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Original Article

Outcomes of Overt and Non-overt Disseminated Intravascular Coagulation Using the ISTH DIC Scoring System in Children: A Single-Center Study

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Abstract. ***Background:*** **Several disseminated intravascular coagulation (DIC) scoring systems are used for prognosticating the clinical outcomes of patients with DIC. However, research on children is scarce. Therefore, this study compared the clinical outcomes of overt and non-overt DIC using the International Society on Thrombosis and Hemostasis (ISTH) DIC scoring system.**
Methods**: This retrospective study reviewed data on children aged one month to 15 years diagnosed with DIC between 2003 and 2014.**
Results**: Of 244 patients, 179 (73.4%) had overt DIC, and 65 (26.6%) had non-overt DIC. The most common causes were infection (84.8%), tissue injury (7%), and malignancies (2.9%). The 28-day case fatality rate was significantly higher for overt than non-overt DIC (76% vs. 15.6%; $P < 0.001$). DIC scores were significantly associated with mortality ($R^2 = 0.89$). Each clinical parameter (platelet count, prothrombin time, and fibrin degradation products) was associated with mortality ($P = 0.01$). On multivariable analysis, the factors associated with death were platelet counts ≤ 50 000 cells/mm^3 (OR, 2.42; 95% CI, 1.08–5.42; $P = 0.031$); overt DIC score (OR, 7.62; 95% CI, 2.94–19.75; $P < 0.001$); renal dysfunction (OR, 2.92; 95% CI, 1.34–6.37; $P = 0.007$); shock (OR, 39.62; 95% CI, 4.99–314.84; $P = 0.001$); and acute respiratory distress syndrome (OR, 25.90; 95% CI, 3.12–214.80; $P = 0.003$).**
Conclusions**: The 28-day case-fatality rate was significantly higher for patients with overt than non-overt DIC and concordant with ISTH scores. ISTH DIC scores can be used as a clinical predictor for DIC in children.**

Keywords: Children; DIC; Infection; Mortality.

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Introduction. Disseminated intravascular coagulation (DIC) is caused by excessive hemostatic system activation. The disease leads to consumptive coagulopathy, microthrombi formation, and severe

bleeding. Ultimately, it results in multiorgan dysfunction, manifested in conditions such as trauma, malignancy, and sepsis.[1] DIC is responsible for mortality in such conditions in both child and adult patients.[2,3]

Several scoring systems have demonstrated value in diagnosing DIC. The International Society on Thrombosis and Haemostasis (ISTH) DIC scoring system draws upon prothrombin time, platelet count, fibrinogen, and D-dimer levels, and it has been widely studied in mainly adult patients with DIC.[4] The ISTH DIC system can prognosticate the outcomes of patients in critical condition due to sepsis and non-sepsis etiologies.[5,6] Nevertheless, research on the efficacy of the scoring system for the pediatric population is scarce. Therefore, evaluating ISTH DIC scores in children with DIC may assist physicians in predicting clinical outcomes. This study aimed to evaluate and compare the clinical outcomes of children with overt DIC and non-overt DIC using the ISTH scoring system.

Patients and Methods. This retrospective study was performed on patients aged 28 days to 15 years who had been diagnosed with DIC during admission at Siriraj Hospital, Mahidol University, Thailand, between January 2005 and December 2014. The clinical parameters of the patients at admission were rated using the ISTH DIC scoring system as follows:[4]

- Platelet count: > 100 000 cells/mm^3 = 0 points; between 50 000 and 100 000 cells/mm^3 = 1 point; and < 50 000 cells/mm^3 = 2 points
- Prolonged prothrombin time: < 3 seconds = 0 points; between 3 and 6 seconds = 1 point; and > 6 seconds = 2 points
- Fibrinogen level: > 100 mg/dL = 0 points, and < 100 mg/dL = 1 point
- D-dimer level: no increase = 0 points; moderate increase = 2 points; and strong increase = 3 points

The patients were classified into two groups: (1) "overt DIC", for those with ISTH DIC scores ≥ 5, and (2) "non-overt DIC", for patients with ISTH DIC scores < 5.

Patients who were previously diagnosed with DIC were treated with blood components within 24 hours before the diagnosis of DIC or had incomplete laboratory parameters of the ISTH DIC scoring system were excluded. Specific organ dysfunctions were classified according to the international pediatric sepsis consensus conference[7] as follows.

