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THE CLINICAL BENEFIT OF SERUM PROCALCITONIN LEVELAS COMPARED TO BISAP SCORING SYSTEM FOR PREDICTINGTHE SEVERITY AND PROGNOSIS OF ACUTE PANCREATITIS

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Abstract

Background: Early accurate severity assessment of patients with acute pancreatitis (AP) is cruicial to decide on the acute management and predict outcomes and prognosis.This is done through multiple scoring systems of which serum procalcitonin (PCT) and BISAP has shown promising results. However,data comparing these methods is still conflicting. Objectives: we aim to assess the role of PCT as a sole indicator and compare it to BISAP in determining severity and prognosis of AP. Methods: Retrospective chart review of all AP cases between June 2012 and February 2017 at Makassed General Hospital, with at least one reading of PCT documented in records. Data regarding patients' demographics and outcomes were collected. Procalcitonin levels and trends were compared to severity classes and BISAP scores regarding various outcomes of AP. Results: Forty-four patients met our inclusion criteria. Based on the revised Atlanta classification, 26 patients had mild, four moderate and 14 severe AP. Mean serum PCT levels were found to correlate with severity classes (1.28 with mild versus 4.81 with moderate-severe AP; P < 0 .0001). This was even more prominent on follow-up testing after 48hours (1.67 vs 12.89 respectively; P=0.01). This proportional relation was again noted with BISAP scores of 0,1 and 2 where the mean PCT was 0.1,5.0 and 19.1 respectively. A trend of decrease in serial PCT was also noted with mild as compared to a trend of rising PCT in moderate-severe AP. Conclusion: Initial and serial PCT levels directly correlated with disease severity and might offer significant additional prognostic value in AP.

Keywords

Prognosis; Severity; Serum procalcitonin; Acute pancreatitis

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ABSTRACT: *Background: Early accurate severity assessment of patients with acute pancreatitis (AP) is cruicial to decide on the acute management and predict outcomes and prognosis.This is done through multiple scoring systems of which serum procalcitonin (PCT) and BISAP has shown promising results. However,data comparing these methods is still conflicting. Objectives: we aim to assess the role of PCT as a sole indicator and compare it to BISAP in determining severity and prognosis of AP. Methods: Retrospective chart review of all AP cases between June2012 and February2017 at Makassed General Hospital, with at least one reading of PCT documented in records. Data regarding patients' demographics and outcomes were collected. Procalcitonin levels and trends were compared to severity classes and BISAP scores regarding various outcomes of AP. Results: Forty-four patients met our inclusion criteria. Based on the revised Atlanta classification, 26 patients had mild, four moderate and 14 severe AP. Mean serum PCT levels were found to correlate with severity classes (1.28 with mild versus 4.81 with moderate-severe AP; P<0.0001). This was even more prominent on follow-up testing after 48hours (1.67 vs 12.89 respectively;P=0.01). This proportional relation was again noted with BISAP scores of 0,1 and 2 where the mean PCT was 0.1,5.0 and 19.1 respectively. A trend of decrease in serial PCT was also noted with mild as compared to a trend of rising PCT in moderate-severe AP.*
Conclusion: Initial and serial PCT levels directly correlated with disease severity and might offer significant additional prognostic value in AP.

