

Dengue Management in Triage using Ultrasound in children from Cambodia: a prospective cohort study

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Summary

Background Dengue is a mosquito-borne viral infection with increasing global prevalence. It is endemic in more than 100 countries, with a heavy burden in Asia. Ultrasound findings including gallbladder wall thickening, ascites, and pleural effusions secondary to plasma leakage have been described in dengue. We aimed to determine if the presence of point-of-care ultrasound findings early in suspected dengue could predict clinical worsening in ambulatory pediatric patients.

Methods We did a prospective, single-blinded, observational cohort study at a children's hospital in Siem Reap, Cambodia during periods of dengue outbreak. Ambulatory patients were screened and children ages > 3 month and ≤ 16 years with suspected acute, non-severe dengue were enrolled. Subjects had chest and abdominal ultrasound exams. Independently, subjects were evaluated by a blinded physician who determined a treatment plan as per usual practice. Follow-up was conducted 7-10 days after the initial visit. Analysis of ultrasound findings was performed to determine their relationship with outcome measures including need for unplanned hospital visits or admissions.

Findings A total of 2,186 children were screened during periods of national dengue outbreak in Cambodia in consecutive years 2018-2019, and 253 children met eligibility criteria. Results showed patients with gallbladder wall thickening (> 3.0 mm) who were discharged had a significantly more likely need for unplanned visit or hospitalization than those with normal gallbladder wall, 67% (95% CI 44 – 84) versus 17% (95% CI 12 – 24), $p < 0.0001$. Subjects with any abnormal ultrasound finding were more likely to be directly admitted versus discharged upon initial presentation, 62.2% (95% CI 46.1 – 76.0) versus 19.5% (95% CI 14.8 – 25.4), $p < 0.0001$.

Interpretation Point-of-care ultrasound findings, particularly gallbladder wall thickening, in suspected early dengue can help predict disease progression in ambulatory patients. Ultrasound has potential to help guide management of suspected dengue patients and resource management during periods of dengue outbreak.

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Introduction

Dengue fever is a highly prevalent viral illness spread by a mosquito vector. There are approximately 100 million symptomatic infections annually worldwide, and the virus is endemic in more than 100 countries.¹ Its economic and health burdens are significant and disproportionately affect lower-income populations.²⁻⁴ Distribution is primarily tropical and sub-tropical with approximately 70% of the global burden in Asia.³ The spread of dengue, however, has increased and more

regions including Europe and North America are experiencing outbreaks due to local transmission and travel-related cases.⁵⁻⁸

Clinical manifestations and severity of dengue vary. In addition to fever, signs and symptoms include myalgias, arthralgias, nausea, vomiting, headache, lethargy, abdominal pain, and mucosal bleeding. Severity of symptomatic infections ranges from a mild febrile illness to shock.^{9,10} The World Health Organization (WHO) has developed a severity classification system to help guide recognition of findings indicating need for treatment or close observation, called warning signs (WS).¹¹ Individuals who develop WS are at higher risk for progression to severe dengue. Overall, mortality due to dengue is less than 1%, but may exceed > 20% in

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Research in context

Evidence before this study

Dengue is endemic in Cambodia and more than 100 countries worldwide. Its incidence is increasing, and it has significant morbidity and mortality in adult and pediatric populations. Early recognition and treatment are important for good outcomes. Identification of individuals with early suspected dengue who are at risk for worsening disease is relevant to treatment decisions and resource management. We searched PubMed without language restrictions up to April 16, 2021 for publications using the search terms “dengue” AND “ultrasound”, which yielded 87 results. We reviewed these articles in order to identify prospective research of the utility of ultrasound in predicting dengue progression or severity. The majority of prior research investigating use of ultrasound in dengue has focused on patients already admitted to the hospital and relied on conventional, radiology-performed ultrasound. Several studies have found a correlation between sonographic findings, gallbladder wall thickening, ascites, pleural effusion, and dengue severity. One study of ambulatory adult subjects found a relationship between sonographic findings and subsequent progression of disease.

Added value of this study

We prospectively enrolled a pediatric cohort of patients with early suspected dengue in Cambodia during periods of dengue outbreak. There are several aspects of our research which are underrepresented in the existing literature. Whereas most prior studies have included patients who have already required hospital admission, we enrolled ambulatory patients early in the course of their illness. 252 children were included with a mean day of illness 3.6 days at the time of enrollment. This allowed us to determine if the early appearance of sonographic findings could predict disease progression and guide decision-making, such as need for admission or close follow-up. Furthermore, we utilized point-of-care ultrasound at triage by emergency providers rather than radiology studies. Use of portable ultrasound across multiple specialties continues to grow, facilitating clinical decisions in ambulatory and even pre-hospital settings, which can be particularly useful in resource-limited settings. We observed a significant difference in need for subsequent admission and unplanned visits in discharged patients who had evidence of gallbladder wall thickening. Additionally, subjects with any abnormal ultrasound finding were more likely to be directly admitted versus discharged at time of presentation.

