Original Research Article

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D-dimer levels in predicting the severity of acute pancreatitis

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ABSTRACT

Background: Coagulative disorder is known to occur in the early phase of acute pancreatitis. (AP) and D-dimer is a commonly used clinical parameter of haemostasis. The aim of this study was to assess the value of the plasma D-dimer level as a marker of severity in the 1.3.5 days after admission in patients with Acute pancreatitis.

Methods: From September 2015 to September 2017, 60 patients admitted for AP were included in this observational study. The D-dimer level was measured during days 1,3,5 after admission and the acute physiology and chronic health evaluation (APACHE) II score, sequential organ failure assessment (SOFA) score, and other clinical parameters were recorded at the same time. The maximum and the mean D-dimer values were used for analysis and compared with other prognostic factors of AP.

Results: Both the maximum and mean levels of D-dimer were significantly different between patients with and without clinical variables such as multiple-organ dysfunction syndrome (MODS), need for surgical intervention, and the mortality. Additionally, the D-dimer level correlated well with two usual markers of AP severity-the APACHE II score and the C-reactive protein level. Conclusion D-dimer measurement is a useful, easy, and inexpensive early prognostic marker of the evolution and complications of AP.

Conclusions: D-dimer measurement is a useful, easy, and inexpensive early prognostic marker of the evolution and complications of SAP.

Keywords: Acute pancreatitis, D-Dimer, Multiple organ dysfunction syndrome, Pancreatic infection

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition characterized by variable severity ranging from a mild, self-limited disease to a severe, systemic disease associated with multiple organ dysfunction. Up to 12-25% of the patients develop severe acute pancreatitis (SAP), which has a mortality rate of 8-25%.

Mortality in SAP 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 AP and are related to its severity.² Coagulative disorders in these patients may range from scattered intravascular thrombosis to severe disseminated intravascular coagulation (DIC).³

In previous studies, some haemostatic system-related parameters have been shown to be potential predictors of AP severity and outcome.^{2,4,5} D-dimer, which is mostly used as an effective diagnostic tool to rule out deep vein thrombosis (DVT) as well as pulmonary embolism (PE).^{6,7} has been reported to have great predictive power

in the early phase of AP. Salomon et al, found that the plasma levels of D-dimer were significantly different between patients with uncomplicated pancreatitis and patients with complications.² 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.⁴

METHODS

In this observational study, all consecutive adult patients (age 18 years) with AP (within 72 h from the onset of the disease) hospitalized in JSS Hospital Mysore in department of General Surgery between January September 2015 to September 2017 were studied. Patients who had suffered prior attacks of acute pancreatitis, patients who had received surgical intervention before admission, and patients with a known history of coagulative disorders or a recent history of myocardial infarction or cerebral infarction were excluded from the study. All patients received standard medical therapy and were followed until discharge from the hospital or hospital death.⁸

Baseline data including age, sex, aetiology, the Ranson score, and the APACHE II score were recorded on admission. The definitions of organ dysfunction were based on a score of 2 or more in the sequential organ failure assessment (SOFA) scoring system. Multiple-organ dysfunction syndrome (MODS) was defined as the combined dysfunction of 2 major organ systems. Pancreatic necrosis was diagnosed according to the results of contrast enhanced computed tomography (CECT) performed at least 48 h after the onset of the disease. Major organ systems.

Both the SOFA score and APACHE II score were assessed on a daily basis during days 1,3,5 days after admission. The development of local complications, such as pancreatic pseudocysts, the computed tomography severity index, the use of vasoactive drugs and mechanical ventilation, the duration of hospital and ICU stay, and the need for surgical intervention were also recorded.¹⁰

In all patients, the plasma D-dimer level was determined on admission and days 3,5 The upper limit of the reference interval for D-dimer was 500 micro g/L. Maximum D-dimer was defined as the highest level reached in all measurements, and the mean D-dimer was defined as the mean level of all measurements. In addition, other routine laboratory parameters such as serum concentrations of creatinine, bilirubin, urea nitrogen, and C-reactive protein (CRP) (all at the Central Laboratory of JSS hospital Mysore) were determined at the same time as the plasma D-dimer level was measured, and at other time points.

