Carbohydrate antigen 19-9 levels in early acute pancreatitis

Akut pankreatitte karbonhidrat antijen 19-9 seviyeleri

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Background and Aims: *There are many etiologic factors responsible for acute pancreatitis. Carbohydrate antigen 19-9 is a well-known tumor marker for gastrointestinal malignancies, especially pancreaticobiliary cancer. Carbohydrate antigen 19-9 levels also increase benign events such as cholestasis. Therefore, the purpose of this study is to retrospectively investigate the relationship between the underlying etiologies and carbohydrate antigen 19-9 levels in patients who were hospitalized due to acute pancreatitis.* ***Materials and Methods:*** *We retrospectively analyzed the data of 109 patients who had increased carbohydrate antigen 19-9 levels in the first 24 hours during hospitalization. Additionally, we divided the patients into two groups, namely biliary and nonbiliary, based on their recent diagnoses in the etiologies of acute pancreatitis.* ***Results:*** *We detected increased carbohydrate antigen 19-9 levels (more than 37 U/mL) in 63 (92%) of the patients in the biliary group, and in 8 (19%) of the patients in the non-biliary group (p <0.001). There was a statistically significant difference between the groups regarding the mean carbohydrate antigen 19-9 values (164.5 vs. 24.1 U/mL, respectively; p <0.005). Also, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and direct bilirubin values were statistically different between the two groups (p <0.05). The receiver operating characteristic curve analysis suggested that the optimum carbohydrate antigen 19-9 level cut-off point for the prediction of pancreatitis caused by biliary reasons was 39.6 U/mL, with a sensitivity and specificity of 92.6% and 85.4%, respectively.* ***Conclusion:*** *High levels of carbohydrate antigen 19-9 (especially above 39.6 U/mL) in patients with acute pancreatitis may be associated with biliary acute pancreatitis.*

Keywords: *Acute pancreatitis, pancreatic diseases, biliary tract diseases, carbohydrate antigen 19-9*

Giriş ve Amaç: *Akut pankreatit için birçok etiyolojik faktör bulunmaktadır. Karbonhidrat antijeni 19-9, gastrointestinal malignitelerde, özellikle pankreatikobiliyer kanserde iyi bilinen tümör belirtecidir. Karbonhidrat antijeni 19-9 seviyeleri ayrıca kolestaz gibi iyi huylu hadiselerde de artış gösterir. Bu nedenle akut pankreatit nedeniyle hastanede yatan hastalarda altta yatan etiyolojiler ile karbonhidrat antijeni 19-9 düzeyleri arasındaki ilişkiyi retrospektif olarak araştırmayı amaçladık.* ***Gereç ve Yöntem:*** *Hastanede yatış sırasında ilk 24 saatte karbonhidrat antijeni 19-9 düzeyi bakılan 109 hastanın verilerini retrospektif olarak inceledik. Hastalar akut pankreatit etiyolojisindeki son tanılarına dayanarak biliyer ve non-biliyer olarak iki gruba ayrıldı.* ***Bulgular:*** *Biliyer gruptaki hastaların 63'ünde (%92), non-biliyer gruptaki hastaların 8'inde (%19) karbonhidrat antijeni 19-9 düzeyi 37 U/mL'den yüksek saptandı (p <0.001). Gruplar arasında ortalama karbonhidrat antijeni 19-9 değerleri açısından istatistiksel olarak anlamlı fark vardı (164.5'e karşı 24.1; p <0.005). Ayrıca aspartat aminotransferaz, alanin aminotransferaz, total bilirübin ve direkt bilirübin değerleri iki grup arasında istatistiksel olarak farklıydı (p <0.05). Receiver operating characteristic eğri analizinde, biliyer nedenlerden dolayı pankreatitin öngörülmesi için optimum karbonhidrat antijeni 19-9 seviyesi kesme noktasının sırasıyla %92.6 ve %85.4 duyarlılık ve özgüllük ile 39.6 U/mL olduğunu görülmüştür.* ***Sonuç:*** *Akut pankreatitli hastalarda yüksek karbonhidrat antijeni 19-9 (özellikle 39.6 U/mL'nin üzerinde) düzeyleri, biliyer nedenli akut pankreatitle ilişkili olabilir.*

Anahtar kelimeler: *Akut pankreatit, pankreas hastalıkları, safra yolu hastalıkları, karbonhidrat antijeni 19-9*

INTRODUCTION

Acute pancreatitis is an inflammatory occurrence of the pancreas that is characterized by the elevation of pancreatic enzymes such as amylase and lipase. In our country, despite regional differences in etiology, gallstones and alcohol consumption (60-80%) are the two most common causes of acute pancreatitis (1-3). The development of new technology and new laboratory tests has decreased the number of idiopathic cases; however, this rate is still around 10–30% (1-3).

