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Early Predictors of Severity in Dengue Fever: An Ambidirectional Cohort Study

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Abstract

Objective: To identify early clinical and laboratory predictors of severe dengue among hospitalized patients during the 2024 outbreak in Islamabad.

Methodology: This ambidirectional (mixed) cohort study included 281 laboratory confirmed dengue cases admitted to tertiary care hospital in Islamabad from July to December 2024. Dengue severity was classified according to the WHO criteria as dengue without warning signs, dengue with warning signs and severe dengue using purposive sampling technique. Detailed Clinical features with initial presenting features and laboratory parameters during first 4 days of illness were extracted from the record of the patients and patients were followed for change in severity and progression in the course of illness were analyzed. Uni-variate and multivariate logistic regression was performed to identify independent predictor of severe dengue at 5% alpha.

Results: Among the 281 study participants, 51.2%, 45.2% and 3.6% progressed to DF without warning signs, Dengue with warning sign & Severe dengue respectively. Severe dengue was significantly associated with age >35years (p<0.001), [dengue with non-severe disease has age 30.7±12.3, while dengue with severe disease has age 38.6±15.8], diabetes (p=0.035), hypertension (p=0.035), nausea, vomiting, diarrhea, arthralgia rash and bleeding manifestations (p<0.01). Early thrombocytopenia (<50,000/µL within 4 days of illness) strongly correlate with severity (p<0.001). IgM+IgG co-positivity increased significantly across severity categories (p<0.001). Multivariate analysis identified shortness of breath [OR:27.8(6.3-123.7) 95%CL p<0.001], bleeding manifestations [9.2 (3.7–22.4 CL 95%)(p<0.001)] and platelet count <50,000/µL within 4 days of illness [OR:8.6 (3.4–22.396%CI) p<0.001) as independent predictors of severe dengue.

Conclusion: Early onset thrombocytopenia, bleeding and shortness of breath are critical independent predictors of severe dengue. Incorporating these clinical indicators in initial assessment may improve risk stratification and reduce morbidity and mortality during outbreak in resource-limited setting.

Keywords: dengue Fever, dengue hemorrhagic fever, outbreak, predictors, severity

Introduction

Over the last decade, dengue fever has emerged as a major global health concern, with a marked surge in both the number and severity of cases. According to the World Health Organization (WHO), there has been a significant increase in the number of dengue cases this year alone.[1] Dengue is estimated to cause approximately 390 million infections annually, with about 96 million resulting in clinically apparent cases.[1] From January to July 2025, over 4 million cases and over 3000 deaths have been reported to WHO from 97 countries.[2]

Dengue is prevalent across all regions of Pakistan. According to the National Institute of Health-Pakistan, 52,929 cases were reported in 2021 and 79,007 cases in 2022, 21018 cases in 2023 and in 2024, 28427 cases have been reported.[4] This year, a large number of patients have presented with warning signs at the time of diagnosis and were subsequently found to have complicated dengue fever. Despite improvement in disease surveillance and reporting systems, early identification of patients at risk of severe outcomes remains a significant clinical challenge.

Dengue is transmitted by the bite of the Aedes aegypti mosquito, which belongs to the Flavivirus family. There are four antigenic variants of the virus, DENV1, DENV2, DENV3, and DENV4.[5] Clinically, it can manifest as an undifferentiated febrile illness to more fatal forms such as Dengue hemorrhagic fever and dengue shock syndrome, associated with multi-organ failure and death. Individuals with underlying comorbidity are even at greater risk of developing severe disease.[6] Risk factors have been identified by several studies that serve as potential Indicators for disease severity.[7,8] Therefore, recognizing significant signs and symptoms earlier in the clinical course is essential for the timely prediction and management of life-threatening complications.

Despite yearly outbreaks and high disease burden of dengue, early prediction of the disease severity remains challenging. While extensive research has already been conducted on the complications of dengue, there is limited data available on early clinical predictors of the disease especially in Pakistan. There is an urgent need to recognize early clinical markers of disease severity and to develop a risk scoring system in resource-limited countries, particularly in Pakistan, to enable timely intervention and reduce mortality.

Our study aims to identify the early clinical and laboratory predictors especially on first 4 days of illness before critical phase begun which are associated with fatal outcomes in patients with dengue fever. Early identification of high-risk patients will enable clinicians to prioritize and optimize management, potentially reducing morbidity and mortality.

