Disseminated Intravascular Coagulation Is an Independent Predictor of Adverse Outcomes in Children in the Emergency Department with Suspected Sepsis

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Objective To evaluate the impact of early disseminated intravascular coagulation (DIC) on illness severity in children using a database of emergency department ED encounters for children with suspected sepsis, in view of similar associations in adults.

Study design Laboratory and clinical data were extracted from a registry of emergency department encounters of children with suspected sepsis between April 1, 2012, and June 26, 2017. International Society of Thrombosis and Hemostasis DIC scores were calculated from laboratory values obtained within 24 hours of emergency department admission. Univariate logistic regression, multivariable logistic regression, and Cox regression were used to assess the influence of DIC scores on vasopressor use (primary outcome), mortality, ventilator requirement, pediatric intensive care unit admission, and hospital duration (secondary outcomes). The optimal DIC score cutoff for outcome prediction was determined.

Results Of 1653 eligible patients, 284 had DIC scores within 24 hours, including 92 who required vasopressors and 23 who died within 1 year. An initial DIC score of ≥3 was the most sensitive and specific DIC score for predicting adverse outcomes. Those with a DIC score of ≥3 vs <3 had increased odds of vasopressor use in both univariate (OR, 4.48; 95% CI, 2.63-7.62; $P < .001$) and multivariable (OR, 3.78; 95% CI, 1.82-7.85; $P < .001$) analyses. Additionally, those with a DIC score of ≥3 vs <3 had increased 1-year mortality with a hazard ratio of 3.55 (95% CI, 1.46-8.64; $P = .005$).

Conclusions A DIC score of ≥3 was an independent predictor for both vasopressor use and mortality in this pediatric cohort, distinct from the adult overt DIC score cutoff of ≥5. *(J Pediatr 2020;225:198-206)*.

Disseminated intravascular coagulation (DIC) is a state of hemostatic dysregulation causing microvascular clotting and consumptive coagulopathy that is seen in a variety of conditions, including sepsis, trauma, and malignancy. Each of these conditions causes cytokine-induced endothelial and mononuclear cell release of tissue factor and generation of excessive thrombin extending outside the local area of injury along with release of fibrinolytic proteins.[1,2] Excessive thrombin generation leads to microvascular thrombi with consumption of platelets, procoagulant and anticoagulant proteins, and inhibition of fibrinolysis, all of which contribute to multiorgan failure.[2]

The predominant condition leading to DIC is sepsis, a major cause of morbidity and mortality in children, affecting >75 000 children per year in the US with estimated mortality rates of 7%-10% across all age groups.[1-6] Organ system dysfunction has been shown to correlate with pediatric sepsis outcome, but measures of hematologic dysfunction in pediatric sepsis have been limited to platelet count, or platelet count and international normalized ratio.[4,7]

The International Society of Thrombosis and Hemostasis (ISTH) delineates overt DIC in a patient with a known associated clinical condition, using a DIC score cutoff of ≥5 based on defined laboratory deviation of platelet count, prothrombin time (PT), fibrin split products (commonly D-dimer), and fibrinogen, although the score was derived from adult data.[8-10] The acronym DIC

CRP	C-Reactive protein
DIC	Disseminated intravascular coagulation
ED	Emergency department
HR	Hazard ratio
ISTH	International Society of Thrombosis and Hemostasis
JAAM	Japanese Academy of Acute Medicine
PICU	Pediatric intensive care unit
PT	Prothrombin time
ROC	Receiver operator characteristic

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was previously noted to be synonymous with "death is coming," reflecting the high mortality rate associated with DIC.[11] Several studies in adults have shown an increased risk of mortality or other poor outcome in patients with overt DIC as defined by the ISTH scoring system.[2,10,12] In an effort to decrease mortality rates in severe sepsis, 3 randomized controlled trials in adults have used anticoagulant factor replacement (antithrombin, tissue factor pathway inhibitor, or activated protein C) to correct sepsis-associated DIC.[13-15] Although all trials failed to show overall survival benefit, subgroup analyses of activated protein C and antithrombin trials showed decreased mortality in the subsets with overt DIC at study entry.[2,16,17] Although a few studies have shown increased risk of mortality in children with overt DIC using these criteria, the uncertainty over applicability of the ISTH definition of DIC to children with less developed hemostatic systems has led to application of diverse scoring systems in pediatric studies.[1,3,18-22]

The aim of this study was to evaluate early ISTH DIC scores as potential predictors of negative outcomes in children presenting to a pediatric tertiary care emergency department (ED) with concern for sepsis, the most common cause of DIC in children.[1] This topic is of particular interest in the era of increasing emphasis on early recognition of end-organ dysfunction and early intervention as a means to improve outcomes in critically ill patients.[17,23,24]

Methods

This observational cohort study took place at an academic tertiary care pediatric hospital with >75 000 ED visits annually, using the Colorado Sepsis Treatment and Recognition Registry. This is a previously established prospective clinical sepsis registry approved by the Children's Hospital Colorado Organization Research Risk and Quality Improvement Review Panel and the Colorado Multiple Institution Review Board (#13-2364). The registry contains data from the Electronic Health Record, including patient demographics, vital signs, medication administration, timing of care events, laboratory values, procedures (such as intubation and lumbar puncture), and hospital events (such as length of stay and mortality), as previously described by Scott et al.[25] Patient encounters were identified in 2 ways. Patients were included if the ED sepsis protocol was activated based on clinical suspicion for sepsis, generally following consensus sepsis definitions and American College of Critical Care Medicine guidelines for sepsis recognition, although the clinical suspicion did not require systemic inflammatory response syndrome criteria to be met.[7,26,27] In addition, ED encounters were screened monthly for cases of severe sepsis missed by the automated system and added as previously described.[25] Data were downloaded into a REDCap database and a deidentified dataset was exported for analysis.

