Early Predictors of Mortality in Children with Severe Dengue Fever: A Prospective Study

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Objective: The aim of the study was to identify early predictors of mortality in children with severe dengue fever admitted to pediatric intensive care unit (PICU).

Materials and Methods: All consecutive children with laboratory-confirmed severe dengue fever were enrolled in this prospective observational study. Besides demographic data, disease severity and organ dysfunction scores, laboratory investigations and interventions are done in PICU were recorded and analyzed.

Results: During the study period of 42 months, 172 patients with dengue fever were admitted to PICU. A total of 78 (45.3%) patients with severe dengue fever were included and analyzed. There were 20 (25.6%) deaths. There were significant differences in disease severity and organ dysfunction scores, transaminases, blood lactate level and serum creatinine between survivors and nonsurvivors. A significantly higher number of nonsurvivors required interventions in first 24 hours of admission. Platelet counts (*P* value 0.22) and hematocrit (*P* value 0.47) were not statistically different in 2 groups. There was a significantly high vasopressor—inotrope score (VIS) (<0.001) and positive fluid balance >10% (0.002) in nonsurvivors. Multivariate stepwise logistic regression analysis identified serum glutamic pyruvic transaminases (≥ 284 IU/L; odds ratio [OR] 1.002, 95% confidence interval [CI]: 1.001–1.003), blood lactate level (≥2.73 mmol/L; OR 2.08, 95% CI: 1.354–3.202), Pediatric Risk of Mortality score at 12 hours (≥14.5; OR 1.35, 95% CI: 1.077–1.693), VIS (≥22.5, OR 1.129, 95% CI: 1.059–1.204) and positive fluid balance >10% (OR 22.937, 95% CI: 2.393–219.84) at 24 hours of admission as independent predictors of mortality.

Conclusion: Disease severity, hyperlactatemia at admission, need for multiple vasoactive drugs and positive fluid balance are predictors of mortality in severe dengue infection in children admitted to PICU.

Key Words: dengue fever, pediatric intensive care unit, hyperlactatemia, fluid overload, outcome

(*Pediatr Infect Dis J* 2021;40:797–801)

Dengue fever, caused by single-stranded RNA virus (flavivirus), is the most rapidly spreading mosquito-borne viral disease in the world.[1] It is a major cause of morbidity and mortality in Southeast Asia, including India.[2] As per the National Vector Borne Disease Control Program data, in 2017, 157,220 dengue infections were reported in India with 250 deaths.[3] In 2009, the World Health Organization (WHO) revised the classification of dengue infection and proposed 7 warning signs that can be used to identify whether a person is at risk of severe dengue infection.[4] The utility and limitation of these 7 warning signs had been highlighted in adult and pediatric dengue infection.[5,6] Patients suffering from dengue fever with warning signs and severe dengue need hospitalization.[7] Patients with unstable hemodynamics, major bleeding, respiratory distress and organ failure are often admitted to critical care unit.[8] Lovera et al[9] from Paraguay reported 12% dengue shock children required at pediatric intensive care unit (PICU). Predicting outcomes of patients with severe dengue admitted to the critical care unit remain challenging. Very few studies have reported the predictors of mortality in adults and children with severe dengue infection admitted to the critical care units.[10,11] There is a need to identify early risk factors for death in children admitted to the PICU with severe dengue fever. Recognition of early risk factors would enable the critical care provider to triage, proper resource utilization and prognostication. The objective of our study was to identify early predictors of mortality in children with severe dengue fever admitted to tertiary level III PICU.

MATERIALS AND METHODS

This study was conducted at Sir Ganga Ram Hospital, New Delhi, located in the north part of India. It is a tertiary level, multispecialty teaching hospital with 12-bedded multidisciplinary medical and surgical PICU with separate 7-bedded pediatric cardiac ICU. In this prospective observational study, consecutive patients admitted to the PICU with laboratory-confirmed dengue infection between July 1, 2016 and December 31, 2019 were enrolled. Diagnostic tests included were reverse transcription-PCR amplification (Altona Diagnostics, Hamberg, Germany), NS1 antigen (Panbio Dengue Early ELISA, Standard Diagnostic Inc, Republic of Korea) and DENG IgM and DENG IgG antibodies (Dengue Duo, Standard Diagnostic Inc, Republic of Korea). Patients suffering from co-infections like enteric fever, Rickettsial fever, malaria, leptospirosis, septicemia and other viral hemorrhagic fevers along with dengue infection were excluded. The following data were captured on excel sheet-demography, clinical manifestations, Pediatric Index of Mortality (PIM) 2 score,[12] Pediatric Risk of Mortality (PRISM) scores at 12 and 24 hours,[13] Pediatric Logistic Organ Dysfunction (PELOD) score,[14] admission laboratory investigations, interventions were done within 24 hours of arrival to the PICU and final outcome. Vasopressor-inotrope score (VIS) was used to objectively compare the severity of shock.[15] Institutional ethical committee approval was obtained for the study.

