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Case Report

Prognostic Ability of Hematological Parameters and Inflammation Based Scores in Acute Pancreatitis

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1. Abstract

1.1. Aims and Background: Appropriate triage is essential in the management of Acute Pancreatitis (AP). Even if AP initially stratified as mild or moderate, it may rapidly progress to severe form and even death may occur. Therefore, to find reliable prognostic and predictive markers in order to customize treatment strategies is really essential. Nutrition-based and/or inflammation-based prognostic indicators such as modified Glasgow Prognostic Score (mGPS), Prognostic Nutritional Index (PNI), C-reactive protein to albumin ratio (CRP/Alb), Neutrophil to lymphocyte ratio (NLR) and Platelet To Lymphocyte Ratio (PLR) have emerged as prognostic factors in some cancers and inflammatory conditions. We evaluated the prognostic ability of inflammation based scores in patients with acute pancreatitis.

1.2. Methods: We retrospectively reviewed the medical records of 299 cases with acute pancreatitis. AP severity assessment was based on Atlanta 2012 classification. To evaluate the inflammation based prognostic scores, laboratory parameters performed at hospital *admission* and *after 48 hours of admission were used.*

1.3. Results: A total of 299 patients with acute pancreatitis were reviewed. Mean age of the patients was 55years, the most common etiology was gallstones (58%). 241 of the patients were classified as mild, 58 of them were classified as severe pancreatitis. There were no significant relationships between mGPS at admission (mGPS 0) and etiology, severity, ICU requirement, surgery requirement, local or systemic complications and mortality. Score of "2" according to the mGPS at 48 hours after admission (mGPS 48) were significantly related with severity (p<0,001, %43.2-%74.5), need for antibiotics (p<0,001, CI: %38.5-%69.3), requirement of ICU (p=0,005, %46.9-%81), systemic complications (p<0,001, %38.7-%73.8) and mortality (p=0,364, %48.3-%100). It was found that PNI 0, PNI 48, NLR 0, NLR 48, PLR 0, PLR 48 and CRP/albumin 48 (but not CRP/albumin 0) were significantly correlated with severity, need for antibiotics and presence of systemic complications (p<0.001,p<0,05 and p <0,05). NLR 48, PLR 48 and CRP/albumin 48 were significantly related with surgery requirement and presence of local complications (p<0,05).

1.4. Conclusions: Nutritional and Hematological scores may be helpful but inflammation based prognostic scores other than mGPS 48 are not reliable at admission for predicting the severity of acute pancreatitis. Combination of other inflammation and nutrition based prognostic scores and mGPS may represent more accurate prognosis of AP.

2. Keywords: Acute pancreatitis; Inflammation based score; Prognosis

3. Introduction

Acute pancreatitis is an inflammatory condition of the pancreas. Local complications of acute pancreatitis include acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis. Systemic complication in AP is defined as an exacerbation of the chronic disease, development of organ failure due to the cytokine cascade was classified

under systemic complications but it became a separate entity in revised 2012

3.1. Atlanta Classification

The overall mortality in acute pancreatitis is approximately 5 percent. However, mortality rates show difference between mild and severe pancreatitis. While mortality rate in acute mild interstitial pancreatitis is estimated to be 3 percent, it reaches to 17 percent in patients with necrotizing pancreatitis [1].

Acute pancreatitis is a heterogeneous disease which can be classified as mild, moderate or severe based on 2012 revised Atlanta classification [2]. Predicting the severity of disease is really an important issue since it allows to stratify the disease severity and to develop management strategies [3]. Several prognostic scoring systems based on clinical, laboratorial and radiological evaluations have been proposed to predict outcome so far. Early and accurate prediction of prognosis enables patients with or at risk of developing severe AP to be identified and closely supported with intensive monitoring [4]. Ranson criteria, the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Modified Glasgow Prognostic score, the bedside index of severity in acute pancreatitis (BISAP) score and the Balthazar index have been used widely and taken their places in various guidelines [5-7]. Various isolated biochemical values such as C-reactive protein, leukocyte count, procalcitonin, CRP/alb ratio, NLR and PLR have been identified as potential markers of the severity of an episode of pancreatitis and some of them are included in a range of scoring systems [5,8-10].

Score based on Ranson criteria, which consist of 11 parameters, was the earliest scoring system for AP severity. Mortality was calculated around 40 percent when the score was ≥3. This scoring system has been used widely for many years. However, a meta-analysis including 110 studies revealed that it is a poor predictor of severity [11].