Cohort Selection

This study included all pediatric patients presenting with suspected sepsis to the ED at a tertiary pediatric center between April 1, 2012, and June 26, 2017. Laboratory evaluation was performed at provider discretion, but DIC laboratory tests were included in the ED sepsis order set and recommended for patients who appeared critically ill. Exclusion criteria included age <60 days or >18 years, transfer from another facility, hospital length of stay of <24 hours, current anticoagulation therapy, neonatal intensive care unit admission, and vasopressor initiation before collection of the laboratory values of interest. In patients with multiple ED encounters, the first encounter with a full DIC evaluation within 24 hours of ED admission was chosen for analysis. If the patient had multiple encounters but did not have a DIC evaluation, the first encounter was used. Clinical data were extracted from the EMR including age, sex, chronic comorbidities, provider sepsis protocol activation, DIC score components (platelet count, fibrinogen, PT, D-dimer), initial lactate level (dichotomized as ≥4 mmol/L vs <4 mmol/L),[25] and C-reactive protein (CRP; dichotomized as above normal for laboratory vs below normal for laboratory, ≥0.9 mg/dL vs <0.9 mg/dL), vasopressor use, mechanical ventilation requirement above baseline, hospital and pediatric intensive care unit (PICU) length of stay, and presence of end-organ dysfunction as defined by the International Pediatric Sepsis Consensus Conference (Goldstein criteria).[7] DIC scores were calculated based on the ISTH criteria[19] as follows: (1) platelet count: >100 000/μL = 0 points, 50 000-100 000/μL = 1 point, <50 000/μL = 2 points; (2) D-dimer: no increase (<0.5 μg/mL) = 0 points, moderate increase (0.5-3.0 μg/mL) = 2 points, strong increase (>3 μg/mL) = 3 points; (3) PT prolongation above the upper limit of normal: ≤3 seconds = 0 points, 3-6 seconds = 1 point, ≥6 seconds = 2 points, (4) fibrinogen: ≥100 mg/dL = 0 points, <100 mg/dL = 1 point (**Table I**; available at www.jpeds.com). The platelet count was additionally analyzed by threshold levels used in the DIC score proposed by the Japanese Academy of Acute Medicine (JAAM) where platelet count was scored 1 point for count <120 000/μL and 2 points for <80 000/μL.[28,29] The JAAM platelet criteria also include points for serial decreases in platelet count, which we were not able to assess using this dataset.

The general practice for treatment of DIC during the study period was to treat the underlying disorder and to support with blood products as needed for bleeding or with invasive procedures. Replacement of antithrombin was not routinely practiced, and tissue factor pathway inhibitor, activated protein C, and thrombomodulin concentrates were not available in the US during the time of this study.

Statistical Analyses

The primary outcome was the relationship between ISTH DIC score and the requirement of vasopressors during hospital admission. The need for vasopressors was used as a surrogate marker of illness severity given the low overall mortality in the pediatric population. Secondary outcomes included

all-cause mortality, hospital and PICU length of stay, duration of vasopressor use, requirement and duration of mechanical ventilation during hospitalization, procedures performed during hospitalization including intubation and lumbar puncture, and end-organ dysfunction. Because of the lack of clear applicability of the adult ISTH DIC score cutoff in pediatrics, proportional stacked bar graphs of vasopressor use and mortality rates with each DIC score were created, and receiver operator characteristic (ROC) curve sensitivity analysis was performed to determine the most appropriate dichotomous DIC score cutoff. Univariate logistic regression analyses for the primary outcome were performed with both continuous and dichotomous DIC score. Secondary outcomes were also assessed with the dichotomous DIC score using univariate logistic regression.

Multivariable regression analysis tested the predictive power of the dichotomous DIC score relative to CRP and lactate levels obtained within 24-hours of ED arrival. CRP and lactate levels were included in the analysis because they are commonly tested biomarkers that are known to be predictive of poor outcomes in this setting.[25,30] They were included in the multivariable regression to evaluate whether or not DIC scores would add additional benefit in predicting outcomes. Time to mortality and hazard ratios (HRs) were assessed using Cox regression analyses. All ORs were calculated using logistic regression analysis. Statistical analyses and data visualization were performed using SPSS v26 and R v3.6 (https://www.r-project.org/).

Results

The study flow diagram is shown in **Figure 1** (available at www.jpeds.com). Of 3053 children with potential sepsis, 1400 met exclusion criteria. Of the remaining 1653 children, laboratory components of ISTH DIC scores were obtained within the first 24 hours of presentation to the ED in 284 children (17.2%), with 160 (56%) male, and a mean (±standard deviation) age of 8.8 ± 5.6 years. Chronic comorbidities were present in 181 of 284 (64% of) children evaluated for DIC, and 62 of 181 (34% of) comorbidities were malignancy (**Table II**; available at www.jpeds.com). Children evaluated for DIC had higher rates of end-organ dysfunction, increased vasopressor use and mechanical ventilation during hospitalization, increased 1-year mortality, and longer mean hospital and PICU lengths of stay than those who were not evaluated for DIC ($P < .05$ for each) (**Table II**).