KEYWORDS: *Prognosis; Severity; Serum procalcitonin; Acute pancreatitis*

1. INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas characterized by severe Characteristic epigastria pain along with an elevation of pancreatic enzymes, namely amylase and lipase (Kusske,1996) .Approximately 20 percent of cases develop moderately severe or severe acute pancreatitis, characterized by local complications or organ failure. Expectedly, patients with severe or necrotizing pancreatitis had a significantly higher mortality when compared to patients with mild interstitial pancreatitis (17 versus 3 percent) (Banks, 2006). Tremendous research efforts were put into assessing the severity and prognostic factors of AP in order to help in the management as well as to determine the best in-hospital setting for such patients. The revised Atlanta classification system stratifies patients to mild, moderate and severe based on the presence or absence of local or systemic complications and of organ failure (Lee, 2016).Different predictive models and scoring systems were developed and validated over the past few decades to aid in prognostication, including the APACHE II and the Ranson's criteria were among the early scoring systems that showed good accuracy inpredicting the severity of pancreatitis; however, they were limited by their complicated multiple parameters and the time delay needed to fulfill its criteria (Yang, 2014). More recently, the bedside index of severity in acute pancreatitis (BISAP) –a more simple and practical score- was tested and validated for this purpose and showed similar sensitivity and predictive value when compared to the other previous scores (Papachristou, 2010).

Aiming at finding better and simpler prognostic indicator, small studies addressed the utility of serum procalcitonin (PCT)levels in determining outcomes of patients with AP. PCT is the inactive pro-peptide of the hormone calcitonin, which is involved in calcium homeostasis. The increased serum PCT correlates closely with the inflammatory response of a host to microbial infections, namely bacterial and fungal infections (Villatoro, 2010). In patients who suffer from acute pancreatitis, PCT has been shown to predict the development of infected pancreatic necrosis (Al-Nawas, 1996) . In addition, it was suggested that PCT might be an early predictor of severity and organ failure in patients with AP (Modrau, 2005). The significance of measuring the PCT level in the assessment of the severity of acute pancreatitis as well as predicting the risk of developing infected pancreatic necrosis was tested inseveral studies. Systematic reviews of these studies yielded contradicting results. The most recent one published in 2009 suggested a valuable role of serum PCT in predicting the severity of acute pancreatitis and the risk of developing infected pancreatic necrosis (Mofidi, 2009). The sensitivity and specificity of PCT for predicting the development of severe AP were 0.72 and 0.86, respectively. Moreover, the sensitivity and specificity of PCT for prediction of infected pancreatic necrosis were 0.80 and 0.91 (95% CI = 13.8--58.3) (Al-Nawas, 1996) .When comparing PCT to BISAP score, data were also contradicting. A Korean study in 2013 compared BISAP to other scoring systems including PCT, showed that BISAP was more accurate than PCT (BISAP 84% accurate and PCT 76%) (Kim, 2013). However, data is still insufficient.

In this study, we aim to assess the role of procalcitonin and to compare it to BISAP in determining the disease severity and prognosis according to revised Atlanta Classification for severity of acute pancreatitis

2. MATERIALS AND METHODS

2.1 Setting and Data Collection

This is a retrospective chart review of all patients diagnosed with acute pancreatitis who were admitted to Makassed General Hospital (MGH) between June 2012 (the date were PCT was first introduced to our laboratory) and February 2017. Data were retrieved from the patients' electronic medical records. Only patients above the age of 18 at diagnosis, with at least one reading of Procalcitonin in their charts and with clear documentation sufficient for the calculation of BISAP score were selected for data collection and comparison. Exclusion criteria included patients with chronic pancreatitis, preceding active sepsis from a definitive focus other than AP and those with incomplete chart documentation. Datathat were collected from the selected charts included: Patients' demographics, associated comorbidities, etiology of AP, results of any imaging performed, the presence of any local complications or the occurrence of any organ failure (needed for the revised atlanta criteria), the criteria for calculating the BISAP score, PCT readings, duration of hospital stay, the use of antibiotics, the need for intervention, and mortality. PCT levels were measured using an immunoturbidimetry method (Roche Diagnostics, Indianapolis, Ind) and an enzyme-linked fluorescent assay (bioMerieux, France), respectively.

Patients were first categorized into mild, moderate and severe AP based on the criteria for the revised Atlanta classification. The BISAP score and the initial as well as the other PCT readings were then plotted and comparison was performed to show the concordance between these three predictive modelswith respect to the various outcomes of AP.

