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Role of D-dimer in Prediction of Severity of Acute Pancreatitis

Dr. Puneet Sharma[1*], Dr. Ashok Kaundal[2], Dr. Anil Malhotra[3], Dr. Amit Sachdeva[4]

[1]Junior resident, Department of General Surgery, Indira Gandhi Medical College, Shimla India
[2]Associate Professor, Department of General Surgery, Indira Gandhi Medical College, Shimla India
[3]Professor, Department of General Surgery, Indira Gandhi Medical College, Shimla India
[4]Senior resident, Department of Community Medicine, Indira Gandhi Medical College, Shimla India

***Corresponding author:** Dr. Puneet Sharma
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Abstract | **Original Research Article**

Background: Acute pancreatitis is a life threatening disease. Multiple scoring systems and biomarkers have been identified for prediction of severity of acute pancreatitis, but none of them does so at time of admission. Importance of using D-dimer lies in that it can predict severity of this disease at time of admission with a single reading. ***Aims and objectives:*** To Determine the relation between D-dimer and early prediction of severity of acute pancreatitis and to determine the predictive value of D-dimer in early prediction of severe acute pancreatitis by comparing with Bed Side Index for severity of acute pancreatitis score. ***Material and methods:*** This study was carried out in the department of surgery, Indira Gandhi Medical College and Hospital, Shimla, HP from July, 2014 to June, 2015.Study involved 50 acute pancreatitis patients (21males and 29 females). D-dimer assay and Bedside Index for Severity of Acute Pancreatitis (BISAP) was calculate at time of admission. ***Results:*** Mean age was 46.4 years. Most common presentation was pain abdomen while most common clinical finding was presence of guarding and tenderness. Total 11 patients had D-dimer of <0.4 mg/l, out of which 4 had mild disease, 5 had moderate and 2 had severe disease. Out of 39 patients with D-dimer value >0.4 mg/l none had mild disease, 21 had moderate and 18 had severe disease. Severe disease could be predicted by D-dimer >0.4mg/l and BISAP >3 in 90% and 80% of patients respectively. ***Conclusion:*** D-dimer is readily available, easy to obtain and cheap alternative of CRP and other scoring systems, which can predict severity of acute pancreatitis with acceptable sensitivity and specificity.
Key words: D-dimer, acute pancreatitis, Bedside Index for Severity of Acute Pancreatitis (BISAP).

INTRODUCTION

Acute pancreatitis, which is inflammation of pancreas, is one of the clinical problems commonly reported in clinical practice. In majority of patients, acute pancreatitis generally runs a benign course. However, in about 20% of cases, it may be severe and can be associated with mortality up to 20% [1].

The incidence of acute pancreatitis is on rise, documented to be increased by 10-folds over past two decades [2]. The incidence of acute pancreatitis is documented to be higher in USA, Finland and Scotland (49.3, 46.6 and 41.9 per 100000 populations, respectively). No prevalence data exists for acute pancreatitis from India.

Mortality in severe acute pancreatitis occurs either early, due to an overwhelming inflammatory reaction or late, owing to sepsis-related complications such as septic shock and major bleeding primarily arising from infected pancreatic necrosis. Coagulative derangements and disturbance of the microcirculation are known to occur in the acute phase of disease and are related to its severity.[3] Coagulative disorders in these patients may range from scattered intravascular thrombosis to severe disseminated intravascular coagulation (DIC) [4].

Identifying the cohort of patients who require critical care support is vital to rationalise health care resources. For this reason, scoring systems and other variables are used, in conjunction with regular clinical review, to ensure prompt and timely intervention. Despite of proliferation of scoring systems for grading, there is no single system which is completely reliable in prediction of severity and mortality.

D-dimer is a fibrin degradation product, a small protein fragment present in blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross linked D fragments of fibrin protein. D-dimer measurement is a useful, easy, and inexpensive early prognostic marker of the evolution and complications of severe acute pancreatitis.

