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Acute Phase Reactants and Their Clinical Correlation in Patients with Dengue Hemorrhagic Fever

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Abstract **Original Research Article**

Background: Early recognition and risk stratification in dengue hemorrhagic fever (DHF) are essential, as it can progress to dengue shock syndrome (DSS), contributing significantly to morbidity and mortality. An optimal biomarker is required to predict the severity of an illness. Acute phase reactants, including serum ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), exhibit rapid changes in response to infection and may serve as valuable indicators for early diagnosis and prognosis ***Methods*:** This descriptive cross-sectional study was conducted in the Department of Medicine, Dhaka Medical College Hospital, from February to July 2020. 140 patients diagnosed with DHF based on WHO criteria were enrolled. Clinical features and laboratory data were collected, including ESR, CRP, and serum ferritin. Associations between acute phase reactants and clinical parameters such as bleeding, shock, plasma leakage, hepatomegaly, and hospital stay were analyzed using SPSS v23.0. A p-value <0.05 was considered statistically significant ***Results*:** Of the 140 patients, 112 (80%) had DHF without shock, and 28 (20%) had DSS. The mean ESR, CRP, and ferritin levels during the critical phase significantly differed between DHF and DSS groups ($p<0.05$), indicating a correlation with disease severity. However, differences during the convalescent phase were not statistically significant ***Conclusion*:** Serum ferritin and CRP are promising acute phase reactants for assessing disease severity in DHF. Their routine evaluation may support the early identification of high-risk patients and guide clinical management.

Keywords: Dengue Hemorrhagic Fever, acute phase reactants, serum ferritin, C-reactive protein, ESR.

INTRODUCTION

Dengue fever is currently one of the most significant arboviral infections worldwide. It has affected more than 100 countries in tropical and subtropical regions. According to WHO estimates, between 50 and 100 million dengue illnesses occur each year, and the incidence has increased 30 times worldwide within the previous 50 years. The dengue virus is a serious hazard to public health today, and about two-fifths of the world's population is susceptible to contracting the virus [1–3]. Bangladesh has achieved remarkable progress in controlling communicable diseases in recent years. However, the country still faces tremendous pressure regarding public health problems, especially controlling emerging or re-emerging diseases. The upsurge in dengue cases introduces a major threat to the community's health, and its emerging situation warrants an increased level of interventions in the health sector of Bangladesh [4].

Aedes mosquitoes, including Aedes aegypti and Aedes albopictus, are the vectors of dengue illness. Clinical signs of dengue infection include asymptomatic infection, undifferentiated fever, dengue fever, a symptom similar to influenza, and dengue hemorrhagic fever (DHF), a severe and occasionally fatal illness marked by bleeding and shock. The first and second epidemics of DHF occurred in Manila in 1954 and 1956, followed by the third in Bangkok in 1958. Since then, DHF has spread throughout tropical Asian countries and has expanded globally. There are four distinct serotypes, namely dengue 1 to 4. Infection with any of the four serotypes causes similar clinical symptoms that may vary in severity, depending on several risk factors, including virus virulence, viral load and host response [5–7]

Most dengue patients recover without problems after 5–7 days of acute illness. However, in DHF, the initial febrile period is followed by a rapid onset of vascular leakage, thrombocytopenia, and hemorrhage. The continual loss of intravascular volume from plasma leakage can very rapidly lead to hypotension and cardiovascular collapse, which may lead to dengue shock syndrome (DSS). If this is not managed carefully, it can cause significant mortality. The lack of knowledge regarding the mechanisms that cause the progression from moderate DF to more serious DHF has hampered the early identification of dengue patients who will develop DHF. This causes treatment delays and often leads to over-hospitalization, which greatly increases the cost burden of dengue. Triaging patients for treatment may benefit from the availability of trustworthy indicators that forecast DHF in the early stages of infection [8,9]

Studies have identified various biomarkers for immune and endothelial cell activation and biochemical and genetic markers to predict the severity of dengue. The clinical utility of these markers is limited since measurement of these markers like soluble receptors, growth factors, genetic profiling etc. is technically difficult and not widely available [10]. Hence, a reliable and useful simple biomarker to distinguish between severe and mild illness of dengue during the early phase of infection is needed in deciding as to whether or not to admit the patient for management [11]. Acute phase reactants (APR) are inflammation markers that increase or decrease in the patient's serum during times of acute tissue injury or inflammation. They are also important mediators in the inflammatory process that is activated after such stress has been inflicted on the body, and it is feasible to measure their levels. The most commonly measured positive APR include C- reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) [12]. Other acute phase reactants like ferritin levels, cytokines, coagulation factors, long pentraxin, and pentraxin 3 have been studied to predict the severity of dengue infection in clinical practice. In some cases, a positive correlation has been found [13,14] However, there are no accepted clinical guidelines for the early recognition and stratification of DHF. Therefore, the study aims to evaluate the use of APR and its clinical correlation in dengue haemorrhagic fever.