Definitions

Revised Atlanta classification system: divides patients with AP into a. mild AP, characterized by the absence of any organ failure and local or systemic complications. (ii) Moderately severe AP, characterized by transient organ failure (resolving within 48 hours) and/or local or systemic complications without persistent organ failure. (iii) Severe acute pancreatitis, characterized by persistent organ failure that may involve one or multiple organs

BISAP "Bedside Index for Severity in Acute Pancreatitis": is a score that has been developed to identify patients at high risk for mortality or severe disease early during the course of acute pancreatitis. It gives one point to each of the following five criteria: Serum BUN of more than 25mg/dl, Impaired mental status, presence of systemic immune response syndrome (SIRS), age > 60 years, and the presence of pleural effusion.

Procalcitonin: A biochemical marker (a peptide precursor of hormone calcitonin) composed of 116amino acids and produced by cells of thyroid, lungs, and intestines. Its level rise in bacterial infections, not in viral or non-infectious inflammations. It is used as a marker for sepsis with sensitivity (85%) and specificity (91%) for differentiating patients with systemic inflammatory response syndrome (SIRS) from those with sepsis (Gurda-Duda, 20

2.2 Statistical analysis

The Statistical Package for Social Sciences (SPSS, version 21) program was used for data entry, management, and analyses. A p-value of <0.05 is used to indicate statistical significance.Categorical variables are presented as number and percent, whereas continuous variables are presented as mean and standard deviation. Bivariate analysis was carried out by using the chi square for comparing categorical variables, whereas continuous ones were compared using the Student's t-test.

3. RESULTS:

The total number of patients who met the study's inclusion criteria was 44 patients. Twenty-six patients (59%) were found to have mild APaccording to the revised Atlanta classification, whereas 4 patients (9%) had moderately severe AP and 14 patients (32%) had severe AP. Because of the small number of patients with moderate AP, and because this category shares some similar characteristics with patients having severe AP, these two groups were combined together under "moderate-severe AP" category, and were compared to patients with "mild AP".

The two groups were similar with respect to baseline characteristics including age and gender (Table 1).

Table 1: Characteristics of 44 Patients with Acute Pancreatitis

	Pancreatitis		
	Mild N=26	**Moderate-Severe N=18**	**P-value**
Age, mean (±SD)	59.50 (±20.67)	61.28 (±20.97)	0.77
Gender			
Male	15 (57.7%)	6 (33.3%)	0.14
Female	11 (42.3%)	12 (66.7%)	
Etiology			
Alcoholic	2 (7.7%)	1 (5.6%)	1.00
Biliary	11 (42.3%)	7 (38.9%)	0.75
Hypertriglyceridemia	3 (11.5%)	3 (16.7%)	0.68
Hypercalcemia	0 (0.0%)	0 (0.0%)	NA
Drug induced	3	1 (5.6%)	NS
Post-ERCP	1 (5.6%)	1 (5.6%)	
Other	11 (42.3%)	7 (38.9%)	1.00
Outcome			
ICU admission	0 (0.0%)	13 (72.2%)	<0.0001
Mechanical ventilation	0 (0.0%)	9 (50.0%)	<0.0001
Necrosis	0 (0.0%)	1 (5.6%)	0.41
Antibiotic use	20 (76.9%)	18 (100.0%)	0.07
Intervention	8 (30.8%)	3 (16.7%)	0.48
Mortality	0 (0.0%)	6 (33.3%)	0.003
Duration of hospitalization, mean (±SD)	6.69 (±3.80)	17.11 (±9.40)	<0.0001

The most common etiology for AP was biliary(40.9%). Other causes included alcohol (6.6%), and hypertriglyceridemia (14.1%), drug induced (9%) and post ERCP pancreatitis (4.5%). Expectedly, patients with moderate-severe AP had worse outcomes with 13 cases requiring ICU admissions (72.2%) of which 9 needed mechanical ventilation (50%) and a total of 6 in-hospital mortalities (33.3%) as compared to none in the mild AP group. Both groups had similar surgical intervention (mainly cholecystectomy) and antibiotics use rates.

