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Does Elevated Serum Levels of Procalcitonin Potentially Correlate with Severity of Acute Pancreatitis: A Prospective Study

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Abstract

Objective: Acute pancreatitis (AP) is not consistent in terms of its clinical presentation and severity. Various biochemical parameters, computerized tomography and certain scoring systems are used for this purpose and to determine the need for intensive care.

Methods: In this study patients of AP, who presented with the onset of symptoms by or before 48 hours were included. Blood samples were collected for the estimation of procalcitonin (PCT) on day of admission. Chemiluminescent immunoassay (Elecsy Brahms PCT Roche Diagnostic) was used for measuring serum PCT concentration. In this study Revised Atlanta classification was used as the gold standard to stratify severity of acute pancreatitis.

Results: Of the 115 patients of AP, 58.3% were male; mean age of presentation was 47 (ranged 18-90) years, 14.8% had severe pancreatitis with organ failure, 16.5% had moderately severe pancreatitis and 68.7% were acute mild pancreatitis. Death occurred in 7%. Commonest risk factor for AP was gall stone disease (53.9%) followed by alcohol (21.7%). In 14.8% of the patients, cause was idiopathic. Mean ± SD value of serum PCT for mild, moderately severe and severe pancreatitis on day of admission were 0.46 ± 1.35 ng/ml, 1.45 ± 1.21ng/ml and 2.58 ± 3.2 ng/ml respectively. Best cut off value of serum PCT was 0.42 ng/ml between mild and moderately severe pancreatitis (ROC curve (AUC):0.785 95% CI (0.691 to 0.861) p 0.0001 with 65% sensitivity and 89.9% specificity. While best cut off value of serum PCT was 0.53 ng/ml between moderately severe and acute severe pancreatitis (ROC curve (AUC):0.70% CI (0.528 to 0.842) P 0.025 with 81.3% sensitivity and 55% specificity.

Conclusion: Serum PCT is potentially a simple and a reliable early biomarker in predicting the severity of AP; however require further research to confirm its accuracy. We have best cut off values that stratify AP into mild, moderately severe and severe pancreatitis with sensitivity ranges between 65% to 81.3% at day of admission.

Keywords: Procalcitonin; Acute Pancreatitis; Severity; Biomarker

Abbreviations AP: Acute Pancreatitis; AUC: Area under Curve; APHACE: Acute Physiology and Chronic Health Evaluation; BISAP: Bedside Index of Severity of Acute Pancreatitis; CT: Computed Tomography; CTSI: Computed Tomography Severity Index; ERCP: Endoscopic Retrograde Cholangio-Pancreatography; PCT: Procalcitonin, ROC: Receiver Operating Characteristic Curve; SAP: Severe Acute Pancreatitis.

Introduction

Acute pancreatitis (AP) is an essential medical condition and carries significant mortality and morbidity if not recognized and managed properly. Accurate diagnosis of severe acute pancreatitis (SAP) on admission to the hospital is of paramount importance and there is, therefore need for finding predictors of severe disease to identify patients who are at risk of morbidity and death. At the moment we have different scoring systems including clinical, biochemical and imaging systems, to stratify severity of AP. However, all these systems incorporate numerous parameters and require appropriate timing to arrive at a conclusion. These constrains persuade the researchers to look for serum procalcitonin (PCT) a comparatively simple, accurate and convenient marker for predicting the severity in AP.

According to the Revised Atlanta Classification [1] severity of the disease is designated into 3 grades: mild, moderately severe, and severe. This classification is based on modified Marshal scoring system and imaging (computed tomography (CT) findings). Mild acute pancreatitis is known with absence of both organ failure and local complications. Moderately acute pancreatitis is transient organ failure lasts for duration of 48 hours, local complications, and/or exacerbation of comorbid disease. Severe acute pancreatitis (SAP) is defined as presence of both organ failure (organ failure that persists for ≥ 48 hours) and local complications. Early severe acute pancreatitis is rapid development of multiple organ dysfunction within 72 h of symptom onset characterized by early respiratory failure, extensive pancreatic necrosis, and abdominal compartment syndrome [2]. The presence of multiorgan dysfunction syndrome, substantial pancreatic necrosis, infection, and sepsis are key factors that affects the outcome of patient in terms of the mortality in AP [3,4]. Mortality reported in various studies ranged between (20%-60%) in SAP. At the moment various prognostic markers and scoring systems are available to stratify the

