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Letter to the Editor

Is serum neutrophil gelatinase-associated lipocalin a useful marker in acute pancreatitis?

1. Introduction

Acute pancreatitis (AP) is the reversible inflammation of pancreas. Annually from 4.9 to 35 cases per 100,000 of AP is reported. About one-fourth of patients with AP, develop severe acute pancreatitis (SAP) which may lead to a life-threatening complications and mortality rate is reported up to 5% [1].

A delay in hospitalizing patients after the onset of symptoms and a prior discrimination in the severity of AP within the first 48 h cause difficulties in managing the disease. Several clinical scoring systems and biochemical markers are studied for the prediction of the severity of AP [2]. Unfortunately scoring systems (eg, Ranson, Glaskow) in predicting the severity of AP takes 48 h to be completed and do not have a high degree of sensitivity and specificity. Therefore markers that can predict the severity of the disease within the admission of patients has been on research focus.

Neutrophil gelatinase-associated lipocalin (NGAL) is a member of the lipocalin superfamily. It is a 24 kDa glycoprotein released from activated neutrophils at the sites of infection and inflammation. NGAL is upregulated and expressed in the kidney after renal ischemia and is accepted as a promising marker in diagnosing early acute tubular necrosis [3]. Moniaux et al. had reported that NGAL is expressed de novo during the progression of pancreatic adenocarcinoma. They also observed in the same study that NGAL levels were significantly higher in patients with AP in comparison to healthy individuals [4]. Later on Chakraborty et al. published a study evaluating serum NGAL (sNGAL) levels in the course of AP. The study proposed sNGAL as a distinguishing marker of SAP and mild acute pancreatitis (MAP) [5].

In our prospective study we aimed to evaluate the prognostic value of sNGAL levels in AP. Our study included 66 adult patients diagnosed AP and 30 healthy volunteers. The patients were admitted to the internal medicine clinic of our hospital between March and December 2016. We obtained an informed consent from every subject and the study was approved by the hospital's ethical committee. AP was diagnosed and classified according to the revised Atlanta classification. Patients who admitted to the emergency department of the hospital within the first 24 h by the onset of symptoms were included. Patients who underwent to contrast enhanced imagining for any reason were excluded.

We used one of the earliest scoring systems, Ranson's criteria for classifying the severity of acute pancreatitis. Patients with non-biliary etiology were scored due to the Ranson's criteria and the patients with biliary etiology were scored the modified version of Ranson's criteria [6]. Mortality is predicted as 0 to 3% when the score was < 3, 11 to 15% when the score is ≥3, and 40% when the score is ≥6 [6]. The first group was regarded as mild pancreatitis ($n = 38$) had a Ranson's score up to 2, and the second group as severe pancreatitis had a Ranson's score of ≥3 ($n = 28$).

Blood samples for the laboratory testing were obtained by the

admission and by the 48th hour from the onset of the symptoms. The samples for testing sNGAL level were stored at −80 °C. The sNGAL concentrations were measured using the Lipocalin-2/NGAL ELISA kit (Aviscera Bioscience, USA) and the Synergy/HTX and BioTek 405/LS devices.

Definitive statistics for categorical variabilities were number and percentage, for numeric variabilities were mean, standard deviation, minimum and maximum. Numeric variabilities were performed with Student t-Test if two independent group were compared and had a normal distribution, One Way ANOVA test if more than two groups were compared, and Mann Whitney U test and Kruskal Wallis Test if normal distribution was not fulfilled. The subgroup analyses were performed with Mann Whitney U test in nonparametric tests and were interpreted with Bonferroni correction. Paired t-Test were performed when dependent groups were compared and the difference of the numerical variabilities had the normal distribution; Wilcoxson test were the test of choices wen dependent groups did not fulfill the normal distribution. Since the numeric variabilities did not fulfill the parametric test requirements, Spearman Correlation Analysis was applied. The determinant factors for numeric variabilities were evaluated with Linear Regression Analysis and the determinant factors in categorical variabilities were evaluated with Logistic Regression Analysis. The statistical alfa significance level was accepted as $p < 0{,}05$.

