Correlation of Disease Activity, IL-6 & CRP Levels and Leukocytes/Lymphocyte Ratio Among Patients with Acute Pancreatitis

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Keywords: Acute pancreatitis; Scorings; CRP; IL-6; leukocytes/lymphocyte ratio

Introduction

Acute pancreatitis (AP) is described as activation of pancreas enzymes inside the pancreas and digestion of pancreas tissue via its own enzymes (autodigestion) [1]. Acute pancreatitis is diagnosed according to criteria indicated in Atlanta symposium in 1992, namely abdominal pain accompanied by three-fold increase in serum amylase or lipase levels [2]. According to this symposium, acute pancreatitis is classified into two groups, as mild and severe disease states. While rate of mild disease is 70-80% in acute pancreatitis, severe cases present with a rate of 20-30%.

Though certain variations in etiology are seen in different countries, gallbladder stones and alcohol is held responsible in approximately 70-80% of cases [1,3]. Various scoring systems are being used to determine clinical severity and prognosis in acute pancreatitis [2-6]. Ranson is a specific scoring system for acute pancreatitis and is based on certain clinical and laboratory findings of patients at referral and at 48th hour. APACHE II is rather a general scoring system; beginning from initial referral to hospital, it provides evaluation of certain physiological functions and general health status of patients at 24-hour intervals. BISAP score are also newer scoring system for pancreatitis [4]. Balthazar scoring describes anatomic structures more precisely and may indicate complications like pancreatic inflammation and necrosis. Endogenous inflammatory mediators play a significant role in pathogenesis of AP [7-10]. Best known among these mediators is interleukin-6 (IL-6) and it’s released at an early stage as a response to inflammation, enabling the synthesis of acute phase proteins, primarily C-reactive protein (CRP), in liver. While measuring IL-6 levels are beneficial in determining early reaction of the organism to inflammation, serum CRP levels will be helpful in evaluating early phase response.

Since acute pancreatitis (AP) leads to serious morbidity and mortality, determination of severity of acute pancreatitis at an early stage via scoring and inflammatory mediators indicated above accompanied by appropriate treatment and intensive care will decrease mortality in these cases. The aim of this trial is to investigate whether the comparison of Ranson, APACHE II and Balthazar scoring systems with inflammatory mediators CRP, leukocytes/lymphocytes ratio and IL-6 is statistically significant.

Material and Method

A total of 52 patients were enrolled in this trial. Basic scoring (Ranson criteria and APACHE II) and inflammatory indicators were used in our trial. Serum levels of IL-6 were measured (pg/ml), which is known to express the earliest and the most efficient response. During the first 24 hours after referral, blood samples of 10 ml were obtained from each patient; serum was separated and placed in a dry tube to be kept frozen at -20°C until examination. Quantitative measurements were performed by immunoassay method using Immulite™-IL-6 kit in Immulite™-1000 device. For normal reference values, IL-6 levels were measured in samples obtained from 10 healthy adult volunteers; values between 0-10 pg/ml were accepted as normal reference range.

Acute phase response: To determine acute phase response against inflammation, serum CRP levels were measured. Blood samples of 5 ml were obtained from cases during 48th hours after referral and quantitative measurements were carried out in biochemistry laboratory in Behring Turbittmer” device (Behringwerke AG, Marburg, Germany) using turbiquant CRP kit (anthuman CRP from rabbit, Behring, Germany) using turbiquant CRP kit (anthuman CRP from rabbit, Behring, Germany)

For this measurement, normal reference values for CRP

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Received December 02, 2011; Accepted June 08, 2012; Published June 10, 2012

Citation: Goral V, Berekatoglu1 Mete N (2012) Correlation of Disease Activity, IL-6 & CRP Levels and Leukocytes/Lymphocyte Ratio Among Patients with Acute Pancreatitis. J Gastroint Dig Syst 2:112. doi:10.4172/2161-069X.1000112

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were 0-5 mg/L. Cut-off value for severe inflammation was accepted as 150 mg/L. Whole blood samples of patients, required for APACHE II or Ransom scorings, were placed in tubes containing EDTA and were evaluated by automatic laser system in CELL-DYN 3700 device. Other parameters like amylase, glucose, urea, creatinine, Na⁺, K⁺, Cl⁻, Ca++, LDH, AST, albumin, T.cholesterol, TG, LDL, HDL were studied in biochemistry tubes with gel using enzymatic method in Architect C 1600. Arterial blood gas was obtained with heparinized injector and was measured in Siemens rapid lab 1265 device.

