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Serial bedside echocardiography identifies children at risk of recurrent Dengue shock: a prospective cohort study

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Abstract

Background Dengue shock syndrome (DSS) is characterised by vascular leakage, although myocardial impairment may contribute to haemodynamic instability. The dynamic interplay between volume depletion and cardiac function during resuscitation remains incompletely understood.

Methods We conducted a prospective cohort study of children aged 6–15 years with DSS admitted to Hospital for Tropical Diseases in Ho Chi Minh City (2018–2020). Serial bedside echocardiography was performed at shock presentation and at 1, 3, 6, 12, and 24 h post-resuscitation, daily until hospital discharge, at follow-up 1–2 weeks later, and during recurrent shock.

Results 90 patients were enrolled; 16 (18%) developed recurrent shock at a median of 14 (IQR 11–17) hours after initial resuscitation. During shock, reduced SVI and CI during shock occurred in the presence of preserved LVEF and small IVC diameters, consistent with a preload-limited state. Transient myocardial impairment (MPI > 0.45) occurred in 40 patients (44%), and improved with fluid replacement. At 6 hours after resuscitation, patients who subsequently developed recurrent shock showed distinct haemodynamic profiles, including higher heart rate, lower SVI, lower lateral e′ velocity, higher E/e′, and lower TAPSE. Reduced lateral e′ velocity was also associated with respiratory distress.

Conclusions In DSS, preload reduction due to vascular leakage appears to be a major contributor to recurrent shock, although transient myocardial involvement may coexist. Focused echocardiographic assessment 6 h after resuscitation may help identify children at risk of recurrent shock before overt deterioration, supporting earlier risk stratification and more targeted fluid management.

Take home message

In dengue shock syndrome, hypovolaemia is the main cause of recurrent shock, though transient myocardial involvement may also contribute. Echocardiographic measures, including stroke volume index, lateral e′ velocity, E/e′ ratio, and TAPSE, assessed six hours after resuscitation can identify children at risk before clinical deterioration.

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Combined with vital sign monitoring, these parameters enhance early recognition and guide targeted, personalised fluid management.

Keywords Dengue, Echocardiography, Vascular leakage, Cardiac function, Dengue shock syndrome

Introduction

Myocardial impairment is common in dengue, with reported incidence ranging from 20 to 50% and associated with severe disease [1–4]. One study of 79 Vietnamese patients with dengue demonstrated that 45% had systolic impairment, particularly affecting septal and right ventricular walls, and 42% had diastolic impairment [5]. Reduced cardiac output in dengue has been associated with both reduced preload and ventricular dysfunction, without blood pressure changes [4]. The mechanisms are still incompletely understood, but vascular leakage, coronary hypoperfusion, and altered myocardial oedema likely play key roles [1].

Fluid resuscitation is the cornerstone of dengue shock syndrome (DSS) management. However, despite fluid therapy, about 30% of patients develop recurrent episodes of shock. These patients often require higher fluid volumes, particularly colloids, increasing the risks of fluid overload and poor outcomes, and necessitating care in settings with respiratory support and experienced staff [6, 7]. Cardiac dysfunction may compound this haemodynamic instability and has been associated with respiratory distress in DSS patients admitted to ICU [8]. Yet it remains challenging to identify these high-risk patients early in the resuscitation process. Understanding the contribution of myocardial impairment and identifying early predictors of recurrent shock may help tailor fluid management and improve outcomes in DSS.

Echocardiography offers non-invasive, bedside assessment of preload and cardiac performance. With portable devices, serial evaluation has become increasingly feasible in critically ill patients [9]. We therefore conducted prospective serial echocardiographic assessments in children with DSS to characterise haemodynamics, intravascular volume changes, and cardiac performance during fluid resuscitation, and to explore associations with the clinically relevant outcomes recurrent shock and respiratory distress.

Methods

Study design and participants

This was a prospective cohort study conducted at the Hospital for Tropical Diseases (HTD), Ho Chi Minh City, Vietnam, from 2018 to 2020 [10]. Children aged 5–15 years admitted to the PICU at HTD with clinically suspected DSS were eligible. Additional requirements included written informed consent and availability of staff and equipment for haemodynamic assessment. Exclusion criteria were prior fluid resuscitation before consent (either at another hospital or at HTD), and pre-existing significant underlying diseases that may be likely to affect haemodynamic assessment.

Enrolled patients underwent repeated bedside echocardiography at pre-defined time points, daily clinical examinations and research blood samples for up to 4 days or until ICU discharge, whichever occurred first. Patients were invited for follow-up echocardiographic and laboratory evaluation 1–2 weeks after discharge. All patients were managed according to hospital guidelines for DSS. Details on fluid therapy, vital signs, and clinical/biochemical assessments were recorded in case report forms.

Point-of-care echocardiography

Serial echocardiography was performed at predefined time points: shock diagnosis, 1, 3, 6, 12, and 24 h, then daily until ICU discharge. Examinations were performed by two trained investigators (HQC and HTT) using Samsung Medison U6 and GE Vivid iQ devices, with inter-operator variability $<10\%$. Standard 2D, M-mode, and Doppler images were acquired.

At enrolment (before initial resuscitation), only left ventricular (LV) output and extravascular fluid accumulation were assessed to avoid delaying urgent care. In cases of recurrent shock, the full scan schedule was repeated. LV output was assessed by stroke volume index (SVI) and cardiac index (CI), derived from LV outflow tract diameter, velocity–time integral, heart rate, and body surface area. Combined systolic and diastolic ventricular function was assessed by myocardial performance index (MPI); LV systolic function by ejection fraction (M-mode; Teichholz method); LV diastolic function by lateral e′ velocity (relaxation) and E/e′ ratio (filling pressure); right ventricular (RV) systolic function by tricuspid annular plane systolic excursion (TAPSE). Maximal and minimal inferior vena cava (IVC) diameters were measured 2 cm from the right atrial junction in the subcostal long-axis view. Definitions of echocardiographic parameters and the corresponding ultrasound views required for their acquisition are provided in Appendix Tables 1 and 2.

Extravascular fluid accummulation, including pleural effusion, gallbladder wall thickening, and ascites, was assessed using using a high-frequency transducer. Pleural effusion was assessed using a standardised operating procedure based on the Kigali ARDS protocol [11]. If any visible anechoic space above the diaphragm was present, the maximal depth of pleural effusion was measured at each lung base. Gallbladder wall thickness was measured at the anterior wall in the supine position, and ascites was assessed by scanning the hepatorenal and splenorenal recesses, paracolic gutters, and pelvis for free intraperitoneal fluid.

