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**DIAGNOSTIC VALUE OF FIBRIN MONOMER AND SELECTED
PHYSIOLOGICAL ANTICOAGULANT FACTORS FOR
DISSEMINATED INTRAVASCULAR COAGULATION AND
MORTALITY PREDICTION IN CHILDREN WITH SEPSIS**

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SUMMARY OF DOCTORAL THESIS IN MEDICINE

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The dissertation will be defended before the University-level Dissertation
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The thesis can be found at:

- National Library
- Hanoi Medical University Library

LIST OF PUBLICATIONS RELATED TO THE THESIS

1. Xoay TD, Tuan TA, Ha NT, Quan TQ, Duyen NT, My TTK. Antithrombin and Activated Protein C in Pediatric Sepsis: Prospective Observational Study of Outcome. *Pediatr Crit Care Med*. 2025;26(2): e197-e205.
2. Tran Dang Xoay, Tran Thi Kieu My, Nguyen Tat Kien, Nguyen Thi Trang, Nguyen Thi Duyen, Ta Anh Tuan. Diagnostic value of multiple organ dysfunction syndrome and mortality of fibrin monomer in children with sepsis. *Journal of Medical Research*, Vol. 191, No. 6, 2025: 296-302.

INTRODUCTION TO THE THESIS

1. Rationale

Sepsis-induced coagulopathy (SIC), most commonly manifesting as disseminated intravascular coagulation (DIC), has been shown to be closely associated with disease severity and increased mortality in patients with sepsis. However, pediatric studies establishing diagnostic thresholds for DIC and the prognostic value of fibrin monomer, antithrombin, and protein C remain limited. Therefore, this study, entitled "Diagnostic value of fibrin monomer and selected physiological anticoagulant factors for disseminated intravascular coagulation and mortality prediction in children with sepsis" was conducted with the following two objectives:

Objective 1:

To analyze the diagnostic value of fibrin monomer and selected physiological anticoagulant factors for disseminated intravascular coagulation in children with sepsis treated in the Pediatric Intensive Care Unit, National Children's Hospital.

Objective 2:

To determine the prognostic value of fibrin monomer and selected physiological anticoagulant factors for mortality in children with sepsis.

2. New contributions of the thesis

A study of 206 children with sepsis in the Pediatric Intensive Care Unit of the National Children's Hospital from March 2021 to October 2024 yielded the following important conclusions:

- To determine the optimal cut-off values of fibrin monomer, antithrombin, and protein C for diagnosing DIC in children with sepsis.
- To analyze the roles of fibrin monomer, antithrombin, and protein C in predicting mortality in children with sepsis.
- To propose the use of fibrin monomer, antithrombin, and protein C as coagulation biomarkers for the clinical diagnosis of DIC.

3. Structure of the thesis

The thesis comprises 116 pages, including 02 pages of introduction, 32 pages of literature review, 16 pages of materials and methods, 29 pages of research results, 34 pages of discussion, 01 page of conclusion, and 01 page of recommendations. The thesis includes 31 tables, 13 figures, 17 charts, and 127 references.

The doctoral candidate has two published articles in reputable professional journals, including one in English and one in Vietnamese.

CHAPTER 1

OVERVIEW OF THE LITERATURE

1.1. Sepsis and coagulation disorders in children

1.1.1. Diagnostic criteria for pediatric sepsis

Pediatric sepsis is a serious medical condition that, if not adequately controlled, can lead to multiple organ dysfunction syndrome and death. The IPSCC-2005 criteria have long been the most widely used in both clinical practice and research because they are easy to apply and highly sensitive. However, they also have important limitations, including low specificity and development based mainly on expert consensus from high-resource countries. The new Phoenix criteria for pediatric sepsis were therefore developed from real-world data to replace the older IPSCC-2005 criteria. These criteria can be applied in both high-resource and low-resource settings and can also stratify disease severity. However, there have been few studies in Vietnam using the new criteria to evaluate their diagnostic value.

1.1.2. Sepsis-induced coagulopathy

Sepsis-induced coagulopathy (SIC) is a common complication in patients with sepsis, with a prevalence of approximately 29% in adults. Among these, disseminated intravascular coagulation (DIC) is the most common, with a prevalence of 30-50%. In Vietnam, according to a 2021 study by Ta Anh Tuan et al. on 55 pediatric patients with sepsis, the prevalence of DIC was clearly very high, at 20%. The mortality rate of children with sepsis and DIC was also very high compared to the group without DIC (55% versus 31%).

Early diagnosis of DIC plays a crucial role in enabling early intervention and treatment, thereby reducing mortality rates in pediatric patients with sepsis. However, to date, there is no gold standard for early diagnosis of DIC. Therefore, the International Society on Thrombosis and Haemostasis (ISTH) has issued guidelines for early diagnosis of DIC based on several coagulation factors, including fibrin monomer (FM), antithrombin, and activated protein C (aPC). FM is released from fibrinogen by thrombin during the early stages of hypercoagulation, in contrast to the elevated D-dimer levels after secondary fibrinolysis when a thrombus has formed. Therefore, FM is expected to be a key factor in early diagnosis of DIC. In fact, studies have shown that FM has higher sensitivity, specificity, positive predictive value, and negative predictive

value compared to D-dimer for definitively differentiating between the no DIC group and overt DIC group.

Antithrombin and aPC are physiological anticoagulant proteins that play a crucial role in the pathogenesis of DIC. One study found that elevated D-dimer and decreased fibrinogen are indicative of late-stage DIC, but combining the ISTH score with antithrombin and aPC helps in the early diagnosis of DIC in patients with bacterial infections.