Statistical analysis

Results were expressed as medians (interquartile ranges), unless mentioned otherwise. Categoric variables were described in absolute numbers and in percentages. Continuous variables were compared using the Mann-Whitney U-test. To establish optimal cut-off points, a receiver operating characteristic (ROC) curve was used. Other tests are Kruskal-Wllis test, independent t test, ANOVA test.

RESULTS

A total of 60 patients with AP were enrolled in this observational study. Table 1 shows the demographic and clinical data of these patients. The incidence rates of organ dysfunction during the episodes of pancreatitis were high: renal dysfunction in 34 patients (56.7%), and pulmonary dysfunction developed in 28 patients (46.6%).

Table 1: Demographic data and clinical characteristics.

Clinical characteristics				
	<30 (20)			
Age (years)	31-50 (27)			
	51-70 (10)			
	>71 (3)			
Gender	Male	53		
Gender	Female	7		
Aetiology	Alcohol	48		
	Gallstone	14		
	Drug induced	1		
APACHE II score on admission	17			
Ranson score 48 h after admission	5			
CRP level on admission(mg/dl)	104			
Balthazar index	6			
Hospital mortality (%)	3 (5%)			
Pancreatic necrosis	36 (60%)			
Organ dysfunction	40 (66.7%)			
MODS	13 (21.7%)			
Surgical intervention	10 (16.7%)			
	13.05			

D-Dimer and presence or absence of clinical variables

As shown in Table 2, the maximum level of D-dimer was significantly greater in patients who have Pancreatic necrosis, need for mechanical ventilation, organ dysfunction, and who expired. (P<0.0001).

Moreover, patients who presented with MODS (P value-0.013), need for vasoactive drugs (P value-0.18), need for operation intervention (P value-0.18) also showed higher maximum levels of D-dimer. The mean D-dimer levels showed tendencies similar to those of the maximum D-dimer levels in relation to clinical variables (Table 3). Thus, the utility of the maximum D-dimer level seemed

to be equivalent to the mean level as a marker of the severity of AP.

Table 2: Values of maximum D-dimer levels in relation to the presence or absence of clinical variables.

Clinical variables	Presence D-dimer (lg/L)	n	Absence D-dimer (lg/L)	n	P value
Death	4200	3	1165	57	0.025
Operative intervention required	3573	10	1230	50	0.18
MODS	4200	13	1100	47	0.013
Need for vasoactive drugs	4580	29	1600	31	< 0.0001
Pancreatic necrosis	4200	36	1165	24	< 0.0001
Need for mechanical ventilation	3288	8	1600	52	< 0.0001
Organ dysfunction	4050	40	980	20	< 0.0001

MODS: Multiple organ dysfunction syndrome.

Table 3: Values of mean D-dimer levels in relation to the presence or absence of clinical variables.

Clinical variables	Presence D-dimer (lg/L)	n	Absence D-dimer (lg/L)	n	P value
Death	3866	3	876	57	< 0.024
Operative intervention required	2946	10	1095	50	0.17
MODS	3867	13	877	47	0.02
Need for vasoactive drugs	3560	29	1142	31	< 0.0001
Pancreatic necrosis	3405	36	975	24	< 0.0001
Need for mechanical ventilation	4540	8	1100	52	< 0.0001
Organ dysfunction	2895	40	905	20	< 0.0001

Comparison of D dimer values in patients with MODS, need for surgical interventions and mortality.

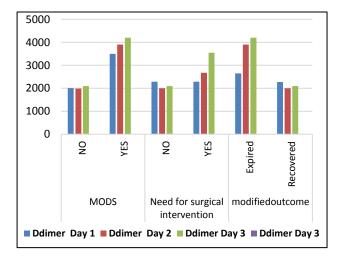


Figure 1: Comparison of D-dimer levels in patients with MODS, need for surgical intervention and mortality.

As Figure 1 shows, patients who presented with MODS, compared with those without MODS, had a consistently higher level of D-dimer in the days 1, 3, 5 after admission. Also, plasma levels of D dimer in the days 1, 3, 5 after admission were significantly different between

patients with and those without, surgical intervention, mortality (Figure 1).

