Ultrasound findings of plasma leakage as imaging adjunct in clinical management of dengue fever without warning signs

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ABSTRACT

Introduction: Plasma leakage is a major cause of morbidity and mortality in dengue fever. Few studies have shown the sensitivity of thoracoabdominal ultrasound in detecting plasma leakage in severe dengue, however its sensitivity in the early presentation of dengue fever without warning signs remains unknown. This study is aimed to determine the role of serial ultrasound in order to detect plasma leakage in dengue fever without warning signs.

Methods: This prospective cohort study was conducted at Hospital Universiti Sains Malaysia (USM) from 1st October 2016 to 30th November 2017. Serial bedside ultrasound procedures were performed for 83 patients who were diagnosed as having dengue fever without warning signs and were initially treated as outpatients. Ultrasonography evidence of plasma leakage either pleural effusion, thickened gallbladder wall, ascites or pericardial effusion were compared with clinical findings and laboratory parameters for plasma leakage.

Results: Of the 83 dengue patients, eventually 72.3% had dengue fever with warning signs and 6.0% had severe dengue fever. There were 38 patients who had subclinical plasma leakage at initial presentation, 84.2% and 7.9% of them then progressed to dengue fever with warning signs and severe dengue respectively. There was a minimal agreement between serial bedside ultrasound and haematocrit level in the detection of plasma leakage (observed kappa 0.135).

Conclusions: Serial bedside ultrasound is an adjunct procedure to physical examination and may detect plasma leakage earlier compared to haemoconcentration. The early usage of serial ultrasound is of paramount importance in detecting dengue patients who are at risk of progressing to severe dengue.

KEYWORDS:
Dengue fever, haemoconcentration, plasma leakage, ultrasonography

INTRODUCTION

Dengue fever is one of the most important mosquito-borne viral diseases that causes significant health threat to populations living in tropical and subtropical regions. The incidence of dengue has increased dramatically around the world in recent decades. The number of cases reported by the World Health Organization (WHO) increased from 2.2 million in 2010 to 3.2 million in 2015.[1] Besides that, it was reported that the dengue infection had expanded geographically to many previously unaffected regions.[2] In Malaysia, the reported overall dengue case fatality rate was 0.2%.[3]

Dengue infection is a dynamic disease that results in a broad spectrum of illness, ranging from asymptomatic infection to severe life-threatening illness.[4] Based on Clinical Practice Guideline (CPG), there are 3 broad categories of dengue infection which are dengue fever, dengue fever with warning signs (abdominal pain, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, hepatomegaly and increase in haematocrit level) and severe dengue. A patient with severe plasma leakage and/or haemorrhage and/or organ dysfunction is diagnosed to have severe dengue fever.[1,5] Admission to the ward is warranted for patients with dengue fever with warning signs and severe dengue.[4]

A typical dengue infection has three phases which include a febrile phase, critical phase and recovery phase. During the early febrile phase, it is impossible to predict whether a dengue patient will progress to dengue with warning signs or severe dengue.[4] Once a patient enters a critical phase, there is a risk of increasing plasma leakage that lead to shock and organ hypoperfusion. Therefore, plasma leakage is considered as the hallmark of severe dengue.[6]

Multiple studies have shown that plasma leakage is the major cause of mortality and morbidity in patients with dengue fever.[6,7] Yet, the onset of plasma leakage was difficult to predict.[7] To date, WHO has suggested a rapid decrease in platelet count in parallel with a rising haematocrit level to be used as a guide to the onset of plasma leakage. The degree of

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increase in haematocrit reading compared to baseline haematocrit correlates well with the severity of plasma leakage.[1] However, interpretation of haematocrit can be difficult in a situation such as unknown baseline haematocrit levels, haemorrhage, dehydration, excessive fluid replacement or in the haemodilutional state.[8]

Besides haematocrit count, the evidence of plasma leakage can be detected clinically or radiologically like pleural effusions or ascites. A few studies advocated the usage of ultrasound to detect plasma leakage. The features to look for during ultrasound procedure are gallbladder wall thickness, pericardial effusion, pleural effusion and ascites.[8-10] Since thoracoabdominal ultrasound is more sensitive than clinical examination in detecting pleural effusion or ascites,[9,10] it may serve as a better guide in detecting plasma leakage. Plasma leakage may occur in any stage of the illness rather than a specific timing. Thus, serial ultrasound during the follow up and course of illness could detect the presence of plasma leakage more accurately.[7]