As evaluating the results there was not statistical difference in gender, age and body mass index (BMI) between the groups. The patients admitted to our hospital's emergency department $13{,}9 \pm 6{,}2$ h after the onset of the symptoms. The etiology was found to be biliary in 53%, idiopathic in 20%, hypertriglyceridemia in 9%, alcohol-related in 3%, post-ERCP in 1,5%, drug-related in 1,5% and mass related in 1,5% of the patients. Mean sNGAL level in admission was significantly higher in all patients in comparison to the control group. There were significantly differences in BMI, WBC, CRP, and sNGAL level in admission. Age and BMI were higher in patients with SAP ($p = 0{,}006$, $p = 0{,}01$ respectively). The average CRP value in SAP patient group was significantly higher than the MAP patient group ($p = 0{,}009$). sNGAL level in patients with MAP were higher than patients with SAP on the 48 h after the onset of the symptoms and serum NGAL levels did not discriminate the cases of SAP from MAP (table).

The Ranson's score at 48 h had a positive correlation with Ranson's score on admission, age and BMI ($p = 0{,}001$, and $p = 0{,}015$).

In our study, two patients were admitted to the intensive care unit (ICU), and one of them died. Multi organ dysfunction was diagnosed in two patients. Three patients had pseudocyst (one of them with pancreatic necrosis) as a local complication.

Acute pancreatitis can be diagnosed by typical abdominal pain and a raise in serum lipase or amylase level within three fold upper of the normal limit. No imaging is required to diagnose the patients when these two findings exist. It was important not to use contrast enhanced imagining within admission of the patients since such agents may cause

acute kidney injury and raise sNGAL level.

sNGAL level has been studied as an early diagnostic marker recently after Moniaux et al. had suggested sNGAL levels were significantly higher in patients with AP [4]. Our study confirms this finding as mean sNGAL levels were significantly higher in patients with AP in comparison to healthy individuals.

The first human study within the literature was performed by Chakraborty et al. on 102 individuals. Chakraborty et al. found a significantly higher value of sNGAL levels in patients with SAP, after 48 h of the onset of symptoms, in comparison to patient with MAP. The sensitivity and specificity of sNGAL was both reported 100% within the 48 h [5].

Lipinski et al. conducted a study in 104 patients with AP. They obtained urine samples in admission and 24 h of collection (urine first day). Urinay neutrophil associated gelatinase lipocalin (uNGAL) was significantly higher in patients with SAP, than in cases with mild-severe AP and MAP both in admission and the first day. The sensitivity and specificity were 81% and 71% in admission and 87% and 85% in the first day, respectively. Lipinski et al. suggested uNGAL as a possible predictive marker during the early course of the disease [7].

Sporek et al. studying 65 patients with AP reported the sensitivity and specificity of sNGAL as %90 and %72 respectively on day 2 in a similar study model. uNGAL is proposed as a useful prognostic marker within the 24 h after the onset of the disease by Sporek et al. as well [8,9].

It is not clear in the studies of Chakraborty, Lipinski and or Sporek if contrast-enhanced CT scan has been used in diagnosing AP.

The sNGAL level in patients with local complications, multi organ failure had higher sNGAL levels in our study. An additional statistical analyses was applied to compare the seven patients with severe outcomes with the rest of 58 patients, and sNGAL level still did not reach a statistical significance neither on admission nor on the 48th hour, but CRP did in the 48th hour. Levels of CRP above 150 mg/L at 48 h after the onset of acute pancreatitis is associated with severe acute pancreatitis (sensitivity %80, specificity %76) [10].

Being older, having a BMI ≥ 30, persisting organ failure (over 48 h), acute kidney disease in the onset of the disease has been associated with higher mortality rates [11]. We support these findings.

Our study had some limitations. It was performed in a single center. We had few number of patients, especially patients with severe complications. This may have restricted us to evaluate the diagnostic value of sNGAL in a clinical based approach for SAP. We found CRP levels in the 48th hour useful as managing the patients. Larger and standardized studies are needed to evaluate sNGAL levels as an early prognostic marker to determine the severity of AP.

Declaration of Competing Interest

As the authors of text we declare that there is no conflict of interests.

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