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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Role of Biomarkers in the Differentiation of Acute Pancreatitis from Chronic Pancreatitis

Akut Pankreatitin Kronik Pankreatitten Ayırımında Biyobelirteçlerin Yeri

Meltem Gümüş[1], Alaaddin Yorulmaz[2], Ersin Başkocagil[3], Halil Haldun Emiroğlu[1]

[1]Department of Pediatrics, Division of Pediatric Gastroenterology, Selcuk University Medical School, Konya, Turkey
[2]Department of Pediatrics, Selçuk University Medical School, Konya, Turkey
[3]Department of Pediatrics, Beyhekim Hospital, Konya, Turkey

ABSTRACT

Aim: The objective of this study was to develop biomarkers that can be used to forecast the subsequent development of chronic pancreatitis in patients who experienced acute pancreatitis during childhood.

Material and Method: From 2011 to December 2023, a total of 156 pediatric patients with pancreatitis (129 with acute pancreatitis and 27 with chronic pancreatitis) were assessed at the Pediatric Gastroenterology Clinic of Selçuk University Faculty of Medicine Hospital, following the criteria established by INSPPIRE.

Results: Among the patients, 85 (54.48%) were female and 71 (45.52%) were male. The F/M ratio was calculated to be 1.19. The ROC analysis of pancreatitis types revealed that the following factors were statistically significant: Albumin/CRP, 48th hour amylase and lipase levels, Prognostic Nutrition Index, Albumin/amylase ratio, and albumin levels upon admission to the hospital.

Conclusion: The prevalence of pancreatitis has shown an upward trend in recent times. The symptoms presented by patients seeking admission for pancreatitis may differ based on their age group. To arrive at a diagnosis, it is imperative to first suspect the presence of the disease. The establishment of standardized approaches for the early diagnosis and treatment of patients, along with their implementation, will not only enhance the prognosis but also prevent potential complications. Further research in the field of pediatrics is warranted in order to devise a scoring system applicable to the pediatric age group and identify the most efficacious treatment modalities.

Keywords: Biomarker, child, pancreatitis, INSPPIRE criteria

ÖZ

Giriş: Bu çalışmada, çocukluk çağında akut pankreatit geçiren hastalarda sonrasında kronik pankreatit gelişip gelişmeyeceğini tahmin etmek için biyobeliteçler geliştirmeyi amaçladık.

Gereç ve Yöntem: 2011 ile Aralık 2023 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Hastanesi Çocuk Gastroenteroloji Kliniğinde INSPPIRE tarafından belirlenen kriterlere göre tanı konan 129 (%82,70) hasta Akut, 27 (%17,30) kronik toplam 156 çocuk pankreatit hastası değerlendirildi.

Bulgular: Hastaların 85'i (%54,48) kız, 71'i (%45,52) erkekti. K/E oranı 1,19 idi. Pankreatit tiplerine ROC analiz incelendiğinde; hastaların hastaneye başvuru anı Albümin/CRP, 48. saat amilaz, lipaz, Prognostik Nutrisyon İndeksi, Albümin/amilaz oranı ve albümin değerleri anlamlı bulunmuştur.

Sonuç: Pankreatit insidansı son yıllarda artan bir seyir göstermektedir. Pankreatit başvuru şikayetleri yaş grubuna göre değişiklik gösterebilmektedir. Tanı konulması için öncelikle hastalıktan şüphe duyulması gerekmektedir. Hastaların erken tanısı ve tedavisi konusunda standart yaklaşımların oluşturulması ve bunların uygulanması prognozu iyileştirici ve komplikasyonları önleyici etkilere yol açacaktır. Çocukluk yaş grubunda kullanılabilecek bir skorlama sistemi geliştirmek ve en etkili tedavi yöntemlerini bulmak için daha çok pediatrik çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Biyobelirteç, çocuk, pankreatit, INSPPIRE kriterleri

Corresponding Author: Meltem GÜMÜŞ
Address: Department of Pediatrics, Division of Pediatric Gastroenterology, Selçuk University Medical School, Konya, Turkey
E-mail: meltemdorum@gmail.com, meltem.dorum@selcuk.edu.tr

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INTRODUCTION

Acute Pancreatitis (AP) is a mostly reversible inflammatory disease damaging the pancreas as a result of increased enzyme activation in the pancreatic parenchyma for various reasons, and Chronic Pancreatitis is the permanent inflammation of the tissue (1). In children, AP is often mild and self-limiting and does not require treatment (2). Although it usually resolves without complications, some might develop into Chronic Pancreatitis (CP). The incidence of AP has increased to 13/100.000 per year in the pediatric population (3). Recurrent attacks are detected in 9-35% of patients who had AP, and the annual incidence of CP is 0.5 per 100.000 (4, 5). CP might develop in patients diagnosed with Acute Recurrent Pancreatitis (ARP) over time, and it is unclear how long it will take to progress to the chronic stage. In a previous study with 300 child patients, 84% of the patients who had CP had previously had recurrent pancreatitis attacks and were diagnosed with CP in an average of one year (1.5 months-14.3 years) following the pancreatitis attack initiated (6).

Systemic diseases, drugs, traumas, and congenital anomalies (e.g., choledochal cysts and pancreaticobiliary junction anomalies) are common causes of AP during childhood, and 15-30% of cases are idiopathic. Patients who have ARP and CP also have common etiological causes like Toxic/Metabolic, Idiopathic, Genetic, Autoimmune, Recurrent Pancreatitis, and Obstructive causes etc., and more than one risk factor might cause disease development simultaneously (7). CP is characterized by irreversible damage to the pancreatic tissue such as fibrosis and necrosis, and its diagnosis is made when at least one of the following is detected; abdominal pain, endocrine insufficiency, or exocrine insufficiency, accompanied by imaging findings compatible with chronic pancreatic damage. Having imaging findings supporting CP is sufficient (8). The rate of development of ARP in children after the first attack of AP was reported to be 21.5%, and the rate of development of CP after ARP was 2% (9).

