To Access the Role of Serum Procalcitonin in Predicting the Severity of Acute Pancreatitis

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ABSTRACT

Background

Acute Pancreatitis remains a common disorder with devastating consequences in severe form of disease. In this study we assessed serum procalcitonin for early prediction of severity of acute pancreatitis and compared it with multiple scoring systems and biomarkers.

Objective

This is a prospective comparative study in which 125 patients with diagnosis of acute pancreatitis were enrolled. All blood samples and imaging studies were obtained within 24-72 hours of admission and the severity was predicted.

Method

This is a prospective comparative study in which 125 patients with diagnosis of acute pancreatitis were enrolled. All blood samples and imaging studies were obtained within 24-72 hours of admission and the severity was predicted.

Result

Acute pancreatitis was graded severe in 54 patients and mild in 71 patients as per the Atlanta criteria. Receiver operating characteristic curve showed the area under curve of serum procalcitonin was higher (area under curve: 0.887, Confidence interval: 0.825-0.948) compared to computed tomography severity index scoring system (Area under curve: 0.841, Confidence interval: 0.771-0.911), Ranson's score (Area under curve: 0.796, Confidence interval: 0.715-0.876) and C-reactive protein (Area under curve: 0.717, Confidence interval: 0.628-0.8.7) in predicting the severity of acute pancreatitis. The best cut-off value of serum procalcitonin to predict severe acute pancreatitis was 0.9 ng/ml with 92.6% sensitivity, 80.3% specificity. The accuracy of serum procalcitonin (85.6%) was better than computed tomography severity index score (73.6 %), Ranson's score (76.8%) and C-reactive protein (64.8%).

Conclusion

Multifactorial scoring systems are complex and hard to use in clinical basis. Serum procalcitonin can be used as a promising single biomarker, easily done in all setup with better accuracy. And it is comparable to computed tomography severity index and Ranson's scores in earlier prediction of severity of acute pancreatitis.

KEY WORDS

Acute pancreatitis, serum procalcitonin, pancreatic necrosis

INTRODUCTION

Acute pancreatitis (AP) is a disorder with devastating consequences.[1] Although most episodes are mild and self-limiting, about one fifth patient develops a severe attack that can be fatal.[2,3] Early deaths in AP, within the first week, are due to multi-organ dysfunction syndrome (MODS) whereas late mortality is a consequence of local or systemic infections.[4] Therefore, early prediction of severe attacks is important, as it enables the timely administration of intensive supportive therapy and the early detection of complications. Ranson's score, Glasgow score and Computed tomography severity index (CTSI) are established as important methods for assessing the severity of AP but these multifactorial scoring systems are complex and hard to use in clinical basis.

Serum PCT is an 116-amino acid propeptide of calcitonin with a molecular weight of 13 kDa is an early marker of systemic bacterial infection, sepsis, and multi-organ failure.[4] It is shown to predict the severe AP (SAP) in the form of infected necrosis or organ failure within first 24 hours (hrs) after hospital admission.[5-7] C-reactive protein (CRP) is acute-phase protein, applied as a single marker for prediction of SAP.[8] In 1974, Ranson first made a risk stratification model to include 11 factors on admission and at 48 hrs to predict morbidity and mortality in AP.[9] Balthazar used contrast-enhanced CT scan (CECT) findings for the same, however, has the drawback of not reflecting the systemic response.[10] This study aims to analyze the efficacy of plasma PCT and compare it with Ranson's score, CRP and CTSI scores in predicting SAP.