Variable definitions

Dengue shock was defined as hypotension for age, or pulse pressure (PP) ≤ 20 mmHg, with signs of circulatory compromise requiring fluid boluses or inotropic support. Patients with DSS were sub-classified as compensated and decompensated shock according to their blood pressures (BP) [12]. Compensated DSS was defined as the patient having systolic blood pressure maintained with a PP of > 10 to 20 mmHg at shock diagnosis. Decompensated DSS was defined as the patient having a PP ≤ 10 mmHg or hypotensive for age or unmeasurable BP at shock diagnosis. Myocardial impairment was defined as LV or RV MPI > 0.45, which were pre-specified based on paediatric studies [13, 14].

The primary endpoint was recurrent shock, defined as a new episode of clinical shock occurring after the patient had reached haemodynamic stability during fluid resuscitation. Haemodyanmic stability was defined as normal systolic blood pressure with pulse pressure ≥ 25mmHg for at least 6 consecutive hours, a duration considered sufficient to allow for full clinical response following initial fluid resuscitation. The secondary endpoint was respiratory distress, defined by a sustained increase in respiratory effort or rate (age 5–12: >30 breaths/min; age 12–16: >20 breaths/min) and/or the need for respiratory support (nasal CPAP or mechanical ventilation).

Fluid management

Fluid resuscitation followed a standardised, protocol-driven regimen based on hospital dengue management guidelines. Escalation from crystalloid to colloid was determined by predefined clinical criteria (e.g., persistent shock after initial bolus, recurrent shock).

Briefly, patients with compensated DSS receive crystalloid fluids at 15 ml/kg/h initially, tapered to 10, 7.5, 5, and 3 ml/kg/h over 24 h if clinically improving (normalised heart rate, blood pressure, improved urine output, etc.). Decompensated shock is managed with colloid boluses (15 ml/kg/h for 1 h, then 10 ml/kg/h for 2 h), after which fluids are switched to crystalloids. In patients who do not respond to initial crystalloid resuscitation or who develop recurrent shock, colloid boluses are administered, followed by a return to crystalloid infusion. The colloid type used depends on local availability. Details of fluid regimens are shown in Appendix Fig. 1. Vital signs are monitored hourly and haematocrit at 0-, 1-, 3-, and 5-hours post-shock or more frequently if clinically indicated.

Statistical analysis

Continuous data are summarised as median (interquantile (IQR)), categorical data as n (%). Data distribution was assessed visually using histograms. Echocardiographic parameters were analysed as absolute values. Comparisons between compensated vs. decompensated shock groups were perfomed using Wilcoxon rank-sum or Fisher's exact tests as appropriate.

Longitudinal changes in echocardiographic parameters were analysed using linear mixed-effects models, with each parameter as the dependent variable. Fixed effects included time (continous, modelled with natural cubic splines with four knots), shock group (categorical), their interaction, and fluid type used at the measurement time (categorical: crystalloid vs. colloid). Fluid type was treated as a time-varying covariate to account for changes in resuscitation strategy over time. Each patient was included as a random effect with a random slope for time to account for individual trajectories. Results from the mixed-effect models are mainly reported by visualisation of the predicted values for the two groups. P-values from joint tests in these models indicate whether the parameters changed over time, differed between groups, or had group-specific time trends. Logistic regression was employed to investigate associations between the various clinical and haemodynamic parameters with recurrent shock and respiratory distress, adjusted for age and shock severity. Statistical significance was set at $p < 0.05$. Analyses were performed in R v4.2.1.

Ethical review

Ethical approvals for this study were obtained from the Oxford Tropical Research Ethics Committee (03–18) and the HTD Ethics Committee (CS/BND/18/27). For each participant, written informed consent was obtained from a parent/guardian, together with assent from children ≥ 12 years.

Results

Baseline characteristics and clinical outcomes

Of the 92 patients enrolled between 2018 and 2020, two withdrew. Thus a total of 90 patients were included in the final analysis.

The median age was 12 years (IQR 10–13). 17/90 patients (19%) presented with decompensated shock at enrolment (Table 1). In addition to differences in blood pressure, patients who presented with decompensated shock had higher heart rates (120 vs. 110 bpm, $p = 0.036$) compared with those with compensated shock. Median venous lactate was 3.2 mmol/l (IQR 2.5–3.8) for all patients, with no difference between the two severity groups. Other biochemical tests were within normal limits. Troponin I levels were ≤ 40 pg/mL in 87 patients. Amongst the three patients with elevated troponin I

Table 1 Baseline characteristics of paediatric patients with dengue shock syndrome (DSS)

Characteristic	*n*	Overall, *N* = 90	*n*	Compensated DSS, *N* = 73	*n*	Decompensated DSS*, *N* = 17	*p*-values
Age, years	90	12 (10, 13)	73	12 (10, 13)	17	10 (8, 13)	0.300
Female sex	90	37 (42)	73	29 (40)	17	9 (53)	0.300
Day of illness at presentation, day	90	5 (5, 6)	73	5 (5, 6)	17	5 (5, 6)	0.200
BMI, kg/m^2	90	20.1 (17.2, 22.9)	73	20.2 (17.4, 22.8)	17	19.2 (14.7, 22.9)	0.300
Heart rate, bpm	90	110 (105, 123)	73	110 (104, 120)	17	120 (110, 127)	0.036
Systolic BP, mmHg	84**	100 (90, 100)	73	100 (90, 100)	11	100 (90, 102)	0.800
Diastolic BP, mmHg	84**	80 (75, 90)	73	80 (70, 85)	11	90 (80, 95)	0.005
Pulse pressure, mmHg	90**	20 (15,20)	73	20 (20, 20)	17	10 (5, 10)	< 0.001
Respiratory rate, breaths/min	90	24 (22, 26)	73	24 (22, 26)	17	24 (22, 26)	0.591
Temperature, °C	90	37.0 (37.0, 37.4)	73	37.1 (37.0, 37.5)	17	37.0 (37.0, 37.2)	0.208
WBC, k/µl	90	4.51 (0.99, 2.40)	73	4.35 (3.37, 6.19)	17	5.36 (4.12, 6.45)	0.216
POC haematocrit, %	90	50 (48, 52)	73	50 (47, 52)	17	52 (50, 55)	0.466
Platelets, k/µl	90	30 (20,40)	73	32 (22, 40)	17	29 (17, 34)	0.400
Albumin, g/l	90	36.9 (33.1, 39.3)	73	36.8 (33.3, 39.3)	17	37.0 (33.0, 39.2)	> 0.900
Venous lactate, mmol/l	90	3.2 (2.5, 3.8)	73	3.1 (2.4, 3.8)	17	3.2 (2.7, 3.8)	0.523
SVI, ml/m^2	90	17.2 (14.0, 20.7)	73	17.5 (14.8, 21.0)	17	14.0 (11.3, 18.7)	0.010
CI, l/min/m^2	90	1.8 (1.6, 2.1)	73	1.8 (1.6, 2.2)	17	1.6 (1.4, 2.0)	0.110
Gallbladder wall thickness, mm	90	0.87 (0.65, 1.00)	73	0.87 (0.67, 1.03)	17	0.73 (0.56, 0.89)	0.062
Pleural effusion	72***	56 (77)	57	45 (79)	15	11 (73)	0.700
Ascites	86***	46 (53)	69	37 (54)	17	9 (53)	> 0.900