Central nervous system dysfunction was defined as a Glasgow coma score ≤ 11 or decreased Glasgow coma score ≥ 3 from baseline.

Respiratory system dysfunction was defined as the ratio of partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2), PaO2/FiO2 < 300 without evidence of cyanotic heart disease and preexisting pulmonary disease or PaCO2 > 65 torr or > 20 mmHg of baseline or requiring oxygen FiO2 > 0.5 to maintain oxygen saturation ≥ 92% or requiring non-elective invasive or non-invasive mechanical ventilator

Renal dysfunction was defined as the serum creatinine ≥ 2 times for age or increased serum creatinine > 2 times from baseline.

Hepatic dysfunction was defined as total bilirubin ≥ 4 mg/dL or alanine transaminase > 2 times from baseline.

Descriptive statistics were used to detail demographic and clinical characteristic data. Continuous data are presented as medians and ranges, while categorical data are reported as numbers and percentages. Pearson's chi-squared test was used to compare the proportions of groups with categorical data, and Student's t-test or the Mann–Whitney U test was used to compare medians for continuous data. Univariable and multivariable predictors of death were evaluated using binary logistic regression analysis (backward method), with results presented as the odds ratio (OR) and 95% confidence interval (CI). A probability (*P*) value < 0.05 was considered statistically significant. All analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc, Chicago, IL, USA).

Results. Of the 67 992 inpatient cases, 244 patients were diagnosed with DIC, giving a frequency of DIC of 0.35. There were 118 male patients (48.4%) and 126 female patients (51.6%); the age group breakdown of 1 month – 1 year, 1-5 years, 5-10 years, and more than 10 years were 71 (29.1%), 78 (32%), 50 (20.5%) and 45 (18.4%) patients, respectively. Infection was the most common cause of DIC (84.8%), with tissue injury being the second most common cause (7%); other causes are detailed in **Table 1**. Gram-negative bacterial infection was the most common cause of infection-associated DIC. The other causative organisms are detailed in **Table 2**. Of the 17 patients with DIC secondary to tissue injury and surgery, open-heart surgery for congenital heart disease (9 patients) was the most common cause. Postorgan transplantation ranked second with 5 patients (liver transplantation, 4 patients; kidney transplantation, 1 patient), followed by intra-abdominal surgery (2 patients) and thermal injury (1 patient). There were 7

Table 1. Underlying causes of DIC.

Underlying condition	Number of patients with DIC (%)
Infection	207 (84.8)
Tissue injury	17 (7)
Malignancy	7 (2.9)
Acute liver failure	2 (0.8)
Microangiopathic disorders	3 (1.2)
Others	8 (3.3)
Total	244

DIC, disseminated intravascular coagulation.

Table 2. Causative organisms of DIC.

Organisms	Number of patients (n, %)
Bacteria	
1.1 Gram-positive septicemia	35 (14.3)
Coagulase-negative Staphylococci	3 (1.4)
Methicillin-resistant *Staphylococcus aureus*	4 (1.9)
Methicillin-resistant coagulase-negative staphylococci	13 (6.3)
Methicillin-sensitive *Staphylococcus aureus*	7 (3.3)
Streptococcus pneumonia	2 (0.9)
Enterococcus faecalis	4 (1.9)
Streptococcus agalactiae	2 (0.9)
1.2 Gram-negative septicemia	55 (26.5)
Acinetobacter baumannii	14 (6.7)
Pseudomonas aeruginosa	5 (2.4)
Klebsiella pneumonia	16 (7.7)
Escherichia coli	13 (6.3)
Salmonella spp.	3 (1.4)
Enternobacter cloacae	2 (0.9)
Stenotrophomonas maltophilia	2 (0.9)
1.3 Sepsis unspecified	78 (37.6)
Viruses	
1.4 Dengue	12 (5.8)
1.5 Influenza	6 (2.8)
1.6 Cytomegalovirus	4 (1.9)
1.7 Human immunodeficiency virus	2 (0.9)
1.8 Epstein-Barr virus	1 (0.4)
1.9 Enterovirus	1 (0.4)
Fungi	
1.10 *Candida* spp.	6 (2.8)
1.11 *Aspergillus* spp.	1 (0.4)
1.12 *Penicillosis* spp.	1 (0.4)
Others	
1.13 Disseminated tuberculosis	3 (1.4)
1.14 Disseminated strongyloidiasis	1 (0.4)
Total	207 (100)