Moreover, the hospitalization duration was significantly higher (mean =17.11 ±9.40) among moderate-severe pancreatitis patients.

Both BISAP score and PCT levels were significantly higher in moderate-severe acute pancreatitis patients when compared to those of mild disease (p<0.0001) (Table2).

Table 2: Correlation between revised Atlanta classification and the mean BISAP score and mean PCT levels.

	Pancreatitis		
	Mild N=26	**Moderate-Severe N=18**	**P-value**
Scoring/biochemical markers			
BISAP score, mean (±SD)	1.12 (±1.18)	2.89 (±1.18)	<0.001
Procalcitonin (PCT1), mean (±SD)	1.28 (±3.73)	4.81 (±6.05)	<0.001
Procalcitonin (PCT2), mean (±SD)	1.67 (±4.61)	12.89 (±26.28)	0.01
Procalcitonin (PCT1+PCT2), mean (±SD)	2.05 (±6.71)	14.84 (±25.92)	<0.001

Interestingly, there was a clear and linear quantitative correlation between the mean PCT level upon admission and after 48 hours with the severity of AP and with the BISAP score. Even when we subdivided the patients into mild , moderate and severe categories, the mean PCT level seemed to proportionally rise with the increase in the severity, from 1.27 in patients with mild, to 2.20 in moderate and 5.56 in severe AP. Fifty percent of patients with moderate-severe AP had a PCT level above the cutoff of 2 as compared to only 7% in patients with mild AP. Moreover, there was a greater tendency of having a rising PCT level by more than 50% after 48 hours in severe cases (30%) as compared to mild cases (8%). Similarly, 75% of patients with mild AP showed a drop of PCT within the first 48 hours as compared to 50% of patients with moderate and severe cases (Appendix1).

When subdividing the patients into the 5 possible BISAP score, PCT levels were correlating with severity from 0 to 2 and to a lesser extent at BISAP 3, however this relation was lost at higher BISAP scores, probably due to the small number of patients (table 3).

Table 3: Correlation between different BISAP scores and Procalcitonin Levels in Acute Pancreatitis.

	Pro-calcitonin	**p-value**
BISAP score (n)		
0 (n=10)	0.11 (±0.63)	
1 (n=10)	5.00 (±0.63)	
2 (n=10)	19.08 (±33.36)	0.010
3 (n=6)	8.12 (±14.48)	
4 (n=7)	2.05 (±1.72)	
5 (n=1)	15.54 (NA)	

There was no correlation between the duration of hospitalization with respect to PCT levels (Figure1).

