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Comparison of the Prognostic Value of Hematologic Inflammatory Markers in Patients with Acute Pancreatitis

Akut Pankreatit Hastalarındaki Hematolojik İnflamatuvar Belirteçlerin Prognoz Üzerindeki Etkilerinin Karşılaştırılması

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ABSTRACT

Introduction: Acute pancreatitis (AP) is an inflammatory disease that can also cause a life-threatening clinical picture. AP causes the disease by activating the inflammatory system. Therefore, hematological parameters used as inflammatory markers help to determine the disease progression.
Objective: In this study, we investigated the relationship between hematological parameters and imaging findings with AP severity and survival.
Methods: Data from 312 patients over 18 years of age diagnosed with acute pancreatitis were used for this study. Demographic data, hematologic parameters, and computed tomography of the abdomen were analyzed during hospitalization.
Results: When platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte raito (NLR), amylase/neutrophil and lipase/neutrophil ratios were analyzed according to the severity of AP; while elevated NRL, amylase/neutrophil and lipase/neutrophil ratios were significant in distinguishing between mild and moderate pancreatitis ($p < 0.001$, $p=0.001$, $p=0.001$ and $p=0.001$, respectively), PLR was not significant ($p=0.055$). High amylase/neutrophil and lipase/neutrophil ratios were statistically significant in discriminating between moderate and severe pancreatitis ($p < 0.001$, $p=0.01$, respectively). When patient survival rates were analyzed after discharge regardless of pancreatitis onset, 90.2% (n=229) of patients were alive, while 9.8% (n=25) died. Statistically, there was no significant difference between pancreatitis severity and death ($p=0.837$).
Conclusion: The results of our study suggest that systemic immune inflammatory index (SII), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and modified CT severity index (MCTSI) are valuable in the diagnosis of AP. In addition, the ratios of amylase/neutrophilia and lipase/neutrophilia, which we coincidentally found to be significant in our study, have the potential to lead many studies in determining the severity of pancreatitis.

Keywords: Pancreatit, Neutrophil, Lymphocyte.

ÖZET

Giriş: Akut pankreatit (AP) mortalitesi yüksek olan enflamatuvar hastalıklardan biridir. AP inflamatuvar sistemi aktive ederek hastalığa neden olur. Bu nedenle inflamatuvar hematolojik parametreler hastalığın seyrini belirleme amacıyla kullanılabilir.
Amaç: Bu çalışmada hematolojik parametreler ile görüntüleme bulgularının AP şiddeti ve sağkalım arasındaki ilişkilerinin araştırılması hedeflendi.
Yöntem: Bu çalışma için akut pankreatit tanısı almış 18 yaş üstü 312 hastanın verileri kullanıldı. Demografik veriler, hematolojik parametreler, batın tomografisi sonuçları ve hastanede yatış süreleri analiz edildi.
Bulgular: Platelet lenfosit oranı (PLR), nötrofil lenfosit oranı (NLR), amilaz/nötrofil ve lipaz/nötrofil oranları akut pankreatit AP şiddetine göre incelendiğinde; yüksek nötrofil lenfosit (NLR), amilaz/nötrofil ve lipaz/nötrofil oranları hafif ve orta şiddetli pankreatit arasındaki ayrımda anlamlı bulunurken (sırasıyla $p < 0.001$, $p=0.001$, $p=0.001$ ve $p=0.001$), platelet lenfosit oranı (PLR) sonuçları anlamlı bulunmamıştır ($p=0.055$). Orta şiddetli ve şiddetli pankreatit arasındaki ayrımda ise yüksek amilaz/nötrofil ve lipaz/nötrofil oranları istatistiksel olarak anlamlı bulunmuştur (sırasıyla $p < 0.001$, $p=0.01$). Pankreatit tanı zamanı dikkate alınmaksızın hastaların taburculuk sonrası hayatta kalma oranları incelendiğinde, %90.2'si (n=229) hayatta iken %9.8'i (n=25) vefat etmiştir. İstatistiksel olarak pankreatit şiddeti ile mortalite arasında anlamlı fark bulunmamıştır ($p=0.837$).
Sonuç: Bu çalışmanın sonuçları sistemik immün inflamasyon indeksi (SII), nötrofil lenfosit oranı (NLR), platelet lenfosit oranı (PLR) ve modifiye bilgisayarlı tomografi şiddet indeksi (MCTSI) değerlerinin AP tanısında kullanılabileceğini göstermektedir. Ayrıca çalışmamızda insidental olarak anlamlı bulunan amilaz/nötrofil ve lipaz/nötrofil oranları pankreatit şiddetini belirlemek için yapılacak başka çalışmalarda yol gösterici olabilir.

Anahtar Kelimeler: Pankreatit, Nötrofil, Lenfosit.

