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Acute Diarrhoea in Dengue Patients – A Hospital-Based Cross-Sectional Study

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Abstract

Introduction: ***In Bangladesh, dengue fever is an endemic illness, with high rates of mortality during outbreaks. Acute diarrhoea is a common symptom of dengue fever. This study aimed to identify the frequency of acute diarrhoea in dengue virus infection, and its association with various factors and the in-hospital outcome.***

Methods: ***This cross-sectional study involved 203 dengue patients who were admitted to a tertiary-level teaching hospital in Dhaka, Bangladesh, between July and October 2023. The frequency of acute diarrhoea in dengue patients was calculated, and its associations with various demographic, clinical and haematological parameters, complications, categories of dengue virus infection, ICU/HDU transfer and length of hospital stay were assessed.***

Results: ***Diarrhoea developed in 17.7% of dengue patients. The study identified an association of platelet count less than 50,000/cumm with acute diarrhoea in dengue patients (p-value <0.001). Organ dysfunctions (p-value <0.001), particularly cholecystitis (p-value 0.03), acute kidney injury (p-value 0.04) and pancreatitis (p-value 0.02), as well as multiorgan dysfunctions (p-value 0.02), were significantly more frequent in dengue patients with acute diarrhoea. Dengue shock syndrome (p-value 0.047), expanded dengue syndrome (p-value 0.04) and severe dengue (p-value 0.01) were found in higher frequencies in dengue patients with acute diarrhoea, who also had longer hospital stays (p-value <0.001).***

Conclusion: ***This study demonstrates that acute diarrhoea is significantly associated with severe clinical outcomes in dengue, including organ dysfunction and prolonged hospitalization. Incorporating this symptom into early risk stratification may enhance clinical decision-making and patient care.***

Key words: ***Acute diarrhoea in dengue, dengue shock syndrome, expanded dengue syndrome, severe dengue, prolonged hospital stay***

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Introduction

Dengue fever is caused by four serotypes of dengue virus transmitted by Aedes aegypti and Aedes albopictus[1]. Dengue fever is a global concern, placing nearly half of the world population at risk[2]. In 2023, over 5,000 fatalities associated with dengue were documented across more than 100 nations[3]. Notably, Bangladesh recorded the highest incidence of dengue in Asia, with 277,801 cases and 1,393 deaths that year[4].

Although not mentioned as a typical symptom, acute diarrhoea is found as a common manifestation in dengue virus infection in recent studies. A recent study in Dhaka, Bangladesh, found a 56% frequency of diarrhoea in dengue fever[5]. A study on 260 confirmed Dengue virus infections in Peshwar, Pakistan, found acute diarrhoea in 54.4%[6]. Another study in Bengaluru, India, revealed a 13% frequency of diarrhoea[7]. Hasan et al. in a study on 747 dengue virus infections in Dhaka, Bangladesh showed a 25.6% frequency of diarrhoea[8]. A 26.2% frequency of diarrhoea was reported in a study in Venezuela.[9] A Mexican study exhibited a 17% frequency of diarrhoea in dengue fever[10].

Duran et al. analyzed the frequency of diarrhoea in dengue virus infection of different classes and observed a higher frequency of diarrhoea in severe dengue (77.4%) than dengue with warning signs (28.8%) and dengue

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without warning signs (17.9%)[9]. Medina et al. in a study on 8559 dengue patients found a higher proportion of diarrhoea among the hospitalized ones (24%) than those who did not require hospitalization (15.6%)[10]. A recent meta-analysis found diarrhoea as a risk factor for severe dengue with an odds ratio of 1.2 (p-value 0.04)[11]. Ullah et al. in a recent study in Dhaka, Bangladesh, found a positive correlation between diarrhoea and severity of dengue[5].

This research was conducted to estimate how frequently diarrhoea manifests in patients with dengue virus infection. The associations of acute diarrhoea in dengue with demographic, clinical and haematological parameters and categories of dengue virus infection were evaluated. Additionally, the analysis considered the necessity for transfer to intensive care or high-dependency units and the duration of hospital stays in cases of acute diarrhoea in dengue virus infection.

