Original Article

D-dimer as a Marker of Severity and Prognosis in Acute Pancreatitis

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Abstract

Background and Objectives: Acute pancreatitis (AP) scores need a battery of tests that are not helpful at an early stage. Can a single test predict Complicated Acute Pancreatitis (CAP) which includes moderate and severe AP, local complications, and need for intensive care unit (ICU). **Methodology:** 30 patients of AP. D-dimer, C-reactive protein levels done within 3 days of AP onset. APACHE II, Ranson's score, CT severity index were done. Inhospital disease course for development of organ failure and need for ICU care was followed daily. **Results:** D-dimer in CAP was 2732 ng/L (MAP 567 ng/L), in abnormal computed tomography (CT) was 1916 ng/L (normal CT 363 ng/L), and in organ failure was 4776 ng/L (776.5 ng/L absent organ failure). D-dimer increases as the severity of organ failure increases (P = 0.04). D-dimer in ICU patients was significantly elevated (P = 0.021). D-dimer correlates with APACHE II score well, with an increase in predictive mortality rate (P = 0.01). On receiver operator characteristics, D-dimer >933.5 ng/L predicts CAP, >827.5 ng/L predicts positive CT findings (local complications), and >1060.5 ng/L predicts the development of organ failure. **Conclusion:** Coagulopathy and microthrombi play a significant role in early pathogenesis. D-dimer test acts at the level of this core pathogenesis, even before the complications set in. D-dimer within 72 h of AP correlates well with the CT findings after 72 h. This is the first study that correlates D-dimer levels with CT scores, ICU requirement. D-dimer can guide primary care physicians in selecting AP patients for referral to a higher center in a resource-limited setting.

Keywords: *Alcoholic pancreatitis, chronic pancreatitis, D-dimer, lipase, multiple organ failure, pancreatitis, prognosis*

Introduction

Acute pancreatitis (AP) with a narrow therapeutic window is a common acute condition seen by emergency and primary care physicians.[1] AP can be mild, moderately severe, and severe. Usually mild AP resolves by itself whereas severe AP seen in 20% has a good chance of fatal complications.[2] There is a wide variation of morbidity and mortality rates between mild AP and severe AP (<5% vs. 25%).[3,4] Natural history of AP has 2 phases: early (first 14 days due to systemic inflammatory response syndrome) and late phase (begins 2 weeks after the onset of AP, due to infection of the pancreatic necrosis seen in 40%–70%).[5,6] To improve the clinical outcome in AP, an accurate assessment of severity and an appropriate management plan is essential to avoid fatal outcomes. Prediction of severity is usually done by various scores and predictive models based on clinical, laboratory, and radiological investigations. Many of these scores require a battery of tests. In some semi-urban and rural areas, computed tomography (CT) facility is not available. Therefore, in the setting of financial constraints for the patient or due to the nonavailability of CT scan, there is a hindrance in planning active referral management of the patient from a resource-limited setup to a high dependency unit, tertiary referral setup. This is important not only in SAP but also in mild AP. Because AP is a dynamic disease, mild AP can progress to SAP and become fatal during the course of treatment.[7] It needs triage of patients because of the implications of management, prognostication, and allocation of health-care resources. Patients requiring early aggressive resuscitation in high dependency or intensive care units (ICUs) would be benefitted from early transfer to an expert center.[8] More than 50% of deaths occur in the 1st week from the disease onset in AP and deaths occur frequently within 1 week after the onset of multi-organ dysfunction syndrome (MODS).[9] Therefore, anticipation and prediction of MODS becomes crucial in the initial few days.

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Intensive care management is essential and effective in managing SAP, and early identification of patients who might require transfer to an ICU is essential.[10,11] Hence, even mild AP should be monitored with the greatest care and anticipation. Therefore, in the resource-limited setting, prediction and anticipation of SAP becomes difficult even among the mild cases. It would be of great help, if there is a simple test that is widely known and available, that is cost-effective and can predict SAP, the clinical progression and disease outcome in AP. An ideal prognostic marker is yet to be found. Preferably, it should be a single safe test, simple, quick, cheap, can be done at hospital admission, readily available, repeatable, reproducible, and observer independent.[8] There is increasing evidence of pancreatic and systemic microvascular disturbances in the pathogenesis of pancreatitis in the form of vasoconstriction, shunting, inadequate perfusion, increased blood viscosity, and coagulation.[12] Impaired microcirculatory blood flow is a well-recognized risk factor for moderate and severe AP and progression of severity. Superimposition of ischemia on reversible edematous pancreatitis leads to irreversible necrotizing pancreatitis.[13] This is the first study to correlate D-dimer levels with CT findings and ICU stay.

