ORIGINAL ARTICLE

Is there a correlation between the initial calcium level and Balthazar classification in patients with acute pancreatitis?

Mehmet Ali Bilgili, M.D.,[1] Ramazan Dertli, M.D.,[2] Abdullah Al Kafee, M.D.,[3] Guner Kılıç, M.D.,[2] Yusuf Kayar, M.D.[2]

[1]Department of Emergency, Van Training and Research Hospital, Van-*Turkey*
[2]Department of Internal Medicine, Division of Gastroenterology, Van Training and Research Hospital, Van-*Turkey*
[3]Department of Biomedical Engineering, Boğaziçi University Faculty of Engineering, İstanbul-*Turkey*

ABSTRACT

BACKGROUND: While a life-threatening course is observed in 2–3% of patients with acute pancreatitis (AP), mortality can be up to 50% in severe AP. In our study, we research relationship between calcium level and Modified Balthazar (MB) score.

METHODS: 354 patients who were followed up with a diagnosis of AP between 2013 and 2019 were included in our study. Serum calcium level was measured within the first 24 h. Abdominal computed tomography (CT) was performed in all patients in the first 12 h and between 3 and 7 days. The severity of AP was determined according to the MB classification. The correlation between calcium level and MB classification was examined.

RESULTS: 206 (58.2%) of the patients were women. Mean age was 54.8±17.9 years (range: 18–100). It was observed that the rate of severe AP was significantly higher in the low calcium group compared to the MB classification in which tomographies taken at admission and 72 h after were evaluated ($p<0.05$). Furthermore, progression was higher in low calcium group ($p<0.05$). The cutoff value was 9.35 mg/dl for the ROC analysis performed to distinguish mild pancreatitis from moderate-severe pancreatitis according to the MB classification performed by CT obtained after 72 h based on the Ca values. For the cutoff value of 9.35 mg/dl (AUC: 0.581, p=0.018, 95% CI: 0.514–0.649), the sensitivity was 57.4% and the specificity was 53.1%.

CONCLUSION: Since there is a correlation between the initial calcium level and the severity of the disease according to the CT-scan obtained later, the calcium level gives us an idea of the course of the disease.

Keywords: Acute pancreatitis; Balthazar classification; hypocalcemia.

INTRODUCTION

Acute pancreatitis (AP) is an inflammation of the pancreatic tissue that can show a different course from a simple and self-limiting clinical to death.[1] The severe systemic response that develops due to inflammation results in a severe picture that can lead to multiple organ failure. While over 80% of patients have mild, self-limiting AP requiring only brief hospitalization, <20% have severe AP, which may cause various complications.[2] While a life-threatening course is observed in 2–3% of the patients, the mortality can be up to 50% in severe AP.[3–8]

Many laboratory and radiological parameters are used to determine the severity of AP. Imrie, Ranson, Bedside Index of Severity in AP, Acute Physiology and Chronic Health Evaluation II, harmless AP score are some of them.[2] Despite certain limitations, imaging scoring, which was developed by Balthazar and can be used to evaluate pancreatic and peripancreatic inflammation and pancreatic necrosis, is also one of the important classifications that determine the severity of AP.[9] However, it is thought that these scoring systems alone are not sufficient prognostically in AP patients. In addition, it has been shown in the laboratory that parameters such as pro-inflammatory cytokines, pancreatic enzymes, and C-re-

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Address for correspondence: Yusuf Kayar, M.D.
Van Eğitim ve Araştırma Hastanesi, Gastroenteroloji Bölümü, Van, Turkey
Tel: +90 432 - 222 00 10 E-mail: ykayar@yahoo.com

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active protein are significantly correlated with the severity of AP.[2,10] It has been previously reported in various studies that hypocalcemia develops in the course of severe pancreatitis and that calcium levels are associated with the severe course of the disease. This hypocalcemia has been associated with calcium accumulation in soft tissues secondary to inflammation.[5,6,11] In addition, in a study in which parathormone was examined in the course of AP, it was observed that there was an irregular hormone response to inflammation, and different studies emphasized that a similar picture could be present in other systemic inflammatory conditions.[12–15]

It has been reported that computed tomography (CT) performed at an early stage shows the normal appearance of the pancreas in 14–30% of AP. Since necrosis is not seen in the early hours, it is recommended not to perform CT before 72 h.[16] There are a few studies investigating changes in imaging findings during the course of AP and evaluating biochemical markers and radiological examinations together.[17] In this study, we tried to determine the relationship between calcium level and the Balthazar score calculated in tomographic scans performed 12 h and 72 h later.