The Acute Physiology and Chronic Health Examination (APACHE II) score is a widely used score for AP severity which was originally developed for patients in ICU. It is performed every single day and increasing values suggest a severe pancreatitis attack. Mortality is 11 to 18 percent when APACHE II score >8. However, it is a complex and time consuming score and it has a poor predictive value at 24 hours [1].

BISAP score is a simple and well validated score for predicting mortality. It is commonly used nowadays. Though, it has not been validated in terms of length of hospitalization and ICU requirement [12].

CT severity index (Balthazar score) is basically based on necrosis, fluid collections and inflammation. It is obvious that pancreatic necrosis predicts a severe attack. Nevertheless, there are no proven correlation between extent of necrosis and mortality [13].

In brief, every scoring system for prediction of AP severity has a handicap and none has proven to be perfect so far. In this study, we evaluated the efficacy of nutritional, hematological and inflammation based scores in determining the outcome of acute pancreatitis compared to other classical prognostic scores.

4. Methods

A total of 299 patients who were admitted to our hospital between 2010 and 2015 were evaluated retrospectively from medical records. Diagnostic criteria for acute pancreatitis were a serum amylase level higher than three times the upper limit of normal in patients with upper abdominal pain or radiological evidence of acute pancreatic inflammation. Patients not meeting these criteria were excluded from the study. Patients age, sex, number of AP attacks, etiology of pancreatitis, Ranson score at admission and 48th hour after admission, APACHE II score, severity according to 2012 revised Atlanta classification, need for antibiotics, intensive care unit requirement, need for surgery, local complications, systemic complications, length of hospitalization and mortality were recorded. Organ failure was evaluated as systemic complication in this study. All patients with CRP level more than 150 mg/L after 48 hours of admission started on broad spectrum antibiotics. All of the patients who needed antibiotics were started on imipenem/cilastatin. Standard imipenem/cilastatin dosage was 2gr/day. Dose adjustments due to the renal or hepatic impairment were done accordingly. Only pseudocyst and necrosis were evaluated as local complication in this study. Organ failure and exacerbation of underlying chronic illnesses were evaluated as systemic complication. Additionally, neutrophil counts, lymphocyte counts and platelet counts, serum albumin and C-reactive protein levels at admission and 48th hour after admission were recorded and used for calculation of scores. mGPS, PNI, NLR, PLR and CRP/Alb ratio at admission and 48th hour of hospitalization were calculated using these data. The definition of the scoring systems was summarized in (Table 1). Statistical correlation between these scoring systems and disease severity was carried out with confidence interval of 95%.

Table 1: Definitions of prognostic scores

Scoring systems	Score
GPS	
CRP (≤ 10 mg/L) and albumin (≥ 35 g/L)	0
CRP (≤ 10 mg/L) and albumin (< 35 g/L)	1
CRP (> 10 mg/L) and albumin (≥ 35 g/L)	1
CRP (> 10 mg/L) and albumin (< 35 g/L)	2
Modified GPS	
CRP (≤ 10 mg/L) and albumin (≥ 35 g/L)	0
CRP (≤ 10 mg/L) and albumin (< 35 g/L)	0
CRP (> 10 mg/L) and albumin (≥ 35 g/L)	1
CRP (> 10 mg/L) and albumin (< 35 g/L)	2
PLR	
Platelet count: lymphocyte count < 150	Low
Platelet count: lymphocyte count ≥ 150	High
NLR	
Neutrophil count: lymphocyte count < 3	Low
Neutrophil count: lymphocyte count ≥ 3	High
PNI	
Albumin (g/L) + 5 × total lymphocyte count ≥ 45	0
Albumin (g/L) + 5 × total lymphocyte count < 45	1

Statistical analyses were performed using Statistica version 13.3. Shapiro–Wilk test was used to test the normal distribution of continuous variables. The continuous data were presented as mean ± standard deviation (mean ± SD) and the categorical variables were expressed as number (n) and percentage (%).The numerical data were compared across the independent groups using Student's t test, with comparisons of more than 2 independent groups being performed with the ANOVA test. Bonferroni post-hoc statistic was used to determine the differential group/groups. Paired sample *t*-test was used for 2 dependent groups' comparisons. Ordinal categorical variables were assessed by marginal homogeneity test. The relationship between categorical variables was evaluated by Chi square and Fisher's exact test. Tests were interpreted at a significance level alpha = 0.05.