For all patients, parameters like gender, age, etiology, findings of imaging techniques and total stay in hospital were recorded, in addition to concomitant diseases either known to be existent at referral or detected during hospitalization, additional morbidities which developed during hospitalization (including organ failure), surgical interventions during hospitalization, if any, ERCP requirement, invasive radiological procedures and number of mortalities.

As per existing findings, patients with Ranson score ≥3, APACHE II score ≥8 and CRP value ≥150 mg/L were accepted as severe AP cases; CT was performed in these patients and scored according to Balthazar classification.

For statistical evaluations, data were electronically recorded and studied in SPSS 17.0 program and Student's t test was used for testing of two independent groups and for testing of categorical variables.

**Results**

Among patients diagnosed as acute pancreatitis, 36 (69.2%) were women and 16 (30.8%) were men; ages varied between 17 and 86 (mean age: 55.7), mean age was 54.4 for women and 56.9 for men. Upon investigation of etiology of acute pancreatitis; biliary causes were found in 30 patients (57.6%), hypertriglyceridemia in 1 patient (1.9%) and post-ERCP in 2 patients (3.8%). No cases were considered as idiopathic conditions (38.4%). ERCP was performed in 16 patients diagnosed with biliary AP and cholangitis, presenting with high direct bilirubin values and stones in biliary tract detected by imaging techniques. ERCP results revealed choledocholithiasis in 12 patients; no prominent cause was determined in 4 patients. Length of stay in hospital among patients was 10 ± 4 days.

Patients were classified into two groups as mild and severe AP cases according to the Atlanta classification [2]. In mild AP cases, APACHE II was <8, Ranson <3 and CRP was <150 mg/L while in patients with severe AP, APACHE II was ≥8, Ranson ≥3 and CRP was ≥150 mg/L.

Among patients with mild AP, mean Ranson score was found as 1 and APACHE-II score for the same group was calculated as 3.1. In mild AP group, mean CRP value was 49 mg/L and mean IL-6 was 7.7 pg/ml. Among severe AP patients, mean Ranson score was determined as 3.2 and mean APACHE-II score was calculated as 10.5. In severe AP group, mean CRP was 188 mg/L and mean IL-6 was measured as 30.2 pg/ml. Leukocytes/lymphocyte ratio was 12.71 (34.7 ± 1.95) in patients with acute pancreatitis (normal ratio: 2.63) (P<0.001), especially in patients with severe pancreatitis.

**APACHE II, Ranson and CRP values of patients at 48th hour was compared to IL-6 values in first 24 hours (Table 1). Based on this correlation, a statistically significant relation was found in APACHE II with CRP and Ranson score (P<0.001). CRP was determined to exhibit a statistically significant correlation with Ranson score and interleukin 6 (P<0.001); a significant correlation was observed between Ranson score and IL-6 levels (P<0.05). Patient group was evaluated statistically.

Patients were classified into two groups as mild and severe AP cases (Severe AP: APACHE II≥8, Ranson≥3 and CRP≥150 mg/L) (Table 2). Based on this classification, different APACHE II, Ranson and CRP values in mild and severe cases were found to be significantly correlated with primarily IL-6, duration of hospitalization, age groups and blood urea nitrogen (BUN) (P=0.03, P=0.02, P=0.001, P=0.03, respectively).

In addition, patients with Ranson score<3 and APACHE II<8 were compared with cases with values of Ranson≥3 and APACHE II≥8 in terms of CRP values. This comparison was found to be significant by Chi-square test, as P: 0.01 and P: 0.001, respectively. In addition, according to study protocol, abdominal CT was performed in 17 patients, who complied with criteria of severe AP and Balthazar scoring was applied. Scores obtained were compared with APACHE II, Ranson, CRP, IL-6 and blood urea nitrogen (BUN) (Table 2). Based on Balthazar scoring system; increases were determined in Ranson, APACHE II scores and CRP, interleukin 6 values in parallel to the rise in Balthazar scores. Statistical evaluation also revealed significant values of P<0.001, as indicated in table above.

Among statistical tests, Student's t test (One Way Analysis of Variance) was used to compare mean values of two independent groups. ANOVA statistical test was used. Significance levels of differential groups were indicated.