MATERIALS AND METHODS

Study Design

354 patients hospitalized with the diagnosis of AP in the Gastroenterology Service of our Hospital between 2013 and 2019 were included in our study. The diagnosis of AP was made on the basis of the American College of Gastroenterology guidelines.[1] Those with contrast material allergy, chronic pancreatitis, malnutrition, malabsorption, malignancy, and those who did not want to participate in the study and pregnant women were excluded from the study. The age and gender data of all patients were documented.

Serum Calcium Level Measurement

Total serum calcium level was measured within the first 24 h. These values were then corrected for the serum albumin level. Thus, serum calcium level corrected with albumin level was determined. Corrected serum calcium level = Total serum calcium level + (0.8 * [4 – serum albumin concentration]).[4,5] The patients were divided into two groups as those with low and normal calcium levels. The relationship between the severity of AP assessed according to the Modified Balthazar (MB) classification between the two groups was examined.

AP Severity

Abdominal CT was performed in all patients included in the study. In addition to pancreatic necrosis and peripancreatic fluid accumulation, ascites, pleural fluid, extrapancreatic parenchymal abnormalities (subcapsular fluid accumulation, hemorrhage or infarction), vascular complications (arterial hemorrhage, venous thrombosis, or pseudoaneurysm), and gastrointestinal tract involvement (inflammation, and intramural fluid accumulation) extrapancreatic findings were evaluated. AP was graded and classified according to the MB classification. According to the Balthazar score, patients with scores of 0–2, 4–6, and 8–10 were evaluated as mild, moderate, and severe AP, respectively.[17]

Imaging Analysis

Helical CT (chapter 64, Aquilion; Toshiba Medical Systems, Tokyo) was performed on all patients within the first 12 h and on days 3–7. Contrast-enhanced CT scan (collimation, 4×2.5 mm; slice thickness, 5 mm; reconstruction interval, 5 mm) was obtained at a rate of 3 ml/s, 65 s after 100 ml Iohexol (Omnipaque 300) administration. All images were analyzed by the radiologist. Pancreatic, peripancreatic, and extrapancreatic findings and complications were examined.

Ethics Statement

All participants gave written consent to participate in the study. Ethical approval for this study was done in our hospital Ethics Committee (Turkey) was included in the study. All procedures were in accordance with the ethical standards of our institution's human experiment committee and the Declaration of Helsinki.

Statistical Analysis

The results of our study were analyzed with the program "The Statistical Package for the Social Sciences 22.0 (SPSS Armonk, NY: IBM Corp.)." Categorical data were given as frequency and percentage (n,%), data with continuous values were given as mean (± standard deviation [SD]). Data were tested for compliance with normal distribution using the Kolmogorov–Simonov test, histogram, and ± SD. Chi-square test was used to test categorical data. Parametric data of the groups were compared using Independent T test and non-parametric data using Mann–Whitney U test. The cutoff values were calculated using the receiver operating characteristic (ROC). The cases with $p<0.05$ were considered statistically significant.