Methodology

Study Design: This was an ambidirectional (mixed) Cohort study as all inpatients cases of dengue were enrolled in the study and data for initial four days of disease regarding their laboratory investigations and day of onset of disease were collected retrospectively and they were followed for the development of outcome in the form of severity of dengue fever.

Study sites: The study is carried out at the inpatient department of the Pakistan Air Force Hospital Islamabad, a tertiary care hospital, well equipped with the facilities of high dependency units (HDU), Intensive care units (ICU) and advanced imaging and laboratory services for the diagnosis and management of infectious diseases, including dengue.

Study Population, Sampling technique and Sample Size: A total of 281 patients with dengue confirmed either with positive NS-1 Ag or Dengue Serology (IgG, IgM) were enrolled in the study using purposive sampling. The sample size was calculated by using WHO sample size calculator with a 95% confidence level, estimated dengue prevalence of 30 %9 based on regional epidemiological studies from Pakistan. and 5% precision yielding a minimum required sample of 260 patients.

Inclusion and exclusion criteria

All patients aged 18 years or older, who had laboratory confirmed dengue fever were included in the study during July to December 2024.

Patients excluded were those who had any preexisting hematological disorder, febrile illness due to another co-infection such as malaria or enteric fever, who were receiving any kind of immunosuppression therapy and were pregnant at the time of enrollment. Patients with incomplete data record were also excluded.

Data collection procedure

Clinical Laboratory and imaging data of enrolled participants were collected from hospital record using standardized data sheet by researcher themselves. These data sheet was self-developed by researcher after thorough literature search. The socio-demographic variables and those pertaining to dengue fever were included in this data sheet. To ensure the accuracy, internal validity and clinical relevance, the data sheet was reviewed by two senior medical specialists and modified as per their suggestions.

Dengue specific data include clinical onset, symptoms, laboratory findings and outcome in the form of dengue fever (D), dengue with warning signs (DW) & Severe Dengue (SD). Illness onset was defined as the first day of fever onset. Clinical symptoms and relevant laboratory parameters for initial 4 days of disease were observed. All patients were followed up till their admission in hospital for final outcome in the form of DF

without warning signs: these are confirmed dengue in febrile phase.

Dengue with warning signs: these are dengue patients who are having confirm key indicators like abdominal pain vomiting mucosal bleeding or raising hematocrit who needs close monitoring.

Severe Dengue these are dengue patients who are having at least one of the following severe plasma leakage leading to shock or respiratory distress, severe bleeding or severe organ impairment.28

Statistical Analysis: Statistical analysis was made using SPSS version 27. Continuous and categorical variables were compared using Student's t-test and Chi-square or Fisher's exact test respectively. Variables with p<0.10 in uni-variate analysis were entered into multivariate logistic regression model to identify independent predictors of severe dengue. Significance was set at p<0.05.

Ethical Consideration: Ethical letter was obtained from hospital ethical committee letter no: 250307-B. Moreover individual consent was taken from each participants.

Results

281 patients with suspected dengue fever were enrolled in the study, conducted from July to December 2024 corresponds to the outbreak of dengue fever. Data revealed that there were 144 (51%) patients with dengue fever without warning sign,127 (45%) dengue with warning sign and 10 (3.5%) with severe Dengue.

Among all study participants, 274 (97.2%) patients had positive NS1 Ag and 241 (85%) patients had Dengue serology positive, of which 142(50.4%) were IgM and 5(1.8%) were IgG positive and 94 (33.3%) had both IgG and IgM positive.

In present study, more males 191 (67.6%) were affected as compared to females. Total 86 (45.3%) males and almost similar ratio of female 41 (41.5%) had DW. It was observed that mean age of participants with serious dengue was slightly higher 38.6 ± 15.8 years as compared to those with non-serious dengue fever 30.7± 12.3 years and this difference was significant statistically (p<0.001) on student's t-test as shown in Table I.

