

Gallbladder Wall Thickening for Early Detection of Plasma Leakage Among Children with Dengue Fever Admitted in a Tertiary Care Hospital

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Abstract:

Background: Plasma leakage is defined as a 20% elevation of hematocrit from baseline or evidence of plasma leakages such as pleural effusion, ascites, or hypoalbuminemia. In the early phase, these signs of plasma leakage are usually difficult to ascertain by physical examination and laboratory tests.

Objective: This study aimed to investigate whether gallbladder wall thickening (GBWT) in the febrile phase of the disease can be used to detect the occurrence of plasma leakage in dengue patients.

Methods: A cross-sectional analytical study was conducted during a 4-month period in Dr. MR Khan Shishu Hospital and ICH from September 2021 to December 2021. Children from 6 months to 14 years who were admitted with acute onset of fever less than 3 days with NS1 positivity were included consecutively. Laboratory tests and abdominal Ultrasonography were also performed to confirm the occurrence of plasma leakage.

Result: Out of 114 patients, the majority were male (64%), in the 5-<10-year age group (48.25%). Common presentations include fever (100%), flushed appearance (66.7%), abdominal pain (66.7%), vomiting (44.7%), bodyache (39.5%). During the febrile phase, 56 patients were presented with GBWT, 49 of which showed plasma leakage during treatment. The sensitivity and specificity of GBWT during fever were 89% and 88%. PPV and NPV were 87% and 90% respectively. In risk factor analysis, Gallbladder wall thickening was found statistically significant (<.009) predictor of plasma leakage in dengue.

Conclusion: Gallbladder wall thickening during the febrile phase is a predictor of plasma leakage in Dengue.

Keywords: Dengue Fever, Plasma Leakage, Thickening of Gall bladder Wall, Children.

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Introduction:

Dengue Fever is the most common viral disease across the world, including Bangladesh.¹ This virus can bring out substantial morbidity and mortality in adults as well as in children. According to the World

Health Organization, 390 million people are affected worldwide yearly, with around a 1% mortality rate.² Dengue has been a major public health problem in the world for several decades, and the first official dengue outbreak in our country in 2000.³ Since then, Bangladesh has faced a mild to moderate outbreak every year.⁴ In 2018, Bangladesh experienced an unusual outbreak of Dengue with the highest incidence of recorded cases.⁴ There are four dengue virus serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Even though these four serotypes have comparable antigenicity, nevertheless, they produce cross-protection for a few months. Secondary infection with another serotype or multiple infections with different serotypes augments the chances of occurring more severe diseases.⁵ Patients with dengue may be

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asymptomatic or may present with severe and non-severe clinical manifestations. Common presentations include fever, body aches, rashes, etc. But if bleeding and plasma leakage develops, it may be fatal and life-threatening.¹

Several studies have suggested that plasma leakage is the main hallmark of dengue pathogenesis. A complex interaction between virus, host immune response, and endothelial cells maintains endothelial cells' integrity and functions, leading to plasma leakage. It is essential to detect signs of plasma leakage because this is responsible for the loss of intravascular volume and circulatory insufficiency, shock, and even death. Early detection of plasma leakage is essential to improve management and decrease the mortality rate of dengue infection. When the patient has a mild degree of plasma leakage, the signs of plasma leakage, like pleural effusion, ascites, or hypoalbuminemia, are usually difficult to ascertain by physical examination and laboratory tests. Several studies have demonstrated that ultrasonography is useful in detecting plasma leakage signs such as gallbladder wall thickening (GBWT), ascites, and pleural effusion. A few other studies suggest that gallbladder wall thickening, or gallbladder sub serosal edema is the most common initial ultrasound finding compared to ascites and pleural effusion.^{4,5}

Hypothetically the underlying mechanism of gallbladder wall thickening is subserosal edema is one manifestation of increased capillary permeability due to antibody-dependent enhancement.⁶ So, this study aims to investigate whether gallbladder wall thickening in the early phase of the disease can be used to detect the occurrence of plasma leakage in children.

Materials and Methods:

Study Procedure-A cross-sectional analytical study was carried out at the Pediatric Department of Dr. M R Khan Shishu Hospital and ICH from September 2021 to December 2021 to see the clinical profile of dengue fever and find out the gall bladder wall thickening as an early predictor of plasma leakage in children with Dengue Fever. This study had been approved by Ethical Review Committee of Dr. M R Khan Shishu Hospital and ICH. Children from 6 months to 14 years old who were admitted with acute onset of fever less than 3 days with NS1 positivity were included in our study. However, children with Dengue Fever admitted with plasma leakage or during the convalescent phase and

unwilling to give consent were excluded from the study.