Descriptive statistics of laboratory values from the 284 - children who had DIC screens demonstrated: PT: median, 15.4 seconds (IQR, 14.3-17.1 seconds; range, 11.5-47.2 seconds); D-dimer: median, 1.24 μg/mL [IQR, 0.59-2.81 μg/mL; range, 0.22-19.1 μg/mL]; platelet count: median, 196 × 10^3/μL (IQR, 114-286 × 10^3/μL; range, 2-722 × 10^3/μL); and fibrinogen: median, 373.5 mg/dL [IQR, 288-489 mg/dL; range, 53-887 mg/dL]. Initial examination of the distribution of DIC scores for vasopressor use and mortality indicated a sharp increase in the proportion of children with adverse outcomes at a DIC score of 3 (**Figure 2**, A and C). ROC curve analyses showed that a DIC score of ≥3 was the best cutoff for maximizing sensitivity and specificity for both vasopressor use (sensitivity, 0.65; specificity, 0.71; area under the curve, 0.70) and 1-year mortality (sensitivity, 0.70; specificity, 0.62; area under the curve, 0.69) (**Figure 2**, B and D). Among those evaluated for DIC, there were no statistical differences between those with DIC score ≥3 vs <3 in demographic data, including age ($P = .24$), sex ($P = .88$), underlying comorbidities ($P = .13$), or presence of a central venous catheter ($P = .49$). DIC scores were dichotomized as ≥3 (n = 116) vs <3 (n = 168) for subsequent analyses.

Primary Outcome, Vasopressor Use

Patients with initial DIC scores of ≥3 vs <3 had increased vasopressor use, with an OR of 4.48 (95% CI, 2.63-7.62; $P < .001$) (**Table III**). Of those requiring vasopressors, 28 of 60 patients (46.6%) with a DIC score of ≥3 and 14 of 32 (43.8%) with a score of <3 initiated vasopressors while still in the ED. An initial lactate level of ≥4 mmol/L and CRP of ≥0.9 mg/dL were also associated with increased vasopressor use (OR, 3.29 [95% CI, 2.18-4.96; $P < .001$] and OR, 2.07 [95% CI, 1.08-3.98; $P = .03$], respectively). When the 3 significant univariate predictors of vasopressor use were all included in a multivariable regression model, a DIC score of ≥3 remained a significant predictor of vasopressor use (OR, 4.46; 95% CI, 2.22-8.95; $P < .001$) (**Table III**).

Examination of the individual DIC score components demonstrated that prolonged PT and elevated D-dimer were each significant predictors of vasopressor use, decreased platelet count using JAAM thresholds was marginally significant, and fibrinogen showed no independent predictive value (**Table III**). When applying the JAAM criteria for platelet number, platelet count may have been more predictive of vasopressor use, but the change in predictive value was small, and the study was not powered to allow for multiple comparisons of each DIC score component (**Table III**). A prolonged PT was the strongest predictor of the individual DIC components (OR, 3.50; 95% CI, 2.24-5.47; $P < .001$).

Secondary Outcomes

A DIC score of ≥3 significantly predicted increased duration of hospital admission, PICU admission, days on vasopressors, and days on ventilator support (all $P < .01$) (**Table IV**). There was an increased OR for mortality in patients with a DIC score of ≥3 at 1 year (OR, 3.72; 95% CI, 1.48, 9.35; $P = .005$). An initial lactate level of ≥4 mmol/L and CRP of ≥0.9 mg/dL did not significantly predict mortality at 1 year ($P = .08$; $P = .45$). Given previous studies showing an increased 30-day mortality with elevated lactate, we evaluated the effect of DIC score and lactate values on 30-day and 90-day mortality risk in addition to 1-year mortality risk.[25] A DIC score of ≥3 predicted an increased mortality risk at 1 year, but not at