24 patients have DM out of them 8 (33.3%) have simple DF, 14 (58.3%) have DW and 2 (8.3%) have SD. 28 patients have Hypertension out of them 10(35.7%) have DF,17(60.7%) have DW, and 1 (3.6%) have SD, for asthmatic patients total no. was 5, out of them 2(40%) have DF 2(40%) have DW and 1(20%) have SD, 7 patients have IHD 1 (14.3%) have DF, 6(85.7%) have DW, 209 patients do not have any comorbidities out of which 118(56.5%) have DF ,127(45.2%) have DW 10(3.6%) have SD. the Fisher-Freeman-Halton Exact test(P=0.035) and Linear-by-Linear Association(p=0.002) suggest a strong increasing trend showing that patients with comorbidities are more likely to develop severe dengue than those without. (Table 1)

Table II focuses on potential utility of certain clinical manifestations as supportive clinical indicators. It shows that a range of clinical features showed extremely significant association with dengue severity like nausea, vomiting, diarrhea, abdominal pain, shortness of breath, arthralgia and bleeding disorders (mucosal bleeding, vaginal bleeding and bleeding per rectum) with p-value <0.001. The proportion of all these symptoms showed linear tendency by increasing with severity levels and suggesting them all as strong clinical predictors. Clinical manifestations like myalgia and rash also showed highly significant association with p-value <0.01.

In contrast no significant associations were found for cough (χ^2 =1.94, p=0.748), headache (χ^2 =1.22, p+_0.544), or fever (χ^2 =1.94, p=0.379) which were uniformly present across all severity levels, indicating limited utility in predicting disease progression. Retro-orbital pain showed a possible trend (χ^2 =3.44, p=0.179), though this did not reach statistical significance. All (100%) patients had fever along with headache and body aches and we have observed the clinical features of the patients from the time of onset of fever, which was taken as day 1 of disease for the present study.

Patients with Dengue showed neutropenia with mean TLC of 4.5×109/l ± 3.6x10 9 /l in dengue fever and much lower in severe dengue 3.5×10 9/l.(p<0.001). The mean HCT was 42.8±4 in patients with dengue fever and low in patients with severe disease 5.3±8.

There is a strong and statistically significant relationship between platelet count and dengue severity, patients with lowered platelets counts on less than 4 days of presentation are predictive of more severe form of disease like DW and SD as shown in Table III.

Analysis of serological markers IgG and IgM positivity increase significantly with severity of the disease(p<0.001). In dengue fever cases, IgM positivity predeominates (58.5%) with 28% seronegative for both markers, whereas in dengue hemarrhagic fever, 52.7% patients showed presence of both IgM and IgG. All SD patients were dual positive. this trend indicates that secondary or reinfection cases were associated with severe forms of the disease. (Table 3)

Table IV shows that patients aged >35 years had 2.8 times higher odds of developing severe dengue (p<0.001). Similarly, co-morbid conditions such as diabetes mellitus OR=1.6 (95%CI: 1.1-2.5), p=0.03 and hypertension OR=1.7 (95%CI: 1.1-2.6), p=0.03 were significant predictors, indicating an increased risk among patients with underlying diseases.

Among clinical features, nausea (OR=2.5), vomiting (OR=2.9), and diarrhea (OR=2.2) were all significantly

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associated with severe dengue (p<0.001), suggesting that gastrointestinal symptoms are important early indicators of disease severity. Bleeding manifestations showed strongest association of all , with OR=4.5 (95%CI= 3.0-6.6), P <0.001, highlighting its clinical significance.

A markedly strong association was observed with thrombocytopenia, where patients with platelet count <50,000/μL at presentation (days 1–4) had 5.8 times higher odds of severe dengue (p<0.001), making it one of the strongest predictors in this analysis.

Multivariate analysis demonstrates that shortness of breath [OR=27.8, (95%CI: 6.3–123.7) showed positive association with severe dengue. Moreover, early development of bleeding manifestation [OR=7.2, (95%CI: 1.7–29.5)), p=0.006], platelet count <50,000 [OR=8.6, (95%CI: 3.4–22.3), p<0.001], diarrhea [OR=9.2, (95%CI: 3.7-22.4) and nausea [OR=6.5, (95%CI: 2.2-19.0), p<0.001], were also strong independent predictors of severe dengue. While vomiting and comorbidities were

