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Original Article

Clinicopathological profile & outcome of critically ill patients suffering from Dengue: Single Centre Experience during COVID Pandemic

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Abstract:

Introduction: *Dengue is endemic in our country contributing significantly in morbidity & mortality. This study was conducted to observe the clinic-pathological profile, presentation & outcome of critically ill dengue patients who required Intensive Care Unit admission.*

Methods: *This observational study was conducted in ICU of a tertiary care hospital in Dhaka city from July 2021 to September 2021. Laboratory confirmed cases of Dengue patients admitted in ICU were included in the study.*

Results: *Total patients were 40 with equal male-female distribution. Mean age of the patients was 39.17 ± 13.83 years with most of them (70%) in age group of 18-40 years. Direct admission through Emergency Room (42.5%) was more than transfer-in from indoor of same hospital & other hospitals (35% & 22.5% respectively). There were multiple reasons for ICU admission including hypotension (commonest reason), breathlessness, diarrhoea, abdominal distension, altered level of consciousness etc. Only 13 (32.5%) patients had co-morbidities like DM, HTN etc, and mean age of them was significantly higher than patients without co-morbidities (50.3 ± 13.31, vs 32.23 ± 6.88). Biochemical parameters showed that TWBC count was normal in most patients (n=27, 67.5%), thrombocytopenia was present in 35 (87.5%) patients during admission, hypocalcaemia was present in most patients (90%), liver enzymes were raised in most patients (87.5% & 95% respectively for AST & ALT) and three patients had AKI. Twenty percent patients needed vasopressor support for shock & 5% needed mechanical ventilator support for respiratory failure. Clinical condition was improved in 38 patients & most of them (82.5%) were transferred out from ICU within 6 days. Only two among forty patients expired despite resuscitative efforts. There was no significant difference in the biochemical parameters between survivors & non-survivors.*

Conclusion: *As dengue specific treatment is not yet available, early recognition of the critically ill patients and immediate supportive treatment along with close monitoring in Intensive Care Unit is life-saving for the patients.*

Key words: *Dengue, Intensive Care Unit, Critically ill patients.*

Introduction:

Dengue is an arthropod-borne arboviral disease occurring mainly in tropical & subtropical regions. Causative organism is a small single-stranded RNA virus named Dengue virus (DEN). It comprises of four distinct types of serotypes (DEN-1 to -4). Distinct genotypes have been identified within each serotypes. Among these, 'Asian' genotypes of DEN-2 and -3 are frequently associated with severe disease.[1]

Incidence has increased 30-fold in last 50 years with geographic expansion to new countries.[2] Bangladesh, one of the world's densely populated country with its tropical location, has suitable climate for the vector Aedes. Dengue was documented in Bangladesh from the mid-1960s to the mid 1990s.[3,4] Since the first official outbreak in 2000, our country is affected by Dengue in every year with more than thousands of people requiring hospital admission.[5,6] Prevalence in Bangladesh was 2.7 per 1000 in 2019; and alarming fact is that it is increasing gradually.[7] As per 2011 revised World Health Organization (WHO) guidelines, symptomatic Dengue patients are divided into Undifferentiated fever, Dengue fever (DF) with or without unusual hemorrhage, Dengue hemorrhagic fever (DHF) with or without shock, and Expanded dengue syndrome (EDS).[2] Dengue fever is a self-limited viral illness. Supportive care with judicious fluid replacement, proper rest and antipyretics like paracetamol is usually sufficient. Patients of DF with warning signs, DHF and EDS require admission in hospitals and careful IV fluid administration. If their condition does not improve after management or worsen, then they are shifted to Intensive Care Unit (ICU) for further better management.