The use of ultrasound to detect plasma leakage in severe dengue (previously known as dengue haemorrhagic fever) is quite established.[6,7,11] However, the use of ultrasound in the early phase of dengue fever is not yet established. There are a few studies that look into the role of ultrasound in early phase of dengue fever with warning signs that warrants admission.[11-14] All those studies were conducted in India with a relatively small sample sizes and the ultrasounds were conducted one-off during the admission, except for Nakum J et al.[11] Therefore, there is still a lack of evidence about early dengue fever, especially for those without warning signs and can be treated as outpatients.

The aim of the study was to determine the use of serial ultrasound procedure in detecting plasma leakage as part of the clinical management of dengue fever without warning signs.

MATERIALS AND METHODS

The patients in this prospective study who were diagnosed with dengue fever without warning signs based on the WHO classification at the emergency department (ED) of Hospital Universiti Sains Malaysia (USM) from 1st October 2016 to 30th November 2017 were included.[1]

The inclusion criteria were that patients were Malaysian citizens aged ≥ 18 years, confirmed dengue case, either in febrile phase or critical phase but haemodynamically stable and can be treated as an outpatient based on the WHO guideline.[1] The diagnosis of dengue fever was confirmed by detection of non-structural protein (NS-1 Antigen) and/or dengue serology such as serum IgM and serum IgG. Those patients with underlying cholelithiasis, cholecystitis, chronic heart failure, chronic kidney disease, liver cirrhosis or nephrotic syndrome were excluded because the ultrasound findings might be affected by these underlying diseases. None of the patients were required to fast prior to the ultrasound procedure. Based on the previous studies, patients need not fast[11,13,14] whereas one study required patients to fast.[12] Studies have shown that there were no differences in technical success and quality of images obtained from patients who fasted or not.[15,16] In fact, dengue patients are known to have reduced oral intake[17] and fasting itself might be inappropriate for them.

Point-of-care ultrasound (POCUS) was performed from the first diagnosis and every time the dengue patients had their daily follow up and routine blood taking. POCUS was used to answer simple and specific questions relevant to the condition of the patients such as whether the pleural effusion or ascites was presence or not.[18] It is different from conventional comprehensive ultrasound performed by radiologists.[19] Monitoring of dengue patients began on the day of enrolment until the haematocrit and platelet counts had shown a substantial increase and also the patient had shown improved clinically, i.e., enter the recovery phase. Once patients enter the recovery phase, they were discharged from follow up.

During each follow up, the patient underwent a thorough clinical history, physical examination, routine full blood count and bedside ultrasound (POCUS) procedure to look for any evidence of plasma leakage. Laboratory evidence of plasma leakage (haemoconcentration) was based only on the haematocrit level as it is a marker of plasma leakage.[4,11] It is defined as single high haematocrit values (≥46% for men ≤60 years old, ≥42% for men >60 years old and ≥40% for women of all age group) as described in the CPG.[4]

Ultrasonography evidence of plasma leakage was considered to be present if either pleural effusion, ascites (including perirenal fluid collection and/or rectovesical/rectovaginal spaces fluid collection), pericardial effusion or gallbladder wall thickenings were detected.

Ultrasound examinations or POCUS were also performed according to a predetermined protocol using ultrasound model Logiq S7 (GE Healthcare). The procedure was performed using a curvilinear transducer with 2-5MHz frequency with the patient in a supine position. The probe was placed on the right and left upper quadrant of the abdomen. The patient was considered to have pleural effusion if any fluid collection was visible at the pleural space. The abdomen was screened for the presence of ascites in hepatorenal pouch, splenorenal area and rectovesical/rectovaginal space. Any evidence of free fluid intra-abdominally is considered pathological except for fluid in rectovaginal space. In this study, the female patients were considered to have ascites only when free fluid was detected in the perirenal region as well. The measurement of gall bladder was taken at the anterior gall bladder wall. The wall thickness of 3mm or more was considered as thickened gallbladder wall, and were identified as positive for gallbladder wall oedema.[20,21] Pericardial effusion was screened with the probe at subxiphoid region, using liver as the window.