CHAPTER 2

RESEARCH SUBJECTS AND METHODS

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria

All children aged 1 month to 18 years who met the following criteria were included in the study:

- Admitted to the Pediatric Intensive Care Unit (PICU), National Children's Hospital.
- Diagnosed with sepsis.

2.1.2. Case definition

Diagnostic criteria for sepsis:

- Children admitted from March 2021 to January 2024 were diagnosed with sepsis according to the 2005 International Pediatric Sepsis Consensus Conference (IPSCC-2005) criteria.
- Children admitted from February 2024 onward were diagnosed with sepsis according to the updated Phoenix criteria (February 2024).

2.1.3. Exclusion criteria

Patients were excluded if they had congenital coagulopathy, were receiving anticoagulant therapy before admission, had received blood or blood products within the preceding 7 days, had concomitant conditions such as chronic liver disease, cancer, or major trauma, or lacked sufficient study data.

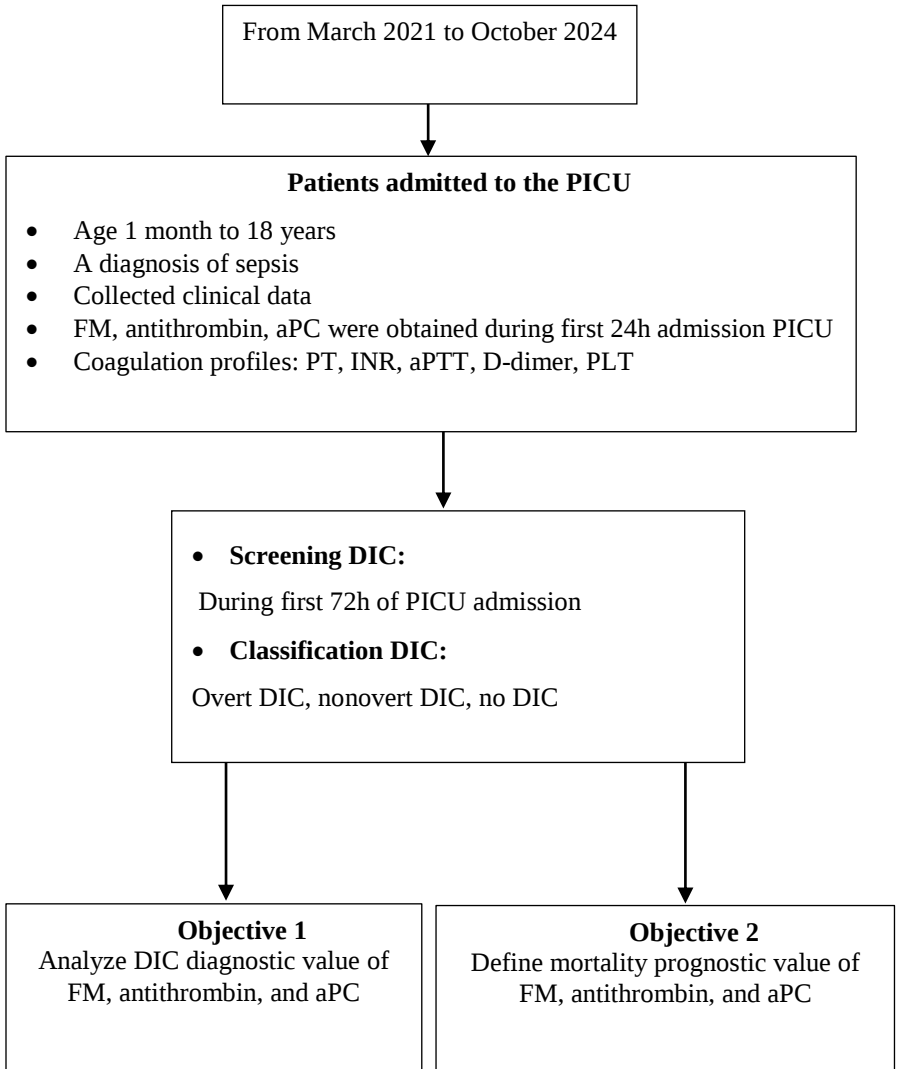
2.2. Study setting and period

- Study location: the Pediatric Intensive Care Unit, National Children's Hospital.

The retrospective data collection period was from March 2021 to April 2023, and the prospective data collection period was from April 2023 to October 2024.

2.3. Research Design

- Descriptive observational study of a case series.

RESEARCH FLOWCHART**Figure 2.1. Study flowchart**

2.4. Sample size and method

- A convenience sampling method was used: all patients meeting the inclusion criteria for sepsis were enrolled and tested for FM, antithrombin, and aPC.

2.5. Study content and variables

a. Demographic and clinical variables

- + Age (months): continuous quantitative variable.
- + Gender : male/female, categorical variable.
- + Weight at PICU admission (kg): continuous quantitative variable.
- + Underlying conditions: categorical variable according to ICD-10.
- + Septic shock: categorical variable.
- + Positive blood culture: categorical variable.
- + Length of mechanical ventilation (days): from the start of mechanical ventilation to the time of weaning, continuous quantitative variable.
- + Length of PICU stay (days): from PICU admission to discharge, continuous quantitative variable.
- + Treatment modalities: hemodialysis and ECMO; categorical variables.
- + PRISM III score: assessed within the first 24 hours after PICU admission according to Pollack.
- + Multiple organ dysfunction syndrome (MODS):

Patients diagnosed with MODS within the first 72 hours after sepsis diagnosis were classified according to the 2022 PODIUM criteria, including respiratory, circulatory, neurologic, renal, hepatic, gastrointestinal, endocrine, and immunologic dysfunction. Hematologic and coagulation dysfunction were excluded from the MODS definition because of their positive correlation with the hematologic predictors under study, which could bias the results.

