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Original Research Article

Serial estimation of urinary trypsinogen-2 levels in patients of acute pancreatitis: a new prognostic indicator

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ABSTRACT

Background: Acute abdominal discomfort is a common symptom of acute pancreatitis (AP). However, because most clinics are unable to rapidly monitor pancreatic enzymes, early detection of AP is challenging. Therefore, the purpose of this study is to investigate the utility of serial urine trypsinogen-2 measurement as a prognostic indicator in individuals with AP.
Methods: A total of 60 patients with AP who presented to the surgical emergency department within 72 hours of symptom onset were included in the study, regardless of sex orage. AP was classified into mild, moderate and severe according to the revisedAtlanta classification. Patient's urine samples were collected at admission, day 3, day 5, and day 7 for determination of urine trypsinogen-2 level.
Results: The mean value of S. amylase (IU/l), S. lipase (IU/l), C-reactive protein **(**CRP) (mg/l), and urinary trypsinogen 2were increased in severe compared with mild AP. The mean value of urinary trypsinogen 2 was significantly decreased from day 1 to day 7 after treatment in the mild, moderate, and severe AP groups. With these cut-off values, urinary trypsinogen2 had a sensitivity of 92.3%, specificity of 42.9%, positive productive value (PPV) of 75%, and negative productive value (NPV) of 75% for diagnosing the severity of AP. These tests demonstrate the accuracy of urinary trypsinogen-2 to determine severity of AP.
Conclusions: In a cross-sectional study, urinary trypsinogen-2 can be used as both diagnostic and prognostic indicator for AP.

Keywords: AP, Trypsinogen-2, Amylase, Lipase, CRP

INTRODUCTION

Acute abdominal discomfort is a common symptom of AP. In all patients admitted to the emergency department as acute abdomen, the cause was AP in up to 5% AP. AP can mimic clinical symptoms such as perforated duodenal ulcer, acute cholecystitis, gastritis, etc. in most patients with acute abdomen.[1] AP is a condition in which the pancreas becomes inflamed over a short period of time, which is characterized by a wide range of clinical features, ranging from a mild, self-limiting form (no organ failure) to severe, systemic disease requiring treatment in the intensive care unit. Most patients exhibited a mild form of AP, but up to 20-30% of patients may develop a severe form of AP, which can be associated with multiple organ dysfunction and a mortality rate of 10-30%. In patients

with AP, gallstones and alcohol are the two most common etiologic factors, accounting for up to 80% of all cases.[2,3]

The exact pathogenesis of AP is still unknown, and several treatment options have been proposed. The most widely accepted is the uncontrolled release and intraductal activation of trypsin and the lack of adequate trypsin clearance, leading to pancreatic inflammation and subsequent initiation of the inflammatory cascade, which in turn triggers AP.[4] Leukocyte activation and migration is the key determinant of local and systemic complications in AP.[4,5] Several strategies are currently used to assess severity and predict outcome. There are several clinical scoring systems (Ranson criteria, modified Glasgow criteria, BISAP, APACHE II, modified ATLANTA, Imrie).[8] Of all the scoring systems, APACHE II, although very laborious due to the many parameters involved, seems to be the best validated scoring system for AP. Some biological and genetic markers have also been used for this purpose. Contrast-enhanced CT scanning of the abdomen is a widely available and useful investigation for predicting the outcome of AP using CT-severity scoring systems.[6,7] Although a number of single- and multiparameter predictors for the diagnosis and prognosis of AP have been investigated and described in recent years, most of them are still far from being perfect predictors.[8]

Trypsinogen (25-kd pancreatic proteinase) is a precursor form of trypsin. Trypsinogen has two main isoforms, trypsinogen-1 (cationic) and trypsinogen-2 (anionic), which are secreted in high concentrations into various body fluids such as blood, urine, and the peritoneal cavity. Because of their relatively small size, trypsinogens are easily filtered through the glomeruli and excreted in the urine.[9] The tubular reabsorption of trypsinogen-2 is lower than that of trypsinogen-1 for unknown reasons, so the concentration of trypsinogen-2 in urine is higher than that of trypsinogen-1. Some of the recent studies suggest that the concentration in urine TAP directly correlates with the severity of AP. In healthy individuals, the concentration of trypsinogen-1 in urine is higher than in AP patients, who preferentially have elevated concentrations of trypsinogen-2 in urine, making this trypsinogen-2 in urine a more accurate diagnostic marker and can be used as a prognostic marker.[10,11] Trypsinogen activation peptide (TAP) is an amino-terminal peptide released by activation of trypsinogen. Intrapancreatic activation of serum trypsinogen to trypsin by enterokinase is thought to play a central role in the pathophysiology of AP.[11]

For the early detection of trypsinogen-2 in the urine of patients with AP, arapid test strip has been used for several years, and its sensitivity and specificity have been verified by many centers.[12] Urinary trypsinogen-2 concentration has also been previously described as a prognostic marker for severe AP. The present study aims to investigate the role of serial determination of urinary trypsinogen-2 as a prognostic marker in patients with the AP.