Table 1. Patient Demographics and Baseline Data

Characteristics	Frequency n=281(100%)	DF 144 (51.2%)	DW 127 (45.2%)	SD 10 (3.6%)	P value
Age in years (mean ± SD		30.7±12.3	38.6±15.8		<0.001
Male	191 (67.6%)	99(52.1%)	86(45.3%)	5(2.6%)	0.001
Female	91 (32.4%)	45(49.5%)	41(45.5%)	5 (5.5%)	
Comorbidities present	209 (74.4%)	118(56.5%)	81(38.8%)	10 (4.7%)	0.097
Diabetes Mellitus (DM)	24(8.5%)	8(33.3%)	14(58.3%)	2 (8.3%)	0.003*
Hypertension (HTN)	28(10.0%)	10(35.7)	17(60.7%)	1(3.6%)	0.003*
Asthma	5(1.8%)	2(40.0%)	2(40.0%)	1(20.0%)	0.097
Ischemic Heart Disease (IHD)	7(2.5%)	1(14.3%)	6(85.7%)	(0%)	0.097

*Fisher Exact p=0.03; Linear-by-Linear trend p=0.002

Table 2. Association of Clinical Manifestations with Severity of Dengue Infection

Symptoms	DF(n=142) n (%)	DW(n=129) n (%)	SD (n=10) n (%)	Total (%) n (%)	p-value	Significant association Trends
Nausea	78 (54.9%)	177 (90.7%)	10 (100%)	205 (73%)	<0.001	Yes ↑with severity
Vomiting	34 (23.9%)	117 (90.7%)	10 (100%)	138 (49.1%)	<0.001	Yes ↑with severity
Cough	23 (16.2%)	25 (19.4%)	02 (20%)	50 (17.8%)	0.786	No
Diarrhea	15 (10.6%)	76 (58.9%)	07 (70%)	98 (34.9%)	<0.001	Yes ↑with severity
Abdominal Pain	24 (16.9%)	83 (64.3%)	08 (80%)	115 (40.9%)	<0.001	Yes ↑with severity
Shortness of breath	4 (2.8%)	40 (31.0%)	05 (50%)	49 (17.4%)	<0.001	Yes ↑with severity
Headache	142 (100%)	128 (99.2%)	10 (100%)	280 (99.6%)	0.554	No
Retro-orbital Pain	29 (20.4%)	35 (27.1%)	04 (40%)	68 (24.2%)	0.215	No

Myalgia	88 (62.0%)	100 (77.5%)	09 (90%)	197 (70.1%)	0.008	Yes ↑with severity
Fever	136 (95.8%)	127 (98.4%)	10 (100%)	273 (97.2%)	0.358	No
Rash	18 (12.7%)	31 (24.0%)	05 (50%)	54 (19.2%)	0.003	Yes ↑with severity
Arthralgia	18 (12.7%)	52 (40.3%)	08 (80%)	78 (27.8%)	<0.001	Yes ↑with severity
Mucosal bleeding (gum/ nose)	02 (1.4%)	31 (24.0%)	07 (70%)	40 (14.2%)	<0.001	Yes ↑with severity
Vaginal Bleeding	(0%)	10 (7.8%)	02 (4.3%)	12 (4.3%)1	<0.001	Yes ↑with severity
Bleeding per rectum	(0%)	09 (7.0%)	04 (40%)	03 (4.6%)	<0.001	Yes ↑with severity

Table 3. Association of Dengue Severity with Laboratory Parameters

Symptoms	DF (n=142)	DW (n=129)	SD (n=10)	P-value	Significant association &Trends
ALT (U/L)	Mostly Normal/ Mild (20-60)	Majority Markedly elevated (61-200)	Very high (>200)	<0.001	Yes; ↑ ALT with severity
Platelet on presentation	Majority >100,000/ µL	Majority <100,000/ µL	60% had <50,000/ µL	<0.001	Yes; platelets↓ with severity
USG Finding	Mostly Normal	GB wall thickness and fluid(40+70 cases)	Fluid +GB Changes (80%)	<0.001	Yes; abnormal USG↑ with severity
Chest X-ray Fluid	None	63(48.8%)	9(90%)	<0.001	Yes; pleural fluid ↑ with severity
NS1 Antigen	97.2%positive	97.7%positive	100%positive	0.847	No; (uniformly positive, not severity related)
Serology (IgM/IgG	IgM most frequent (58.5%),28% negative	Mixed: Ig-M45%Both IgM+IgG 52.7%	All had IgM+IgG	<0.001	Yes; IgM+IgG positivity ↑ with severity
Lowest Platelets count	Mostly >50,000/µL	Majority <50,000/ µL	All <20,000/µL	<0.001	Yes; lowest platelets correlate with severity
Day of presenta-tion	Early=1-4 days (55.6%)	5-8 days (62%)	After 5 days (90%)	0.005	Yes; later presentation ↑risk of severity

