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Original Article

Role of Serum Ferritin as An Early Prognostic Marker in Dengue Fever: A Prospective Observational Study

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Abstract

Background: *Early detection of progression to severe dengue using simple and measurable tests is crucial for initiating appropriate supportive therapy. This research investigated if blood ferritin levels can be used as a marker of seriousness in individuals with dengue.* ***Methods:*** *A hospital-based, forward-looking study was performed on 70 individuals admitted to the Bangladesh Shishu Hospital & Institute. Dengue diagnoses were made based on NS1 antigen detection on days 2–3 and/or IgM presence on days 6–10. Blood ferritin levels were quantified using ELISA on the day of defervescence.* ***Results:*** *Mean age was 5.5 ± 4.02 years, with 42.9% between 1–5 years and a male predominance (62.9%). Dengue shock syndrome developed in 28.6% of patients. The mean serum ferritin level was 931.50 ± 1009.56 ng/ml. significantly higher levels (2222.60 ± 739.60 ng/ml) were observed in dengue shock syndrome cases.* ***Conclusion:*** *Elevated serum ferritin levels during the defervescence period are significantly associated with dengue shock syndrome and may be used as an early prognostic marker.*

Keywords: *Progression, Dengue Fever, ferritin levels, defervescence, predominance*

Introduction: Dengue virus (DENV), a member of the flavivirus family, is mainly spread through the bites of Aedes aegypti and Aedes albopictus mosquitoes. Four main serotypes of the virus are known: DENV-1 to DENV-4. Infection with one serotype provides lifelong protection against that specific serotype, but not against the others. Subsequent infections with different serotypes can increase the risk of severe dengue due to a phenomenon called antibody-dependent enhancement[1,2]. DENV1 and DENV3 are generally considered less dangerous than DENV2 and DENV4, with Type 4 being less virulent than Type 2. Experiencing dengue infection with one serotype provides lifelong immunity to that specific serotype but may increase the risk of complications upon later infection with a different serotype. Dengue is a major cause of sickness and death among children in Southeast Asia[1,2]. The World Health Organization (WHO) estimates that there are roughly 50-100 million new dengue infections worldwide annually, with 50,000 severe cases requiring hospitalization and a mortality rate of about 2.5%. The number of cases has dramatically increased over the last two decades, rising nearly eightfold from 505,430 in 2000 to approximately 5.2 million in 2019[3,4]. The first dengue hemorrhagic fever outbreak in Bangladesh occurred in mid-2000, with 5,551 reported cases from Dhaka, Chittagong, and Khulna. Of these, 4,385 (62.4%) were classified as Dengue Fever (DF) and 1,186 (37.6%) as Dengue Hemorrhagic Fever (DHF). The Case-Fatality Rate (CFR) was 1.7%, with 93 deaths reported. In 2019, 101,354 dengue cases were recorded, along with 179 related deaths[5]. The severity of dengue can range from a mild fever to more serious conditions like dengue hemorrhagic fever and dengue shock syndrome[6]. Dengue fever usually presents as a sudden fever lasting 2 to 7 days, accompanied by symptoms such as headache, pain behind the eyes, muscle aches, joint pain, rash, and bleeding problems[7].

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The NS1 antigen test, using the enzyme-linked immunosorbent assay (ELISA), is used for dengue diagnosis during the initial five days of fever. The NS1 test shows a diagnostic sensitivity exceeding 90% within the first two to three days of illness. However, its sensitivity gradually decreases and becomes significantly lower after the fifth day[8]. Dengue virus-specific IgM can be identified and used to diagnose dengue infections with considerable accuracy. Individuals who have never had dengue before show a gradual IgM response, increasing by 50% within three to five days, 80% after more than five days, and reaching 100% after ten days [9],[10]. According to the WHO, severe dengue includes dengue hemorrhagic fever and dengue shock syndrome[11]. Ferritin is a protein that stores iron, making it readily available for essential cell functions while protecting other important molecules from the potentially damaging effects of this metal. It also plays a role in various other health conditions, including inflammatory, neurodegenerative, and cancerous diseases[9]. Some studies have indicated that serum ferritin might serve as a marker for feverish thrombocytopenia caused by viral infections like dengue fever[12],[13]. Elevated ferritin levels in dengue patients suggest a strong immune response and problems with blood clotting, indicating more severe disease requiring close observation[14],[15]. This research investigated whether measuring ferritin early in the illness could predict the severity of dengue, potentially helping with patient sorting and proper care.

Materials & Methods

This prospective observational study, carried out at Bangladesh Shishu Hospital & Institute in Dhaka, Bangladesh, aimed to investigate the relationship between serum ferritin levels and dengue severity during the defervescence period.