RESULTS

354 patients followed up with a diagnosis of AP were included in the study. 206 (58.2%) of the patients included in the study were women and their mean age was 54.8±17.9 years (age range: 18–100). While total serum calcium level was low in 30 (8.4%) patients, albumin-corrected calcium level was found to be low in 19 (5.3%) patients. There was no significant difference in demographic terms (age and gender) between the two groups made according to the total calcium level ($p>0.05$). In the comparison made in terms of AP severity in both groups; According to the MB classification, in which tomographies taken at the time of application were evaluated, it was observed that the ratio of moderate and severe AP was significantly higher in the low calcium group ($p<0.05$). According to the MB classification, in which tomog-

raphies taken after 72 h were evaluated, the ratio of mild AP was significantly lower and the rate of severe AP was significantly higher in the low calcium group (p<0.05 and p<0.001, respectively). In addition, in the comparison made in terms of changes in the severity of the disease (regression, progression, or no-change) during the application and subsequent imaging; the proportion of those who progressed was significantly higher in the low calcium group (p<0.001) (Table 1).

In the demographic comparison between the two groups made according to albumin-corrected calcium level, there was no significant difference in gender ratio, while the group with low calcium was found to be younger (p<0.001). In the comparison made in terms of AP severity in both groups; it was observed that the rate of severe AP was significantly higher in the low calcium group compared to the MB classification, in which tomographies taken at the time of application were evaluated (p<0.05). According to the MB classification, in which tomographies taken after 72 h were evaluated, the ratio of mild AP was significantly lower and the rate of severe AP was significantly higher in the low calcium group (p<0.05 and p<0.001, respectively). In addition, in the comparison made in terms of changes in the severity of the disease (regression, progression, or no-change) during the application and subsequent imaging; the proportion of those who progressed was significantly higher in the low calcium group (p<0.05) (Table 2).

ROC analysis was performed to distinguish mild pancreatitis from moderate-severe pancreatitis according to the modified baltazar classification performed by tomography taken at the first 12th h based on the total calcium values of the patients at the time of admission. The cutoff value for total Ca value was 9.35 mg/dl. For the cutt-of value of 9.35 mg/dl (AUC: 0.616, p=0.001, 95% CI: 0.551–0.680), the sensitivity was 59.4% and the specificity was 57.3%. ROC analysis was performed to distinguish mild pancreatitis from moderate-severe pancreatitis according to the modified baltazar classification performed by tomography taken after 72 h based on the total Ca values of the patients at the time of admission. The cut-off value for total Ca value was 9.35 mg/dl. For the cutoff value of 9.35 mg/dl (AUC: 0.581, p=0.018, 95% CI: 0.514–0.649), the sensitivity was 57.4% and the specificity was 53.1% (Fig. 1).

ROC analysis was performed to distinguish mild pancreatitis from moderate-severe pancreatitis according to the modified baltazar classification performed by tomography taken at the first 12th h based on the corrected Ca values of the patients at the time of admission. The cutoff value for the corrected Ca value was found to be 9.29 mg/dl. For the cutoff value of 9.29 mg/dl (AUC: 0.628, p<0.001, 95% CI: 0.562–0.694), the sensitivity was 70.5% and the specificity was 51.5%. ROC analysis was performed to distinguish mild pancreatitis from moderate-severe pancreatitis according to the modified baltazar classification performed by tomography taken after 72 h based on the corrected Ca values of the patients at the time of admission. The cutoff value for the corrected Ca value was 9.29 mg/dl. For the cutoff value of 9.29 mg/dl (AUC: 0.554, P

Table 1. Relationship between total calcium level and demographic characteristics, Balthazar classification

	Patients with low calcium levels n=30 (8.4%)	Patients without low calcium levels n=324 (91.6%)	Total n=336	p-value
Age (year)	55±17.6	54.7±17.8	54.1±17.9	0.065
(Mean, Standard deviation, Range)	(24–85)	(18–100)	(18–100)	
Sex, n (%)				
Male	14 (46.7)	134 (41.4)	148 (41.8)	0.573
Female	16 (53.3)	190 (58.6)	206 (58.2)	
Balthazar classification (on admission), n (%)				<0.001
Mild	14 (46.7)	237 (73.1)	251 (70.9)	0.002
Moderate	14 (46.7)	86 (26.5)	100 (28.2)	0.019
Severe	2 (6.6)	1 (0.4)	3 (0.9)	<0.001
Balthazar classification (after 72 hours), n (%)			<0.001	
Mild	16 (53.3)	240 (74.1)	256 (72.3)	0.015
Moderate	5 (16.7)	73 (22.5)	78 (22.0)	0.458
Severe	9 (30.0)	11 (3.4)	20 (5.7)	<0.001
Computed tomography changes, n (%)				<0.001
Regression	7 (23.3)	70 (21.6)	77 (21.8)	0.826
Progression	15 (50)	72 (20.3)	72 (20.3)	<0.001
No change	8 (26.7)	205 (57.9)	205(57.9)	<0.001