METHODS

In this cross- sectional study, 60 patients with AP were enrolled in this study inthe department of general surgery, King George's medical university, Lucknow and duration of study was 1 year (October 2021 to October 2022). Patients of AP who presented to surgery emergency within 72 hours of symptom onset of either sex or any age were included. After a detailed description of the procedure, written informed consent was obtained from all patients. This study was approved by the institution's ethics committee (X- PGTSC-IIA/P16). Patients with AP admitted to the emergency department after 72 hours from the onset of pain, patients with other acute abdominal diseases (perforation, obstruction, cholecystitis, etc.) admitted to the surgical emergency department, chronic diseases such as chronic infectious diseases, malignant diseases, and patients who had left the surgical ward against medical advice were excluded.

AP was diagnosed according to the revised Atlanta classification. Patientswere also classified into mild, moderate, and severe AP according to therevised Atlanta classification on the basis of disease severity. According to the modified Marshall score, organ failure was defined by a score of ≥2 for one or more of the organ systems (renal, cardiovascular, pulmonary).

Patients' urine samples were collected at admission, day 3, day 5, and day 7 and stored in freezer (-20 degrees Celsius). All patients with signs and symptoms of AP were treated according to the applicable criteria: USG of the whole abdomen, CECT of theabdomen and biochemical parameters-were assessed. The age, sex, and other parameters of each patient were recorded according USG whole abdomen instrument developed for the study. Each patient was evaluated using the modified Atlanta score, CT severity index, BISAP, and modified Glass-Gow scoring system. Serial urinary trypsinogen-2 levels were correlated with existing predictive criteria.

Serum amylase, lipase, and CPR were measured by the hospital laboratory with routinely used reference values. Urinary trypsinogen-2 concentration was measured with the human PRSS2 (Protease, serine, 2) ELISA kit, which uses the sandwich ELISA principle according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed with the SPSS for Windows programme, version 23.0 (SPSS, Chicago, Illinois). Values are expressed as mean, median, ±SD, minimum, maximum,number, and percentage. Continuous variables were presented as mean±SD and categorical variables as absolute numbers and percentages. Normally distributed continuous variables were compared with the unpaired t test. Categorical variables were analysed with either the chi-square test or Fisher's exact test. More than two groups were analysed with the ANOVA test.

Trypsinogen-2 urine level at different time periods (day 1, day 3, day 5, and day 7) was compared with the post hoc test for significance of the mean difference between groups (time periods), and Pearson correlation analysis was performed to determine the relationship between trypsinogen-2 urine level and other variables (S. amylase, S. lipase, CRP, and CT severity). Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic and prognostic significance (sensitivity and specificity) of urinary trypsinogen-2 level in relation to severity CT. A value of $p<0.05$ was considered statistically significant.

RESULTS

The percentage of mild (0-2), moderate (4-6), and severe (8-10) pancreatitis was 16.67%, 63.33%, and 20.0%, respectively. Accordingly, most patients in our study (63.33%) fell into the moderate CT severity group.

The mean age, weight (kg), height (cm), and BMI (kg/m2) were 39.00±13.65, 57.10±4.72, 157.90±6.45, and 23.21±1.74 in the mild group, 39.76±14.81, 57.55±6.05, 158.03±4.97, and 23.02±1.83 in the moderate group and 46.42±16.29, 60.67±12.69, 157.33±6.53, and 24.21±3.70 in the severe AP group. Mean age, weight (kg), height (cm), and BMI (kg/m^2) did not differ significantly among the mild, moderate, and severe AP groups. The percentages of men and women were 60.00% and 40.00% in themild group, 42.11% and 57.89% in the moderate group, and 75.00% and 25.00% in thesevere AP group. According to these data, in my study the severe form of AP was more common in men and the moderate form of AP was more common in women (Table 1).

The mean values of S. amylase, S. lipase, and CRP were 129.80±106.61, 78.10±48.03, 94.10±25.85 in mild, 528.82±508.76, 393.39±443.72, and 115.58±35.51 in moderate, and 737.25±890.45, 286.50±262.11, and 135.25±41.32 in severe AP. The mean value of S. amylase and CRP were significantly increased in severe compared with mild AP, but the mean value of S. lipase was higher in the moderate AP group than in the severe form (Table 2).

