ORIGINAL ARTICLE

Investigating the correlation between severe acute pancreatitis and pancreatic necrosis with some serum parameters

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ABSTRACT

BACKGROUND: Acute pancreatitis (AP) is a disease related to significant morbidity and even mortality. Various factors are involved in the etiology, especially gallstones and excessive alcohol consumption. Although, the course of the disease in most of the cases is generally mild, in some cases, the disease can be severe and lead to pancreatic or peripancreatic necrosis. Radiologically, "Balthazar computed tomography severity index" (CTSI) is used to assess the severity and presence of necrosis in pancreatitis. In this study, we classified the severity of AP in patients with Balthazar CTSI and investigated whether there is a correlation between some serum parameters and AP severity and which serum parameters can be used as a safe marker to predict the AP severity and the development of pancreatic necrosis (PN).

METHODS: A total of 341 patients diagnosed with AP and hospitalized in our general surgery clinic between the years 2012 and 2018 were included in this study. Hematological and biochemical parameters of the patients were recorded. Abdominal CT's of the patients were evaluated according to the Balthazar CTSI. The correlation between these parameters and AP severity evaluated by Balthazar CTSI was investigated.

RESULTS: PN was detected in 19.4% of 341 patients who participated in the study. Patients whose PN detected in their abdominal CT's by Balthazar CTSI; neutrophil counts, neutrophil/lymphocyte ratio (NLR), thrombocyte/lymphocyte ratio, platelet-lymphocyte ratio, and neutrophil/monocyte ratio (NMR) were significantly higher and the serum albumin was significantly lower than patients with PN.

CONCLUSION: Neutrophil count, serum albumin levels, NLR, LR, and NMR can be used as predictive markers to determine AP severity.

Keywords: Acute pancreatitis; Balthazar score; pancreatic necrosis; serum parameters.

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disorder of the pancreas and one of the leading causes of gastrointestinal disorders requiring hospitalization worldwide. Its incidence is gradually increasing.[1–3] Severe AP is a subform of AP with systemic inflammatory response syndrome and organ failure. Pancreatic necrosis (PN) develops in about 20% of the patients with AP and this situation requires more advanced medical or invasive intervention.[4,5]

To evaluate AP severity, many different methods developed such as Ranson criteria, Acute Physiology and Chronic Health Evaluation 2 (APACHE 2) classification system, and various scoring systems such as the Balthazar score system were developed. At the time of patient admission, the effects of many

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different factors on the prognosis of AP such as advanced age, obesity, hemoconcentration, C-reactive protein (CRP), and procalcitonin levels have been studied separately. Among these, Balthazar computed tomography severity index (CTSI) is a scoring system that is widely used in AP and based on CT findings.[6,7]

In this study, we identified cases with severe pancreatitis/PN according to Balthazar CTSI, and in these severe cases, we investigated the correlation between some hematological and biochemical markers in the serum with the severity of the disease.

MATERIALS AND METHODS

Study Design

The study includes 341 patients who were admitted to Istanbul University-Cerrahpasa, School of Medicine Department of General Surgery between the years 2012 and 2018. About 43.4% (n=148) of them were women and 56.6% (n=193) of them were men. Hematological and biochemical parameters of the patients were measured. Contrast-enhanced abdominal CT was performed. All CT imaging of the patients were evaluated by 5 years of abdominal radiology experienced radiologist (S.Ş.).

The radiologist evaluated CT images using the PACS (ExtremePACS, Ankara, Turkey) program and laboratory findings of the patients in a blinded fashion and classified the findings according to the Balthazar CTSI (Fig. 1a-f) (Table 1).[8] According to this classification, the hematological and biochemical parameters of the severe AP patients with PN are compared with mild AP patients to see if there was a statistically significant difference.

Statistical Analysis

Number Cruncher Statistical System (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used while evaluating the study data. The suitability of the quantitative data to normal distribution was tested by Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical evaluations. Student's t-test was used for two-group comparisons of quantitative data with normal distribution, and the Mann-Whitney U-test was used for two-group comparisons of data not showing normal distribution. Pearson's Chi-squared test was used to compare qualitative data. Diagnostic screening tests (sensitivity, specificity, PKD, and NKD) and ROC curve analysis were used to determine cutoffs for parameters. The significance level was assessed at least $p<0.05$.

