

## Ultrasound As An Aid To Diagnosis In Dengue

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<sup>1,2,3,4,6</sup> Experimentation/Study Conduction  
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## Abstract

**Objective:** To determine the ultrasound findings in patients with dengue fever and to evaluate their relationship with laboratory parameters.

**Study Design and Setting:** This prospective cross-sectional study was conducted at Creek General Hospital, United Medical and Dental College, Karachi from September 2020 to August 2021.

**Methodology:** A total of 248 patients diagnosed with dengue fever, fulfilling the exclusion and inclusion criteria, were included in the study. Demographic data were recorded on a structured proforma. Serological confirmation along with complete blood counts and liver function tests were obtained. Abdominal and chest ultrasounds were conducted in all patients. The ultrasonographic features of these patients were analyzed with laboratory investigations through SPSS version 23. Student's t-test and Chi-square tests were used to assess the association between the ultrasonographic findings and laboratory features. A P-value of <0.05 was considered significant.

**Results:** The most common ultrasonographic feature among dengue patients was acalculous cholecystitis (49.6%) followed by hepatomegaly (47.2%), splenomegaly (46.8%), altered echotexture of the liver (46.4%), ascites (37.5%) and pleural effusion (7.3%).

Acalculous cholecystitis and ascites were significantly associated with severe thrombocytopenia and increasing hematocrit. Acalculous cholecystitis, ascites, pleural effusion, and altered echotexture of the liver were associated with raised transaminases.

A low platelet count showed the strongest relationship with sonographic features of capillary leak syndrome.

**Conclusion:** Ultrasound is a useful investigation to diagnose severe, critical dengue. The development of ultrasonographic features should prompt proactive management of these patients in order to prevent the emergence of severe complicated dengue.

**Keywords:** Acalculous cholecystitis, ascites, dengue, hepatomegaly, pleural effusion, ultrasound.

## Introduction

Around half of the world's population is exposed to the dengue virus.<sup>1</sup> Among the vector-borne viral diseases, dengue fever (DF) causes high mortality and morbidity in tropical and sub-tropical regions of the world.<sup>2</sup> The incidence of dengue has increased around 30 times in recent decades. We have witnessed a rising incidence of dengue outbreaks in Pakistan since the beginning of this century. Climate change, urbanization, increased international travel, internally displaced populations, unplanned urban development and natural disasters like urban flooding have all contributed to this increase.<sup>3</sup> The mosquitoes *Aedes aegypti* and *albopictus* grow prolifically in stagnant water and have been demonstrated in various parts of the country.<sup>3</sup>

Dengue virus infection may present as mild febrile illness and also as potentially fatal dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Classical dengue fever, DHF, and DSS are the most recognized forms but there are reports of other unusual presentations like hepatitis, encephalopathy, cardiomyopathy, acute pancreatitis, and acalculous cholecystitis.<sup>4,5</sup> Keeping in mind the various organ systems involved in the infection WHO (World Health Organization), in 2012, introduced a new term "Expanded Dengue Syndrome". These presentations have now become increasingly common.<sup>6</sup> In dengue endemic regions expanded dengue syndrome should be suspected in febrile patients who have organ system involvement along with fever and bicytopenia. Many of the clinical features of DF are similar to other febrile diseases endemic in regions where dengue itself is found. The monsoon season, in which DF incidence surges, also heralds an increase in cases of malaria and enteric fever in Pakistan. It is important to establish the correct diagnosis so that precious resources are not wasted in unnecessary or invasive investigations and unwarranted treatment regimens. It is therefore important to know the various presentations of DF which may be encountered by the physician.

DF is suspected on the basis of clinical findings, laboratory investigations and confirmed by serological tests for dengue-specific antigens or antibodies. Many of the features have to be confirmed through ultrasound. Ultrasonography has demonstrated hepatomegaly, splenomegaly, altered liver texture, pancreatitis, presence of ascites, pleural effusion,

acalculous cholecystitis, and rarely pericardial effusion in patients with Dengue fever.