DIC, disseminated intravascular coagulation.

patients with malignancies; of these, hematologic malignancies (4 patients) were the most common cause (2 patients with acute lymphoblastic leukemia, 1 patient with acute myeloid leukemia, and 1 patient with non-Hodgkin lymphoma). The other 3 patients had solid tumors: 1 with hepatoblastoma, another with neuroblastoma, and the third with an endodermal sinus tumor. Hemorrhage was the most common manifestation (153 patients; 62.7%), with gastrointestinal hemorrhage being the most common site (41.8%), followed by endotracheal hemorrhage (24.2%) and hematuria (7.8%). Thrombosis was diagnosed in 20 patients (8.1%); venous thrombosis was the most common site (45%), followed by peripheral gangrene (40%).

The laboratory parameters of the patients with overt and non-overt DIC are compared in **Table 3**. Of the 244 patients with DIC, 179 (73.3%) were diagnosed with overt DIC, and the remaining 65 (26.7%) had non-overt DIC. The 28-day case fatality rate for overt DIC (76%) was significantly higher than that for non-overt DIC (15.4%; $P < 0.001$). The median time from the diagnosis of DIC to death was 7.1 days (0–37 days), while the median time from diagnosis of DIC to recovery was 14 days (2–61 days). The correlation between mortality and the ISTH DIC scores is illustrated in **Figure 1** ($R^2 = 0.89$).

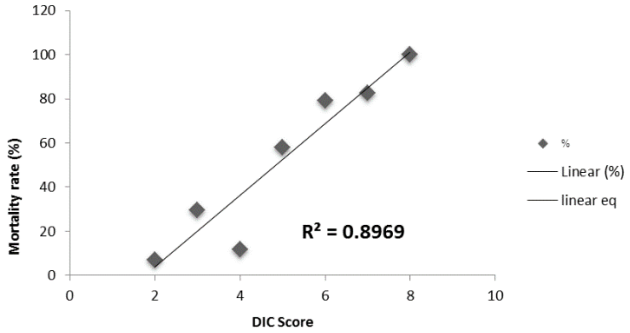

Figure 1. Correlation between the DIC scores and the 28-day case fatality rate.

In terms of admission, 209 patients (85.7%) were admitted to the intensive care unit (ICU), whereas the other 35 patients (14.3%) were not. The rates of ICU admission of the patients with overt and non-overt DIC were not significantly different ($P = 0.129$). Anticoagulant was prescribed for 9 patients; the most commonly used anticoagulant was unfractionated heparin (4 patients), followed by low molecular weight heparin (3 patients) and warfarin (2 patients). Of the 9 patients requiring anticoagulant therapy, 4 had venous thrombosis, 4 had arterial thrombosis, and one prophylactically received an anticoagulant to prevent clotting after cardiac surgery. Recombinant factor VIIa was prescribed for 9 patients. Neither treatment-associated hemorrhage nor thrombosis was observed. The most typical indication was dengue hemorrhagic fever with severe hemorrhage (6 patients). The other indications were cancer with severe hemorrhage (2 patients) and chronic liver disease requiring a postsurgery bleeding prophylactic (1 patient). The factors associated with the death of DIC patients are presented in **Table 4**, and the laboratory parameters of the decedents and survivors are compared in **Table 5**. Univariable and multivariable factors associated with death in DIC are detailed in **Table 6**.

Discussion. Studies regarding DIC in children are scarce. Oren et al. reported that the frequency of DIC in the pediatric population was 1.12 hospitalized in a Turkey University Hospital,[8] similar to the present study's finding of 0.35. However, the frequency in children is lower than in adults (34.4).[9] Additionally, the present

Table 3. Comparison of laboratory parameters of patients with overt and non-overt DIC.