RESULTS

The ages of 341 cases included in the study ranged from 18 to 94 years, with an average of 58.29±18.54 years. The distribution of demographic characteristics of the patients, Balthazar

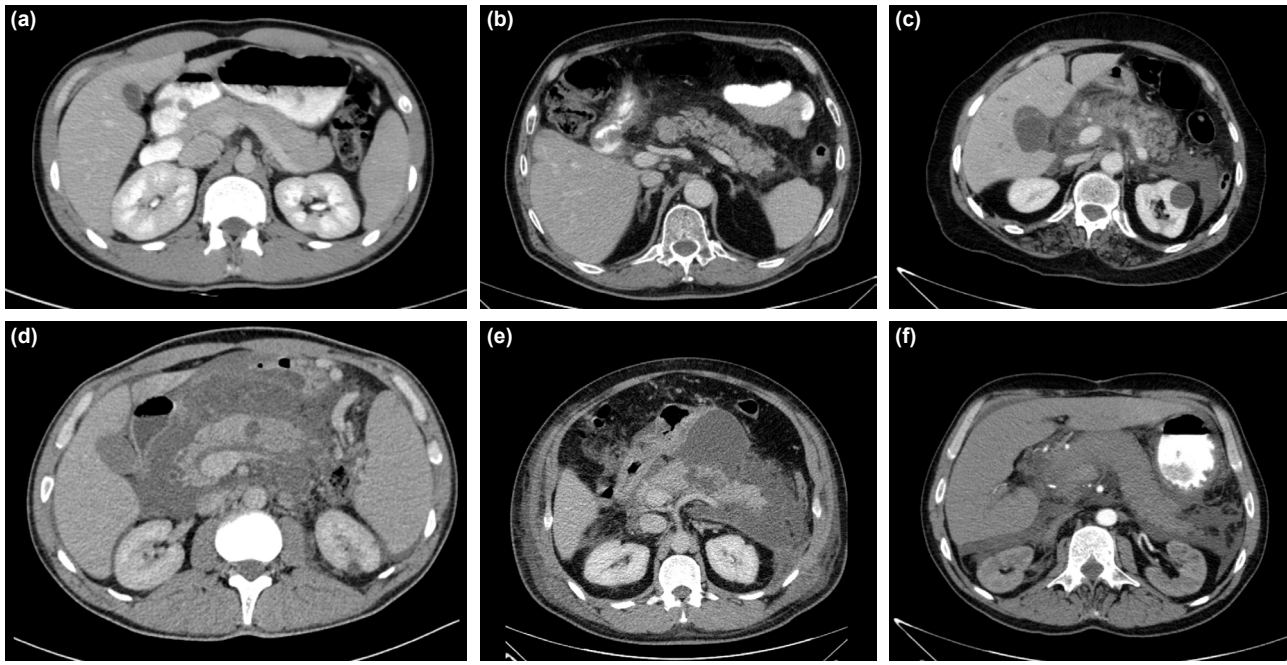

Figure 1. (a) A coronal section of the abdominal CT scan shows normal pancreatic parenchyma with homogeneous contrast enhancement. **(b)** Inflammation of the peripancreatic fatty tissue, parenchymal contrast enhancement still homogeneous. **(c)** Edematous and homogeneously enhanced effusions around the pancreatic parenchyma extending to the right and left pararenal areas. Effusion is chosen in the pericholecystic area. There is an incidental cyst in the left kidney. **(d)** The non-enhancing necrosis area is selected in the middle of the pancreatic body with significant retroperitoneal and intraperitoneal (perihepatic and perisplenic) effusions. **(e)** Areas of non-enhancing necrosis on the pancreatic body and tail (not shown) are noted. There are fluid collections in the bilateral pararenal area and the lesser sac. **(f)** Edematous and non-enhancing pancreatic parenchyma with bilateral pararenal effusions.