severity in acute pancreatitis. These scoring systems are based on clinical and biochemical criteria's include Ranson score (11 criteria) [5], the Glasgow score (eight criteria) [6], Bed side Index for Severity in Acute Pancreatitis (BISAP) score (5 criteria), and the acute physiology and chronic health evaluation (APACHE II) score (14 criteria) [7]. These scoring system predicts severity in AP with sensitivity and specificity of range between 55% and 90%, depending on the cut-off number and the timing of scoring [8]. However, these scoring systems have constrains, for instance (APACHE II) is the cumbersome scoring system, likewise (Ranson and Glasgow scores) takes at least 48 hours into the illness to obtain composite score.

Procalcitonin is a calcitonin propeptide contains 116 amino acids with molecular mass 13 kDa. In general population, PCT is synthesized as the intracellular prohormone of calcitonin in the C cells of the thyroid gland and it is found in plasma as traces (~0.1 ng/ml). PCT was measured earlier by manual immunochemistry based method BRAHMS Kryptor assay; nowadays newer generation PCT assays are available like (Siemens and Roche), these are fully automated diagnostic analysers. In systemic infection or inflammatory state, PCT blood level increase within 3-6 hours, and continues till inflammatory process stays. Research says neuroendocrine cells of kidneys and lungs are possible source of PCT during state of sepsis and severe inflammation, the plasma concentration may ranges between 1 ng/ml and 1000 ng/ml; [9-12]. Serum PCT is an ideal marker to diagnosis early sepsis and inflammatory condition due to its short half-life (approximately 24 hours) and thereby helps in monitoring disease progression [13]. The major complications of acute pancreatitis are infected pancreatic necrosis, sepsis, and multi-organ failure and expect increase serum PCT levels; values above 0.5 ng/ml are considered abnormal [14]. In this study we have investigated the appropriate cut-off values of serum PCT in different degree of severity of AP and assessed its validity as a prognostic marker.

Patients and Methods

It was prospective study and all patients who are fulfilling inclusion/exclusion criteria were enrolled. The diagnosis of AP was made on criteria, presence of two of the following three features:

- Abdominal pain (epigastric region often radiating to back, acute onset, severe, continuous and aggravated by meals).
- Serum amylase and/or lipase more than 3 times the upper limit of normal.
- Abdominal imaging findings, ultrasound shows diffuse/focal enlarged hypo echoic pancreas or diffuse/focal enlarged heterogeneous enhancement of pancreas on CT.

Onset of typical abdominal symptoms ≤ 48 hours prior to study inclusion.

Exclusion criteria were Patients with previous pancreatic interventions or surgery due to the current attack of acute pancreatitis and major psychiatric disorders.

A written informed consent was taken from all patients. Blood samples were collected on admission and were centrifuged for 10 minutes at 3,000 rotations per minute for serum PCT. The serum PCT concentration was measured using a chemiluminescent immunoassay (Elecsy Brahms PCT Roche Diagnostic) with the reference value range (0.05 ng/mL) for healthy subjects. The study protocol was in agreement with the current revisions of the Helsinki Declaration and was endorsed by the ethics committee at the Institution. The diagnostic cut-off values of serum PCT were determined by the receiver operating characteristic (ROC) curves. SPSS software version 20.0 was used for the two samples t-test and chi-square test. $P<0.05$ was deemed statistically significant.

Results

Among 115 patients 67 (58.3%) were males and 48 (41.7%) were females. Mean age of presentation in cohort of 115 AP was 47.7 years (range 18-91), with mean age of males and females were 45.3 years and 51.08 years respectively. In our study on analyzing the etiology, we observed that the etiologies of AP included gallstone (53.9%), alcoholic (25%), idiopathic (14.8%), drug (5.2%), hypercalcemia (1.7%), hypertriglyceridemia (0.9%) and post-ERCP (1.7%) shown in Table 1. Of 115 AP patients, 79 patients (68.7%) had mild pancreatitis, 19 patients (16.5%) had moderately severe and 17 patients (14.8%) had severe pancreatitis.