Parameter	Patients with overt DIC N = 179	Patients with non-overt DIC N = 65	*P* value
Hemoglobin, mean ± SD (g/dl)	10.19 ± 2.94	9.84 ± 2.94	0.419
White blood cell, median (IQR) (cell/mm^3)	8550 (2640–15 470)	8600 (4785–15 155)	0.513
Platelet count, median (IQR) (cell/mm^3)	35 000 (21 000–550 000)	76 000 (46 500–109 000)	< 0.001
Prothrombin time, median (IQR) (sec)	22.70 (19.20–29.10)	15.30 (13.55–17.15)	< 0.001
D-dimer, median (IQR) (µg/ml)	4.80 (2.57–9.72)	2.02(1.17–3.90)	< 0.001
Fibrinogen, median (IQR) (mg/dl)	171.50 (112.70–326.00)	251.90 (170.00–353.40)	0.002
APTT, median (IQR) (sec)	51.50 (39.20–72.80)	36.20 (28.25–46.10)	< 0.001
AST, median (IQR) (U/L)	152.50 (52.50–659.50)	51.50 (32.00–171.50)	< 0.001
ALT, median (IQR) (U/L)	81 (29–307)	30 (17–65)	< 0.001
TB, median (IQR) (mg/dl)	1.90 (0.70–7.10)	0.70 (0.30–2.87)	< 0.001
DB, median (IQR) (mg/dl)	0.85 (0.28–4.25)	0.13 (0.05–0.71)	< 0.001
BUN, median (IQR) (mg/dl)	21.70 (11.50–38.00)	11.10 (6.60–22.35)	< 0.001
GFR, median (IQR) (ml/min/1.73 m^2)	44.80 (27.80–90.83)	81.30 (46.25–120.0)	0.002
Albumin, mean ± SD (g/dl)	2.88 ± 0.62	3.04 ± 0.59	0.083

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; DB, direct bilirubin; DIC, disseminated intravascular coagulation; GFR, glomerular filtration rate; SD, standard deviation; TB, total bilirubin.

Table 4. Factors associated with death of DIC patients.

Factor	Death n (%)	Survive n (%)	Odds ratio (95% CI)	*P* value
Total	146	98		
Ward				
Non-ICU	13 (8.9)	22 (22.4)	2.96 (1.41–6.22)	0.003
ICU	133 (91.1)	76 (77.6)		
ISTH score				
Non-overt DIC	10 (6.8)	55 (56.1)	17.40 (8.17–37.05)	< 0.001
Overt DIC	136 (93.2)	43 (43.9)		
Sex				
Male	71 (48.6)	47 (48.0)	0.97 (0.58–1.63)	0.918
Female	75 (51.4)	51 (52.0)		
Underlying conditions				
Infection	121 (82.9)	86 (87.8)	0.67 (0.32–1.42)	0.298
Malignancy	6 (4.1)	1 (1.0)	4.15 (0.46–17.70)	0.247
Tissue injury	11 (7.5)	6 (6.1)	1.24 (0.45–3.50)	0.671
Liver failure	2 (1.4)	0 (0)	NA	0.517
Microangiopathic disorder	1 (0.7)	2 (2)	0.33 (0.03–3.70)	0.566
Miscellaneous	5 (3.4)	3 (3.1)	1.12 (0.26–4.81)	1.000
Clinical presentations				
Bleeding	153 (62.7)	124 (69.3)	2.87 (1.68–4.92)	<0.001
Thrombosis	12 (8.2)	8 (8.2)	1.01 (0.57–1.76)	0.988
CNS dysfunction	49 (33.6)	14 (14.3)	3.03 (1.56–5.88)	0.001
CVS dysfunction	146 (100)	61(62.2)	3.39 (2.75–4.19)	< 0.001
RS dysfunction	145 (99.3)	63 (64.3)	80.5 (10.80–601.0)	< 0.001
Renal dysfunction	112 (76.7)	41 (41.8)	4.58 (2.63–7.98)	< 0.001
Hepatic dysfunction	88 (60.3)	37 (37.8)	2.50 (1.48–4.23)	0.001
Shock	145 (99.3)	59 (60.2)	95.8 (12.87–713.82)	< 0.001
MODS	146 (100)	64 (65.3)	NA	< 0.001
ARDS	44 (30.1)	1 (1.0)	41.84 (5.65–309.65)	0.001