Table 2. Relationship between corrected calcium level and demographic characteristics, Balthazar classification

	Patients with low calcium levels n=19 (5.3%)	Patients without low calcium levels n=335 (94.7%)	Total n=336	p-value
Age (year)	46.5±15.3	55.2±17.9	54.1±17.9	<0.001
(Mean, Standard deviation, Range)	(24–69)	(18–100)	(18–100)	
Sex, n (%)				
Male	8 (42.1)	140 (41.8)	148 (41.8)	0.978
Female	11 (57.9)	195 (58.2)	206 (58.2)	
Balthazar classification (on admission), n (%)				0.031
Mild	10 (52.6)	241 (71.9)	251 (70.9)	0.071
Moderate	8 (42.1)	92 (27.5)	100 (28.2)	0.168
Severe	1 (5.3)	2 (0.6)	3 (0.9)	0.031
Balthazar classification (after 72 hours)				<0.001
Mild	10 (52.6)	246 (73.4)	256 (72.3)	0.049
Moderate	3 (15.8)	75 (22.4)	78 (22.0)	0.500
Severe	6 (31.6)	14 (4.2)	20 (5.6)	<0.001
Computed tomography changes, n (%)				0.044
Regression	2 (10.5)	75 (22.4)	77 (21.8)	0.223
Progression	8 (42.1)	64 (19.1)	72 (20.3)	0.015
No change	9 (47.4)	196 (58.5)	205 (57.9)	0.339

= 0.118, 95% CI: 0.484–0.624), the sensitivity was 66.8% and the specificity was 42.9% (Fig. 2).

The progress of AP severity in the two groups made according to the total calcium level was analyzed in detail. In the group with low calcium; in the images taken after 72 h of Stage B, 2 (33.3%) patients remained Stage B, 2 (33.3%) patients regressed to Stages A, and 2 (33.3%) patients progressed to Stage C. It was seen that two patients with Stage B remained Stage B in 2 (100%) images taken after 72 h. In the imaging performed after 72 h of 6 patients with Stage C, 2 (33.3%) patients remained Stage C, and 4 (66.7%) patients regressed to Stage A. In the imaging performed after 72 h of 5 patients with stage D, it was seen that 2 (40%) patients re-

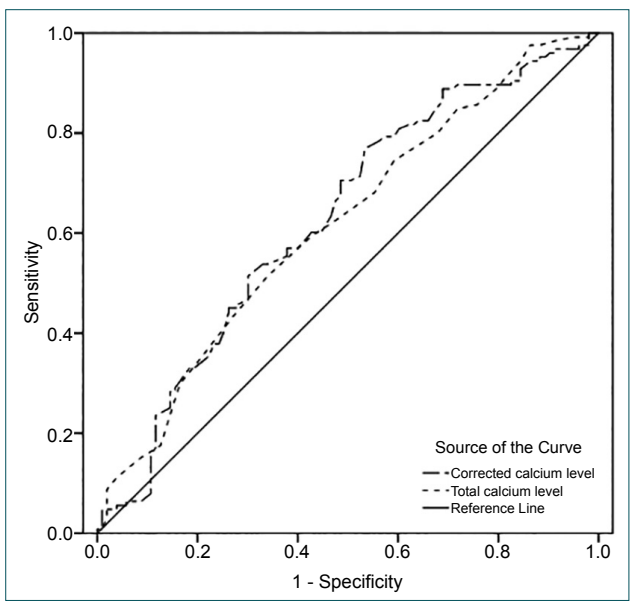

Figure 1. Relationship between calcium level and Balthazar classification calculated in the first 12 h.