*Decompensated DSS is defined as pulse pressure $\leq$ 10 mmHg or hypotension for age or unmeasurable blood pressure

**6 patients had unmeasurable blood pressure. Their pulse pressure were imputed as 5 mmHg

***Pleural effusion scanning was not performed in 18 patients, and ascites scanning was not performed in 4 patients because of the urgency of resuscitation at the time of shock presentation

Data are presented as absolute count (%) for categorical variables and median (IQR) for continuous data. Comparisons between group were assessed using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. N: number of patients, n: number of measurements. BMI: body mass index, BP: blood pressure, WBC: white blood count, POC: point of care, SVI: stroke volume index, CI: cardiac index, AST: aspartate aminotransferase, ALT: alanin aminotransferase

Table 2 Clinical outcomes of patients with dengue shock syndrome (DSS)

Characteristic	*n*	Overall, *N* = 90	*n*	Compensated DSS, *N* = 73	*n*	Decompensated DSS*, *N* = 17	*p*-values
Recurrent shock	90	16 (18)	73	10 (14)	17	6 (35)	0.072
1 episode	90	12 (13)	73	7 (10)	17	5 (29)	0.990
2 episodes	90	4 (4)	73	3 (4)	17	1 (6)	-
Time to 1st re-shock, hours	16	14 (11, 17)	10	14 (8, 16)	6	16 (13, 17)	0.533
Time to 2nd re-shock, hours	4	25 (25, 26)	2	25 (25, 25)	2	29 (29, 29)	0.500
Respiratory distress	90	10 (11)	73	6 (8)	17	4 (24)	0.093
Percentage haemoconcentration**, %	90	32 (25, 42)	73	32 (23, 39)	17	48 (31, 52)	0.013
Total IV fluid volume, ml/kg	90	130 (122, 149)	73	129 (121, 144)	17	133 (125, 175)	0.100
Colloid use (ml/kg)	34	35 (35, 47)	17	35 (33, 43)	17	36 (35, 58)	0.032
Crystalloid (ml/kg)	90	123 (117, 134)	73	125 (118, 136)	17	95 (89, 118)	< 0 001
IV fluid duration, hours	90	27.3 (24.9, 30.9)	73	27.2 (24.3, 30.2)	17	27.4 (27.0, 35.3)	0.150
PICU duration, day	90	3 (3, 4)	73	3 (3, 4)	17	4 (3, 4)	0.033
Death	90	0	73	0	17	0	-

*Decompensated DSS is defined as pulse pressure $\leq$ 10 mmHg or hypotension for age or unmeasurable blood pressure

**Percentage haemonconcentration was calculated as (enrolment– FU haematocrit/FU haematocrit)*100

Data are presented as absolute count (%) for categorical variables and median (IQR) for continuous data. Comparisons between group were assessed using Wilcoxon rank sum test for continuous variables, and Fisher's exact test for categorical variables. N: number of patients, n: number of measurements, IV: intravenous, PICU: paediatric intensivecare unit

levels (46, 61, and 359 pg/mL), none had impaired systolic function, defined as an EF < 60%.

Recurrent shock occurred in 16/90 (18%) patients; 12 had one episode and 4 had two episodes of recurrent shock (Table 2). The median time to the first recurrent shock was 14 h after the initial DSS diagnosis (range, 6–26 h). Rates of recurrent shock were higher amongst patients who presented with decompensated compared to compensated shock (35% versus 14%, $p = 0.072$). Respiratory distress developed in 10/90 (11%) patients, though none required NCPAP or mechanical ventilation. The median ICU stay was 3 days (IQR 3–4), and no deaths occurred.

The median total IV fluid volume was 130 ml/kg (IQR 122–149) over 27 h (IQR 25–31), with heterogeneous patterns of crystalloid and colloid use across patients, ranging from crystalloid-only resuscitation to mixed regimens using colloids at different stages (Fig. 1). Patients who required more than two administrations of colloids (for decompensated shock, inadequate response to initial crystalloid resuscitation, or recurrent shock) were more likely to receive larger total fluid volumes and undergo longer resuscitation.

Changes of cardiac function over time

At the time of shock or recurrent shock diagnosis, 89/90 patients demonstrated reduced SVI, CI, worse functional parameters, along with elevated MPIs and reduced IVC diameters. One patient presented with a narrow pulse pressure but was normovolemic (SVI = 40 ml/m²) and normal systolic function (EF = 72%). The echocardiographic parameters had significant non-linear changes over time with substantial inter-patient variability during the resuscitation period and generally returned to normal ranges by follow-up (Table 3**).**

During resuscitation, MPIs > 0.45, indicative of global ventricular dysfunction, were transiently observed in 40/90 patients (44%), involving predominantly the LV (39 cases), with fewer RV [5] and biventricular [3] cases. Most abnormalities coincided with hypovolaemia and resolved as the volume status improved.

a. **Trajectories of echocardiographic parameters by shock severity**.