Methodology

Study design

This prospective observational study was conducted in a tertiary care-level teaching hospital, which caters to a large section of economically weaker patients and rural population from within and neighboring states.

Study population

Thirty patients with AP presenting within 3 days of the onset of AP were recruited for this study by consecutive sampling. None of them had organ failure and needed ICU at the time of admission. For estimation of D-dimer levels in AP with 30% relative precision and 95% confidence interval, the sample size required was 30. The onset of AP is defined as the time of onset of abdominal pain and not the time of admission to the hospital. The time interval between the onset of abdominal pain and first admission to the hospital was noted. The exclusion criteria were patients with recurrent pancreatitis, chronic pancreatitis, delayed presentation to the hospital after disease onset, known coagulopathy disorders, pregnancy, trauma, chronic liver disease, previous deep vein thrombosis, ischemic heart disease, cerebrovascular disease, anticoagulants/hormonal replacement therapy, known organ failure, admitted to ICU on presentation, and immune-compromised patients.

Data collection

The diagnosis of AP, classification of severity (into mild, moderately severe, and severe), organ failure based on the modified Marshall scoring system (MMSS), CT morphological features of AP, and CT severity index were made based on revised Atlanta criteria. At the time of admission, D-dimer and C-reactive protein (CRP) levels were done along with other routine blood tests such as arterial blood gas, complete hemogram, renal function tests, liver function tests, prothrombin time, and amylase and lipase levels. The patients were followed up and monitored daily in the hospital. Development of organ failure (transient/permanent), need for ICU care, ventilator support, inotropic support, dialysis, etc., during the course of hospital stay was recorded. Findings on CT imaging and transabdominal ultrasonography were noted. All patients had an ultrasound, and 14 patients underwent contrast-enhanced CT (CECT). Patients were managed appropriately as per routine protocols. Inclusion in the study or D-dimer test values were not informed to the treating team, hence the study did not influence the treatment management protocol of any patients. In our study, the study population was divided into two categories: mild AP and complicated pancreatitis (with organ failure and local/systemic complications) which included moderately severe and severe AP. Ranson's score, APACHE II score, and computed tomography severity index (CTSI) were calculated for all these patients.

Data analysis

Continuous variables were expressed as mean with standard deviation, and nonparametric data were expressed as median with a 25–75th interquartile range. Mann–Whitney *U*-test was done to assess the statistical significance. Categorical values are expressed as numbers and percentages. The Chi-square test and analysis of variance were used to assess statistically significant association. $P < 0.05$ was considered to be statistically significant. Receiver operating characteristic (ROC) curves were plotted to find the predictive diagnostic capacity, cutoff values, and sensitivity and specificity.

Ethical consideration

The study was approved by the Institutional Ethics Committee with signed informed consent taken from all the participants.

Results

The basic demographics of the study population, etiological factors are given in Table 1. Table 2 shows the study population distribution into varying grades of severity of AP and CT morphological features according to revised Atlanta criteria and CT severity index score. The D-dimer level (ng/L) showed a statistically significant ($P = 0.001$) increasing trend as the severity of AP increases, as in mild AP (557.9 ± 244.1), moderately severe (2653 ± 2009.5), and severe AP (5911 ± 111.6). Table 3 demonstrates the D-dimer levels in different grades of severity of pancreatitis, with grades of CT severity index scores and with the development of organ failure and the need for ICU care. The D-dimer levels (ng/L) increased as the

CTSI increased, the D-dimer levels (ng/L) in normal CT was 363, CTSI 4 was 1079.5, CTSI 6 was 3375.3, CTSI was 4084.2 (P = 0.04). The CRP level (mg/dl) in mild AP was 9.64 (±7.78) and complicated AP was 20.88 (±5.68), $P < 0.001$. The CRP level (mg/dl) in organ dysfunction was 19.7, single-organ failure was 22.4, and multiorgan failure 20.4; no significant correlation was seen between CRP and organ failure (P = 0.5). The Ranson's score did not show a statistically significant correlation between mild AP and complicated AP (P = 0.256), between no organ failure and the presence of organ failure (P = 0.193). There was no significant correlation (P = 0.256) between the Ranson's score and D-dimer levels. Figure 1 shows increasing mean D-dimer levels with increasing levels of organ failure, and APACHE II scores. It demonstrates the increasing levels of D-dimer as the respiratory failure (Pao2/FiO2) increases leading to multi-organ failure, as per Modified Marshall Scoring System; the D-dimer levels show an increasing trend as the APACHE II scores with predicted mortality risk increase. Figure 2 shows the ROC curves, where D-dimer levels of 933.5 ng/l and above are highly suggestive of the development of complicated pancreatitis, D-dimer levels of 827.5 ng/l and above are highly suggestive of the development of local complications in CT, D-dimer levels of 1060.5 ng/L and above are highly suggestive of development of organ failure.