It still remains a problem to determine which cases will progress with severe clinical findings or complications in advance, and therefore, how many days of hospital treatment will be required. Also, it is not known which patients will develop CP. The epidemiology and the natural history of pediatric ARP and CP are not well-understood, and there are no evidence-based diagnostic, prognostic and treatment guidelines for these disorders. Although there are many classification and scoring systems in the adult literature, the search for reliable biomarkers that might make early predictions of patients that might develop serious AP, are easy to apply, and provide rapid results (10). The revised ATLANTA classification of acute pancreatitis identified two phases of the disease Severity is classified as mild, moderate or severe. Mild acute pancreatitis, the most common form, has no organ failure, local or systemic complications and usually resolves in the first week. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications or exacerbation of co-morbid disease. Severe acute pancreatitis is defined by persistent organ failure, that is, organ failure >48 h. Ransons criteria are one of the earliest scoring systems to assess the severity of acute pancreatitis and continue to be widely used. The original Ranson criteria is a scoring system that uses 11 parameters to assess the severity of acute pancreatitis. The 11 parameters are age, white blood cell count (WBC), blood glucose, serum aspartate transaminase (AST), serum lactate dehydrogenase (LDH), serum calcium, fall in hematocrit, arterial oxygen (PaO2), blood urea nitrogen (BUN), base deficit, and sequestration of fluids. (11-13).

The purpose of the present study was to evaluate the etiology, clinical, laboratory, and imaging findings and treatment methods of patients presenting with AP and CP. It was also aimed to develop biomarkers to predict whether pediatric patients who have AP might later develop CP.

MATERIAL AND METHOD

The study was carried out with the permission of Selçuk University Faculty f Medicine Ethics Committee (Decision No:2023/467). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Group and Protocol

The study included 156 patients who were diagnosed with acute and Chronic Pancreatitis, followed up by the Department of Pediatric Gastroenterology of Selçuk University between 2011 and 2023. The data of the patients were scanned retrospectively on the hospital automation system and patient files.

The criteria that were set by INSPPIRE were taken as the basis and the types of pancreatitis were identified. The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) Group defined Acute Pancreatitis (AP), Acute Recurrent Pancreatitis (ARP), and Chronic Pancreatitis (CP) in children in 2012. Abdominal pain that was suggestive of pancreatitis, serum Amylase and/or Lipase values more than three-fold the upper limit of normal, at least two of the criteria in imaging findings compatible with AP, at least one of the AP exocrine pancreatic insufficiency, endocrine pancreatic insufficiency, or abdominal pain suggestive of pancreatitis, and presence of radiological imaging findings compatible with CP was accepted as CP. In order to call it ARP, we need at least 2 separate AP episode and at least 1 month without pain or amylase/lipase between episodes values must be fully normalized (6)

The age, gender, height, weight, previous disease, follow-up periods, etiological reasons for the diagnosis, types of pancreatitis, radiological imaging and laboratory results, hospital stays, treatments, and complications that developed in patients were recorded. Measured weight and height values and calculated Body Mass Index (BMI) values were evaluated in percentiles according to age and gender by using the Neyzi Growth Curves. The body weight of the patients was recorded in kilograms and their height in centimeters.

Leukocyte, neutrophil, lymphocyte, and platelet values were recorded in the admission and in the 48th-hour complete blood count. From the full blood test results of the individuals who participated in the study, the number of neutrophils was proportioned to the number of lymphocytes, and the Neutrophil-Lymphocyte Ratio (NLR) values were calculated by dividing the number of PLR platelets by the number of lymphocytes.

The biochemical parameters of the patients who were included in the study, Calcium (Ca), Phosphorus (P), Alkaline Phosphatase (ALP), Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Albumin, Amylase, Lipase, ESR and CRP blood test results were recorded at the time of admission and the 48th hour. It was also recorded on which day of follow-up the Amylase and Lipase values of the patients initiated to decrease, and if they reached normal, on which day they returned to normal. Serum ALT:0-41U/L and AST:0-32U/L were considered normal values. The upper limit of Amylase value was 53 U/L and 67 U/L for Lipase.

In the biochemical parameters of the patients, AST/ALT Ratio was calculated by dividing the ratio of the serum albumin value by the CRP value, Albumin/CRP Ratio (ACR) was calculated by dividing the ratio of the Amylase value by the Lipase value, Amylase/Lipase Ratio (ALR) was calculated by dividing the Lipase value by the Albumin value, Lipase/Albumin Ratio (LAR) was determined by dividing the Amylase value by the Albumin value, Amylase/Albumin Ratio (AAR) was determined by dividing the AST value by the ALT value. The Prognostic Nutritional Index was calculated as follows.

PNI = [10 x Serum Albumin (g/dl)] + [0.005 x Total Lymphocyte Count]

The Systemic Immune Inflammation Index (SII) values of the patients were calculated by using Neutrophil, Platelet, and Lymphocyte values according to the following formula.

SII=N×T/L

As well as blood tests, Abdominal Ultrasonography was performed in the first step to show the etiology and evaluate it for complications, and then Magnetic Resonance Cholangio-Pancreaticography (MRCP) and Upper Abdominal Computed Tomography (CT) were performed, especially in patients whose etiology could not be elucidated.

The treatments of the patients were recorded by scanning the Epicrisis in the hospital automation system and the digital system. The day of treatment and the number of days TPN was given were recorded in patients who were initiated on Total Parenteral Nutrition (TPN). The day on which the treatment was initiated for the patients whose oral intake was stopped and the day on which the diet was switched to the Regimen 3 diet were evaluated. Patients who received octreotide, analgesics, and antibiotics for treatment were also recorded. It was evaluated which antibiotic was given. Which groups of patients needed surgery were also examined.