Table 1. Balthazar Score (CT Severity Index [CTSI])

Grade	Findings of the abdominal CT *(without contrast enhancement)*	Score
A	Normal pancreas – flat regular shape with sharp margins, homogenous contrast enhancement, with no peripancreatic or retroperitoneal contrast enhancement.	0
B	Diffuse or focal pancreatic enlargement may have an irregular shape, also may have heterogeneity in contrast enhancement but there is no contrast enhancement in the inflamed peripancreatic area.	1
C	Abnormal pancreatic parenchymal findings with peripancreatic inflammation.	2
D	Single located, intrapancreatic, or extrapancreatic fluid accumulation.	3
E	Two or more located intrapancreatic or extrapancreatic fluid accumulation w orw/o pancreatic/peripancreatic gas images.	4
	Necrosis ratio (%) in the abdominal CT *(with contrast enhancement)*	
0		0
<30		2
30–50		4
≥50		6

CTSI = CT without contrast score + CT with contrast enhancement: maximum = 10, ≥6 = severe pancreatitis, Balthazar, EJ, Robinson, DL, Megibow, AJ, Ranson, JH, Radiology 1990; 174:331.

Table 2. The distribution of demographic characteristics

		n	%
Age (year)	Min-Max (median)	18–94 (60)	
	Mean±SD	58.29±18.54	
Gender	Female	148	43.4
	Male	193	56.6
Balthazar Score	Min-Max (median)	0–10 (2)	
	Mean±SD	2.03±1.72	
Pancreatitis severity	Mild (0–3)	275	80.6
	Moderate (4–6)	63	18.5
	Severe (7–10)	3	0.9
Pancreatic necrosis	Absent (<4)	275	80.6
	Present (≥4)	66	19.4

SD: Standard deviation.

Table 3. Comparison of pancreatic necrosis by age and gender

	Pancreatic necrosis (-) (n=275)	Pancreatic necrosis (+) (n=66)	p
Age (year)			
Min-Max (median)	18–94 (62)	19–86 (52)	[a]0.001**
Mean±SD	59.92±18.64	51.48±16.60	
Gender, n (%)			
Female	122 (44.4)	26 (39.4)	[b]0.464
Male	153 (55.6)	40 (60.6)	

[a]Student t Test; [b]Pearson Chi-squared Test; **p<0.01. SD: Standard deviation.

score, pancreatitis levels, and the presence of PN are shown in Table 2.

A statistically significant difference was found between the ages of the cases according to the presence of PN (p=0.001 and p<0.01); the ages of patients with PN tend to be younger. No statistically significant difference was found between the gender distributions of the cases according to the presence of PN (p>0.05) (Table 3).

Laboratory parameters of the cases were compared statistically according to the presence of PN. No statistically significant difference was found in the ratios of amylase, lymphocyte, monocyte, platelet, CRP, aspartate aminotransferase (AST), LDH measurements and lymphocyte/monocyte, CRP/albumin, AST/platelet, and neutrophil/albumin between patients with and without PN.

A statistically significant difference was found between neutrophil measurements (p=0.010 and p<0.05) and albumin measurements (p=0.042 and p<0.05) according to the presence of PN. Neutrophil measurements are higher and albumin measurements are lower in patients with PN. Depending on the presence of PN, a statistically significant difference was found between; neutrophil/lymphocyte measurements (p=0.007 and p<0.01), platelet/lymphocyte measurements (p=0.045 and p<0.05), and neutrophil/monocyte measurements (P=0.014 and p<0.5). Neutrophil/lymphocyte (NLR), platelet-lymphocyte ratio (PLR), and neutrophil/monocyte (NMR) measurements are higher in patients with PN. Findings are compiled in Table 4.

