

# Gallbladder Wall Thickness to Predict Severe Dengue in Children

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## ABSTRACT

**Introduction:** Significant increase in plasma leakage is characteristic of severe dengue. This results in collection of fluid in serous cavities. Gall bladder wall thickening (GBWT) often precedes the development of pleural effusion and ascites. Early detection of plasma leakage and management is shown to reduce mortality in dengue illness. Ultrasonography is a point of care investigation to identify GBWT. The aim of this study was to determine the cut-off value of GBWT to predict severe dengue in the early phase of the illness.

**Methods:** This was a prospective study done on 310 children with dengue illness. Abdomen and chest ultrasound was done in all these children between third and sixth day of illness. GBWT of more than 3.5 mm was taken as a thickened gall bladder wall. Maximum severity of the illness was considered for categorising the severity of dengue.

**Results:** Out of 310 children, 160 (51.6%) were categorized as dengue fever, 91 (29.4%) as dengue with warning signs and 59 (19%) as severe dengue. The incidence of thickened gall bladder wall was 27.5% in DF (Dengue fever), 68% in DF with warning signs and 96.6% in severe dengue. The odds of finding thickened gall bladder wall in severe dengue are 3.5 times that of dengue fever. GBWT increases as the severity of the illness increases. GBWT of 5 mm has sensitivity of 93.7% and specificity of 70% to predict progress to severe dengue. There was a fair correlation of 46% between thickened gall bladder wall and thrombocytopenia. Gall bladder wall thickness of 2.5 mm had sensitivity of 86.3% and specificity of 80% for ascites. GBWT of 3.5 mm had a sensitivity of 77.6% and specificity of 85% for pleural effusion.

**Conclusions:** GBWT assessment by ultrasonography in early phase of illness can be used as a point of care modality to predict severe dengue. The sensitivity and specificity to predict the progression to severe dengue is 93.7% & 70% respectively for the cut-off value of five mm of GBWT.

**Key Words:** Dengue; Gall bladder wall thickness (GBWT); Severe dengue; Ultrasonography



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## INTRODUCTION

The incidence of dengue has increased substantially in recent decades around the world. In the last two decades there has been eight-fold increase in the number of dengue cases reported. Statistical data shows a steady increase in mortality related to dengue illness.<sup>1</sup> Significant plasma leakage is an important feature of severe dengue infection.<sup>2,3</sup> Plasma leakage can be determined by an elevation of haematocrit by  $\geq 20\%$  from the baseline. Apart from this, the presence of pleural effusion, ascites or hypoproteinaemia / hypoalbuminemia also indicates plasma leakage.<sup>3</sup> Plasma leakage can lead to hypotension and shock. Predicting the progress of the illness to severe form is challenging. In the early phase of the illness, the signs of plasma leakage are usually difficult to ascertain by clinical examination.<sup>2,3</sup> Change in haematocrit as a marker of plasma leakage may not be of clinical benefit.<sup>2</sup> Pleural effusion / ascites detected by ultrasonography are helpful in diagnosing plasma leakage. Leakage of plasma into the interstitium precedes its collection in the serous cavities. This can be identified by abdominal ultrasonography as increased thickness of gall bladder wall. Identifying gall bladder wall thickness (GBWT) in early phase of illness can be used to detect the occurrence of plasma leakage.<sup>3</sup> This finding may alert the clinician for intensive monitoring of patients for the development of complications.<sup>2</sup> Therefore GBWT may be useful as early warning sign for plasma leakage in dengue illness.<sup>2,4</sup> Reticular pattern of GBWT can be considered as typical reliable sign of plasma leakage in DF.<sup>4</sup> GBWT has not been included in the WHO criteria for classification of dengue illness.<sup>3</sup> Even though there are several studies regarding sonographic findings, only few studies are available to predict the severity of dengue by GBWT in the early phase of the disease.<sup>2-6</sup> Therefore this study was undertaken to determine the cut-off value of GB wall thickness in the early phase of the illness to predict severe dengue.

## METHODS

This hospital-based study was conducted in JSS Medical College Hospital, Mysore, India between January 2017 to November 2017. All children with