Salomone *et al*. [3] found that the plasma levels of D-dimer were significantly different between patients with uncomplicated pancreatitis and patients with complications. Radenkovic *et al*. suggested that the measurement of plasma levels of D-dimer, irrespective of whether D-dimer concentrations were measured during the first hour of admission or 24 h later, was an accurate method for the identification of patients who would develop organ failure in the further course of AP [5]. The extent of fibrinolysis (as indicated by D-dimer levels) is related to the severity of the disease and can be correlated with multi-organ failure.

Only few studies of D-dimer for prediction of severity of acute pancreatitis have been conducted worldwide. Highlight of study is to use cheaper and easily available laboratory investigation i.e. D-dimer and Bed Side Index for Severity of Acute Pancreatitis (BISAP), which also includes minimal laboratory tests to predict severity of acute pancreatitis within 24 hrs of admission.

Aims and objectives

- Determine the relation between D-dimer and early prediction of severity of acute pancreatitis.
- To determine the predictive value of D-dimer in early prediction of severe acute pancreatitis by comparing with Bed Side Index for severity of acute pancreatitis score and CT Severity Index.
- To determine if patients could be stratified into having mild, moderate or severe pancreatitis based on various cut-off D-dimer values.

MATERIALS AND METHODS

This study was carried out in the department of surgery, Indira Gandhi Medical College and Hospital, Shimla, HP. The period of study was from July, 2014 to June, 2015. Patients admitted with diagnosis of acute pancreatitis were considered for this study, after taking informed consent.Study involved 50 patients (21males and 29 females).

Inclusion criteria

All patients admitted with diagnosis of acute pancreatitis irrespective of the etiology.

Exclusion criteria

- Immunocompromised patients in whom deranged D-dimer values maybe attributed to other causes
- Patients who are known cases of coagulative disorders
- Pregnant females who will not be subjected to radiation for CT scan to assess for pancreatic necrosis.
- Patients with previous episode of proven pancreatitis.
- Patients who have surgical interventions prior to admission
- Patients with recent history of myocardial infarction or cerebral insult.

Study procedure

Acute pancreatitis was diagnosed according to the clinical symptoms, radiological evidence (USG and/or CT scan) and elevation of serum amylase more than three times or raised serum amylase levels. Onset of pancreatitis was taken as the time when patient developed symptoms rather than the time when he was admitted. Detailed history of the patient and physical examination were done at time of admission. Patients were stratified into mild, moderate and sever pancreatitis as per revised Atlanta guidelines. 2 groups were made: mild pancreatitis and moderate+severe pancreatitis. For D-dimer two groups were created with value of <0.4mg/l and >0.4mg/l and BISAP score group was divided into 2 groups of <3 and >3. Following investigations were done:

- Complete haemogram, Serum Glucose, Renal function test, Liver function tests - Bilirubin (total and conjugated), AST, ALT, ALP, Serum Amylase and /or serum Lipase, Serum Ca^{++} levels, ECG, Chest and Abdominal X-rays, Ultrasonography of the abdomen.
- Quantitative serum high sensitivity D-dimer assay was done at time of admission.
- Bedside Index for Severity of Acute Pancreatitis was calculating at time of admission.

D-dimer Estimation

3ml of clotted blood samples was taken. The concentration of D-dimer was measured By Nycocard D-dimer Single Test Kit and Using Nycocard Reader II (Axis-Shield Poc as Norway).

Test Procedure

- Preparation of plasma: venous blood was drawn in evacuated blood collecting tubes for coagulation analysis (0.11 or 0.13 M Na-citrate). One volume of this solution was added to volumes of whole blood in a tube. Sample was centrifuged for 15 minutes at 2000g.
- Prewashing: 50 µl of washing solution was applied to test device.
- Sample: 50 µl of undiluted platelet free citrated plasma or control was applied to device.
- Conjugate: 50 µl of conjugate was applied to test device.
- Washing: 50 µl of washing solution was applied to test device.
- Test response was measured within 2 minutes. Nycocard reader II was used for measuring results. Results were expressed as D-dimer concentration in mg/l.

Bed side index for severity of acute pancreatitis Score (BISAP)

This score was calculated at 24 h of admission using BUN level > 25 mg/dL, Impaired mental status,

Systemic Inflammatory Response Syndrome (SIRS), Age > 60 years and Pleural effusion (on chest radiography or CT).