- + Treatment outcome: survival or death by day 28; categorical variable.
- + Primary site of infection: respiratory, skin and soft tissue, nervous system, gastrointestinal tract, urinary tract, abdominal cavity, or undetermined site; categorized according to ICD-10 based on the medical history, clinical examination, and paraclinical findings within the first 24 hours of hospitalization.
- + Vasoactive-inotropic score (VIS) at 24 hours after PICU admission; continuous variable.

$$\text{VIS} = \text{dopamine } (\mu\text{g/kg/min}) + \text{dobutamine } (\mu\text{g/kg/min}) + 100 \times \text{epinephrine } (\mu\text{g/kg/min}) + 100 \times \text{norepinephrine } (\mu\text{g/kg/min}) + 10 \times \text{milrinone } (\mu\text{g/kg/min}) + 10,000 \times \text{vasopressin } (\text{U/kg/min}).$$

+ Clinical manifestations of hemostatic complications within 72 hours after sepsis diagnosis: bleeding, thrombosis, or both. Thrombosis was identified based on clinical examination combined with vascular Doppler ultrasonography, computed tomography (CT), and magnetic resonance angiography (MRA).

+ Patients were considered hypercoagulable when r-aPTT < 0.8 and hypocoagulable when r-aPTT > 1.2, according to Tripodi et al.

+ White blood cells, neutrophils, lymphocytes, hemoglobin, platelets, urea, creatinine, AST, ALT, bilirubin, Na⁺, K⁺, Cl⁻, calcium, pH, HCO₃⁻, lactate, glucose, blood culture results.

+ Coagulation markers:

- FM (μg/mL), antithrombin (%), aPC (%) within the first 24 hours of PICU admission.
- Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen (g/L), and D-dimer were measured at PICU admission and again at 24, 48, and 72 hours.

b. Analysis of the diagnostic value of fibrin monomer and selected physiological anticoagulant factors for DIC in children with sepsis

- The DIC score was assessed on PICU admission and then 24-, 48-, and 72-hour post-PICU admission.

The DIC score was calculated according to the 2001 ISTH criteria.

Overt DIC was defined as a DIC score of ≥5, while a score of 1-4 was considered non-overt DIC.

- Compare selected factors among the overt DIC, non-overt DIC, and no-DIC groups at PICU admission.

- Analyze the DIC diagnostic values of FM, antithrombin, and aPC.

2.5.2. Content and variables of objective 2

- Compare selected clinical and treatment factors between the survivor and nonsurvivor groups.

- Analyze the correlations of FM, antithrombin, and aPC with VIS, PICU length of stay, and the number of dysfunctional organs.

- Compare several clinical factors, coagulation tests, at the time of PICU admission between the groups:

+ Survival group vs. non-survival group.

+ Group with shock vs. no shock.

+ MODS group vs. no MODS group.

- Analyze the mortality prognostic value of FM, antithrombin, and aPC.

- Multivariate analysis was used to identify independent factors associated with mortality.

Variables were assessed several times each day, and the worst value was selected for analysis.

2.6. Methods/Tools for Information Collection

+ Retrospective patient data: retrospectively collected from archived medical records and digital software during the period from March 2021 to April 2023 using the research medical record form.

+ Prospective patient data: variables in the study were collected from medical records, digital software, and prospective observations in the research medical record form, then the data were entered and coded into Excel.

2.7. Intervention techniques used in the study

2.7.1. Sampling and testing procedures

Two milliliters of whole blood were drawn into a tube containing 3.2% sodium citrate, and the tests were performed at the Department of Hematology, National Children's Hospital.

2.7.2. Fibrin monomer testing procedure

The FM assay was performed using an immunoturbidimetric method on the STA-R system (Diagnostica Stago, France).

2.7.3. Procedure for testing antithrombin and activated protein C

Antithrombin activity (%) and aPC (%) were measured using an ACL TOP 750 LAS machine (Werfen, Barcelona, Spain) according to ISO 15189:2012 standards. Reference values for antithrombin activity were (69.1–121.8%) and aPC (46.6–150.9%).

Conventional coagulation tests were conducted according to ISO 15189:2012 standards.

2.7.4. Procedures for performing other tests

- Biochemistry tests were performed on the AU 5800 analyzer in the Department of Biochemistry, National Children's Hospital, according to ISO 15189:2012 standards.

- Microbiological tests were performed in the Department of Microbiology, National Children's Hospital, according to ISO 15189:2012 standards.

2.8. Potential Errors and Control Measures

2.8.1. Data Management Methods

Data were collected using a standardized case report form and then entered and coded in an Excel file.

2.8.2. Potential Errors and Control Measures

- Clearly define the inclusion and exclusion criteria for recruitment.
- Use uniform sample medical records to collect information.
- Enter and verify the data multiple times.
- Use data analysis tests that match the corresponding variables.

2.9. Statistical analysis

- The collected clinical and laboratory data were processed and presented as follows:

- + Categorical variables were expressed as n (%).
- + Non-standard distributed continuous variables were expressed as median and interquartile range (IQR, 25th-75th percentile).
- Data analysis:

+ AUROC curve analysis was used to evaluate the diagnostic performance of FM, antithrombin, and aPC, including the area under the curve, cut-off value, sensitivity, and specificity. Larger AUROC values indicate better diagnostic or prognostic performance. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Post-test probabilities were estimated from disease frequency, sensitivity, and specificity to calculate the positive and negative predictive values of FM, antithrombin, and aPC using a Fagan nomogram.

