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Original Article

A comparative Analysis of Socio-Demographics, Clinical Features, and Acute Phase Reactant (ESR, CRP, Serum Ferritin) in DHF and DSS Patients

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ABSTRACT

Background: *Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are severe forms of dengue infection associated with significant morbidity. Acute phase reactants like ESR, CRP, and serum ferritin may play a role in predicting disease severity.* ***Methods & Materials:*** *This cross-sectional study was conducted in the Department of Medicine, Dhaka Medical College Hospital, from February to July 2020. A total of 140 patients diagnosed with DHF based on WHO 1997 criteria were enrolled using purposive sampling. Among them, 28 developed DSS. Data were collected using a structured questionnaire. ESR, CRP, and ferritin were measured during both critical and convalescent phases. Data were analyzed using SPSS v23.* ***Results:*** *Of the 140 patients, 51.43% were male. Most (58.57%) came from urban areas. Fever (100%), headache (84.29%), and rash (77.86%) were common symptoms. During the critical phase, mean ESR was significantly lower in DSS (8.01 mm/hr) compared to DHF (12.63 mm/hr, p<0.001). Mean CRP was significantly higher in DSS (36.63 mg/L) than DHF (20.1 mg/L, p<0.001). Ferritin was also significantly elevated in DSS (1503 ng/mL) compared to DHF (1213 ng/mL, p=0.04).* ***Conclusion:*** *Acute phase reactants, particularly CRP and serum ferritin, showed significant elevation in DSS and can serve as useful biomarkers in assessing the severity of dengue. ESR was significantly lower in DSS, likely due to hemoconcentration and DIC. These markers may aid in early identification of severe cases.*

Keywords: *Dengue hemorrhagic fever, Dengue shock syndrome, CRP, ESR, Ferritin, Acute phase reactants.*

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INTRODUCTION

Dengue fever is a rapidly spreading, mosquito-borne viral disease that has emerged as a major public health problem in tropical and subtropical nations, including Bangladesh[1]. It is transmitted by the dengue virus, a Flavivirus, through the Aedes aegypti mosquito[2]. There are approximately one million cases of dengue infections reported each year globally, with most of them evolving into its severe manifestations, i.e., dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)[3]. DHF is characterized by increased vascular permeability, thrombocytopenia, and hemorrhagic manifestations, whereas DSS includes all the manifestations of DHF along with circulatory failure, which poses a major threat to patient survival[4]. There are recurrent epidemics of dengue in Bangladesh in recent years that have led to increased hospitalization and put a heavy burden on the health care system[5]. Early recognition and appropriate treatment of DHF are necessary in order to prevent the development of DSS, which is associated with increased morbidity and mortality[6]. While clinical presentation and routine laboratory findings are helpful in the evaluation of the disease, the need now is for strong biomarkers that would help predict the severity of the disease and guide early intervention[7]. Acute phase reactants such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum ferritin are employed as routine inflammatory markers in clinical practice[8]. These proteins continuously alter their concentration with infection, inflammation, or tissue injury. CRP is an acute phase reactant with early rise in acute inflammation, and ferritin, apart from its function in iron storage, acts as an acute phase reactant during systemic inflammation[9, 10]. ESR is the red blood cell accumulation due to the presence of inflammatory mediators. Although these markers are non-specific, their level may be inversely proportional to the severity of the disease and may add value in DHF/DSS differentiation[11]. There are a number of studies on the role of acute phase reactants in infections and inflammation, but little data exist on their applicability in dengue, particularly in DHF and DSS[12]. Clarification of the

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interaction of these markers and disease severity can enable early diagnosis, risk stratification, and improved clinical outcomes[13]. In dengue, the immune response is central to pathogenesis, and excessive activation of inflammatory pathways is considered to be the cause of capillary leakage, shock, and multi-organ failure[8]. Therefore, the quantitation of these biomarkers in the different phases of illness may prove useful in delineating disease progression and prognosis[14]. The aim of the study was to compare socio-demographic and clinical characteristics of patients with DHF and DSS and their acute phase reactants—ESR, CRP, and serum ferritin—levels at critical and convalescent phases of the disease. By unmasking significant differences between these two groups, we wanted to know whether the aforementioned biomarkers would have the potential to be an indicator of the severity of disease. This could finally support enhanced clinical judgment and resource management in outbreaks of dengue, particularly from resource-constrained settings like Bangladesh.