METHODS

This is a prospective comparative study conducted at the department of gastrointestinal surgery of College of medical sciences, Bharatpur, Nepal in between January 2014 to January 2016. After approval by the Institutional Review Board and taking informed written consent, 125 patients who were clinically suspected to have AP were included in the study. The diagnosis of AP was based on acute upper abdominal pain radiating to back associated with a serum amylase level greater than three times the normal value or an elevated serum lipase level. Case who had the features suggestive of chronic pancreatitis, patients not giving written consent, patients with a history of trauma were excluded from the study. The cases were evaluated thoroughly in accordance with the standard practice, which included thorough history taking, general examination, systemic examination, laboratory investigations and imaging studies. Blood samples were sent for estimation of serum amylase level, serum lipase level, serum electrolytes, creatinine, blood urea nitrogen, liver function test, arterial blood gas analysis, complete haemogram, coagulation profile, lipid profile, CRP levels, and blood or urine culture in febrile patients. These investigations were repeated in accordance to the need and as per hospital protocols after admission. Serum PCT was measured within first 24 h after admission. For serum PCT, blood samples were centrifuged for 10 minutes at 3,000 rotations per minute at -4°C. The serum was removed and stored at -80°C until biochemical analysis. Plasma PCT was estimated using a chemiluminescent immunoassay (LUMI test PCT, Brahms Diagnostica, Berlin, Germany). Appropriate data were recorded to permit calculation of the Ranson's scores. Ranson's score was calculated at and 48 hrs after admission. Patients with Ranson's score ≥ 3 was considered severe form of AP.[11] Computed tomography (CT) scan was performed in all patients after 48 h after arrival at the hospital for detection of the development of fluid collections, the extent of inflammation, and necrotic changes. CT was repeated weekly if the symptoms worsened. Accordingly, CTSI was calculated. Here, CTSI score ≥3 was taken as the cut-off value to label them as SAP.[10] All patients were classified as mild or severe AP according to the Atlanta criteria. SAP is defined by the occurrence of one or more systemic (organ failure) or local complications during the course of the disease. Organ failure included shock (systolic blood pressure < 90 mmHg), pulmonary insufficiency (arterial PO_2 < 60 mmHg at room air or the need for mechanical ventilation), renal failure (serum creatinine level > 2 mg/dl after rehydration or hemodialysis), gastrointestinal bleeding (>500 ml/24 h), coagulopathy (platelets 100,000/mm^3 or less, fibrinogen less than 1.0 g/l and fibrin split products more than 80 µg/ml) or metabolic disturbances (serum calcium <7.5 mg/dl).

Patients were considered to have alcoholic pancreatitis if they consumed alcohol on a regular basis, or had alcohol binge prior to the onset of symptoms. Patients were diagnosed as a case of gallstone pancreatitis if gallstones are found in USG or with the previous history of gallstones. Rest of all were labeled as idiopathic pancreatitis.

All the patients were admitted and managed with adequate intravenous fluids, analgesics, and prophylactic antibiotic therapy if indicated. Patients with vomiting were kept nil per oral soon after admission and nasogastric aspiration was done. Oral feeding was permitted as early as possible. Ionotropic support was given to those patients who were hemodynamically unstable i.e. blood pressure (systolic <90 mmHg) in spite of proper hydration. Mechanical ventilator support was given in needy patients especially who had a respiratory compromise. When patients remained asymptomatic with oral intake, patients were discharged or underwent cholecystectomy if indicated. Surgical intervention was done in cases in which deterioration of clinical status was found despite aggressive medical management. Patients were regularly assessed clinically as well as with appropriate laboratory investigations and imaging studies whenever indicated. Once all the clinical and laboratory parameters were normal the patients were discharged on oral adjunctive medication with follow up advice.

The data was collected and were analyzed using descriptive and inferential statistics. In descriptive statistics, a different tool such as frequency distribution was used to show outcome. Independent t-test was applied for normally distributed, descriptive continuous variables and Mann-Whitney U test were applied for a data which are not distributed normally. Receiver operating characteristic (ROC) curves and the respective areas under the curve (AUC) was used as a global measure of the diagnostic accuracy of the single markers and multiple scoring systems. The optimal cut-off values to predict severe pancreatitis were derived from the receiver operating characteristic curves. The diagnostic cut-off value was expressed as its sensitivity, specificity, positive predictive value, negative predictive value, accuracy and odds ratio. Differences were considered statistically significant if the p-value was less than 0.05 with 95% confidence interval. All of the statistical analyses was carried out using the SPSS software, version 20.0 (Chicago, Illinois, USA).