+ Group proportions were compared using the Chi-square test. Non-standard distributed continuous variables were compared using the *Mann-Whitney U* test. Associations for categorical variables were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). Spearman correlation coefficients were used to assess the associations of FM, antithrombin and aPC with VIS and PICU length of stay.

+ Multivariable logistic regression was performed to identify independent prognostic factors.

+ Statistical analyses were performed using SPSS version 31.0 (Armonk, NY: IBM Corp.).

2.10. Research ethics

- The study was approved by the Ethics Council of the National Children's Hospital where the research was conducted (No. 641/BVNTW-HDDD, dated April 10, 2023) and Hanoi Medical University.

- Parents or legal guardians of participating patients were informed about the study and signed written consent forms.

- This is a descriptive observational study, so it does not affect the patient's treatment results.

- Conventional coagulation tests, antithrombin, and aPC are routine tests performed during patient monitoring and treatment and are covered by insurance.

- FM was measured from blood collected at the same time as routine coagulation tests; no additional blood samples were obtained. The cost was covered by the researcher, and the patient did not pay any fee.

- All information on the study participants was anonymized and kept confidential for research purposes only.

CHAPTER 3: RESEARCH RESULTS

From March 2021 to October 2024, the study included 206 eligible patients, comprising 67 retrospective cases and 139 prospective cases.

The research results are analyzed based on two research objectives:

3.1. Objective 1

Analysis of the diagnostic value of fibrin monomer and selected physiological anticoagulant factors for DIC in children with sepsis at the Pediatric Intensive Care Unit, National Children's Hospital.

3.1.1. Baseline patient characteristics

Table 3.1. Baseline patient's characteristics

Variable	Total (n = 206)	Ratio (%)
Age (months), median (IQR)	9 (3–32)	-
Male gender, n (%)	126	61,2
Weight (kg), median (IQR)	8 (5–12,4)	-
Underlying condition *, n (%)	47	22.8
Septic shock, n (%)	153	74.3
Multiple organ dysfunction syndrome, n (%)	185	89.8
Total PRISM III score, median (IQR)	11 (7–20)	-
Blood culture (+), n (%)	81	39.3
Hemodialysis, n (%)	38	18.4
ECMO, n (%)	4	1.9
Duration of mechanical ventilation (days), median (IQR)	5 (3–8.3)	-
Length of PICU stay (days), median (IQR)	8 (5–13)	-
Death, n (%)	40	19.4

Categorical variables are presented as n (%); IQR, 25th-75th percentile.

** Note: 47 (22.8 %) patients had underlying conditions: 9 premature, 5 Down syndrome, 4 cerebral palsy, 3 epilepsy, 3 congenital heart defects, 2 multiple malformations, 2 immunodeficiency, 2 congenital megacolon, 2 psychomotor developmental delay, 1 anal fistula, 1 imperforate anus, 1 biliary atresia, 1 bowel obstruction, 1 cleft palate, 1 epilepsy and cerebral palsy, 1 hypotonia, 1 lupus, 1 obesity, 1 pompe disease, 1 Prader-Willi syndrome, 1 renal atrophy, 1 short bowel syndrome and malnutrition, 1 thalassemia, 1 urea cycle disorder.*

Distribution by age group

Table 3.2. Distribution by age group

Age group	Number of patients	Ratio (%)
< 12 months	113	54.9
12-36 months	44	21.3
≥ 36 months	49	23.8
Total	206	100

3.1.2. Primary site of infection

Table 3.3. Primary site of infection

Primary site of infection	Number of patients	Ratio (%)
Respiratory tract, n (%)	88	42.7
Skin and soft tissues, n (%)	41	19.9
Nervous system, n (%)	31	15
Gastrointestinal tract, n (%)	25	12.1
Abdominal cavity, n (%)	10	4.9
Urinary tract, n (%)	5	2.4
Undetermined site, n (%)	7	3.4
Total	206	100

Categorical variables are presented as n (%).

3.1.3. Clinical presentation of hemostatic events

Table 3.4. Clinical presentation of hemostatic events

Clinical presentation of hemostatic events	Number of patients	Ratio (%)
Hemorrhage present, n (%)	20	9.7
Thrombosis present, n (%)	12	5.8
Hemorrhage with thrombosis present, n (%)	8	3.9
No bleeding or thrombosis, n (%)	166	80.6
Total number	206	100

Categorical variables are presented as n (%).

3.1.4. Characteristics of coagulation disorders on laboratory tests at the time of PICU admission

Table 3.5. Coagulation status

Status	Number of patients (n = 206)	Ratio (%)
Hypercoagulation	1	0.5
Hypocoagulation	77	37.4
Total	78	37.9

Table 3.6. Proportion of patients with coagulation abnormalities on laboratory testing

Tests	Number of patients (n = 206)	Ratio (%)
Platelets < 150 ($\times 10^9/L$)	36	17.5
INR ≥ 1.4	82	39.8
aPTT ≥ 40 (s)	68	33
Fibrinogen < 1 (g/L)	7	3.4
D-dimer ≥ 400	186	90.3
Fibrin monomer ≥ 7 ($\mu g/L$)	88	42.7
Antithrombin < 69 (%)	79	38.3
Protein C < 46 (%)	71	34.5