Patients who had PCR or NS1 antigen test positive with DENG IgM antibodies positive and DENG IgG antibodies negative at admission were considered to have a primary dengue infection. In the absence of PCR or NS1 antigen test positive, positive DENG IgM antibodies with negative DENG IgG antibodies were also considered to be a primary infection. Patients with PCR or NS1 antigen test positive at admission with DENG IgG positive (with or without DENG IgM antibodies positive) were considered to have a secondary dengue infection.

Accepted for publication April 5, 2021

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The authors have no funding or conflicts of interest to disclose.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/21/4009-0797
DOI: 10.1097/INF.0000000000003179

Initial Fluid Management

In our unit, we start initially with normal saline at 3–5 mL/kg/h in hemodynamically stable, 5–10 mL/kg/h in the presence of poor perfusion with normal blood pressure and 10–20 mL/kg/h in hypoperfusion and hypotensive cases at the time of admission in the PICU. Hourly urine output, hemodynamic parameters, point of care hematocrit values, ultrasonography of lungs and functional echocardiography to assess the status of inferior venacava, ejection fraction and velocity–time integral were considered for further intravenous fluid therapy. If shock remained unresolved after 3 hours of fluid therapy, 1 g/kg albumin infusion was initiated over 2 hours. Intra-abdominal pressure was measured every 2 hours through indwelling urinary catheter in cases of nonresolving shock, hypoxemia, oliguria and worsening acidosis. When indicated, controlled drainage of peritoneal fluid under intra-abdominal pressure monitoring was done. Pigtail catheter was inserted under ultrasound guidance to minimize the risk of bleeding. Appropriate blood components were also used to prevent bleeding. Intake–output charting was done every hour and cumulative fluid balance was calculated after 24 hours.

Respiratory Support

Patients with increased work of breathing were provided with respiratory assist devices, high flow nasal cannulae, noninvasive ventilation with mask interface and invasive mechanical ventilation. The selection of the device was based on clinical assessment and oxygen saturation which was targeted above 92%.

Blood Component Therapy

Appropriate blood components, packed red blood cells, fresh frozen plasma, platelets transfusion, cryoprecipitate were used only in patients with major bleeding and when invasive procedures were performed. Platelet transfusion was also given in children with platelet counts ≤10,000/mm^3.

Fluid Removal Methods and Dialysis

Diuretics and albumin infusion in the presence of hypoalbuminemia were used for fluid overload state in hemodynamically stable patients. Renal replacement therapy (RRT), peritoneal dialysis (PD) or continuous RRT was used in diuretic resistant fluid overload state and in cases with established acute kidney injury (AKI). Pediatric Risk, Injury, Failure, Loss and End-stage renal disease (pRIFLE) criteria were used to identify AKI.[16] Organ dysfunction was defined according to previously published criteria.[17]

STATISTICAL ANALYSIS

Statistical testing was conducted with the statistical package for the Social Science System version SPSS 17.0 (SPSS, Chicago, IL). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Nominal categorical data between the groups were compared using χ^2 test or Fisher exact test as appropriate. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired *t* test, whereas the Mann-Whitney *U* test was used for those variables that were not normally distributed. For all statistical tests, a *P* value less than 0.05 was taken to indicate a significant difference.

To identify the potential factors associated with mortality, multivariate logistic regression model was used to identify independent risk factors for mortality after removing variables PIM2 and PRISM 24, which showed a strong sign of multicollinearity. Hosmer and Lameshow test value was 0.756 and Nagelkerke R^2 was 0.786. A stepwise approach was used to enter new terms into the model, with a limit of $P < 0.05$ to enter the terms.

