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# D-DIMER - AN ESSENTIAL MARKER IN SEVERITY PREDICTION OF ACUTE PANCREATITIS

General Surgery

**Dr. Mrinal Talukdar** Associate Professor of Surgery, Silchar Medical College, Silchar -788014, Assam.

**Dr. Prashanth K R** Senior Resident, Lady Hardinge Medical College, Shahid Bhagat Singh Marg, DIZ Area, Connaught Place, New Delhi 110001.

**Dr. Ratnadeep Paul*** Senior Resident, Silchar Medical College, Silchar -788014, Assam. *Corresponding Author

## ABSTRACT

**Introduction:** Acute pancreatitis (AP) is characterized by a spectrum of symptoms, ranging from a local inflammatory process to the more severe form (acute necrotizing pancreatitis) which is associated with a systemic inflammatory response. The overall mortality rate of AP is between 5% and 15%, reaching 30 % in severe acute pancreatitis (SAP). Early optimized care may improve prognosis in patients with severe forms but it remains a challenge to identify these poor prognosis cases especially in the first 48 hours. This study will evaluate the efficacy of serum D-Dimer in prediction of severity and outcome of acute pancreatitis. **Methods:** A prospective observational study of 60 patients presenting with AP was done at Silchar Medical College from 1st June 2017 to 31st May 2018. APACHE-II, Ranson criteria, and CT severity index (CTSI) of all patients were calculated,. D-Dimer was done for all patients. The patients were stratified into categories of severe pancreatitis, organ failure and pancreatic necrosis, as well as the number of deaths. The comparison of D-Dimer with other scoring systems was done by area under the receiver-operating curve (AUC) to predict severity, organ failure, necrosis, and death. **Result:** Of the 60 patients, 15 (25%) developed SAP, 12 (20%) Organ failure (OF), 22 (36.7%) pancreatic necrosis and 3 (5%) died. ROC curves were generated and following cut-off were selected for comparison of severity, organ failure, necrosis and death; Ranson ≥ 3, APACHE II ≥ 8, CTSI ≥ 4. Cut-off of D-Dimer value for severity, organ failure, necrosis and death are ≥1397µg/L, ≥1886µg/L, ≥1890µg/L and ≥5769µg/L respectively. The AUC of D-Dimer (0.914) in predicting severity of disease is similar to that of Apache 2 (0.958) and Ranson (0.899). CTSI (0.715) had lowest AUC among them. The AUC of D-Dimer (0.833) in predicting of organ failure of disease is similar to that of Ranson (0.908) and lower than Apache 2 (0.980). CTSI (0.715) had lowest AUC among them. The AUC of CTSI (0.892) in predicting the necrosis was higher than Apache 2 (0.590), Ranson score (0.578) system and D-Dimer. The AUC of D-Dimer (0.953) in predicting of mortality of disease is similar to that of Apache 2 (0.933), CTSI (0.953) and lower than Ranson score (0.816). **Conclusion:** D-Dimer is an easy tool for assessment of severity and prognosis of acute pancreatitis. CTSI is best for predicting pancreatic necrosis.

## KEYWORDS

Acute pancreatitis; severity assessment; organ failure; mortality prediction; D-Dimer.

## INTRODUCTION

Acute pancreatitis is best defined clinically by a patient presenting with two of the following three criteria[1] : (1)symptoms (epigastric pain) consistent with pancreatitis, (2) a serum amylase or lipase greater than three times the upper limit of normal and (3) radiologic imaging consistent with pancreatitis, usually using computed tomography (CT) or magnetic resonance imaging (MRI)[2]. Most patients develop a mild and self-limited course; however, 10% to 20% of patients have a rapidly progressive inflammatory response associated with prolonged length of hospital stay and significant morbidity and mortality. Patients with mild pancreatitis have a mortality rate of less than 1% but, in severe pancreatitis, this increases up to 10% to 30%.[3]

The most common cause of death in this group of patients is multiorgan dysfunction syndrome. Mortality in pancreatitis has a bimodal distribution; in the first 2 weeks, also known as the early phase, the multiorgan dysfunction syndrome is the final result of an intense inflammatory cascade triggered initially by pancreatic inflammation. Mortality after 2 weeks, also known as the late period, is often caused by septic complications. [4] The high mortality of the severe acute pancreatitis (SAP) calls for methods to assess the severity of the disease early and accurately for initiating more aggressive interventions that will decrease adverse outcomes and high mortality. Therefore, careful ongoing clinical assessments along with multi-factorial scoring systems and imaging studies are required for the prediction of the SAP [5,6,and7]