METHODS & MATERIALS

This cross-sectional descriptive study was conducted at the Department of Medicine, Dhaka Medical College Hospital, over six months from February 2020 to July 2020. The purpose of the study was to determine the clinical and laboratory profiles, particularly acute phase reactants—erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum ferritin—among Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) patients. 140 patients admitted with a diagnosis of DHF were recruited using purposive sampling. Patients aged 18 years or more of either sex, diagnosed according to WHO 1997 criteria for DHF, and who provided informed written consent were included. Patients with co-infections, steroid or immunosuppressant drug-taking patients, those with sideroblastic anemia, thalassemia, or liver disease, pregnant women were all excluded from study. A validated case record form was employed in gathering data with face-to-face interviews and clinical examination. Socio-demographic profile, clinical features, comorbidities were documented. Patients were divided into DHF and DSS groups based on the presence or absence of shock features using WHO criteria. ESR, CRP, and serum ferritin levels were measured both in critical (on admission) and convalescent phases. ESR was analyzed by the Westergren method, CRP by high-sensitivity turbidimetric immunoassay with monoclonal antibodies, and serum ferritin by electrochemiluminescence immunoassay.

Ethical approval for conducting the study was provided by the Ethical Review Committee of Dhaka Medical College. All the respondents were informed about the objectives, methods, and potential benefits of the study prior to participation, and confidentiality was maintained with utmost care. The collected data were cross-checked for accuracy and consistency prior to their entry into a database. Statistical analysis was done on SPSS version 23. The results were presented in text, tables, and graphs. In all analyses, a p-value of less than 0.05 was considered statistically significant.

RESULTS

Table – I: Baseline characteristics of the participants (*n*=140)

	Mean (±SD)*	Count**	Percentage**
Sex	Male	72	51.43
	Female	68	48.57
Age group	Age group 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
Address	Rural	58	41.43
	Urban	82	58.57
Occupation	Govt. employee	26	18.57
	Non govt. employee	24	17.14
	Business	33	23.57
	Housewife	32	22.86
	Unemployed	14	10
	Others	11	7.86
Level of education	Uneducated	23	16.43
	Below SSC	52	37.14
	SSC	33	23.57
	HSC	27	19.29
	Graduate and above	5	3.57

Baseline characteristics of the participants are shown in Table 1. Among the participants (N=140), males were 72 (51.43%) and females were 68 (48.57%). Most of the patients came from urban area 82 (58.57%). Most common profession among male was businessman 30 (41.67%), followed by government employee 18 (25%). Most common profession among female was housewife 32 (47.06%), followed by non-government employee 12 (17.65%). Most common educational standard was below SSC 52 (37.14%), followed by SSC 33 (23.57%) and HSC 27 (19.29%).

Table – II: Clinical features (*n*=140)

	Total	DHF	DSS	P value*
Clinical features	**Count (%)**	**Count (%)**	**Count (%)**	
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

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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

Common clinical features are shown in Table 2. Fever was present in all patients 140 (100.00%) followed by headache 118 (84.29%) are the two commonest clinical features followed by rash 109 (77.86%) and vomiting 92 (65.71%). There was no statistically significant difference (calculated by Pearson's chi square test of independence) between the prevalence of these symptoms between DHF and DSS groups.

Table – III: Investigation findings of the participants (*n*=140)

Variable		DHF (n=112)	DSS (n=28)	P value*
ESR (mm at 1st Critical period hour)		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(±2.45)	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)	0.80
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 III shows comparison of results of laboratory investigations between group of patients with DHF and patients with DSS. In critical period ESR was found higher in DHF whether CRP and serum ferritin was found lower in DHF. The differences of ESR, CRP and ferritin between DHF and DSS were statistically significant (p values <0.001, <0.001 and 0.04 respectively). During Convalescence period, the differences of ESR, CRP and ferritin between DHF and DSS were not statistically significant. Difference of HB, total WBC and platelet between DHF and DSS were not statistically significant. Difference of serum creatinine and SGPT between DHF and DSS groups were not statistically significant.