At the end of 2019, infection with a new strain of coronavirus (SARS-CoV-2) outbreak occurred in Wuhan, China; and ultimately spread worldwide. World Health Organization (WHO) declared this Corona Virus Disease-19 (COVID-19) as a 'Public Health Emergency of International Concern' on 30th January 2020, and a 'Pandemic' on 11th March of the same year.[8] First case in Bangladesh was detected in the late March 2020. Since then, millions of people have been affected with this deadly virus.[9] In 2020, people were afraid to go to hospital due to fear of getting COVID-19 disease even if they had any emergency. Due to availability of vaccines and treatment for

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this deadly infection, there has been increased number of patients' admission in hospitals due to other diseases in 2021. At the same time, Dengue infection has raised again in the post monsoon time resulting in dengue patients seeking medical advices amongst COVID-19 pandemic.

Various studies on Dengue patients had been done previously in different settings in Bangladesh. But study on critically ill patients of Dengue requiring ICU support is lacking. We tried to compile the characteristics of the Dengue patients requiring ICU support and their outcome in a tertiary care hospital in Dhaka, capital of Bangladesh. This may help in future planning of dengue management.

Methods:

This is an observational cross-sectional study done in ICU of Islami Bank Central Hospital Kakrail (IBCHK) from 1st July 2021 to 30th September 2021. There are 250 beds in the hospital. And the ICU has twelve beds dealing with critically ill adult patients with medical, surgical and/or gynaecological problem. Data were collected retrospectively from hospital records. So, consent was waived. Ethical permission was taken from hospital authority. Patients aged 18 years or more and laboratory confirmed cases of Dengue presenting within 7 days of onset of fever, who were admitted into ICU, were included in this study. Diagnosis of Dengue was confirmed by either positive dengue specific non-structural antigen-1 (NS1), or positive dengue IgM antibody. Laboratory tests for dengue diagnosis were done just after admission in ICU in case of symptomatic patients, or before ICU admission in patients who were referred to ICU from inpatient department of same hospital or different hospitals. Patients were excluded if they presented with diseases other than Dengue like Pneumonia, Urinary tract infection etc with H/O Dengue more than 2 weeks back. Cases are classified into Dengue fever (DF), Dengue hemorrhagic fever- non shock (DHF), Dengue shock syndrome (DSS) and Expanded dengue syndrome (EDS) according to WHO classification and case definition[2]. Demographic data, co-morbidity, reason for ICU admission, duration of fever, complications, length of ICU stay and organ support data were collected from history sheet and ICU files. Relevant investigations were done as per requirements of patients' management in ICU. Platelet count less than 150,000 cells/mm^3 blood was defined as thrombocytopenia. Leukocyte count of 4000 to 11000 cells/mm^3 had been counted as normal; below this was labeled as leucopenia, and more than 11000 was labeled as leukocytosis. The values of alanine aminotransferase (ALT) and asparate aminotransferase (AST) above 40 U/ml (for both) were considered as elevated. Corrected Ca^{2+} level less than 8.5 mg/dl was labeled as hypocalcaemia, and serum creatinine more than 1.2 mg/dl was considered as elevated.

All patients were managed as per National Guideline[10] and as per Intensivists' decisions based on individual clinical condition. Collected data were analyzed by SPSS 20, and formulated in tables and diagrams. P-value <0.05 was considered as significant.

Results

A total of 43 Dengue patients were admitted in ICU during the study period. Three patients were excluded from the study as one of them was brought in ICU with generalized tonic clonic seizure & shock, and died within one hour of admission despite all resuscitative effort. The other two patients were discharged against medical advice with risk bond by their family members within few hours of admission. So, we lack baseline data of them along with outcome.

Mean age of the patients was 39.17 ± 13.83 years. Predominant age groups were 18-30 years and 31-40 years (n=14 in each group, 35%) (Figure 1). Half (n=20, 50%) of the study patients were male & half were female (M:F ratio 1:1).