3.1.5. Distribution of DIC in the first 72 hours of PICU admission

Table 3.7. Distribution of DIC within the first 72 hours after PICU admission

DIC	Number of patients	Ratio (%)
Overt DIC, n (%)	64	31.1
Nonovert DIC, n (%)	137	66.5
No DIC, n (%)	5	2.4
Total	206	100

Categorical variables are presented as: n (%)

3.1.5. Comparison of selected factors between the overt DIC and nonovert DIC groups

Table 3.8. Comparison of selected factors between the overt DIC and nonovert DIC groups

DIC Parameters	Overt DIC (n = 64)	Nonovert DIC (n = 137)	OR (95% CI)	p*
Age (months), median (IQR)	12 (5–44)	7 (2–29)	1.01 (1.00–1.01)	0.037
Number of days on mechanical ventilation, median (IQR)	7 (4–12,8)	5 (3–8)	1.07 (1.02–1.12)	0.005
Number of days in the PICU, median (IQR)	9 (5–14)	8 (5–12)	1.01 (0.98–1.05)	0.441
Hemodialysis, n (%)	40 (62.5)	16 (11.7)	6.04 (2.65–13.74)	< 0.001
ECMO, n (%)	4 (6,3)	0 (0)	-	0.999
Death, n (%)	24 (37.5)	16 (11.7)	4.54 (2.19–9.38)	< 0.001

IQR: interquartile range (25th–75th percentile)

OR: odds ratio; 95% CI: 95% confidence interval

** Logistic regression; p < 0.05 was considered statistically significant.*

3.1.6. Test performance of FM in relation to overt DIC

Table 3.5. Test performance of FM in relation to overt DIC

Predictor	Fibrin monomer
Area under the curve (95% CI)	0.71 (0.6–0.8)
p*	< 0.001
Cut-off value (Sensitivity; specificity)	6.94 (0.81; 0.56)
Positive predictive value	0.45
Negative predictive value	0.86

Post-test probability calculated using Fagan nomogram

Boldface values are p < 0.05, which were statistically significant.

3.1.7. Test performance of FM in relation to non-overt DIC

Table 3.6. Test performance of FM in relation to non-overt DIC

Predictor	Fibrin monomer
Area under the curve (95% CI)	0.69 (0.6–0.8)
p^*	< 0.001
Cut-off value (Sensitivity; specificity)	6.67 (0.77; 0.54)
Positive predictive value	0.77
Negative predictive value	0.54

Post-test probability calculated using Fagan nomogram

Boldface values are $p < 0.05$, which were statistically significant.

3.1.8. Test performance of antithrombin in relation to overt DIC

Table 3.7. Test performance of antithrombin in relation to overt DIC

Predictor	Antithrombin
Area under the curve (95% CI)	0.78 (0.70–0.87)
p^*	< 0.001
Cut-off value (Sensitivity; specificity)	55.5 (0.72; 0.73)
Positive predictive value	0.54
Negative predictive value	0.85

Post-test probability calculated using Fagan nomogram

Boldface values are $p < 0.05$, which were statistically significant.

3.1.9. Test performance of antithrombin in relation to non-overt DIC

Table 3.8. Test performance of antithrombin in relation to non-overt DIC

Predictor	Antithrombin
Area under the curve (95% CI)	0.74 (0.64–0.83)
p^*	< 0.001
Cut-off value (Sensitivity; specificity)	73.5 (0.43; 0.93)
Positive predictive value	0.92
Negative predictive value	0.45

Post-test probability calculated using Fagan nomogram

Boldface values are $p < 0.05$, which were statistically significant.

3.1.10. Test performance of protein C in relation to overt DIC

Table 3.9. Test performance of protein C in relation to overt DIC

Predictor	Protein C
Area under the curve (95% CI)	0.74 (0.62–0.85)
p^*	< 0.001
Cut-off value (Sensitivity; specificity)	33.5 (0.67; 0.71)
Positive predictive value	0.51
Negative predictive value	0.82

Post-test probability calculated using Fagan nomogram

Boldface values are $p < 0.05$, which were statistically significant.

3.1.11. Test performance of protein C in relation to non-overt DIC

Table 3.10. Test performance of protein C in relation to non-overt DIC

Predictor	Protein C
Area under the curve (95% CI)	0.69 (0.58–0.81)
p^*	0.001
Cut-off value (Sensitivity; specificity)	33.5 (0.67; 0.66)
Positive predictive value	0.79
Negative predictive value	0.50

Post-test probability calculated using Fagan nomogram

3.2. Objective 2

Determining the prognostic value of fibrin monomer and selected physiological anticoagulant factors for mortality in children with sepsis

3.2.1. Comparison of clinical characteristics between the survivor and nonsurvivor groups

Table 3.15. Comparison of clinical characteristics between the survivor and nonsurvivor groups

Characteristic	Survival group (n = 166)	Nonsurvival group (n = 40)	OR (95% CI)	p^*
Age (months), median (IQR)	7 (2–26.3)	25 (6.3–73.5)	1.01 (1.00–1.02)	0.002
Male, n (%)	99 (59.6%)	27 (67.5%)	1.41 (0.68–2.92)	0.361
Hemorrhage, n (%)	10 (6%)	10 (25%)	5.20 (1.99–13.58)	< 0.001
Thrombosis, n (%)	10 (6%)	2 (5%)	0.82 (0.17–3.90)	0.804
Hemorrhage with thrombosis, n (%)	1 (0.6%)	7 (17.5%)	35.00 (4.17–294.04)	0.001
Overt DIC, n (%)	40 (24.1%)	24 (60%)	4.73 (2.29–9.76)	< 0.001
Number of organs dysfunction, median (IQR)	3 (2–4)	4 (3–5)	2.71 (1.87–3.92)	< 0.001