Coagulative disorders are known to occur in acute pancreatitis and are related to its severity [8,9,and10] Coagulative abnormalities may range from scattered intravascular thrombosis to severe disseminated intravascular coagulation (DIC) [11]. Pancreatic enzymes, cytokines, and other active peptides, liberated from the inflamed pancreas, convert inflammation of the pancreas (a single-organ disease of the retroperitoneum) to a multisystem disease [12,13,14,15,16].These coagulative abnormalities could result in the development of disseminated intravascular coagulation (DIC), which is often associated with MOF through its bleeding tendency and disturbance of tissue microcirculation. DIC and associated multiorgan failure are often the terminal events of a variety of acute systemic conditions [16,17]. Therefore, markers of coagulation including serum D-Dimer, usually increase in AP and platelet count, prothrombin time or antithrombin III decrease. A few studies have evaluated the value of coagulation markers in the prediction of pancreatitis severity and outcomes including D-Dimer, but a definitive predictive biomarker have not yet to be established.[18]

D-Dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross linked D fragments of the fibrin protein.[19]D-Dimer which is mostly used as an effective diagnostic tool to rule out deep vein thrombosis (DVT) as well as pulmonary embolism (PE) [20,21] has been reported to have great predictive power in the early phase of AP. Serum D-Dimer has been introduced as an early marker of severe inflammation and it may play a vital role in predicting the severity of acute pancreatitis. Several studies have been conducted to establish its role in the early prediction of severity of acute pancreatitis.

During the past years, very few studies have been conducted in India to validate the accuracy of D-Dimer in estimating the severity of AP, but no studies have been done to validate D-Dimer in the north eastern part of India. The aim of this study was to evaluate the usefulness of D-Dimer for the early prediction of the severity, organ failure, pancreatic necrosis and death in acute pancreatitis in our hospital and compare it with the existing systems.

## MATERIALS AND METHODS:

A prospective observational study was carried out in Silchar Medical College from 1st June 2017 to 30th May 2018 for a period of one year after ethical committee approval. The study was funded by DBT, New Delhi, the DBT nodal cell, Tezpur University.

Patients presenting with features of acute pancreatitis to emergency and outdoor were admitted, thoroughly examined and investigated further.

## INCLUSION CRITERIA:

Patients admitted with abdominal pain and fulfilling the diagnostic

criteria of acute pancreatitis by clinical history, physical examination, biochemical tests and different imaging modalities and patients aged more than 18 years and less than 70 years were included in this study.

**EXCLUSION CRITERIA:**
Patients attending after 24 hours of onset of abdominal pain, having acute on chronic pancreatitis, pulmonary embolism and/or Deep vein thrombosis and patients unwilling to give voluntary consent to participate in the study were excluded from this study.

Laboratory and biochemical tests were done either at the time of admission or within 24 hrs. of admission and at 48 hours. Tests included total leukocyte count, hematocrit, blood glucose level, blood urea, serum creatinine, serum calcium, serum electrolytes, Liver function tests, and serum amylase and lipase and Arterial Blood Gas (ABG) analysis. D-Dimer was also done within 24 hours of admission. An ultrasound scan of the abdomen and plain radiograph of the abdomen and chest was done on the day of admission.

APACHE II scores were calculated from the laboratory values and radiological reports obtained within first 24 hours after admission. Ranson score was calculated from the laboratory values obtained within the first 48 hours. CTSI was obtained from the report of the CT scan which was done after 72 hours and within 7 days. The reporting of the scans was done by same set of radiologists.

**Definitions:**
Acute pancreatitis is best defined clinically by a patient presenting with two of the following three criteria: (1) symptoms (epigastric pain) consistent with pancreatitis, (2) serum amylase or lipase greater than three times the upper limit of normal, and (3) radiologic imaging consistent with pancreatitis, usually using computed tomography (CT) or magnetic resonance imaging (MRI) [22].

The presence or absence of organ failure and/or local complications such as peripancreatic fluid collections and infected necrosis was used to classify AP as mild or severe according to revised Atlanta classification. Duration of organ failure defined it to be transient (48 hours). Local complications include peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocyst, and walled-off necrosis.