Implications of all the available evidence

This study shows the potential for point-of-care ultrasound to guide management of children with early, suspected dengue. During periods of dengue outbreaks, decisions to admit patients, arrange follow-up, and referrals to tertiary centers are complex. Use of clinical criteria such as presence or absence of warning signs,

physical examination, and laboratory studies are imperfect. Sonographic assessment is easy to perform in a variety of settings, safe, and may be a useful adjunctive tool for the evaluation of dengue patients early in their disease course. Further research and evaluation of standardized protocols for point-of-care ultrasound in dengue is warranted.

cases of untreated severe dengue.¹ Thus, early recognition, monitoring and treatment is important for good outcomes.

Ultrasonography has been shown to be a useful adjunctive tool in recognition and management of dengue patients.¹² The disease can cause increased capillary permeability and leakage.⁹ Sonographic findings include gallbladder wall thickening, pericholecystic fluid, ascites, pleural effusions, and hepatomegaly and splenomegaly. Presence of these findings in a patient with suspected dengue strongly supports the diagnosis, particularly in endemic areas during periods of outbreak.^{13–16} Several studies have found gallbladder wall thickening to be a finding that correlates with dengue severity in pediatric and adult patients.^{17–23} However, most prior research has been conducted with subjects who have already been hospitalized. A review of ultrasound in dengue by Dewan and colleagues reported only 5% of studies were conducted in ambulatory settings, and the most studies utilized conventional, non-portable ultrasound.²⁴

Dengue is often diagnosed clinically by recognition of signs and symptoms in the appropriate setting, such as a seasonal dengue outbreak in an endemic area. Non-specific testing such as a complete blood count can aid diagnosis and management. Dengue-specific serum testing can provide confirmation via viral isolation, antigen or immunoglobulin detection. However, such testing may be limited by availability, timeliness, and inability to predict progression of disease.^{25,26} Use of point-of-care ultrasound has expanded over the past two decades including its use in resource-limited settings due to its wide number of applications, relative affordability, and portability.^{27,28} The fundamental advantage of point-of-care ultrasound compared with conventional studies is the ability of the performing clinician to quickly perform a study and make immediate decisions based on their findings. While different sonographic findings in dengue patients have demonstrated correlation with severity, less is known about whether these same sonographic findings at early stages are predictive of disease progression. In one study of adult early dengue patients there was evidence of disease progression in patients with ultrasound findings even in the absence of dengue warning signs.²³ Such findings could influence patient treatment plans, follow-up, hospital admission, and associated resource management.

In this prospective, observational study, our objective was to determine if point-of-care ultrasound implemented at triage could identify children with early suspected dengue who are at risk for progression of disease and need for hospitalization. We hypothesized that presence of early sonographic findings could be predictive of disease progression independently of other clinical and laboratory markers.

Methods

Study design and participants

This was a prospective, observational study designed to investigate the ability of point-of-care ultrasound findings to predict worsening condition of children presenting to the hospital with suspected dengue. The study was conducted at an urban children's hospital in Siem Reap, Cambodia. Patients presenting for unscheduled, non-traumatic, acute visits were consecutively screened and enrolled over two 3-week periods during national dengue outbreaks in 2018 and 2019. Institutional IRB approval was obtained for all participating research institutes as well as regional and national IRB approval for the enrolling institution. All guardians provided informed consent for enrolled subjects and all children seven years or older provided assent. The study was registered on ClinicalTrials.gov (NCT03632486).

All patients presenting to the outpatient department of the hospital were screened. This outpatient department functions as the equivalent of a low-acuity emergency department. Research staff were on-site during all hours of department operation to facilitate consecutive enrollment. Patients and their guardians were approached at triage by research nurses fluent in the national language (Khmer). Inclusion criteria were reported febrile illness, clinical suspicion of dengue, age > 3 months and ≤ 16 years, and ability for parent/guardian to give informed consent. Exclusion criteria were severe dengue, hemodynamic instability, known pleural, pericardial, or intraperitoneal fluid, gallbladder disease, or known adverse skin reaction to ultrasound gel. Clinical suspicion as per WHO guidelines was determined by physicians in triage. Suspected dengue patients had fever and at least two of the following criteria: nausea/vomiting, rash, arthralgia or myalgia, leukopenia, or any WS. Warning signs included abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, hepatomegaly, increased haematocrit and decreased platelet count.¹¹ Severe dengue patients were excluded because these patients had already reached a critical disease state and the objective of the study was to predict progression in lower acuity patients. After screening, subjects underwent bedside ultrasound performed by research physicians with expertise in ultrasound. Separately, they underwent a history and physical by a host institution physician who

determined their treatment plan and disposition as per usual practice. These clinicians were blinded to the findings of the ultrasounds performed by the research physicians.