IQR: interquartile range (25th–75th percentile)

OR: odds ratio; 95% CI: 95% confidence interval

** Logistic regression; $p < 0.05$ was considered statistically significant.*

3.2.2. Correlation between FM, antithrombin, protein C, and VIS

Table 3.11. Correlation between FM, antithrombin, protein C, and VIS

VIS at the time 24h Coagulation parameters	Survival group (n = 166, median VIS 15)		Nonsurvival group (n = 40 , median VIS 45)	
	r_s	p	r_s	p
Fibrin monomer	0.07	0.513	0.42	0.039
Antithrombin	- 0.30	0.002	- 0.43	0.048
Protein C	- 0.30	0.005	- 0.30	0.278

r_s : Spearman correlation coefficient

3.2.3. Correlation between FM, antithrombin, protein C, and the number of dysfunctional organs at the time of PICU admission

Table 3.12. Correlation between FM, antithrombin, protein C, and the number of dysfunctional organs at the time of PICU admission

MODS Coagulation parameters	Number of dysfunctional organs (n = 206, median 3)	
	r_s	p
Fibrin monomer	0.36	< 0.001
Antithrombin	- 0.31	< 0.001
Protein C	- 0.20	0.04

r_s : Spearman correlation coefficient

3.2.4. Correlation between FM, antithrombin, protein C and length of PICU stay

Table 3.13. Correlation between FM, antithrombin, protein C and length of PICU stay

Length of PICU stay Coagulation parameters	Survival group (n = 166, median 8 day)		Nonsurvival group (n = 40, median 5.5 day)	
	r_s	p	r_s	p
Fibrin monomer	0.20	0.037	- 0.24	0.212
Antithrombin	- 0.1 7	0,083	0.08	0 , 717
Activated Protein C	-0.19	0,070	-0.02	0,950

r_s : Spearman correlation coefficient

3.2.5. Comparison of coagulation parameters between the shock group and the non-shock group at the time of PICU admission

Table 3.19. Comparison of coagulation parameters between the shock and non-shock groups at PICU admission

Coagulation parameters	Shock group (n = 153)	Non-shock group (n = 53)	OR (95% CI)	<i>p</i>[*]
Platelets (x10⁹/L), median (IQR)	246 (130–367)	309 (161–500)	0.99 (0.99–1.00)	0.034
International Normalized Ratio, median (IQR)	1.3 (1.2–1.7)	1.2 (1.1–1.4)	1.97 (0.94–4.15)	0.074
Activated Partial Thromboplastin Time(s), median (IQR)	37.4 (32.9–45.5)	33.4 (29.7–38.4)	1.07 (1.02–1.12)	0.003
Fibrinogen (g/L), median (IQR)	3.0 (2.0–4.1)	4.1 (2.6–5.2)	0.72 (0.59–0.89)	0.002
D-dimer (ng/mL FEU), median (IQR)	3355 (1429–10241)	3605 (1485–7096)	1.00 (1.00–1.00)	0.708
Fibrin monomer (µg/mL), median (IQR)	7.85 (3.94–16.57)	6.05 (3.89–11.77)	1.00 (0.99–1.02)	0.590
Antithrombin (%), median (IQR)	59 (43–75)	79.5 (54.5–97.5)	0.98 (0.96–0.99)	0.003
Protein C (%), median (IQR)	35.5 (23.8–49.5)	49 (35–70)	0.97 (0.95–0.99)	0.003

IQR: interquartile range (25th–75th percentile)

OR: odds ratio; 95% CI: 95% confidence interval

** Logistic regression; $p < 0.05$ was considered statistically significant.*

3.2.6. Comparison of coagulation parameters between the MODS (+) group and the MODS (-) group at the time of PICU admission

Table 3.20. Comparison of coagulation parameters between the MODS and non-MODS groups at PICU admission

Coagulation parameters	MODS (+) (n = 185)	MODS (-) (n = 21)	OR (95% CI)	p *
Platelets (x10⁹/L), median (IQR)	244 (122–372)	424 (306–551)	0.99 (0.99–1.00)	0.003
International Normalized Ratio, median (IQR)	1.3 (1.1–1.6)	1,2 (1.1–1.4)	3.15 (0.75– 13.24)	0.118
Activated Partial Thromboplastin Time (s), median (IQR)	36.5 (32.3–44.2)	32.6 (29.2–39.4)	1.06 (0.99–1.13)	0.066
Fibrinogen (g/L), median (IQR)	3.1 (2.0–4.4)	4.4 (3.3–5.8)	0.62 (0.46–0.82)	< 0.001
D-dimer (ng/mL FEU), median (IQR)	3609 (1492–9277)	3092 (940–7252)	1.00 (1.00–1.00)	0.497
Fibrin monomer (µg/mL), median (IQR)	7.69 (3.97–15.83)	4.80 (2.43–8.51)	1.06 (0.95–1.19)	0.310
Antithrombin (%) median (IQR)	59 (43–75)	89 (59.5–104.5)	0.97 (0.95–0.99)	0.002
Protein C (%), median (IQR)	35 (24–52)	49.5 (29.8–72)	0.98 (0.96–1.00)	0.031

IQR: interquartile range (25th-75th percentile)