Table 1: Characteristics of the study population

Basic demographics	*n* (%)		
Sex			
Male	24 (80)		
Female	6 (20)		
Age			
18–30	10 (33.3)		
31–40	14 (46.7)		
41–50	3 (10)		
51–60	2 (6.7)		
>60	1 (3.3)		
Etiological cause	**Male (*n*)**	**Female (*n*)**	**Total, *n* (%)**
Alcohol	21	0	21 (70)
Biliary stones	2	4	6 (20)
Idiopathic	1	2	3 (10)

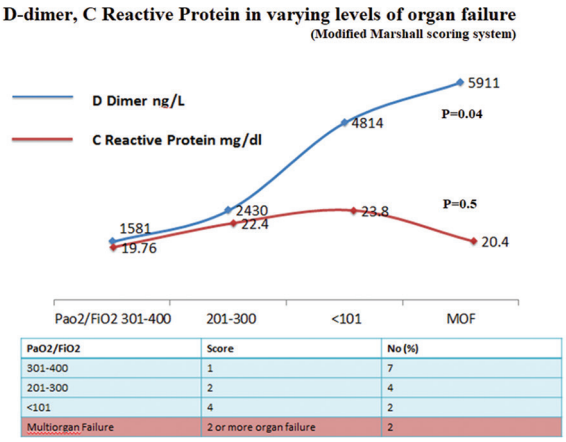
Table 2: Grades of severity of acute pancreatitis and computed tomography findings

	n (%)
Severity of pancreatitis	
Mild	15 (50)
Moderately severe	13 (43.3)
Severe	2 (6.7)
CTMF	
Normal	3 (21.4)
Interstitial edematous pancreatitis	4 (28.6)
Necrotizing pancreatitis	2 (14.3)
Acute necrotic collection	2 (14.3)
Walled-off necrosis	2 (14.3)
Acute peripancreatic fluid collection	1 (7.1)
CTSI	
Normal	3 (21.4)
4	3 (21.4)
6	3 (21.4)
8	5 (35.7)

CTSI: Computed tomography severity index; CTMF: Computed tomography morphological feature

Discussion

Alcohol is the primary cause of both acute and chronic pancreatitis in most countries. Autopsy studies have revealed subclinical pancreatitis in 10% of alcohol abusers.[14] Gallstone pancreatitis is more common in female subjects, and alcoholic pancreatitis is more common in middle-aged male subjects.[15,16] Abstinence after the first attack of AP protects from further attacks and decreases pancreatic dysfunction (endocrine and exocrine).[17] Studies have found that the severity of AP is independent of the elevation in serum amylase and lipase levels on admission. Patients with only a slight increase in these enzymes can also have or develop severe AP. This is especially true for patients with alcohol-induced AP whose amylase levels are lower than in other etiological groups.[18] Similarly, they do not correlate



D-dimer levels & APACHE II scores in varying grades of acute pancreatitis

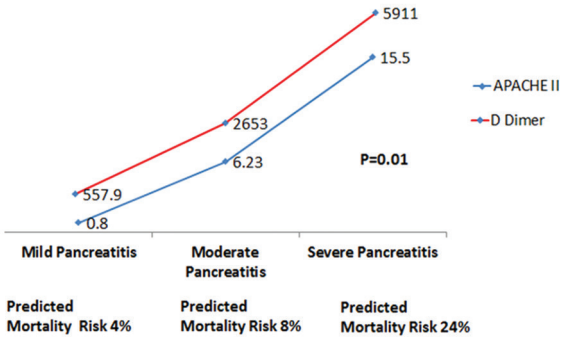
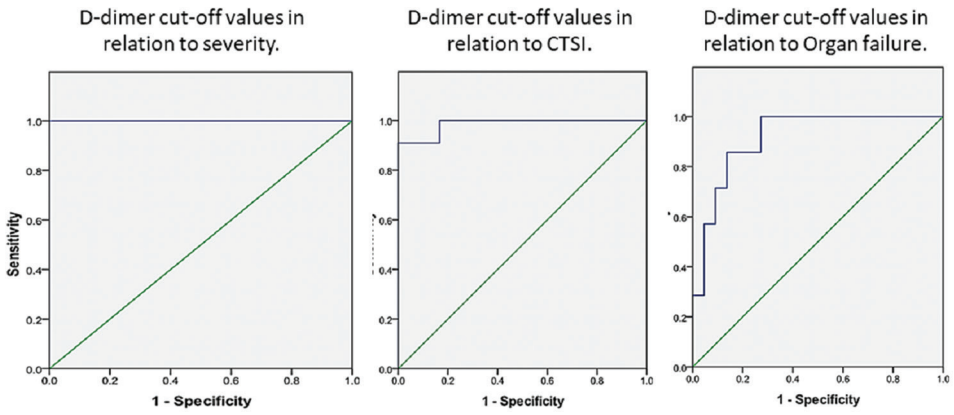