Methods

This cross-sectional study was performed using the data collected from the hospital records on patients admitted to the Department of Medicine at Shaheed Monsur Ali Medical College Hospital in Dhaka, Bangladesh, during the timeframe of July to October 2023. The study participants consisted of 203 consecutive individuals with confirmed dengue virus infections, as determined by positive NS1 antigen and/or anti-Dengue IgM testing[12]. The sample size approximately matches the calculated sample size of 217 derived employing the formula for cross-sectional studies with a presumed proportion of diarrhoea in dengue 17%[10].

Age, gender, pre-existing hypertension, diabetes mellitus, days before hospital admission and length of hospital stay were documented. From the test reports, the peak values for haematocrit, SGPT, and serum creatinine were noted, alongside the lowest values for total white blood cell (WBC) count and platelet count. The neutrophil-lymphocyte ratio (NLR) was computed based on the absolute counts of neutrophils and lymphocytes at the point of the lowest total WBC count.

The different categories of dengue virus infection, namely dengue fever (DF), dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS), and expanded dengue syndrome (EDS), were recorded. DF was defined as dengue virus infection without DHF, DSS or EDS[12]. Dengue virus infections with evidence of plasma leakage, such as pleural effusion, ascites and a rise of haematocrit by ≥20% of baseline, were considered as DHF[12]. DHF patients who had narrow pulse pressure (≤20 mmHg), low systolic and/or diastolic blood pressure (<90 mmHg and <60 mmHg, respectively) alongside low volume pulse and/or cold peripheries, or who experienced syncope were designated as DSS[12].

Cases of dengue that exhibit major organ involvement, which did not meet the criteria for DHF or DSS, were classified as EDS[13]. The following were considered as major organ involvement: (1) Encephalopathy/encephalitis - Impaired consciousness, abnormal behaviour and/or seizure with normal serum sodium level or diffuse brain swelling in CT scan[14], (2) Hepatitis - SGPT ≥200 U/L, (five-times of upper limit of the normal range, according to the reference value of the hospital laboratory)[15], (3) Cholecystitis - Positive Murphy's sign and thickness of gall bladder wall ≥3 mm in ultrasonogram[16], (4) Pancreatitis - Swollen pancreas in ultrasonogram, serum lipase >500 U/L and/or serum amylase >300 U/L (three-times of upper limit of the normal range, according to the reference value of the hospital laboratory)[17,18], (5) Acute kidney injury (AKI) - a serum creatinine increase of 50% or more, or an elevation of at least 0.3 mg/dl from the baseline in a 48-hour window[19] and (6) Myocarditis - Diffuse ST segment and/or T wave change and serum troponin-I >0.1 ng/ml[20,21]. Involvement of two or more organs was considered as multi-organ dysfunction (MOD)[22]. A diagnosis of severe dengue was made when a dengue virus infection exhibited any of the major hemorrhagic events, DHF, DSS or critical organ dysfunction[12]. Delayed hospitalization was defined as admission after 5 days of fever onset[23].

Acute diarrhoea was defined as the expulsion of ≥3 unformed stools within 24 hours[24]. All the study participants with acute diarrhoea received adequate rehydration with oral rehydration salts (ORS) as per standard protocol. Patients with severe dehydration or insufficient oral intake received additional intravenous Cholera saline[24].

Participants in the study were split into two groups: the first group, known as the dengue with acute diarrhoea (Den-D) group, included individuals with acute

diarrhoea, while the second group served as the control group and consisted of individuals without acute diarrhoea. The two groups were analyzed for differences in demographic, clinical and haematological parameters, haemorrhagic manifestations, organ dysfunctions, categories of dengue virus infection, transfers to ICU/HDU, and the length of their hospital stays.

Qualitative and quantitative variables were compared using odds ratio and mean difference (for normally distributed data) or median difference (for skewed data), respectively[25-27]. 95% confidence interval (qualitative and normally distributed quantitative data) or Bootstrap confidence interval (skewed quantitative data) were calculated[28]. Chi-square test, Fisher's exact test, Student's t-test and Mann-Whitney U test were employed as appropriate. A p-value below 0.05 was accepted as an indicator of statistical significance. Microsoft Excel 2016 and STATA 19 were employed to carry out the statistical procedures.