RESULTS

A total of 135 cases of AP were admitted in College of Medical Sciences and Teaching Hospital, Bharatpur, Nepal in the year January 2014 - January 2016. Only 125 cases who meet the study criteria were included in this study. Those who did not meet the inclusion criteria and denied to undergo the required investigations were excluded from the study.

In this study population, 59.2% (n=74) patients were male, and 40.8% (n= 51) patients were female. The mean age of the patient was 46.78 ± 14.16 years. As per the Atlanta criteria, patients were classified as mild AP or SAP. Mild AP was seen in 56.8% (n=71) of patients and SAP was seen in 43.2% (n =54) of patients. There were no significant statistical differences as per the age (p = 0.714) and sex (p = 0.276) in both the groups. (Table1)

Table 1. Characteristics of the patients with acute pancreatitis

Characteristics	Severe Pancreatitis (n=54)	Mild pancreatitis (n=71)	Total (n=125)	p-value
Male/ female	29/25	45/26	74/51	0.276
Age	46.24±14.96	47.18±13.62	46.78±14.16	0.714
Etiology				
Alcoholic	24(44.4%)	25(35.2%)	49	0.333
Biliary	18(33.3%)	33(46.5%)	51	
Idiopathic	12(22.2%)	13(18.3%)	25	
Mortality	4(3.2%)	0	4(3.2%)	
Mean Value	mean±SD	mean±SD		
PCT at admission	2.41±2.24	0.49±0.55	1.32±1.79	<0.001
CRP at 48 hrs	134.46±56.14	91.46±53.46	110.03±58.46	<0.001
CTSI at 48 hrs	4.44±1.84	2.21±1.31	3.17±1.91	<0.001
Ransons at 48 hrs	3.81±2.01	1.92±1.30	2.74±1.89	<0.001

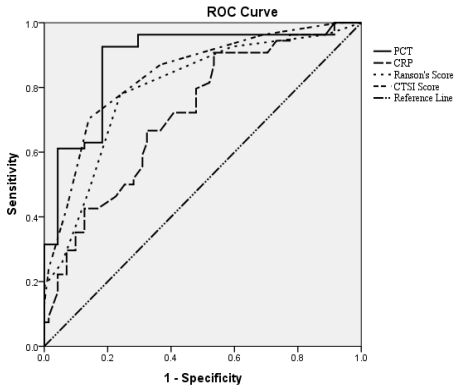

Figure 1. ROC curve for the serum PCT, CTSI score, Ranson's score and serum CRP and for predicting the severe form of acute pancreatitis.

The major cause of pancreatitis were biliary, alcohol and idiopathic in both the mild and severe form of diseases. Gallstone followed by alcohol were most common cause of acute pancreatitis. However, there was no statistical difference in the etiology. A mild form of the disease was found to be more common with biliary pancreatitis and severe form of the disease was found to be more common with alcohol-induced pancreatitis (p = 0.333). The mean value of different markers is shown in Table 1. In this study, mortality was seen in 3.2% (n = 4) of cases and all patients had a severe form of the disease. The most common cause of mortality was MODS in three patients, and acute respiratory distress syndrome in one patient.

We analyzed all of the four parameters using the AUC for predicting SAP. AUCs for each scoring system in predicting SAP are shown in Table 2.

Table 2. AUCs for PCT, CTSI score, Ranson's Score, and CRP in predicting SAP

Characteristics	AUC	p valve	Confidence Interval	
			Lower bound	Upper bound
Ransons at 48 hrs	.796	<0.001	.715	.876
PCT at admission	.887	<0.001	.825	.948
CRP at 48 hrs	.717	<0.001	.628	.807
CTSI at 48hrs	.841	<0.001	.771	.911

Serum PCT showed slightly higher accuracy (AUC: 0.887, CI: 0.825-0.948) compared to CTSI scoring system (AUC: 0.841, CI: 0.771-0.911), Ranson's score (AUC: 0.796, CI: 0.715-0.876) and CRP (AUC: 0.717, CI: 0.628-0.8.7) in predicting the severe form of acute pancreatitis. However, all four parameters were statistically significant in terms of predicting the severity of AP (p < 0.001).