All bedside ultrasound procedures were carried out by a single operator, who first received a one-month training to ensure good technique and competency on performing

bedside ultrasound for dengue patients. The training included detecting pleural effusion, perirenal fluid collection, pericardial effusion, gallbladder wall thickening or rectovesical/rectovaginal fluid collection, i.e., all findings measured in the study. Inter-rater reliability test was performed and scored 0.9. All the ultrasound scan clips in the study were reviewed and verified by the emergency medicine consultant who is certified and had undergone fellowship training in POCUS under the Emergency Ultrasound Fellowship, Massachusetts General Hospital-Harvard Medical School.

Socio-demographic, clinical, laboratory and ultrasonography data were collected using a proforma form. The first day of fever was defined as the first day of illness. The clinical management of the dengue patients were based on the recommendation by the WHO guideline and CPG.[1,4] Ultrasonography was part of the routine clinical care. Patients with ultrasonography evidence of plasma leakage were admitted to the observation ward of ED for close monitoring and frequent full blood count.

Admission to the ward was warranted once patients developed warning signs or severe dengue based on CPG. Once the patients were admitted to the hospital, the management would be continued by the medical team in the ward. Ultrasound examination or POCUS would be discontinued as it was not a standard procedure in the ward, unless specifically requested by the team. The progresses of the patients were followed up in order to observe for the outcome of the disease.

All data analysis was performed using IBM SPSS version 24. Numerical data were expressed as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). The agreement of detecting plasma leakage based on bedside ultrasound and haematocrit level in dengue fever patient without warning signs was analysed using the kappa agreement calculator from website http://vassarstats.net/kappa.html.

The Human Research Ethics Committee of USM approved all legal, ethical, radiological aspects of the study, (reference number: USM/JEPeM/16100392).

RESULTS

A total of 90 patients were initially enrolled in the study and one patient had no gallbladder ultrasonography assessment due to the surgical history of cholecystectomy. There were 7 patients who defaulted follow up at ED, Hospital USM due to logistic issues. Of the 83 patients with the diagnosis of confirmed dengue fever without warning signs and treated as an outpatient, eventually only 18 (21.7%) patients remained dengue fever without warning signs; 60 (72.3%) and 5 (6.0%) of the them developed dengue fever with warning signs and severe dengue fever respectively. All the patients with severe dengue fever had intravascular depletion due to significant plasma leakage. Those who developed dengue fever with warning signs and severe dengue at later stage of disease were admitted for close monitoring. All of them were discharged from the hospital without any mortality or morbidity (Figure 1).

Socio-demographic and clinical characteristics of the patients are presented in Table I. The youngest patient was 18 years old whereas the oldest was 76 years old. Overall mean age was 34.6 years (SD±14.23 years). The mean day of illness presented to the ED was on day five of illness, with the earliest day of presentation was on day one of illness. None of the socio-demographic profile had a significant association with the detection of plasma leakage using ultrasound throughout the disease (Table I).

At the time of presentation, none of the patients had clinical signs or laboratory findings suggesting plasma leakage. However, based on the ultrasound, there were 38 patients who had plasma leakage (7.9% of the patients had pleural effusion, 7.9% of the patients had ascites and 92.1% of the patients had thickened gallbladder wall). Upon completion of the follow up, of those 38 patients who had subclinical plasma leakage at enrolment, 3 of them (7.9%) recovered from the disease as dengue fever without warning signs. Whereas 32 of them (84.2%) progressed to dengue fever with warning signs and three of them (7.9%) developed severe dengue (Table II).

Meanwhile, of the 45 patients without ultrasonography evidence of plasma leakage on enrolment, 27 of them progressed to dengue fever with warning signs or severe dengue during subsequent follow up. Eventually there were 15 (33.3%), 28 (62.2%) and two (4.4%) cases of dengue fever without warning sign, dengue fever with warning sign and severe dengue respectively (Table II).