Altered mental status was defined as any record of disorientation, lethargy, somnolence, coma or stupor in the medical record. The SIRS was defined by the presence of 2 of the following criteria: pulse > 90 beats/min; respirations > 20/min or $PaCO_2$ < 32 mm Hg; body temperature > 38°C or < 36°C; white blood cells (WBC) count >12 000 or < 4000 cells/mm^3 or >10% immature neutrophils (bands). Each point on the BISAP scores worth 1 point. Score of >3 were taken as cut-off for severe acute pancreatitis

STATISTICAL ANALYSIS

ANOVA test for independent data was used to compare concentrations of D-dimer and bedside index for severity of acute pancreatitis between groups. The prognostic value of D-dimer in prediction of severity of acute pancreatitis was compared to that of bedside index of severity of acute pancreatitis.

RESULTS

In the present study the age of patients ranged between 16 years to 77years. Mean age was 46.4 years. Maximum number of patients was in age group of 30-50 years and 50-70 years. 4 patients had mild pancreatitis, 26 had moderate and 20 had severe pancreatitis. It was also observed, that as the age increased number of patients with severe disease also increased. Among total 50 patients 21 were males and 29 were females. Male to female ratio was 1:1.38

Table-1: Age and Gender distribution of study participants

Age group (in years)	Acute pancreatitis			Total
	Mild	Moderate	Severe	
10-30	3	2	2	7
30-50	2	9	9	20
50-70	1	12	7	20
>70	0	1	2	3
Mean & SD	36.25 ± 15.74	47± 13.98	47.1 ± 15.9	
Male	3	11	7	21
Female	3	13	13	29
Total	6	24	20	50

Most common presentation was pain abdomen. All patients presented to hospital with this complaint. Fever was present in 20 patients. It was observed in patients with moderate to severe disease. Most common clinical finding was presence of guarding and tenderness. It could be elicited in 90% of patients. It was followed by presence of pleural effusion, in 50% of patients. None of the patients with mild disease had pleural effusion, 34.6% patients with moderate disease and 80% of patients with severe disease had pleural effusion. Ascitis was not a common finding and was present in 20% of patients and mostly in patients with severe disease. 12% of patients had lump in epigastric region at the time of presentation to hospital. Grey turner and Cullen's signs couldn't be elicited in any patient.

Table-2: Clinical presentation of the study participants

Sign and symptoms	Mild acute pancreatitis	Moderate acute pancreatitis	Severe acute pancreatitis	Total	Percentage
Pain abdomen	4	26	20	50	100%
Fever	0	6	14	20	40%
Guarding & tenderness	3	22	20	45	90%
Pleural effusion	0	9	16	25	50%
Ascitis	0	2	8	10	20%
Lump	0	0	6	6	12%
Grey turner & cullen's sign	0	0	0	0	0%

Single reading of D-dimer was taken within 24 hours of admission after the patient was diagnosed to have acute pancreatitis. All patients were divided into 2 groups, one with D-dimer of <0.4 mg/l and other with >0.4mg/l. Total 11 patients had D-dimer of <0.4 mg/l, out of which 4 had mild disease, 5 had moderate and 2 had severe disease. Out of 39 patients with D-dimer value >0.4 mg/l none had mild disease, 21 had moderate and 18 had severe disease. Mean values of D-dimer for patients with mild, moderate and severe disease were 0.15, 0.583 and 0.954 mg/l respectively.

Table-3: D-dimer reading after 24 hours of admission

D-dimer (mg/l)	Acute pancreatitis			Total
	Mild	Moderate	Severe	
<0.4	4	5	2	11
>0.4	0	21	18	39
Total	4	26	20	50
Mean ±2SD	0.15± 0.10	0.583± 0.357	0.954± 0.632	
p-value	0.001			

BISAP (Bedside index for severity of acute pancreatitis) score was calculated at time of admission to hospital and Patients were divided in two groups, one with BISAP score <3 and other with >3 as shown in table 4. Out of 19 patients with BISAP score of <3, 4 (21.05%) had mild disease, 11 (57.89%) had moderate and 4 (21.05%) had severe disease. Out of 31 patients with score of >3, none had mild disease, 15 (48.39%) had moderate and 16 (51.61%) had severe disease. Out of all 20 patients with severe disease on CECT abdomen 16 (80%) had BISAP of >3.