Procedures

The bedside ultrasound protocol consisted of chest and abdominal scans performed in a stepwise fashion. Subjects were supine on an examination table with their guardian and a nurse fluent in Khmer present to explain actions of the research staff. Sonographic evaluation of the lungs to assess for b-lines consisted of obtaining images at the mid-clavicular, anterior axillary, and posterior axillary lines. A positive finding was defined as three or more b-lines in two or more zones in each hemithorax. Images of the short and long axes of gallbladder were obtained to assess for gallbladder wall-thickening. The gallbladder was measured at the anterior wall in either short or long axis, and a positive finding was defined as wall thickness > 3.0 mm. Lastly, a FAST (focused assessment with sonography for trauma) exam was performed to assess for pleural effusion, pericardial effusion, and intraperitoneal free fluid.²⁹ A positive finding was detection of any fluid. All imaging was performed using a Sonosite MicroMaxx machine and C60e/5-2 MHz convex transducer. Sonographers included emergency ultrasound fellowship-trained attending physicians and ultrasound fellows from the visiting and host institutions. Each sonographer had extensive experience performing and interpreting the ultrasound examinations. Interpretation occurred in real-time, and a second physician sonographer was available to review any uncertain findings or assist with a second ultrasound exam if necessary. Findings were entered into an electronic database (Excel, Version15.32; Microsoft, Redmond, WA).

Each subject had a medical evaluation performed by a staff physician per standard protocol at the hospital. These clinicians were blinded to the ultrasound findings. The patient's physician determined need for laboratory studies or additional imaging, admission to the hospital, or discharge and any follow-up plan. In certain cases, the treating clinician recommended short-term follow-up in one to three days, and as such these visits were not considered unplanned. Routine lab studies were available, however definitive dengue tests were not. Laboratory results were recorded in the study data sheets and abstracted from the patient's chart in addition to patient demographics, symptoms, vital signs, and presence of dengue WS. Mobile telephone numbers were collected, and guardians were contacted for follow up interviews. These follow-up efforts were initiated 7 days after the initial encounter and terminated after day 10 if no one could be reached. If a telephone number was not available, the electronic medical record was screened for subsequent encounters. Follow-up

assessment included a brief interview to determine if the subject's condition worsened and if there was need for repeat hospital visits or admission. The telephone interviews were conducted by research nursing staff fluent in the native language and in the presence of a research physician.

Statistical analysis

The primary outcome was progression of disease as defined by the need for an unplanned hospital visit or admission within the follow-up period. Secondary outcome was need for admission at the time of initial presentation.

Descriptive statistics were used for the characteristics of the study population. Continuous variables were reported as means and 95% confidence intervals (95% CI). Categorical variables were reported as proportions. We analyzed ultrasound findings in the study population and their relationship with outcome measures and calculated 95% confidence intervals (CI) using the modified Wald technique. Comparison between groups was performed using Fisher's exact test. Logistic regression was used to calculate odds ratios for the association of findings with the primary and secondary outcomes. All data analysis was performed using JMP (Version 19, Cary, NC).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

During the study period, nursing staff screened 2,186 patients who presented to the outpatient department at the study hospital (Figure 1). A total of 253 patients with early suspected dengue met eligibility criteria. One patient/guardian declined to participate. The remaining 252 subjects were enrolled. A completion follow-up interview was conducted for 220 of the 252 enrolled patients. Seven of the 32 lost to follow-up had been admitted and discharged in a healthy state after the initial visit. Baseline characteristics including clinical severity and laboratory findings were similar in both follow-up groups and are described in Table 1.

Of the 252 subjects enrolled, 215 (85.3%) were initially discharged home. Of those discharged, 42 subjects (19.5%) had a subsequent unplanned visit or admission to the hospital within the follow-up period. Subjects who had a thickened gallbladder wall (> 3.0 mm) were significantly more likely to have an unplanned visit or admission versus subjects with a normal gallbladder wall, 67% ($n/N = 12/18$) versus 17% ($n/N = 30/172$), $p \leq 0.0001$. Mean gallbladder wall thickness in the

abnormal group was 6.1 mm. Other ultrasound examinations did not show a similar association with the primary outcome. Test characteristics for ultrasound are shown in Table 2. However, taken as a whole, an increasing number of ultrasound findings was associated with an increase in return visits and hospitalization. 18% percent of individuals with no ultrasound findings had a subsequent unplanned visit or admission compared with 22% with one ultrasound finding, and 78% with two ultrasound findings.

Overall, 65 subjects (25.8%) had at least one abnormal ultrasound finding, and some had several findings. Specific findings and their prevalence in the study population are displayed in Figure 2. The most common ultrasound findings were ascites and thickened gallbladder wall. Example images of these sonographic findings are shown in Figure 3. Pericardial or pleural effusions were rare. The presence of pulmonary b-lines, which to our knowledge has not previously been investigated in dengue patients, was also rare.