Cutoff points were determined for NLR, PLR, and NMR ratios in cases with PN. Statistical significance was found between the presence of PN and the cutoff value of 7.6 for NLR measurement (p=0.027 and p<0.05). The risk of developing PN is 1.838 times higher in patients with NLR measurement of 7.6 and above. The ODDS ratio for NLR measurement is 1,838 (95% confidence interval [CI]: 1.066–3.172). A statistically significant correlation exists between the presence of PN and the 276.1 cutoff value of PLR measurement

Table 4. Evaluation of laboratory findings according to the presence of pancreatic necrosis

		Pancreatic necrosis (-) (n=275)	Pancreatic necrosis (+) (n=66)	ᶜp
Amylase	Min-Max (median)	502–2364 (1005)	509–2039 (1083.5)	0.437
	Mean±SD	1074.13±423.29	1120.09±438.26	
Neutrophil	Min-Max (median)	0.3–59.3 (8)	0.6–28.7 (10.2)	0.010*
	Mean±SD	9.20±5.72	11.01±6.05	
Lymphocyte	Min-Max (median)	0.1–9.1 (1.2)	0–7.3 (1.1)	0.284
	Mean±SD	1.37±0.90	1.37±1.16	
Monocyte	Min-Max (median)	0–3.6 (0.6)	0.1–1.8 (0.6)	0.998
	Mean±SD	0.65±0.42	0.65±0.38	
Platelet	Min-Max (median)	24.4–756 (232)	31.7–906.4 (239)	0.252
	Mean±SD	245.01±104.42	270.18±135.97	
CRP	Min-Max (median)	0–397 (20.2)	0–480 (27.3)	0.455
	Mean±SD	62.04±82.18	78.31±112.13	
AST	Min-Max (median)	3–9620 (55)	3–1318 (52)	0.417
	Mean±SD	198.75±746.55	122.76±199.32	
LDH	Min-Max (median)	109–11200 (268)	124–1374 (293)	0.259
	Mean±SD	436.00±845.73	382.35±262.41	
Albumin	Min-Max (median)	1.7–5.3 (4)	2.8–5.7 (4.2)	0.042*
	Mean±SD	3.98±0.60	4.16±0.59	
Neutrophil/Lymphocyte	Min-Max (median)	0.6–138.5 (6.6)	0.6–60 (9.5)	0.007**
	Mean±SD	10.15±12.35	14.03±13.04	
Lymphocyte/Monocyte	Min-Max (median)	0.1–35 (2.2)	0.1–8.1 (2.2)	0.462
	Mean±SD	2.77±2.93	2.47±1.83	
Platelet/Lymphocyte	Min-Max (median)	7.4–2429 (193.6)	38.5–3170 (226.9)	0.045*
	Mean±SD	242.51±203.10	345.93±440.15	
CRP/Albumin	Min-Max (median)	0–2488 (21)	0–26921 (28.9)	0.334
	Mean±SD	84.72±203.55	490.52±3306.27	
Neutrophil/Monocyte	Min-Max (median)	2.8–194 (13.1)	2.4–90 (18.1)	0.014*
	Mean±SD	19.43±23.28	21.16±16.66	
AST/Platelet	Min-Max (median)	0–123.3 (0.2)	0–4.6 (0.2)	0.336
	Mean±SD	1.52±8.62	0.55±0.82	
Neutrophil/Albumin	Min-Max (median)	0.1–19 (2)	0.2–8.4 (2.4)	0.053
	Mean±SD	2.42±1.83	2.75±1.69	

ᶜMann-Whitney U Test; *p<0.05; **p<0.01. SD: Standard deviation; CRP: C-reactive protein; AST: Aminotransferase; LDH: Lactate dehydrogenase.

(p=0.019 and p<0.05). The risk of developing PN is 1.929 times higher in patients with a PLR measurement of 276.1 and above. The ODDS ratio for PLR measurement is 1.929 (95% CI: 1.107–3.361). A statistically significant correlation was found between the presence of PN and the cutoff value of 15.3 NMR (p=0.013 and p<0.05). The risk of developing PN risk is 1,980 times higher in cases with NMR of 15.3 and above. ODDS ratio for NMR measurement is 1,980 (95% CI: 1.147–3.418) (Table 5). The ROC curve for neutrophil/lymphocyte, platelet/lymphocyte, and neutrophil/monocyte measurements according to PN presence is also shown in Figure 2.