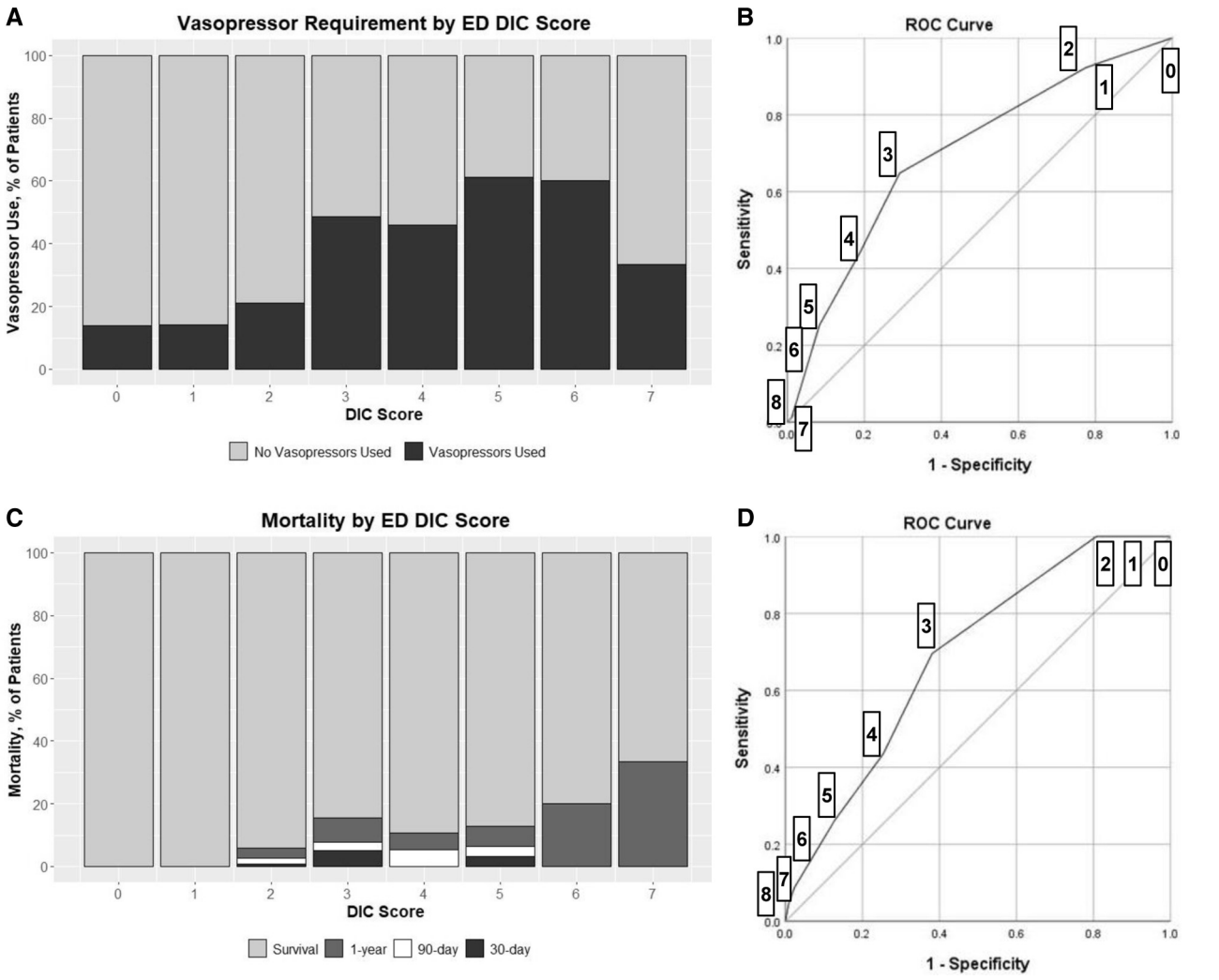

Figure 2. Analysis of vasopressor requirement and 1-year mortality by DIC score. **A,** Vasopressor requirement percentages by ED DIC score. **B,** ROC curve of DIC score prediction of vasopressor use. Boxed numbers signify ROC curve points of individual DIC scores. Area under ROC curve = 0.70. **C,** Mortality by ED DIC score. **D,** ROC curve of DIC score prediction of 1-year mortality. Boxed numbers signify ROC curve points of individual DIC scores. Area under the ROC curve = 0.69. Total number of patients (n) with each DIC score: 0 (n = 43); 1 (n = 7); 2 (n = 118); 3 (n = 39), 4 (n = 37), 5 (n = 32), 6 (n = 5), 7 (n = 3); there were no DIC scores of >7 in this population.

30 or 90 days (P = .22; P = .07). An initial lactate level of ≥4 mmol/L predicted an increased risk of mortality at the 30- and 90-day time points (OR, 3.96 [95% CI, 1.35-11.58; P = .01] and OR, 3.07 [95% CI, 1.27-7.41; P = .01]), but not at 1 year.

In a time-to-event Cox regression analysis, a DIC score of ≥3 predicted an increased mortality risk up to 1 year (HR, 3.55; 95% CI, 1.46-8.64; P = .005) (Figure 3, A), and this risk remained significant even when adjusting for malignancy (HR, 3.19; 95% CI, 1.30-7.81; P = .01). An elevated lactate level of ≥4 mmol/L had an increased mortality risk up to 90 days (HR 3.03; 95% CI, 1.28-7.72; P = .012) (Figure 3, B).

Procedures performed during the admission available in the dataset included intubation and lumbar puncture. Of the 1653 patients in the study, 146 (8.8%) were intubated, including 60 of 146 (41.1%) screened for DIC in the ED, 37 of 60 (61.6%) of whom had a DIC score of ≥3. Lumbar punctures were performed in 149 (9.0%) of the 1653 patients, including 35 of the 149 screened for DIC (23.4%), with 13 of those 35 (37.1%) with a DIC score of ≥3 (8.7%).