Of all subjects enrolled, 37 (14.7%) were admitted to the hospital at the time of their initial visit. Of those subjects, 23 (62.2%) demonstrated an abnormality on their ultrasound examinations. See Table 3. Of the 35 patients with gallbladder wall thickness, 14 (40%) were admitted following their initial encounter. Of the 46 patients with abdominal free fluid on FAST exam, 14 (30%) were admitted following their initial encounter. Presence of any abnormal ultrasound finding correlated significantly with need for admission at the time of initial presentation. Subjects with any abnormal ultrasound finding were more likely to be directly admitted versus discharged, 62.2% ($n/N = 23/37$) versus 19.5% ($n/N = 42/215$), $p < 0.0001$.

Associations between clinical characteristics and laboratory studies with the primary outcome are shown in Table 4. All patients had a complaint of a fever during their illness, but a measured temperature $\geq 38.0^\circ\text{C}$ in triage showed a significant association with the need for a return visit/hospitalization. These febrile subjects were more likely to have an unplanned visit or admission versus those with normal temperature, 32.0% ($n/N = 28/87$) versus 13.6% ($n/N = 14/103$), $p = 0.0056$. The presence or absence of warning signs, other symptoms, physical exam findings, or laboratory values did not show a significant relationship. Patients admitted to the hospital demonstrated a higher percentage of warning signs and vital sign abnormalities compared to those discharged. Table 5 compares the number of warning signs for admitted and discharged patients. A sensitivity analysis was performed on the number of dengue warning signs to assess the validity of our primary finding (Supplemental Table 1). Increasing number of warning signs corresponded to increasing association with gallbladder wall thickening.

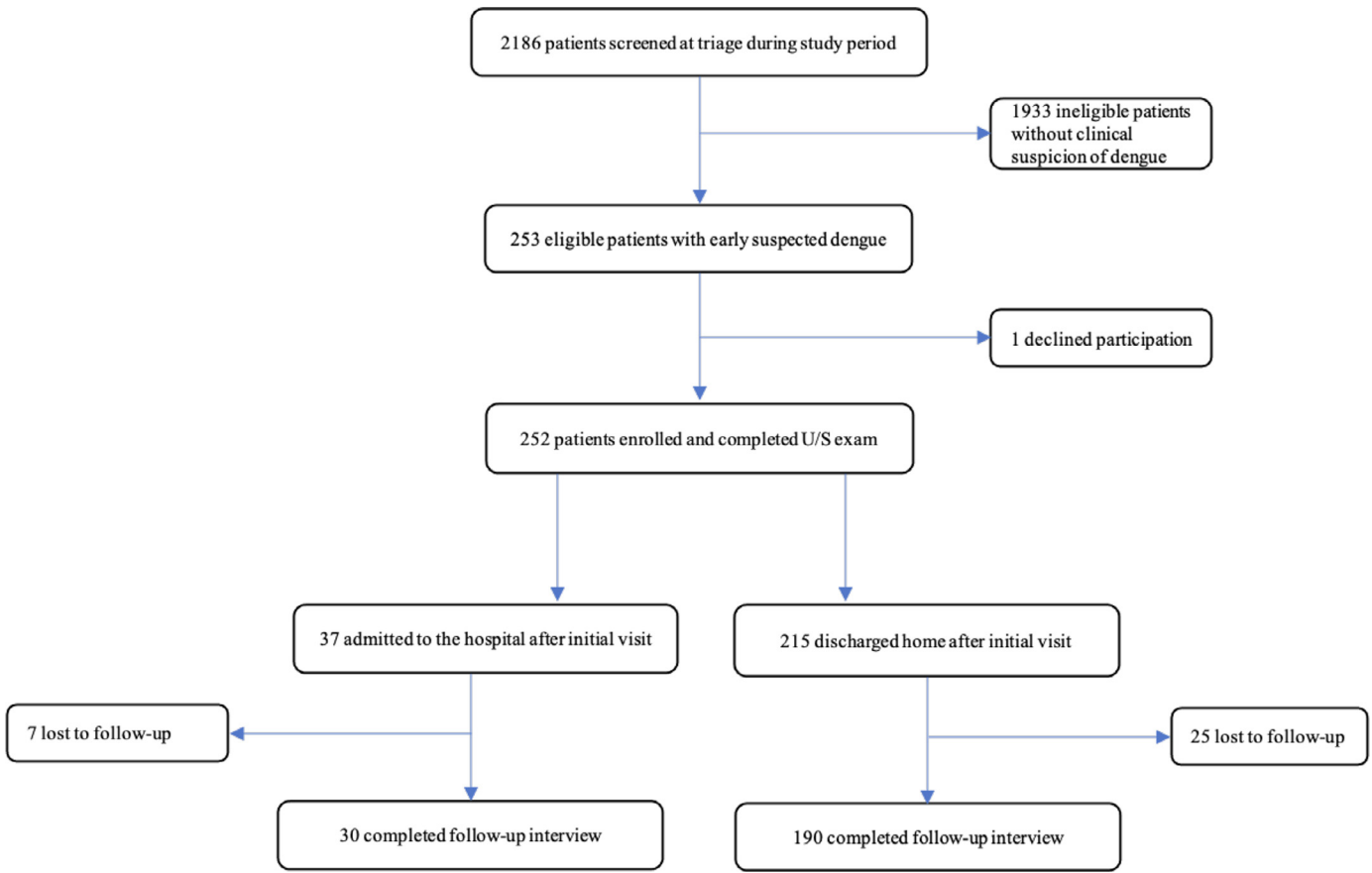


Figure 1. Flow diagram of subject enrollment and follow-up.