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INTRODUCTION

Acute pancreatitis (AP) is an inflammatory disease that can be self-limiting or develop into severe pancreatitis, resulting in high mortality and morbidity. It has been reported that the mortality rate of severe pancreatitis (15~20%) is still high (1,2).

AP causes the disease by activating an inflammatory cascade-like system (3). Molecular studies focusing on cytokine activation, macrophage-mediated inflammatory response, and neutrophil infiltration have shown associations with acute pancreatitis. Systemic inflammatory scores calculated by a formula using inflammatory cell counts such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) and systemic immune inflammatory index (SII) have been associated with many inflammatory diseases (4). In many publications, SII, PLR, and NLR have been found to be effective in determining the severity of AP (5).

Although various scoring systems such as BISAP scoring and MARSHALL scoring are used to determine prognosis, cases of severe pancreatitis are still not well defined at the time of diagnosis (6). The modified computed tomography (CT) severity index (MCTSI) is a version of the original CT severity index developed by Balthazar and colleagues in 1990 to distinguish mild, moderate, and severe forms of acute pancreatitis (7, 8). Its advantage over other scores is that the severity of disease can be classified based on radiologic appearance alone (9). Any delay in the diagnosis and treatment of high-risk patients leads to an increase in morbidity and mortality. Therefore, criteria that can easily determine the progression of AP are needed.

In our study, we investigated the association between hematologic parameters, AP severity, and mortality in patients diagnosed with acute pancreatitis.

METHOD

Study Design

Data were accessed from 312 patients aged ≥18 years with a diagnosis of acute pancreatitis who underwent contrast-enhanced abdominal CT at the Adult Emergency Medicine Clinic of Manisa City Hospital between January 2019 and January 2022. 254 patients who met the inclusion criteria were enrolled in the study.

Exclusion criteria: Patients whose laboratory data were not available and/or patients who had not undergone contrast-enhanced abdominal computed tomography (n:19). Patients with chronic and recurrent pancreatitis attacks, renal dysfunction, patients receiving chemotherapy, immunosuppressive patients, pregnant women, patients with hematologic and immunologic disorders (n:26) Patients referred to another health care facility (n:13). A total of 254 patients were enrolled in the study.

Patients' demographic data (age, sex), blood count values (leukocyte count, neutrophil count and plt and pdw), biochemical values (serum amylase, lipase, C-Reactive Protein (CRP), lactate dehydrogenase (LDH), blood glucose, blood urea nitrogen, creatinine) were recorded during hospitalization. Laboratory values of patients diagnosed at admission AP and the efficacy of these prognostic markers in determining mortality and severity of AP were analyzed.

The diagnosis of acute pancreatitis was made based on the results of clinical examination, laboratory tests, and radiological examination. These included (i) abdominal pain characteristic of acute pancreatitis, (ii) elevated amylase and/or lipase levels (at least three times higher than the upper limit), and (iii) characteristic findings of acute pancreatitis in the pancreas verified by computed tomography.

The MCTSI was classified using a scoring based on the images of inflammation and necrosis detected on contrast-enhanced tomographic images of the pancreas. MCTSI was calculated in patients after

contrast-enhanced computed tomography performed during the first days of hospitalization. MCTSI data were collected by radiologists. Patients were classified into three groups according to MCTSI criteria: mild, moderate, and severe.

Ethical approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (decision no: 393, date: 27/04/2022).

Statistical analysis

SPSS Windows version 22 software was used for statistical analysis. Continuous variables were analyzed for normal distribution using histograms, Q-Q plots, and Shaphiro-Wilk or Kolmogorov-Smirnov tests, depending on the number of variables. Normally distributed continuous variables were presented as mean ± standard deviation throughout the study, and the t test for independent variables was used to compare the two groups. Other continuous variables were presented as median (minimum-maximum), and the nonparametric Mann-Whitney U test was used to compare the groups. Categorical variables were presented as frequencies and percentages, and the Pearson chi-square test or Fischer's exact probability test was used to compare the groups. Values with a p value of 0.05 or less at the 95 percent confidence interval were considered statistically significant.

RESULTS

There were 254 patients who participated in the study. Of the patients, 145 (57.1%) were female and 109 (42.9%) were male. The mean age of the patients was 58.13 ± 18.21 years and there was no statistically significant difference between gender and mean age (p=0.454). Pancreatic imaging findings showed that 166 (58.7%) patients had mild pancreatitis, 71 (28%) had moderate pancreatitis, and 17 (6.7%) had severe pancreatitis. 101 (39.8%) patients had gallstones, and 217 (85.4%) patients were treated in the ward and 37 (14.6%) in the intensive care unit.

When the post-discharge survival rates of the patients were analyzed independently of pancreatitis attack, 90.2% (n=229) of patients were alive, whereas 9.8% (n=25) had died. Of those who died, 60% (n=15) were male and 40% (n=10) were female. There was no statistically significant difference between pancreatitis severity and death (p=0.837).