Written informed consent was obtained from all the patients or a legal guardian where necessary. A case record form, like clinical demography, was constructed to collect baseline information. A detailed physical examination was done. Investigations like Complete blood count, Serum creatinine, Serum albumin, SGPT, and USG of the abdomen were done in every patient during the admission. If USG finds no evidence of gall bladder wall thickening during admission, Repeat USG will be done daily for consequent febrile days.

During the hospital course, we detected restlessness, cold clammy skin, systolic Pressure <5th centile, Pulse pressure <20 mm of Hg, capillary Refill Time >3 seconds, raised Hematocrit >20%, ascites, pleural effusion, bleeding manifestations as a feature of Plasma leakage. All the investigations were done in the lab of Dr. M R Khan Shishu Hospital and ICH.

The ultrasound examination was performed by an experienced sonographer who did not know the clinical and laboratory data of the subjects examined. Ultrasound examination was performed using USG Logic P9 R4 series using convex probe with the frequency of 3-5 MHz. Inspection results will be printed and recorded.

Definition:

Gallbladder Wall Thickening- GB Wall thickness of 3 mm is the upper limit of normal. GB wall thickening above 3 mm was considered as GB wall thickening.⁷

Statistical analysis:

Statistical analysis was carried out with SPSS Statistics software version 23. Univariate analyses are shown in the form of a subject characteristic table. Categorical and numerical variables are presented in numbers and percentages. The Chi Square test determined statistical significance for continuous variables. The P-value of 0.05 was taken as the significant cut of value. Qualitative variables were expressed in n(%). Diagnostic ability was estimated as sensitivity and specificity along with ROC curve for obtaining cut off value of parameter of interest.

Result

A total of 114 children with dengue fever were enrolled in our study. Among the study population, males were predominant (65.5%), and 48.2% of patients were between 5-10 years old. (Table-I)

Table-I
Baseline characteristics of the study population (n-114)

Variable	Number (n)	Frequency(%)
Age group		
<1 year	2	1.75
1-<5 year	35	30.7
5-<10 year	55	48.25
10 -14 year	22	19.2
Sex		
Male	73	64.03
Female	41	35.96

During admission, dengue cases presented with a diversity of clinical features. High-grade continued fever was present in 100% of patients, and the mean duration of fever was 4±2 days. Along with fever, other predominant clinical presentations included flushed appearance (66.7%), rash (17.5%), vomiting (44.7%), Headache (47.4%), Orbital pain (11.4%), abdominal pain (66.7%), Arthralgia (15.8%), Body ache (39.5%), Bleeding manifestation (17.5%). (Figure-1)

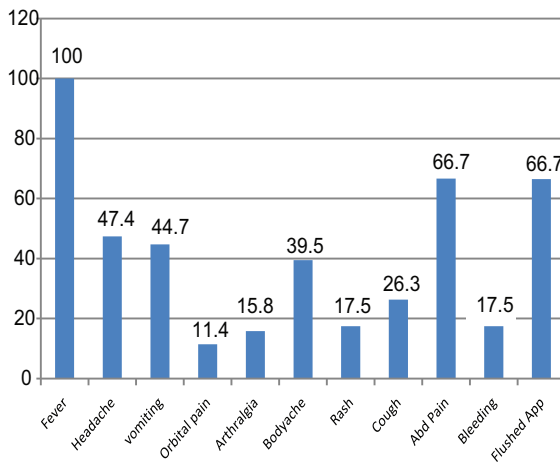


Fig.-1: Clinical presentations of children with Dengue Fever (n-114)

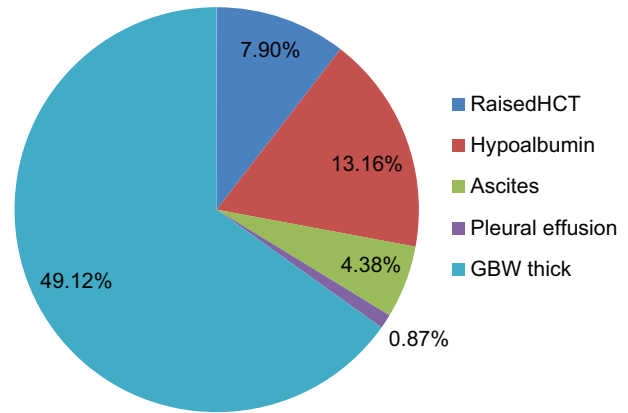


Fig.-2: Signs of plasma leakage during febrile period among children with dengue(n-114).