OR: odds ratio; 95% CI: 95% confidence interval

** Logistic regression; p < 0.05 was considered statistically significant.*

3.2.10. Comparison of coagulation parameters between the survivor and nonsurvivor groups at PICU admission

Table 3.21. Comparison of coagulation parameters between the survivor and nonsurvivor groups at PICU admission

Coagulation parameters	Survival group (n = 166)	Nonsurvival group (n = 40)	OR (95% CI)	<i>p</i> *
Platelets ($\times 10^9/L$), median (IQR)	279 (174–417)	137 (67–266)	0.99 (0.99–1.00)	0.003
International Normalized Ratio, median (IQR)	1.3 (1.1–1.6)	1.5 (1.3–1.9)	2.04 (1.27–3.27)	0.003
Activated Partial Thromboplastin Time (s), median (IQR)	35.7 (31.8–41.7)	40.8 (34.2–62.9)	1.03 (1.01–1.05)	< 0.001
Fibrinogen (g/L), median (IQR)	3.4 (2.3–4.8)	2.2 (1.3–3.4)	0.64 (0.49–0.83)	< 0.001
D-dimer (ng/mL FEU), median (IQR)	2740 (1383–7272)	6024 (1783–20000)	1.00 (1.00–1.00)	0.120
Fibrin monomer ($\mu g/mL$), median (IQR)	7.10 (3.89–12.87)	10.81 (4.72–33.14)	1.01 (0.99–1.02)	0.391
Antithrombin (%), median (IQR)	64 (49–80)	53 (27–67)	0.98 (0.96–1.00)	0.027
Activated protein C (%), median (IQR)	37 (26–56)	28 (16.3–50.5)	0.98 (0.95–1.01)	0.140

IQR: interquartile range (25th–75th percentile)

OR: odds ratio; 95% CI: 95% confidence interval

** Logistic regression; $p < 0.05$ was considered statistically significant.*

3.2.11. Test performance of FM in relation to mortality

Table 3.14. Test performance of FM in relation to mortality

Predictor	Fibrin monomer
Area under the curve (95% CI)	0.61 (0.49–0.73)
<i>p</i> *	0.062
Cut-off value (sensitivity; specificity)	7.69 (0.71; 0.58)
Positive predictive value	0.29
Negative predictive value	0.89

Post-test probability calculated using Fagan nomogram; $p < 0.05$ is considered statistically significant.

3.2.12. Test performance of antithrombin in relation to mortality

Table 3.15. Test performance of antithrombin in relation to mortality

Predictor	Antithrombin
Area under the curve (95% CI)	0.64 (0.51–0.77)
p^*	0.037
Cut-off value (sensitivity; specificity)	63.5 (0.51;0.74)
Positive predictive value	0.32
Negative predictive value	0.86

Post-test probability calculated using Fagan nomogram; $p < 0.05$ is considered statistically significant.

3.2.13. Test performance of protein C in relation to mortality

Table 3.16. Test performance of protein C in relation to mortality

Predictor	Protein C
Area under the curve (95% CI)	0.63 (0.47–0.79)
p^*	0.111
Cut-off value (sensitivity; specificity)	29.5 (0.68; 0.56)
Positive predictive value	0.27
Negative predictive value	0.88

Post-test probability calculated using Fagan nomogram; $p < 0.05$ is considered statistically significant.

3.2.14. Multivariate analysis of factors associated with mortality

Table 3.17. Multivariate analysis of factors associated with mortality

Predictor	OR (95% CI)	p^*
Age	1.01 (0.99–1.01)	0.242
Overt DIC present	2.27 (1.01–5.11)	0.048
MODS	2.26 (1.52–3.36)	< 0.001

MODS = Multiple organ dysfunction syndrome;

OR: odds ratio; 95% CI: 95% confidence interval;

** Logistic regression; $p < 0.05$ was considered statistically significant.*

CHAPTER 4: DISCUSSION

4.1. Baseline characteristics of the study population

4.1.1. Age

Age plays an important role in studies of pediatric sepsis. Previous studies have shown that younger children are at greater risk of severe infection because their immune systems are immature, making them more susceptible to severe disease and worse progression.

The results shown in Table 3.1 indicate that the study population was predominantly very young, with a median age of 9 months, and that children younger than 12 months accounted for 54.9% of cases. The study also found that the nonsurvivor group was older, whereas antithrombin and aPC levels were lower than in the survivor group (Table 3.15, Table 3.19). This suggests that differences in antithrombin and aPC activity may be related to patient age. This finding is consistent with a 2018 study by Niederwanger et al. in Austria involving 164 children (42 aged <1 year; 122 aged ≥ 1 year), which found that antithrombin activity above 41.5% in children younger than 1 year was associated with better survival (AUROC 0.83, good prognostic value), whereas in children aged 1 year or older the threshold was above 67.5% (AUROC 0.68, poor prognostic value). According to Niederwanger et al., the risk of death was significantly higher when antithrombin was below these thresholds (41.7% vs. 3.3% in children <1 year; 32.2% vs. 9.5% in children ≥ 1 year). Their study also found that reduced antithrombin was associated with MODS. The differences between their cut-off values and ours may be explained by differences in study populations and sample sizes.

4.1.5. Mortality rate

Mortality rates in studies of sepsis vary according to the patient population and the stage of disease. DIC has been shown to be closely associated with disease severity in sepsis and to be an important factor related to mortality. In this study, the mortality rate was 40/206 (19.4%), which is relatively high.