dengue infection between one month to 18 years of age confirmed by either IgM or NS1 antigen test by ELISA were included in the study group. Those with coexisting infections proved by blood culture, smear for MP, chest X-ray, Widal test and Weil-Felix test were excluded. JSS Institutional Ethical Committee approved this study, and a written consent was taken from the parents. The prevalence of GBWT in children with confirmed dengue illness reported to be 75.9%.<sup>6</sup> The sensitivity of this finding in severe dengue fever is 89.6%. Considering these values and a precision of 5% using the appropriate formula we needed to recruit a minimum of 188 cases. During the study period we could recruit 310 patients. All the eligible patients were admitted and managed as per the standard protocol. Fasting could not be done for all the children especially infants and small children. We however tried the fasting rule for the older children especially adolescents. Ultrasonography of abdomen and thorax was performed between third and sixth day of illness. A designated radiologist conducted the ultrasound examination using 3.5 MHz and 5 MHz probes on Philips CX 30 machine. GBWT was measured by placing the callipers between the inner wall to the outer wall of gall bladder. A measurement of greater than 3.5 mm GBWT was considered as thickened gall bladder. All the four quadrants of abdomen were screened for the evidence of ascites. Sonography of thorax was done in either supine or sitting position to look for effusion in costophrenic angles. Maximum severity of the illness was determined at the time of discharge for categorising the severity as per WHO criterion.<sup>7</sup> The data were entered into a purpose designed case report form. Analysis was done using Analyse-it for excel v 4.3. Quantitative variables were summarised as mean and standard deviation or median and interquartile range depending on their distribution. Categorical variables were summarised as proportions. Proportions were compared for association using Chi Square test. Diagnostic ability was estimated as sensitivity and specificity along with ROC curve for obtaining cut off value of parameter of interest. Comparison of median was done using Sign test.

## RESULTS

Table 1. Demographic and ultrasound findings at admission

Parameters	Median (IQR)	
Age in years	9 (6 - 12)	
Ultrasound done at admission (day of illness)	6 (5 - 6) Range 3 to 6 days	
		N (%)
Gender	M (%) / F (%)	179 (57.7) / 131 (42.3)
Ultrasound Findings	Ascites	191 (61.6)
	Pleural effusion	171 (55.2)
	Thickened gall bladder wall	167 (53.8)
Serology	NSI	221 (71)
	IgM	34 (11)
	Both	55 (18)

We studied 310 children with dengue illness confirmed by serology. One hundred and sixty (51.6%) were categorized as dengue fever, 91 (29.4%) as dengue with warning signs and 59 (19%) as severe dengue. Demography and sonographic findings are depicted in the table 1. The incidence of GBWT was 27.5% in DF, 68% in DF with warning signs and 96.6% in severe dengue. The odds of finding thickened gall bladder wall in severe dengue are 3.5 times that of dengue fever (Table 2). It is interesting to note that the thickness of the gall bladder wall increases as the severity of the illness increases (Graph 1).

Table 2. Cases with Thickened Gall Bladder Wall in various severity of dengue illness

	N =310	GBWT
Dengue fever (DF)	160 (51.6%)	44 (27.5%)
Dengue with Warning signs (WS)	91 (29.4%)	66 (68%)
Severe Dengue illness (SD)	59 (19%)	57 (96.6%)
Odds ratio for WS against DF		2.63
Odds ratio for DF + WS against SD		2.2
Odds ratio for SD against DF		3.51

\*Dengue illness classified according to WHO criteria  
GBWT - Gall Bladder Wall Thickening

Presence of GBWT predicted development of severe dengue illness. GBWT of 5 mm has sensitivity of 93.7% and specificity of 70% to predict progression to severe dengue illness. Specificity of this could be improved to 79% by considering a cut-off value of 6 mm when the sensitivity dropped to 86.7%. Area under the curve was 90% (Graph 2 A). Positive predictive value was observed to be 46% with negative predictive value of 98%. GBWT more than 2.5 mm was associated with presence of ascites in 83.2% of cases. Conversely 93.2% of children who had GBWT of less than 2.5 mm did not have ascites (P < 0.00001). The area under the ROC curve was 91.7%. GBWT of 2.5 mm had sensitivity of 86.3% and specificity of 80% in determining presence of