Cutoff values were estimated using ROC curve with maximum sensitivity and specificity. AUC was found to significantly higher with serum PCT than CTSI, serum CRP, and Ranson's score. To assess its significance, the cutoff values of serum PCT and CRP were analyzed at different levels (Table 3). It was seen that serum PCT at 0.9 ng/ml had a maximum sensitivity of 92.60% and specificity of 80.30%

Table 3. **Analysis of cutoff values of serum PCT and CRP**

PCT	Value	Sensitivity	Specificity	PPV	NPV	Accuracy	Odds Ratio (OR)
	0.55 ng/ml	92.6	71.8	71.4	92.7	80.8	31.87 (10.17-99.88)
	0.9 ng/ml	92.6	80.3	78.1	93.4	85.6	50.89 (15.71-164.68)
	1.51 ng/ml	61.1	95.8	91.7	76.4	78.9	35.62 (9.91-128)
CRP							
	87 mg/ml	72.2	52.1	53.4	71.2	60.8	2.82 (1.32-6.02)
	110 mg/ml	59.3	69	59.3	69	64.8	2.96 (1.36-6.41)
	153 mg/ml	46.3	77.5	61	65.5	64	3.24 (1.54-6.79)

with an accuracy of 85.6%. The patients with serum PCT more than 0.9ng/ml had 51 times risk of developing a SAP.

Similarly, CRP at a cut-off value of 110 mg/ml had a sensitivity of 59.3% and specificity of 69% and accuracy of 64.8% with 3.24 time the risk for developing SAP. This was least accurate than that of PCT in predicting the severity of acute pancreatitis.

Table 4. **Comparison of cutoff value**

Value	Sensitivity	Specificity	PPV	NPV	Accuracy	Odds Ratio(OR)
PCT at 0.9 ng/ml	92.6	80.3	78.1	93.4	85.6	50.89(15.71-164.68)
CRP at 110 mg/ml	59.3	69	59.3	69	64.8	3.24(1.54-6.79)
Ransons ≥3	77.8	76.1	71.2	81.8	76.8	11.11(4.79-25.8)
CTSI≥3	87	63.4	64.4	86.5	73.6	11.62(4.58-29.43)

On the basis of highest sensitivity and specificity values generated from the receiver operating characteristic curves, the best cutoff of serum PCT and CRP were further analyzed with Ranson's ≥ 3 and CTSI ≥ 3. (Table 4) There was higher level of sensitivity, specificity, PPV, NPV and accuracy with serum PCT in comparison to other severity markers.

DISCUSSION

AP is a major surgical challenge and assessment of severity of AP is important for early identification of risk of complications and mortality and also in improving outcome.[12] The ideal predictor of the severity of AP is described as being simple, highly sensitive, highly specific, safe, reproducible and cheap and can be rapidly performed.[13] The nature and purpose of this research work was to evaluate the ability of the serum PCT as a single biochemical marker in predicting the SAP which was demonstrated by AUC.

In 2000 Toh et al. conducted a prospective study and they found AP was more common in males with male to female ratio of 1.3.[14] Similarly, in our study there was male predominance and male to female ratio was 1.45. Toouli et al. found AP is more common in the age group 40-60 years, however in our study it was 40-50 years.[15]

Forsmark et al. mentioned in their review article that gallstones (40%) was most common cause of AP followed by alcohol (30%).[16] In our study also, gallstones (41%) was found the commonest cause of AP followed by alcohol (39%) and idiopathic (20%). This finding was also justified as recommendation laid down by the UK guidelines.[14]

Serum PCT is a prognostic marker of AP, focusing on systemic inflammation and organ failure in the early stage of AP.[7] We analyzed three cut-off values for serum PCT levels 0.55, 0.9 and 1.5 ng/mL to predict the SAP. The results of this study showed that the threshold values of PCT at 0.9 ng/ml can be taken into consideration as a statistically significant predictor for SAP. The NPV of 93.4% showed that SAP can be excluded in a maximum number of patient with its negative result. Patients with PCT more than 0.9 ng/ml had 51 times increased risk of developing severe form of AP and can be used as a promising parameter for identifying the patients who are at risk to develop infectious complications.