RESULTS

During the study period of 42 months including 4 disease seasons, 172 patients with dengue fever were admitted to the PICU. Seventy-eight (45.3%) patients with severe dengue fever were included and analyzed (Supplemental Digital Content 1; http://links.lww.com/INF/E391). Of 78 patients, 27 (34.6%) patients had primary dengue infection and the rest had the secondary infection. The majority were male (49/78, 62.8%) and the median (interquartile range [IQR]) age was 10 (6.2–12) years. There was no difference in age (median; IQR 10 [6.7–12]) vs. 10 (5.7–14.7); $P = 0.67$) and gender distribution (67.2% vs. 50%; $P = 0.16$) between survivors and nonsurvivors. There was no significant difference (*P* value 0.5) in the duration of illness before PICU admission between survivors (mean ± SD; 4.36 ± 2.12 days) and nonsurvivors (4.7 ± 2.27 days). Admission characteristics and laboratory parameters are summarized in Tables 1 and 2. Fifty-four (69.2%) children had ≥2 organs dysfunction at admission. Respiratory and cardiovascular dysfunctions were commonest. AKI and multiorgan dysfunction syndrome (MODS) were present in 16 (80%) and 100% of nonsurvivors at admission ($P < 0.001$). Interventions done after admission in the first 24 hours are compared as shown in Table 3. Fifty-seven (73%) patients required mechanical ventilation at admission. Forty-five (57.7%) children required inotropes at admission to manage shock whereas 12 cases had fluid responsive shock. Pleural drainage and paracentesis were performed in 5 cases within 24 hours of admission. Multivariate logistic regression analysis identified admission serum glutamic pyruvic transaminases (SGPTs ≥ 284 IU/L), hyperlactatemia (≥2.73 mmol/L), PRISM score at 12 hours (≥14.5), VIS (≥22.5) and positive fluid balance >10% at 24 hours of admission as independent risk factors for mortality (Table 4). Operative characteristics of significant clinical and laboratory parameters are shown in Table 5. The nonsurvivors had a shorter stay in the PICU as compared with survivors (median, IQR 2 [2–9] vs. 5.5 [4–10]; $P = 0.03$). Twenty (25.6%) patients died, of which 11 (55%) expired within 48 hours of admission. There was 100% mortality in children with 5 organs dysfunction (Fig. 1).

TABLE 1. Comparison of Admission Parameters and Disease Severity Scores Between Survivors and Nonsurvivors

Variable	Survivors (n = 58)	Nonsurvivors (n = 20)	*P*
INR	1.3 (1.14, 1.54)	1.94 (1.42, 2.94)	<0.001
Platelets	31,000 (20,000, 55,250)	39,000 (26,000, 70,750)	0.22
PaO_2/FiO_2 ratio	278 (227, 374.5)	256 (179.5, 344.5)	0.65
S.Cr	0.6 (0.48, 0.92)	1.53 (0.6, 2.43)	<0.001
SGOT	291 (143, 1343.2)	2211.5 (357.7, 10,600)	0.001
SGPT	137 (62, 685.2)	1192.5 (291, 2864.2)	<0.001
S. Lactate	2.15 (1.6, 3)	6.23 (2.95, 9.65)	<0.001
PIM2	8.15 (5.4, 10.3)	19 (17.1, 21.4)	<0.001
PRISM 12	9 (5.7, 13.2)	16 (10.28)	0.001
PRISM 24	6 (3.7, 8)	22 (14, 31.5)	<0.001
PELODS Adm	3.5 (2, 12)	20 (5.2, 39.2)	<0.001
PICU stay (d)	5.5 (4, 10)	2 (2, 9)	0.03

Arterial blood lactate level in mmol/L; FiO_2, fraction of inhaled oxygen; INR, International normalized ratio; PaO_2, partial pressure of oxygen; PIM, Pediatric Index of mortality; PRISM, Pediatric Risk of Mortality score at 12 and 24 hours; PELODS, Pediatric Logistic Organ Dysfunction score at admission; PICU, pediatric intensive care unit; S.Cr, serum creatinine (mg/dl); SGOT, serum glutamic oxaloacetic transaminases (IU/L); SGPTs, serum glutamic pyruvic transaminases (IU/L); VIS, vasopressor-inotrope score.