Ethical consideration

The Institutional Ethical Review Board (IERB) of Shaheed Monsur Ali Medical College Hospital granted formal approval for the study (Reference: SMAMC/04/2023/1789). Informed consent (and assent from the guardian of the under-18 patients) for using the clinical and laboratory data was obtained at the time of admission.

Results

From July to October 2023, the Department of Medicine recorded a total of 316 admissions for dengue patients. Among them, complete records on the desired parameters were found in 203 patients; all of them were included as the study participants. Among the study participants, 36 had acute diarrhoea as per the operational definition. The frequency of acute diarrhoea in dengue was 17.7%. The remaining 167 participants were grouped as controls.

Participants in the study had a mean age of 32.7± 12.2 years, and their ages varied from 13 to 75 years. The largest age group represented was 21 to 40 years, comprising 64.5% of the total participants. Of the total, 115 individuals (56.6%) were male, and 88 individuals (43.4%) were female. There were no notable statistical differences in age or gender between the two groups.

Table-I compares the frequencies of co-morbidities, delayed admission and other gastrointestinal manifestations between dengue patients with and without acute diarrhoea. Frequencies of hypertension, diabetes mellitus, delayed hospital admission, vomiting and abdominal pain did not differ significantly between the two groups.

Different haematological parameters were compared between the two groups in Table-II. The Den-D group exhibited a significantly lower platelet count (p-value 0.005). The frequency of platelet count <50,000/cumm was greater in the Den-D group (p-value <0.001). There were no substantial differences observed between the two groups concerning haematocrit, WBC count and neutrophil-lymphocyte ratio.

Table-I

Co-morbidities, delayed admission and other gastrointestinal symptoms in the study participants (n=203)

Variables	Den-D(n_1=36)	Control(n_2=167)	Odds ratio	95% Confidence interval	p-value
Hypertension[1]	3 (8.3)	4 (2.4)	3.7	0.8-17.3	0.11[a]
Diabetes mellitus[1]	3 (8.3)	11 (6.6)	1.3	0.3-4.9	0.72[a]
Delayed admission[1]	27 (75.0)	131 (78.4)	0.8	0.4-1.9	0.65[b]
Vomiting[1]	35 (97.2)	156 (93.4)	2.5	0.3-19.7	0.69[a]
Abdominal pain[1]	11 (30.6)	44 (26.3)	1.2	0.6-2.7	0.61[b]

1-n(%)

a-Fisher's exact test, b-Chi square test

Table-II

Haematological parameters in the study participants (n=203)

Variables	Den-D (n_1=36)	Control (n_2=167)	Odds ratio / Mean difference / Median difference	Confidence interval	p-value
Haematocrit[1]	42.4±5.1	41.0±5.6	1.3[4]	(-0.6)-3.4[7]	0.17[a]
WBC count (1000/cumm)[1]	3.4±1.3	3.9±1.5	-0.5[4]	(-1.0)-0.1[7]	0.08[a]
WBC <4000/cumm[2]	26 (72.2)	92 (55.1)	2.1[5]	1.0-4.7[7]	0.09[b]
NLR[3]	2.9 (1.7-10.0)	2.5 (1.5-4.7)	0.4[6]	(-0.5)-4.6[8]	0.17[c]
Platelet count (1000/cumm)[3]	41.0 (23.5-69.5)	78.0 (35.0-110.0)	-37.0[6]	(-57.0)-(-12.5)[8]	**0.005[c]**
Platelet <50000/cumm[2]	19 (52.8)	17 (10.2)	9.9[5]	4.3-22.5[7]	**<0.001[b]**

1-mean±standard deviation, 2-n(%), 3-median(IQR)
4-mean difference, 5-odds ratio, 6-median difference
7-95% confidence interval, 8-Bootstrap confidence interval
a- Student's t-test, b-Chi square test, c-Mann-Whitney U test

Haemorrhagic manifestations occurred in 15(7.9%) participants. Gum bleeding was the most frequent haemorrhage observed in 7 participants. Other haemorrhagic manifestations were epistaxis (6), melaena (4), menorrhagia (2) and haematemesis (1). Bleeding from multiple sites was observed in 4 participants - epistaxis, gum bleeding, haematemesis and melaena in 1, gum bleeding with epistaxis in 1, epistaxis with menorrhagia in 1 and epistaxis with melaena in 1 (Figure-1).