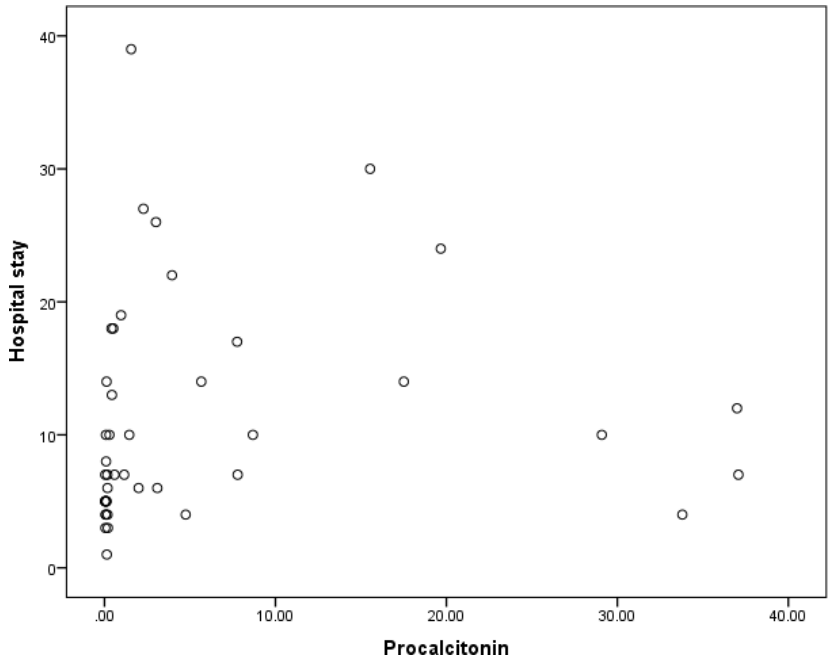

Fig. 1 Relationship between the duration of hospitalization and PCT levels

Of notice, there is a wide distribution for PCT in BISAP score 2 as compared to BISAP score of 3 and 4 (Figure 2).

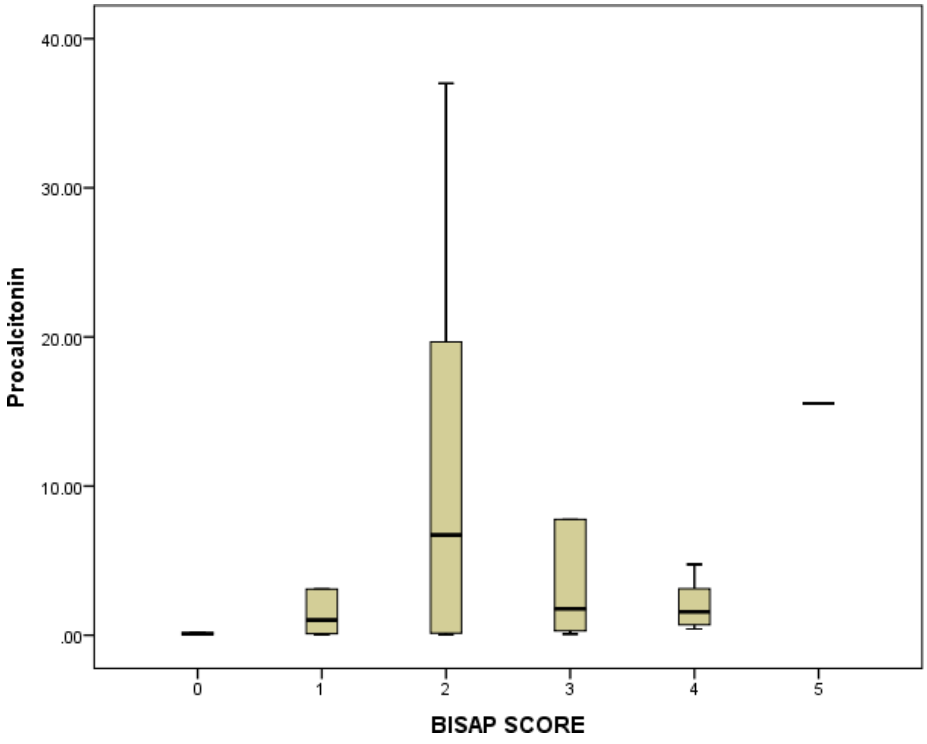

Fig. 2 Relationship between Procalcitonin Levels and BISAP score

4. DISCUSSION:

AP is a serious medical condition that places a considerable burden on the healthcare system. It is of utmost importance to adequately categorize patients into the various severity classes and to accurately determine the patients with the worse prognosis in order to manage these cases aggressively and thus reduce the high mortality rates of such condition. Unfortunately, the scoring systems used at present are often inadequate in patients with severe AP, which is characterized by rapidly progressive multiple system organ dysfunction. Therefore, a simple scoring systems or single specific biomarkers that can predict the prognosis of AP are needed.