The revised ATLANTA classification of acute pancreatitis identified two phases of the disease Severity is classified as mild, moderate or severe. Mild acute pancreatitis, the most common form, has no organ failure, local or systemic complications and usually resolves in the first week. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications or exacerbation of co-morbid disease. Severe acute pancreatitis is defined by persistent organ failure, that is, organ failure >48 h. Ransons criteria are one of the earliest scoring systems to assess the severity of acute pancreatitis and continue to be widely used. The original Ranson criteria is a scoring system that uses 11 parameters to assess the severity of acute pancreatitis. The 11 parameters are age, white blood cell count (WBC), blood glucose, serum aspartate transaminase (AST), serum lactate dehydrogenase (LDH), serum calcium, fall in hematocrit, arterial oxygen (PaO2), blood urea nitrogen (BUN), base deficit, and sequestration of fluids. It was recorded how many days the patients needed to stay in the hospital and whether they were admitted to the Intensive Care Unit or not. The complications, on what day they developed, and on what day they regressed were examined and were grouped as mild, moderate, and severe according to Atlanta and Ranson Criteria (11-13).

Statistical Analysis

The IBM SPSS Statistics 23 package program was used for statistical analysis. Descriptive statistics for numerical variables were presented as mean and standard deviation or median and range. Categorical data were presented as % frequency. The Kolmogorov-Smirnov Test was used to examine whether the variables that were used in the analysis showed normal distribution. The Student's T-Test was used in independent groups to examine the relationship between variables with normal distribution in the statistical analysis of binary groups, and Mann Whitney U Test was used for the variables that had non-normal distribution. The cut-off value was determined by using the Youden Index with ROC Curve Analysis. Sensitivity and specificity rates were calculated. The categorical variables were compared by using the Chi-Square Test. The significance level was taken as $p<0.05$.

RESULTS

A total of 156 patients, who were followed up with the diagnosis of acute and Chronic Pancreatitis based on history, clinical, laboratory findings, and radiological imaging in the Department of Pediatric Gastroenterology, Department of Child Health and Diseases, Faculty of Medicine, Selçuk University, were included in the study. According to the diagnostic criteria of INSPPIRE, 129 (82.70%) patients were diagnosed as AP and 27 (17.30%) as CP.

A total of 85 (54.48%) of the patients were girls 71 (45.52%) were boys and the F/M ratio was 1.19. The distribution of the demographic data of the patients is given in **Table 1**.

When the complete blood count results of the patients who participated in the study were examined, leukopenia was detected in 6 (3.84%) of the patients, and all of the patients had AP. Leukocytosis was detected in 64 (41.02%) of the patients, and leukocytosis was detected in only 9 (5.76%) of the patients who had CP. Neutropenia was detected in 6 (3.84%) of the patients, and all of the patients had AP. Thrombocytopenia was detected in 7 of the patients (4.48%), and only 2 of these patients (1.28%) had Chronic Pancreatitis. When the complete blood count results of the patients were examined, the WBC value was found to be 10.33 ±5.06 in patients who had Acute Pancreatitis and 9.72 ±4.04 in patients who had CP. When the WBC values of the patients who participated in the study were compared statistically, no significant differences were detected (p: 0.671). The comparison of the patients' complete blood count results, ESR, CRP, and biochemical values at the time of admission to the hospital and the 48th-hour follow-up according to the type of pancreatitis is given in **Table 2**.

Amylase values were within normal limits in 11 (9.5%) of the patients who were included in the study and Lipase values were within normal limits in 3 (8.9%). The Amylase levels of the patients increased up to 2-fold in 43 (57.1%) patients, 2-5-fold in 40 (11.9%) patients, 5-10-fold in 15 (20.2%) patients, and 20 (78%) patients. It was found to be increased more than 10 times in the patient. The increase rates in ALT, AST, Lipase, and Amylase values of the patients are given in **Table 3**.

When radiological imaging results were evaluated, USI findings were evaluated as normal in 81 (51.92%) of the patients who had AP and in 15 (9.61%) of the patients who had CP. The comparison of the Abdominal USI, CT, and MRI findings of the patients according to pancreatitis types is given in **Table 4**.

When the treatment modalities used were evaluated, 151 (94.79%) patients were initially given oral nutrition and intravenous saline solution that contained sodium concentration appropriate to their ages. Although 124 (79.50%) of these patients were diagnosed with AP, 27 (17.30%) were diagnosed with CP, and this was not found to be statistically significant. The treatments used for the patients and the distribution of clinical results according to pancreatitis types are given in **Table 5**.

When the scores of the patients who had pancreatitis were evaluated in terms of clinical prognosis according to the Atlanta Criteria, 110 (70.50%) of them who had AP had mild, 19 (12.20%) moderate, and 20 (13.30%) of the patients who had CP had mild and 7 (4.50%) had moderate scores. According to the Atlanta Criteria, we did not have any patients in the severe group. When compared in statistical terms, no significant differences were detected (**Table 5**). The Ranson 48th-hour scores were not statistically significant in patients who had AP and CP. However, the Ranson admission score was found to be higher in the patient group with AP than in patients who had Chronic Pancreatitis (p:0.026).

Table 1: The Demographic characteristics of patients according to pancreatitis types

	Acute Pancreatitis	Chronic Pancreatitis	Total	p
	n (%)	n (%)	n (%)	
Gender				0.224
Girl	68 (80.0)	17 (20.0)	85 (54.48)	
Boy	61 (85.90)	10 (14.10)	71 (45.52)	
Age Group				0.362
1-5 age	33 (89.20)	4 (10.80)	37 (23.70)	
6-10 age	29 (76.30)	9 (23.70)	38 (24.40)	
>11 age	67 (82.70)	14 (17.3)	81 (51.90)	
Total	129 (82.70)	27 (17.30)	156 (100.0)	

	Acute Pancreatitis		Non-acute Pancreatitis		Total		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
Age	10.91±5.13	11 (1.0 - 17.0)	10.74± 4.20	11.0 (2.0-17.0)	10.28±4.97	11 (1.0 - 17.0)	0.786
Weight Percentile	29.56±31.93	17.50 (1.0 - 99.0)	31.04±27.41	26.0 (1.0-88.0)	29.84±31.03	18.0 (1.0 -99.0)	0.357
Lenght Percentile	37.79±30.76	20.50 (1.0 - 99.0)	37.59±27.34	32.50 (1.0 -86.0)	32.89±30.12	24.50 (1.0 - 99.0)	0.229
BMI	17.92±4.41	17.03 (11.0-33.79)	17.88±2.62	17.85 (13.78 - 22.21)	18.12±4.62	17.91 (11.0 - 33.79)	0.556