4.2. Coagulation characteristics of the study population

4.2.1. Prevalence of disseminated intravascular coagulation

In our study, overt DIC was present in 64/206 patients (31.1%) and non-overt DIC in 137/206 patients (66.5%) (Table 3.7). The nonsurvivor group had a clearly higher rate of overt DIC than the survivor group (Table 3.17). These findings show that overt DIC is very common in children with sepsis. Multivariable analysis further showed that overt DIC was an independent factor associated with mortality (Table 3.27).

The incidence of DIC in patients with sepsis or septic shock varies significantly depending on the diagnostic criteria as well as the study patient group.

4.2.2. Characteristics of coagulation disorders

One of the main findings of this study was that bleeding complications occurred in 20/206 patients (9.7%), thrombotic complications in 12/206 (5.8%), and both bleeding and thrombosis in 8/206 (3.9%) (Table 3.4). The nonsurvivor group had a markedly higher odds of bleeding complications, or both complications, than the survivor group (Table 3.17). This finding is consistent with the 2023 study by Bui Thi Hanh Duyen in adults with sepsis in Vietnam.

4.3. Diagnostic value of fibrin monomer for DIC

When evaluating the ability of FM to diagnose overt DIC, FM showed fair diagnostic performance, with an AUROC of 0.71. The prevalence of overt DIC was 31.1%; at the cut-off value of 6.94, sensitivity was 0.81, specificity was 0.56, positive predictive value was 45%, and negative predictive value was 86%.

The largest study evaluating FM's ability to diagnose DIC was by Park et al. in South Korea in 2011. The study concluded that FM's DIC diagnostic ability was equivalent to D-dimer. FM can have a higher sensitivity and specificity than D-dimer in discriminating overt DIC, and not superior at discriminating non-overt DIC.

4.4. Prognostic value of fibrin monomer for mortality

When evaluating the prognostic value of FM for mortality in children with sepsis, FM showed poor performance, with an AUROC of only 0.61. At the cut-off value of 7.69, the positive predictive value was only 29%. We were unable to identify comparable published studies on this issue in either adults or children with sepsis.

4.5. Diagnostic value of antithrombin and protein C for DIC

When comparing the overt DIC group with the non-overt DIC group, it was found that the overt DIC group had statistically significant lower antithrombin and aPC activity. The findings in our study are consistent with an earlier study in 2001 by Levi et al. in adult subjects.

4.6. Prognostic value of antithrombin and protein C for mortality

In this study, comparison of the nonsurvivor and survivor groups showed that antithrombin activity was clearly lower in the nonsurvivor group. When antithrombin was used as a prognostic test for mortality, the positive predictive value was 32% and the negative predictive value was 86%. These results are not sufficiently strong for clinical decision-making; however, they may still be useful for risk stratification in future clinical trials. The implications of these findings may support the use of fresh frozen plasma transfusion in patients with severe coagulopathy because it contains antithrombin, which may help improve DIC and mortality.

4.7. Limitations of the study

Although our study yielded several positive findings, it still has important limitations. First, this was a single-center observational study with a relatively small sample size. Second, the frequencies of some events, such as death and the no-DIC group, were low. As a result, some findings in the nonsurvivor group did not reach statistical significance. The use of two different diagnostic criteria for pediatric sepsis after implementation of the new Phoenix 2024 criteria may also have introduced heterogeneity in the results.

Finally, because of limited time and resources, we were unable to perform a kinetic study of FM, antithrombin, and aPC. Nevertheless, these findings provide a basis for future multicenter pediatric studies with larger sample sizes to confirm the proposed hypotheses.

CONCLUSION

A study of 206 children with sepsis treated in the PICU, National Children's Hospital, from March 2021 to October 2024 yielded the following main conclusions:

1. Diagnostic value of fibrin monomer and selected physiological anticoagulant factors for DIC in children with sepsis

In children with sepsis, DIC was common, with overt DIC accounting for approximately one-third of cases (31.1%).

Fibrin monomer, antithrombin, and activated protein C all showed fair diagnostic performance for overt DIC, with antithrombin demonstrating the best discriminative ability (cutoff value 6.94 µg/mL, 55.5%, and 33.5%, respectively).

Antithrombin, particularly at higher cutoff values, showed high specificity and positive predictive value, suggesting a role in stratifying high-risk DIC group; fibrin monomer was more sensitive and may be useful for screening.

2. Prognostic value of fibrin monomer and selected physiological anticoagulant factors for mortality in children with sepsis

Children with sepsis had a high mortality rate (19.4%). The nonsurvivor group had a markedly higher prevalence of overt DIC and MODS than the survivor group.

Antithrombin activity was significantly lower in the nonsurvivor group than in the survivor group; both antithrombin and activated protein C were also significantly lower in patients with MODS.

Although fibrin monomer levels were higher and activated protein C levels were lower in the nonsurvivor group, these differences were not statistically significant.

The prognostic performance of fibrin monomer, antithrombin, and activated protein C for mortality was limited.

RECOMMENDATIONS

The role of coagulopathy in the pathogenesis of pediatric sepsis is becoming increasingly well understood. Based on the findings regarding the ability of FM, antithrombin, and aPC to diagnose late-stage DIC (overt DIC), we recommend early use of these tests within the first 24 hours for children with sepsis admitted to the PICU to facilitate timely detection and intervention.

We also recommend continued investigation of FM, antithrombin, and aPC kinetics for the diagnosis of early-stage DIC according to the updated 2025 ISTH DIC criteria, using a multicenter study design and a larger sample size. In addition, further studies should evaluate SIC-specific criteria for patients with sepsis.

Finally, we recommend further studies evaluating the role of FM, antithrombin, and aPC in the diagnosis of thrombosis and the prognosis of MODS in children with sepsis.