According to MCTSI classification, 65.4% (n=166) had mild pancreatitis, 28% had moderate pancreatitis, and 6.7% (n=17) had severe pancreatitis.

In a subgroup analysis of PLR, NLR, amylase/neutrophil, and lipase/neutrophil according to AP severity, PLR was statistically significant ($p < 0.001$). NLR was also statistically significant (p=0.001). Amylase/neutrophil, and lipase/neutrophil likewise were statistically significant (p=0.001, and p=0.001, respectively), while PLR was not significant (p=0.055) (Table 1).

The ratio of amylase/neutrophil and lipase/neutrophil was statistically significant in distinguishing moderate and severe pancreatitis ($p < 0.001$ and p=0.01, respectively) (Table 1).

When comparing the number of intensive care unit and ward hospitalizations, PLR, NLR and SII values were significant (p=0.007, p=0.005 and p=0.036, respectively), while no significant difference was found between the amylase/neutrophil and lipase/neutrophil ratios (p=0.01057 and p=0.292, respectively) (Table 1).

When the expected overall survival of patients with AP was evaluated by Kaplan-Meier analysis, the expected survival was 36.1 months (95%CI, 35-37.7) (Figure 1).

Table 1. Comparison of acute pancreatitis severity score (MCTS) with PLR, NLR, amylase/neutrophil and lipase/neutrophil ratios

Pancreatitis Severity		PLR	NLR	Amylase/ Neutrophil	Lipase/ Neutrophil	SII
Mild		152, (110,1)	4 (5,65)	46,1 (112,4)	77,6 (219,5)	1015 (1509,8)
Moderate		179,3 (227,6)	6,2 (7,7)	103,7 (192,3)	159,7 (305,1)	1436,3 (2113,3)
Severe		271,4 (207,9)	5,6 (9)	144,6 (217,2)	239,3 (302,1)	1459,8 (2427,5)
MCTSI						
Mild/Moderate	P value	0,055	**0,001**	**<0,001**	**0,001**	**0,009**
Mild/Severe		0,07	**0,151**	**0,001**	**0,01**	0,113
Moderate/ Severe		0,708	0,68	0,239	0,444	0,837
Hospitalization						
Ward		150,9 (123,6)	4,3 (5,7)	69,5 (160,6)	106,6 (255,5)	1123 (1582,3)
Intensive Care Unit		227,6 (236,7)	8,7 (13,2)	99,4 (123,4)	145,4 (294)	2158 (3441,3)
Ward/ Intensive Care unit	P value	**0,007**	**0,005**	0,105	0,292	**0,036**

*__MCTSI__ Modifiye Computer tomography severity index
*__PLR:__ Platelet lymphocyte ratio, __NLR:__ Neutrophil lymphocyte ratio __SII:__ Systemic Inflammatory Index.

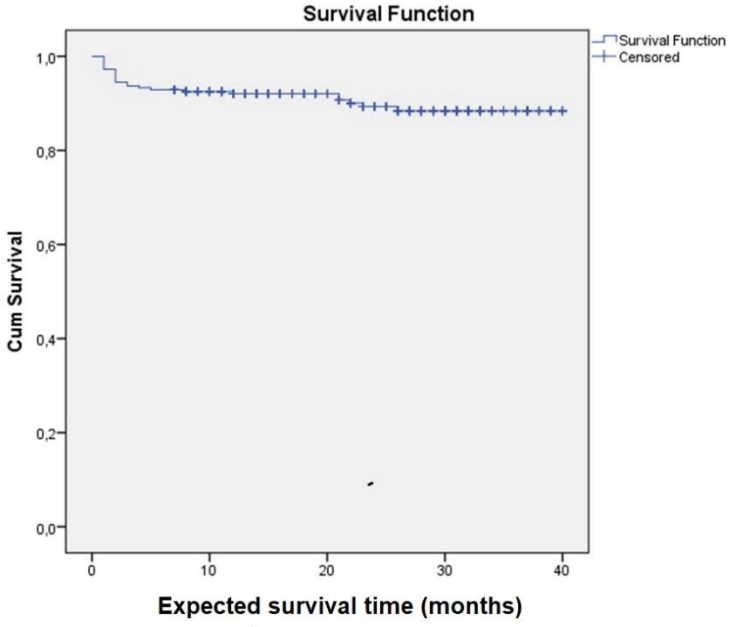

Figure 1. Kaplan-Meier expected overall survival of patients with AP.

When the expected survival time of patients with mild, moderate, and severe pancreatitis was evaluated by Kaplan-Meier analysis, the expected survival time was 36.8 months (95%CI, 35.2-38.3) in patients with mild pancreatitis, 35.7 months (95%CI, 32.9-38.5) in patients with moderate pancreatitis, and 35.4 months (29.4-41.3) in patients with severe pancreatitis. The difference was not statistically significant (p=0.767) (Figure 2).