The number of patients with ultrasound findings suggestive of plasma leakage is presented in Table III. The number of patients decreased by each follow up as the patient either recovered or warded. Once the patients were admitted to the hospital, bedside ultrasound would be discontinued unless specifically requested by the medical team. Thus, Table III only shows the findings for patient that had been treated as outpatient. Gallbladder wall thickening was the most common ultrasound finding followed by pleural effusion and ascites. Pericardial effusion was not detected in any of the patients. Gallbladder wall thickening generally lasted for two to three days before it resolved. Majority of the patients recovered from the illness two to three days after the resolution of the thickened gallbladder wall. Serial bedside ultrasound was able to detect plasma leakage as early as day three of illness. The mean day of detecting plasma leakage based on ultrasound findings was 5.16 days of illness (SD±1.78). Meanwhile the mean day of haemoconcentration was 5.6 days of illness (SD±1.5). There was a small/minimal agreement between serial bedside ultrasound and haematocrit level in detection of plasma leakage (observed kappa 0.135) (Table IV).

DISCUSSION

POCUS is part of the changing landscape of healthcare delivery, particularly in ED, critical care and prehospital care.[19] It is routinely used by physicians with varying levels of training for many diagnostic purposes and procedural guidance, often with little to no supervision by radiologists.[22] The use of POCUS has even expanded to assess and diagnose some tropical infectious diseases.[18] In fact, it has also been

Table I: Socio-demographic of the patients and the association of socio-demographic profile with ultrasonography evidence of plasma leakage (n=83)

Socio-demographic characteristic	n (%)	p-value
Gender		0.730
Male	47 (56.6)	
Female	36 (43.4)	
Ethnicity		0.096
Malay	81 (97.6)	
Chinese	2 (2.4)	
Smoking history		0.532
Smoker	60 (83.1)	
Non smoker	14 (16.9)	
Phase of fever on presentation		0.179
Febrile phase	71 (85.5)	
Critical phase	12 (14.5)	
Day of illness on presentation to hospital	5 (1.66) *	0.814
History of dengue fever		0.230
Yes	3 (3.6)	
No	80 (96.4)	

*mean (SD)
Pearson chi-square or Fisher exact test were applied for categorical data.
Independent t-test was applied for numerical data.
p-value of < 0.05 is significant.

Table II: Final diagnosis of patient with or without subclinical plasma leakage at enrolment

Subclinical plasma leakage	Dengue fever without warning signs n (%)	Dengue fever with warning signs n (%)	Severe dengue n (%)
No	15 (33.3)	28 (62.2)	2 (4.4)
Yes	3 (7.9)	32 (84.2)	3 (7.9)

Table III: Ultrasonography evidence of plasma leakage at enrolment and follow up

	Pleural effusion n (%)	Ascites n (%)	Gallbladder wall thickening n (%)	Pericardial effusion n (%)
At enrollment, n = 83	3 (3.6)	3 (3.6)	35 (42.2)	0
First follow up, n = 83	4 (4.8)	4 (4.8)	36 (43.4)	0
Second follow up, n = 58	1 (1.7)	2 (3.4)	24 (41.4)	0
Third follow up, n = 30	0	1 (3.3)	11 (36.7)	0
Subsequent follow up, n = 20	1 (5)	0	5 (25)	0

Note: The findings might be overlapped in a single patient.

Table IV: Agreement between plasma leakage detected via ultrasound and haematocrit level (n=83)

		Haemoconcentration	
		Yes	No
Ultrasonography evidence of plasma leakage	Yes	34	23
	No	12	14

incorporated into a medical undergraduate curriculum, especially in North America and Canada.[23]

This study shows that bedside ultrasound or POCUS can be a useful imaging adjunct in recognising patients with plasma leakage. Early recognition of this feature can lead to prompt medical treatment and subsequently reduce the morbidity and mortality due to dengue infection.[8,24] At enrolment, a significant number of dengue patients without warning signs (45.8%) already had subclinical plasma leakage that could not be detected despite careful physical examination and laboratory investigation. Majority of the patients (92.1%) progressed to dengue fever with a warning signs or severe dengue, indicating the presence of subclinical plasma leakage at the early stage of fever which is a risk factor for progression to severe dengue. Our finding is comparable to a few studies, which reported 72.7 to 91.4% of patients with dengue haemorrhagic fever/severe dengue had ultrasonographic evidence of plasma leakage.[6,8,25]