Discussion

DIC is a well-recognized complication of sepsis, with reported rates of 20%-50% and mortality of 25%-45% in adults.[2,10,12] Pediatric studies also report high rates of DIC in sepsis and high mortality rates in patients with DIC, up to 50% in 1 PICU study.[18] Adult studies have shown significantly increased mortality in patients with

Table III. Unadjusted and aORs for requirement of vasopressors

Variables	Unadjusted OR (95% CI)	*P* value
DIC score ≥3	4.48 (2.63-7.62)	<.001
DIC score (continuous)	1.57 (1.32-1.87)	<.001
CRP ≥0.9 mg/dL	2.07 (1.08-3.98)	.03
Lactate ≥4 mmol/L	3.29 (2.18-4.96)	<.001
DIC score components		
PT	3.50 (2.24-5.47)	<.001
D-Dimer	1.69 (1.26-2.28)	.001
Platelets (ISTH thresholds)	1.36 (0.98-1.88)	.07
Platelets (JAAM thresholds)	1.24 (1.01-1.52)	.04
Fibrinogen	0.69 (0.07-6.75)	.75
	aOR (95% CI)	*P* value
DIC score ≥3	4.46 (2.22-8.95)	<.001
CRP ≥0.9 mg/dL	1.35 (0.50-3.66)	.56
Lactate ≥4 mmol/L	2.34 (0.98-5.59)	.055

Neither platelet count component evaluation was statistically significant when correcting for multiple comparisons.

overt DIC in the ED based on the ISTH criteria.[7,31,32] These data suggest that the DIC score can be a valuable objective tool that should be incorporated into the emergency care setting.

Researchers and clinicians have noted that sepsis is heterogeneous in terms of pathogen, patient, and organ systems affected, although many treatment elements are similar.[33] Although there is ongoing investigation of molecular techniques that can help to delineate different sepsis endotypes responsive to precision therapeutics, there is likely also an important role for identifying distinct clinical subgroups, what Scicluna called "treatable traits," including a coagulopathic subtype of sepsis.[33-36] Although hematologic dysfunction is incorporated into previously defined sepsis and organ dysfunction scoring systems, it is not as routinely emphasized in the clinical setting as other types of end-organ dysfunction such as kidney, liver, cardiovascular or respiratory dysfunction.[7,37] We found that DIC is an important trait to identify in pediatric sepsis. It delineates a group of patients at greater risk for severe outcomes and is immediately clinically actionable when planning for procedures that may be complicated by coagulopathic bleeding, such as lumbar puncture or thrombosis associated with central venous catheter placement.[38-40]

The DIC score identified a group of children at risk for long-term (1 year) mortality, likely related to residual organ dysfunction following the sepsis/DIC episode and/or underlying patient factors that could guide postsepsis monitoring and treatment. Future studies might determine whether it is beneficial to offer therapies addressing specific abnormal elements of the DIC profile, especially early in the course of illness. Finally, we found that a concerning number of patients at risk for this potentially treatable trait were not tested for DIC. The results of our study suggest that it would be important to focus clinical and quality improvement efforts on consistent testing for DIC in children with severe sepsis.[4] Although an ISTH DIC score of ≥5 traditionally signifies overt DIC in adults, our results showed an ISTH DIC score of ≥3 to be more predictive of adverse outcomes in children. Those with an ISTH DIC score of ≥3 had a 4.5 times greater odds of vasopressor use, a 2.3 times greater odds of requiring

Table IV. Clinical outcomes for patients with DIC scores ≥3 vs DIC scores <3

Outcome variables	DIC score ≥3 n = 116	DIC score <3 n = 168	Unadjusted OR (95% CI)	*P* value
Vasopressors				
Required	60 (51.7)	32 (19.0)	4.48 (2.63-7.62)	<.001
Started in ED	28 (24)	14 (8.3)		
Duration	1.7 ± 2.7	0.6 ± 1.6		<.001
Mechanical ventilation above baseline				
Required	39 (33.6)	27 (16.1)	2.65 (1.51-4.65)	<.001
Duration	2.3 ± 5.1	0.8 ± 2.9		.002
Hospital admission				
Hospital LOS	12.6 ± 11.2	6.7 ± 6.8		<.001
PICU admission	96 (82.8)	104 (62.0)	2.95 (1.66-5.24)	<.001
PICU LOS	5.3 ± 7.3	2.4 ± 4.7		<.001
Mortality				
30-day	4 (3.4)	2 (1.2)	2.99 (0.54-16.6)	.21
90-day	7 (6.0)	3 (1.8)	3.57 (0.90-14.09)	.07
1-year	16 (13.8)	7 (4.2)	3.72 (1.48-9.35)	.005
End-organ dysfunction present during hospitalization*				
Hepatic	41 (35.3)	25 (14.9)	3.13 (1.77-5.53)	<.001
Hematologic	63 (54.3)	16 (9.5)	11.29 (6.01-21.24)	<.001
Renal	19 (16.3)	10 (6.0)	3.09 (1.37-6.91)	.006
Cardiovascular	96 (82.8)	113 (67.3)	2.34 (1.31-4.17)	.004
Respiratory	40 (34.5)	34 (20.2)	2.07 (1.21-3.55)	.008
Procedures				
Intubation	37 (31.9)	23 (13.7)	2.95 (1.64-5.32)	<.001
Lumbar Puncture	13 (11.2)	22 (13.1)	0.84 (0.40-1.74)	.63

LOS, length of stay.
Values are number (%) or mean ± SD.
*Presence of end-organ dysfunction defined by the International Pediatric Sepsis Consensus Conference.[7]