At presentation, the medians of SVI and CI were 17.2 ml/m² (IQR 14.0–20.8) and 1.8 l/min/m² (IQR 1.6–2.1) respectively. Patients with decompensated shock had

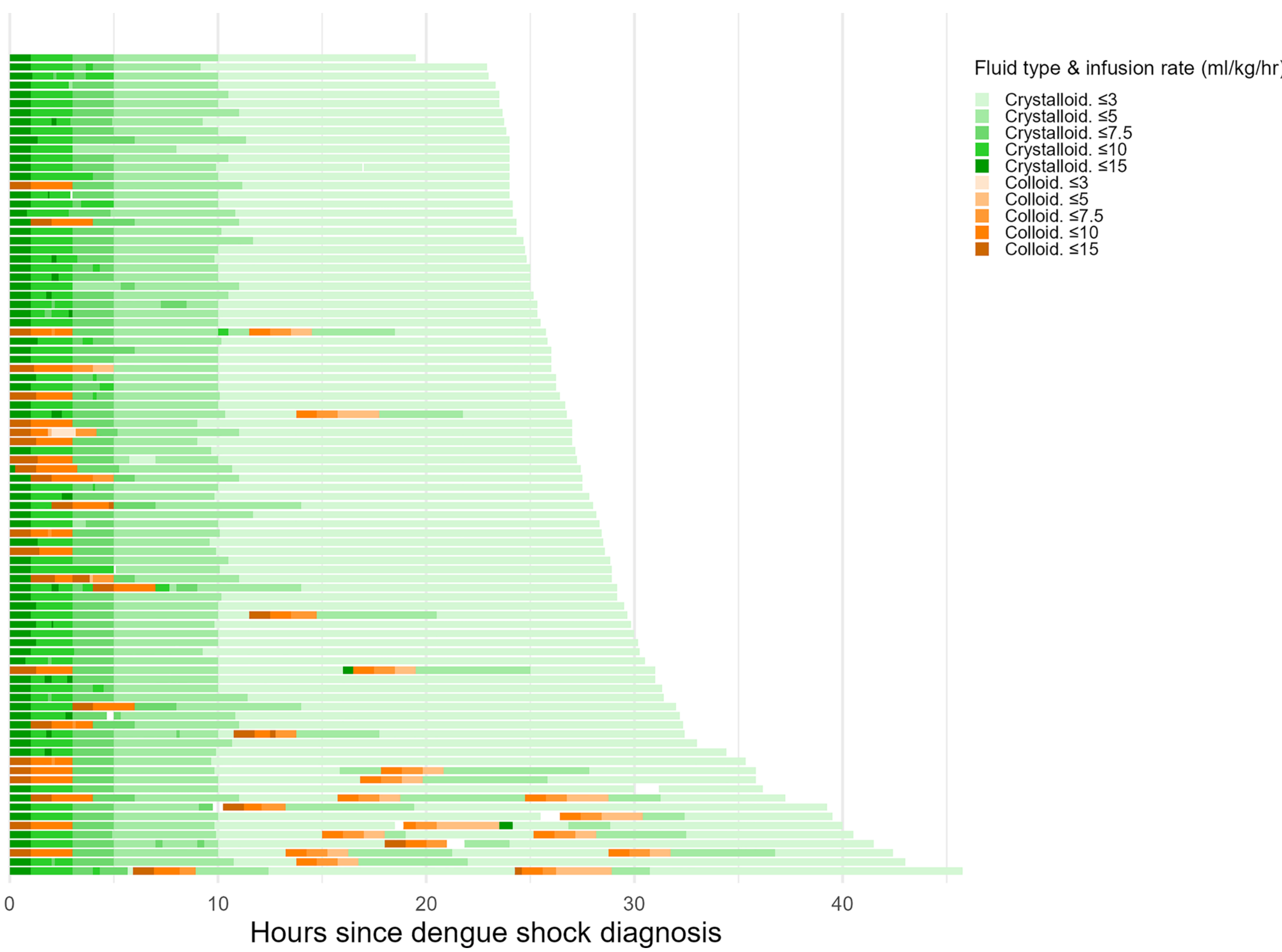

Fig. 1 Summary of fluid resuscitation of paediatric patients with dengue shock syndrome. Each horizontal bar represents the total duration and composition of intravenous (IV) fluid resuscitation for an individual patient. Green segments indicate crystalloid infusion, and orange segments indicate colloid infusion. Patients are arranged in ascending order of total IV fluid infusion duration

Table 3 Haemodynamic and echocardiographic parameters of paediatric patients with dengue shock at the diagnosis of shock and the first recurrent shock

Characteristic	*n*	At the presentation of dengue shock, *N* = 90	*n*	At the diagnosis of the first recurrent shock, *N* = 16	*n*	Follow-up visit, *N* = 90
Hours since the first shock	90	(0,0)	16	14 (11,17)	87	227 (193, 242)
Heart rate, beats/min	90	110 (105, 121)	16	105 (97, 120)	87	85 (77, 92)
SBP, mmHg	90	100 (90,100)	16	90 (86, 100)	87	100 (100, 110)
DBP, mmHg	90	80 (75,85)	16	70 (70, 80)	87	60 (60, 70)
POC Haematocrit, %	90	50 (48, 52)	16	49 (47, 50)	87	38 (36, 40)
LVOT VTI, cm	90	10.7 (9.5, 12.6)	14	12.2 (10.1, 14.4)	87	21.5 (19.4, 24.5)
SVI, ml/m^2	90	17.2 (14.0, 20.8)	14	17.2 (15.8, 20.6)	87	34 (29, 38)
CI, l/min/m^2	90	1.8 (1.6, 2.2)	14	2.0 (1.6, 2.2)	87	2.8 (2.5, 3.3)
EF, %	89	64 (60, 69)*	9	63 (60, 68)	86	70 (67, 74)
e' lat, cm/s	89	15.0 (11.9, 17.7)*	9	11.7 (10.3, 13.5)	86	19.0 (16.3, 20.6)
E/e' ratio	88	5.2 (4.2, 6.2)*	8	5.1 (4.7, 6.4)	84	5.2 (4.6, 5.9)
TAPSE, mm	90	17.6 (16.0, 19.0)*	7	15.0 (10.9, 15.8)	84	21.0 (19.7, 23.0)
LMPI	89	0.34 (0.26, 0.42)*	8	0.38 (0.30, 0.50)	86	0.18 (0.14, 0.24)
RMPI	89	0.10 (0.07, 0.18)*	8	0.19 (0.15, 0.25)	82	0.11 (0.06, 0.16)
Maximal IVC diameter, mm	87	1.03 (0.77, 1.23)	10	1.05 (0.53, 1.26)	84	1.37 (1.15, 1.59)
Minimal IVC diameter, mm	87	0.77 (0.58, 0.96)	10	0.83 (0.43, 0.97)	84	0.94 (0.76, 1.18)
Left pleural effusion size, cm	90	0.7 (0.4, 1.0)*	10	1.9 (1.0, 2.4)	87	0 (0, 0)
Right pleural effusion size, cm	90	1.6 (0.9, 2.4)*	10	3.1 (3.0, 5.0)	87	0 (0, 0)
Gallbladder wall size, cm	90	0.8 (0.7, 1.0)*	10	0.9 (0.7, 1.0)	87	0.2 (0.2, 0.2)