Mofdi et al. in their systematic review of 24 studies found serum PCT had 73% sensitivity and 87% specificity at the cutoff value of 0.5 ng/ml in predicting the severity of acute pancreatitis.[18] Ammori et al., Olah et al. and Bulbüller et al. in their studies also mentioned the best cutoff value of 0.5 ng/ml.[6,19,20] According to Mandi et al. and Madrau et al. the best cutoff value was 1.2 ng/ml and 0.7 ng/ml respectively.[21] In most of these studies the best cutoff value of serum PCT varied from 0.5-1.2 ng/ml. However, all these studies showed serum PCT is a significant biochemical marker for early diagnosis of SAP.[17,22]

Another most commonly used single severity marker is CRP. According to Puolakkainen et al. circulating CRP levels start to rise significantly to reach its peak at 48 hrs after the onset of the disease and declines thereafter.[23,24] Here we measured serum CRP at 48 hrs after the presentation to the hospital. The best cutoff value was found to be at 110 mg/ml. Serum CRP at 110 mg/ml had 59.3% sensitivity, 69% specificity and 64.8% accuracy. Similarly, Bota et al. in 2013 mentioned CRP with a cut-off value >120 mg/L, had 77.2% sensitivity, 89.9% specificity and 85% accuracy for predicting SAP.[25] In keeping with previous published data, our results finds a low diagnostic value of CRP in SAP.

Ranson's score was recorded as binary values on admission and at 48 hrs, and its primary aim was to evaluate the function of early operative intervention in patients with AP.[11,26] In 2013, Khanna et al. mentioned the Ranson's score had 83.9% sensitivity, 78% specificity with 85% accuracy.[27] However, in our series, it was 77.8% sensitivity, 76.1% specificity and 76.8% accuracy. Though the patients with Ranson's score ≥ 3 had 11 times risk of developing SAP, but the results are available only after 48 hrs of the admission until then the spectrum of MODS had already ensured.

In 2010, in the study conducted by Papachristou et al. CTSI score ≥ 3 had 85.7% sensitivity, 71.0% specificity to predict the severity of AP.[26] Similarly, in our study CTSI score ≥ 3 had 87% sensitivity, 63.4% specificity. CTSI mainly predicts the local complication rather than systemic complications of the disease and the pancreatic necrosis become evident after 48-72 hrs the onset disease process.

In our series, Serum PCT had the greatest accuracy of 85.6% followed by the Ranson's score 76.8%, CTSI score 73.6% and CRP 64.6% in predicting the severity of AP. However, all four parameters were statistically significant in terms of predicting the severity of AP ($p < 0.001$). So we can use serum PCT as a single biochemical marker to assess the severity of pancreatitis earlier in primary ,secondary and tertiary level care were multifactorial scoring system are difficult to apply.

The results that we found in our study may not correlate directly with the results seen in the larger population. By increasing the sample size and the duration of the study, better prediction of AP can be done. We did not measure serial PCT levels because this study investigated the potential role of the PCT level in the early prediction (on the day of admission) of disease severity in patients. Currently, both the major scoring systems, including CTSI score and Ranson's score, use threshold values to change continuous variables into binary values, giving equal weighted points to calculate a score. They fail to capture synergistic or multiplicative effects on the interactions of interdependent systems.

CONCLUSION

Certain predictive methods, such as the Ranson's score, CTSI score have been established as important methods for assessing the severity of AP but these multifactorial scoring systems are complex and hard to use in clinical bases. Serum PCT is an early marker of systemic bacterial infection, sepsis, and multi-organ failure. In this study, it was found that increased serum levels of PCT serve as a promising simple biomarker of prediction of severity of AP with better accuracy when compared with other scoring systems. Therefore, serum PCT as an index marker to assess the severity of AP can be used instead of complex scoring systems like Ranson's and BCTSI and CRP.

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