**Discussion**

AP is one of the most significant diseases of pancreas. Though certain variations in etiology are seen in different countries, gallbladder stones and alcohol are considered to be responsible in approximately 70-80% of cases [1-3]. While alcohol is the leading cause in etiology of AP in Western countries, biliary causes constitute the primary reasons in our country. Among other causes, abdominal trauma, hypertriglyceridemia, pancreas or ampulla vater tumors, drugs, infectious causes, endoscopic retrograde cholangiopancreatography...
or surgical procedures may be specified. In around 10% of cases, no cause is determined. In the current trial, evaluation of etiology of acute pancreatitis revealed biliary causes (57.6%), idiopathic causes (38.4%), hypertriglyceridemia (1.9%) and post-ERCP (3.8%). Results of our trial indicate biliary and idiopathic causes as the two leading etiological factors, in compliance with data in literature.

In acute pancreatitis, various scoring systems are being used to determine clinical severity and prognosis [3-6]. The purpose of scoring is to correlate metabolic disorders and organ failure in pancreatitis with morbidity and mortality. Therefore, more than one scoring system is utilized in AP cases. The most common and well known scoring systems are Ranson criteria, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Glasgow criteria and Balthazar scoring. Ranson criteria is a reliable indicator of clinical severity and prognosis in acute pancreatitis. In a review of etiological and prognostic factors in acute pancreatitis, projected mortality rate among patients with Ranson score>3 was indicated as approximately 1%, as 15% in patients with scores 3-4, as 40% among patients with scores 5-6 and as 100% for patients with scores over 6; based on Atlanta criteria, Ranson score>3 is described as severe pancreatitis [1-6]. In 70-80% of cases, acute pancreatitis is mild while in 20-30%, severe disease is observed [4,5]. Among patients treated and followed up in our department, 37 cases (71%) were mild and 15 (29%) were severe acute pancreatitis cases.

In a number of trials conducted on AP, APACHE II scoring system was used. A large scale literature search performed by Bollen TL et al. [11], showed that APACHE II scores ≥ 8 indicated a severe disease [11-16]. Advantage of APACHE II scoring is its applicability both at referral and re-evaluation at intervals of 24-hours; therefore, it provides information on prognosis and response to treatment. Main disadvantages of APACHE II scoring are overaging of age of patients and high scores obtained among elderly patients presenting with mild-moderate attacks. In contrast to Ranson score, APACHE II scoring system is not specific for AP.

For evaluation of patients in our trial, Computed Tomography Severity Index (CT severity score-CTSS) described by Balthazar et al. [12] was used. In this scoring system, clinical severity is described by the extent of inflammation and necrosis in pancreas [11-16]. CT with contrast is the gold standard in diagnosis of acute pancreatitis and evaluation of cases. CT examination describes anatomic structures more efficiently and may reveal complications like pancreatic inflammation and necrosis. Besides, CT is also beneficial in terms of determining clinical severity and prognosis. Vriens et al. [15], found a positive correlation between CTSS and Ranson criteria [3]. In a trial conducted by Ting-Kai L et al. [16] on 121 patients, mild or severe CTSS was found to produce variable APACHE II and Ranson scores [12]. In our trial, among patients with severe AP who were subjected to abdominal CT, comparison of score results with Ranson, APACHE II, CRP and IL-6 values was P<0.001. In parallel to elevation of CTSS, Ranson, APACHE II score and CRP, IL-6 values were determined to be increased and these results were calculated to be statistically significant. Though Balthazar CT index is the best method, increasingly being used in recent years to indicate local complications in acute pancreatitis, it’s still inadequate in predicting mortality and systemic morbidity. For indication of organ failure, APACHE II and Ranson criteria are the two valid scores which are currently in use.

CRP, an acute phase reactant, is widely used to differentiate mild and severe AP attacks [2-4]. Cytokines also have very important role of pathogenesis of acute pancreatitis [3-7]. Serum CRP level>150 mg/L is an indicator of poor prognosis. During acute inflammations, IL-6 increases at an early stage which is followed by acute phase response developed by hepatocytes, which are in turn stimulated by IL-6; therefore, CRP level reaches to maximum in about 48 hours. CRP value measured at 48th hours after the onset of symptoms was shown to be more beneficial than earlier values. Chen et al. [16], in their study of 50 patients, reported that IL-6 is more efficient in determining prognosis at an early stage, as compared to other inflammatory mediators [9]. In the current trial, mean values of IL-6 measured in severe AP cases during first 48 hours were 30.2 (P: 0.03). This value was found to be statistically significant. Evaluation of correlation of IL-6 with each of the following parameters, namely Ranson, APACHE II and CRP, revealed findings of Ranson (p: 0.014), CRP (P: 0.000) and APACHE II (P: 0.199). Based on these findings, a significant correlation was determined for IL-6 with Ranson and CRP.