The study included children between 1 month to 15 years old who had dengue fever with warning signs upon arrival at the hospital. Children were not included if they had dengue shock syndrome, dengue hemorrhagic fever, significant long-term illnesses, or had received a blood transfusion recently. Participants were selected based on the World Health Organization's (WHO) 2012 criteria for dengue fever with warning signs. Patients with fever and positive dengue blood tests from other labs were also considered. Individuals were excluded if permission to participate was not granted by their parents or legal guardians. Dengue cases were confirmed by positive NS1 antigen tests within the first 3 days of illness, and/or positive IgM antibody tests between days 6 and 10. Patients with other identified causes for their fever were classified as having different febrile diseases. Severe dengue was characterized by severely low platelet counts, substantial bleeding, fluid leaking from blood vessels, shock, or failure of multiple organs. All other cases were classified as non-severe dengue. Serum ferritin levels were measured during the defervescence period via immunoluminescence using the ADVIA Centaur CP instrument. Blood tests were performed using the Sysmex Hematology Analyzer (Model 1000) to measure hemoglobin, total white blood cell count, types of white blood cells, platelet count, and hematocrit. The main goal of the study was to evaluate the relationship between serum ferritin concentrations and the severity of dengue illness.

Statistical Analysis: Data analysis was done using the Statistical Package for the Social Science (SPSS) Version 25. Continuous variables were summarized using mean and standard deviation (SD) and categorical variables as frequencies and percentages. Kruskal Wallis test was done to compare the median values among groups. A probability value of <0.05 was accepted as the level of statistical significance.

Results

Table I: Demographic profile of the study subjects (N=70)

	Frequency (n)	Percentage (%)
Age (years)		
< 1	8	11.4
1 - 5	30	42.9
>5 - 10	22	31.4
>10 - 15	10	14.3
Mean ± SD	5.50 ± 4.02	
Min - max	0.33 - 15	
Gender		
Male	44	62.9
Female	26	37.1

Mean age of the study subjects was 5.5 ± 4.02 years, with 42.9% of patients between 1–5 years of age. There was a male predominance (62.9%) among the study population.

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Table II: Symptoms of dengue of the study subjects (N=70)

Symptoms	Frequency (n)	Percentage (%)
Fever	70	100.0
Rash	23	32.8
Joint pain/Arthralgia	1	1.4
Persisting vomiting	13	18.6
Headache	3	4.3
Constipation	1	1.4
Diarrhea	5	7.1
Abdominal pain	13	18.6
Retro-orbital pain	4	5.7
Urine output reduced	9	12.9
Duration of illness (days)		
Febrile [Mean ± SD]	4.52 ± 2.51	

During admission, all dengue cases presented with fever (100%) and mean duration of fever was 4.52 ± 2.51 days. Other predominant clinical features included rash (32.8%), vomiting (18.6%), abdominal pain (18.6%), reduced urine output (12.9%), and diarrhea (7.1%), as shown in Table II.

Table III: Dengue NS1 antigen of the study subjects (N=70)

	Frequency (n)	Percentage (%)
Dengue NS1		
Positive	42	60.0
ICT for Dengue		
IgM (positive)	25	35.7
IgM & IgG (positive)	3	4.3

Regarding serological tests, NS1 antigen was positive in 60.0% of cases (based on prior reports before admission), while 35.7% tested positive for IgM antibodies and 4.3% tested positive for both IgM and IgG (Table III)

Table IV: CBC parameter at admission of the study subjects (N=70)

	Mean ± SD	Min - max
Hemoglobin (g/dl)	10.83 ± 1.42	6.40 - 13.90
HCT	34.61 ± 4.19	22.50 - 49.00
TWBC	6654 ± 3328	430 – 20250
Platelet count	186739 ± 108414	20000 – 442000

Baseline hematological data at admission showed a mean hemoglobin level of 10.83 ± 1.42 g/dL, hematocrit (HCT) 34.61 ± 4.19%, total leukocyte count (TWBC) 6,654 ± 3,328 /mm³, and platelet count 186,739 ± 108,414 /mm³ (Table IV).

Table V: Liver function test at admission of the study subjects (N=70)

	Mean ± SD	Min - max
SGOT (U/L)	128.56 ± 317.67	12.00 - 2504.00
SGPT (U/L)	82.46 ± 172.39	14.00 - 998.00
Serum Albumin (gm/L)	33.89 ± 4.68	22.80 - 41.00

Liver function tests showed a higher mean SGOT (AST) level (128.56 ± 317.67 U/L) compared to SGPT (ALT) (82.46 ± 172.39 U/L). Mean serum albumin level was 33.89 ± 4.68 g/L (Table V).

Table VI: Serum ferritin level during the defervescence period of the study subjects (N=70)

	Mean ± SD	Min - max
Serum Ferritin (ng/ml)	931.50 ± 1009.56	18.50 - 4130.00

Mean serum ferritin level at the defervescence period was 931.50 ± 1009.56 ng/mL, with values ranging from 18.50 to 4,130.00 ng/mL (Table VI).

