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Association of D-Dimer Level with Severity of Acute Pancreatitis in Children

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Abstract **Original Research Article**

Background: Early identification of severe acute pancreatitis (AP) in children is essential for appropriate risk stratification and timely management. Conventional biochemical markers have limited ability to predict disease severity. D-dimer, a fibrin degradation product reflecting activation of coagulation and fibrinolysis, has shown promising results as an early predictor of severe AP in adults; however, evidence in children remains limited. ***Objective:*** To determine the association between serum D-dimer level and the severity of acute pancreatitis in children. ***Materials and Methods:*** This cross-sectional observational study was conducted in the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from March 2021 to June 2022. Twenty children diagnosed with acute pancreatitis according to the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) criteria were enrolled consecutively. Serum D-dimer was measured on the day of admission. Patients were classified into mild and severe acute pancreatitis using the Pediatric Acute Pancreatitis Severity Score (PAPS). Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of serum D-dimer were calculated. ***Results:*** Severe acute pancreatitis was identified in 30.0% of patients, while 70.0% had mild disease. The mean serum D-dimer level was significantly higher in children with severe acute pancreatitis than in those with mild disease (3.89 ± 3.39 vs. 1.28 ± 1.60 µg/mL; $p<0.001$). ROC curve analysis demonstrated good diagnostic performance of serum D-dimer for predicting severe acute pancreatitis. At the optimal cutoff value (>1.66 µg/mL), serum D-dimer showed satisfactory sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy for identifying severe disease. ***Conclusion:*** Serum D-dimer level was significantly associated with the severity of acute pancreatitis in children and demonstrated good diagnostic performance in differentiating severe from mild disease. It may serve as a simple and useful early biomarker for severity assessment, although larger multicenter studies are required to validate these findings.

Keywords: Acute pancreatitis; Children; D-dimer; Disease severity; Pediatric Acute Pancreatitis Severity Score.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas resulting from premature activation of digestive enzymes within pancreatic acinar cells, leading to pancreatic injury and varying degrees of local and systemic inflammation [1,2]. The diagnosis of pediatric AP is established when at least two of the following criteria are present: abdominal pain suggestive of pancreatitis, serum amylase and/or lipase levels more than three times the upper limit of normal, and characteristic imaging findings [3].

The incidence of pediatric AP has increased considerably over the last two decades, with an estimated annual incidence of 3–13 cases per 100,000 children [4]. Although most children recover completely, approximately 15–20% develop severe disease characterized by pancreatic necrosis, organ dysfunction, systemic inflammatory response syndrome (SIRS), or

other local and systemic complications, contributing to increased morbidity and mortality [5, 6].

Early identification of severe AP is essential because timely intensive management can reduce complications and improve clinical outcomes. Several scoring systems, including the Pediatric Acute Pancreatitis Severity Score (PAPS), have been developed to assess disease severity in children. However, these scoring systems have only moderate predictive accuracy and often require multiple clinical and laboratory parameters collected over time [7,8]. Conventional biochemical markers such as serum amylase and lipase are useful for diagnosis but correlate poorly with disease severity [3].

Acute pancreatitis is associated with activation of inflammatory and coagulation pathways. Systemic inflammation induces endothelial injury, activation of the coagulation cascade, and microvascular thrombosis, which contribute to pancreatic necrosis and multiple organ dysfunction. D-dimer, a fibrin degradation product, reflects activation of coagulation and fibrinolysis and has emerged as a potential biomarker for predicting disease severity[9]. Elevated D-dimer levels indicate a hypercoagulable state and microvascular coagulopathy, which may worsen pancreatic injury and increase the risk of complications, including disseminated intravascular coagulation [10].

Several studies in adults have demonstrated that elevated D-dimer levels at admission are significantly associated with severe AP, pancreatic necrosis, organ failure, and poor clinical outcomes [11,12]. In Bangladesh, a study among adults reported that serum D-dimer levels could reliably predict severe AP with a cutoff value of 3.3 µg/mL on the first day of admission [13]. However, evidence regarding the role of D-dimer in pediatric AP remains scarce, particularly in developing countries.

Considering the increasing incidence of pediatric AP and the lack of reliable early biomarkers for predicting disease severity, this study was undertaken to evaluate the association between serum D-dimer levels and the severity of acute pancreatitis in children.

Objective

General Objective

To determine the association between serum D-dimer level and the severity of acute pancreatitis in children.

Specific Objectives

1. To classify children with acute pancreatitis into mild and severe acute pancreatitis using the Pediatric Acute Pancreatitis Severity Score (PAPS).
2. To measure serum D-dimer levels in children with acute pancreatitis at admission.
3. To compare serum D-dimer levels between children with mild and severe acute pancreatitis.

MATERIALS AND METHODS

Study Design: It was a cross-sectional observational study.