The mean trypsinogen 2 in urine on day 1, day 3, day 5, and day 7 and average were 6.37±2.16, 5.59±2.14, 2.80±1.81, 1.24±1.15, 4.02±0.60 in mild, 7.55±2.92, 7.30±3.27, 4.75±2.89, 2.47±2.18, 5.49±1.67 in moderate and 10.66±2.71, 9.11±3.26, 6.70±3.05, 4.18±2.62 and 7.56±2.19 in severe AP group. Mean urinary trypsinogen 2 was significantly increased in severe AP compared with mild and moderate AP on day 1, day 3, day 5, and day 7, and on average (Table 3).

Mean urinary trypsinogen 2 was significantly decreased from day 1 to day 7 in the mild,moderate, and severe AP groups (Table 4).

The urine trypsinogen 2 with CT severity of AP. The Pearson correlation coefficient of urinary trypsinogen-2 was significantly positively correlated with CT severity of AP, CRP level, S. lipase level, and S. amylase value (Table 5).

Sensitivity, specificity, PPV, and NPV were used to analyse urinary trypsinogen-2 level for severity of AP (Table 6 and Figure 1). The cut-off value for urinary trypsinogen 2 was 6.0 (median) to diagnose the severity of AP. With these cut-off values, urine trypsinogen 2 had a sensitivity of 92.3%, specificity of 42.9%, PPV of 75%, and NPV of 75% in diagnosing the severity of AP. These tests demonstrated the accuracy of the risk factors for the severity of AP. Urinary trypsinogen-2 level was significantly different from thelarge area under the curve (AUC) on the ROC curve.

Table 1: Comparisons of baseline characteristics with severity of AP.

Variables	Mild (n=10)		Moderate (n=38)		Severe (n=12)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
Age (in years)	39.00	13.65	39.76	14.81	46.42	16.29	0.371
Weight (kg)	57.10	4.72	57.55	6.05	60.67	12.69	0.429
Height (cm)	157.90	6.45	158.03	4.97	157.33	6.53	0.931
BMI (kg/m^2)	23.21	1.74	23.02	1.83	24.21	3.70	0.304
Gender	**N**	**%**	**N**	**%**	**N**	**%**	
Male	6	60.00	16	42.11	9	75.00	0.117
Female	4	40.00	22	57.89	3	25.00	

Table 2: Comparisons of mean S. amylase, S. lipase and CRP in between mild, moderate and severe AP group.

Variables	Mild (n=10)		Moderate (n=38)		Severe (n=12)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
S. amylase	129.80	106.61	528.82	508.76	737.25	890.45	0.047*
S. lipase	78.10	48.03	393.39	443.72	286.50	262.11	0.067
CRP	94.10	25.85	115.58	35.51	135.25	41.32	0.031*

*Significant ($p<0.05$).

Table 3: Comparisons of mean urinary trypsinogen 2 in between mild, moderate and severe AP group.

Urinary trypsinogen 2	Mild		Moderate		Severe		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
At day 1	6.37	2.16	7.55	2.92	10.66	2.71	0.001*
At day 3	5.59	2.14	7.30	3.27	9.11	3.26	0.037*
At day 5	2.80	1.81	4.75	2.89	6.70	3.05	0.007*
At day 7	1.24	1.15	2.47	2.18	4.18	2.62	0.008*
Average	4.02	0.60	5.49	1.67	7.56	2.19	<0.001*

*Significant (p<0.05).

Table 4: Change in mean Urinary Trypsinogen 2 from day 1 to day 7 in mild, moderateand severe AP.

Variables	At day 1		At day 3		At day 5		At day 7		P value
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	
Mile	6.37	2.16	5.59	2.14	2.80	1.81	1.24	1.15	<0.001*
Moderate	7.55	2.92	7.30	3.27	4.75	2.89	2.47	2.18	<0.001*
Severe	10.66	2.71	9.11	3.26	6.70	3.05	4.18	2.62	<0.001*

*Significant (p<0.05).

Table 5: Correlation of urinary trypsinogen 2 with severity of AP, CRP level, S. lipase level and S. amylase level.

Urinary trypsinogen 2	Pearson correlation coefficient	P value
Severity of AP	0.582	<0.001*
CRP level	0.315	<0.031
S. lipase level	0.170	<0.067
S. amylase level	0.215	<0.047

*Significant (p<0.05).