Organ dysfunctions were observed in 65(32.0%) participants. Cholecystitis (22,10.8%) was the most frequent organ dysfunction, followed by AKI (16,7.9%), hepatitis (15,7.4%), pancreatitis (7,3.4%) and myocarditis (5,2.5%). Eighteen (8.9%) participants had multiorgan dysfunction (MOD) (Figure-2).

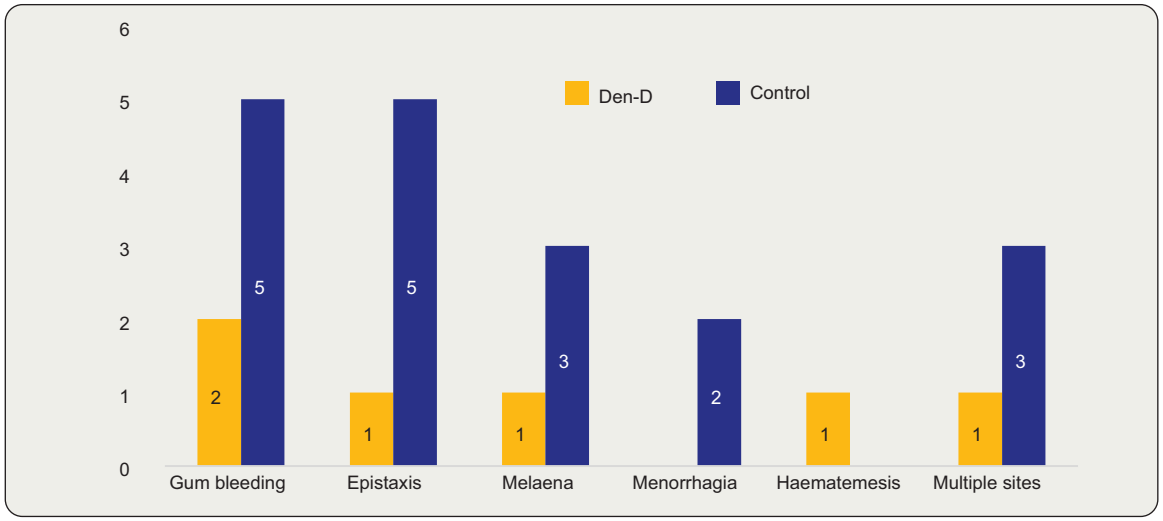

Figure-1: *Haemorrhagic manifestations observed in the participants (n=203). Parameters are not mutually exclusive.*