BMI: Body Mass Index

Table 2: Comparison of complete blood count, sedimentation, CRP and biochemical values at the time of admission and 48th hour control according to the type of pancreatitis

	Acut Pancreatitis		Chronic Pancreatitis		p
	Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	
At the time of admission					
WBC (U/L)	10.33 ±5.06	9.4 (1.8 - 29.8)	9.72 ±4.04	8.3 (5.1 - 20.7)	0.671
Neutrophil (U/L)	6.97 ±4.7	5.9 (1.1 - 23.1)	6.5 ±3.92	5.4 (2.7 - 5378)	0.833
Lymphocyte (U/L)	3.36 ±1.90	3.2 (0.3 - 15.0)	3.18 ±1.42	3.1 (0.91- 6.46)	0.860
Plateletes (mm3)	308.85 ±121.83	306 (30 - 835)	331.22 ±116.6	316 (88 - 625)	0.248
CRP (mg/dL)	14.67 ±32.06	3.65 (0.1 - 205)	8.08 ±20.45	1.4 (0.1 - 98)	0.016
Sedimentation	15.19 ±14.87	9.5 (2 - 56)	13.54 ±13.4	10 (2 - 53)	0.846
ALT (U/L)	63.31 ±167.87	17 (3 - 1530)	33.44 ±42.08	15 (7 - 171)	0.797
AST(U/L)	109.67 ±451.19	30 (10 - 4881)	43.89 ±46.79	24 (16 - 227)	0.772
Albumin (g/dL)	4.13 ±0.56	4.2 (2.7 - 5.2)	4.28 ±0.45	4.4 (2.9 - 5)	0.205
Amylase (U/L)	584.27 ±1126.33	232 (22 - 10110)	538.19 ±637.17	227 (128 - 2551)	0.447
Lipase (U/L)	1203.63 ±4138.66	344 (10 - 45552)	943.19 ±1214.18	320 (11 - 4415)	0.826
NLR	2.76 ±2.68	1.68 (0.36-14.0)	2.80 ±2.70	1.87 (0.63-10.2)	0.890
PLR	111.2 ±60.14	93.94 (5.1-341.43)	132.83±95.10	116.87 (20.47- 419.0)	0.556
ACR	3.42 ±8.64	1.12 (0.02 - 48.0)	7.64 ±12.68	2.23 (0.04 - 43.0)	0.006
PNI	41.37 ±5.52	42.02 (27.01 - 52.02)	42.79 ±4.49	44.01 (29.02 - 50.02)	0.225
SII	815.49 ±757.25	520.89 (20.77 - 3794)	950.38 ±974.75	508.65 (55.26 - 4273.8)	0.650
ALR	2.56 ±11.77	0.64 (0.05 - 100.4)	1.74 ±3.57	0.63 (0.19 - 18.73)	0.321
LAR	288.73 ±928.22	89.38 (2.11 - 9902.61)	221.31 ±282.19	73.95 (2.56 - 1003.41)	0.630
AAR	145.13 ±283.39	53.67 (4.23 - 2407.14)	127.18 ±150.27	50.68 (29.77 - 614.7)	0.606
48th Hour Control					
WBC (U/L)	7.66 ±3.44	6.7 (2.3 - 20)	8.31 ±3.34	7.7 (3 - 14.4)	0.319
Neutrophil (U/L)	4.66 ±3.2	3.8 (0.82 - 15.5)	4.74 ±2.22	4.55 (1.2 - 10.7)	0.302
Lymphocyte (U/L)	2.81 ±1.27	2.7 (1.1 - 8.9)	3.27 ±1.68	2.7 (1.45 - 6.85)	0.395
Plateletes(mm3)	292.97 ±115.53	278 (40 - 867)	305.82 ±106.5	317.5 (95 - 462)	0.331
CRP (mg/dL)	20.37 ±41.24	5 (0.1 - 241)	15.59 ±43.33	3 (0.4 - 153)	0.140
Sedimentation	15.68 ±18.47	7 (1 - 68)	8.0 ±11.49	2.5 (2 - 39)	0.232
ALT (U/L)	66.53 ±277.12	14 (3 - 2817)	26.31 ±29.08	11.5 (6 - 110)	0.527
AST (U/L)	93.8 ±563.81	24 (8 - 6111)	35.29 ±28.96	24.5 (11 - 132)	0.978
Albumin (g/dL)	3.76 ±0.49	3.8 (2.5 - 4.9)	3.96 ±0.47	4 (2.6 - 4.6)	0.012
Amylase(U/L)	167.6 ±138.93	130 (15 - 904)	238.89 ±184.82	197 (14 - 829)	0.030
Lipase(U/L)	239.69 ±291.32	150 (4 - 1743)	307.12 ±280.51	234 (5 - 990)	0.081
NLR	1.94 ±1.7	1.51 (0.17 - 10.15)	1.68 ±1.05	1.39 (0.61 - 5.1)	0.971
PLR	119.82 ±71.72	106.26 (30.77 - 619.29)	116.36 ±66.85	99.32 (14.29 - 291.03)	0.838
ACR	3.4 ±8.38	0.71 (0.01 - 42)	2.59 ±3.02	1.27 (0.02 - 10.75)	0.099
PNI	37.75 ±4.77	38.01 (25.01 - 49.01)	39.46 ±5.1	40.03 (26.03 - 46.01)	0.126
SII	568.34 ±559.25	404.69 (44.62 - 3591.86)	548.98 ±466.57	431.87 (64.29 - 2094.14)	0.787
ALR	1.56 ±1.81	0.99 (0.08 - 12.14)	2.91 ±9.46	0.9 (0.15 - 49.2)	0.853
LAR	63.16 ±69.39	39.71 (1.05 - 349.74)	78.8 ±70.58	55.68 (1.22 - 254.74)	0.152
AAR	46.36 ±39.26	32.65 (3.42 - 205.45)	63.25 ±52.6	45.85 (10.73 - 218.16)	0.062