Table 6: Sensitivity, specificity of diagnosing of severity of AP by urinary tTrypsinogen 2.

Test	Cut-off (median)	Sensitivity	Specificity	PPV	NPV	Area	Significant
Urinary trypsinogen 2	6.0	92.3%	42.9%	75.0%	75.0%	0.790	0.002*

*Significant (p<0.05).

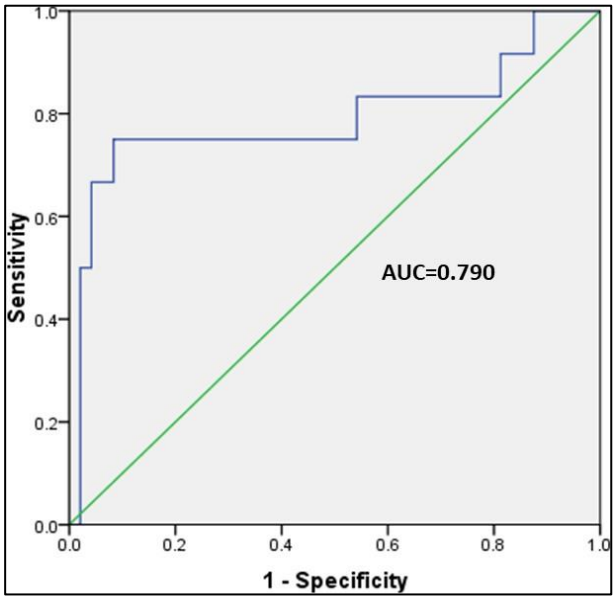

Figure 1: ROC curve analysis of diagnosing of severity of AP patients. Each receiver characteristic curve is expressed as a solid line.

DISCUSSION

In our study, of the total 60 patients according to the CT severity index, 16.67% were patients with mild AP, 63.33% were patients with moderate AP, and 20.0% were patients with severe AP in the study population. Approximately 20-30% of patients with AP develop a severe form of the disease, oftenassociated with single or multiple organ dysfunction, requiring urgent treatment. One of the major obstacles in the treatment of AP is the early recognition of the severe form. About 20-40% of patients with severe AP develop pancreatic infection and peripancreatic necrosis.[13] A previous study reported that the 20% of people with AP go on to develop severe disease with complications and a significant risk of death.[14]

In our study, the mean S. amylase and CRP were significantly elevated in severe compared with mild AP. The CRP value of 150 mg/l measured 48 hours after admission is a very accurate predictor of acute severe pancreatitis. The absolute CRP value >of 150 mg/dL within 48 hours of admission is the value establishedby international consensus for predicting severe AP.[15] With a sensitivity of 83% and a specificity of 85%, CRP values

greater than 210 mg/l in AP distinguish between mild and severe cases.[16] CRP is a more sensitive marker than erythrocyte sedimentation rate, and when clinical signs of acute cholecystitis coexist with CRP levels above 30 mg/L, the correct diagnosis of acute cholecystitis can be made with a sensitivity of 78% (ESR).[17] CRP levels greater than 210 mg/L could differentiate between mild and severe cases of AP with a sensitivity of 83% and a specificity of 85%.

Previous research has identified numerous predictors of pancreatic necrosis and infected necrosis, including CRP, lactate dehydrogenase, and procalcitonin.[18-20] These elements can serve as proxy indicators for these local problems, as they are involved in a variety of inflammatory and infectious processes. In contrast, trypsinogen-2 and lipase are released after AP, which play a role in inflammation and self-digestion of pancreatic and peripancreatic tissues, explaining how they may help determine the likelihood of local problems in the future.[21,22] Although local perfusion disturbance is a major factor in necrotizing pancreatitis perfusion CT, which is not commonly used in routine clinical practice, is necessary for diagnosis.[23]