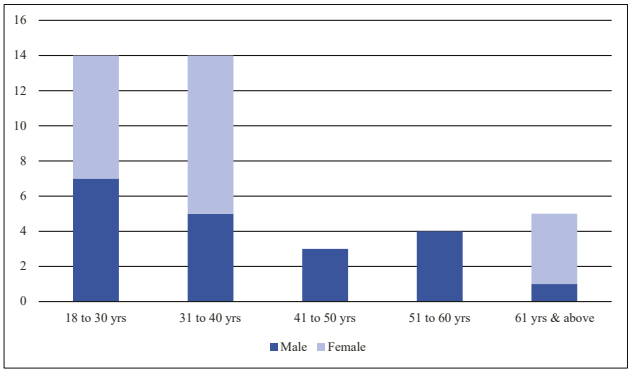

Figure 1: Age & gender distribution of study patients

Critically ill patients were admitted in ICU either directly through emergency room, or transferred in from inpatient department of same hospital, or referred from other hospitals where ICU support was not available (Table I). Maximum patients (n=36, 90%) were diagnosed as Dengue on basis of positive NS1 test; rest (n=4) were IgM +ve. As COVID pandemic was going at that time, so RT-PCR for SARS CoV-2 test was done in all patients and result was negative in all.

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Causes of ICU admissions have been shown in table-II. There were variable reasons including hypotension, breathlessness, diarrhoea etc for ICU admission.

Table I: Admission pattern of study subjects (N=40)

	Frequency	%
Emergency Room	17	42.5
Inpatient department of same hospital	14	35
Referred from another hospital	9	22.5

Table 2: Reasons for ICU admissions*

	Frequency
Hypotension	26
Breathlessness	9
Diarrhoea	4
Abdominal distension &/or pain	2
Convulsion	1
Altered level of consciousness	1
Thrombocytopenia	1

*Multiple response table has been used as some patients had more than one reasons for ICU admission

Thirteen (32.5%) out of forty patients had co-morbidities which are shown in table III. Mean age of the patients having co-morbidity was significantly higher than the mean age of the patients who did not have any co-morbidity (table IV).

Table III: Co-morbidities of study patients (n=13)*

Diseases	Frequency
Diabetes Mellitus (DM)	6
Hypertension (HTN)	11
Ischemic heart disease (IHD)	2
Chronic kidney disease (CKD)	2
Bronchial asthma (BA)	1
Chronic obstructive pulmonary disease (COPD)	1
Hypothyroidism	2
Other	1

*Multiple response table has been used as some patients had more than one co-morbidity

Table IV: Mean Age difference between patients with co-morbidities and without co-morbidities

	Frequency	Percentage	Mean Age ± SD	*p* value
Co-morbidities present	13	32.5%	50.3 ± 13.31	<0.01
Co-morbidities Absent	27	67.5%	32.23 ± 6.88	

Patients were diagnosed as per WHO guideline after ICU admission (table V). All patients had fever with mean duration of 4.72 ± 0.66 days at the time of ICU admission (table VI). Baseline biochemical variables of study subjects have been shown in table VII. White cell count was normal in 67.5% patients (n=27). Leucopenia was present in 7 patients (17.5%) and leukocytosis was present in 6 patients (15%). Thirty five (87.5%) patients had thrombocytopenia at time of ICU admission. During their stay in ICU, all patients developed low platelet count with the lowest recorded count 2000 cells/mm^3 (range 2000-1,09,000, with median 12,000 & IQR 11,000). Thirty five (87.5%) out of forty, and thirty-three (82.5%) patients had raised asparate aminotransferase (AST) and alanine aminotransferase (ALT) levels respectively. Two patients had very high AST (3130, 6200) and ALT (2999, 4710) levels. We considered those two as outliers. Severe hepatitis was defined if AST and/or ALT levels were more than 1000 U/L.[11] If serum creatinine level was increased by 0.3 mg/dl, or more within 48 hours, or elevated to 1.5-fold or more from the baseline (done within 6 months before current Dengue infection), then the patients were categorized as acute kidney injury (AKI).[12]

Table V: Diagnoses of study subjects (N=40)

	Frequency	%
Dengue Fever with hemorrhage	1	2.5
Dengue Hemorrhagic Fever (without shock)	30	75
DHF with shock (Dengue Shock Syndrome)	6	15
Expanded Dengue Syndrome	3	7.5