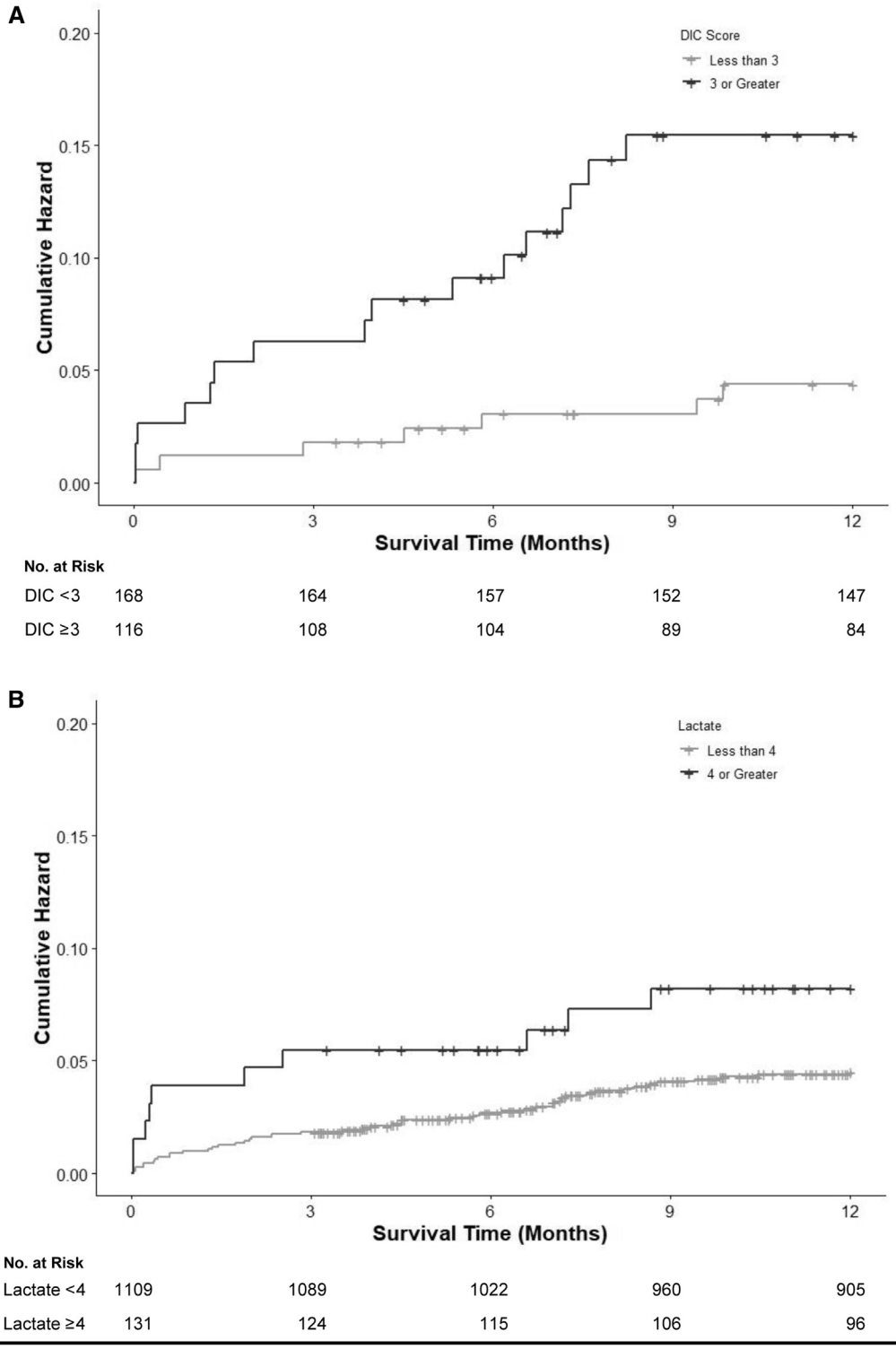

Figure 3. Kaplan-Meier mortality curve based on **A,** DIC score of ≥3 vs a DIC score of <3 within 24 hours of admission to ED (HR, 3.55; 95% CI, 1.46-8.64; *P* = .005) and **B,** based on Lactate level within 24 hours of admission to ED (HR, 3.03; 95% CI, 1.28-7.72; *P* = .012).

mechanical ventilation, and had a longer hospitalizations and PICU stays by an average of 6 and 3 days, respectively.

Evolving concepts in sepsis-induced coagulopathy focus on thrombin generation and inhibition of fibrinolysis resulting in diminished organ perfusion and function leading to increased mortality and morbidity.[28,29] The JAAM, in particular, has used these results to address the pathophysiology directly with replacement of tissue factor pathway inhibitor and antithrombin, although the US approach has been supportive care to limit bleeding and clotting complications.[41]

Our analysis of JAAM and ISTH platelet cutoffs indicate that a future examination of varying platelet cutoffs may be helpful. Of note, these data are associated with DIC in the setting of sepsis specifically. Additional studies are necessary to evaluate the applicability of a cutoff score of 3 for patients with DIC in the setting of other pathophysiologic states, such as trauma or malignancy without sepsis.