WBC: White Blood Cell, CRP: C Reactive Protein, ALT: Alanin Aminotransferase, AST: Aspartat Aminotransferase, NLR: Neutrophil / Lymphocyte Ratio; PLR: Platelet/ Lymphocyte Ratio; ACR:Albumin/CRP Ratio, PNI:Prognostic Nutritional Index [10 x serum albumin (g/dl)]+ [0.005 x total lymphocite], SII: Systemic Immune Inflammation Index, ALR: Amylase /lymphocite Ratio, LAR: Lipase/Albumin Ratio, AAR: Amylase/Albumin Ratio.

Tablo 3: Increases in ALT, AST, lipase and amylase values and rates of increase of our patients.

	Pancreatitis Type		Total	p	Pancreatitis Type		Total	p
	Acute pancreatitis	Chronic pancreatitis			Acute pancreatitis	Chronic pancreatitis		
ALT								
Normal	107	22	129		98	22	120	
Increase up to 2 times	6	2	8	0.282	6	2	8	
2-5 times increase	6	3	9		12	2	14	0.785
>5 times increase	9	0	9		3	0	3	
AST								
Normal	94	21	115		100	18	118	
Increase up to 2 times	18	3	21		10	5	15	
2-5 times increase	6	3	9	0.273	6	1	7	0.287
>5 times increase	10	0	10		3	0	3	
Amylase								
Normal	11 (8.52)	0 (0)	11 (90.9)		47	7	54	
Increase up to 2 times	43	9	52		47	6	53	
2-5 times increase	40	12	52	0.287	30	11	41	0.075
5-10 times increase	15	1	16		5	3	8	
>10 times increase	20	5	25		0	0	0	
Lipase								
Normal	3 (2.32)	1 (3.70)	4 (2.56)		19	2	21	
Increase up to 2 times	3 (2.32)	1 (3.70)	4 (2.56)		21	0	19	
2-5 times increase	35	7	42	0.983	38	8	46	0.088
5-10 times increase	27	6	33		27	9	36	
>10 times increase	61	12	73		20	7	27	

ALT: Alanin Aminotransferase (U/L); AST: Aspartat Aminotrasferase (U/L). Amylase (U/L), Lipase (U/L).

Table 5: Distribution of Treatments and Clinical Outcomes According to Pancreatitis Types

		Acute Pancreatitis		Chronic Pancreatitis		p
		n (%)		n (%)		
Hidration	-	5 (3.20)		0 (0)		0.298
	+	124 (79.50)		27 (17.30)		
TPN	-	80 (51.30)		21 (13.50)		0.119
	+	49 (31.40)		6 (3.80)		
PPI	-	13 (8.30)		5 (3.20)		0.212
	+	116 (74.40)		22 (14.10)		
Oktreotide	-	87 (55.80)		21 (13.50)		0.290
	+	42 (67.8)		6 (10.2)		
Antibiotics	-	84 (53.80)		22 (14.10)		0.098
	+	45 (26.90)		5 (3.20)		
Analgesics	-	106 (69.30)		21 (13.70)		0.739
	+	21 (13.70)		5 (16.30)		
Surgical procedure	Not required	125 (80.10)		26 (16.60)		0.872
	Required	4 (2.60)		1 (0.70)		
Intensive care hospitalization	Not required	123 (78.80)		26 (16.60)		0.829
	Required	6 (3.80)		1 (0.60)		
Nutrition	Not interrupted	25 (16.40)		7 (4.60)		0.444
	Interupted	104 (68.80)		20 (13.20)		
Complication	No developed	110 (70.50)		22 (14.10)		0.620
	Developed	19 (12.20)		5 (3.20)		
Atlanta score	Mild	110 (70.50)		20 (12.80)		0.156
	Modarate	19 (12.20)		7 (4.50)		
		Mean±SD	Median (Min-max)	Mean±SD	Median (Min-max)	p
Follow-up period		7.98 ±12.28	2.8 (1- 60)	26.3 ±30.11	16.0 (1 - 99)	0.001
Duration of hospitalization		10.53 ±8.24	8.0 (2-50)	9.44 ±7.49	6.0 (2-30)	0.393
Duration of intensive care hospitalization		3.0 ±1.54	2.50 (2-6)	3.0 ±0.01	3.0 (1-3)	0.589
Time to start feeding (day)		3.83±3.15	3.0 (1-23)	3.55±1.95	3.0 (1-8)	0.775
Time to start normal feeding (day)		6.78±5.12	5.0 (2-40)	6.16±3.67	4.0 (3-15)	0.663
Time to start TPN (day)		2.82 ± 3.02	2.0 (1-16)	2.0 ± 1.73	1.0 (1-5)	0.399
Duration of TPN (day)		6.84 ± 5.46	5.0 (2-34)	6.60 ± 2.60	7.0 (4-10)	0.631
On the day when the amylase value starts to decrease		2.69 ±1.99	2 (1 - 14)	2.44 ±1.09	2 (1 - 6)	0.905
On the day when the lipase value starts to decrease		3.11 ±2.58	2 (1 - 18)	2.71 ±1.64	2 (1 - 8)	0.689
The day the amylase value normalises		12.14 ±15.37	5 (1 - 87)	11.38 ±13.03	4.0 (2- 40)	0.807
The day the lipase value normalises		16.63 ±21.18	10.0 (2 - 165)	17.0 ±15.97	11.50 (2- 45)	0.754
Ranson score		0.36±0.68	0 (0-4)	0.07 ±0.26	0 (0-1)	0.026
Ranson 48th hour score		0.19 ±0.41	0 (0-2)	0.07 ±0.26	0 (0-1)	0.155