DISCUSSION

This cross-sectional study was conducted among patients diagnosed with dengue haemorrhagic fever at Dhaka Medical College Hospital (DMCH) to evaluate the levels of acute phase reactants (ESR, CRP, and serum ferritin) and explore their correlation with clinical features and disease severity, particularly in differentiating DHF and DSS.

A total number of 140 dengue haemorrhagic fever patients presenting at the Medicine department during the period of February, 2020 to July, 2020 were included. Among the respondents 112 (80%) had dengue haemorrhagic fever and 28 (20%) had dengue shock syndrome. Chen et al. showed among 191 Dengue patients 69 had DHF of whom 63 (91.3%) had non-shock DHF and 6 had DSS (8.69%)[15]. This difference might be due to delayed admission in the hospital in our perspective.

Among the participants in this study (N=140), there was male preponderance; male were 72 (51.43%) and female were 68 (48.57%). Chen et al. found comparable findings with female preponderance; female were 52.4% and male were 42.7%[15]. This slight difference might be due to women in our country lagged behind in getting healthcare as a result of socio-economic inequalities based on gender discrimination. Age group 18-30 years had the highest number of patients with 30.71% in number, followed by age group 31-40 years 19.29%, 51-60 years 15.71%, 41-50 years 12.86%, 61-70 years 11.43% and >70 years 10%. In the current study 50% of patients were less than 40 years of age. Petchiappan V et al. found about 50% of patients were less than 25 years of age[16]. This difference could be due to selection criteria of patients.

The distribution of living area was recorded. 58.57% patients hailed from the urban area while 41.43% patients came from rural area. This pattern was due to the usual distribution of vectors of DHF in the peripheral areas of urban cities and inadequate mosquito control measures in the urban areas. The occupation of the participants was recorded. Most common profession among male was businessman 30 (41.67%), followed by government employee 18 (25%). Most common profession among female was 32 (47.06%), followed by non- government employee 12 (17.65%). In this study the level of education among the participants was recorded. Most common educational standard was below SSC 37.14%, followed by SSC 23.57%, HSC 19.29%, uneducated 16.43% and graduate and above 3.57%. Current level of achieving educational facilities corresponds strongly with the pattern of educational qualification shown in this study.

Clinical features of the responded were recorded in this study. Fever was present in all patients (100%), followed by headache 84.29% were the two commonest clinical features

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followed by rash 77.86%, vomiting 65.71%, eye-ache 54.28%, pleural effusion 52.14%, generalised body-ache 47.86%, bleeding manifestation 33.57%, ascites 31.43% and abdominal pain 27.14%. There was no statistically significant difference (calculated by Pearson's chi square test of independence) between the prevalence of these symptoms between DHF and DSS group. Chen et al. got some clinical features quite similar to this study with some difference in other features. Chen et al. found clinical features like fever 95.3%, myalgia 54.5%, bone pain 36.1%, headache 35.1%, abdominal pain, cough, nausea/vomiting 24.6%, diarrhoea, dizziness 22.5%, rashes 20%, orbital pain 13.6%, gum bleeding 12% and gastrointestinal bleeding 7.9%[15]. In a retrospective, hospital-based study conducted at a university hospital in southern Taiwan by Ho T-S et al. found most common symptoms/signs on admission were myalgia 46.8%, petechiae 36.9% and nausea/vomiting 33.5%[17].

ESR was measured in this study during critical and convalescence phases of DHF and DSS. The mean (±SD) ESR in DHF during critical period was 12.63 (±0.45), mean (±SD) ESR during critical phase of DSS was 8.01 (±0.35). The ESR was lower in shock cases of DHF. The difference in ESR during critical phases of DHF and DSS was statistically significant ($p<0.001$). Kalyanarooj and Nimmannitya determined Erythrocyte sedimentation rate (ESR) in 180 DHF patients and 70 patients with various viral and bacterial infections using the Wintrobe method. The mean ESR in non-shock DHF cases was 13.87 mm/hour while in shock cases it was 7.63 mm/hour and there was statistically significant difference (p value less than 0.05)[18]. We also found similar findings and our results are congruent with those reported by Kalyanarooj and Nimmannitya. The mean ESR during the time of shock was lower than in the pre-shock and post-shock period. Hemoconcentration, low level of albumin and fibrinogen and the presence of disseminated intravascular clotting (DIC) in a majority of DHF patients are most likely responsible to this observed lower ESR especially during shock period[18].