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Table 4. Univariate Analysis of predictors of severe Dengue

Predictors	Odds ratio (95% Confidence Interval)	P value
Age> 35 years	2.8 (1.9-4.0)	<0.001
Diabetes mellitus	1.6 (1.1-2.5)	0.035
Hypertension	1.7 (1.1-2.6)	0.035
Nausea	2.5 (1.8-3.4)	<0.001
Vomiting	2.9 (2.0-4.2)	<0.001
Diarrhea	2.2 (1.6-3.1)	<0.001
SOB	2.4(1.9-3.2)	<0.001
Bleeding manifestation	4.5 (3.0-6.6)	<0.001
Platelets<50,000/µL on presentation(1-4 day)	5.8 (3.9-8.7)	<0.001

Table 5. Predictors of severe Dengue on Multivariate Analysis

Predictors	Adjusted OR (95% CI)	P value
Shortness of breath	27.8 (6.3–123.7)	<0.001
Platelets <50,000/µL	8.6 (3.4–22.3)	<0.001
Bleeding manifestation	9.2 (3.7–22.4)	<0.001
Diarrhea	7.2 (1.7–29.5)	0.006
Nausea	6.5 (2.2–19.0)	0.001
Vomiting*	0.24 (0.10–0.59)	0.002
Comorbidities	0.97 (0.36–2.59)	0.958

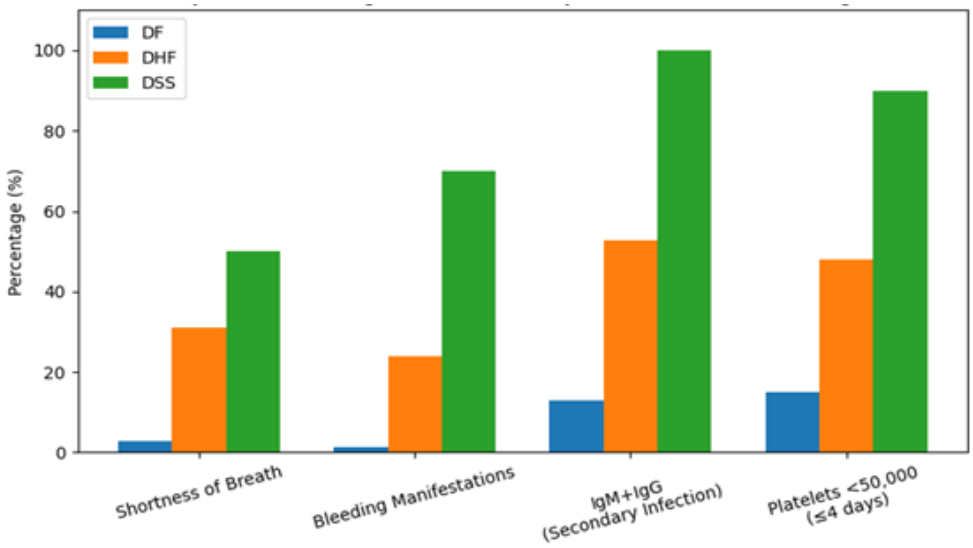

Figure 1: Distribution of various Predictors in accordance with severity of Dengue

not found to be independent predictors after adjustment suggesting that although these features may be common, they do not reliably predict progression to severe disease as shown in Table V.

Discussion

In this retrospective observational cohort study 281 confirmed dengue patients were included in outbreak of 2024 from July till December. Substantial portion of patients (49%) developed severe form of disease, including DW (45%) and SD (3.5%) This severity rate is higher than some regional reports, which typically estimates severe disease 10-30% of hospitalized dengue cases.9

The findings of our study show a male predominance (67.6%) this finding is consistent with regional studies from endemic areas, where behavioral and occupational exposure pattern predispose males to more contact with mosquitoes.10,11,12 However severe Dengue was not limited to either sex, suggesting that gender is not an independent determinant of severity. Our study shows that the patient with DW were significantly older than those with simple Dengue fever. (Mean 38.7 vs 30.7 years p<0.001) it is aligning with reports previously published sighting that advancing age is associated with worse outcome, possibly due to association of co morbid conditions.12,13