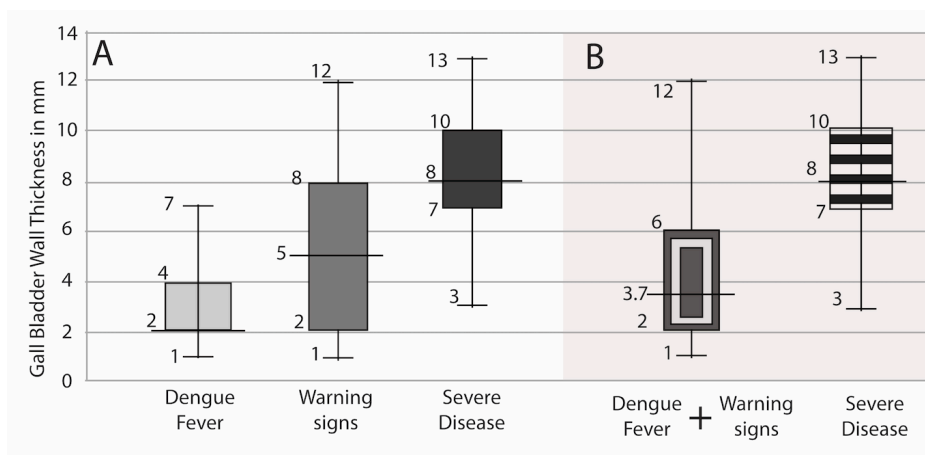


Figure 1. Gall Bladder Thickness in various severity of dengue illness

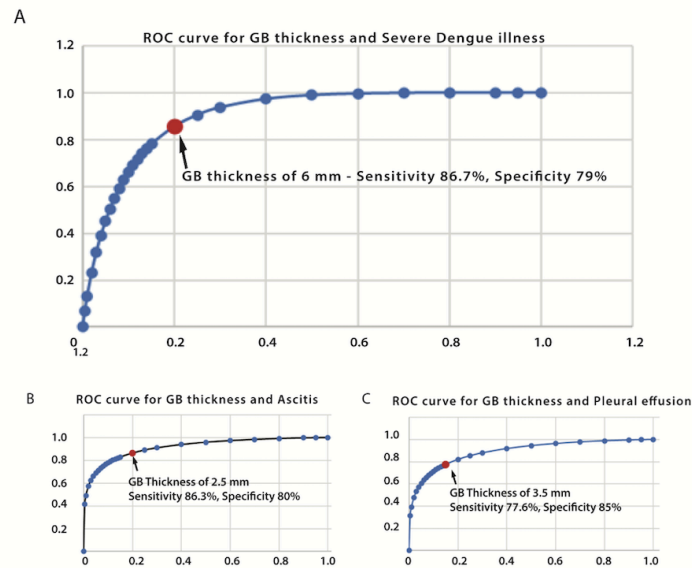


Figure 2. (A) ROC curve for gall bladder wall thickness and severe dengue illness  
(B) ROC curve for gall bladder wall thickness and Ascites  
(C) ROC curve for gall bladder wall thickness and pleural effusion

ascites (Graph 2B). Presence of GBWT of > 3.5 mm was associated with pleural effusion as well. 85.3% of subjects who had GBWT of > 3.5 mm also had pleural effusion. Conversely 84.9% of children who had GBWT of < 3.5 mm did not have pleural effusion ( $P < 0.00001$ ). The area under the ROC curve was 89.3%. GBWT of 3.5 mm has sensitivity of 77.6% and specificity of 85% in determining presence of pleural effusion (Graph 2C).

The median platelet count was 105500 /  $\text{mm}^3$  in dengue fever, 45000 /  $\text{mm}^3$  in children with dengue

fever with warning signs and 26000 /  $\text{mm}^3$  in severe dengue. There was a fair correlation ( $r = -0.46$ ) between GBWT and thrombocytopenia (Graph 3).

## DISCUSSION

Sonography of chest and abdomen was performed between the third and sixth day of illness and the findings were correlated with maximum severity of the illness as per WHO classification.<sup>7</sup> Our study revealed the sensitivity and specificity to predict the progression of severe dengue as 93.7% & 70%

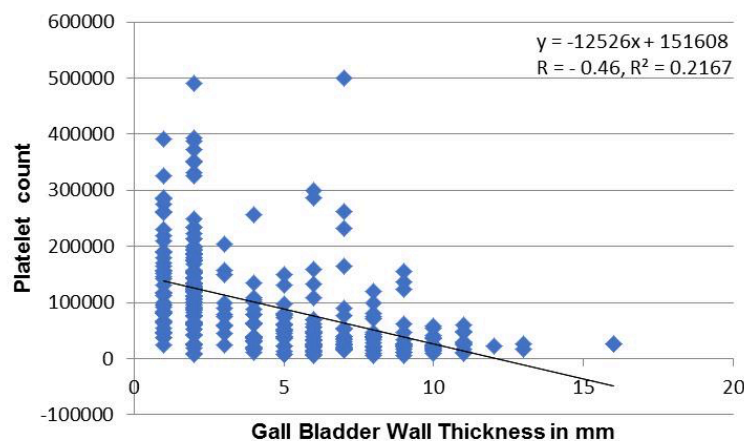


Figure 3. Graph showing correlation between GBWT and Platelet count

respectively for the cut-off value of 5 mm of GBWT on third to sixth day of illness.