5. Results

Mean age of the patients were 55(±17) years. Male and female gender distribution was similar. Most common etiology was biliary causes (59%). 243 (81%) of the patients were classified as mild acute pancreatitis, 56 (%19) of them were classified as severe acute pancreatitis (Table 2). 51 (17%) of the patients had a history of previous pancreatitis. Median hospitalization time of the patients was 4 (±3.5) days.

Table 2: Baseline patient characteristics

Age, y	
Median (SD)	55±17
Sex, n (%)	
Male	153 (51%)
Female	146 (49%)
Etiology, n(%)	
Biliary	175 (59%)
Alcoholism	32 (11%)
Hypertriglyceridemia	19 (6%)
Other	73 (24%)
Disease severity	
Mild acute pancreatitis	243 (81%)
Severe acute pancreatitis	56 (19%)

The mGPS at 48th hour after admission was0 (15.3%) in 42 patients, 1 (35.3%) in 97 patients and 2 (48.5%) in 131 patients. A total of 88 patients (32.5%) needed for antibiotics during their follow-up due to local or systemic complications and rapid CRP level progression at first 48 hours of hospitalization. The mGPS48 score was 2 in 61 (69.3%) of the patients who needed for antibiotics. 21 (7.7%) of the total patients needed for ICU during their follow up. The mGPS 48 score was 2 in 17 of these 21 patients who had ICU requirement. 9 (3.3%) of the patients had surgery because of local complications and mGPS 48 score was 2 in 7 of them. While 22 of the patients had local complications, 84 of the patients had systemic complications. The mGPS 48 score was 2 in 16 and 62 of these patients, respectively. A total of 6 deaths occurred and mGPS 48 score was 2 in all of them. In the patients whose mGPS 48 score was 2, antibiotic requirement (p<0.001), ICU requirement (p=0.008), indication for surgery (p=0.039), local complications (p=0.035), systemic complications (p<0.001) and mortality (p=0.044) were significantly higher when compared with mGPS 48 score 0 and mGPS 48 score 1 groups (Table 3).

Table 3: mGPS at 48th hour as a prognostic tool.

	Antibioticrequirement					
		no	yes	total	CI	p value
0	Number	37	5	42		p<0,001
	%	20.3	5.7	15.3		
1	Number	75	22	97		
	%	41.2	25	35.3		
2	Number	70	61	131		
	%	38.5	69.3	48.5		
	ICU requirement					
		no	yes	total	CI	p value
0	Number	42	0	42		p=0,008
	%	16.5	0	15.3		
1	Number	93	4	97		
	%	36.6	19	35.3		
2	Number	119	17	136		
	%	46.9	81	49.5		
	Indication for surgery					
		no	yes	total	CI	p value
0	Number	42	0	42		p=0,039
	%	15,8	0	15,3		
1	Number	95	2	97		
	%	35.7	22.2	35.3		
2	Number	129	7	136		
	%	48.5	77.8	49.5		
	Local complications*					
		no	yes	total	CI	p value
0	Number	42	0	42		p=0,035
	%	16.6.	0	15.3		
1	Number	91	6	97		
	%	36	27.3	35.3		
2	Number	120	16	136		
	%	47.4	72.7	49.5		
	Systemic complications**					
		no	yes	total	CI	p value
0	Number	38	4	42		p<0,001
	%	19,9	4,8	15.3		
1	Number	79	18	97		
	%	41.4	21.4	35.3		
2	Number	74	62	136		
	%	38.7	73.8	49.5		
	Mortality					
		no	yes	total	CI	p value
0	Number	42	0	42		P=0.044
	%	15.6	0	15.3		
1	Number	97	0	97		
	%	36.1	0	35.3		
2	Number	130	6	136		
	%	48.3	100	49.5		

*14 of the patients had necrosis, 4 had pseudocyst, 5 had both pseudocyst and necrosis.

**includes fever, circulatory failure, respiratory failure or renal failure

Lower levels of NLR were associated with more severe form of pancreatitis. In addition; frequency of ICU requirement and indication for surgery, local and systemic complication probability and mortality were higher in lower NLR 0 levels. Increased NLR 48 levels were related with severity of disease and it was statistically significant (p=0.002). On the other hand, decreased NLR 48 levels were associated with ICU requirement, indication for surgery, local and