**Outcome of acute pancreatitis:**
Outcome of acute pancreatitis was categorized into acute pancreatitis without any complication, acute pancreatitis with complication and death from sequel of acute pancreatitis.

**Organ failure:** It was defined according to the Modified Marshall Scoring System, a universally applicable scoring system for identifying organ failure.

**Data were collected in a predesigned data-sheet which contained questionnaire, clinical findings and biochemical and imaging findings.**

**STATISTICALANALYSIS**
Median and interquartile ranges were used for representation of continuous variables and proportions for categorical data. Cochran-Armitage trend test was used for assessing the distributions of severity, necrosis, organ failure, and death by BISAP point score. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for individual scoring systems.

The optimal Ranson, APACHE-II and CTSI scores and D-Dimer level for predicting severity, necrosis, organ failure, and death was determined by their characteristic Receiver-operating (ROC) curves. The Area under the Curve (AUC) of the scoring systems was compared with each other at a time by the nonparametric approach developed by DeLong et al [24]. A p-value of $< 0.05$ was chosen to be significant for all tests. XL Stat 2016 was used for performing all the statistical calculations.

**RESULTS**
A prospective and observational study was carried out to evaluate the role of serum D-Dimer in predicting severity and outcome of acute pancreatitis. Total 60 patients with acute pancreatitis, who fulfilled the inclusion criteria, were included in this study. The result of the study was presented in following tables and figures.

**Table 2 : Demographic, clinical and biochemical characteristics of the study population (n=60)**

| VARIABLES | DATA |
|---|---|
| MALE:FEMALE | 1.85:1(39/21) |
| Mean age (years) | 35+/-13 |
| etiology:<br>1. alcoholic<br>2. gall stone<br>3. idiopathic | <br>23(38.3%)<br>26(43.3%)<br>11(18.3%) |
| severity:<br>1. Mild ap<br>2. severe ap | <br>45(75%)<br>15(25%) |
| organ failure:<br>1. absent<br>2. present | <br>648(80%)<br>12(20%) |
| necrosis<br>1. absent<br>2. present | <br>38(63.3%)<br>22(36.7%) |
| mortality | 3(5%) |
| hematocrit | 39.045+/-5.165 |
| bmi | 25.483+/-4.168 |
| crp | 92.667+/-54.645 |
| hospital stay<br>1 mild ap<br>2 severe ap | <br>7.52+/-3.053<br>10.429+/-5.872 |
| icu admission | 13(21.6%) |

**AP:** Acute Pancreatitis, **BMI:** body Mass index, **CRP:** C-reactive protein, **ICU:** Intensive Care Unit

**Table 3: D-dimer In Predicting Severity Of Pancreatitis**

| VARIABLE | AUC | CUTOFF | 95% CONFIDENCE INTERVAL | |
|---|---|---|---|---|
| | | | LOWER BOUND | UPPER BOUND |
| D-DIMER | 0.914 | 1397 | 0.836 | 0.992 |

**Table 4 : 2×2 Contingency table (D-DIMER and SEVERITY)**

| D-DIMER | SEVERE AP | MILD AP | TOTAL |
|---|---|---|---|
| ≥1397µg/L | 12 | 7 | 19(31.6%) |
| <1397 µg/L | 3 | 38 | 41(68.3%) |
| TOTAL | 15(25%) | 45(75%) | 60(100%) |

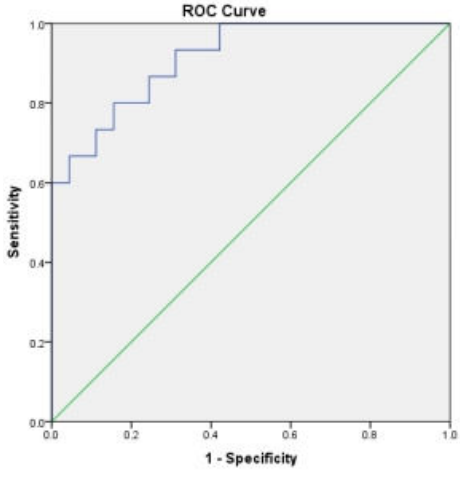


**Fig 1 : Receiver operating curve (ROC) of D-Dimer for severity prediction**.
D-Dimer cut off for severity in AP was 1397µg/L. D-Dimer had high sensitivity and specificity of 80% and 84% respectively in prediction of Severity of Acute Pancreatitis (AP). Accuracy of D-Dimer was 83.3% for development of a severe disease. AUC of D-Dimer for prediction of severity of disease was high (0.914) with a p value <0.0001.