Keeping in mind the mortality and morbidity of this disease, the development of accurate and timely diagnostic modalities and parameters is required. Early identification of cases that can develop critical and severe diseases is important. This can help timely decisions to initiate appropriate management strategies.<sup>7</sup> DF usually has 3 stages; the first is the febrile stage followed by the critical stage leading to the recovery stage.<sup>8</sup> In some patients the febrile stage can proceed to recovery without going through the critical phase. The critical stage, which usually occurs immediately after fever effervescence, is characterized by increased capillary permeability and plasma leakage. This can be the harbinger of DHF or DSS. This is also associated with hemoconcentration, thrombocytopenia, leucopenia, and an increase in hepatic transaminases.<sup>9</sup> Increased capillary permeability leads to third space sequestration of fluid which can present as acalculous cholecystitis, ascites, and pleural effusion. This is the stage where close monitoring and early intervention will improve the outcomes of the disease. There is no specific management available to prevent or treat DSS or organ failure associated with DF.<sup>10</sup> Many of these features, although diagnosed clinically are confirmed by ultrasound. This study was undertaken to recognize the various sonographic features seen in patients with dengue fever and to assess their association with different laboratory parameters.

## Materials and Methods

This is a descriptive cross-sectional study conducted at Creek General Hospital, United Medical and Dental College, Karachi. The study was conducted over a period of one year from September 2020 to August 2021. The patients were included in the study through consecutive sampling.

This study was approved by the Institutional Review Board (UMDC/IRB-Ethics/2020/2/9/267). All adult patients presenting with clinical features of dengue fever and who were serologically confirmed to have the infection were included in the study, after informed consent. Cases with other acute infections, chronic liver disease, chronic kidney disease, nephrotic syndrome, congestive cardiac failure, malaria, enteric fever, hemolytic anemia, recent surgery, and trauma, using contraceptive pills, pregnant females, and patients with cholelithiasis

were excluded. Dengue was diagnosed on the basis of clinical presentation and appropriate serological tests including a non-structural protein-1 (NS-1) Antigen test or dengue immunoglobulin M/ immunoglobulin G.

Ultrasound scanning of the abdomen and thorax was performed on patients with a confirmed diagnosis of dengue. The ultrasounds were performed with an ultrasound machine (Toshiba 730 Pro model) using a 7.5 MHz probe. A single sonographer performed all the ultrasounds. Acalculous cholecystitis was diagnosed if the gallbladder (GB) wall thickening was measured to be more than 3.5 mm, there was an ultrasonographical positive Murphy’s sign, and a gall bladder without stones.<sup>11</sup> Both the pleural spaces were assessed using an intercostal approach. A liver span more than 15 cm was taken as hepatomegaly and splenomegaly was defined as a spleen measuring more than 12 cm.<sup>12</sup> Laboratory tests including complete blood picture, liver function test, renal function tests, and blood film for malarial parasite were obtained for all cases. Tests like complete blood count and biochemical tests were repeated as required. The data were analyzed through SPSS 23.0. Qualitative variables were expressed as numbers and percentages. Quantitative variables were evaluated with mean and

standard deviation. Associations of various sonographic features like hepatomegaly, splenomegaly, acalculous cholecystitis, and pleural effusion; with different laboratory parameters like hemoconcentration, thrombocyte count, leucocyte count were assessed through Student’s t-test and Chi-square test. Bivariate correlation was assessed to estimate the relationship between the different sonographic features and significantly associated variables. P-the value of <0.05 was considered significant.

**Results**

Among the study population, the mean ( $\pm$  standard deviation) age was 28.14 $\pm$ 11.14 years, and 54% of the population was male. (Table-1)

The most common sonographic finding was acalculous cholecystitis (49.6%), followed by hepatomegaly (47.2%), splenomegaly (46.8%), and altered liver echotexture (46.4%). Out of the 248 patients, 37.5% had ascites and 7.3% had pleural effusion. (Table-1)

**Table-1:**

Variable	Values	
Age (mean $\pm$ SD)	28.14 $\pm$ 11.14	
Gender -n(%)	Male	134 (54%)
	Female	114 (46%)
Outcome - n(%)	Discharged	246 (99.2%)
	Expired	2 (0.8)
<b>LABORATORY PARAMETERS</b>		
Maximum hemoglobin (g/dl) mean $\pm$ SD	13.83 $\pm$ 2.21	
Minimum hemoglobin (g/dl) mean $\pm$ SD	11.71 $\pm$ 2.06	
Hemoconcentration -n(%)	Yes	154 (62.1%)
	No	94 (37.9%)
Total leucocyte count (x10 <sup>9</sup> /L) mean $\pm$ SD	3.98 $\pm$ 1.93	
Leucopenia - n(%)	Yes	172 (69.4%)
	No	76 (30.6%)
Absolute neutrophil count (x10 <sup>9</sup> /L) mean $\pm$ SD	2.24 $\pm$ 1.42	
Platelet count (x10 <sup>9</sup> /L) mean $\pm$ SD	77.84 $\pm$ 63.74	
Thrombocytopenia - n(%)	Yes	216 (87.1%)
	No	32 (12.9%)
Transaminitis - n(%)	Yes	201 (81%)
	No	47 (19%)
<b>ULTRASONOGRAPHIC FINDINGS</b>		
Splenomegaly -n(%)	Yes	116 (46.8%)
	No	132 (53.2%)
Hepatomegaly - n(%)	Yes	117 (47.2%)
	No	131 (52.8%)
Altered liver echotexture - n(%)	Yes	115 (46.4%)
	No	133 (53.6%)
Acalculous cholecystitis - n(%)	Yes	123 (49.6%)
	No	125 (50.4%)
Ascites - n(%)	Yes	93 (37.5%)
	No	155 (62.5%)
Pleural effusion - n(%)	Yes	18 (7.3%)
	No	230 (92.7%)