OBJECTIVE

The objective of this study was to evaluate the use of acute phase reactants and their clinical correlation in dengue haemorrhagic fever.

METHODOLOGY & MATERIALS

This descriptive cross-sectional study was conducted at the Department of Medicine, Dhaka Medical College Hospital, from February to July 2020. It included 140 people who were diagnosed with dengue hemorrhagic fever and admitted to the hospital.

Selection criteria:

Inclusion Criteria:

- Age above 18 years
- Diagnosed as a case of dengue haemorrhagic fever
- Willing to participate.

Exclusion Criteria:

- Dengue patients with co-infections.
- Patients on drugs like steroids, antimalarials and immunosuppressants.
- Patients with sideroblastic anemia, thalassemia, and liver disease.
- Pregnant women

Data Collection Procedure: The study was conducted in the Medicine Ward of Dhaka Medical College Hospital after obtaining ethical clearance. A pretested case record form and structured questionnaire collected data from 140 purposively selected DHF patients with informed consent. Face-to-face interviews gathered socio-demographic and clinical data, followed by physical examinations. ESR, CRP, and serum ferritin levels were assessed using conventional techniques during critical and convalescent stages. Equipment included consent forms and questionnaires capturing patient details and acute phase reactant levels relevant to disease severity assessment.

Data Analysis: After collecting information, these data were checked, verified for consistency, and edited for final results. The data were entered into the computer and analyzed using statistical packages like Statistical Package for Social Sciences, SPSS version 23 (International Business Machines Corporation, IBM, USA). Text, tables, charts and graphs presented the result. A significance level (p-value) of <0.05 was taken for all statistical analyses.

Ethical Implication: The study was conducted after obtaining ethical clearance from the ethical review committee of Dhaka Medical College before commencement. Before data collection, informed written/verbal consent was taken from the respondents. Moreover, the confidentiality of collected data was maintained with the highest priority. Before data collection, the objectives, procedure, and benefits of the study were explained to the participants. The privacy of the participants was also maintained during data collection.

RESULTS

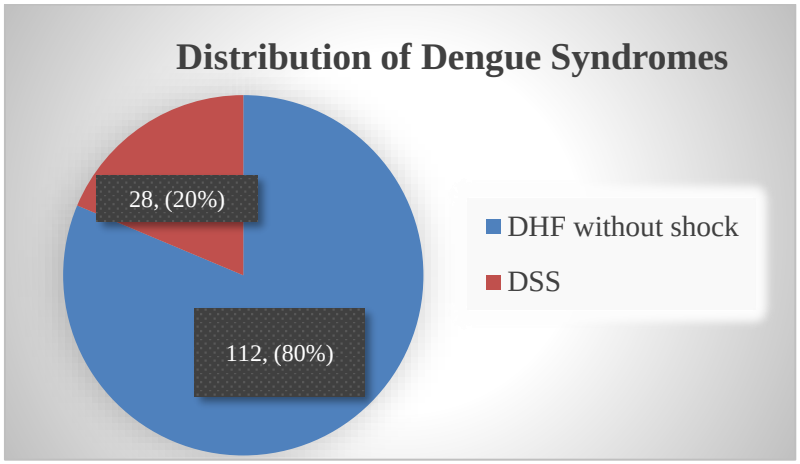

Figure 1: Distribution of Dengue Syndromes Among the Patients

Figure 1 shows that among the 140 patients included in this study, DHF without shock was 112 (80%), and DSS was 28 (20%).

Table 1: Baseline Characteristics of the Participants (n=140)

Variables	Group	Number of patients (n)	Percentage (%)
Age group (years)	18-30	43	30.71
	31-40	27	19.29
	41-50	18	12.86
	51-60	22	15.71
	61-70	16	11.43
	>70	14	10
Sex	Male	72	51.43
	Female	68	48.57
BMI (kg/m^2)		20.38±5.12	
Resident	Rural	58	41.43
	Urban	82	58.57

Table 1 shows the baseline characteristics of the participants. Among the participants (N=140), 72 were males (51.43%), and 68 were females (48.57%). Most of the patients came from urban areas (82, 58.57%). BMI was 20.38 (±5.12) kg/m^2.