TABLE 2. Comparison of Laboratory Parameters at Admission Between Survivors and Nonsurvivors

Parameter	Survivor (n = 58) n (%)	Nonsurvivor (n = 20) n (%)	*P*
PCV			
<30	10 (17.2)	6 (30)	
30–45	35 (60.3)	10 (50)	0.47
>45	13 (22.4)	4 (20)	
Platelets			
<50,000	16 (27.6)	8 (40)	
10,000–50,000	41 (70.7)	11 (55)	0.38
<10,000	1 (1.7)	1 (5)	
TLC			
<4000	7 (12.1)	3 (15)	
4000–10,000	40 (69)	7 (35)	0.01
>10,000	11 (19)	10 (50)	
INR			
>1.5	15 (25.9)	14 (70)	0.001
SGOT			
40–120	12 (20.7)	1 (5)	
121–1000	27 (46.6)	8 (40)	0.11
>1000	19 (32.8)	11 (55)	
SGPT			
<40	10 (17.2)	0	
41–120	18 (31)	5 (25)	0.03
121–1000	20 (34.5)	6 (30)	
>1000	10 (17.2)	9 (45)	
S. Cr			
≤1	46 (79.3)	6 (30)	
1.1–2.0	10 (17.2)	7 (35)	
≥2.1	2 (3.4)	7 (35)	<0.001
Lactate			
<2	25 (43.1)	1 (5)	
≥2	33 (56.9)	19 (95)	0.002

Arterial blood lactate level in mmol/L; INR, international normalized ratio; PCV, packed cell volume in percentage; Platelet count in cumm; SGOT, serum glutamic oxaloacetic transaminases in IU/L; SGPT, serum glutamic pyruvic transaminases in IU/L; Serum creatinine in mg/dL; TLC, total leukocyte count in cumm.

DISCUSSION

In this prospective observational study spanning over three and half years, we had 172 children admitted to PICU with dengue fever. All 94 children manifesting only warning signs survived whereas 58 of 78 children with severe dengue survived. High SGPT and serum lactate levels at admission, PRISM 12 score, high VIS and fluid overloading >10% at 24 of admission were independent predictors of mortality.

In 1997, WHO classified dengue infection into dengue fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[18] It emphasized the need for fluid administration and hemodynamic instability. Considering its limitations, WHO revised the classification in 2009.[1] The dengue infection cases were categorized into dengue fever with or without warning signs and severe dengue. A study categorizing cases using 1997 and 2009 classifications revealed sensitivity and specificity to capture ICU care for DHF/DSS were 39.0% and 75.5%, respectively, while sensitivity and specificity for severe dengue were 92.1% and 78.5%, respectively.[19] The high sensitivity of 2009 revised classification is likely to label large number of cases as severe dengue as suggested by Narvaez et al (positive predictive value 67.4%) while some patients may not be actually sick enough to require ICU care.[19] So there was a need to study clinical and laboratory parameters to capture patients of severe dengue requiring ICU monitoring and treatment.

TABLE 3. Comparison of Interventions in First 24 hours of Admission in Nonsurvivors and Survivors

Parameter	Survivor (n = 58)	Nonsurvivor (n = 20)	*P*
Albumin transfusion	30 (51.7)*	15 (75)	0.11
Mechanical ventilation	38 (65.5)	19 (95)	0.009
Platelet transfusion	27 (46.6)	18 (90)	0.004
Fluid balance (%)			
≤10	36 (62.1)†	4 (20)	
>10	22 (37.9)	16 (80)	0.002
VIS	00 (0–10)‡	40 (21.2, 65)	<0.001
RRT	13 (22.4)	15 (75)	<0.001

*Value in number and percentage.
†Cumulative fluid balance at 24 hours of admission.
‡Value median and interquartile range.
RRT, renal replacement therapy; VIS, vasopressor-inotrope score.

TABLE 4. Multivariate Logistic Regression Analysis

Parameter	Odds Ratio (95% CI)	*P*
Admission variable		
SGPT	1.002 (1.001–1.003)	0.007
S. Lactate	2.08 (1.354–3.202)	0.001
PRISM 12	1.35 (1.077–1.693)	0.009
Intervention variable		
VIS	1.129 (1.059–1.2040	<0.001
Fluid balance (>10%)	22.937 (2.393–219.84)	0.007

CI, confidence interval; PRISM, Pediatric Risk of Mortality score at 12 hr; SGPT, serum glutamic pyruvic transaminases in IU/L; VIS, vasopressor-inotrope score.