*The values of the first episode were measured at 1-hour after the shock diagnosis to avoid the emergency treatment

Data are presented as median (IQR). Two patients did not undergo echocardiography at the time of the first recurrent-shock diagnosis due to the unavailability of ultrasound operators. Another two patients did not attend the follow-up visit and therefore had no echocardiographic data. The remaining missing data were non-systematic and resulted from absent images or inadequate image quality that prevented measurement. SBP: systolic blood pressure, DBP: diastolic blood pressure, POC: point-of-care, Bilateral PE size: total pleural effusion thickness on both lungs, LVOT VTI: left ventricular outflow tract velocity time integral, SVI: stroke volume index, CI: cardiac output index, EF: ejection fraction, e' lat: the early diastolic myocardial velocity measured at the lateral mitral annulus, E/e': The ratio of early diastolic mitral inflow velocity to early diastolic myocardial velocity, TAPSE: tricuspid annular plane systolic excursion, LMPI: left myocardial performance index, RMPI: right myocardial performance index, IVC: inferior vene cava

significantly lower SVI compared with those with compensated shock (14.0 vs. 17.5 ml/m², $p = 0.010$). Although CI was lower in the decompensated group, the difference was not statistically significant (1.6 vs. 1.8 l/min/m², $p = 0.110$).

Both groups showed substantial increases in SVI and CI following resuscitation (Fig. 2). Patients with decompensated shock had a steeper initial rise in SVI and CI after colloid administration. However, throughout the resuscitation period, the decompensated group maintained lower SVI and CI compared to the compensated group ($p < 0.001$ for severity). There were no significant overall differences in functional parameters between compensated and decompensated shock ($p > 0.05$ for severity in all parameters) (Appendix Fig. 2).

b. **Trajectories of echocardiographic parameters by recurrent shock**.

The trajectory of SVI differed significantly between patients with and without recurrent shock ($p < 0.001$ for time and recurrent shock interaction) (Fig. 2). After the 6-hour time point, when most patients were receiving maintenance fluids at 5 ml/kg/hour, those who subsequently developed recurrent shock showed a progressive decline in SVI compared with patients without recurrence, reaching a nadir of 17.2 ml/m² (IQR 15.8–20.6) at the time of recurrent shock. CI followed a similar trend, although differences in trajectory were not statistically significant ($p = 0.195$ for time and recurrent shock interaction).

Similarly, the trajectories of lateral e′ velocity (rexalation), TAPSE (right ventricular contraction), and RMPI appeared to differ from the non-recurrent shock group within the first 6–12 hours post-resuscitation, reaching nadirs at the time of the recurrence (lateral e ' 11.7 cm/s, IQR 10.3–13.5; TAPSE 15.0 mm, IQR 10.9–15.8; RMPI 0.19, IQR 0.15–0.25) (Fig. 3). The trajectories of EF and LMPI did not differ significantly between patients with and without recurrent shock ($p > 0.05$ for time and recurrent shock interaction). Finally, E/e' ratio (filling pressure) was significantly higher overall in patients who developed recurrent shock ($p = 0.002$ for recurrent shock), particularly during the first 12 h.

Changes in fluid accumulation over time

Pleural effusion thickness increased steadily during the ICU stay, while the gallbladder wall thickness decreased