systemic complications and mortality. All of these differences between NLR 48 and these variables seemed to be statistically significant. As PLR 0 level increased; disease severity, ICU and surgery requirement, complications and mortality were increased also. However; only disease severity, ICU requirement and systemic complications were statistically significant. Higher PLR 48 levels were associated with severe AP, increased ICU requirement, more surgical procedures, increased local and systemic complications and mortality. All of the associations with these variables were statistically significant. There was no statistically significant relationship between CRP/ALB 0 and these variables. Higher CRP/ALB 48 levels were associated with severe disease, more surgery requirement and increased local and systemic complications. Although seemed to be statistically significant, ICU requirement and mortality were more common in patients with lower levels of CRP/ALB 48.Low PNI score were associated with increased antibiotics usage. While mean PNI score in patients who were started on antibiotics was 42.67 (±6.67), it was 45.83 (±7.25) in patients who were not started on antibiotics. This difference was statistically significant (p=0.001). Patients who needed ICU had lower levels of PNI score and this difference was statistically significant (mean 42.67±8.50 vs 44.93±7.09, p=0.005). Patients who had systemic complications had lower levels of PNI score and this difference was statistically significant also (mean 42.61±6.72 vs 45.58±7.24, p=0.001). In terms of need for surgery, local complications and mortality; there were no significant association according to PNI score (Table 4).

Table 4: Analysis of relationships of NLR, PLR and CRP/ALB ratio with some clinical conditions

	Atlanta classification				ICU requirement				İndication for surgery			
		n	mean±SD	p value		n	mean±SD	p value		n	mean±SD	p value
NLR 0	Mild	240	7,51±6,5	p<0.001	yes	21	1.76±1.67	p<0.001	Yes	9	1.51±1.76	p=0.312
	Severe	55	1,49±1,36		no	276	8.28±7.48		no	288	8.75±8.32	
NLR 48	Mild	235	5,28±9,01	p=0.002	yes	20	1.22±6.85	p=0.002	Yes	9	1.57±8.52	p=0.001
	Severe	55	9,58±9,25		no	271	5.64±9.18		no	282	5.79±9.05	
PLR 0	Mild	240	2,08±1,51	p<0.001	yes	21	4.08±2.87	p<0.001	Yes	9	4.37±4.01	p=0.154
	Severe	55	3,34±2,13		no	276	2.19±1.51		no	288	2.26±1.56	
PLR 48	Mild	235	1,48±8,89	p=0.001	yes	20	2.59±1.11	p<0.001	Yes	9	2.67±1.16	p<0.001
	Severe	55	1,96±1,06		no	271	1.50±8.84		no	282	1.54±9.14	
CRP/ALB 0	Mild	224	7,14±8,87	p=0.674	yes	19	2.73±3.24	p=0.847	Yes	10	3.02±2.98	p=0.524
	Severe	51	1,90±2,81		no	257	6.40±8.28		no	266	6.27±8.14	
CRP/ALB 48	Mild	225	3,21±3,82	p<0.001	yes	21	8.93±5.46	p<0.001	Yes	9	9.15±5.11	p<0.001
	Severe	52	5,96±4,43		no	258	3.40±3.86		no	270	3.64±4.11	
	Local complications				Systemic complications				Mortality			
		n	mean±SD	p value		n	mean±SD	p value		n	mean±SD	p value
NLR 0	yes	22	1.35±1.21	p=0.01	yes	89	1.20±1.14	p<0.001	yes	7	1.21±7.84	p=0.327
	no	275	8.57±9.35		no	208	7.60±6.92		no	290	8.86±8.78	
NLR 48	yes	21	1.35±7.29	p<0.001	yes	87	1.03±1.38	p<0.001	yes	6	1.61±1.05	p=0.006
	no	270	5.52±9.07		no	204	4.29±5.35		no	285	5.89±9.06	
PLR 0	yes	22	3.40±2.76	p=0.065	yes	89	2.83±2.03	p=0.001	yes	7	5.18±3.30	p=0.58
	no	275	2.24±1.57		no	208	2.11±1.50		no	290	2.26±1.60	
PLR 48	yes	21	2.83±1.33	p<0.001	yes	87	2.04±1.11	p<0.001	yes	6	2.66±1.20	p=0.004
	no	270	1.47±8.30		no	204	1.38±7.77		no	285	1.55±9.24	
CRP/ALB 0	yes	22	3.88±4.07	p=0.89	yes	81	2.14±2.89	p=0.593	yes	6	7.63±5.05	p=0.868
	no	254	6.35±8.33		no	195	7.81±9.51		no	270	6.27±8.08	
CRP/ALB 48	yes	22	9.72±5.51	p<0.001	yes	86	6.71±5.07	p<0.001	yes	6	1.44±5.89	p<0.001
	no	257	3.32±3.72		no	193	2.53±3.05		no	273	3.59±3.91	

6. Discussion

Pancreatitis is a heterogeneous disease which is difficult to predict the severe forms at admission. Prediction of the severity as early as possible is important for early intervention. One of the major challenges about pancreatitis is to develop new scoring systems to predict the outcome earlier. Some of the inflammation based scores has been utilized for this entity so far.