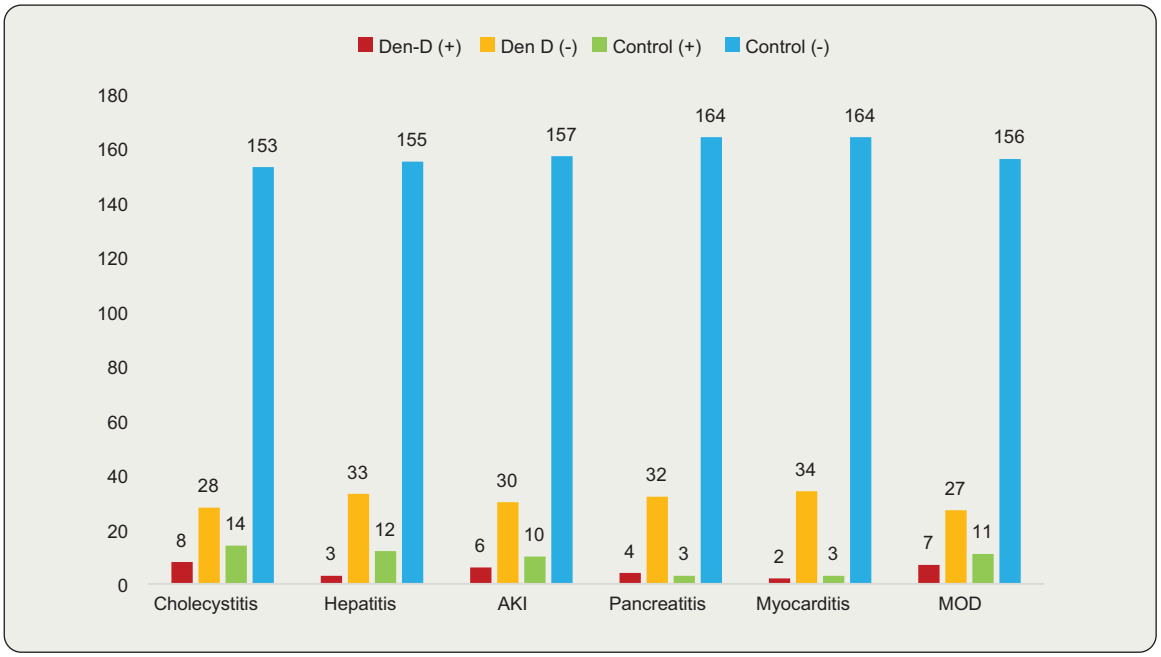

Figure-2: Organ dysfunctions observed in the participants (n=203). Parameters are not mutually exclusive. (+ and – indicate presence and absence of organ dysfunctions, respectively).

Table-III compares the frequency of haemorrhagic manifestations and various organ dysfunctions between the participants with and without acute diarrhoea. Haemorrhagic manifestations occurred at a higher frequency in the Den-D group, but that did not reach statistical significance. The Den-D group had a significantly greater frequency of organ dysfunctions (p-value <0.001). Cholecystitis, AKI and pancreatitis occurred in significantly higher frequency in the Den-D group (p-value 0.03, 0.04 and 0.02, respectively). Multi-organ dysfunction was found in a greater proportion in the Den-D group (p-value 0.02).

Among the 65 participants exhibiting organ dysfunction, 23 belonged to DHF/DSS. The remaining 42 were labelled as EDS.

Figure-3 shows the different categories of dengue virus infection among the study participants. The number of DF, DHF, DSS, EDS and severe dengue was 92(45.3%), 69(34.0%), 29(14.3%), 42(20.7%) and 111(54.7%), respectively.

Table-III

Haemorrhagic manifestations and organ dysfunctions in dengue patients with and without acute diarrhoea (n=203)

Variables	Den-D (n_1=36)	Control (n_2=167)	Odds ratio	95% Confidence interval	p-value
Haemorrhage[1]	3 (8.3)	12 (7.1)	1.2	0.3-4.4	0.73[a]
Cholecystitis[1]	8 (22.2)	14 (8.3)	3.1	1.2-8.1	0.03[a]
AKI[1]	6 (16.7)	10 (6.0)	3.1	1.1-9.3	0.04[a]
Hepatitis[1]	3 (8.3)	12 (7.2)	1.2	0.3-4.4	0.73[a]
Pancreatitis[1]	4 (11.1)	3 (1.8)	6.8	1.5-32.1	0.02[a]
Myocarditis[1]	2 (5.6)	3 (1.8)	3.2	0.5-20.0	0.22[a]
MOD[1]	7 (19.4)	11 (6.6)	3.4	1.2-9.6	0.02[a]
Total organ dysfunctions[1]	23 (63.9)	42 (25.1)	5.3	2.5-11.3	<0.001[b]