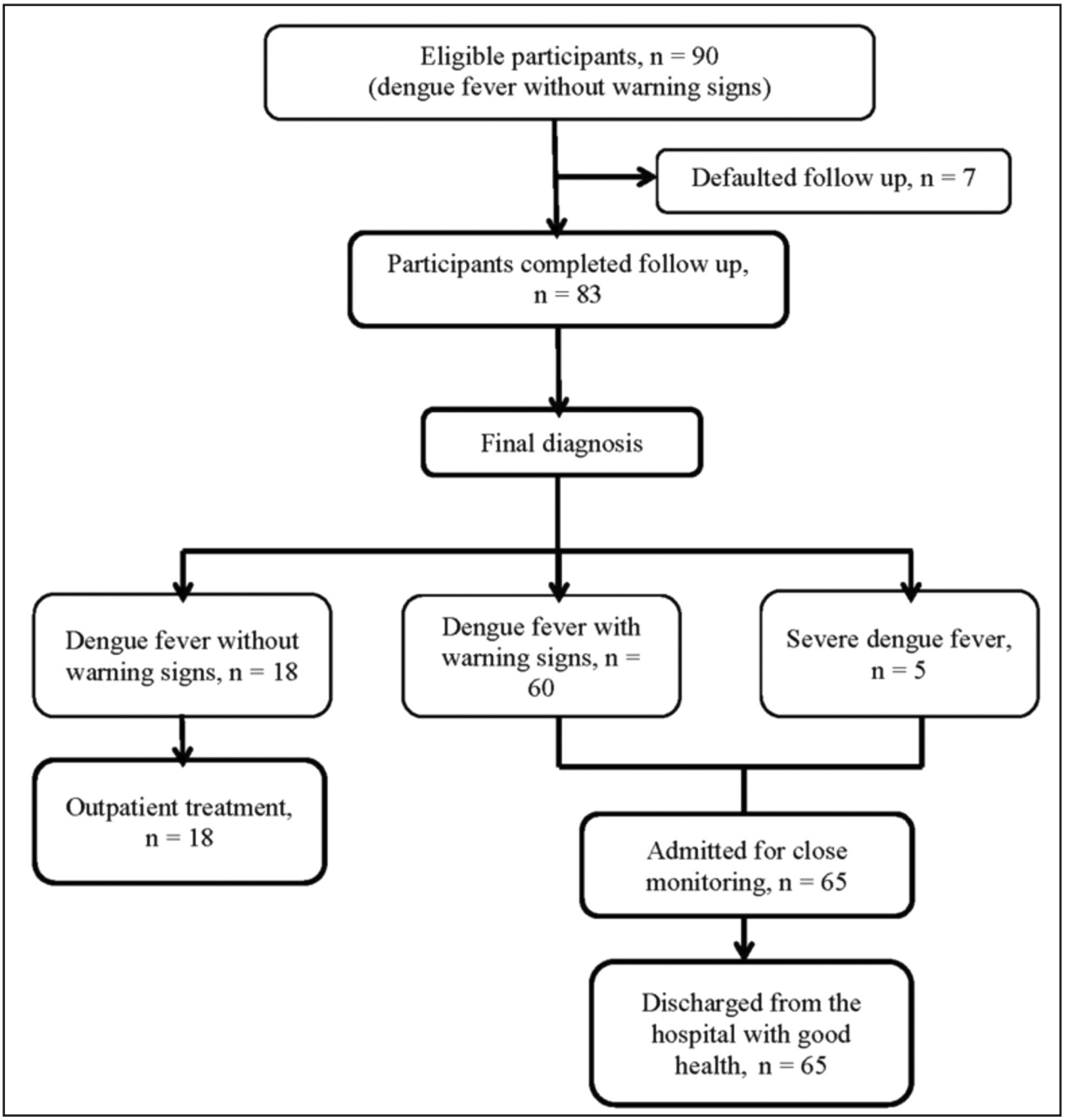

Fig. 1: Flow of patients in the study.

Our finding is particularly important and helpful during dengue outbreaks in dengue endemic country. Despite normal haematocrit readings, those patients with ultrasonography evidence of ascites, pleural effusion or gallbladder wall thickening should receive special attention as they have a high chance of developing warning signs or severe dengue during the dengue infection. On the other hand, in the case delay of diagnosis where dengue serology test is not immediately available, patients present with undifferentiated fever and ultrasonography evidence of plasma leakage are most probably having dengue fever, thus warrant immediate medical treatment. We suggest this group of patient to be admitted to the ward for close monitoring while waiting for results of the serology test.