Figure 1: Correlation between D-dimer levels and respiratory failure, multi-organ dysfunction, and APACHE II scores with predicted mortality risk



D-dimer Cut-off, ng/L	Severity
>=933.5	Complicated Pancreatitis
<933.5	Mild Pancreatitis
Sensitivity	1
Specificity	1

D-dimer cut-off, ng/L	CT
>=827.5	Abnormal CT
<827.5	Normal CT
Sensitivity	0.909090909
Specificity	0.833333

D-dimer cut-off, ng/L	Organ failure
>=1060.5	Present
<1060.5	Absent
Sensitivity	0.857142857
Specificity	0.727273

Figure 2: The receiver operator characteristic curves, D-dimer levels, and development of complicated pancreatitis, local complications, and organ failure

Table 3: D-dimer levels in severity grades, computed tomography severity index, organ failure, and intensive care unit

Severity of AP versus laboratory parameters, median (IQ)			
Severity	**Amylase (IU)**	**Lipase (IU)**	**D-dimer (ng/L)**
Mild pancreatitis	314 (328)	2351 (4961)	567 (444)
Complicated pancreatitis	551 (856)	2967 (7214)	2732 (4034)
P	0.245	0.2	<0.001
CTSI versus D-dimer levels			
CTSI			**D-dimer (ng/L), median (IQ)**
Normal CT			363 (483)
CTSI 4, 6, 8			1916.5 (4356)
P			0.005
Organ failure versus D-dimer			
Organ failure			**D-dimer (ng/L), median (IQ)**
No organ failure			776.5 (670)
Organ failure present			4776 (5142)
P			0.001
Need for ICU versus D-dimer			
Level of care			**D-dimer (ng/L), median (IQ)**
ICU care			2732 (4805)
Non ICU care			847 (685)
P			0.021

ICU: Intensive care unit; CTSI: Computed tomography severity index; IQ: Interquartile; AP: Acute pancreatitis

with the etiology of pancreatitis or severity.[19] D-dimer levels were significantly different among patients with mild pancreatitis and complicated pancreatitis which includes moderately severe and severe pancreatitis ($P < 0.001$). The D-dimer levels increase as the grade of severity increases in AP ($P = 0.001$). In AP, CRP rises due to inflammation and infection if present; it is not specific to the pathogenesis. However, D-dimer operates at the level of the pathogenesis of microcirculatory disturbances seen in AP. For a prognostic score to be ideal, it should operate at the level of pathogenesis. Coagulation abnormalities are frequent in AP, and they correlate with severity.[20] In AP, there is concurrent activation of inflammatory and procoagulant pathways. D-dimer is significantly raised in SAP compared to Mild AP.[21] D-dimer levels increase significantly as CTSI increases ($P = 0.04$). All these CTs were done after 72 h in our study as an early CT will not be of help. Because more reliable results are obtained 72 h after the onset.[22] Hence, CT does not help assess the severity and predict prognosis in <72 h. D-dimer levels done in the first 72 h of AP correlate well with the findings on CT done after 72 h, thereby precious time of therapeutic window is not lost. D-dimer levels were significantly elevated in patients with organ failure compared to patients with no organ failure ($P = 0.001$). Similarly, as the organ dysfunction (MMSS score 1) becomes organ