Table VI: Duration of fever at the time of ICU admission (N=40)

	Mean ± SD Days
DF with Hemorrhage (n=1)	4
DHF (non shock) (n=30)	4.77 ± 1.72
DHF with shock (DSS) (n=6)	4.6 ± 0.89
EDS (n=3)	5.6 ± 0.57
Total (N=40)	4.72 ± 0.66

Table VII: Laboratory parameters of study subjects (N=40) during ICU admission

Variables	**Mean ± SD**	Range
Hemoglobin	13.52 ± 2.13	9.9 to 18.2
Hematocrit	39.84 ± 5.65	30 to 53
Ca^{2+}	7.54 ± 0.73	5.7 to 9.1
Hypocalcaemia (n=36)	7.41± 0.65	5.7 to 8.4
Serum Creatinine	0.96 ± 0.47	0.2 to 2.51
Raised S. creatinine (n=8)	1.71 ± 0.52	1.3 to 2.5
	Median [IQR]	
Total WBC (TWBC)	6505 [4135]	2700 to 24,100
Normal TWBC (n=27)	6510 [2590]	4100 to 9840
Leucocytosis (n=6)	14750 [4780]	12580 to 24100
Leucopenia (n=7)	2930 [320]	2700 to 3860
Platelet count (n=40)	43,500 [93,000]	8000 to 1,70,000
On admission Thrombocytopenia (n=35)	35,000 [79000]	8000 to 140,000
Lowest Platelet count during ICU stay (n=40)	10500 [8500]	2000 to 38000
AST (n=38)	158 [222]	14 to 1810
Raised AST (n=35)	161 [220]	44 to 1810
ALT (n=38)	110.5 [188]	18 to 1993
Raised ALT (n=33)	119 [184]	43 to 1993

Complications of the patients, which they had during admission or developed during ICU stay, have been shown in table VIII. Pleural effusion is the commonest complication followed by ascites and pulmonary oedema. Patients were managed according to the National Guideline and treating Intensivists' decisions. Twenty-six patients (65%) had hypotension at the time of ICU admission and needed bolus IV fluid. Most of the patients improved within 6 days of ICU admission (Figure 2). No patients stayed in ICU for more than 12 days.

Table VIII: Complications of study patients (N=40)*

	Frequency
Bilateral pleural effusion	25
Unilateral pleural effusion	2
Ascites	19
Pulmonary oedema	11
Carditis	1
Pancreatitis	1
Secondary bacterial infection	3
Acute kidney injury	3
Melaena	4
Menorrhagia	1

*Multiple response table has been used as some patients had more than one complication

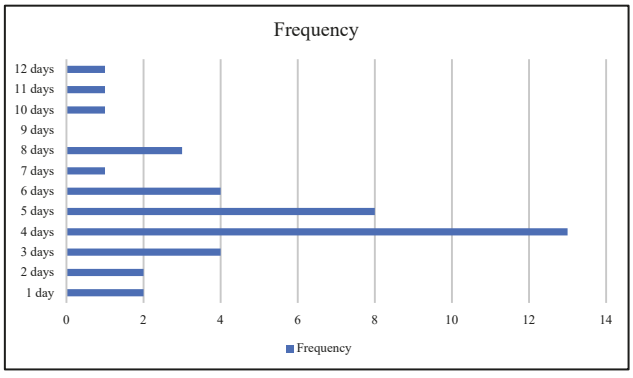

Figure 2: Duration of ICU stay

Table IX: Outcome and Organ support of study patients (N=40)

	Frequency	Percentage
Cured	38	95%
Expired	2	5%
Organ Support		
Mechanical Ventilator	2	5%
Vasopressor	8	20%
Renal replacement therapy	None	-

Outcome of the study patients & organ support requirement have been shown in table IX. We had two fatal cases (5%)

who expired despite all resuscitative efforts. Both (one male, aged 48 yrs, and one female, aged 28 yrs) of them were suffering from DSS with hypotension, bilateral pleural effusions, ascites and pulmonary oedema. One of them had secondary infection and was put on mechanical ventilator. Both required inotropes. Their biochemical parameters were not significantly different from the survivors (table X).