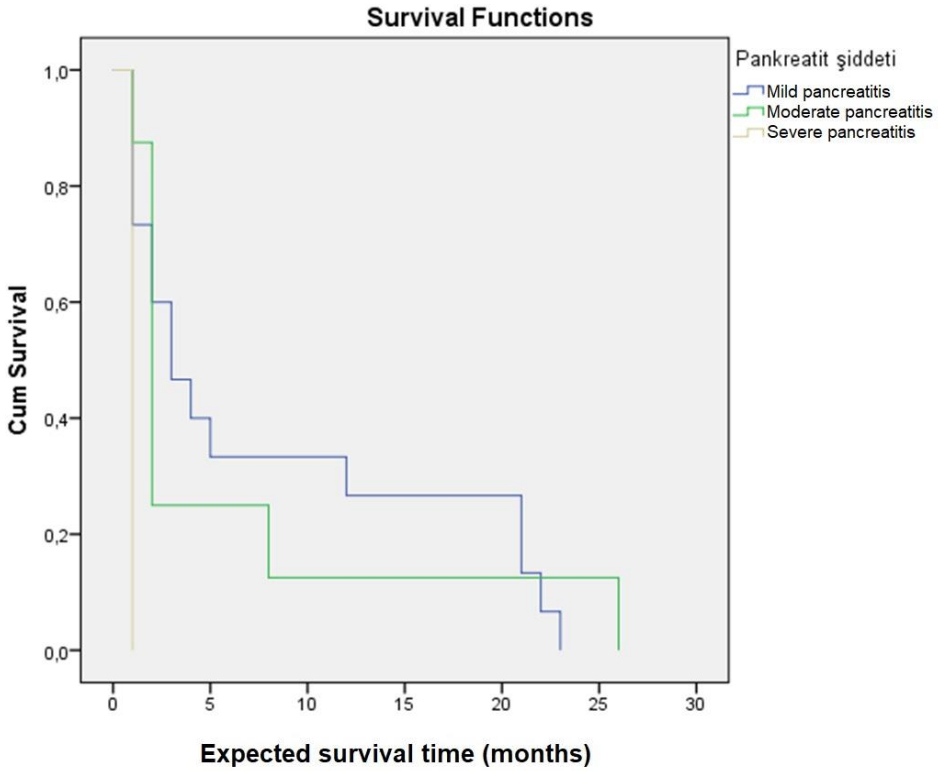

Figure 2. Kaplan-Meier expected survival analysis according to pancreatitis severity.

DISCUSSION

The prognosis of AP patients must be accurately determined. There are many methods to assess the prognosis of AP. However, none of these methods is sensitive or specific enough. The SII is an index that reflects the balance between inflammatory and immune responses and has been found to be a predictor of the severity of acute pancreatitis (8). Another study showed that SII was significantly associated with AP mortality (10). NLR scores have been used as diagnostic indicators in many inflammatory and neoplastic diseases (11, 12). NLR has been described as an independent risk factor for persistent organ failure, prolonged intensive care unit (ICU) stay, and higher in-hospital mortality in AP (8, 13). Moreover, NLR and PLR levels have been shown to be significant in severe acute pancreatitis (14). In our study, a significant association was found between SII and elevated NLR and PLR levels and hospitalization of patients to the intensive care unit.

In our analysis with amylase/neutrophil and lipase/neutrophil ratios, significant results were found in distinguishing mild/moderate pancreatitis from mild/severe pancreatitis. The amylase/neutrophil and lipase/neutrophil ratios are proportional values found randomly within the scope of our special engineering studies, and we have not yet encountered the use of these values in the literature. We think that these new ratios can be used in future scientific clinical studies.

Recently, some clinicians have used CT imaging to predict disease progression (15). The use of CT to determine the severity of AP is becoming increasingly common (15-17). The MCTSI is most commonly used for CT assessment (15 - 18). Several studies have found a significant association between MCTSI score determined at admission and mortality and morbidity (19). In our study, no statistically significant difference was found between the survival of patients with mild pancreatitis and patients with moderate and severe pancreatitis. We suggest that the reason for this is that acute pancreatitis is not the sole

determinant of mortality, but with comorbid conditions it may have an increasing impact on mortality (Figure 1,2).

CONCLUSION

The results of this study show that SII, NLR PLR, and MCTSI are valuable in determining the severity of acute pancreatitis at presentation. In addition, the ratios of amylase/neutrophilia and lipase/neutrophilia may be useful in determining the severity of pancreatitis. Therefore, they can be used as an early indicator to determine the severity of acute pancreatitis. However, large-scale, prospective, and well-designed studies should be performed to confirm the results.

DESCRIPTIONS

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