Variable	Enrolled subjects n = 252	Subjects with follow-up n = 220	Subjects lost to follow-up n = 32
Age in yr., mean (SD)	7.5 (3.8)	7.6 (3.8)	6.8 (3.5)
Sex			
Male	136 (53.6%)	121 (55.0%)	15 (46.9%)
Female	116 (46.4%)	99 (45.0%)	17 (53.1%)
Clinical characteristics			
Day of illness, mean (SD)	3.6 (1.3)	3.6 (1.3)	3.5 (1.2)
Temp $\geq 38^{\circ}\text{C}$ in triage	117 (46.4%)	100 (45.5%)	17 (53.1%)
Tachycardia	99 (39.3%)	89 (40.5%)	10 (31.3%)
Warning signs present	157 (62.3%)	133 (60.5%)	24 (75.0%)
Laboratory studies			
Leukopenia	88 (41.7%)	73 (40.1%)	15 (51.7%)
Thrombocytopenia	77 (36.6%)	67 (37.0%)	10 (34.4%)
Disposition			
Initial admission	37 (14.7%)	30 (13.6%)	7 (21.9%)
Initial discharge	215 (85.3%)	190 (86.3%)	25 (78.1%)

Table 1: Baseline demographics and clinical characteristics of subjects at initial presentation.

	Number with Return Visit or Hospitalization (n/N)	Percent of Return Visit or Hospitalization (%; (95% CI))	Odds Ratio (OR (95% CI))	P Value
GB Wall Thickness (>3.0 mm)	12/18	67% (44 – 84)	11.1 (3.4 – 36.6)	<0.0001
GB Wall Thickness (<3.0 mm)	30/172	17% (12 – 24)	0.1 (0.04 – 0.3)	<0.0001
Abdominal Fluid (+)	10/30	33% (19 – 51)	1.0 (0.3 – 3.0)	0.97
Abdominal Fluid (-)	32/160	20% (15 – 27)	0.5 (0.2 – 1.2)	0.11
Pleural Fluid (+)	1/2	50% (9 – 90)	1.4 (0.05 – 43)	0.85
Pleural Fluid (-)	41/188	22% (17 – 28)	0.3 (0.02 – 4.6)	0.37
Pericardial Fluid (+)	0/1	n/a	n/a	n/a
Pericardial Fluid (-)	42/189	22% (17 – 29)	n/a	n/a
Lung B-Lines (+)	0/0	n/a	n/a	n/a
Lung B-Lines (-)	42/190	22% (17 – 29)	n/a	n/a

Table 2: Ultrasound findings in discharged ambulatory subjects and their association with unexpected return visits or hospitalizations. n = number of subjects with ultrasound finding who had an unplanned return visit or hospitalization. N = total with ultrasound finding discharged.

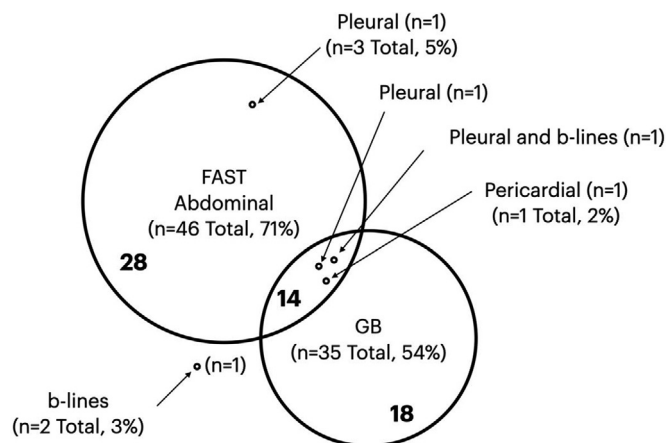


Figure 2. Abnormal ultrasound examinations in study subjects with totals for sub-group categories listed as (n, %). n = number of ultrasounds with finding. % is calculated with denominator = 65 patients with any ultrasound finding. GB = gallbladder.