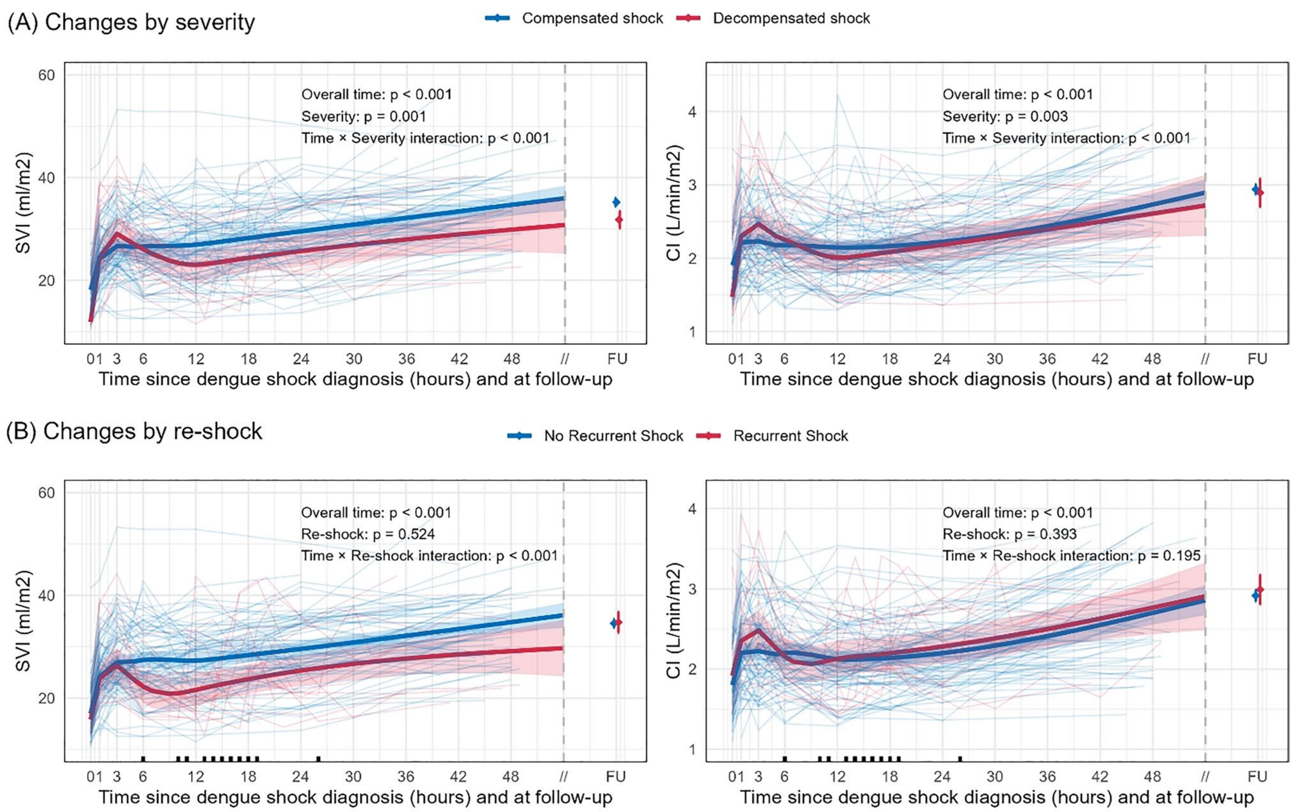

Fig. 2 Trajectories of stroke volume index (SVI) and cardiac index (CI) in children with dengue shock syndrome during ICU stay and at the follow-up visit, by shock severity at admission and by the occurrence of recurrent shock. Panel (A) shows changes in stroke volume index (SVI) and cardiac index (CI) by severity group (blue = compensated shock, red = decompensated shock). Panel (B) shows changes in SVI and CI by recurrent shock status (blue = no re-shock, red = re-shock). Thin lines represent individual patient trajectories; solid lines represent model-estimated means; shaded bands are 95% confidence intervals; and symbols at FU indicate group means ± 95% CI at follow-up. In panel (B), short rug marks along the x-axis indicate the timing of recurrent shock events. Linear mixed-effects models were fit with each echocardiographic parameter as the outcome, including time, shock group (severity or recurrent shock), their interaction, and fluid type used at the measurement time as fixed effects, with patient included as a random effect and time as a random slope. P-values are from joint tests in these models and indicate whether parameters change over time, whether groups differ overall, and whether time trends differ between groups

after 24 h (Appendix Fig. 3). Patients with recurrent shock tended to develop greater pleural effusions after 12 h of infusion as they tended to received higher volumes of IV fluid.

Associations of haemodynamic and echocardiographic parameters with recurrent shock and respiratory distress

At presentation only an earlier day of illness at the time of shock was significantly associated with recurrent shock (OR 0.35, 95%CI 0.15, 0.74). At 6 h post-resuscitation, higher heart rate, lower SVI, lower lateral e′ velocity, higher E/e′, and lower TAPSE were associated with increased risk of recurrent shock (Fig. 4). Among these, lateral e′ velocity had the best predictive performance, with an AUC of 0.91 (95% CI 0.81–1.00) with a cut-off of 14.0 cm/s achieving 79% sensitivity and 68% specificity (Appendix Fig. 4). For SVI, a cut-off of 25 ml/m² yielded 73% sensitivity and 56% specificity.

Only lateral e′ velocity at 6 h was associated with subsequent respiratory distress (OR 0.79, 95%CI 0.62–0.97) (Appendix Table 3).

Discussion

In this prospective study, reduced LV output emerged as a defining haemodynamic feature of both initial and recurrent shock in paediatric patients with severe dengue. Differences in echocardiographic parameters between patients with and without recurrent shock were detectable as early as 6 hours after initial resusictation, occuring from 0 to 20 hours before overt haemodynamic deterioration. Lower SVI, reduced lateral e′ velocity and TAPSE, together higher E/e′ and heart rate, were early indicators of recurrent shock. These findings demonstrate that clinically relevant haemodynamic changes occurs well before blood pressure alter, providing a potential window for proactive intervention.