TPN: Total Parenteral Nutrition, PPI: Proton Pump Inhibitors

Table 4: Comparison of Abdominal Ultrasonography, Computed Tomography and Magnetic Resonance findings according to the type of pancreatitis

	Acute Pancreatitis n (%)	Chronic Pancreatitis n (%)	p
USG Findings			
Normal	81	15	0.311
Biliary sludge	10	3	0.566
Increase in pancreatic size	10	1	0.400
Gallstone	9	2	0.932
Peripancreatic fluid	10	1	0.455
Pancreas could not be valuated	7	2	0.688
Pancretic edema	6	2	0.555
Increased pancreatic echogenicity	5	3	0.121
LAP	5	0	0.298
Choledocal duct width	3	2	0.173
Pancretics cyst	2	1	0.459
Pancreas duct dilatation	0	2	0.002
BT Findings			
Normal	13	2	0.699
Increase in pancreatic size	6	1	0.851
Peripancreatic fluid	2	2	0.133
Pancreas edema	2	0	0.521
Gallstone	2	0	0.521
Pancreas duct dilatation	0	1	0.026
Pancreatic necrosis	1	0	0.651
Pancreas density changes	0	1	0.026
LAP	0	1	0.026
MR Findings			
Normal	45	13	0.205
Increase in pancreatic size	12	5	0.167
Peripancreatic fluid	8	3	0.371
Pancreas duct dilatation	3	7	0.001
Bile duct dilatation	3	5	0.001
Pancreas density changes	5	3	0.124
Gallstone	3	2	0.176
Pancreatic pseudocyst	2	1	0.463
Choledochal cyst	1	0	0.645
Pancreatic necrosis	1	0	0.645
Pancreatic atrophy	0	1	0.029
Pancreas divisium	1	1	0.221

LAP: Lymphadenopathy

When the ROC Analysis made for pancreatitis types was evaluated, Albumin/CRP, 48th-hour Amylase, Lipase, PNI, Albumin/Amylase Ratios, and Albumin values of the patients at the time of admission to the hospital were found to be significant. When the Albumin/CRP Ratio was taken at a cut-off value of 1.60, the AUC value was 0.683 (0.557-0.809), the sensitivity was 65.20%, and the specificity was 70.40%. The ROC Curve Analysis results of the patients who participated in the study according to the pancreatitis types are given in **Table 6**.

DISCUSSION

The number of patients who are diagnosed with pancreatitis has been increasing in recent years with the understanding of the physio-pathogenesis of pancreatic diseases, advances in diagnostic methods, and increased awareness of physicians. The factors that lead to this increase appear to be multifactorial. Patients who are complicated by pancreatitis are increasing in the pediatric population and there are more referrals to tertiary healthcare centers. INSPPIRE Criteria were developed to identify AP, ARP, and CP in pediatric cases (14). Prospective clinical studies are lacking on the natural history of AP and the factors influencing disease progression to CP. In the present study, under what circumstances patients who have AP might progress to CP were investigated.

AP can be detected in all age groups. In a previous study that was conducted by Nydegger et al. with 279 pediatric patients, the median age was reported to be 10 years at presentation, and the number of male patients was found to be 1.4-fold that of female patients (15). Some studies reported that it is more common in female patients. In the study conducted with 130 pediatric patients by Fonseca et al., female patients were found to be 1.65-fold more common than male patients (16). Also, in a meta-analysis study that consisted of 589 patients published in 2016, the average age was found to be 9.2±2.4 years (17). Similarly, in the present study, the average age was found to be 10.91±5.13 years in patients who had AP and 10.74±4.20 years in patients who had CP. No statistical difference was detected in mean age between patients who had AP and CP (p:0.786).

Table 6: The ROC curve analysis results according to the pancreatitis types of the patients participating in the study.

	AUC (%95 CI)	Cut Off	p	Sensitivity (%)	Specificity (%)
Albumin/CRP Ratio	0.683 (0.557-0.809)	1.60	0.006	65.20	70.40
48th hour Amylase	0.633 (0.512-0.753)	237.50	0.030	40.70	82.20
48th hour Lipase	0.618 (0.540-0.696)	202.50	0.021	61.50	64.80
48th hour PNI	0.654 (0.526-0.781)	39.90	0.026	66.70	67.30
48th hour Amylase/Albumin Ratio	0.665 (0.583-0.746)	0.011	0.035	80.00	44.70
48th hour Albumin	0.661 (0.547-0.774)	3.79	0.012	84.00	49.10

In a 12-year study that was conducted by Poddar et al. with 320 patients, it was found that 50% of the patients were diagnosed with AP, 21% with ARP, and 29% with CP. The rate of male patients diagnosed with AP to female patients was 2.4, the rate of male patients diagnosed with ARP to female patients was 1.03, and the rate of male patients who had CP to female patients was 3.2 (18). In a recent study conducted in our country, nearly two-thirds of the patients with acute pancreatitis resolved spontaneously, 30.9% and 4.3% of the cases developed acute recurrent pancreatitis and chronic pancreatitis, respectively. Furthermore, 27.4% patients with acute recurrent pancreatitis progressed to chronic pancreatitis, and eventually, 12.7% of cases developed chronic pancreatitis within 3-4 years. The result of this study confirmed the increased incidence of acute pancreatitis in recent years. Conversely, the length of hospital stay decreased over the years (19). In the present study, the rate of male patients diagnosed with AP to female patients was 0.89, and the rate of male patients who had CP to female patients was 0.59.

The most valuable biochemical markers employed for the diagnosis of pancreatitis are high Amylase and Lipase levels. The sensitivity of high Amylase in the diagnosis of pancreatitis varied between 50% and 85% in pediatric studies. Although high Lipase levels are considered to be more sensitive than Amylase, only high Amylase was detected in some cases of pancreatitis (20). Serum Amylase and Lipase values increased by three-fold the upper limit of normal are always significant. However, there is no relationship between the severity of the inflammatory process and prognosis and Amylase and Lipase levels (21). In a study that was conducted by Werlin et al., the average value was found to be 485 IU/L for Amylase and 1841 IU/L for Lipase (4). In the present study, the Amylase value was found to be 584.27±1126.33 and the Lipase value was 1203.63±4138.66. No statistically significant differences were detected in terms of AP and CP levels in the patients who participated in the study.