DISCUSSION

According to the Atlanta classification presented in 1992 and revised in 2012, AP divided into three groups: Mild AP (without organ failure or complications such as necrosis, pseudocyst), moderate AP (organ failure subsides within 48 h with local complications), and severe AP (with organ failure lasting more than 48 h).[9,10] Although AP is mostly mild as shown in our study, it can be fatal in 1–2% of cases. This rate increases to 10% if the patient has temporary organ failure, to 20–30% if there is a persistent single organ failure, to 30% if there is infected necrosis, and to 40–60% if there

Table 5. Diagnostic Screening Tests and ROC curve results for neutrophil/lymphocyte, platelet/lymphocyte and neutrophil/monocyte measurements by presence of pancreatic necrosis

	Diagnostic Scan					ROC Curve		p
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% Confidence interval	
NLR	≥7.6	59.09	56.00	24.38	85.08	0.607	0.528–0.687	0.007**
PLR	≥276.1	42.42	72.36	26.92	83.97	0.579	0.44–0.659	0.045*
NMR	≥15.3	59.09	57.82	25.16	85.48	0.597	0.523–0.672	0.014*

**p<0.01; *p<0.05. NLR: Neutrophil/lymphocyte ratio; PLR: Thrombocyte/lymphocyte ratio; NMR: Neutrophil/monocyte ratio; ROC: Receiver operating characteristic

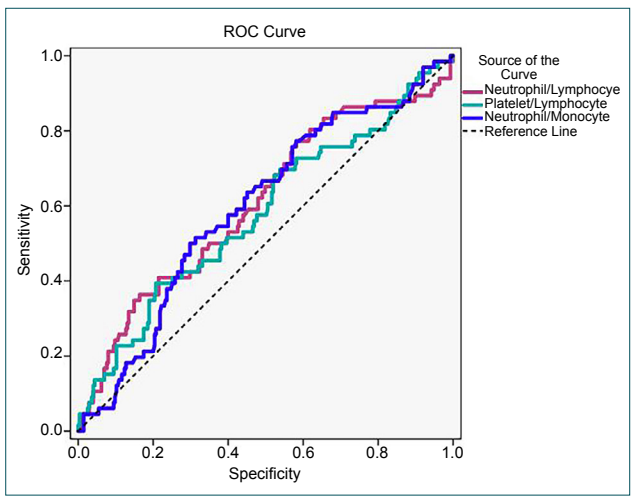

Figure 2. ROC curve of neutrophil/lymphocyte, platelet/lymphocyte, and neutrophil/monocyte measurements by the presence of pancreatic necrosis.

is persistent multiorgan failure.[9,10]

For the clinical course of the disease and especially the severe AP course, various scoring systems such as Ranson criteria, Glasgow criteria, APACHE 2, CT imaging scoring systems, Bedside Index of Severity in AP (BISAP) score, PANC 3, Harmless AP Score, and Japanese Severity Score have been developed.[6,7,11,12] Yet according to various studies, Balthazar CTSI,[8] which is a CT-based scoring system, has proven its effectiveness.[13,14] In a retrospective study, it was shown that those with a CT index >5 had an 8 times higher risk of death, a 17 times hospital stay, and a 10 times higher risk of undergoing necrosectomy than those with a CT index of <5.[15] Especially APACHE 2 score stands out among clinical scoring systems in studies; BISAP has also been found to be highly effective.[16,17]

Studies on the predictive value of biochemical markers in AP as in our study are still ongoing. Bezmarević et al.[17] found the predictive value of procalcitonin higher than CRP. In our study, CRP was found insufficient in predicting the presence of severe AP. The result of our series is consistent with the study of Hong et al.,[18] showing that low albumin level is also an indicator of severe AP and mortality. Neutrophil/lymphocyte ratio (NLR) has been suggested as an effective marker in predicting severe AP and organ failure due to AP in recent years. Similarly, in our study, we found that both neutrophil count and NLR were effective in predicting severe AP.[19–21] Suppiah et al.,[20] among their studies to determine optimal cutoff values for NLR, found that day 0: 10.6, day 1: 8.1, and day 2: 4.8, these results were found consistent with our 7.6 value. Platelet/lymphocyte ratio (PLR) has also recently been presented as a good prognostic factor that can be combined with NLR.[22,23]

The inflammatory process in AP begins with the migration of circulating monocytes and neutrophils to the pancreatic interstitial area. These infiltrating neutrophils and monocytes lead to the production of various cytokines and other inflammatory mediators. Macrophage activation may thus be an important factor determining AP severity.[24] For this reason, recent studies have focused on the lymphocyte/monocyte ratio (LMR). Low LMR is considered to be an important prognostic factor.[25] In our study, we evaluated the neutrophil/monocyte ratio (NMR) for severe AP and concluded that it can be used as a predictive factor.