Study Period: Study period was from March 2021 to June 2022.

Place of Study: Study was carried out at the Department of Pediatric Gastroenterology and Nutrition, BSMMU, Dhaka, Bangladesh.

Study Population: Children with abdominal pain diagnosed as acute pancreatitis, admitted at Department of Pediatric Gastroenterology and nutrition, BSMMU, Dhaka, Bangladesh were the cases.

Sample Size:

Calculation of sample size:

$$N\ (sN) = \frac{(SN(1-SN)}{W^2}$$

Where

$$TP+FN = z^2 \times \frac{TP+FN}{P}$$

TP True Positive
FN False Negative
SN Sensitivity
W Accuracy
Z Confidence interval normal distribution value, i.e for 95%= CI, Z=1.96
P Prevalence of disease in the test population.

Example:

SN	0.99
W	0.075
Z	1.96
P	0.33
TP+FN	6.76
Then s (SN)	20

Total sample size was 20.

Jones, Carley, and Harrison (2003). An introduction to power and sample size Estimation; Emergency Medical Journal vol.20, pp.453–458.

*Due to COVID-19 condition, sample size was small as admission of patient in hospital was adversely affected.

Sampling Method: Consecutive sampling method was followed.

Sample Selection Criteria:

Inclusion Criteria:

Children of either gender, age less than 18 years admitted and diagnosed as acute pancreatitis by any 2 or more of the following criteria.

1. Abdominal pain suggestive of, or compitable with AP (ie: abdominal pain of acute onset, especially in the epigastric region)
2. Serum lipase and/or serum amylase level at least 3 times greater than the upper limit of normal;
3. Characteristic findings of AP with imaging methods (Using USG, CECT, EUS, MRI/MRCP).

Exclusion Criteria:

1. Patients with abdominal pain due to other organic cause.
2. Patient with coagulopathy disorders.
3. Refusal of the parents to give consent.

Sampling Procedure:

- Patients who admitted at the Department of Pediatric Gastroenterology and Nutrition, BSMMU having abdominal pain fulfilled the INSPPIRE criteria of acute pancreatitis were initially enrolled for the study.
- During recruitment, objectives of the study were explained to the parents and a written consent was obtained.
- The detailed clinical history, physical examination findings and investigation reports were recorded in a predesigned standard data sheet by the researcher herself.
- History was obtained directly from the patients/ parents/ caregivers and physical examination of all cases were done by researcher herself at the day of admission under supervision of guide. Assurance was given about the safety of the patient.
- In each case, history were taken in details especially regarding abdominal pain (pattern, location, and duration of pain).
- Examination of each case specially heart rate, respiratory rate, temperature, any feature of shock, dehydration, blood pressure, weight, was done meticulously at admission by researcher. Other general and abdominal status like tenderness, guarding, abdominal distension, epigastric fullness, presence of ascites and bowel sound also were examined.
- Patients were managed with supportive therapy such as bowel rest when needed, proper hydration by intravenous fluid, injectable analgesic and antibiotics in case of infection. Fluid sequestration was calculated after 48 hours from administrated fluid and fluid output.
- For investigation purpose, venous blood was drawn aseptically for laboratory workup.

Data Collection Tool:

- Data collection tool: Data were collected by the researcher herself. A preformed structured questionnaire was filled up for each case which included all the variables of interest (APPENDIX-I).

Statistical Analysis:

After collection, all the data were checked manually. Then they were entered to a data-sheet in the computer-based program SPSS for Windows. Categorical data were presented as frequency with percentage and numerical data were presented as mean with standard deviation in case of normal distribution. Statistical analysis was performed by using SPSS 23.0 and p values <0.001 was considered statistically significant. Statistical significance was demonstrated by unpaired t test to see the association of D-dimer with severity of acute pancreatitis and construction of ROC curve. Sensitivity, Specificity, positive predictive value, negative predictive value, accuracy of D-dimer level were observed by comparing with severe acute pancreatitis and mild acute pancreatitis which was classified by pediatric Acute Pancreatitis severity (PAPS) score.

RESULT

Table 1: Laboratory findings of the study subjects (N=20)

	Frequency	Percent
Hb% (g/dl)		
6 – 9	2	10.0
9 – 12	10	50.0
>12	8	40.0
TC (/cumm)		
>18500	5	25.0
<18500	15	75.0
Hct (%)		
<35	5	25.0
35 – 40	10	50.0

	Frequency	Percent
>40	5	25.0
LDH (U/L)		90.0
<2000	18	10.0
>2000	2	
Blood Urea nitrogen (mg/dl) after 48 hours		70.0
<21	14	30.0
≥26	6	
Serum calcium (mg/dl) (after 48 hours)		
<8.3	4	20.0
≥8.3	16	80.0
Serum Albumin g/dl (after 48 hours)		
<2.6 gm/dl	3	15.0
>2.6 gm/dl	17	85.0