Procalcitonin, an early marker of systemic bacterial infection, sepsis, and multiorgan failure, was introduced as a prognostic marker of AP in the recent years, focusing on systemic inflammation and organ failure in the early stage of AP (Modrau, 2005). Review of literature about its efficacy revealed some debate about the role of this biochemical marker as a prognostic factor.One study in 2008 by Gurda-Duda et al.(Gurda-Duda, 2008), stated that the early prediction of severe AP was achievable by measuring PCT on admission and following it up within

48 hours. Subsequent studies have compared the value of serum Procalcitonin to other prognostic markers such as CRP and Interleukin-6(IL-6) where it showed a higher significance. However, results were variable in relation to Procalcitonin due to small study sample size and multi-center studies. A Korean study in 2012 by Kim et al compared the clinical significance between BISAP and PCT. It stated that a BISAP score (≥ 2) was more accurate (84%) at predicting severity of AP and superior to serum PCT (≥ 3.29 ng/mL, 76% Accuracy) [10].

In our study, we aimed to study the value of serum Procalcitonin in severity assessment of AP and to compare it to BISAP. The relation between the absolute quantitative levels of PCT and the severity class was clear and proportional, denoting a significant additional role that can help in the prognostication of patients presenting with AP. Although the correlation of the PCT level was less evident with higher BISAP scores, which is mostly attributed to the very small number of patients having a score of 5 (only 1 patient), the results shown above suggest a good association with the other BISAP categories. Although current data could not support the use of PCT alone as a solo test, these findings might support the suggestion that adding PCT levels to the routine admission panel for such patient will be complementary to the already validated available scores to improve the prognostication process. Further data is needed in order to integrate the PCT level into the other scoring systems and develop modified predictive models with higher accuracy and clinical value.Our data also suggested that serum Procalcitonin is significant in predicting severity of AP at an early stage with cut-off value of 1.28 (±3.73) ng/ml in mild form of the disease and 4.81 (±6.05) ng/ml for moderate-severe AP (p-value<0.001). Regarding BISAP, it was evident that the best cutoff score of BISAP was 2 which is similar to the result stated by Kim et al. [], although some other studies have proposed 3 to be the best cutoff score [].We aimed to see the relation between the duration of hospitalization with the severity of the disease and found that patients with severe disease are likely to spend more time in the hospital with an average of 17.11 (±9.40) days (p-value <0.0001). Beside our primary aim of our study, we noticedthat the use of antibiotics in this study population was surprisingly very high even in the mild AP group (76.9%). This shows a deficiency in following the current guidelines [6], which recommend against the routine use of antibiotics in AP except in the case of severe necrotizing AP (we had only 1 such case in this series) or with the evidence of local infected collections.

Our study had several major limitations. We had only 44 patients over the past 5 years since Procalcitonin was first introduced to Makassed General Hospital. This was attributed to deficiencies in documentation in our medical records, the lack of knowledge about the importance of PCT in patients with AP, and the recurrent occasions of shortage of the laboratory kits supplies. This number is small and a larger number is needed to provide better results especially in the nigh BISAP score category. We also were not able to compare the PCT to other predictive models like the Ranson's criteria and the Balthazar score due to the lack of documentation in this retrospective study.

5. CONCLUSION

Serum procalcitonin level is a valuable complementary prognostic marker for assessing the severity of AP. We suggest to routinely measure and follow-up serial serum PCT levels on patients presenting with AP. It directly correlates with the three classes of the revised Atlanta classification and best correlates with BISAP scores of 0 to 3. We suggest a mean cut off value of 2 for denoting a worse prognosis.

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Conflicts of Interest: The authors declare that they have no conflict of interest.

Ethical approval: Makassed General Hospital Institutional Review Board committee approved this study.

Informed consent: No informed consent was required due to the retrospective nature of this study. During the data collection phase, a special form was used where patient initials and case numbers were only included. At a later stage, a different number was assigned to each of our cases to safeguard patient privacy.

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