The diagnostic value of Amylase is high, especially in the first 24 hours when symptoms begin to appear, and then decrease. Lipase remains at high levels longer than Amylase and is more reliable in the diagnosis of AP. However, as is true for both of them, the level of these enzymes cannot be interpreted for the degree of severity and clinical course of the disease (22). In a study conducted by Sanchez et al., serum Amylase was found to be increased in 85.5% of the patients and Lipase was increased in 87.1% (23). There was a 6-8-fold increase in both enzymes. In another study conducted by Werlin et al., it was observed that serum Amylase was increased in 83% of the patients and Lipase was increased at least 3-fold the upper limit of normal in 82% of patients (4). Four of these patients had abnormal Amylase values vs. normal Lipase values, and 2 patients had abnormal Lipase values vs. normal Amylase values. In the present study, Amylase levels were high in 90.9% of the patients, and Amylase values were normal in 8.52% of the patients who had AP. Lipase was found to be diagnostically high in 97.4% of the patients, and Lipase levels were found to be at normal levels in 2.32% of patients who had AP and 3.70% of patients who had CP. These results were consistent with the literature data. However, as a result of these results, no statistical difference was detected in terms of elevation in patients who had AP and CP.

Lipase begins to rise in the first 6 hours, reaches its peak value in the 24-30th hour, and decreases to normal values after 8-14 days. Amylase begins to rise in 2-12 hours, reaches its peak value in 10-72 hours, and decreases to normal values after 3-5 days (24). In the present study, the average day when Amylase values initiated to decrease was found to be 2.69±1.99 days in patients who had AP and 2.44±1.09 days in patients who had CP. The average normalization of Amylase value was 12.14±15.37 days in patients who had AP and 11.38±13.03 days in patients who had CP. The average day when the Lipase values initiated to decrease was 3.11±2.58 days in patients who had AP and 2.71±1.64 days in patients who had CP. The average Lipase value normalization was 16.63±21.18 days in patients who had AP and 17.0±15.97 days in patients who had CP. Similar to previous studies, the Lipase value was normalized over time. According to these results, Amylase and Lipase values initiated to decrease in patients who had AP and CP, and no statistically significant differences were detected in terms of normalization times.

Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and SII are ideal and easily available and low-cost biomarkers that can be calculated from laboratory parameters at the time of application and were identified as inflammatory prognostic biomarkers in some malignant and inflammatory diseases (including AP) for adults (10). SII, which is calculated by Neutrophil, Platelet, and Lymphocyte counts, is a novel marker that reflects the balance between immune and inflammatory states. First identified in patients who had hepatocellular carcinoma, SII was used in adult AP patients in 2021 and was reported to be a better marker than NLR in the early prediction of the development of serious disease (25, 26). In the present study, whether these biomarkers could be used to differentiate AP and KP in children was investigated. As a result of the study, no significant differences were detected in NLR, PLR, SII, and Prognostic Nutrition Index (PNI) values in differentiating AP and CP at the time of hospital admission and in the 48-hour blood levels of the patients.

Scoring systems are underway to predict the prognosis of pediatric patients who have AP. CRP levels are also considered an important test in showing the prognosis

of the disease as a positive acute phase reactant increased in many infections and autoimmune diseases. Albumin is a negative acute phase reactant and has an inverse correlation with the severity of inflammation in various diseases (27). A CRP level above 15 mg/dL at the 48th hour of an AP attack is an indicator of poor prognosis (28). In patients who are diagnosed with pancreatitis, elevated leukocyte counts and ESR also provide the clinician with an idea about the severity of the disease. In a previous study conducted by Kaya et al. with 199 patients, it was reported that leukocytosis and CRP elevation were important markers in predicting prognosis (29). In the present study, leukocytosis was detected in 64 (41.02%) of the patients, and leukocytosis was detected in only 9 (5.76%) of the patients who had Chronic Pancreatitis. In a previous study, the frequency of leukocytosis was reported to be 32.9% in patients who had AP (30). CRP elevation was detected in 41.66% of the patients and was detected in only 5 (18.51%) of the patients who had CP. In the present study, these results were compatible with the literature data. A statistically significant difference was detected in distinguishing patients who had AP and CP in terms of CRP elevation at the time of admission to the hospital.

In previous studies, the CRP/albumin ratios were found to be a more sensitive marker in many diseases, from malignancies to cardiovascular diseases, from infections to autoimmune diseases (27). A better understanding of the value of Albumin in predicting the chronic course and prognosis of the disease and the role of CRP in the acute period and in monitoring inflammation leads to the idea that the CRP/Albumin Ratio might be considered a more sensitive biomarker. In immunocompetent patients, as the severity of inflammation increases, cytokine storm occurs more frequently and secondary CRP production increase in hepatocytes becomes inevitable. The negative effects of cytokine increase on albumin production are well-known. CRP/Albumin Ratio appears as a biomarker that can be used in the follow-up and prognosis of patients. In the present study, the Albumin/CRP Ratios were evaluated in patients who had AP and CP. According to our results, it was found that the levels at the time of admission to the hospital were statistically significant in patients who had AP and CP and that when the cut-off value for the albumin/CRP ratio was taken as 1.60 (AUC: 0.683), the sensitivity and specificity were 65.20% and 70.40%, and patients could turn into CP. Also, blood albumin levels taken at the 48th hour were statistically higher in patients who had CP than in patients who had AP. The 48th-hour Amylase levels of the patients were determined to be higher in patients who had Chronic Pancreatitis than in patients who had Acute Pancreatitis. When ROC Analysis was used to determine which patients who had Acute Pancreatitis would become chronic in the patients who participated in the study, the sensitivity was found to be 40.70% and the specificity was 82.20% (with the 48th-hour Amylase level cut-off value as 237.50) (AUC: 0.633).