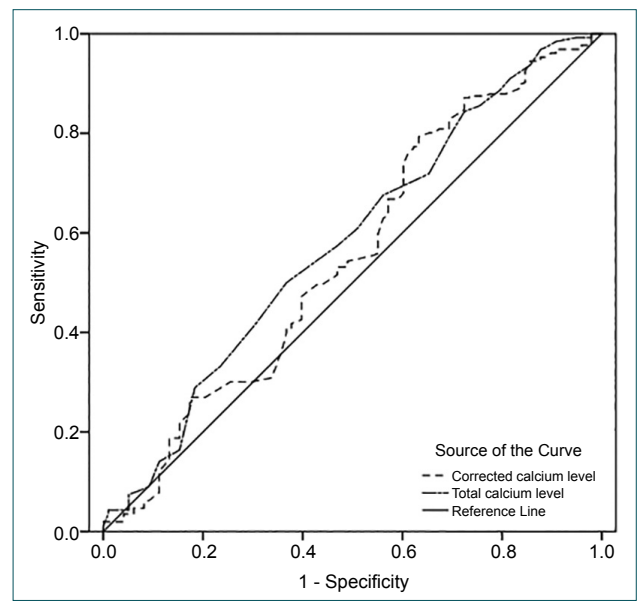

Figure 2. Relationship between calcium level and Balthazar classification calculated after 72 h.

mained stage D, and 3 (60%) patients progressed to Stage E. In the imaging performed after 72 h of 11 patients with Stage E, 9 (81.8%) patients remained Stage E, and 2 (18.2%) patients regressed to Stages A and C (Table 3).

In the group with normal calcium levels; in the imaging performed after 72 h of 56 patients with Stage A, 46 (82.1%) patients remained Stage A, and 10 (27.9%) patients progressed to Stages B, C and D. In the imaging performed after 72 h of 36 patients with Stage B, 22 (61.1%) patients remained Stage B, 8 (22.2%) patients regressed to Stage A, and 6 (16.7%) patients progressed to Stage C. In the imaging performed after 72 h of 145 patients with Stage C, 91 (62.8%) patients remained Stage C, 30 (20.7%) patients regressed to Stages A and B, and 24 (16.6%) patients had Stages D and E ' It was seen to be progressed. In the imaging performed after 72 h of 40 patients with Stage D, 11 (27.5%) patients remained Stage D, 22 (55%) patients regressed to Stages A, B, and C, 7 (17.5%) patients progressed to Stage E was seen to be. In the imaging performed after 72 h of 47 patients with Stage E, 37 (78.7%) patients remained Stage E, and 10 (21.3%) patients regressed to Stages A, B, C, and D (Table 4).

DISCUSSION

The pancreas is one of the important organs of the intestinal system with endocrine and exocrine functions. Enzymes involved in digestion cause damage to the pancreatic tissue due to pancreatic damage that occurs due to inflammation in patients with pancreatitis clinic.[1,4,5] While mild and moderate pancreatitis affects only itself and adjacent organs locally, multiple organ failure may develop in severe pancreatitis due to both local and systemic effects.[1,3,4,8] It is known that morbidity and mortality decrease in patients with severe AP with early initiation of treatment and close monitoring.[18] For this reason, it is important to determine the course of the disease using laboratory and radiological parameters.

Although there are many parameters used in the course of AP, it has been reported in studies that there is a significant relationship between calcium level and AP severity.[19,20] Calcium is involved in bone metabolism as well as in many metabolisms in the body. Ca metabolism is regulated with parathyroid hormone and calcitonin. Various theories have been proposed regarding the pathophysiology of hypo-

Table 3. Evaluation of the changes in CT scan performed on the 3th-7th day compared to the one performed within the first 12 hours in patients with low total calcium level

CT 3th-7th day	CT: On admission					
	Stage A n (%)	Stage B n (%)	Stage C n (%)	Stage D n (%)	Stage E n (%)	Total n (%)
Stage A	2 (33.3)	0 (0)	4 (64.7)	0 (0)	1 (9.1)	7 (23.3)
Stage B	2 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6.7)
Stage C	2 (33.3)	2 (100)	2 (33.3)	0 (0)	1 (9.1)	7 (23.3)
Stage D	0 (0)	0 (0)	0 (0)	2 (40)	0 (0)	2 (6.7)
Stage E	0 (0)	0 (0)	0 (0)	3 (60)	9 (81.8)	12 (40)
Total	6 (100)	2 (100)	6 (100)	5 (100)	11 (100)	30 (100

CT: Computed tomography.