Clinical and routine laboratory findings had been studied to assess the risk of DHF or DSS in patients with dengue fever.[20–24] Common clinical features and laboratory findings associated with progression of severity of dengue were lethargy, hepatomegaly, persistent vomiting, pain abdomen, major gastrointestinal bleeding, hemoptysis, capillary leak, pleural effusion, ascitis, high transaminases, prolonged activated partial thromboplastin time and high hematocrit. Presence of thrombocytopenia and high or low leukocyte counts had inconsistent association with severity of dengue.[9,20] In present study, hematocrit and platelet counts were not different in survivors and nonsurvivors but high SGPT level (≥284 IU/L) differentiated the outcome. A study on Brazilian children did not find any abnormal laboratory finding as risk factor for death.[25] Mortality had been associated with severe refractory shock, disseminated intravascular coagulation, acute respiratory distress syndrome, hepatic failure and neurologic complication singly or in combination.[26] In present study, presence of AKI, need for high inotropes and vasopressors, and use mechanical ventilation were significantly higher in nonsurvivors.

With univariate analysis, we found disease severity and organ dysfunction scores (PIM 2, PRISM 12, 24 hours and PELOD score at admission) were significantly different in survivors and nonsurvivors. Interestingly, only PRISM 12 score was found to be independent predictors of mortality. In adult studies, APACHE II and SOFA scores were determined as independent risk factor for mortality in ICU.[10,27] A study from Taiwan found Glasgow Coma Score as determinant of mortality in adult ICU.[28]

Blood lactate estimation is frequently measured in critical care setting for the management of sick patients. With admission arterial blood lactate level ≥2.73 mmol/L, the risk of death was 2 times higher in our study. In a retrospective study from Malaysia in adult cases of severe dengue reported serum bicarbonate and lactate levels as mortality risk factors.[29] It had been reported that for every mmol/L increase in arterial lactates, the risk of mortality increases by a factor of 1.27.[30] We did not find any pediatric study on dengue fever reporting blood lactate level as risk factor as mortality predictor.

TABLE 5. Outcome Predictors

Variable	Cutoff	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Acc (%)	AUC ± SE (95% CI)	*P*
SGPT (IU/L)	<284 ≥284	80	69	47	90	71.8	0.77 ± 0.064 (0.64–0.89)	<0.001
S. Lactate (mmol/L)	<2.73 ≥2.73	90	72.4	53	96	77	0.85 ± 0.05 (0.75–0.95)	<0.001
PRISM 12	<14.5 ≥14.5	65	79.3	52	86.8	75.6	0.75 ± 0.07 (0.614–0.87)	<0.001 <0.001
VIS	<22.5 ≥22.5	75	94.8	83.3	91.7	89.7	0.88 ± 0.05 (0.78–0.98)	<0.001
FB (% at 24 hr)	≤10 >10	80	62	42	90	66.7	0.71 ± 0.065 (0.58–0.84)	0.002

Acc, accuracy; AUC, area under receiver operative characteristics curve; CI, confidence interval; FB, fluid balance at 24 hr of admission; NPV, negative predictive value; PRISM, Pediatric Risk of Mortality score at 12 hr of admission; PPV, positive predictive value; Sn, sensitivity; Sp, specificity; SE, standard error; SGPT, serum glutamic pyruvic transaminases; VIS, vasopressor-inotrope score.

Shock in severe dengue results from capillary plasma leak leading to hypovolemia, myocardial dysfunction and major hemorrhage particularly in gastrointestinal tract.[8] Meticulous fluid therapy with frequent clinical assessment, hourly urine output monitoring and point-of-care hematocrit estimation are required for early recognition. Role of bed-side ultrasonography and functional echocardiography is gaining popularity and are very useful tools to assess intravascular volume status, cardiac contractility including systolic and diastolic dysfunction and pericardial and pleural effusion and ascites.[31,32] Fifty-seven children in our cohort had shock at arrival in PICU. VIS was calculated as an objective tool to compare the survivors with nonsurvivors. Thirty patients had VIS ≥15 and 17 of these patients did not survive. Presence of shock had been reported in adult and pediatric literature as a poor outcome parameter but no previous study had used objective criteria for the severity of shock.[10,11,27,33]