Patient characteristics	No of cases	Percentage (%)
Sex		
Male	67	58.3
Female	48	41.7
Age group		
<20	4	3.5
20-29	18	15.6
30-39	21	18.2
40-49	19	16.5
50-59	25	21.7
60-69	13	11.3
>70	15	13
BMI		
<18.5	5	4.3
18.5-25	64	55.7
25.1-30	36	31.3
>30	10	8.7
Etiology		
Biliary	62	53.9
Alcohol	25	25
Idiopathic	17	14.8
Drug	6	5.2
Hypercalcemia	2	1.7
Hypertriglyceridemia	1	0.9
Post-ERCP	2	1.7
Clinical presentation		
Pain radiating to back	27	23

Non radiating pain	84	73
Vomiting	71	61.7
Abdomen tenderness	55	47.5
Guarding	26	22.6
Ileus	23	20
Co-morbidities		
Present	68	59.1
Absent	47	41.2
Total	N=115	

Table 1: Clinical characteristics of patients with acute pancreatitis.

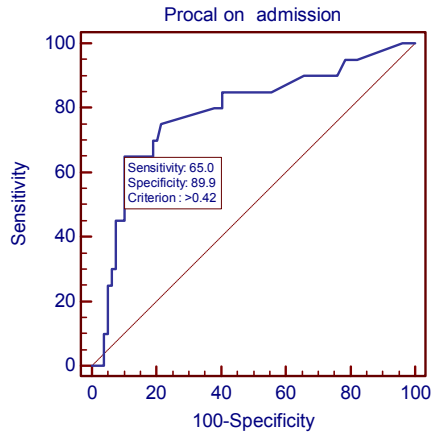

Figure 1: ROC between mild vs moderately severe on admission.

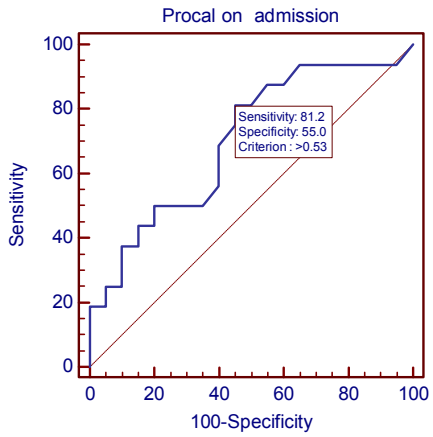

Figure 2: ROC between moderately severe vs severe on admission.

In our study, it was observed out of 115 patients of AP, 8 patients died, 1 patient discharged against medical advice. Overall mortality was 7% observed in patients of AP in current study. The mean values of PCT on day of admission for mild cases were 0.46 ng/ml with SD 1.35 ng/ml range (0.01-8.91),moderately severe was 1.45 ng/ml with SD 1.21 ng/ml range (0.02-4.97) and severe AP was 2.58 ng/ml with SD 3.2 ng/ml range (0.02-11.97) .The area under curve (AUC) was plotted for serum PCTon day of admission in predicting severity in AP, given in Table 2 and Figure 1 and 2.

	Area under the ROC curve(AUC)	95% Confidence interval (CI)	p value	Cut-off point	Sensitivity	Specificity
Mild vs. Moderately severe	0.785	0.6911 to 0.8613	<0.0001	>0.42	65%	89.87%
Moderately severe vs. Severe	0.701	0.526 to 0.8420	0.0252	>0.53	81.25%	55%

Table 2: Receiver-Operating Characteristic Curve (ROC) for Procalcitonin in the study.