The presence of co-morbid conditions particularly diabetes, hypertension, asthma and ischemic heart diseases were significantly associated with increased risk of severe disease (Fisher-freeman Halton p=0.035, linear trends p=0.002).6,14,15 Patients with IHD and hypertension shows severe disease in most of the patients, consistent with earlier studies showing that cardiovascular diseases and metabolic disorders predispose to endothelial dysfunction and impaired immune regulation during dengue infection.16,17,18 These findings reinforce the need for early risk stratification and vigilant monitoring of patients with chronic conditions.12

In our study we have observed that severe gastrointestinal symptoms and constitutional symptoms demonstrate strong association with disease severity. nausea and vomiting in moderate to severe grades were highly prevalent in DW and SD. (P<0.001). This finding echoing WHO guidelines that persistent vomiting is a warning sign.19 Similarly, Diarrhea myalgia rash arthralgia body aches and shortness of breath showed significant association with severe dengue. showing that their values are supporting clinical indicators.20,21 Hemorrhagic manifestations, including epistaxis, gum bleeding, vaginal bleeding and per rectal bleed developing during first 4 days of illness leads to development of severe disease in our cohort.22,15 It is noted that fever and headache which are universally present in all patients did not discriminate between severity categories, indicating their limited prognostic utility.23 Retro orbital pain though showed a non-significant trend toward higher severity, suggesting it may not serve as a reliable early predictor.

Our study confirms the prognostic value of hematological parameters as neutropenia was more pronounced in severe dengue (mean 3.5×10^9/L in Severe disease and 4.5×10^9/L in simple DF).24,25

In this study thrombocytopenia emerged as a strong predictor of severity, as the patients who have lower platelets counts at presentation (<4 days of illness) were found to end up in severe disease as compared to the one who has a higher platelet counts at presentation. This finding is aligning with previous literature stating platelet trend as an accessible and reliable marker for anticipating clinical deterioration.26,27

We observed that increase in IgG and mixed IgG+ IgM positivity among DW and SD patients in our cohort suggest that secondary dengue infection was associated with more severe clinical manifestations. This aligns with prior evidence that hetrotypic secondary infection predispose to severe disease through antibody dependent antibodies from previous infection which enhance viral entry and immune activation during reinfection.

Similar findings have been reported globally, secondary infection were significantly linked to plasma leakage, thrombocytopenia and elevated transaminase. Katzelnick et al. Demonstrated that individuals with intermediate non neutralizing antibodies level were at greatest risk of severe dengue. Likewise, studies from Srilanka and Thiland have shown that high IgG titers or IgM/IgG co-positivity correlate with severe dengue outcomes.

Our findings highlight that it is important to integrate simple clinical observations like persistent vomiting abdominal pain, shortness of breath and bleeding manifestations with readily available simple base line tests of complete blood count showing neutrophils and platelets for early identification of patients at risk of severe disease. In an outbreak this combined approach could guide triage, help in optimizing hospital resource utilization and potentially reduce mortality.

Conclusion

This study demonstrates that increasing age, male gender, and the presence of comorbidities are associated with a higher risk of severe dengue. Clinical symptoms such as nausea, vomiting, shortness of breath and bleeding manifestation along with thrombocytopenia and elevated liver enzymes, indicate disease progression. Multivariate analysis identified shortness of breath, bleeding manifestation and platelet count <50,000 with in first 4 days of illness as the strongest independent predictor of severe dengue. Reinfection, reflected by higher IgG or mixed IgG and IgM was strongly associated with severe dengue. Early recognition of these factors is crucial for timely intervention

and improved patient outcomes.

Limitation

It is single Center study therefore may restrict generalization and potential referral bias toward more severe cases.

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Authors' Contribution Statement

HS contributed to the conception, design, acquisition, and analysis of data, drafting of the manuscript, critical review of the manuscript, and final approval of the version to be published. SUR contributed to the acquisition of data, editing, and formatting of the manuscript. AB contributed to the analysis and interpretation of data. All authors are accountable for their work and ensure the accuracy and integrity of the study.

Conflict of Interest

Authors declared no conflict of interest

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None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.