**Table 5: D-dimer In Prediction Of Organ Failure:**

| VARIABLE | AUC | CUTOFF | 95% CONFIDENCE INTERVAL | |
|---|---|---|---|---|
| | | | LOWER BOUND | UPPER BOUND |
| D DIMER | 0.950 | 1886 | 0.894 | 1.000 |

**Table 6: 2×2 Contingency table (D-DIMER and ORGAN FAILURE)**

| D-DIMER | ORGAN FAILURE ( +) | ORGAN FAILURE( -) | TOTAL |
|---|---|---|---|
| ≥1886 µg/L | **10** | **7** | **17(28.3%)** |
| <1886 µg/L | **2** | **41** | **43(71.6%)** |
| TOTAL | **12(20%)** | **48(80%)** | **60(100%)** |

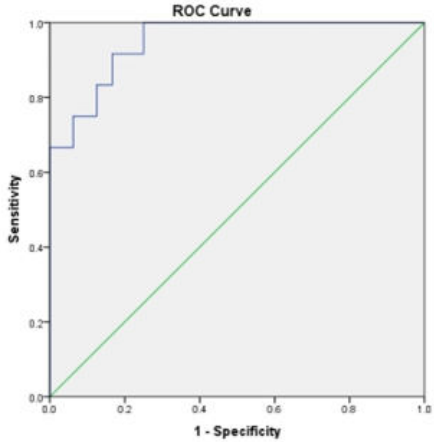


**Fig 2- Receiver Operating Curve (ROC) of D-Dimer for organ failure prediction**

D-Dimer cut off for organ failure in AP was 1886µg/L. D-Dimer had high sensitivity and specificity of 83.3% and 85.4% respectively in prediction of development of Organ Failure in AP. Accuracy of D-Dimer was 85% for development of a organ failure. AUC of D-Dimer for prediction of organ failure in AP was high (0.950) with p value <0.001.

**Table 7 : D-dimer In Prediction Of Pancreatic Necrosis:**

| VARIABLE | AUC | CUTOFF | 95% CONFIDENCE INTERVAL | |
|---|---|---|---|---|
| | | | LOWER BOUND | UPPER BOUND |
| **D DIMER** | 0.715 | 1890 | 0.586 | 0.845 |

**Table 8: 2×2 Contingency table (D-DIMER and PANCREATIC NECROSIS)**

| D-DIMER | ORGAN FAILURE (+) | ORGAN FAILURE( -) | TOTAL |
|---|---|---|---|
| ≥1890 µg/L | 10 | 8 | 18(30%) |
| <1890 µg/L | 12 | 30 | 42(70%) |
| TOTAL | 22(36.6%) | 38(63.3%) | 60(100%) |

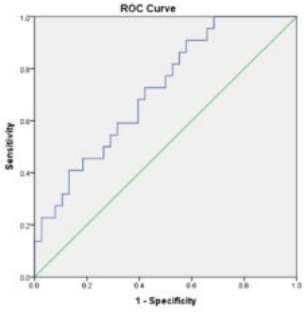


**Fig 3: Receiver operating curve (ROC) of D-Dimer for Pancreatic Necrosis prediction**

D-Dimer cut off for necrosis in AP was 1890µg/L. D-Dimer had low sensitivity and high specificity of 45.4% and 78.9% respectively in prediction of development of Pancreatic Necrosis in AP. Accuracy of D-Dimer was 66.6% for development of a pancreatic necrosis. AUC of D-Dimer for prediction of pancreatic necrosis in AP was low (0.715) with p value 0.006.

**Table 9: D-dimer Score In Prediction Of Mortality:**

| VARIABLE | AUC | CUTOFF | 95% CONFIDENCE INTERVAL | |
|---|---|---|---|---|
| | | | LOWER BOUND | UPPER BOUND |
| D DIMER | 0.959 | 5769 | 0.901 | 1.000 |

**Table 10: 2×2 Contingency table (D-DIMER and MORTALITY)**

| D-DIMER | DEATH( +) | DEATH(-) | TOTAL |
|---|---|---|---|
| ≥ 5769 µg/L | 2 | 18 | 22(36.6%) |
| <5769 µg/L | 1 | 56 | 38(63.3%) |
| TOTAL | 3(5%) | 57(95%) | 60(100%) |