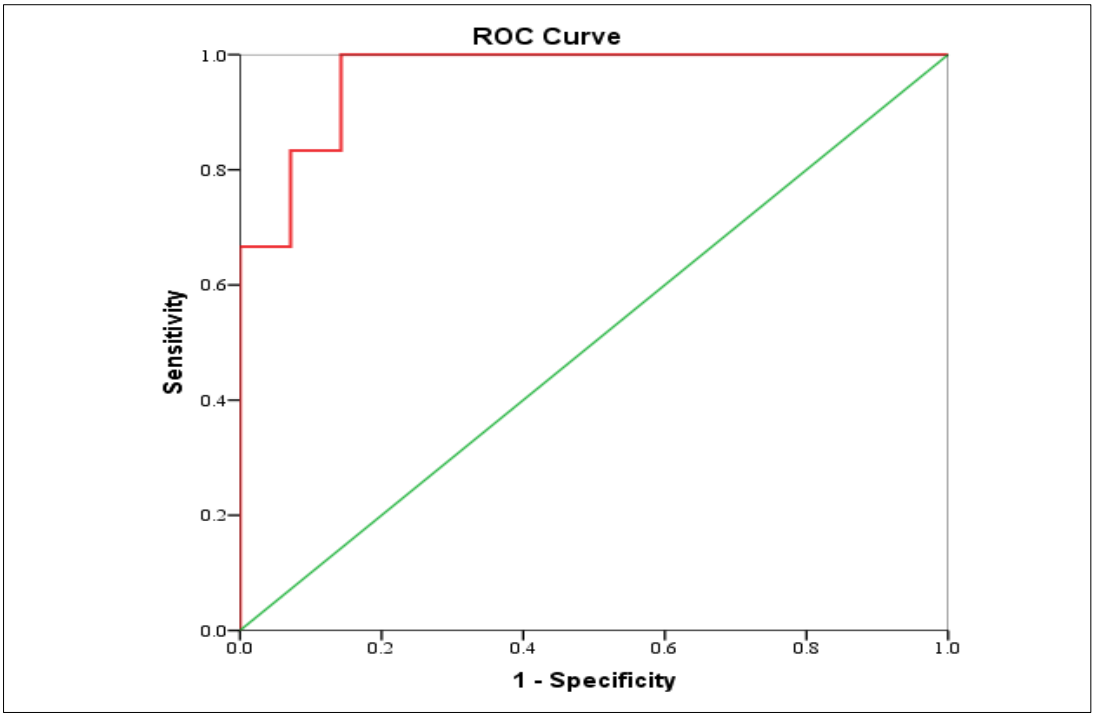

Figure 1: D-dimer receiver operating characteristic (ROC) curve for the differentiation of severity of acute pancreatitis. Area under the curve, 0.964 (95% CI 0.981 – 1.000), Youden index for the optimal cut-off point (D-dimer>1.66), 0.857

Table 2 shows lab findings of the study subjects. Hemoglobin was 6-9 g/dl in 5.0% case, 9 – 12 g/dl in 50.0% cases and >12 g/dl in 45.0% cases. TC was >18500 cumm in 25.0% cases. HCT was <35 in 5.0% case, 35 – 40 in 90.0% cases and >40 in 5.0% cases. LDH was >2000 U/L in 10.0% cases. BUN was <21.0 mg/dl in 70.0% cases and >26.0 mg/dl (rise 5 mg/dl from normal level) in 30.0% cases. Serum calcium was <8.3 mg/dl in 20.0% cases and serum albumin was >2.6 g/dl in 85.0% cases.

Table 2: Association of d-dimer with severity of acute pancreatitis (N=20)

D-dimer(µg/ml)	Mild	Severe	p-value
n (%)	14 (70.0)	6 (30.0)	
Mean ± SD	0.87 ± 0.58	3.39 ± 1.31	<0.001

Unpaired t test was done

Severe acute pancreatitis was found among 30.0% children. D-dimer was found significantly higher among the patients with severe acute pancreatitis than mild acute pancreatitis. In mild AP, it was 0.87 ± 0.58 µg/ml and in severe AP it was 3.39 ± 1.31 µg/ml which was statistically significant (p=<0.001)

Table 3: Diagnostic efficacy parameters for the use of D-dimer in the differentiation of severity of acute pancreatitis for different cut-off point (N=20)

D-dimer(µg/ml)	Sensitivity	Specificity	PPV	NPV	Youden Index
0.510	1.000	0.429	0.636	1.000	0.429
0.535	1.000	0.500	0.667	1.000	0.500
0.775	1.000	0.571	0.700	1.000	0.571
1.100	1.000	0.714	0.778	1.000	0.714
1.365	1.000	0.786	0.824	1.000	0.786
1.665	1.000	0.857	0.875	1.000	0.857
1.815	0.833	0.857	0.854	0.837	0.690
1.900	0.833	0.929	0.921	0.848	0.762
2.035	0.667	0.929	0.903	0.736	0.595
2.550	0.667	1.000	1.000	0.750	0.667

Table 3 Shows Youden index is maximum 0.857 and its cut off value for D-dimer level is 1.665 µg/ml.