Factor	Death n (%)	Survive n (%)	Odds ratio (95% CI)	*P* value
Treatment				
Blood component	146 (100)	94 (95.9)	NA	0.025
Inotropic	143 (97.9)	59 (60.2)	31.51 (9.37–105.96)	< 0.001
Ventilator	136 (93.2)	62 (63.3)	7.90 (3.69–16.92)	< 0.001
Albumin	108 (74)	37 (37.8)	4.69 (2.70–8.13)	< 0.001
Anticoagulant	5 (3.4)	4 (4.1)	0.83 (2.22–3.18)	1.000
Recombinant factor VIIa	7 (4.8)	2 (2.0)	2.78 (0.58–13.39)	0.263
Vitamin K	128 (87.7)	72 (73.5)	2.57 (1.32–5.00)	0.005
Tranexamic acid	7 (4.8)	3 (3.1)	1.59 (0.40–6.32)	0.744
Dialysis	46 (31.5)	8 (8.2)	5.18 (2.32–11.55)	< 0.001
Antibiotic	146 (100)	97 (99.0)	NA	0.402
Age at diagnosis (years)				
1 month to 1 years	44 (30.1)	27 (27.6)	1.09 (0.51–2.34)	0.832
> 1–5 years	45 (30.8)	33 (33.7)	0.91 (0.43–1.92)	0.802
> 5–10 years	30 (20.5)	20 (20.4)	1.00 (0.44–2.75)	1.00
> 10 years	27 (18.5)	18 (18.4)	1	
Age at diagnosis (years)				
≤ 10	119 (81.5)	80 (81.6)	0.99 (0.51–1.92)	0.980
> 10	27 (18.5)	18 (18.4)	1	

ARDS, acute respiratory distress syndrome; CNS, central nervous system; DIC, disseminated intravascular coagulation; ICU, intensive care unit; ISTH, International Society on Thrombosis and Haemostasis; MODS, multiple organ dysfunction syndrome; NA, not available; RS, respiratory system.

Table 5. Comparison of laboratory parameters of decedents and survivors.

Laboratory	Death	Survive	*P* value	Odds ratio (95% CI)
Hemoglobin, mean ± SD (g/dl)	10.28 ± 3.05	9.82 ± 2.76	0.225	1.06 (0.97–1.15)
White blood cell, median (IQR)	8560 (2620–15 620)	8530 (4460–14 910)	0.484	0.99 (0.99–1.00)
Platelet count, median (IQR) (cell/mm^3)	35 000 (21 000–55 0000)	62 000 (31 000–89 050)	< 0.001	0.98 (0.98–0.99)
Prothrombin time, median (IQR) (sec)	22.40 (19.20–29.20)	16.75 (14.10–19.90)	< 0.001	1.14 (1.08–1.19)
D-dimer, median (IQR) (ng/ml)	4453.21 (2379.68–9720.8)	3214.52 (1445.70–6491.71)	0.010	1.01 (1.01–1.02)
Fibrinogen, median (IQR) (mg/dl)	175.45 (118.50–345.90)	236.20 (128.80–347.70)	0.141	1.00 (0.99–1.00)

Table 6. Univariable and multivariable factors associated with death.

Factors	Univariable		Multivariable	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age at diagnosis > 10 years	1.01 (0.52–1.95)	0.980	–	–
Platelet ≤ 50 000/mm^3	3.66 (2.13–6.29)	< 0.001	2.42 (1.08–5.42)	0.031
Prothrombin time ≥ 20 sec	7.39 (4.13–13.22)	< 0.001	–	–
Strong increased D-dimer	2.08 (1.24–3.50)	0.006	–	–
Fibrinogen < 100 mg/dl	2.28 (1.06–4.90)	0.036	–	–
Overt DIC score	17.40 (8.17–37.05)	< 0.001	7.62 (2.94–19.75)	< 0.001
Bleeding	2.88 (1.68–4.92)	< 0.001	–	–
CNS dysfunction	3.03 (1.56–5.88)	0.001	–	–
RS dysfunction	80.56 (10.80–601.0)	< 0.001	–	–
Renal dysfunction	4.58 (2.63–7.98)	< 0.001	2.92 (1.34–6.37)	0.007
Hepatic dysfunction	2.50 (1.48–4.23)	0.001	–	–
Shock	95.85 (12.87–713.82)	< 0.001	39.62 (4.99–314.84)	0.001
ARDS	41.84 (5.65–309.65)	< 0.001	25.90 (3.12–214.80)	0.003