For the cases of acute pancreatitis, it is crucial to determine the etiology to regulate the treatment and determine the need for endoscopic retrograde cholangiopancreatography (ERCP). Until now, there has been not a single laboratory test to distinguish between stasis-induced mechanical (biliary) pancreatitis and nonmechanical (nonbiliary) pancreatitis. There are so many developed scoring systems, which are not easy to use in the routine clinical practice because they are complicated and include many

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Binicier ÖB, Paköz ZB. Carbohydrate antigen 19-9 levels in early acute pancreatitis. The Turkish Journal of Academic Gastroenterology 2020;19:5-10.
DOI: 10.17941/agd.728662

Manuscript received: 09.12.2019 • **Accepted:** 17.04.2020

akademik gastroenteroloji dergisi 2020; 19(1): 5-10

laboratory data and imaging methods (4,5). Carbohydrate antigen (CA) 19-9 is one of the most frequently used tumor biomarkers in gastrointestinal malignancies, especially pancreaticobiliary cancer. In the literature, many studies have demonstrated that CA 19-9 levels were increased in the benign events with cholestasis apart from pancreaticobiliary cancer (6-10). CA 19-9, a sialyl Lewis-A blood group antigen, is defined by a murine monoclonal antibody against a colorectal carcinoma epithelial cell (11). This carbohydrate antigen may also exist in benign events, just as it is shown in pancreatic or biliary ductal epithelium cancers (11-13). Increased CA 19-9 levels do not differentiate between benign and malignant patients with obstructive jaundice. CA 19-9 levels were also found to be increased in other biliary tract–related diseases such as cholecystitis, cholangitis, choledocholithiasis, primary biliary cirrhosis, viral hepatitis, and pancreatitis (9,14-19). High levels of CA 19-9 have also been reported in the case reports of respiratory, rheumatologic, renal, and infectious diseases (20-22).

The purpose of this retrospective study is to investigate the relationship between the underlying etiologies of acute pancreatitis and CA 19-9 levels.

MATERIALS and METHODS

Patient Selection and Data Collection

In this study, we included the patients who were admitted to the emergency department of our hospital between June 2018 and December 2019 with complaints of abdominal pain and patients who were diagnosed with mild or moderate acute pancreatitis and aged more than 18 years old. Of the 421 patients reviewed, 121 patients had higher CA 19-9 levels as well as standard blood tests within the first 24 hours after admission due to the suspicion of obstruction or malignancy in the biliary tract. Table 1 summarizes the inclusion and exclusion criteria of this study. After following the exclusion criteria, we included the remaining 109 patients in this study.

We determined the etiologies of acute pancreatitis according to medical history, laboratory findings, imaging methods (ultrasonography, computerized tomography (CT), magnetic resonance imaging, endoscopic ultrasonography (EUS) and ERCP) and, if necessary, pathology results.

The local ethical committee of XXX hospital (No: 2019/4-22) approved this study's protocol.

Statistical Analysis

We expressed continuous and categorical variables as mean ± standard deviation and percentage, respectively. We used chi-square test to compare the categorical values and the Mann–Whitney U test to compare the continuous variables between the groups. Moreover, we used the receiver operating characteristics (ROC) curve to determine the level of CA19-9 to differentiate the mechanical and nonmechanical causes with an optimum sensitivity and specificity. Thereafter, we obtained area under curve (AUC), positive (PPV) and negative predictive (NPV) values. We conducted statistical analysis of the study by using SPSS 22.0 (IBM Statistical Package for Social Sciences software version 22). $P<0.05$ was considered as statistically significant for this study.

Table 1. The inclusion and exclusion criteria

Inclusion Criteria
• More than 18 years old
• Abdominal pain
• Amylase or lipase > three times upper normal limit
• Onset of abdominal pain within 24 hours
Exclusion Criteria
• Pneumonia
• Rheumatologic disease
• Renal disease
• Malignancy
• Chronic pancreatitis
• Trauma
• Surgery
• Post-ERCP pancreatitis

ERCP: Endoscopic retrograde cholangiopancreatography.

RESULTS

Baseline Characteristics of the Study Population

We included 109 patients (58 females and 51 males) in this study. There were 68 (62%; 34 females, 34 males) patients in the biliary acute pancreatitis (BAP) group and 41 (38%; 24 females, 17 males) patients in the nonbiliary acute pancreatitis (NBAP) group. There was no statistically significant difference between the groups regarding sex distribution ($p=0.387$). Additionally, the mean age of the patients had a statistically significant difference between these groups (63 vs. 54 years; $p=0.007$) (Table 2).