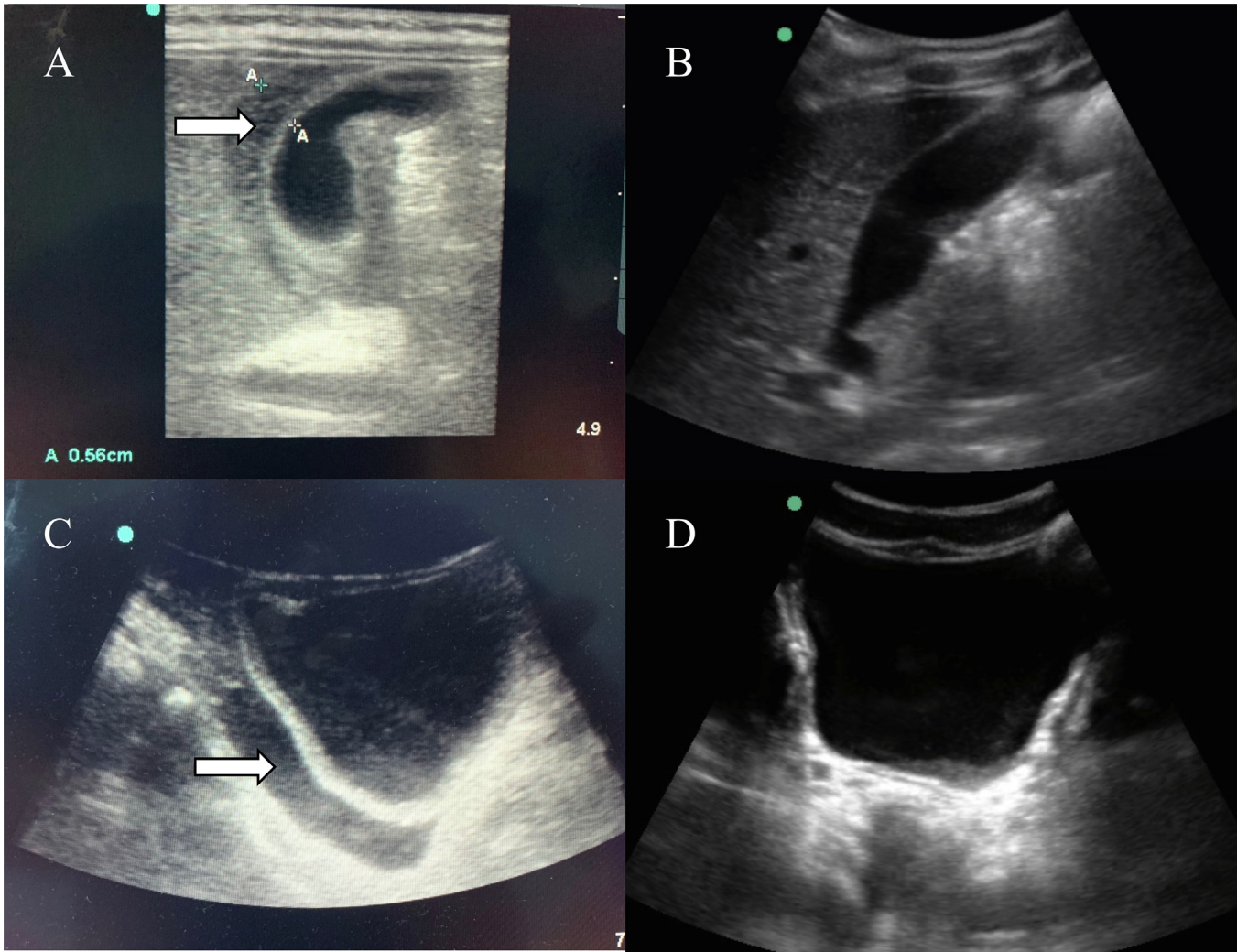


Figure 3. a) Abnormal gallbladder with thickened anterior wall (arrow). b) Normal thin-walled gallbladder. c) Intraperitoneal free fluid (arrow) adjacent to urinary bladder. d) Normal urinary bladder view without free fluid.

	Number Admitted with U/S Finding (n/N)	Percent of Admitted with U/S Finding (% (95% CI))	Odds Ratio (OR (95% CI))	P Value
GB Wall Thickness (>3.0 mm)	14/35	40% (26-56)	4.6 (1.9-11.1)	0.0006
GB Wall Thickness (<3.0 mm)	23/217	11% (7 – 15)	0.2 (0.1 – 0.4)	<0.0001
Abdominal Fluid (+)	14/46	30% (19-45)	2.6 (1.1-6.0)	0.031
Abdominal Fluid (-)	23/206	11% (8 – 16)	0.3 (0.1 – 0.6)	0.0014
Pleural Fluid (+)	1/3	33% (6-79)	n/a	0.99
Pleural Fluid (-)	36/249	14% (11 – 19)	0.3 (0.1 – 3.8)	0.38
Pericardial Fluid (+)	0/1	n/a	n/a	0.99
Pericardial Fluid (-)	37/251	15% (11 – 20)	n/a	n/a
Lung B-Lines (+)	2/2	100% (34-100)	n/a	0.99
Lung B-Lines (-)	35/250	14% (10 – 19)	n/a	n/a

Table 3: Ultrasound findings in subjects admitted at time of initial presentation to hospital.

n = number of subjects with ultrasound finding who were admitted. N = total with ultrasound finding.