1-n(%)

a-Fisher's exact test, b-Chi square test

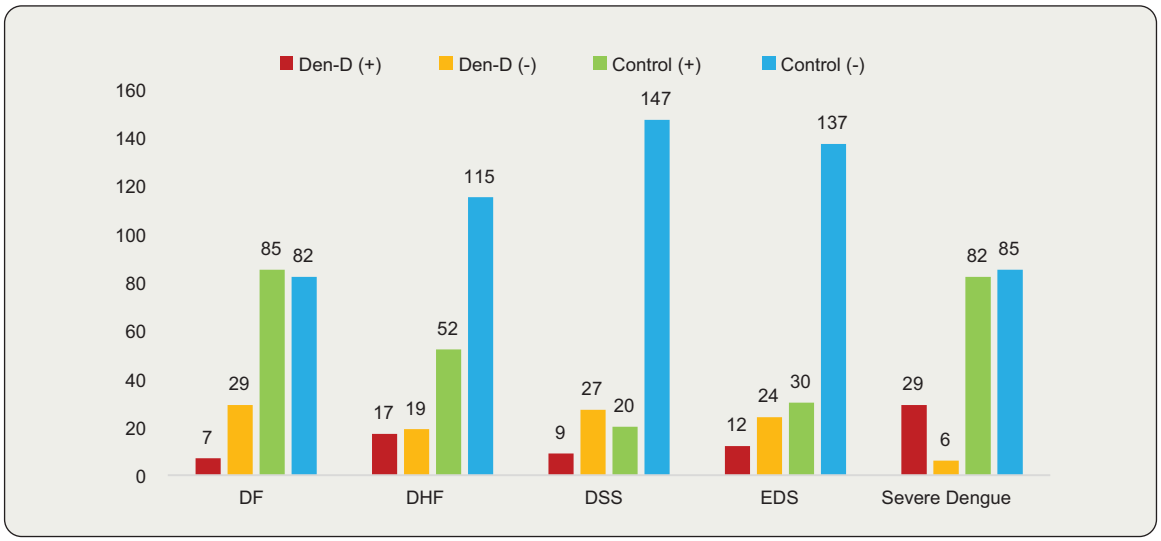

Figure-3: *Categories of dengue virus infection among the participants (n=203). Parameters are not mutually exclusive. DHF includes all DSS cases. Severe dengue includes all DHF and EDS cases. (+ and – indicate the presence and absence of disease categories, respectively).*

The frequency of different categories of dengue virus infection was compared between the two groups in Table-IV. The Den-D group had a significantly higher frequency of DSS (p-value 0.047), EDS (p-value 0.04) and severe dengue (p-value 0.001). On the other hand, uncomplicated dengue fever was found in a greater proportion among controls (p-value 0.001).

The rates of transfer to the ICU/HDU were comparable across both groups. Participants with acute diarrhoea had a significantly longer hospital stay (p-value <0.001) (Table-V).

Table-IV

Categories of dengue virus infection in dengue patients with or without acute diarrhoea (n=203)

Variables	Den-D(n_1=36)	Control(n_2=167)	Odds ratio	95% Confidence interval	p-value
DF[1]	7 (19.4)	85 (50.9)	4.3[2]	1.8-10.3[2]	0.001[a]
DHF[1]	17 (47.2)	52 (31.1)	2.0	1.0-4.1	0.067[a]
DSS[1]	9 (25.0)	20 (13.3)	2.0	1.0-6.0	0.047[a]
EDS[1]	12 (33.3)	30 (18.6)	2.3	1.0-5.1	0.04[b]
Severe Dengue[1]	29 (80.6)	82 (49.1)	4.3	1.8-10.3	0.001[a]

1-n(%), 2- Calculated keeping dengue without diarrhoea as exposure
a-Fisher's exact test, b-Chi square test

Table-V

ICU/HDU transfer and hospital stay in the participants (n=203)

Variables	Den-D (n_1=36)	Control (n_2=167)	Odds ratio / Mean difference	95% Confidence interval	p-value
ICU/HDU transfer[1]	1 (2.8)	1 (0.6)	5.8[3]	0.4-94.4	0.28[a]
Hospital stay (days)[2]	4.6±1.5	3.5±1.7	1.1[4]	0.5-1.7	<0.001[b]

1-n(%), 2-mean±standard deviation
a-Chi square test, b-Student's t test

Discussion

This study utilized a cross-sectional design to analyze a limited number of hospitalized dengue patients encompassing individuals of both sexes and a diverse age spectrum. The demographic breakdown of the study revealed that 56.6% of participants were male and 43.4% were female, with 64.5% of individuals aged between 21 and 40 years. The majority of contemporary studies have revealed a similar pattern in the age and gender demographics of dengue patients[4,5,29].