Table 4: True positive, false positive, false negative and true negative value of D-dimer in diagnosis of severity of acute pancreatitis at a cut-off point >1.66

D-dimer (µg/ml)	Severe		Mild		p-value
≥1.66	6 (100.0)	TP	2 (14.3)	FP	<0.001
<1.66	0 (0.0)	FN	12 (85.7)	TN	

Among the six severe AP patients all had D-dimer ≥1.66 µg/ml and among 14 mild acute pancreatitis patients 14.3% had D-dimer level ≥1.66 µg/ml and 85.7% had D-dimer level <1.66 µg/ml.

Table 5: Diagnostic efficacy parameters for the use of D-dimer levels in the diagnosis of severity of acute pancreatitis at a cut-off point >1.66

Sensitivity	100.0
Specificity	85.7
Positive predictive value	75.0
Negative predictive value	100.0
Accuracy	90.0
Youden index	0.857

Table 5 shows diagnostic efficacy parameters for the use of D-dimer levels in the diagnosis of severity of acute pancreatitis at a cut-off point >1.66. Sensitivity, specificity, PPV and NPV of D-dimer were 100.0%, 85.7%, 75.0% and 100.0% respectively in the prediction of severity of acute pancreatitis at a cut-off point>1.66.

DISCUSSION

Acute pancreatitis is associated with activation of inflammatory and coagulation pathways, resulting in endothelial injury, microvascular thrombosis, and organ dysfunction. D-dimer, a fibrin degradation product, reflects activation of coagulation and fibrinolysis and has been proposed as an early biomarker for predicting disease severity. Early identification of severe acute pancreatitis is essential because prompt intensive management can reduce morbidity and improve clinical outcomes.

The present study demonstrated that serum D-dimer levels were significantly higher in children with severe acute pancreatitis than in those with mild disease. These findings support the hypothesis that increased activation of the coagulation and fibrinolytic systems accompanies severe pancreatic inflammation. Similar observations have been reported in adult studies. Yang *et al.,* (2017) [14] found significantly higher D-dimer levels in patients with moderately severe acute pancreatitis than in those with mild disease. Likewise, Wan *et al.,* (2019) [15] reported significantly elevated D-dimer concentrations among patients with severe acute pancreatitis. Al Mamun *et al.,* (2019) also demonstrated progressively increasing D-dimer levels from mild to severe acute pancreatitis in adults, suggesting that D-dimer reflects disease progression [13].

The present findings are also consistent with those of Radenkovic *et al.,* (2009), who validated D-dimer as an early predictor of organ failure in acute pancreatitis with high sensitivity and negative predictive value [13]. Ke *et al.,* (2011) further suggested that D-dimer may outperform several conventional single laboratory markers in predicting disease severity [16]. Although most previous studies have been conducted in adults, the present study provides evidence that serum D-

dimer may also serve as a useful biomarker in pediatric acute pancreatitis.

Receiver operating characteristic analysis demonstrated satisfactory diagnostic performance of serum D-dimer for predicting severe acute pancreatitis. At the optimal cut-off value (>1.66 µg/mL), serum D-dimer showed good sensitivity, specificity, positive predictive value, and negative predictive value. Although the optimal cut-off value differed from that reported by Al Mamun *et al.,* (2019), these differences may be explained by variations in study population, age group, disease severity classification, laboratory methods, and sample size [13]. Nevertheless, the overall diagnostic performance observed in the present study was comparable to previous reports.

The findings of this study suggest that serum D-dimer measurement at admission may be a simple, rapid, and inexpensive adjunctive biomarker for early severity assessment in children with acute pancreatitis. Early identification of high-risk patients could facilitate closer monitoring, timely referral to intensive care, and appropriate therapeutic interventions. However, the relatively small sample size and single-center design may limit the generalizability of the findings. Larger multicenter studies are recommended to validate the diagnostic utility and optimal cutoff value of serum D-dimer in pediatric acute pancreatitis.

CONCLUSION

The present study demonstrated that serum D-dimer levels were significantly higher in children with severe acute pancreatitis than in those with mild disease. Serum D-dimer showed good diagnostic performance in differentiating severe from mild acute pancreatitis, suggesting that it may serve as a simple, rapid, and useful early biomarker for severity assessment. Measurement of D-dimer at admission may facilitate early risk stratification and timely clinical management of pediatric acute pancreatitis. However, larger multicenter studies are recommended to validate the optimal cutoff value and its routine clinical application.

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