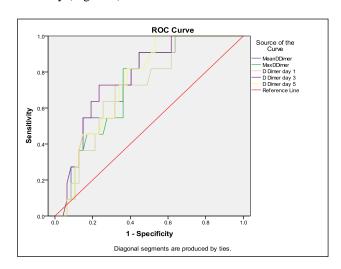


Figure 2: ROC curve for D-dimer levels and other variables in prediction of MODS.

In the prediction of the development of MODS, the areas under the curve (AUCs) for the maximum and mean plasma levels of D dimer were .743 and .727 respectively. In the prediction of mortality, the AUCs for D-dimer levels on day's 1.3.5 days after admission were

0.615, 0.739 and 0.756 respectively. In the prediction of need of surgical intervention, the AUC for max and mean D dimer are 0.650 and 0.65 respectively. The accuracies of the maximum and mean D-dimer values, with an optimal cut-off value (derived from the ROC curves), in predicting the occurrence of MODS, and mortality and surgical intervention are shown in Figures 2, 3 and 4. Comparison of D dimer with usual markers of severity in predicting mortality.

As shown in Table 4, both the maximum and mean levels of D-dimer in the days 1, 3, 5 after admission correlated well with the APACHE II scores and CRP levels (i.e., common prognostic factor and scoring system for the severity of acute pancreatitis), Ransom's score, SOFA score.

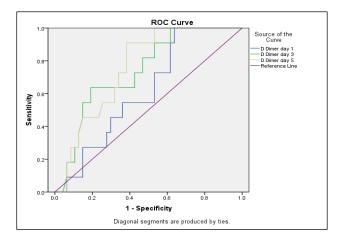


Figure 3: ROC curve for D-dimer and in predicting the mortality.

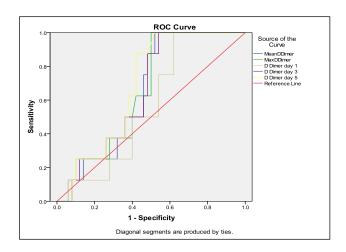


Figure 4: ROC curve for D-dimer and need for surgical intervention.

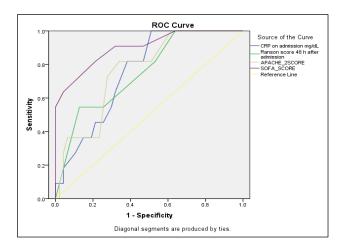


Figure 5: ROC curve analysis for usual markers in predicting the mortality.

Table 4: Correlating the D-dimer with usual markers of severity in predicting the severity of acute pancreatitis.

Test result variable (s)	Area	р	Asymptotic 95% confidence interval		
	Area		Lower bound	Upper bound	
D-Dimer day 1	0.615	0.238	0.457	0.773	
D-Dimer day 3	0.739	0.014	0.594	0.884	
D-Dimer day 5	0.756	0.009	0.627	0.885	
Mean D-Dimer	0.720	0.024	0.574	0.865	
Max D-Dimer	0.719	0.025	0.574	0.863	
APACHE_2SCORE	0.763	0.007	0.625	0.901	
SOFA_SCORE	0.900	0.000	0.794	1.000	
CRP on admission mg/dL	0.753	0.009	0.622	0.885	
Ranson score 48 h after admission	0.751	0.010	0.601	0.902	
CT SEVERITY SCORE	0.813	0.001	0.701	0.926	

ROC curve analysis was also applied for these parameters Figure 5. According to the AUCs of each parameter, Ddimer seemed to have predictive power similar to that of the APACHE II score, and greater than that of the CRP level, and Ransom's criteria.

Table 5: Area under the curve.