Modified Glasgow Prognostic Score (mGPS) is a score which includes CRP and albumin levels. Jones, Michael J et al [4]. revealed that both mGPS0 and mGPS 48 is a reliable marker for predicting the prognosis of AP. In our study, mGPS 0 was not associated with predicting the prognosis of AP. mGPS 48, conversely, was found to be the most reliable and consistent inflammation based score (Table 3).

Gauli Liu et al[14] evaluated some of the hematological parameters based scores and found that NLR 0 was associated with severity of the pancreatitis but NLR 48 was not evaluated in their study Kokulu et al [15] evaluated both NLR 0 and NLR 48 in acute pancreatitis. They revealed that both ratios in the severe AP group was found to be statistically higher than the mild AP group ($p<0.01$). Although NLR 0 values seemed statistically significant regarding severity according to Atlanta classification, ICU requirement, local and systemic complications; it is not relevant. Inflammation is expected to be correlated with higher NLR values. As it is shown in (Table 3), higher NLR 0 values were associated with less severity unlike expected. Therefore, NLR 0 is not a useful marker to predict the severity of acute pancreatitis according to our study. Unlike NLR 0 ratios, higher NLR 48 ratios were associated with more severe disease and mortality. However, association with other variables (ICU or surgery need, local/systemic complications) was irrelevant (similar to NLR 0). For this reason, both NLR 0 and NLR 48 are not reliable markers in predicting the severity or outcomes of patients with acute pancreatitis in our opinion.

Kaplan et al [16] evaluated PLR and NLR combination as a new marker to determine prognosis of acute pancreatitis. In their study, it was shown that both PLR 0 and NLR 0 ratios were associated with severity. We could not found a study which evaluated the PLR 48 in acute pancreatitis. This study showed that higher PLR 48 levels were significantly associated with worse prognosis for each variable as distinct from PLR 0.

In a recent metanalysis [17], it has been shown that CRP/Alb ratio was related with poor prognosis in human malignancies except colorectal cancer. As we know, albumin is a negative acute phase reactant in inflammatory processes. Therefore, inflammatory scores including albumin levels were expected to be more indicating in the following days of hospitalization. CRP/Alb 0 ratios were not associated with disease severity as we expected. Only in terms of mortality, there were higher CRP/Alb 0 ratios which was not statistically significant ($p=0.868$). Higher CRP/Alb 48 ratios seemed to indicate worse prognosis in terms of five variables other than mortality. As a result, CRP/Alb 0 was not a reliable marker. Although CRP/Alb 48 seemed to be a better marker, it was failed to predict the mortality.

One of the most significant limitations of our study is number of deaths. Even though most of the scores seem to be related with mortality, association of scores with mortality was unreliable due to the small number of deaths (%2 of total).

There are much more markers and scores other than these scores. Urinary trypsinogen-2 and trypsinogen activation peptide (TAP) concentration has been shown to be useful prognostic markers [18]. A model combining serum amylase level and body mass index has been developed and shown to be useful [19]. Interleukin-6 and macrophage migration inhibitory factor seem to be new promising parameters for use in clinical routine [20]. A recent study proposed that elevated plasma mitochondrial DNA content in may be used as a more accurate early predictor of pancreatic necrosis in contrast to traditional CRP [21]. Numerous new biomarkers have been studied also [22]. In addition, there are also various radiological scores in predicting severity and outcome [23]. However, none of these novel markers and scoring systems is not optimal and has not been included in clinical routine.

7. Conclusion

Scores at 48th hour seem to be more reliable than admission scores. PNI was the only useful score among admission time (0) scores. Among the 48th hour scores; NLR 48, PLR 48, CRP/ALB 48 and mGPS 48 were significantly related with surgery requirement and presence of local complications ($p<0.05$). mGPS 48 seemed to be the most reliable and useful score regarding antibiotic requirement, ICU requirement, indication for surgery, mortality, local and systemic complications. Predicting severity and outcome in AP as early as possible is one of the most important issues about AP at the present time. There are many clinical researches in progress worldwide.

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