Table 4. Evaluation of the changes in CT scan performed on the 3th-7th day compared to the one performed within the first 12 hours in in patients without low total calcium level

CT 3th-7th day	CT: On admission					
	Stage A n (%)	Stage B n (%)	Stage C n (%)	Stage D n (%)	Stage E n (%)	Total n (%)
Stage A	46 (82.1)	8 (22.2)	20 (13.8)	11 (27.5)	2 (4.3)	87 (26.9)
Stage B	2 (3.6)	22 (61.1)	10 (6.9)	1 (2.5)	1 (2.1)	36 (11.1)
Stage C	6 (10.7)	6 (16.7)	91 (62.8)	10 (25.0)	4 (8.5)	117 (36.1)
Stage D	2 (3.6)	0 (0)	14 (9.7)	11 (27.5)	3 (6.4)	30 (9.3)
Stage E	0 (0)	0 (0)	10 (6.9)	7 (17.5)	37 (78.7)	54 (16.7)
Total	56 (100)	36 (100)	145 (100)	40 (100)	47 (100)	324 (100)

CT: Computed tomography.

calcemia in AP. The most accepted theories; saponification due to adipose tissue necrosis and the precipitation of calcium in tissues due to this, hypoalbuminemia and hormonal disorders. In fact, it has been stated in recent studies that hypocalcemia develops as a response to acute inflammation and there is a similar systemic response in most inflammatory conditions (infection, trauma, malignancy, etc.) in the body.[4,21–23]

Although studies on Ca level in the course of AP have been reported to be closely related to the course of the disease, there are rare studies on the relationship between calcium levels and radiological findings.[2,15–19] Chhabra et al.[24] emphasized that, regardless of the etiology, hypocalcemia had an effect on both the severe course of the disease and mortality in 105 patients followed-up with AP. Pokharel et al.[25] reported that in the course of AP, serum calcium level and corrected calcium level in the first 24 h were effective in the course of the disease, and that pancreatitis had a more severe course in patients with low calcium levels and corrected calcium levels. Tan et al.[20] in a study they conducted with 379 patients with AP, 77 of whom were in intensive care unit, they compared Ca levels with three different scoring systems and it was reported that scoring systems which National Early Warning Score ($r=-0.46$; $p<0.001$), Modified Early Warning Score ($r=-0.37$; $p<0.001$), and Bedside Index of Severity in AP ($r=-0.39$; $p<0.001$) were correlated with calcium level. Therefore, they recommended that Ca level and scoring systems should be integrated with each other. Tasić et al.[19] in their study with 273 patients, he made a classification according to the Baltazar score and found that there was a low level of negative correlation between ionized Ca and the course of the disease. The disease progressed severely as the ionized calcium decreased. In addition, Ammori et al.[26] observed that in the course of AP, endotoxin is released due to hypocalcemia and the development of endotoxemia is effective in mortality. In our study, the rate of moderate and severe pancreatitis was found to be higher in the group with low calcium compared to the total Ca and corrected Ca levels at the time of admission compared to the Baltazar score, which was performed by CT scan at the time of admission and 72 h later. In addition, the rate of disease progression was higher in the group with low calcium.

This study has some limitations. First, being a single-center retrospective study and not mentioning other risk factors that play a role in the progression of the disease are important limitations. In addition, since the data are obtained only from a single tertiary center, it may not include all patients hospitalized with a diagnosis of AP. The strengths of our study include the large number of samples, the clear presentation of all patient etiologies, the evaluation of the abdominal tomography taken at the time of the first application and the 72nd h by the same person (radiology specialist), and the corrected calcium level as well as the total calcium level.