The lower DIC score cutoff in our pediatric population compared with the adult population suggests that the adult cutoff is likely too high to predict the majority of adverse outcomes in children. Fibrinogen is an acute phase reactant and is rarely consumed to a pathologically low level in children with healthy liver function. Similarly, the healthy pediatric bone marrow releases abundant platelets in response to stress, such as infection, such that mild thrombocytopenia reflects significant consumption. Other pediatric studies have suggested that sequential measurement of DIC score components may be important in correctly identifying DIC in children.[19] The Texas Children's Hospital scoring system requires multiple blood draws and subjective interpretation by transfusion medicine specialists, and was not used in this study because it could not be applied retrospectively.[19] The JAAM DIC criteria similarly were not fully able to be applied to this dataset because of the need for antithrombin levels and serial platelet count measurements, which were not consistently available.[20,42]

In concordance with the limited number of prior studies evaluating the adult ISTH criteria in pediatric patients with sepsis, our results show increased overall mortality with higher DIC scores (in those who met our inclusion criteria), with a plateau with DIC scores of ≥3. Interestingly, DIC scores of ≥3 did not predict short-term mortality (within 30 or 90 days) of ED admission, but only mortality at 1 year from ED admission. This delayed mortality did not seem to be due to malignancy, because the HR for mortality related to DIC score of ≥3 was still significant when adjusting for malignancy. Lactate levels predicted mortality at 30 or 90 days, consistent with previous studies, but did not predict 1-year mortality.[25] Our finding of increased long-term mortality has been seen in previous studies that describe an increased risk of mortality long after an initial sepsis event, but the underlying pathophysiology is not well-elucidated.[43-46] Septic events can cause a variety of downstream sequelae including epigenetic changes, decreased organ functional reserve, cardiac remodeling, and periods of relative immunodeficiency, among others.[47] In a study of pediatric nonsurvivors of sepsis events, Weiss et al reported that 24% of deaths were seen in patients with chronic critical illness who never returned to their baseline state of health despite initial recovery from a sepsis event, further supporting the notion that septic events may catalyze physiologic changes that extend beyond an initial period of improvement and result in increased mortality.[46] Interestingly, 1 study of >7000 pediatric patients with severe sepsis by Czaja et al showed that late mortality occurred with similar frequency as in-hospital or early mortality, and that the presence of hematologic dysfunction during a sentinel admission was associated with increased rates of readmission and late mortality.[48]

Among individual DIC components evaluated, a prolonged PT was the most predictive of increased vasopressor use (3.5 times greater odds of vasopressor use per PT-based DIC score point increase), followed by elevated D-dimer. The differences in platelet count cutoff for the JAAM and ISTH scores suggest that a study better powered to analyze a variety of cutoffs would be helpful. Fibrinogen scores were not predictive as they are rarely reduced, which is congruent with previous studies.[19,49] Several study limitations are notable. The overall mortality in this population was low (<5%), and the DIC score was available for only 30% of those who died, which made mortality a suboptimal outcome measure for the study. Additional confounders related to the choice of DIC scoring tool could not be evaluated. Although the findings of increased 1-year mortality remained significant after controlling for oncologic diagnoses, details of other chronic comorbidities were not available for analysis. Vasopressor use was used as a surrogate marker for significant illness; however, only 50.5% of those who required vasopressors had DIC scores assessed. Furthermore, although all DIC laboratory values were collected before initiation of vasopressors, 45.6% who required vasopressors had them initiated in the ED, likely very soon after laboratory results for DIC scores were obtained. This limits applicability of these results for predicting later need for vasopressors (such as in the PICU). DIC score was performed at provider discretion, and patients with a DIC score evaluation had higher rates of end-organ dysfunction, vasopressor use, mechanical ventilation, and ICU admission. Thus, we cannot overcome confounding by indication wherein those selected to have a DIC evaluation also had other factors that concerned the provider. Future studies should evaluate the usefulness of the DIC score in any patient presenting with suspected sepsis. In addition, adverse bleeding events were not tracked in our database, so we were unable to determine the relationship between DIC score and adverse bleeding events with procedures. Finally, it is unclear if knowledge of the DIC score influenced decisions to admit to the PICU or delayed discharge, potentially biasing those outcomes.

Our study shows that pediatric patients presenting with suspected sepsis to the ED who have DIC scores of ≥3 are more likely to have worse outcomes including increased vasopressor use, increased mortality, prolonged hospital and PICU lengths of stay, increased rates of mechanical ventilation, and increased mortality. This DIC score cutoff is lower than the adult ISTH DIC score cutoff, suggesting a need for increased awareness of illness severity in children with this DIC score. Although there is no substitute for provider assessment and experienced clinical judgment, studies have shown wide variability in provider ability to recognize the signs and symptoms of pediatric sepsis.[50,51] Integrating these objective data into early diagnostic assessments could improve timely recognition of illness severity in pediatric sepsis, aid in the management of patients undergoing invasive procedures, and potentially lead to earlier

therapeutic intervention in this patient population. Finally, the relationship of DIC in children with sepsis to both short- and long-term morbidity and mortality suggests the need to evaluate the potential benefits of specific coagulation therapy directed to laboratory evidence of DIC rather than just clinical bleeding or thrombosis in septic children. ■

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Table I. ISTH scoring system for DIC

Score	0	1	2	3
Platelet count	>100 000/μL	50 000-100 000/μL	<50 000/μL	
D-dimer*	No increase		Moderate increase	Strong increase
PT prolongation†	≤3 seconds	3-6 seconds	≥6 seconds	
Fibrinogen	≥100 mg/dL	<100 mg/dL		

*D-Dimer ranges: <0.5 μg/mL = No increase, 0.5-3 μg/mL = Moderate increase, >3 μg/mL = Strong increase.
†PT scores based on prolongation above upper limit of normal based on previously defined age-based ranges: age 0-3 months, 13.2-16.5 seconds; ≥3 months, 12.0-15.0 seconds.