The association of different sonographic features with different variables including laboratory parameters is shown in Tables 2 and 3. The sonographic features which are associated with capillary leak syndrome (CLS) like ascites and acalculous cholecystitis were associated with a low platelet count, leukopenia, hemoconcentration and transaminitis.

Table-2 Association of ultrasonographic features with independent variables.

VARIABLE		Hepatomegaly			Altered liver echotexture			Splenomegaly		
		Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
AGE		29.9±11.5	27.6±10.6	0.09*	28.5±11.5	28.8±10.7	0.83*	29.4±11.5	28.1±10.7	0.38*
GENDER	MALE	66	68	0.5#	62	72	1#	74	60	0.005#
	FEMALE	51	63		53	61		42	72	
HEMOCONCENTRATION	YES	68	86	0.24#	66	88	0.189#	68	86	0.29#
	NO	49	45		49	45		48	46	
LEUCOPENIA	YES	83	89	0.67#	83	89	0.4#	78	94	0.58#
	NO	34	42		32	44		38	38	
THROMBOCYTOPENIA	YES	105	111	0.26#	103	113	0.34#	96	120	0.06#
	NO	12	20		12	20		20	12	
TRANSAMINITIS		99	102	0.19#	105	96	0.00#	95	106	0.87#

\*student's t-test, #Chi square test

Table-3 Association of ultrasonographic features related to capillary leak syndrome with independent variables (\*student's t-test, #Chi square test)

Variable		Acalculous cholecystitis			Ascites			Pleural effusion		
		Yes	No	P-value	Yes	No	p-value	Yes	No	p-value
Age		28.5±10.3	28.9±11.9	0.76*	27.5±11.1	29.4±11.0	0.17*	30.55±16.4	28.6±10.6	0.47*
Gender	Male	66	68	1#	46	88	0.2#	14	120	0.048#
	Female	57	57		47	67		4	110	
Hemoconcentration	Yes	66	88	0.009#	48	106	0.01#	12	142	0.8#
	No	57	37		45	49		6	88	
Leucopenia	Yes	95	77	0.009#	67	105	0.5#	14	158	0.59#
	No	28	48		26	50		4	72	
Thrombocytopenia	Yes	117	99	0.000#	91	125	0.00#	18	198	0.14#
	No	6	26		2	30		0	32	
Transaminitis	Yes	112	89	0.000#	86	115	0.00#	18	183	0.029#
	No	11	36		7	40		0	47	

## Discussion

This study has shown that a high percentage of patients with dengue have ultrasonographic findings therefore

Ultrasound can be a useful adjunct to the investigations required for establishing the diagnosis of dengue fever and also to categorize the severity of the disease.

The incidence of DF has increased in the region in the last twenty years.<sup>13</sup> According to WHO (World Health Organization) data more than 50 million people worldwide are infected by the dengue virus yearly, a large number of these patients require hospitalization, and half a million patients develop DHF.<sup>14</sup> Dengue virus has become endemic in Pakistan. The factors responsible for this is poor vector control due to climate change with rising temperatures, urban migration, disorganized housing development, and

faulty water management systems. Augmenting these is the absence of health awareness and education of the public and poor public health measures.

Dengue virus belongs to the flaviviridae family and has four serotypes. As there is homotypic immunity to each serotype, re-infection with a different serotype makes it more likely that such a patient will develop severe disease. Atypical presentations of Dengue fever seen in expanded dengue involve many organ systems. Many studies have shown the involvement of the liver, heart, brain, and kidney. Asymptomatic elevation of liver enzymes, hepatitis, and fulminant hepatic failure have also been reported.<sup>15</sup>

Other abdominal organs are also involved with acalculous cholecystitis being observed quite frequently<sup>16</sup> and acute pancreatitis, upper and lower gastrointestinal bleeding are also seen in complicated dengue fever.