Discussion

The present study was intended to ascertain the best cut-off values of PCT to stratify severity in AP and assess efficacy of various severity indices in predicting their end result. Severity is defined by the emergence of local complications and/or distant organ dysfunction: 10% to 20% of patients meet a severe AP attack, associated with both local and systemic complications, resulting a prolonged hospital stay and high morbidity and mortality [15]. Early diagnosis and assessment of disease severity at admission is central to appropriate clinical management. Prognostic criteria can be classified into four categories: clinical signs, biochemical indicators, multi-factor grading systems and imaging procedures. Within 48h of admission, clinical assessment is as accurate, if not better than any other means of assessing the prognosis of acute pancreatitis. Several multi-factor grading systems have been devised to identify patients at higher risk. Various biochemical assays, quantify the products released by the pancreas as consequence of inflammatory reaction, have been developed to identify severe disease and/or pancreatic necrosis before the occurrence of multiple organ

dysfunctions. The scoring systems of patients with AP helps in many ways, clinicians are aware of potential severity of disease and can be used comparison tool to assess effectiveness of new treatment within and between patient series. Sadly, at the moment the scoring systems are often insufficient to predict severity and recognize early organ failure [16-18]. Therefore, a reliable scoring system or single biomarkers that adequately characterize the severity of AP is warranted. In this study; PCT was used a simple single biomarker to predict the severity of AP.

Procalcitonin (PCT) contain 116 amino acid of the propeptide calcitonin with a molecular mass of 12,793 Da that is secreted by renal, hepatocytes, pulmonary, pancreatic tissues, and C-cells of the thyroid gland. During the infection, PCT is released into the blood circulation without increase of calcitonin, and it pent-up with the inflammatory response of a host to microbial infections. In present study; PCT has a sensitivity of 65%for prediction of severity in AP within day of presentation, best cut-off value of 0.42 ng/ml to stratify mild cases from moderately severe and sensitivity of 81.3% for prediction of severity with cut-off value of PCT (0.53 ng/ml) between moderately severe and severe AP. Research had found that increase PCT level potentially predicts early organ failure and pancreatic necrosis in patients with AP [19-22]. In a meta-analysis,a subset of 8 studies concluded that the sensitivity and specificity of PCT (using cut-off value 0.5 ng/ml) for occurrence of SAP were 73% and 87%, respectively [23]. In a study by Woo et al. [24], patients with SAP had significantly higher levels of the serum PCT than in mild AP. However, serum PCT being biochemical marker the accuracy was 77.3% as good to the APACHE-II score, but better than the BCTSI (65.9%). The most effective cut-off level of serum PCT was estimated at 1.77 ng/mL (AUC=0.797, 95% CI=0.658-0.935) in their study. In another study by Gurda-Duda et al. [25], stated that estimation of serum PCT helps in the early prediction of SAP, similar results were reported in many subsequent studies although some argument do exist [26-28]. A study by Kim et al. [29], reported significance of the serum PCT as predictor of severe AP (p=0.018), though it's the accuracy was 76% and the AUC was 0.788. A study by Khanna et al. [30], showed that serum PCT in SAP has 100% and 86.4% sensitivity for prediction of organ failure and mortality respectively. Still best early prognostic assessment is attained by a combination of repeated clinical examination, BISAP score, APACHE II score and CT. The primary goal of this approach is to identify those patients who are likely to need intensive care for early organ dysfunction(s) and life-threatening local complications. Prompt stratification will become more important when specific strategies are introduced for treatment of the inflammatory necrotizing process. At moment we are lacking reliable early marker for the prediction of SAP, however current study evaluated the potential role of the serum PCT in the early prediction of SAP. The blood PCT levels significantly helped to improved stratification patients of AP, who are at risk to develop major complications.

Limitation of the Study

The study has limitations given its relatively small cohort size, nonrandomized and insufficiently powered, thus there is necessity of conducting large randomized control trial to assess efficacy of serum PCT as a reliable early biochemical marker for prediction of SAP. There is complete lack of studies which have assessed serum PCT cut-off values in varied severity of AP.

Conclusion

The best cut -off values of serum PCT levels to stratify mild from moderately severe AP, and moderately severe from severe AP at the presentation were 0.42 ng/ml and 0.53 ng/ml respectively. Serum PCT is a promising simple biomarker in predicting the early severity of pancreatitis with accuracy of 78% between mild and moderately severe and 70% between moderately severe and severe on day of admission.

Conflict of Interest

The authors have none to declare

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