Table VII: Signs of dengue during the defervescence period of the study subjects (N=70)

Signs	Frequency (n)	Percentage (%)
Tourniquet test positive	14	20.0
Low BP	20	28.6
Pulse		
Low	20	28.6
Normal	50	71.4
Bleeding	3	4.3
Ascites	4	5.7
Organ dysfunction	3	4.3

At defervescence, 20.0% of patients had a positive tourniquet test, and 28.6% developed low blood pressure (shock). Bleeding was observed in 4.3%, ascites in 5.7%, and organ dysfunction in 4.3% of cases (Table VII).

Table VIII: Type of dengue of the study subjects (N=70)

	Frequency (n)	Percentage (%)
Dengue Fever with warning sign	40	57.1
Dengue Hemorrhagic fever	7	10.0
Dengue shock syndrome	20	28.6
Expanded dengue syndrome	3	4.3

Based on World Health Organization classifications, the majority of patients in the study (57.1%) presented with dengue fever accompanied by warning signs.

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A smaller proportion had dengue hemorrhagic fever (10.0%), while a little over a quarter (28.6%) progressed to dengue shock syndrome. A small percentage of the subjects (4.3%) developed expanded dengue syndrome (Table VIII).

Table IX: Serum ferritin level according to dengue type of the study subjects (N=70)

	Mean ± SD	p-value
Dengue Fever with warning sign	415.38 ± 559.84	<0.001
Dengue Hemorrhagic fever	559.19 ± 300.93	
Dengue shock syndrome	2222.60 ± 739.60	
Expanded dengue syndrome	74.63 ± 5.92	

Serum ferritin levels varied significantly among dengue types ($p < 0.001$), with the highest mean level in dengue shock syndrome cases (2222.60 ± 739.60 ng/mL) (Table IX).

Discussion:

Currently, there is no single test that can accurately predict the severity and outcome of dengue fever. Therefore, this study aimed to evaluate the association between serum ferritin levels and disease severity in dengue patients, with the goal of identifying an accessible early prognostic marker for improved patient triage and management.

In our study, the majority of patients were male (62.9%). A study from Singapore reported a similar male predominance, with 71% of PCR-positive dengue patients being male [17]. Nadeem et al. [16] Also found a higher proportion of male patients in their cohort.

The mean duration of the febrile phase in our study was 4.52 ± 2.51 days, which is comparable to the findings of Chaiyaratana et al. [18], who reported a median febrile duration of five days (range: 1–10 days).

In our cohort, dengue hemorrhagic fever was identified in 10% of patients, dengue shock syndrome in 28.6%, and dengue fever with warning signs in 57.1%. Severe dengue manifestations included bleeding (4.3%), shock (28.6%), ascites (5.7%), and organ dysfunction (4.3%). These findings are consistent with the observations of Diwakar and Madhu [19], who reported similar complication rates in severe dengue.

A key finding of our study was the significantly higher mean serum ferritin level in patients with dengue shock syndrome (2222.60 ± 739.60 ng/mL) compared to those with dengue fever with warning signs (415.38 ± 559.84 ng/mL), dengue hemorrhagic fever (559.19 ± 300.93 ng/mL), and expanded dengue syndrome (74.63 ± 5.92 ng/mL) ($p < 0.001$).

These results are supported by previous studies. Nadeem et al.[16] reported mean ferritin levels of 3175.4 ± 1095.2 ng/mL in severe dengue compared to 1686.9 ± 1307.0 ng/mL in uncomplicated dengue fever. Similarly, Prakash et al.[20] observed significantly higher median ferritin levels in severe dengue (3985 ng/mL, IQR: 2007 ng/mL) compared to non-severe dengue (1936 ng/mL, IQR: 1940 ng/mL) ($p < 0.001$).

Other studies by Petchiappan et al.[21] and Soundravally et al.[12] also demonstrated that hyperferritinemia is strongly associated with severe dengue and can serve as an early predictor of disease severity. The likely explanation is that elevated ferritin reflects intense immune activation, cytokine release, and associated coagulation abnormalities, all of which contribute to severe clinical outcomes. In contrast, Expanded Dengue Syndrome is a broad category of atypical organ involvement (neurological, renal, hepatic, cardiac etc.). It does not always involve the same degree of systemic cytokine storm or macrophage activation seen in DSS.

Our findings strengthen the evidence that serum ferritin, a widely available laboratory marker, could be used to identify dengue patients at risk of developing severe disease, allowing earlier intervention and closer monitoring.

Conflict of interest

There are no conflicts of interest associate with this study.

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Conclusion:
Elevated serum ferritin levels during the defervescence period were significantly associated with dengue shock syndrome in this study. These findings suggest that serum ferritin can serve as a useful early prognostic marker to identify patients at higher risk for severe dengue. Incorporating serum ferritin measurement into routine dengue evaluation may help guide timely clinical decision-making, optimize patient triage, and improve outcomes through earlier intervention and closer monitoring.

Limitations:
1. The study did not differentiate between compensated and decompensated dengue shock syndrome, which may have provided additional insight into disease progression.
2. Dengue virus genotyping was not performed, limiting the ability to correlate specific serotypes with serum ferritin levels and disease severity.
3. Serum ferritin was not measured during the febrile period.

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