	Number with Return Visit or Hospitalization (n/N)	Percent of Return Visit or Hospitalization (% (95% CI))	Odds Ratio (OR (95% CI))	P Value
Temp > 38°C	28/87	32% (24 – 43)	3.4 (1.4 – 8.2)	0.0056
Temp < 38°C	14/103	14% (8 – 22)	0.3 (0.2 – 0.7)	0.0027
Increased HR	23/77	30% (21 – 41)	1.4 (0.6 – 3.4)	0.41
Normal HR	19/113	17% (11 – 25)	0.5 (0.2 – 0.9)	0.035
Increased RR	31/116	27% (20 – 35)	1.2 (0.5 – 2.9)	0.69
Normal RR	11/72	15% (9 – 25)	0.5 (0.2 – 1.1)	0.07
Any Warning Signs	24/105	23% (16 – 32)	1.1 (0.6 – 2.2)	0.78
No Warning Signs	18/85	21% (14 – 31)	0.9 (0.5 – 1.8)	0.78
Decreased WBC	15/55	27% (17 – 40)	1.5 (0.6 – 3.6)	0.39
Normal WBC	22/97	23% (15 – 32)	0.8 (0.4 – 1.7)	0.53
Decreased PLT	11/42	26% (15 – 41)	1.0 (0.4 – 2.6)	0.97
Normal PLT	26/110	24% (17 – 32)	0.9 (0.4 – 2.0)	0.74
Anorexia	25/108	23% (16 – 32)	0.9 (0.4 – 2.1)	0.81
No Anorexia	17/82	21% (13 – 31)	0.9 (0.4 – 1.7)	0.69
Nausea	12/55	22% (13 – 34)	0.7 (0.3 – 1.7)	0.38
No Nausea	30/135	22% (10 – 30)	1.0 (0.5 – 2.2)	0.95
Vomiting	5/17	29% (13 – 53)	1.6 (0.4 – 7.1)	0.51
No Vomiting	37/173	21% (16 – 28)	0.7 (0.2 – 2.0)	0.45
Rash	5/12	42% (19 – 68)	2.7 (0.8 – 9.1)	0.12
No Rash	37/178	21% (15 – 27)	0.4 (0.1 – 1.2)	0.10
Myalgia	5/23	22% (10 – 42)	0.7 (0.2 – 2.4)	0.56
No Myalgia	37/167	22% (17 – 29)	1.0 (0.4 – 2.9)	0.96
Abdominal pain	16/70	23% (15 – 34)	0.6 (0.2 – 2.4)	0.50
No Abdominal pain	26/120	22% (15 – 30)	0.9 (0.5 – 1.9)	0.85

Table 4: Clinical findings in discharged ambulatory subjects and their association with unexpected return visits or hospitalizations.

n = number of subjects with finding who had an unplanned return visit or hospitalization. N = total with finding.

Discussion

Our study investigated the role of point-of-care ultrasound as a tool to predict worsening of early suspected dengue in an ambulatory, pediatric population. We found that gallbladder wall thickening identified in children presenting during a dengue outbreak with suspected dengue was associated with increased likelihood of disease progression. While ultrasound findings have

been shown to correlate with severity in admitted patients, our objective was to evaluate its role in children whose clinical status may be less clear. Despite clinically appearing well enough for discharge, those with gallbladder wall thickening were more likely to require short-term repeat hospital visits or admission. More generally, independent of clinical characteristics or laboratory test results, patients who had abnormal

	Admitted		Discharged	
	n/N	%, (95% CI)	n/N	%, (95% CI)
Zero Warning Signs	2/37	5% (1 – 19)	93/215	43% (37 – 50)
One Warning Sign	7/37	19% (9 – 34)	90/215	42% (35 – 49)
Two Warning Signs	21/37	57% (41 – 71)	30/215	14% (10 – 19)
Three Warning Signs	7/37	19% (9 – 34)	2/215	1% (0 – 3)

Table 5: Presence of dengue warning signs in subjects admitted or discharged at initial presentation to hospital.