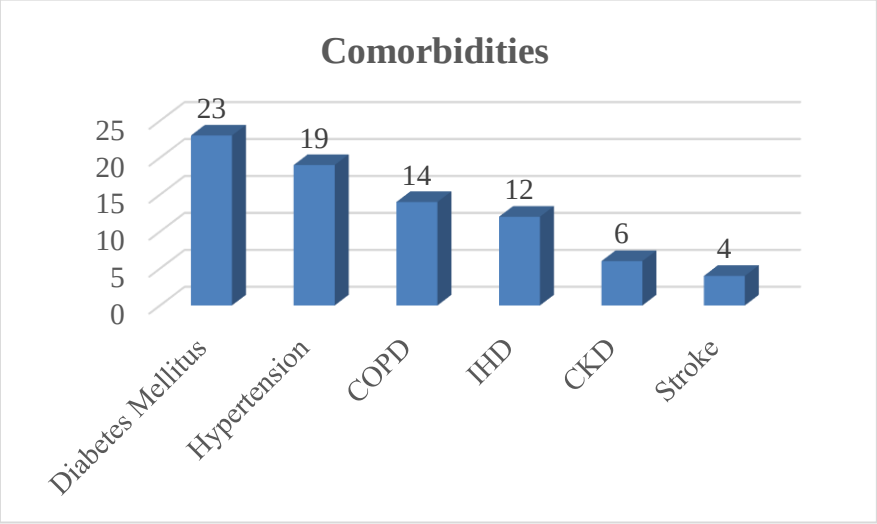

Figure 2: Comorbidities of the patients (n=140)

Common morbidities are shown in Figure 2. Diabetes Mellitus 23 (16.43%) followed by HTN 19 (13.57%) are the two commonest comorbidities followed by COPD 14 (10.0%), IHD 12 (8.57%), CKD 6 (4.29%), and lastly stroke 4 (2.86%).

Table 2: Clinical Features of the Dengue Patients (n=140)

Clinical features	Total	DHF	DSS	P value*
Fever	140 (100.00)	112 (80)	28 (20)	
Headache	118(84.29)	96 (85.71)	22 (78.57)	0.768
Generalized body-ache	67 (47.86)	51 (45.53)	16 (57.14)	0.978
Eye-ache	76 (54.28)	60 (53.57)	16(57.14)	0.324
Rash	109(77.86%)	88(78.57)	21(75)	0.234
Vomiting	92(65.71)	76(67.85)	16(57.14)	0.216
Abdominal Pain	38(27.14)	32(28.57)	6(21.42)	0.436
Pleural effusion	73(52.14)	54(48.21)	19(67.85)	0.412
Ascites	44(31.43)	35(31.25)	9(32.14)	0.327
Bleeding manifestation	47(33.57)	36(32.14)	11(39.28)	0.129

*All p-values were determined by comparison of the proportion between groups by Pearson's chi square test of independence

Table 2 shows the common clinical features in dengue patients. Fever was present in 140 patients (100.00%), followed by headache in 118 (84.29%), and the two most common clinical features were rash in 109 (77.86%) and vomiting in 92 (65.71%). There was no statistically significant difference between the prevalence of these symptoms between DHF and DSS groups.

Table 3: Investigation findings of the participants (N=140)

Parameter		DHF (n=112)	DSS (n=28)	p-value*
ESR (mm at 1st hour)	Critical period	12.63 ± 0.45	8.01 ± 0.35	<0.001
	Convalescence	5.33 ± 0.25	5.91 ± 0.15	0.53
CRP	Critical period	20.1 ± 2.4	36.63 ± 1.79	<0.001
	Convalescence	3.1 ± 0.45	3.63 ± 0.79	0.61
Serum ferritin	Critical period	1213 ± 40	1503 ± 35	0.04
	Convalescence	353 ± 40	313 ± 35	0.8
CBC	Hb (g/dL)	11.3	11.7	0.76
	Total WBC (/mm^3)	3700	2800	0.67
	Platelet (/mm^3)	30000	16000	0.89
Serum creatinine (mg/dL)		1.2	1.3	0.79
SGPT (U/ml)		110	130	0.89

*Derived from comparison of means between DHF and DSS group with Mann-Whitney U non-parametric test.

Table 3 shows a comparison of the results of laboratory investigations between groups of patients with DHF and patients with DSS. In the critical period, ESR was found to be higher in DHF, whereas CRP and serum ferritin were found to be lower in DHF. The ESR, CRP and ferritin differences between DHF and DSS were statistically significant (p values <0.001, <0.001 and 0.04 respectively). During the Convalescence period, the differences in ESR, CRP, and ferritin between DHF and DSS were not statistically significant. The differences in HB, total WBC and platelet between DHF and DSS were not statistically significant. The difference in serum creatinine and SGPT between DHF and DSS groups was insignificant.