Although dengue fever, both classic dengue fever and dengue fever with complications is commoner in older individuals<sup>17</sup> We observed no significant difference in ultrasonographic findings related to age in our study. Male gender is more prone to have dengue,<sup>18</sup> in our study significant differences by gender were observed with splenomegaly and pleural effusion.

Our study showed that splenomegaly was seen in 50% of the patients followed by hepatomegaly (45.6%) and altered liver echotexture (42.2%). 37.9% of the patients had acalculous cholecystitis, 30% had ascites and 5% had pleural effusion. Other studies have shown widely differing incidences of the sonographic findings in DF.<sup>19</sup>

In one study from India, Santhosh et al, showed that 66.7% of patients had cholecystitis while more than 64% of the patients with DF had free fluid in the abdomen and half of the patients showed the presence of pleural effusion. This is different from our study perhaps because of the differences in the populations of the two studies. A vast majority (97.8%) of the patients with acalculous cholecystitis had a platelet count of less than 40,000/mm<sup>3</sup>. Patients with a platelet count of more than 150,000/mm<sup>3</sup> had no ultrasonographic abnormalities in this study.<sup>20</sup>

Another regional study revealed that hepatomegaly was the commonest sonographic finding in patients with DF (44.4%) followed by acalculous cholecystitis

(38.8%) and ascites (25.9%). Splenomegaly was seen in only 6.1% of the patients in this study.<sup>21</sup>

Agarwal et al reviewed dengue patients with CLS showing that 46.3% of patients had polyserositis with ascites, pleural effusion, and gall bladder wall edema while 15.9% had acalculous cholecystitis only and 13.4% had ascites with acalculous cholecystitis. There is such a high percentage of these findings because these patients had critical dengue with increased capillary permeability. It also studied CLS in primary and secondary dengue and revealed no significant statistical difference between the two.<sup>22</sup>

It is also pertinent to note that the incidence of these atypical presentations of DF has increased over the last few years. One of the reasons could be a higher probability of including DF in the differential diagnosis after it is becoming more frequent over the last 20 years. Another reason can be that these are mostly secondary cases and secondary infections are more severe as compared to primary infections. A study involving only expanded dengue syndrome patients showed that 92% of patients had gastrointestinal involvement ranging from asymptomatic transaminitis (57.5%) to acalculous cholecystitis (21.35%) and acute pancreatitis (12.88%) and two cases of subacute intestinal obstruction. 12.5% of the patients either presented with or developed gastrointestinal bleeding. Most of these patients had thrombocytopenia, 40.6% had a platelet count below 20,000/ml.<sup>23</sup>

An Indian study, Chanday et al has shown hepatomegaly to be the most common sonographic finding in Dengue patients being present in 44.44% of patients this was followed by acalculous cholecystitis detected in 210 patients (38.88%) of confirmed dengue fever. Ascites was detected in 140 (25.92%) patients while pleural effusion was seen in 129 (23.88%) patients. Splenomegaly was found in 33 (6.11%) patients. Pancreatitis was a rare clinical and ultrasonography finding seen only in 9 (1.66%).<sup>21</sup> But a study from Karachi, Pakistan showed cholecystitis in 38% of the patients with hepatomegaly and splenomegaly occurring in 4% each, while ascites and pleural effusion were observed in 25% and 20% of the subjects respectively.<sup>24</sup>