The incidence of GBWT was 27.5% in DF, 68% in DF with warning signs and 96.6% in severe dengue. The odds of finding thickened gall bladder wall in severe dengue are 3.5 times higher than that of dengue fever. The odds of finding thickened gall bladder wall in severe dengue is 2.2 times higher than that of dengue fever with warning signs. It is interesting to note that the GBWT increases as the severity of the illness increases. In the present study sonography revealed thickened gall bladder wall in 53.3%, pleural effusion in 54.2% and ascites in 61.1% of children which is similar to study done by others.<sup>2-4,8</sup> The incidence of GBWT in dengue fever in various studies ranged between 28 and 100% depending on the cut off value they have chosen. Same authors have reported the incidence of pleural effusion to be ranging between 32 and 100% and ascites ranging between 15 and 96% in their studies.<sup>2,5</sup> The variations in the frequency of findings may be because of disparate vascular permeability in children and timing of ultrasound study.<sup>2,3,5</sup> Venkata et al showed that GBWT was detected in all 32 children with dengue illness when sonography was done on second to third day of fever.<sup>8</sup>

GBWT is one of the important finding of increased capillary permeability and a common ultrasound finding compared to ascites and pleural effusion.<sup>5,8</sup> Therefore, GBWT between third to sixth day of illness can be used to predict the progression to critical phase as it precedes the development of ascites and pleural effusions. Significant GBWT was noted during third to fifth day of fever, until the critical phase of the illness.<sup>3</sup> Tavares et al observed GBWT in 42.5% of 118 adult dengue patients. GBWT had shown a progressive increase from third to eighth day of illness corresponding to the critical phase of dengue fever. Severe dengue developed more frequently among patients with GBWT when compared to those without GBWT.<sup>5</sup> Michel et al detected GBWT in 65% of non-severe compared to 90% of severe dengue patients at enrollment.<sup>2</sup> Eventually, GBWT was detected in 100% of the severe dengue patients during the subsequent sonography. GBWT preceded development of ascites / pleural effusion by one to three days in 60% non-severe compared to 67% of

the severe patients.<sup>2</sup> Out of 69 adult patients, 37 had GBWT on the third day of fever and was the most common sonographic finding.<sup>3</sup> Among these 37 patients, 30 were proved to have plasma leakage during subsequent days.<sup>3</sup>

The mean GBWT was 3.32 mm in DF without warning signs, 4.95 mm in DF with warning signs and 8.80 mm in severe DF in a study done from Delhi which is similar to our findings.<sup>9</sup> Michel et al observed that the median GBWT at enrollment was 3.6 mm in patients with non-severe dengue versus 5.4 mm in those with severe dengue.<sup>2</sup> Setiawan et al reported significantly higher mean value of GBWT in dengue haemorrhagic fever [DHF] grades III and IV compared to grade I and II (5.14 mm vs 2.39 mm) in children with dengue infection.<sup>10</sup> They also observed GBWT of more than 3 mm in only 33.3% of grade I – II patients when compared to 93.8% in grade III – IV patients. There was a significant positive correlation between GBWT and the severity of illness.<sup>10</sup> Daily sonography revealed a progressive increase in the mean GBWT in DHF patients and it was significantly greater than in DF.<sup>11</sup> Plasma leakage was detected in DHF cases starting from two days before defervescence and was detected in some cases within three days after the onset of fever.<sup>11</sup> Study from Nicaragua also found a similar observation.<sup>12</sup>

In this study, GBWT had a good association with ascites and pleural effusion. Similar correlation was observed by others.<sup>5,10,11</sup> Study from Nicaragua and Indonesia also observed that patients with ascites have significant GBWT than those without ascites.<sup>5,12</sup> In our study there was a fair correlation between GBWT and thrombocytopenia which is similar to study from Nicaragua.<sup>12</sup> However, GBWT did not show any relation to platelet count in another study.<sup>5</sup> In the above study, the admission criteria included thrombocytopenia which might have resulted in skewing of the data resulting in poor correlation with GBWT. Our 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 on third to sixth day of illness. Colbert et al reported sensitivity and specificity for 5 mm cut-off value of GBWT on day three to four as 79.1%, and 86.1% and on day five to six as 87.5% and 86.8%



respectively.<sup>12</sup> Setiwan et al concluded that in DHF children, GBWT between 3 mm to 5 mm, with 93.8% sensitivity can be used as a criterion for admission and monitoring and greater than 5 mm with 91.7% specificity is useful as a criterion for identifying DHF patients at high risk of developing hypovolemic shock.<sup>10</sup>

An interesting argument would be to focus on the serial measurement of GBWT for initial few days to determine the rate of thickening. The rate of thickening depends on the development of capillary leakage and hence useful in identifying the herald of capillary leak even before clinical signs becomes evident.

Our study does have few limitations. One important limitation is that we were unable to perform ultrasound examination within first three days of illness and we also could not perform serial ultrasound after recruitment. Some of the GBWT measurement might have been influenced by the prior feed the child had as it is difficult to keep them fasting always.

## CONCLUSIONS

Thickened gall bladder wall is more frequent in patients with severe dengue illness compared to uncomplicated dengue fever. GBWT increases as the severity of the illness increases. GBWT of more than 5 mm can reliably predict the progression of the illness to severe degree even when clinical features do not indicate so. Sonography can be used as point of care investigation for decision making in clinical practice.

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