Fluid overload state is associated with increased morbidity and mortality in critically ill children. It had been significantly associated with duration of mechanical ventilation, duration of PICU and hospital stay.[34] After adjustment for illness severity, there was a 6% increase in odds of mortality for every 1% increase in percentage fluid overload.[35] WHO emphasized meticulous fluid therapy in children with severe dengue infection to avoid fluid overload.[36] Children presenting with hypoperfusion with or without hypotension are at risk of fluid overload. Other risk factors include inappropriate use of hypotonic fluids, large volume and rapid infusion of fluid bolus, lack of fluid intake–output charting, continuation of intravenous fluid after the resolution of critical phase of illness, inappropriate use of blood components and presence of comorbidity or complications particularly renal and hepatic failure. Use of colloids is suggested in patients of refractory hypotension to prevent fluid overload.[7,8,35,37] We used 5% albumin instead of gelatins and starches in view of the potential adverse effects.[38,39] In our study, fluid balance more than 10% at 24 hours was an independent risk factor for poor outcome. This was in spite of conservative fluid administration from the start of treatment, frequent point of care hematocrit measurement and intensive hemodynamic monitoring including functional echocardiography. It might be extrapolated that liberal fluid administration in patients of dengue fever would have significant adverse effect on the outcome. For fluid overload state, frusemide infusion was used in hemodynamically stable patients without AKI. RRT was used in hemodynamically unstable patients and those with AKI. PD was initiated in 9 children and 19 children required continuous veno-venous hemodia-filtration. Similar approach to tackle fluid overload in severe dengue was reported previously.[11] Selection of RRT modality was based on the age, clinical status of the patient and feasibility and logistics. The final decision was in consultation with pediatric nephrologist.

Organ dysfunction is a frequent complication in patients of severe dengue infection. There may be a single or in combination of 2 or more organ dysfunction.[40] Severe organ impairment including hepatic failure, encephalitis or encephalopathy, acute renal failure and myocardial dysfunction is associated with high mortality even in the absence of plasma leakage and shock.[1] The mortality is directly related to the number of organs involved, more the organs dysfunctional higher is the mortality. In present study, 53 patients had MODS at presentation. The commonest combination was pulmonary and cardiovascular failure in 28.5%. There was also progressive increase in mortality with increase in number of organ failure.

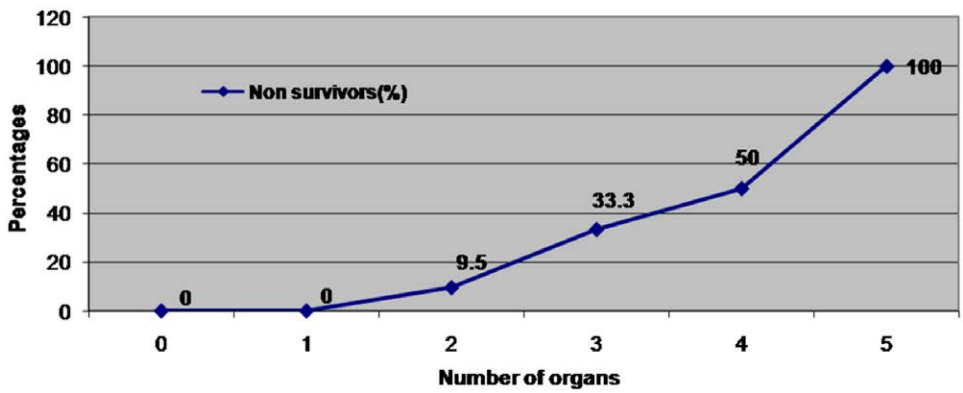

FIGURE 1. Association of number of organ dysfunction and proportion of nonsurvivors. full color online

In a study on pediatric MODS due to varied etiologies, patients with higher organ failure index scores had higher mortality.[41]

There are limitations and strengths in present study. It is a single-center study and only admission parameters of organ dysfunction and disease severity were studied. We did not follow the trends of these parameters during PICU course. Recently, there had been evolving interest in the serum ferritin levels in dengue infection.[42] We did not include serum ferritin and other inflammatory markers to avoid unnecessary financial burden on the parents. The strength of study includes prospective design and inclusion of patients with severe dengue who are at high-risk of mortality. We also analyzed pertinent parameters and interventions which were very important in the management of a critically ill child in the PICU setting.

CONCLUSION

Disease severity, hyperlactatemia at admission, need for multiple vasoactive drugs and positive fluid balance are predictors of mortality in severe dengue infection in children in PICU. Multicenter studies with large cohort of severe dengue patients and to correlate serial changes in organ dysfunction parameters with outcome are desirable.

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