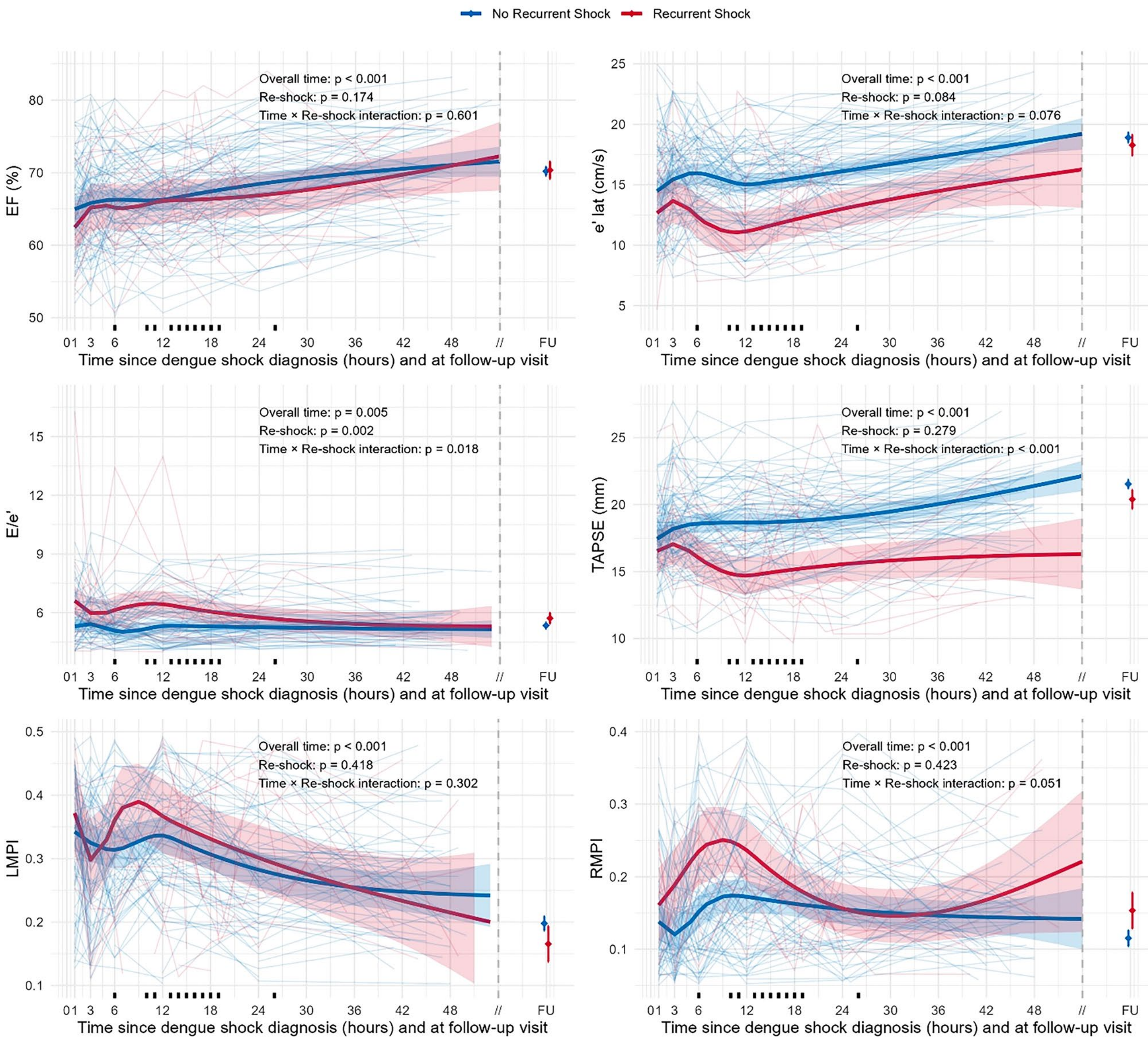

Fig. 3 Trajectories of echocardiographic parameters over the 48 hours following dengue shock diagnosis and at the follow-up visit. Figure shows changes in echocardiographic parameters by recurrent shock status (blue = no re-shock, red = re-shock). Thin lines represent individual patient trajectories; solid lines represent model-estimated means; shaded bands are 95% confidence intervals; and symbols at FU indicate group means ± 95% CI at follow-up. Short rug marks along the x-axis indicate the timing of recurrent shock events. Linear mixed-effects models were fit with each echocardiographic parameter as the outcome, including time, recurrent shock, their interaction, and fluid type as fixed effects, with patient included as a random effect and time as a random slope. P-values are from joint tests in these models and indicate whether parameters change over time, whether groups differ overall, and whether time trends differ between groups. EF: ejection fraction, e' lat: the early diastolic myocardial velocity measured at the lateral mitral annulus, E/e': The ratio of early diastolic mitral inflow velocity to early diastolic myocardial velocity, TAPSE: tricuspid annular plane systolic excursion, LMPI: left myocardial performance index, RMPI: right myocardial performance index

Mechanistically, our data support a major role of vascular leakage and consequent preload reduction in the haemodynamic instability observed in paediatric DSS. Serial echocardiographic assessments illustrated the dynamic interplay between plasma leakage and fluid replacement, reflected by fluctuations in SVI and CI. During shock and recurrent shock, reduced SVI and CI occurred in the presence of preserved LVEF and no evidence of venous congestion (Table 3), a haemodynamic pattern consistent with a preload-limited state as classically described in hypovolemic shock. These observations indicate that diminished ventricular filling is a principal determinant of reduced forward flow in DSS.

Approximately 44% of patients experienced mild and transient myocardial impairment during resuscitation, consistent with previous haemodynamic studies in dengue [8, 15]. These abnormalities typically coincided with hypovolaemic periods and improved following volume