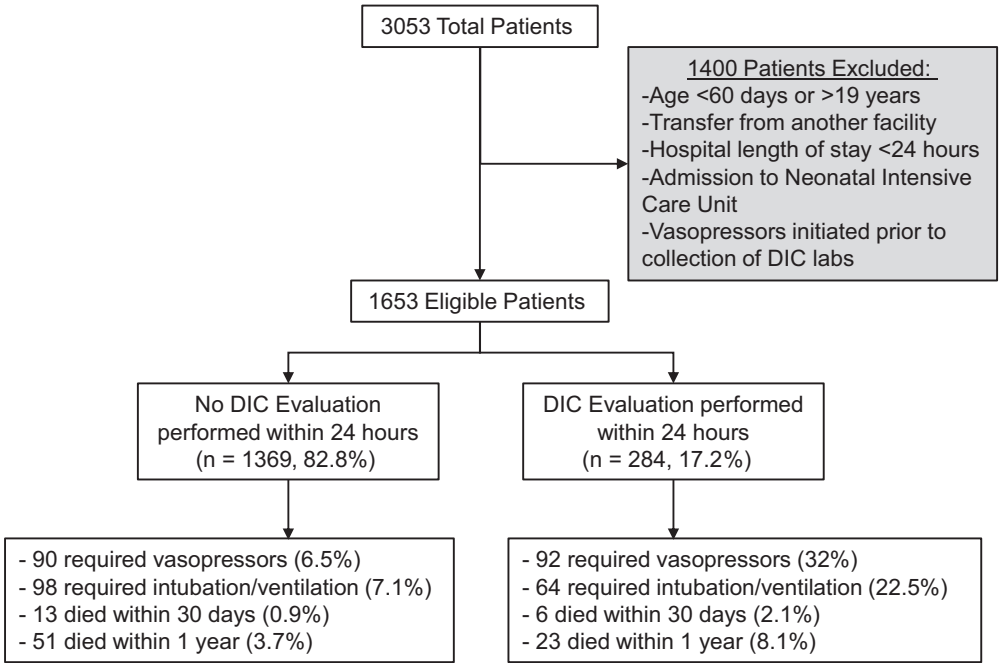

Figure 1. Study flow schematic.

Table II. Patient characteristics and outcomes for patients with and without initial DIC evaluations

Characteristics	DIC evaluated (n = 284) With DIC test, n (%)	DIC not evaluated (n = 1369) Without DIC test, n (%)	*P* value
Sex			.5
Male	160 (56.3)	740 (54.1)	
Female	124 (43.7)	629 (45.9)	
Age			
Average, years	8.8 ± 5.6	7.1 ± 5.7	<.001
<1	15 (5.3)	181 (13.2)	
1-5	78 (27.5)	457 (33.4)	
5-12	92 (32.4)	381 (27.8)	
12-18	99 (24.9)	349 (25.5)	
Chronic comorbidity			
Oncologic	62 (21.8)	374 (27.3)	.06
Nononcologic	119 (41.9)	520 (38.0)	.22
None	103 (36.3)	475 (35.7)	.61
Central line present	54 (19.0)	327 (23.9)	.08
End-organ dysfunction in the ED*			
Hepatic	53 (18.7)	155 (11.3)	.001
Hematologic	69 (24.2)	241 (17.6)	.01
Renal	27 (9.5)	42 (3.1)	<.001
Cardiovascular	171 (60.2)	364 (26.6)	<.001
Respiratory	49 (17.3)	83 (6.1)	<.001

Outcomes	DIC evaluated (n = 284) With DIC test, n (%)	DIC not evaluated (n = 1369) Without DIC test, n (%)	OR (95% CI)	*P* value
Vasopressors				
Required	92 (32.4)	90 (6.6)	6.81 (4.91-9.45)	<.001
Started in ED	42 (14.7)	37 (2.7)		
Duration	1.0 ± 2.2	0.2 ± 1.7		<.001
Mechanical ventilation above baseline				
Required	64 (22.5)	98 (7.1)	3.77 (2.38-4.66)	<.001
Duration	1.4 ± 4.0	0.5 ± 3.3		<.001
Hospital admission				
LOS	9.1 ± 9.3	6.22 ± 8.6		<.001
PICU admission	200 (70.0)	481 (35.1)	4.40 (3.33-5.80)	<.001
LOS	3.6 ± 6.1	1.43 ± 4.4		<.001
Mortality				
30 day	6 (2.1)	13 (0.9)	2.25 (0.85-5.97)	.1
90 day	10 (3.5)	24 (1.8)	2.05 (0.97-4.33)	.06
1 year	23 (8.1)	51 (3.7)	2.28 (1.37-3.79)	.002
Procedures				
Intubation	60 (21.1)	86 (6.3)	4.00 (2.79-5.72)	<.001
Lumbar puncture	35 (12.3)	114 (8.3)	1.55 (1.03-2.31)	.03

LOS, length of stay.
All durations are represented as mean ± SD. *P* value calculations used χ^2, logistic regression, or *t* test.
*Presence of end-organ dysfunction defined by the International Pediatric Sepsis Consensus Conference.[15]