Test result variable (s)	Aros	Area Std. error	Asymptotic	Asymptotic 95% confidence interval		
	Area		Sig.b	Lower bound	Upper bound	
CRP on admission mg/dL	0.753	0.067	0.009	0.622	0.885	
Ranson score 48 h after admission	0.751	0.077	0.010	0.601	0.902	
APACHE_2SCORE	0.763	0.071	0.007	0.625	0.901	
SOFA_SCORE	0.900	0.054	0.000	0.794	1.000	

DISCUSSION

One of the main problems in the management of AP is to anticipate the severity of the disease and the potential complications during its evolution. Our study has demonstrated that both the maximum and the mean levels of D dimer in the 1, 3,5 days after admission appeared to be accurate markers of the severity of AP and were extremely valuable in prediction of multiple organ dysfunction. The mechanism underlying the increases in D dimer levels may be the formation of multiple intravascular thrombi (which can be seen in pathological tissue after acute pancreatitis) and consequently, the process of fibrinolysis. 11,12

The natural course of AP has two major phases, the first of which is characterized by SIRS resulting from the release of inflammatory mediators; the second phase is dominated by secondary infection of pancreatic necrosis, which can lead to sepsis-related complications such as septic shock.^{13,14} Once SAP has occurred, the most important determinant of the ultimate outcome is the of organ dysfunction and presence contamination of pancreatic necrosis. Therefore, the predictive value of the D-dimer level for these two phenomena is of specific interest, as the use of this parameter may enable the selection of individual patients for prompt aggressive intensive care measures. Moreover, the measurement of plasma D-dimer is easy, reproducible, and inexpensive and can be widely applied in almost every clinical laboratory.

Disturbance of the coagulative system has long been thought to be implicated in the pathogenesis of the systemic and local complications of pancreatitis. As for D-dimer, which is a fibrin degradation product, there have been very few studies so far about its value in the prediction of severity during AP, and all of these studies included mild acute pancreatitis as well.^{2,4,5} The present investigation is the first study using D-dimer as an indicator of the disease severity in AP patients only. Another important difference between this study and the previous ones is that, to increase accuracy, we monitored the plasma level of D-dimer for 1,3,5 days and used the maximum and mean values of all results as predictors, instead of using the level on admission. In accordance with previous studies, our results showed that increased levels of D-dimer were associated with the development of organ dysfunction, and we also demonstrated the great precision of D-dimer in the prediction of MODS, with the optimal cut-off values of for maximum and mean values are 4200 and 3867 micro grams/L respectively.⁴

Although the mechanism underlying the elevated D-dimer levels might be complicated, severe coagulative disorder characterized by the diffuse formation of intravascular micro thrombi and activation of fibrinolysis could be the dominant cause of this phenomenon. In SAP patients, compared with AP patients, the more severe coagulative disorder associated with microcirculatory disturbance, especially in pancreatic tissue, could lead to more severe and larger pancreatic necrosis, which could significantly increase the risk of MODS.

Moreover, severe pancreatic necrosis could also increase the intensity of the inflammatory reaction, which might contribute greatly to the occurrence of MODS. Because early assessment during AP is of great importance, a variety of prognostic factors and scoring systems have been developed for the accurate evaluation of the severity of AP and reliable prediction of patients at high risk. Serum CRP and the APACHE II score are the most commonly used and reliable markers with single and multiple variables. Our results showed that both maximum and mean values of D-dimer correlated well with the CRP level and APACHE II score, especially with the APACHE II score, which was thought to be more reliable.

Additionally, the results of ROC curve analysis also support the idea that D dimer could be a better predictor than CRP, as evidenced by significantly greater AUCs for the prediction of MODS. It seems that the D-dimer level could probably replace the CRP level as a single variable prognostic marker for more accurate assessment. Several limitations of our study warrant discussion. Firstly, due to the relatively small sample size, we had to choose a nonparametric test, which led to lower statistical power and brought in some uncertainty as to the conclusion.

The D-dimer levels in most of these patients were very low, which may have contributed to the great statistical significance we observed in this study. Additionally, as some patients may present MODS during the first 3 days after admission, the prognostic value of repeated measurements of D-dimer could be less meaningful in such cases. Therefore, the D-dimer values should be used flexibly, using a combination of D-dimer value on

admission and consecutive values in clinical practice. In conclusion, the results of this study demonstrate that D-dimer measurement is a useful, easy, and inexpensive early prognostic marker of the evolution and complications of SAP, although this observation requires further.

CONCLUSION

D-dimer is a potential parameter to replace currently accepted single-variable predictors with higher predictive precision; a large multicentre study is warranted to affirm these results.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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