Table X: Comparison between survivors and non-survivors

	Survivors (n=38)	Non-survivors (n=2)	*p*
Hemoglobin	13.57 ± 2.16	12.35 ± 0.49	0.43
HCT	40.05 ± 5.69	35.5 ± 2.12	0.27
TWBC	7626 ± 4476.44	3570 ± 749.53	0.21
Thrombocytopenia	12125 ± 8429.11	10000 ± 0.1	0.72
Ca^{2+}	7.54 ± 0.72	7.5 ± 1.2	0.94
SGOT	301.25 ± 421.55	159 ± 2.82	0.64
SGPT	215.06 ± 275.65	106.5 ± 12.02	0.58

Discussion:

Transmission of Dengue peaks during the rainy season due to the optimal conditions for the *Aedes aegypti* and *Aedes albopticus* mosquito. The present study was done in the month of July, August and September, the peak season for Dengue. This pattern is similar to Indian studies as both India and Bangladesh face almost similar monsoon in same times due to geographical location.[13] In Dhaka city, there are thousands of cases every year due to haphazard urbanization, inadequate sanitary facilities, lack of cleanliness in households and presence of abundant mosquito breeding areas. The hospital, where the study was conducted, is situated in South Dhaka and that area is densely populated.

Seventy percent of the study population were in the age group of 18-40 years in the present study. This is consistent with other studies of our country[3,6,14,15]. It may be explained by the fact that this age group is mainly involved in education and work. So, they are exposed more to the mosquitoes than the older people. As the study conducted in an adult ICU, so we exclude children and did not have their prevalence data. Contrast with other studies, we found similar number of male and female Dengue patients in our ICU[3,6,14,15]. Those studies were done in hospitalized patients, ICU patients were not selected separately. But we collected data from ICU patients. This reflects that females with complications are referred to ICU as much as the male patients. Almost similar type of gender distribution was found in the first formal scientific survey in Bangladesh which was done in Chittagong Medical College Hospital in 1997 (male:female 1.5:1)[16,17]. Hasan et al found that number of female patients was rising when they compared number of female patients in 2019 outbreak with previous outbreaks occurred in 2008, 2016 and 2018.[6]

Dengue patients usually develop an abrupt onset of high fever (39-40°C) with headache, retro-orbital pain, malaise, severe body ache, arthralgia, rashes, vomiting and diarrhoea after an average incubation period of 4-6 days[2]. This febrile phase lasts for 2-7 days followed by afebrile phase. As most of our patients presented on 4th day of onset of symptoms, so all of them had fever. For the same reason, 90% of our study patients had positive Dengue NS1 antigen as it remains positive up to six days of onset of fever[18]. IgM antibody appears in blood after five days of fever whereas IgG appears at the end of first week. But IgG appears earlier in case of secondary infection with higher titer than IgM[18]. Only 4 (10%) of our patients had positive IgM report. Though rising titre of positive IgG can be used to detect current infection, no laboratory in our country do quantitative analysis of Dengue antibody as far as we know.

Critically ill patients are admitted in ICU for organ support, or close monitoring to prevent any organ failure. There are several studies on presenting features of Dengue in our country[6]. We did not take data of presenting features; rather we collected data on reasons of the patients' ICU admission or referral to ICU. Sixty five percent patients were admitted to ICU for hypotension as judicial fluid administration under close monitoring is essential for Dengue patients with complications, especially during vascular leakage period. Fortunately, most of them responded to fluid therapy; only 20% (n=8) needed therapy with vasopressors. Hasan et al found that hypotension and GIT features like anorexia, nausea and/or vomiting were common in adult Dengue patients in their study which was conducted in 2019 outbreak[6]. Rapid development of hypotension can be explained by upward shift in disease severity. They also found a reduced trend in hemorrhagic manifestations and joint involvement. We found almost similar picture as cause of ICU admission except less GIT symptoms in our patients.