Our study has some limitations. First, due to the retrospective nature of our study, CT scan and laboratory measurements were not made in a standard timeline after admission. CT scan and laboratory measurements are usually performed recently after admission but standard timeline or simultaneity is not considered. Second, CT scans performed on patients with pancreatitis during the admission, could not be considered enough time for PN development, for this reason, some of these cases may be underestimated. As it is known, PN develops at an early stage within 72 h, for this reason, the CT scan is usually recommended after 72 h to determine the exact extension of PN.[26] Our third limitation is the evaluation of CT images by a single expert. Although the Balthazar CTSI scoring is a high interobserver scoring system,[26] the evaluation by two or more radiology experts could increase the diagnostic value.

Conclusion

Severe AP is a serious disease that can result in mortality. Therefore, it is important to predict the clinical course of the disease at admission and to determine the strategy of

the treatment. In our study, neutrophil count, albumin levels, NLR, LMR, and MNR were noted as biochemical parameters that can be used predictively. This situation is compatible with other similar studies in the existing literature.

Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 06.10.2020, Decision No: 83045809-604.01.02).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Bazı serum parametreleri ile şiddetli akut pankreatit ve pankreas nekrozu arasındaki ilişkinin araştırılması

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AMAÇ: Akut pankreatit (AP), önemli morbidite ve hatta mortalite ile ilişkili bir hastalıktır. Etiyolojide özellikle safra taşları ve aşırı alkol tüketimi olmak üzere çeşitli faktörler rol oynamaktadır. Çoğu olguda hastalığın seyri genellikle hafif olmakla birlikte, bazı durumlarda hastalık şiddetli olabilir ve pankreas veya peripankreatik nekroza yol açabilir. Radyolojik olarak "Balthazar CT şiddet indeksi" (CTSI), pankreatitte nekrozun şiddetini ve varlığını değerlendirmek için kullanılır. Bu çalışmada, Balthazar CTSI ile AP'nin şiddetini sınıflandırarak bazı serum parametreleri ile AP şiddeti arasında korelasyon olup olmadığını, hangi serum parametrelerinin AP şiddetini ve pankreas nekrozunun (PN) gelişimini tahmin etmek için güvenli bir belirteç olarak kullanılabileceği araştırdık.

GEREÇ VE YÖNTEM: 2012–2018 yılları arasında genel cerrahi kliniğimizde yatan ve AP tanısı alan 341 hasta çalışmaya dahil edildi. Hastaların hematolojik ve biyokimyasal parametreleri kaydedildi. Hastaların abdominal BT'leri Balthazar CTSI'ye göre değerlendirildi. Bu parametreler ile Balthazar CTSI tarafından değerlendirilen AP şiddeti arasındaki ilişki araştırıldı.

BULGULAR: Çalışmaya katılan 341 hastanın %19.4'ünde pankreas nekrozu saptandı. Balthazar CTSI tarafından abdominal BT'lerinde pankreas nekrozu saptanan hastalar; nötrofil sayıları, nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR), nötrofil/monosit oranı (NMR) önemli ölçüde daha yüksekti ve serum albümini, pankreas nekrozu olan hastalara göre önemli ölçüde daha düşüktü.

TARTIŞMA: Nötrofil sayısı, serum albümin seviyeleri, NLR, LR ve NMR, AP şiddetini belirlemek için prediktif belirteçler olarak kullanılabilir.

Anahtar sözcükler: Akut pankreatit, Balthazar skoru; pankreas nekrozu; serum parametreleri.

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