DISCUSSION

The research investigated how acute phase reactants relate to dengue hemorrhagic fever clinical severity and their capability to forecast patients who could develop dengue shock syndrome (DSS). DHF without shock was diagnosed in 80% of the 140 patients, whereas 20% developed DSS. The development of DSS in 20% of patients from our population exceeded previous results, where Chen et al. noted DSS in 8.7% of cases [11].

The study data revealed a substantial male medical dominance since males comprised 51.43% of patients, which matched statistics presented in Chen et al., who documented a 52.4% female patient ratio [11].

Socio-cultural factors influencing healthcare access for genders in Bangladesh explain the differences between groups. Individuals between 18 and 30 years old demonstrated the most significant disease burden (30.71%), according to findings that matched Petchiappan *et al.*, Their research showed that about 50% of patients were in this age range due to their high outdoor activity levels and mobility patterns [10].

Most cases came from urban residents, reaching 58.57 percent of the patient population because Aedes mosquitoes usually inhabit urban areas where large numbers of people live, and poor insect control programs help spread disease, according to Mutsuddy *et al.,* [4].

The investigation revealed a 16.43% prevalence of DM, which matched hypertension at 13.57%. Chen *et al.,* reported a similar prevalence of hypertension affecting 31.4% of patients and diabetes affecting 21.5% of patients [11]. The divergence of prevalence results from several aspects, including the study samples and their settings, together with the population's baseline health condition.

These patients experienced fever in every case, while headache came second, and rash and vomiting ranked third. The research from Chen et al. showed that fever (95.3%), myalgia (54.5%), and headache (35.1%) were the most prevalent clinical features in cases [11]. According to Ho *et al.,* patients affected by dengue fever experienced myalgia with petechiae, nausea, and other symptoms [15]. Our findings reaffirm the classical symptom profile of DHF and its overlap with other febrile illnesses.

The significant discovery of this research was the substantial variation between acute phase reactants of patients with DHF compared to patients with DSS during the essential period. The ESR value measured in patients with DHF reached 12.63 mm/hr., which differed significantly ($p < 0.001$) from the DSS patient value of 8.01 mm/hr. Kalayanarooj and Nimmannitya reported small ESR values in patients with DSS since shock affects fibrinogen levels and causes hemoconcentration [16].

Patients with DSS showed a significant rise in CRP levels at 36.63 ± 1.79 mg/L compared to the CRP levels of DHF patients at 20.1 ± 2.4 mg/L, generating a $p < 0.001$ statistical result. Chen et al. established that severe dengue patients had elevated CRP levels, indicating potential use as a prognostic biomarker [11]. Research by Vuong et al. agreed with this discovery by demonstrating that CRP plays a fundamental role in dengue progression evaluation [17].

Patients with DSS experienced elevated serum ferritin measurements of 1503 ng/mL ± 35 ng/mL over DHF patients whose ferritin reached 1213 ng/mL ± 40 ng/mL during the critical phase ($p = 0.04$). The study results match those of Evalda and colleagues, who found that serum ferritin effectively predicted dengue patient shock development [18]. Ferritin evaluation for severity assessment received support from the research conducted by Soundravally *et al.,* and Selvamuthukumaran [19, 20].

The analysis during convalescence failed to show any statistically significant variations in ESR levels and CRP and ferritin across groups. The critical illness stage is the optimal time to use acute phase reactants to provide valuable information about patient severity. The DHF group patients did not exhibit statistically essential variations in their complete blood count results alongside their biochemical parameters like hemoglobin, WBC count, platelet count, serum creatinine, and SGPT compared to DSS group patients. Routine clinical measurements have limited use when predicting shock development in patients. The findings reported by Chen *et al.,* [11] matched those observations.

This research demonstrates that serum CRP and ferritin show significant clinical value as early predictors of disease severity in DHF. These elevated markers in DSS patients illustrate the usefulness of risk analysis and speed up disease management to enhance treatment results.

CONCLUSION

This study highlights the significant association of elevated C-reactive protein and serum ferritin levels with the development of dengue shock syndrome in dengue hemorrhagic fever patients. These acute phase reactants may serve as valuable early indicators of disease severity, aiding timely clinical decision-making and management. Routine assessment of CRP and ferritin could improve risk stratification and outcomes in dengue-endemic settings. Further research is needed to validate their prognostic utility across diverse populations and clinical scenarios.

Limitations and recommendations

This study was limited by a small sample size and conducted solely at a single tertiary hospital, potentially limiting generalizability. Future research should involve more extensive, multicenter studies across diverse settings in Bangladesh. Adequate funding and manpower are essential to enhance study quality, and further investigation is needed to explore additional associations with dengue severity.

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Conflicts of interest: There are no conflicts of interest.

Ethical approval: The study was approved by the Institutional Ethical Review Committee.

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