failure (MMSS 2) and multi-organ failure (2 or more organs), the D-dimer levels rise in a statistically significant manner ($P = 0.04$) whereas the CRP levels did not show such significance ($P = 0.5$), as shown in Figure 1. D-dimer levels in the initial days of disease onset correlate well with the development of organ failure and multi-organ failure. The disturbances of microcirculation in SAP are not confined to the pancreatic capillary bed but are also observed in other organs. Diffused microcirculatory disorders may play a crucial role in the development of MODS in SAP.[23] Various studies suggest that both the initiation and the progression of pancreatitis are characteristically associated with impairment in the gland's microcirculation. Rubidium clearance technique, electromagnetic flow meters, and radioactive microsphere studies have confirmed blood flow impairment in AP.[24] Coagulative derangements and disturbance of the microcirculation are known to occur in the acute phase of AP and are related to its severity.[25] Intravascular thrombosis has been suggested as a mechanism of pancreatitis-associated impairment of the microcirculation.[26] Pathologic examination of severe pancreatitis has shown extensive interstitial fat necrosis, necrotizing vasculitis with occlusions, and thrombosis of small feeding arteries and draining veins, areas of hemorrhage, and devitalized pancreatic parenchyma.[27] There is increasing evidence of pancreatic and systemic microvascular disturbances in the pathogenesis of pancreatitis in the form of vasoconstriction, shunting, inadequate perfusion, and increased blood viscosity and coagulation.[12] The superimposition of ischemia on reversible edematous pancreatitis leads to irreversible necrotizing pancreatitis.[13] Destabilization of the vascular endothelium is commonly seen in AP which leads to vascular bed leak causing vasodilation, hypotension, and complications.[28] This fluid leak with continuing high-volume resuscitation causes intra-abdominal hypertension which compromises intra-abdominal perfusion pressure.[29] Patients with shock can easily have inappropriately low abdominal perfusion pressure even with moderate intra-abdominal hypertension. This leads to bowel mucosal ischemia, bacterial translocation, infection, sepsis, and multi-organ failure.[30,31]

This vascular bed leak causes hemoconcentration which, along with intravascular coagulation, is highly relevant for the development of pancreatitis-associated microvascular instability,[32] improved by isovolemic hemodilution,[33] and heparin administration which counteracts the effects of microvascular thrombosis.[34] D-dimer is a small protein fragment present in the blood after the fibrinolysis of the thrombus happens. It is detected with the availability of monoclonal antibodies that bind to D-dimer.[35]

The mean APACHE II score with predictive mortality risk increases as the severity of AP increases ($P = 0.01$). Various studies suggest higher median APACHE II scores among nonsurvivors versus survivors (score = 26 vs. 19, respectively; $P < 0.001$). An APACHE II cutoff of 24.5 and pre-ICU admission time of 2.5 days were sensitive predictors of fatal outcomes.[36] A significant difference in D-dimer levels was noted between patients needing ICU care and those managed in the ward. Furthermore, it should be noted that the need for ICU is mainly dependent on the clinical condition of the patient. Based on the ROC curve, D-dimer levels above 933.5 ng/L are highly suggestive of pancreatitis with complications that can be moderately severe or severe AP. D-dimer levels of more than 827.5 ng/L are highly suggestive of localized pancreatic complications on the CECT abdomen. D-dimer levels of more than 1060.5 ng/L predict the possible development of organ failure. Thus, D-dimer correlates significantly with the severity and development of local and systemic complications.

This is the first study that has studied the correlation between D-dimer levels and development of local complications, need for ICU care during the course of disease. The small sample size and limited resources for various tests were limitations of the study. This study can be done on a larger sample size for generalizability; the study population can be matched for age and underlying comorbidities. An ideal or desirable detection system should (a) have high sensitivity and PPV, (b) be able to predict necrosis early (48 h), (c) be performed rapidly (4 h), (d) be available in most hospitals, (e) be relatively inexpensive, and (f) be objective and not observer-dependent.[37] In our study, D-dimer satisfies all these requirements.

Conclusion

D-dimer as a single marker can be used to grade the severity of AP, predict the development of local complications and organ failure. Persistent organ failure and mortality are two valid endpoints for the prediction of severity in AP. It is suggested that for accurate prediction of severity, the endpoint of the test/tool should be causally associated with the severity. The most commonly used scores/tools in AP show statistical significance but lack causal association.[38] A particular score correlates well with mortality, but there is a third variable involved in between, for example, organ failure which has led to the fatal outcome. The variables tested in the predictive score do not contribute or have a causal association with the pathophysiology and subsequent fatal outcome. However, D-dimer works based on microvascular abnormality and coagulation abnormalities, the common pathophysiology seen in AP. Hence, it does not detect the endpoint only but shows a causal association.

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Ethical clearance

The study approved by Institutional Ethics Committee of St. John's Medical College & Hospital, Bengaluru, India through its letter no: IEC/1/34/2017.

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Conflicts of interest

There are no conflicts of interest.

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