The frequency of diarrhoea was 17.7% in this study, similar to the studies in Chattogram, Bangladesh and Mumbai, India, that reported frequencies of 17.8% and 21.6%, respectively[30.31].

This study compared the demographic, clinical and haematological parameters between dengue patients with and without acute diarrhoea. Age and gender distribution, pre-existing hypertension or diabetes mellitus, late hospital admission and the presence of other gastrointestinal symptoms did not differ between the two groups. Among various haematological parameters evaluated in this study, platelet count falling below 50,000/cumm was found in a higher proportion among the dengue patients with diarrhoea. This is a unique finding as we could not find any published study exploring the risk factors of acute diarrhoea in dengue virus infection after an extensive search. However, maybe a correlate as found by a few studies that both thrombocytopenia (mean platelet count below 50000/cmm) and diarrhoea were associated with severe dengue[30,32].

A study by Arshad et al. reported a significant relationship between bleeding and diarrhoea. However, no such relationship was found in the present study[33].

Organ dysfunctions developed in a higher proportion of dengue patients with acute diarrhoea. Among various organ dysfunctions, the association of cholecystitis, pancreatitis and AKI with acute diarrhoea in dengue patients was statistically significant. The frequency of multi-organ dysfunction was greater with acute diarrhoea in dengue patients. The dengue patients with organ dysfunction belong to the EDS and DHF/DSS categories. The association of different categories of dengue virus infection with acute diarrhoea in dengue virus infection was also evaluated. The Den-D group in this study developed DSS, EDS and severe dengue in significantly higher proportions. Tsheten et al. and Zhang et al in their meta-analyses did not find any association of acute diarrhoea in dengue patients with DHF or DSS[34,35]. Duran et al. in a Mexican study revealed a higher frequency of acute diarrhoea in severe dengue that included DHF, DSS and EDS[9]. Munmun et al., in a recent study, observed an association between severe dengue and diarrhoea in dengue patients[30].

The underlying pathogenesis of a higher incidence of complications among dengue patients with acute diarrhoea is not well established. According to Reisinger et al. IL-8, which has a major role in the pathogenesis of dengue virus infetion might also be involved in acute diarrhoea in dengue[36].

Dengue patients with acute diarrhoea had a significantly longer hospital stay. The occurrence of dengue-related complications at a higher frequency justifies the longer hospital stay. A study by Aroor et al. from India has revealed longer hospital stays in dengue patients with acute diarrhoea[37].

Limitation & Recommendation

Other potential pathogens of acute diarrhoea were not ruled out in this study. So, this study could not ascertain whether the diarrhoea was caused by the dengue virus or there was a co-infection with a gastrointestinal pathogen. Besides, the hydration status, which was a potential confounder of the outcome, affecting the blood volume and development of shock and AKI, was not compared between the two groups because of the inconsistency of data on the hydration status. This study was conducted at a single institution and utilized a cross-sectional design involving a limited participant pool. Prospective studies conducted across multiple centres on acute diarrhoea in dengue patients with a larger sample, exclusion of other potential pathogens of acute diarrhoea and comparison of hydration status between dengue patients with or without acute diarrhoea are recommended.

Conclusion

Diarrhoea is common in dengue patients. Platelet count <50,000/cu mm was associated with a higher frequency of acute diarrhoea in dengue patients. Acute diarrhoea exhibited a greater proportion of severe dengue and an extended hospital stay.

Conflict of interest

The authors have no conflict of interest to disclose.

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Authors' contribution

Amit Wazib – Formulation of the research concept, review of existing literature, crafting the research methods and analysis of the data. Shaila Rahman – Development of the research protocol. Mahdi Hayat Tonmoy, Shudipta Roy Hamonta and Takambin Tabassum Maya – Acquisition of the data. Mehnaz Kamal – Executing a comprehensive review.

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