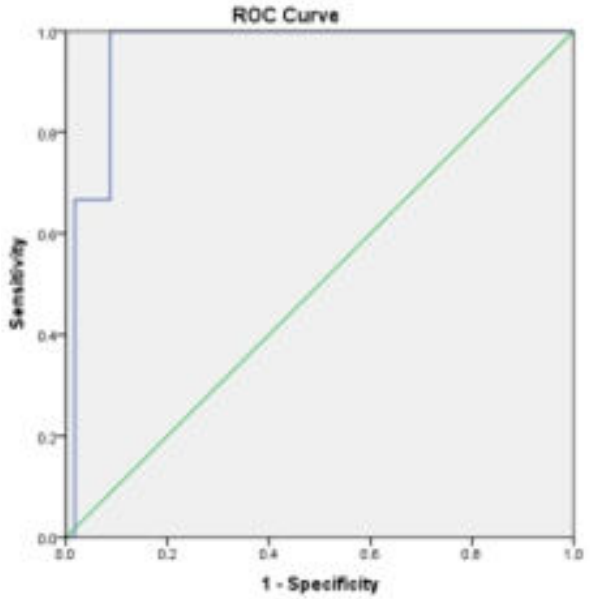


**Fig4 : Receiver operating curve (ROC) of D-Dimer for Mortality prediction**

D-Dimer cut off for mortality in AP was 5769µg/L. D-Dimer had sensitivity and specificity of 66.6% and 98.7% respectively in prediction of development of mortality in AP. Accuracy of D-Dimer was 96.6% for development of mortality. AUC of D-Dimer for prediction of mortality in AP was high (0.959).

**Table 11: AUC of different scoring systems& D-DIMER values in predicting severity, Organ failure, necrosis and mortality**

| AUC (95% <2) | Severity | Organ Failure | Necrosis | Mortality |
|---|---|---|---|---|
| **Ranson** | **0.899(0.820-0.979)** | **0.908(0.827-0.989)** | **0.578(0.476-0.729)** | **0.816(0.623-0.99)** |
| **Apache II** | **0.958(0.913-0.990)** | **0.980(0.952-0.990** | **0.890(0.928-0.751)** | **0.933(0.816-0.99)** |
| **CTSI** | **0.715(0.566-0.813)** | **0.719(0.562-0.875)** | **0.892(0.806-0.978)** | **0.953(0.884-0.99)** |
| **D-DIMER** | **0.914(0.836-0.992)** | **0.950(0.894-1.000)** | **0.715(0.586-0.845)** | **0.959(0.901-1.000)** |