Data shown are n (%). n = number of subjects with 0–3 warning signs. N = total number of admitted (or discharged) subjects. Testing for association between number of warning signs and outcome was performed using Fisher's exact test for trend, $p = 0.03$.

ultrasound findings were more likely to be admitted at the time of initial presentation. The most common sonographic findings were ascites and gallbladder wall thickening, which is consistent with prior research demonstrated by Santosh et al,¹³ and others.^{14–16} Additionally, gallbladder wall thickening has been associated with more severe illness as shown by Setiawan et al,¹⁷ and several other studies,^{18–23} so it is logical that its presence in early disease could portend worsening. Accordingly, in an adult cohort of early dengue patients, Xin Tian et al found > 90% of patients with ultrasound findings, primarily gallbladder wall thickening, progressed to dengue with warning signs or severe dengue.²³

Decisions to admit patients to the hospital are multifactorial. Clinical status, risk for decompensation, social and economic factors, and hospital capacity are considerations. Admitting children who are ill-appearing with an advanced disease state is relatively straightforward, however there is a large proportion of dengue patients in the categories with or without warning signs with whom management has less certainty. In 2009, WHO dengue guidelines were revised and have demonstrated improved test characteristics compared with prior guidelines, particularly for severe disease.¹¹ However, there have been concerns that increased sensitivity for non-severe dengue could lead to excess resource utilization, whereas the guidelines recommend hospitalization of patients with WS.^{30–35} These WS are present in a substantial number of non-severe dengue patients. In our study population, 62.3% of subjects were classified as having WS, similar to other studies.^{30–33,36} While the presence of any warning sign is highly sensitive for severe disease, it lacks specificity and has poor PPV.^{30,32,33,36} Following implementation of the revised WHO classification, Narvaez et al,³⁰ observed an increase in pediatric dengue patients transferred to their study hospital from 11.36% to 83%. Leo et al,³³ estimated a 2.3-fold increase in workload if adopting a warning sign guided admission policy, which would likely exceed capacity in resource-limited endemic areas during periods of outbreak. In our cohort of early suspected dengue patients, presence of WS was not a significant factor in predicting need for return visits or hospitalization in

discharged patients. However, gallbladder wall thickening predicted need for unplanned visits or hospitalization. These point-of-care ultrasound findings could aid decisions for admission, follow-up plans, or referrals to higher levels of care.

Follow-up of patients in resource-limited settings for either clinical or research purposes can be challenging. Our mobile telephone follow-up protocol was successful with an overall follow-up rate approaching 90%. Only 2% (n = 5) of subjects were unable to provide a mobile telephone number. Awareness of local telecommunications technology and behaviors is important for research outside of developed healthcare networks. In Cambodia, most of the population has access to a mobile phone, whereas follow-up via email, land-line telephone, or in-person would have significant limitations. However, many Cambodians use more than one subscriber identification module (SIM) card.³⁷ This complicates follow-up when contact numbers become inactive. To help circumvent this issue we attempted to obtain two contact numbers if available. We observed a 10% increase in successful follow-up for subjects with two numbers versus one.

There are limitations to consider in this study. There was no testing to confirm the diagnosis of dengue and such testing would have allowed for more accurate selection of dengue patients. Confirming the diagnosis of dengue may have improved our external validity but was not imperative as our study population was febrile children with suspected dengue. In resource poor settings, definitive testing may not be commonly available, and our results support the use of ultrasound to triage patients regardless of confirmed presence of dengue. It is possible that our study population included individuals who did not actually have dengue, but this could be interpreted to strengthen our results. It is possible the test characteristics of ultrasound could be different when disease prevalence is lower and additional research during these periods is warranted.

Another potential limitation in our study is selection bias associated with subjects lost to follow-up, who may have had disproportionately worse outcomes. However, we were able to complete follow-up for 87.3% of subjects. Differences between successful and lost follow-up

groups such as admission rates, clinical variables, and ultrasound findings did not appear to be significant. Additionally, enrollment was limited to a single, tertiary pediatric hospital. Assessments of this protocol in smaller hospitals and community and rural sites would have improved generalizability and represents an interesting area of potential research. Lastly, we did test for association between five different ultrasound findings and disease progression, and multiple clinical findings, thus raising the possibility of finding an association by chance.

Point-of-care ultrasound has an important role in patient care in many settings, and its role is growing with the advent of more portable and affordable equipment. In this study, expert bedside sonographers completed the exams, representing an ideal scenario. However, general clinicians may achieve competency in basic assessments of the gallbladder and identification of free fluid with a FAST exam without extensive training. Prior research has demonstrated clinical competence of a limited gallbladder sonographic assessment following 25 scans.³⁸ In developing countries, a variety of training programmes have been described, with variation in structure, content, and length, but many demonstrating successful introductory training.³⁹ As the role of ultrasound in the assessment of dengue patients is still being defined, consideration should also be given to development of specific protocols and training.

Dengue is a major worldwide health problem expanding into areas of the world that have not previously dealt with the disease. Recognition of patients at risk for decompensation and close observation is important for good outcomes. We found that point-of-care ultrasound findings in early suspected dengue patients can predict need for subsequent acute care visits. Its usefulness during dengue outbreaks in endemic, resource-limited settings is promising and warrants further research.

Contributors

TG, RG, and YP conceived and supervised the study. TG and RG performed the data curation, initial formal analysis and manuscript preparation. TG, RG, YP, RL, AS, VP, MH, and EH actively participated in investigation and review and editing of the manuscript. Each author revised the manuscript critically for intellectual content and approved the final version before submission.

Declaration of interests

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2021.100371.

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