Conclusion

Early intensive care unit hospitalization, strict follow-up and early treatment changes the course of the disease in FP patients. Therefore, it is important to know the course of the disease in the early period. In our study, we showed that serum calcium level is an important parameter in the course of AP and has a predictive value regarding the course of the disease. Although CT is an important marker, it is not recommended due to its inability to show the severity of the disease at an early stage. However, since there is a correlation between the initial calcium level and the severity of the disease according to the subsequent CT, the calcium level gives us an idea of the course of the disease.

Ethics Committee Approval: This study was approved by the Van Training and Research Hospital Clinical Research Ethics Committee (Date: 04.02.2021, Decision No: 2023/03).

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ORİJİNAL ÇALIŞMA - *ÖZ*

Akut pankreatit hastalarında başlangıçta bakılan kalsiyum seviyesi ile Balthazar sınıflaması arasında korelasyon var mı?

Dr. Mehmet Ali Bilgili,[1] Dr. Ramazan Dertli,[2] Dr. Abdullah Al Kafee,[3] Dr. Guner Kılıç,[2] Dr. Yusuf Kayar[2]

[1]Van Eğitim ve Araştırma Hastanesi, Acil Ünitesi Bölümü, Van
[2]Van Eğitim ve Araştırma Hastanesi, Gastroenteroloji Bölümü, Van
[3]Boğaziçi Üniversitesi Mühendislik Fakültesi, Biomedikal Mühendisliği Bölümü, İstanbul

AMAÇ: Akut pankreatit (AP) hastalarnın %2–3'ünde hayatı tehdit eden bir seyir görülürken, ağır seyirli AP'de mortalite %50'ye kadar çıkabilmektedir. Çalışmamızda kalsiyum düzeyi ile Modifiye Balthazar (MB) skoru arasındaki ilişkiyi saptamaya çalıştık.

GEREÇ VE YÖNTEM: Çalışmamıza 2013–2019 tarihleri arasında AP tanısı ile takip edilen 354 hasta alındı. İlk 24 saat içinde serum kalsiyum seviyesi ölçüldü. Çalışmaya alınan tüm hastalara ilk 12 saatte ve 3–7 günler arasında abdominal bilgisayarlı tomografi (BT) çekildi. MB sınıflamasına göre AP'nin şiddeti belirlendi. Kalsiyum seviyesi ile MB sınıflaması arasındaki korelasyon incelendi.

BULGULAR: Çalışmaya alınan hastaların 206'sı (%58.2) kadındı. Ortalama yaşları 54.8±17.9 yıl (yaş aralığı: 18–100) idi. Başvuru sırasında ve 72 saat sonrasında çekilen tomografilerin değerlendirilerek yapıldığı MB sınıflamasına göre düşük kalsiyum grubunda ağır AP oranının anlamlı olarak daha yüksek olduğu izlendi ($p<0.05$). Ayrıca düşük kalsiyum gurubunda progresyon daha yüksek oranda gözlendi ($p<0.05$). Hastaların başvuru anındaki total Ca değerleri baz alınarak 72. saat sonrası çekilen BT ile yapılan MB sınıflamasına göre hafif pankreatitleri orta-ağır pankreatitlerden ayırmak için yapılan ROC analizi için kestirim değeri 9.35 mg/dl bulundu. 9.35 mg/dl kestirim değeri için (AUC: 0.581, $p=0.018$, %95 CI: 0.514–0.649) hassasiyet %57.4, özgüllük %53.1 olarak hesaplandı.

TARTIŞMA: Başlangıçta bakılan kalsiyum seviyesi ile daha sonra çekilen BT'ye göre hastalığın ciddiyeti arasında korelasyon olması nedeniyle, kalsiyum seviyesi hastalığın seyrinin nasıl olacağı konusunda bize fikir vermektedir.

Anahtar sözcükler: Akut pankreatit; Balthazar sınıflaması; hipokalsemi.

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