Table-4: Bedside index for severity of acute pancreatitis (BISAP SCORE)

BISAP	Acute pancreatitis			Total
	Mild	Moderate	Severe	
<3	4	11	4	19
>3	0	15	16	31
Total	4	26	20	50
p-value	0.004			

When D-dimer and BISAP score were compared with each other, none of the patients with mild disease had either D-dimer of >0.4mg/l or BISAP >3. In patients with moderate disease D-dimer was >0.4mg/l in 80.76% of patients and BISAP was >3 in 57.7% of patients. Severe disease could be predicted by D-dimer >0.4mg/l and BISAP >3 in 90% and 80% of patients respectively.

Table-5: Comparison of D-dimer with BISAP for prediction of severity of acute pancreatitis

Acute pancreatitis	**D-dimer**		**BISAP**	
	<0.4mg/l	>0.4mg/l	<3	>3
Mild	4/4 (100%)	0/4 (0%)	4/4 (100%)	0/4 (0%)
Moderate	5/26 (19.23%)	21/26 (80.76%)	11/26(42.3%)	15/26 (57.7%)
Severe	2/20 (10%)	18/20 (90%)	4/20 (20%)	16/20 (80%)

DISCUSSION

The age of patients ranged between 16 years to 77years. Mean age was 46.4 years. It was observed, that as the age increased number of patients with severe disease also increased. Male to female ratio was 1:1.38. Age was not found to be a significant factor in the occurrence of acute pancreatitis (p>0.05). Similarly there was no significant difference in the incidence of acute pancreatitis in both the sexes (P= 0.335).

Most common presentation was pain abdomen. Most common clinical finding (90%) was presence of guarding and tenderness. It was followed by presence of pleural effusion, in 50% of patients. Ascitis was not a common finding and was present in 20% of patients and mostly in patients with severe disease.

In the present study BISAP score was calculated at time of admission to hospital. Patients were divided in two groups, one with BISAP score <3 and other with >3. Out of all 20 patients with severe disease on CECT abdomen 16 (80%) had BISAP of >3.

In present study mean value of D-dimer in mild disease was 0.15± 0.1mg/l, for moderate disease was 0.583±0.357mg/l, for sever disease was 0.957±0.632 mg/l. When the cut-off value for the differentiation from mild disease was taken as 0.4 mg/l , it could predict moderate and severe disease in 39 out of 46 patients, with p- value of <0.001. Out of 26 patients with moderate disease it was >0.4 mg/l in 21 patients and in 20 patients with severe disease it was >0.4 mg/l in 18 patients. Raised D-dimer value could predict severe disease in 90% of patients. It could predict severity with sensitivity of 84.7%, specificity of 100%, positive predictive value of 100% and negative predictive value of 36.4%, which is comparable to that in the literature.

When compared with bedside index for severity of acute pancreatitis, in patients with moderate disease D-dimer was >0.4mg/l in 80.76% of patients and BISAP was >3 in 57.7% of patients. Severe disease

could be predicted with D-dimer >0.4mg/l and BISAP >3 in 90% and 80% of patients respectively.

Few studies calculating the sensitivity, specificity of D-dimer in predicting severity of acute pancreatitis:

Table-6

Study	Sensitivity %	Specificity %
Lu-ke, Hai-bin *et al.* [6]	93	81
Radenkovic *et al*. [5]	90	89
Sreekanth A, Jahangeer B *et al*. [7]	95	96
Our study	84.7	100

CONCLUSION AND RECOMENDATION

D-dimer is readily available, easy to obtain and cheap alternative of CRP and other scoring systems, which can predict severity with acceptable sensitivity and specificity. BISAP score can also be a useful bed side tool at time of admission for stratification of patients into mild and moderate to severe disease. We recommend the D-dimer can be used as single biomarker for early prediction of severity of acute pancreatitis.

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