During the febrile period, raised HCT was obtained in 9 patients (7.9%), Hypoalbuminemia in 15 (13.16%), Ascites in 5 (4.38%), and pleural effusion in 1(.87%) in comparison to thickened GB wall 56 (49.12%). (Figure-2)

During the febrile phase, 56 patients were presented with GBWT with a mean thickness of 3.79 mm. Among these 56 patients, 49 were proved to have plasma leakage during treatment. There were 7 patients who did not experience GBWT but were proven to have plasma leakage during treatment. In risk factor analysis, GBW thickening was found statistically significant (<.009) as a predictor of plasma leakage during the febrile phase. The sensitivity of thickening of the gallbladder wall during the febrile period was 89%, whereas its specificity was 88%. The positive predictive value was 49/56 or 87%, while the negative predictive value was 52/58 or of 90%. In risk factor analysis, GBW thickening was found statistically significant (<.009) as a predictor of plasma leakage during the febrile phase. (Table-II)

Table-II
Validity of GB Thickening as a predictor of plasma leakage in dengue fever (n-114)

GB Thickening	Leakage-Present	Leakage-Absent	Total	P-value
Present	49	7	56	
Absent	6	52	58	<.009
Total	55	59	114	

Sensitivity-89%, specificity-88%, PPV-87%, NPV-90%

* Chi –square test was done to measure the level of significance

ROC curve showed Gall bladder wall thickness of 3.25 mm had a sensitivity of 94% and Specificity of 64%. (Fig.-3)

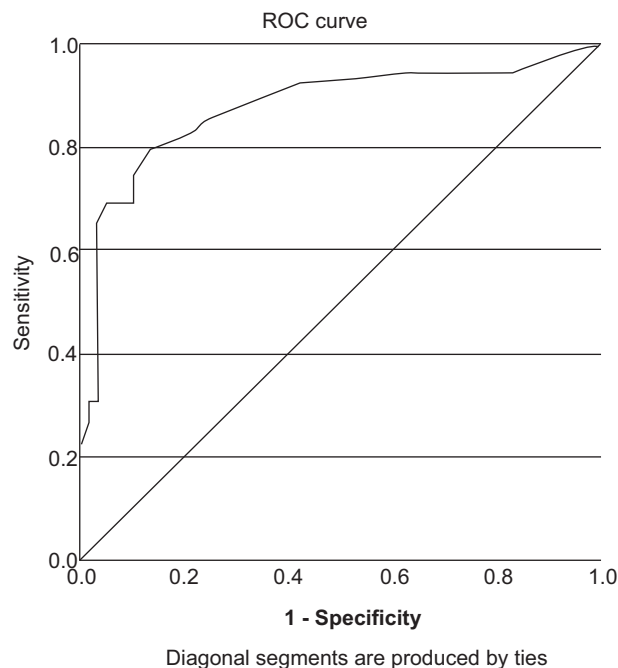


Fig.-3: ROC curve of GB wall thickness against plasma leakage. The ROC shows Gall bladder wall thickness of 3.25 mm had a sensitivity of 94% and Specificity of 64%.

Discussion:

In this study, the common age group affected was between 5 and 10 years. Sarker A et al. and Ahmed FU et al. found that the maximum number of cases was below 10 years in their work^{8,9}, which is like our study findings. Males were affected more (64%) than females in this study, consistent with various previous studies.^{10,11,12,13,14} In this current study, 100% of patients presented with fever followed by a flushed appearance (66.7%), rash (17.5%), vomiting (44.7%), Headache (47.4%), Orbital pain (11.4%), abdominal pain (66.7%), Arthralgia (15.8%), Body ache (39.5%), Bleeding manifestation (17.5%). A similar finding has been reported by Alam S et al., and Mobarak MR et al.^{3,10} According to Ahmed FU et al. and Rahman M et al., headache (85% and 91% respectively) was the main symptom.^{9,15} But headache (47.3%) and retro-orbital pain (10%) were found less in this study. Vomiting (44.7%) and abdominal pain (66.7%) were the commonest presenting symptoms which is similar to a study done by Wang et al and Iman K et al.^{16,17}

Increased capillary permeability is the main hallmark in dengue pathogenesis that leads to plasma leakage, hemoconcentration, hypovolemic shock, and death, which generally occurs in the critical phase.¹ The increased vascular permeability would not change the level of serum albumin upto a certain severe point.¹⁹ Detection of ascites and pleural effusion by clinical and physical examination is difficult when only a small amount of fluid is present. Ultrasonography (USG) is a cheap, safe, rapid, and widely available non-invasive imaging modality. Ultrasonography can detect minimal pleural effusion, ascites, and gallbladder wall thickening.⁶