Early diagnosis of dengue fever is one of the crucial factors in order to improve outcome in the management of dengue infection. It is supported by a study conducted in the year 2015 which state that thickened gallbladder wall was a useful ultrasound finding to confirm suspected cases of dengue haemorrhagic fever, with the positive predictive value of 90%.[26] Some other studies supported usage of thoracoabdominal ultrasound to diagnose dengue fever in a dengue endemic areas, where the parameter that was being studied included thickened gall bladder wall, pleural effusion, hepatosplenomegaly and ascites.[12,20,27]

This study shows that thickened gallbladder wall is the most common ultrasound finding in dengue infection (43.4%).

Variable results have been noted in other studies regarding these findings. A study on the ultrasound findings of 40 patients diagnosed with dengue haemorrhagic fever revealed that there were 53%, 43% and 15% cases of patients with pleural effusion, thickening of the gallbladder wall and mild ascites respectively.[26] In a study conducted in Pakistan, ascites was the most common findings (66.9%) followed by pleural effusion (51.1%) and thickened gallbladder wall (23.7%).[8] Pericardial effusion in dengue fever is uncommon except in severe dengue infection.[28] Our study also had no detection of pericardial effusion in all the patients, including those with severe dengue.

The mean day of detecting plasma leakage based on ultrasound findings was 5.16 days of illness (SD±1.78). Meanwhile the mean day of haemoconcentration was 5.6 days of illness (SD±1.5). This finding demonstrated that bedside ultrasound examination detects plasma leakage earlier compared to haematocrit level. Single haematocrit level was not helpful to identify patients with plasma leakage. The changes in haematocrit level often occur later and lead to a delay in medical treatment. This finding was consistent with a few studies, which reported haematocrit level is a poor indicator of plasma leakage as compared to bedside ultrasound.[6,11]

Currently, haemoconcentration based on laboratory profile is the most widely used criteria for confirming plasma leakage.[8] However, our study shows that serial bedside ultrasound was able to identify plasma leakage as early as day three of illness, which is earlier compared to haemoconcentration. Ultrasonography and laboratory profile had comparable results (slight agreement) for plasma leakage evaluation. Therefore, bedside ultrasound may be a great advantage in the clinical management of dengue infection. Serial bedside ultrasound has not only diagnostic value in undifferentiated fever, but also a prognostic value by recognising patients at risk of severe dengue.

Plasma leakage was already visible by bedside ultrasound in many dengue patients without warning signs at the time of enrolment. This shows its superiority in comparing with the physical examination. This finding also shows that bedside ultrasound should be performed as soon as possible during patient presentation to the health care centre. Once there is evidence of subclinical plasma leakage, we suggest that the patient be admitted to the observation ward in ED for intravenous drip and frequent full blood count. Serial bedside ultrasound can be conducted to see the progress of the patients and help in their disposition.

Since we have more mounting evidences of the role of ultrasound in early dengue fever, systematic review can be conducted in the future to look for its sensitivity, specificity, positive and negative predictive values of detecting subclinical plasma leakage.

There are a few limitations of ultrasonography. It produces images of poor quality in obese patients.[29] In fact, the finding of thickened gallbladder wall in isolation is non-specific if it not associated with underlying diseases of the patients. As such, all the possible diseases that might affect the outcome of this study had to be excluded. Another limitation of this study is the small sample size of patients who developed dengue fever with warning signs and severe dengue, hence we could not perform further analysis. Lastly, ultrasound examination was discontinued after the patient was admitted to the hospital, thus we are unable to analyse the ultrasound finding in this subgroup of patient.

CONCLUSION

Patient diagnosed with dengue fever without warning signs may have plasma leakage even during the initial presentation. Serial bedside ultrasound is an adjunct to physical examination and may detect plasma leakage earlier compared to haemoconcentration. The early usage of ultrasound is of paramount importance in detecting dengue patients who are at risk of progressing to severe dengue and warrant immediate medical treatment.

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DECLARATION

The authors have declared that no conflicting interest throughout the conduct of the study.

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