USI is the imaging method employed as the first choice in the diagnosis of pancreatitis because it is a non-invasive and reliable diagnostic tool. Increased pancreatic size, pancreatic edema, peripancreatic fluid, increased pancreatic echogenicity, and pseudocyst are findings in favor of pancreatitis (31). USI is also a successful examination for imaging the biliary system and gallbladder. The presence of dilatation in the biliary system provides the clinician with clues about causes such as distal obstruction, gallstones, or choledochal cysts. Considering that ultrasonography findings might be normal, the sensitivity of USI varies between 62-95% in the diagnosis of acute pancreatitis (32). In the study that was conducted by Werlin et al., USI was performed in 50% of the patients who had suspected pancreatitis and 75% were evaluated as normal. Pancreatic edema, peripancreatic fluid, gallstones, or sludge were the most common findings in favor of pancreatitis (12). USI will be performed electively and will provide a better evaluation unless the case is an emergency. USI findings were evaluated as normal in 96 (61.53%) of our patients. US findings in patients who had CP are generally nonspecific. Increased pancreatic size or atrophy, calcification, pancreatic duct dilatation or irregularity, pseudocyst, and bile duct dilatation are the findings that can be observed (33). USI findings of patients who had CP were evaluated in the study that was conducted by Alpern et al., and heterogeneity and increased echogenicity was detected in 53% of the patients, focal or diffuse growth was detected in 41%, pseudocyst was detected in 21%, and hypoechoic mass in the head of the pancreas was detected in 7% (34). In the present study, dilatation in the pancreatic duct was detected in 2 (7.40%) patients who had CP and it was statistically significant when compared to AP.

Abdominal CT is more valuable in the diagnosis and determining complications when compared to the ultrasound. The frequency of CT examination in patients who have AP was reported as 60%, and CT imaging is avoided to protect patients from ionizing radiation (30). CT is used when USI is inadequate or when the anatomical definition is more necessary in Acute Pancreatitis. It is especially sensitive in detecting pancreatic necrosis and imaging the spread. Its sensitivity is approximately 92% and its specificity is approximately 100% (29). In the study that was conducted by Urszula et al. with pediatric pancreatitis patients, CT imaging was performed in 73% of the patients, pancreatic edema was detected in 38%, gallstones, bile sludge, and Cholecystitis in 17%, and necrosed pancreas was detected in 6% (30). CT imaging was normal in 15 patients (9.61%), and only 2 of these patients (7.40%) were diagnosed

with Chronic Pancreatitis. In the study that was conducted by Werlin et al., 46% of the patients who had AP and ARP were examined with CT, findings of pancreatitis were detected in 52%, and pancreatic edema, peripancreatic fluid, and gallstones were most frequently detected (4). Pancreatic or intraductal calcifications on CT are pathognomonic findings of CP. Dilated or irregular pancreatic duct is detected with a frequency of 70% (35). In a previous study that was conducted by INSPPIRE, CT was performed for 60% of patients who had CP, and pancreatic duct dilatation was detected in 61%, duct irregularity in 55%, atrophy in 38%, and calcification in 14% (6). In the present study, the occurrence of pancreatic duct enlargement, pancreatic density change, and LAP in patients who had CP compared to patients who had AP was found to be statistically significant.

MRI shows inflammation in the pancreas earlier than other imaging methods and is often used in the etiology rather than the diagnosis (36). MRI has no risks of ionizing radiation and is sensitive in distinguishing between normal parenchyma and inflamed tissue, but because of the long examination time, sedation is required, especially if the children are under five years of age, and it is insufficient for imaging calcifications. Edema, necrosis, and signal increase in peripancreatic fat tissue, pseudocyst, and peripancreatic collection might be observed in the pancreas in this regard. All patients who were diagnosed with CP and AP underwent MRI imaging. It was found to be normal in 58 (37.17%) of the patients. Pancreatic duct dilatation, bile duct dilatation, and pancreatic atrophy were detected more frequently in the patients who had CP than in patients who had AP at statistically significant levels. These results show the superiority of MRI and CT over USI in the investigation of etiology, complications, and chronicity.

Oral intake must be stopped to rest the pancreas in patients who are diagnosed with pancreatitis while the etiology is investigated in the first stage. Then, fluid replacement therapy is initiated to prevent complications (12). In the present study, 151 (96.80%) of the patients were initially given oral intake and intravenous saline solution that contained sodium concentration appropriate for their ages. In a previous study that was conducted by Appak et al., oral intake was stopped in all patients at admission and was resumed within a median of four days (1-48 days) (37). Similar to the present study, oral intake was initiated within a median of three days (1-23 days). When the transition to Nutrition Regimen 3 time of the patients was examined, the average time was found to be 6.78±5.12 days in patients who had AP and 6.16±3.67 days in patients who had CP, and it was not at a statistically significant level. In the study conducted by Appak et al., TPN was initiated in 32.2% of the patients and was given for an average of 15.1± 12.6 days (37). In the present study, 55 (35.2%) of the patients received TPN. The average time to initiate TPN was 2.82±3.02 days in patients who had AP and 2.0±1.73 days in patients who had CP. No significant differences were detected when the TPN initiation times of the patients and the time they received TPN were compared according to the type of pancreatitis. When other treatment methods were evaluated, no significant differences were detected in patients who had AP and CP.

CONCLUSION

The incidence of pancreatitis has been increasing in recent years. Pancreatitis complaints might vary depending on the age group at admission. The disease must first be suspected to make a diagnosis. Laboratory findings and radiological imaging give clues about the differential diagnosis of pancreatitis and the prognosis of the disease at the time of admission. Establishing standard approaches to early diagnosis and treatment of patients and their implementation will improve the prognosis and prevent complications. More pediatric studies are needed to develop a scoring system to be used in the childhood age group and to find the most effective treatment methods.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selcuk University Faculty f Medicine Ethics Committee (Decision No:2023/467).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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