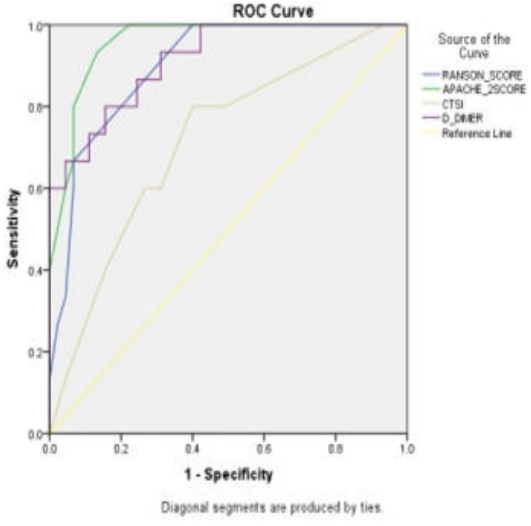


**Fig 5: Receiver operative curve of different scores & D-Dimer in predicting severity**

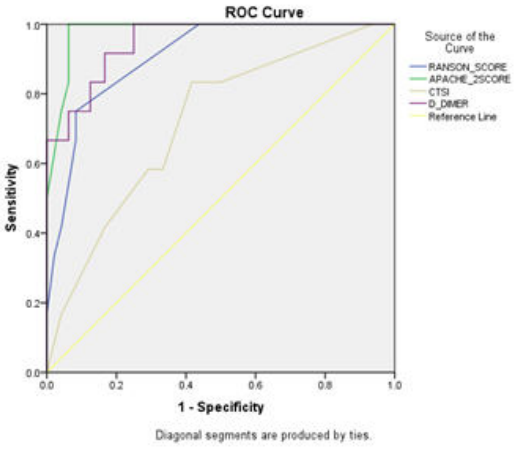


**Fig 6: Receiver operative curve of different scores & D-Dimer in predicting organ failure**

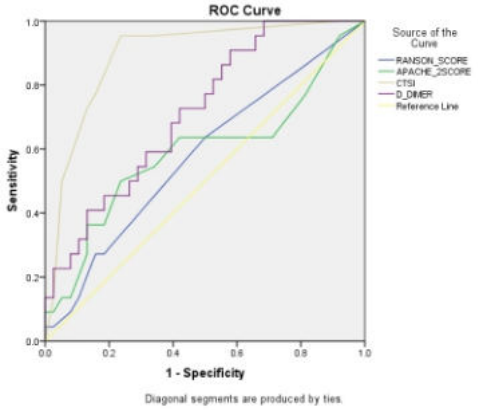


**Fig 7: Receiver operator curve for comparison of prediction of necrosis of different score and D-Dimer**

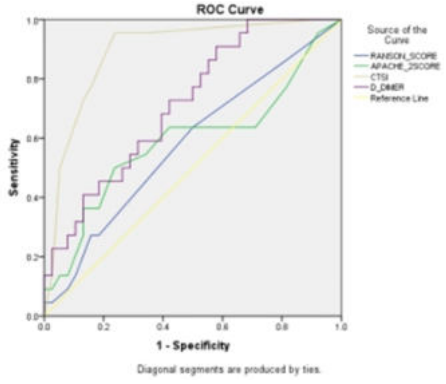


**Fig 8: Receiver operating curve comparing the predictors of mortality of different score and D-Dimer.**

**Table 12: Sensitivity, specificity, Positive predictive value, Negative predictive value and accuracy of different scoring systems and D-Dimer.**

| SEVERITY | SENSITIVITY | SPECIFICITY | PPV | NPV | ACCURACY |
|---|---|---|---|---|---|
| RANSON | 0.600 | 0.933 | 0.75 | 0.875 | 0.850 |
| APACHE ii | 0.800 | 0.955 | 0.857 | 0.934 | 0.916 |
| CTSI | 0.800 | 0.600 | 0.400 | 0.900 | 0.650 |
| D-DIMER | 0.80 | 0.84 | 0.631 | 0.926 | 0.833 |

| ORGAN FAILURE | SENSITIVITY | SPECIFICITY | PPV | NPV | ACCURACY |
|---|---|---|---|---|---|
| RANSON | 0.750 | 0.937 | 0.750 | 0.937 | 0.900 |
| APACHE II | 0.916 | 0.937 | 0.785 | 0.978 | 0.933 |
| CTSI | 0.833 | 0.583 | 0.33 | 0.933 | 0.633 |
| D-DIMER | 0.833 | 0.854 | 0.588 | 0.953 | 0.85 |

| NECROSIS | SENSITIVITY | SPECIFICITY | PPV | NPV | ACCURACY |
|---|---|---|---|---|---|
| RANSON | 0.272 | 0.842 | 0.500 | 0.666 | 0.633 |
| APACHE II | 0.347 | 0.837 | 0.571 | 0.673 | 0.650 |
| CTSI | 0.99 | 0.789 | 0.733 | 1.000 | 0.866 |
| D-DIMER | 0.454 | 0.789 | 0.556 | 0.714 | 0.666 |

| MORTALITY | SENSITIVITY | SPECIFICITY | PPV | NPV | ACCURACY |
|---|---|---|---|---|---|
| RANSONS | 0.666 | 0.824 | 0.166 | 0.979 | 0.816 |
| APACHE II | 0.99 | 0.807 | 0.214 | 0.99 | 0.816 |
| CTSI | 0.666 | 0.508 | 0.066 | 0.966 | 0.516 |
| D-DIMER | 0.666 | 0.987 | 0.666 | 0.982 | 0.966 |

## DISCUSSION

The coagulative system disturbance has long been thought to be implicated in the pathogenesis of the systemic and local complications of acute pancreatitis [25]. 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 acute pancreatitis (AP) In this study the usefulness of D-Dimer was evaluated for the early prediction of the severity, organ failure, pancreatic necrosis and death in acute pancreatitis in our hospital and compared it with existing systems. It was found that D-Dimer was similar to Ranson and APACHE II in prediction of severity of disease and the mortality and was better than Ranson in prediction of organ failure. D-Dimer is an easy tool for assessment of severity and prognosis of acute pancreatitis. CTSI is best for predicting pancreatic necrosis.