In our study the mean urinary trypsinogen-2 level decreased linearly with time. The study showed significant ($p<0.001$) and high positive (direct) correlation of the baseline variables (urinary trypsinogen-2, S. amylase, S. lipase, CPR, CT severity) with each other, suggesting that an increase in one may be associated with an increase in the other or vice versa. The highest correlation was found between CRP and CT severity ($p<0.001$). However, trypsinogen-2 in urine showed significant and direct correlation with S. amylase ($r=0.215$) ($p<0.047$), S. lipase ($r=0.170$) ($p<0.067$) and CRP ($r=0.315$) ($p<0.031$). In addition, urinary trypsinogen-2 showed a significant and direct relationship with the severity of CT ($r=0.581$) ($p<0.001$), suggesting that the severity of CT increases with the increase of urinary trypsinogen-2 or vice versa. Mean urinary trypsinogen-2 showed a linear increase with the increase in CT severity, with severity being the highest, followed by moderate and mild (>moderate >mild). The study showed significantly ($p<0.001$) different and higher mean urinary trypsinogen-2 levels in the severe group compared to both the moderate and mild groups. These observations showed that the urinary trypsinogen-2 level at the time of admission was able to distinguish severe AP from mild and moderate forms of the disease ($p<0.001$) and also to distinguish moderate AP from mild AP. A rapid test strip for the detection of trypsinogen-2 in the urine of patients with AP has been developed in Finland and has been shown to be useful for early detection of the disease, which has also been confirmed in Japan. The results of this study on the sensitivity and specificity of the urinary trypsinogen-2 dipstick test were consistent with those of previous reports. As reported by Mayumi et al the dipstick can be used clinically despite the small number of patients.[24] An innovative method for assessing the severity of AP is the use of the rapid urinary trypsinogen-2 test using diluted urine samples. The PLR forthe presence of severe AP was 4.8 if the test was positive on admission. A positive trypsinogen-2 result increased the probability of severe AP from 28% (pretest probability) to 65% (posttest probability). The PLR for a CRP level >150 mg/L on admission is also quite high (3.7), but the sensitivity is only 38%. Numerous prognostic indicators to assess severity AP have been studied. Most of these indicators should be considered experimental and therefore cannot be used regularly in emergency situations. In a recent European multicenter study of the predictive utility of TAP, PLR was 2.1, specificity 73%, PPV 39%, NPV 86%, and sensitivity 58% 24 hours after symptom onset. at 24 hours after admission, sensitivity, specificity, PPV, NPV, and PLR were 68%, 74%, and 44%, respectively.

In this study, the mean urinary trypsinogen 2 was significantly decreased from day 1 to day 7 in the mild, moderate, and severe AP groups. The cut-off value for urinary trypsinogen 2 was 6.0 (median) to determine the severity of AP. With these cut-off values, urine trypsinogen 2 had a sensitivity of 92.3%, specificity of 42.9%, PPV of 75%, and NPV of 75% for diagnosing the severity of AP. Unlike the routinely measured pancreatic enzymes amylase and lipase, trypsinogen-2 is a pancreatic enzyme, and its levels have been shown to remain elevated over time, with higher levels in urine than serum.

Cut-off values were set to maximise specificity for both moderate and severe AP, as this would dictate ICU admission and, given the limited number of ICU beds, unnecessary ICU admissions should be avoided. With a cut-off value of >6 ng/ml, urinary trypsinogen-2 distinguishes two groups (mild and severe) of cases with a higher sensitivity of92.3%.

The present study showed a positive and direct correlation of urinary trypsinogen-2 with CRP, CT severity index, S. amylase, and S. lipase. Urinary trypsinogen-2 has a sensitivity of 92% and therefore can be used as a single marker for both diagnosis and prognosis in patientswith AP. In order to reduce morbidity and mortality in patients with AP, early diagnosis and assessment of severity is crucial so that early aggressive treatment can be given. In this study, urinary trypsinogen-2 levels were elevated on admission, with significantly higher levels in patients with severe AP. It has been demonstrated that urinary trypsinogen-2 concentration increases in the pathogenesis of AP and is also involved in the process of pancreatic tissue damage. It was found that the expression of trypsinogen-2 in urine is related to the severity of pancreatic tissue damage.

Therefore, urinary trypsinogen-2 can be used as an indicator to assess the prognosis andseverity of AP, and urinary trypsinogen-2 may be a major target for future therapeutic intervention.

Further study will be needed to know the urinary trypsinogen-2 level in other acute abdomen condition who

presented to the emergency and compare their result with AP.

Limitations

Because this study is a pilot, it lacked an appropriate sample size. This study has low specificity (42.9%) value and at present time urinary trypsinogen-2 is expensive and not easily available. This study will only show Urinary trypsinogen-2 level in AP.

CONCLUSION

In this study, the mean values of S. amylase and CRP were significantly increased in severe compared with mild AP. In addition, the mean value of urinary trypsinogen 2 was significantly increased in severe compared with mild and moderateAP on day 1, day 3, day 5, and day 7, and on average. We concluded that urinary trypsinogen-2 may be a novel and effective indicator for diagnosing and predictingthe severity of AP in the presence of necrosis and thus may be used to shorten hospital stay, improve disease management, and make early decisions about the need for endoscopic, percutaneous, or surgical intervention in patients with AP.

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