ARDS, acute respiratory distress syndrome; CNS, central nervous system; DIC, disseminated intravascular coagulation; RS, respiratory system.

investigation found that infections were the most common etiology of DIC, which is consistent with previous studies on adults and children.[8,9] On the other hand, the proportion of children in the current study with infection (approximately 80%) is markedly higher than the corresponding levels previously reported for adults (30%–40%).[10] Furthermore, the rate of malignancy-related DIC seems lower in children than adults, which may indicate differences in the etiologies of the disease in children and adults. Prevalent in tropical regions, dengue hemorrhagic fever can cause thrombocytopenia, plasma leakage, and decreased coagulation factors secondary to hepatic derangement, the combined effects of which lead to DIC.[11] Dengue hemorrhagic fever was the most common cause of viral-associated DIC in the present study; however, this phenomenon might be uncommon in countries where dengue is not endemic. Similarly, our investigation determined that tropical diseases such as disseminated tuberculosis and strongyloidiasis also caused DIC. Therefore, physicians in tropical regions caring for patients with such diseases should be aware of DIC as a peculiar clinical manifestation.

The hemostasis in infants, especially neonates, differs from that in adults. The decreased coagulation factors and natural anticoagulants gradually reach the normal level at approximately six months of age, leading to the counterbalance of hemostasis.[12] The prolonged prothrombin time in such patients might not reflect the proper hemostasis. Therefore, in this cohort, neonates with DIC were excluded from the study.

The clinical severity of hemorrhage and organ failure might be related to the etiologies of DIC in adults. Research on adults showed that multiorgan failure was prevalent in infection-associated DI; in contrast, hemorrhage was common in noninfectious-associated DIC.[13,14] Furthermore, the bleeding tendency in these adult studies appeared to be lower than that of the present pediatric study. The different populations and DIC etiologies of the adult and pediatric investigations may account for the variations in the observed clinical manifestations. The present work identified a thrombosis incidence of 8.1%, comparable with other studies on adult and pediatric populations, and neither arterial nor venous sites predominated.[8,15] Consequently, clinical vigilance of thromboembolic complications is needed in both pediatric and adult patients with DIC. In terms of treatment-associated both hemorrhagic and thrombotic complications, such complications were not observed in this cohort; this may result from the scarcity of patients treated with recombinant factor VIIa, tranexamic acid, and anticoagulant.

Concordant with other studies,[16,17] the 28-day case fatality rate of children with overt DIC or those with organ dysfunction requiring advanced organ support was significantly higher than that for children with non-overt DIC. Additionally, mortality was significantly correlated with the ISTH DIC score and the clinical parameters platelet number, prothrombin time, and D-dimer. Similarly, our multivariable analysis revealed that overt DIC and thrombocytopenia below 50 000/mm^3 were associated with death. These results substantiate the role of the ISTH DIC scoring system in predicting the clinical outcomes of DIC in the pediatric population, with platelet number possibly being a pivotal clinical factor in prognosticating the risk of death in DIC. Although other factors (underlying diseases and age at diagnosis) were not significantly associated with mortality, preexisting cancer tended to be correlated with mortality. Therefore, patients with a high ISTH DIC score, especially those with preexisting cancer, should be closely monitored, and treatment interventions for underlying diseases should be delivered promptly.

Compared to the score of 5, the ISTH score of 3 demonstrated a better mortality prediction in sepsis-associated DIC.[18] Furthermore, other DIC scoring systems, namely Texas Children's Hospital criteria[19] and Japanese Association for Acute Medicine criteria[20] were previously described and demonstrated a good prediction of clinical outcome. However, the former system required sequential evaluation by specialists while the latter required the anti-thrombin level, which was somewhat not performed; these scoring systems might not be applicable in our institute. Taken together, the heterogeneity of results and scoring system substantiated the warrant of further investigation of scoring systems in the pediatric population.

This study had some limitations. First, since this was a retrospective study, there is the possibility of missing or incomplete data. Second, given that the population was drawn from a national tertiary referral hospital, where some tropical diseases appeared to be prevalent, the data may not be generalized to other populations or clinical settings; therefore, the prevalence and causation of DIC may vary from other studies.

Conclusions. Infection was the most common cause of DIC. The children with overt DIC had a higher mortality rate than those with non-overt DIC. The ISTH scoring system can predict the clinical outcomes of children with DIC.

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