In our trial, patients were classified into two groups based on CRP values, namely CRP>150 mg/L and CRP<150 mg/L and compared in terms of Ranson and APACHE II scores. For Ranson, Chi-square=6.609 P=0.01 difference was found to be significant. Similarly for APACHE II, Chi-square=11.65, P=0.001 difference of this comparison was found to be significant. Also, according to the Azab B et al. [10], neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis [16]. In our study, we found that leukocytes/lymphocytes ratio is a simple indicator of severity in patients presenting with acute pancreatitis.

According to results of this prospective trial, taking into account all laboratory indicators and scoring systems, APACHE II, Ranson and Balthazar scores play a significant role in indicating the severity of acute pancreatitis. Correlation between these scoring systems also revealed statistically significant results.

Conclusion

This prospective trial showed that parameters indicating the severity of AP, namely Ranson, APACHE II, Balthazar scoring systems plus IL-6, an early indicator of inflammation and CRP values, which rises at a later stage, were found to be significant, both in terms of separate values and for mutual comparisons. According to our data, we suggest using the leukocytes/lymphocytes ratio is a simple indicator of severity in patients presenting with acute pancreatitis. These methods
may be beneficial in efficient determination of patient group which requires intensive care at an early stage and in reduction of morbidity and mortality.

References

1. Spanier BW, Dijkgraaf MG, Bruno MJ (2008) Epidemiology, aetiology and outcome of acute and chronic pancreatitis: An update. Best Pract Res Clin Gastroenterol 22: 45-63.

2. Bollen TL, Van Santvoort HC, Besselink MG, van Leeuwen MS, Horvath KD, et al. (2008) The Atlanta classification of acute pancreatitis revisited. Br J Surg 95: 6-21.

3. DiMagno MJ, DiMagno EP (2007) New advances in acute pancreatitis. Curr Opin Gastroenterol 23: 494-501.

4. Papachristou GI, Muddana V, Yadav D, O’Connell M, Sanders MK, et al. (2010) Comparison of BISAP, Ranson’s, APACHE-II, and CTSI Scores in Predicting Organ Failure, Complications, and Mortality in Acute Pancreatitis. Am J Gastroenterol 105: 435-441.

5. Viedma JA, Perez-Mateo M, Dominguez JE, Carballo F (1992) Role of interleukin-6 in acute pancreatitis. Comparison with C-reactive protein and phospholipase A. Gut 33: 1264-1267.

8. Stimac D, Fisić E, Milić S, Bilić-Zulle L, Perić R (2006) Prognostic values of IL-6, IL-8, and IL-10 in acute pancreatitis. J Clin Gastroenterol 40: 209-212.

9. Gregoric P, Sijacki A, Stankovic S, Radenkovic D, Ivanecvic N, et al. (2010) SIRS score on admission and initial concentration of IL-6 as severe acute pancreatitis outcome predictors. Hepatogastroenterology 57: 349-353.

10. Azab B, Jaglall N, Atallah JP, Lamet A, Raja-Surya V, et al. (2011) Neutrophil-lymphocyte ratio as a predictor of adverse outcomes of acute pancreatitis. Pancreatology 11: 445-452.

11. Bollen TL, van Santvoort HC, Besselink MG, van Es WH, Gooszen HG, et al. (2007) Update on acute pancreatitis: ultrasound, computed tomography, and magnetic resonance imaging features. Semin Ultrasound CT MR 28: 371-383.

12. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH (1990) Acute pancreatitis: value of CT in establishing prognosis. Radiology 174: 331-336.

13. Chatzicostas C, Roussoumoustaki M, Vardas E, Romanos J, Kouroumalis EA (2003) Balthazar computed tomography severity index is superior to Ranson criteria and APACHE II and III scoring systems in predicting acute pancreatitis outcome. J Clin Gastroenterol 36: 253-259.

14. Vitens P, van de Linde P, Slotema ET, Warmerdam PE, Breslau PJ (2005) Computed tomography severity index is an early prognostic tool for acute pancreatitis. J Am Coll Surg 201: 497-502.

16. Leung TK, Lee CM, Lin SY, Chen HC, Wang HJ, et al. (2005) Balthazar computed tomography severity index is superior to Ranson criteria and APACHE II scoring system in predicting acute pancreatitis outcome. World J Gastroenterol 11: 6049-6052.