Among the critically ill Dengue patients, 32.5% patients had co-morbidities like DM, HTN, IHD etc. It is a well known fact that incidence of co-morbidities like diabetes, hypertension etc is more in elderly population than younger people. The mean age of the patients with co-morbidities was significantly higher than the patients who did not have any co-morbidity (50.3 ± 13.3 vs 32.2 ± 6.8) in present study.

After ICU admission, patients were categorized in different subtypes of Dengue as per WHO guideline. Most of our patients (75%) were diagnosed as DHF (non shock), followed by DHF with shock (15%), EDS (7.5%) and DF with hemorrhage (2.5%) respectively. Uddin et al found 36.9% of their patients had DHF-I followed by DF (33.3%), DHF-II (20.2%), and DHF-III (9.5%) in a one-year study on 84 patients attending a tertiary care hospital in Dhaka city[19]. On the other hand, 46% patients had Classical Dengue in another study done in same hospital[20].

Thrombocytopenia is the most common finding in Dengue infection. Thirty five out of our 40 patients had thrombocytopenia during admission at ICU. During stay in ICU, all had progressive declining number of platelets which became as low as 2000/cmm. Though leucopenia is common near the end of febrile phase, very few number of our patients (n=7) had it. Most of the patients (n=27, 67.5%) had normal leucocyte count (table VII).

Mild to moderate increase in the transaminase levels and hepatomegaly are well recognized features of Dengue[7]. Eighty seven percent of our study population had raised AST levels, & eighty two percent had raised ALT levels; but no patient had hepatomegaly.

DHF is characterized by plasma leakage due to increased capillary permeability. This leads into development of pleural effusion and ascites. Twenty five patients (62.5%) in the current study had bilateral pleural effusion and 19 (47.5%) had ascites. This correlates with the study done by Rahman et al who found 41.7% of their study patients had bilateral pleural effusion, and 34% patients had ascites[3]. Though acalculous cholecystitis has been reported in many studies & case reports of dengue patients, none of our patients had clinical or ultrasonographic features of cholecystitis. Acute pancreatitis is another well known complication of severe Dengue. Only one of our patients had features of acute pancreatitis. The number of patients with pancreatitis was also low (7.7%) in the study by Rahman et al[3]. Capillary fragility and thrombocytopenia may lead to bleeding in Dengue. This bleeding may manifest as petechial skin haemorrhages to life threatening bleeding into internal organs. Four of our patients had gastro-intestinal bleeding manifested us melaena, and one female patient had menorrhagia. Another lethal complication of Dengue infection is Acute Kidney Injury (AKI) which may lead to increased mortality. Three patients (7.5%) in current study had AKI; two of them had acute on chronic kidney disease , and one had de novo AKI. Fortunately their renal functions improved with conservative treatment & none required renal replacement therapy. Study done on 300 Dengue patients in Medicine department of Combined Military Hospital in 2019 showed AKI in 14.3% (n=43) of study patients[3]. Among them, 15 patients (5%) needed hemodialysis. Studies done in India reported incidence of AKI as 14.5%, 13.3% and 10.8%[21,22,23].

Till date there is no specific antiviral therapy for Dengue. Judicious use of parenteral fluid, especially at the time of maximal vascular leakage, and symptomatic treatment is the mainstay of treatment. Most of our patients recovered fully. Unfortunately, two patients with DSS expired. There was no significant difference in the biochemical parameters among the survivors & deceased (table X).

Limitations of the study:

Number of study patients was small in our study. It may indicate that the medical management of Dengue patients in Medicine ward is good enough. As a result, less number of patients was transferred to ICU.

Conclusion:

Dengue has now become a public health problem in Bangladesh. It may present as slight fever, to life threatening DSS or EDS. Intense monitoring of hospitalized Dengue patients with early detection of complications and proper management can be life-saving, even in the critically ill patients requiring ICU support.

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