Table-4: Relationship of sonographic features with independent variables

	Acute cholecystitis	Hepatomegaly	Splenomegaly	Altered liver echotexture	Ascites	Pleural effusion
	p-value (r-value)	(r- p-value)	(r- p-value)	(r- p-value)	(r- p-value)	p-value (r-value)
Age	0.76 (0.01)	0.09 (-0.105)	0.3(-0.05)	0.83 (0.01)	0.17(0.08)	0.47(-0.04)
Gender	0.9(-0.007)	0.48(0.04)	<b>0.004*</b> (0.18)	0.97(-0.002)	0.26(-0.07)	0.03(0.133)
Hemoconcentration	<b>0.006*</b> (0.17)	0.22(-0.07)	0.29(-0.006)	0.15(-0.09)	<b>0.008*</b> (-0.167)	0.68(0.02)
Leucopenia	<b>0.007*</b> (0.17)	0.61(0.03)	0.5(-0.04)	0.37(0.05)	0.47(0.04)	0.42(0.05)
Absolute neutrophil count	<b>0.05*</b> (0.124)	0.42(-0.05)	<b>0.04*</b> (-0.127)	0.1(-0.102)	0.75(0.02)	0.48(-0.04)
Platelet count	<b>0.00*</b> (0.47)	0.07(0.115)	0.1(-0.101)	0.04(0.126)	<b>0.00*</b> (0.40)	<b>0.001*</b> (0.22)
Thrombocytopenia	<b>0.00*</b> (0.237)	0.24(0.115)	0.058(-0.121)	0.28(0.06)	<b>0.00*</b> (0.25)	0.09(0.108)
Transaminitis	<b>0.00*</b> (0.25)	0.17(0.08)	0.75 (0.02)	<b>0.00*</b> (0.243)	<b>0.00*</b> (0.23)	<b>0.03*</b> (0.135)

\*Significant association

The degree of thrombocytopenia and hemoconcentration is positively correlated with acalculous cholecystitis and ascites, but this relationship is not very strong (Table-4). The relationship of other sonographic findings is seen in Table-4.

There are differences observed in ultrasonographic features in different studies. One study revealed 66% of patients had pleural effusion and 50% had ascites. The presence of features like gall bladder wall thickness, ascites, and pleural effusion is associated with a platelet count of less than 40,000/mm<sup>3</sup> and these patients are more likely to require transfusions.<sup>25</sup> Our study has also shown a significant association of a low platelet count, hemoconcentration, leucopenia, and raised transaminases with acalculous cholecystitis while thrombocytopenia, hemoconcentration, and transaminitis were associated with the presence of ascites. This indicates that increased capillary

permeability, which is the pathogenic factor of severe and critical dengue can be predicted by a dropping platelet count, increasing hematocrit, and a low white blood cell count. But when assessing the relationship of the laboratory parameters with sonographic findings it was observed that the degree of thrombocytopenia had the strongest relationship with acalculous cholecystitis, ascites, and pleural effusion. Hemoconcentration was related to the development of acalculous cholecystitis and ascites, but this relationship was not very strong. Although the presence of bicytopenia and hemoconcentration raises the possibility of Dengue fever but prediction or

confirmation of CLS is not possible on this basis. Hemoconcentration in the study population was not strongly associated with CLS in our research. One of the reasons could be the prevalence of anemia in this population. We shall need to develop specific criteria for the diagnosis of hemoconcentration in this population. This can help diagnose hemoconcentration better and aid in the confirmation of critical dengue.

The mortality associated with DF can be reduced with timely and appropriate resuscitative therapy. Such proactive and anticipatory management will prevent the development of complications and thus improve survival. This is only possible when there is high suspicion of this infection, awareness of its manifold presentations, and knowledge of criteria predicting the development of complications.

Predicting the development of severe dengue with complications like DHF and DSS is an important aspect of the management of DF. Ultrasound can be a useful resource to turn to for this purpose. Increased capillary permeability leading to a collection of fluid in the pleural space, peritoneal cavity, or gall bladder wall thickening can be detected by ultrasound and are useful for identifying critical cases. Ultrasound can detect these manifestations before they become clinically evident.<sup>26</sup> Other ultrasound findings like hepatomegaly, splenomegaly, altered liver echotexture, pancreatitis, etc can also be useful in diagnosing DF.<sup>25, 27</sup>

Dengue fever can present with a myriad of symptoms and involve many organs and organ systems. This has been called expanded dengue syndrome. Some manifestations require a specific and proactive management approach. This study has indicated that the inclusion of ultrasound can help develop criteria for the diagnosis of critical and severe dengue and aid to plan aggressive management of DF. Multicentric research involving a large number of patients with DF should be conducted for this purpose.

## Conclusion

Dengue fever can have atypical presentations. Abdominal ultrasound can confirm these diagnoses. Hepatosplenomegaly, ascites, and acalculous cholecystitis are common findings in dengue fever. These are significantly associated with thrombocytopenia, leucopenia, and hemoconcentration. In a population with a high incidence of infectious diseases, especially in the summer and monsoon season, ultrasound should be

used as an adjunct to establish the diagnosis of dengue fever. This can help to differentiate it from other infectious diseases with similar hematological features like malaria and enteric fever. It can also help predict the onset of critical dengue so that proactive supportive management can help save lives.

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