In this study, mean (±SD) CRP in critical period was 20.1(±2.45) for DHF without shock, and 36.63 (±1.79) for DSS, difference between them was statistically significant ($p<0.001$). Our findings were similar to those reported by Chen et al. Chen et al. found that the risk of DHF/DSS and severe dengue is significantly related to the increasing levels of CRP and during the febrile phase, there was significant higher CRP level for DSS versus DF/nonshock DHF and severe dengue versus nonsevere dengue, with CRP cut-off level 30.1 mg/L and 24.2 mg/L respectively[15]. Their study highlighted the utility of the CRP levels in early prediction of DSS and severe dengue in adult patients.

In this study, mean (±SD) ferritin in critical period was 1213(±40) for DHF without shock, and 1503 (±35) for DSS, difference between them was statistically significant ($p=0.04$). Evalda et al. who found that mean serum ferritin concentration in children with dengue shock (mean= 3628.8; SD= 1582.4) was higher than in children without dengue shock (mean= 717.8; SD= 695.8), with $p<0.001$[19]. Therefore, there was a statistically significant association between serum ferritin concentration and dengue shock. We also found significant association in this study. The cut-off point of serum ferritin concentration that could be used to show dengue shock with high sensitivity (0.92) and specificity (0.97) was 2304[19]. Moreover, in a separate study Soundravally et al. found and reported that elevated ferritin level could predict the disease severity with highest sensitivity and specificity of 76.9 and 83.3 %, respectively, on the day of admission and the same was found to be 90 and 91.6 % around defervescence[20]. Selvamuthukumaran S reported that there is a strong correlation between the ferritin levels and the severity of the disease. From the study, it can be concluded that the ferritin levels of the patients can be taken as a biomarker to predict the severity of the dengue fever infection[21]. Our findings are congruent with all of these researchers.

This study was used to measure CBC, serum creatinine and SGPT in critical period of DHF and DSS. In this study mean haemoglobin was 11.3 gm/dl and 11.7 gm/dl during critical period of DHF and DSS respectively, mean total WBC was $3700/mm^3$ and $2800/ mm^3$ during critical period of DHF and DSS respectively, mean platelet count was $30000/mm^3$ and $16000/ mm^3$ during critical period of DHF and DSS respectively, mean serum creatinine was 1.2 mg/dl and 1.3 mg/dl during critical period of DHF and DSS respectively, mean SGPT was 110 U/ml and 130 U/ml during critical period of DHF and DSS respectively. Difference of haemoglobin, WBC and platelet count between DHF and DSS was not statistically significant. Difference of serum creatinine and SGPT between DHF and DSS was not statistically significant. Some discrepancy in those parameters were noted in this study with those conducted by Chen et al. and Ho T-S et al. which might be due to measurement in different phases[15, 17].

LIMITATIONS OF THE STUDY

This study has several limitations that were difficult to avoid. Firstly, due to monetary and time constraints, it was not possible to include a larger number of participants, which may have affected the statistical power of the findings. Secondly, the study was conducted solely at Dhaka Medical College Hospital, a tertiary-level referral center. Therefore, the results may not be generalizable to the broader population across different regions of Bangladesh. Additionally, the relatively small sample size limits the ability to draw strong conclusions and may not fully capture the variability of clinical presentations and laboratory findings of DHF and DSS.

CONCLUSION

This study demonstrated that during the critical period, lower ESR and elevated levels of CRP and serum ferritin were significantly associated with dengue shock syndrome (DSS). These acute phase reactants may serve as useful biomarkers in identifying severe dengue cases, potentially aiding early intervention and better clinical outcomes. Further studies should be conducted with larger, more representative samples to establish stronger associations between acute phase

reactants and disease severity. Efforts should also focus on exploring additional biomarkers and clinical predictors to improve early diagnosis and management of DSS.

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Conflicts of interest
There are no conflicts of interest.

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