### 1) COMPARING THE PREDICTION OF SEVERITY OF DIFFERENT SCORE AND D-DIMER

**Table 13: Comparison Of Auc Of Severity Of Different Scores And D-dimer**

| Score and marker | Our study | Zang et al[27] | Khanna et al[28] | Park et al[26] |
|---|---|---|---|---|
| Ranson's | 0.899 | 0.903 | 0.85 | 0.74 |
| Apache II | 0.958 | 0.836 | 0.88 | 0.80 |
| CTSI | 0.715 | - | 0.66 | 0.67 |

| Marker D-Dimer | Our study | Sreekant apsani etal[31] | Gomercicet al[34] |
|---|---|---|---|
| AUC | 0.914 | 0.965 | 0.76 |
| Cutoff (µg/L) | 1397 | 1265 | 1474 |
| Sensitivity | 0.80 | 0.95 | 0.81 |
| Specificity | 0.84 | 0.96 | 0.66 |

### 2) COMPARING THE PREDICTION OF ORGAN FAILURE BY DIFFERENT SCORES AND D-DIMER

**Table 14: Comparison of AUC of different scores and D-Dimer for organ failure**

| Scoring system | Our study | Park et al[26] |
|---|---|---|
| Ranson's | 0.908 | 0.84 |
| Apache II | 0.980 | 0.95 |
| CTSI | 0.715 | 0.57 |

| D- Dimer | Our study | Aleksandra boskoic et al[29] |
|---|---|---|
| AUC | 0.833 | 0.915 |
| Cut off (µg/L) | 1886 | 1189.5 |
| Sensitivity | 0.853 | 1 |
| Specificity | 0.854 | 0.871 |

### 3) COMPARISON OF PREDICTION OF NECROSIS OF DIFFERENT SCORE AND D-DIMER

**Table 15: Comparison of AUC of different scores and D-Dimer for necrosis**

| Scoring | Our study | Park et al[26] | Aleksandra boskoic et al [33] |
|---|---|---|---|
| Ranson's | 0.578 | 0.48 | - |
| Apache II | 0.590 | 0.55 | - |
| CTSI | 0.892 | 0.98 | - |
| D- Dimer | 0.715 | - | 0.785 |

### 1) COMPARING THE PREDICTORS OF MORTALITY OF DIFFERENT SCORE AND D-DIMER

**Table 16: Comparison of AUC of different scores and D-Dimer for Mortality.**

| Scoring | Our study | Khanna et al[28] | Parachristou et al[30] | Park et al[26] |
|---|---|---|---|---|
| Ranson's | 0.816 | 0.84 | 0.95 | 0.74 |

| | | | | |
|---|---|---|---|---|
| **Apache II** | 0.933 | 0.86 | 0.94 | 0.87 |
| **CTSI** | 0.753 | 0.57 | 0.83 | 0.42 |

| | **Our study** | **Maeda et al[32]** |
|---|---|---|
| AUC | 0.959 | 0.783 |
| Cut off (µg/L) | 5769 | 6000 |
| Sensitivity | 0.666 | 0.85 |
| Specificity | 0.987 | 0.65 |

### Limitations of the study

1. The study population was taken from Silchar Medical College, so the results of this study may not reflect the exact picture of the country.
2. Dependence on the patient, regarding the history.
3. Small sample size was also a limitation of the study.

### Recommendations

Serum D-Dimer measurement among patients with acute pancreatitis may be used as a predictor of severity and outcome of acute pancreatitis. Further studies with larger sample size are recommended.

## CONCLUSION

This study evaluated the diagnostic efficacy of serum D-Dimer in predicting severity and outcome of acute pancreatitis. The difference of serum D-Dimer levels between mild, and severe acute pancreatitis was statistically significant and it was also higher in patients who developed organ failure, necrosis and death following acute pancreatitis than those without complications. Cut-off of D-Dimer value for severity, organ failure, necrosis and death are ≥1397µg/L, ≥ 1886µg/L, ≥1890µg/L and ≥5769µg/L respectively. In the present study serum D-Dimer values within 24 hrs. are found to have a good sensitivity. The test can be used to determine the outcome of acute pancreatitis. This simple, feasible and reproducible marker can be used in clinical practice to improve the early management of acute pancreatitis.

**Conflict of interest:** Nothing to declare

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