A significant occurrence of Gallbladder wall thickening during the 3rd to 5th day of Dengue fever determines that GBWT has started from the febrile phase of the illness.^{20,21} So, we can detect GBWT by ultrasonography in the febrile phase (early phase) to see the presence of plasma leakage and, thus, the severity of the disease before it becomes clinically apparent. A study done in Jakarta showed 53.8% had GBW thickening during febrile phase which was almost similar to our study 56 (49.12%).^{22,23} During febrile period, raised HCT was obtained in 9 patients (7.9%), Ascites in 5 (4.38%), pleural effusion in 1 (0.87%) in comparison to a study done in Indonesia which subsequently showed 12 patients (17.4%), 10 (14.5%) and 2 (2.9%). In this study, among these 9 patients, all (100%) patients had GBW thickening during the febrile phase, but another study showed 9 (75%) patients had gallbladder wall thickening on the third day of fever, and 2 (16.66%) patients on the fifth day of fever and only 1 patient until the end of treatment did not have gallbladder wall thickening. Those findings could be explained by the fact that signs of plasma leakage by gallbladder wall thickening were detectable more than changes in hematocrit level and, furthermore, hypoalbuminemia and hemoconcentration.⁹ In this study, plasma leakage was found in 55 patients (48.25%).²⁴ Hemoconcentration was seen in all patients with plasma leakage during the afebrile period, which was not consistent with the study conducted by N Leonard et al. & Michels et al which showed subsequently 15 patients (21.7%), 21 patients (31.8%).^{24,25} Hypoproteinemia was seen in 37 (32.45%), which was similar to a study that showed 25 patients (36.2%) during the afebrile period.¹⁹

Some researchers suspected that vascular permeability in children is more common than in

adults.²⁶ In current study, gallbladder wall thickening during the febrile phase was found in 49 patients (42.9%), almost like a study done in Indonesia with 37 patients (53.6%). The prevalence of gallbladder thickening during the febrile phase was 49/55 (89%). However, the findings of this study are in accordance with previous studies by Oliveira et al¹² (89.2%) and Vedaraju et al²⁵ (83.3%), which also showed GBWT as the most common initial finding.^{25, 27}

The difference in antigenic strains and patient susceptibility might also have contributed to the difference in the number of incidences of GBWT findings. Furthermore, the presence of gallbladder wall thickening was associated with the severity of the disease. The mean thickness of the gallbladder wall in this study was 3.79 mm (1.7 to 8.9), similar to a study done in Jakarta of 3.30 mm (1.68 to 7.35 mm).²⁴ Kim et al reported a mean gallbladder wall thickness of 6.1 mm (4.0 - 15 mm), but the study was conducted in dengue patients with impaired renal function.²⁸ Other studies that examined gallbladder wall thickening in patients with dengue infection did not mention the average thickness of the gallbladder wall.

In this study, ROC curve showed Gall bladder wall thickness of 3.25 mm had a sensitivity of 94% and Specificity of 64%. Another study revealed the sensitivity and specificity to predict the progression of severe dengue as 93.7% & 70% respectively for the cut-off value of 5 mm of GBWT and Colbert et al reported sensitivity and specificity for 5 mm cut-off value of GBWT as 79.1%, and 86.1%.^{29, 30}

In this study, it has been demonstrated that the sensitivity and specificity of thickening of the gallbladder wall during the febrile period were 89% and 88%, not consistent with a study done in Jakarta which showed 65% and 70%, respectively. Whereas the positive and negative predictive values were 87% and 90%, which was almost like a study done in Indonesia, 81% and 50%, respectively.^{24, 28} In risk factor analysis, GBW thickening was found statistically significant ($<.009$) as a predictor of plasma leakage during the febrile phase. Based on these findings, GBWT, which appears at the beginning of dengue infection, was a good indicator of plasma leakage. Gallbladder wall thickening in dengue often precedes other plasma leakage parameters, and these findings revealed that ultrasound examination of the gallbladder wall during the febrile period has an

important role in detecting plasma leakage in the early phase of dengue infection. Gallbladder wall thickening in the early phase of the disease can be used to detect the occurrence of plasma leakage in dengue-infected children. The early detection of plasma leakage is expected to be able to reduce the mortality rate.

Conclusion- Along with fever, most of the patients presented with GIT symptoms like vomiting and abdominal pain, and the use of gall bladder wall thickening during the febrile phase alone is a good predictor of plasma leakage as a quick initial assessment. So we can use it for predicting disease progression. A further large-scale study is needed to see the effectiveness of Gallbladder Wall thickening as a predictor of plasma leakage

Limitation- It is a single-center study, and the sample size is small.

Abbreviations ALT: AUC: Area under the curve; DF: Dengue fever; DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome; NPV: Negative predictive value; PPV: Positive predictive value; ROC: Respondent operative characteristics; SGPT: Serum glutamate-pyruvate transaminase; WHO: World Health Organization

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