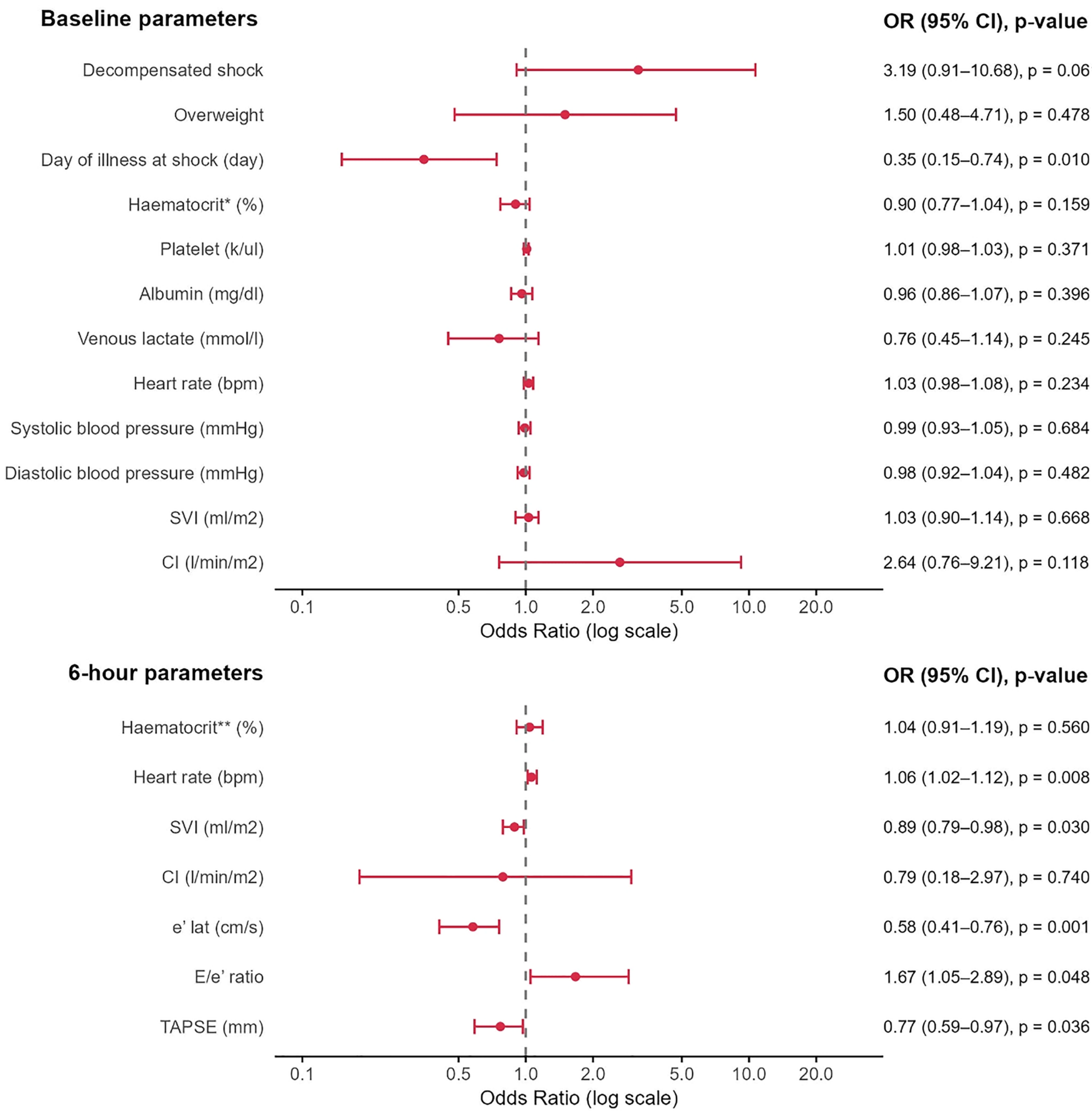

Fig. 4 Odds ratios for baseline and 6-hour parameters in predicting recurrent shock in children with dengue shock syndrome (DSS). Forest plots show odds ratios (ORs) with 95% confidence intervals (CIs) for clinical and echocardiographic parameters measured at baseline (top panel) and six hours after resuscitation (bottom panel). Logistic regression was used to assess the association between each parameter and recurrent shock, with recurrent shock as the outcome and each parameter as a covariate, adjusted for age and shock severity at presentation. SVI: stroke volume index, CI: cardiac index, e′ lat: the early diastolic myocardial velocity measured at the lateral mitral annulus, E/e′: The ratio of early diastolic mitral inflow velocity to early diastolic myocardial velocity, TAPSE: tricuspid annular plane systolic excursion

repletion, suggesting a preload-responsive component. The higher frequency of impairment compared with that reported by Yacoub and colleagues (18% in paediatric patients with dengue using MPIs cutoff > 0.45) may be explained by our repeated assessments, which captured transient hypovolaemic episodes that single-timepoint studies may have missed. In association with elevated MPIs, we observed features indicative of impaired LV relaxation (lower lateral e′ velocity), elevated filling pressures (higher E/e′), and reduced RV function (lower TAPSE), among patients who developed recurrent shock. While TAPSE is load-dependent, tissue Doppler indices are relatively less influenced by preload, raising the possibility of mild intrinsic transient myocardial involvement in a subset of patients [16, 17]. Recurrent shock may therefore represent a spectrum ranging from predominant preload reduction to myocardial impairment that reduces compliance and elevates filling pressures [18]. Futher studies incorporating strain imaging or cardiac MRI are required to clarify the extent and mechanisims of myocardial involvement in severe dengue [19].

Beyond mechanistic considerations, early day of illness at shock presentation was the only factor associated with subsequent recurrent shock (Fig. 4), consistent with findings from a large cohort study of patients with DSS [7]. Early presentation likely reflects a subgroup of patient experiencing rapid and severe leakage that quickly overwhelms their circulatory compensation. Patients presenting with decompensated shock demonstrated more profound preload limitation at admission and throughout their ICU stay (Table 1; Fig. 2), supporting greater leakage severity and recurrent shock risk. Notably, haematocrit showed limited ability to distinguish between compensated and decompensated shock (Table 1), underscoring the limitations of conventional markers of intravascular volume.

At the individual level, reductions in SVI and CI preceded clinical deterioration amongst patients who developed recurrent shock (Fig. 2). Tracking SVI may therefore enable identification of subclinical volume depletion before blood pressure changes, offering a clinically actionable window for intensified monitoring and fluid optimisation. Nevertheless, progression to overt recurrent shock likely reflect inter-individual variability in tolerance to hypovolemia, among other factors, as substantial differences were observed in both SVI levels and timing of recurrent shock. The occurrence of recurrent shock even in initially compensated patients may further emphasise the evolving nature of DSS.

Clinically, combining simple clinical parameters such as heart rate with focused echocardiographic measures may enhance risk stratification in paediatric DSS. Our findings suggest that a limited set of parameters, particularly SVI and lateral e’ velocity, may suffice for early identification of high-risk patients, improving feasibility in acute care settings. Although operator expertise may limit immediate widespread implementation, advances in portable and AI-assisted ultrasound technology may facilitate broader application [20]. Integration with emerging non-invasive technologies, such as the compensatory reserve index derived from photoplethysmography [21, 22], bioimpedance-based devices [23], and machine-learning approaches using pulse oximeters [24, 25], may further extend these insights toward earlier intervention and more personalised fluid management.

This study has several strengths, including its prospective design, dense temporal sampling, and standardised echocardiographic acquisition by trained operators. Serial echocardiography at predefined time points enabled detailed characterisation of haemodynamic trajectories. Fluid therapy followed a protocol-driven regimen, which could reduce variability related to clinician discretion, although residual confounding by indication cannot be excluded. Limitations include the specialised paediatric ICU, which may limit generalisability to frontline or adult settings or less structured care environments. Intensive data collection and strict enrolment criteria resulted in inclusion of only 92 of the 735 potentially eligible ICU admissions. Although patient characteristics and outcomes were broadly comparable with other DSS cohorts, the lower rates of recurrent shock and respiratory distress may reflect selection bias or optimal management in a specialised unit. In addition, while echocardiographic cut-offs were based on established paediatric references, DSS-specific thresholds warrant external confirmation.

In conclusion, preload limitation due to vascular leakage appears to be a major contributor of recurrent shock in DSS, although transient myocardial involvement may contribute in selected patients. Echocardiographic parameters including SVI, lateral e’ velocity, E/e′, and TAPSE measured six hours after fluid resuscitation can help identify patients at risk of recurrent shock before overt clinical deterioration. When combined with clinical monitoring, focused echocardiography may support earlier recognition and more targeted fluid management in paediatric patients with severe dengue.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

HQC was involved in data collection, data analysis and interpretation, and manuscript writing. HTT was involved in the study design, data collection, and manuscript review. TKH, VHNT were involved in data collection. HTLD was involved in sample processing and biomarker measurement. TKNT was involved in data collection and management. NNM, TQP were involved in study management and manuscript review. V DTHT was involved in data verification and manuscript review. NLV and LPK were involved in analysis development, result interpretation and manuscript review. AM was involved in result interpretation and manuscript writing. BW was involved in the study design and manuscript review. SY was involved in the study design, manuscript review and supervision.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The investigators declared that this study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approvals for this study were obtained from the Oxford Tropical Research Ethics Committee (03–18) and the HTD Ethics Committee (CS/BND/18/27). For each participant, written informed consent was obtained from a parent/guardian, together with assent from children ≥ 12 years.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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