Table 2. Demographic characteristics and laboratory findings of patients

	(BAP) (n = 68)	(NBAP) (n =41)	p
Sex			
Male, n (%)	34 (50%)	17 (41.4%)	0.387
Female, n (%)	34 (50%)	24 (58.6%)	
Age (years), mean±std	63±15	54±17	**0.007**
Mean CA 19-9 (U/mL) (range)	164.5 (3.7-1098.7)	24.1 (0.8-101.9)	**< 0.005**
Positive CA 19-9 (> 37 U / mL), n (%)	63 (92%)	8 (19%)	**< 0.001**
Amylase (U/L), mean±std	1,666±1098	1,234±986	0.176
Lipase (U/L), mean±std	3,337±2627	3,735±4058	0.687
AST (U/L), mean±std	294±273	151±210	**< 0.05**
ALT (U/L), mean±std	262±216	97±132	**< 0.05**
Total bilirubin (mg/dL), mean±std	4±3	1.2±1.17	**< 0.05**
Direct bilirubin (mg/dL), mean±std	2.3±1.89	0.42±0.67	**< 0.05**
White blood cell (/mm^3), mean±std	14,147±19811	11,424±3383	0.621
Hematocrit (%), mean±std	40.4±5	41.5±7.3	0.788
Glucose (mg/dL), mean±std	136±41	142±47	0.548
LDH (U/L), mean±std	341±219	343±182	0.827
CRP mg/L, mean±std	89±85	94.8±78	0.724

BAP: biliary acute pancreatitis; NBAP: Nonbiliary acute pancreatitis; std: Standard deviation; CA: Carbohydrate antigen; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; CRP: C-reactive protein.

CA-19-9 Levels Between the Groups and Cut-off Value for Prediction

We detected CA 19-9, more than 37 U/mL (normal range of CA 19-9: 0–37 U/mL), in 63 (92%) patients of the BAP group, and in 8 (19%) patients of the NBAP group, (p<0.001). There was also a statistically significant difference between the groups regarding mean CA 19-9 values (164.5 vs. 24.137 U/mL; p<0.005). Figure 1 shows the boxplot representation between the groups.

The ROC curve analysis suggested that the optimum cut-off point of CA 19-9 level for the prediction of pancreatitis because of mechanical reasons was 39.6 U/mL, with a sensitivity and specificity of 92.6% and 85.4%, respectively (AUC: 0.925, PPV: 91.3%, NPV: 87.5%) (Figure 2).

Other Laboratory Findings

We have also analyzed the other laboratory parameters. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and direct bilirubin values were statistically different between the groups (p<0.05). However, amylase, lipase, white blood cells, hematocrit, glucose, lactate dehydrogenase, and C-reactive protein values were not statistically different between the groups (Table 2).

Tables 2 and 3 summarize the demographic data of the patients and baseline characteristic findings at the time of presentation.

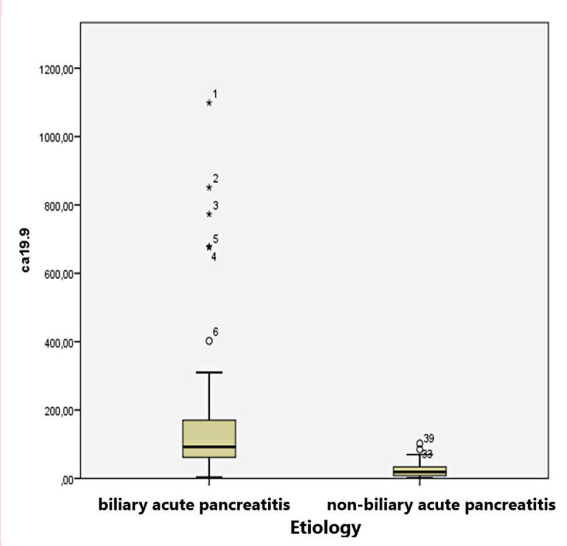

Figure 1. The boxplot representation of carbohydrate antigen (CA) 19-9 levels in biliary acute pancreatitis and nonbiliary acute pancreatitis.

Table 3. Characteristics of the patients who were included in the study	
Patient Groups	**% (n)**
Biliary acute pancreatitis	**62% (68)**
• Bile duct stones	53% (58)
• Diverticulum compression in the common bile duct	4% (5)
• Common bile duct structure	4% (5)
Nonbiliary acute pancreatitis	**38% (41)**
• Idiopathic	11% (12)
• Toxic causes (alcohol)	11% (12)
• Metabolic causes (hyperlipidemia, hypercalcemia, etc.)	7% (8)
• Drug	4% (4)
• Infection	3% (3)
• Congenital pancreatic duct anomaly (pancreas division)	2% (2)

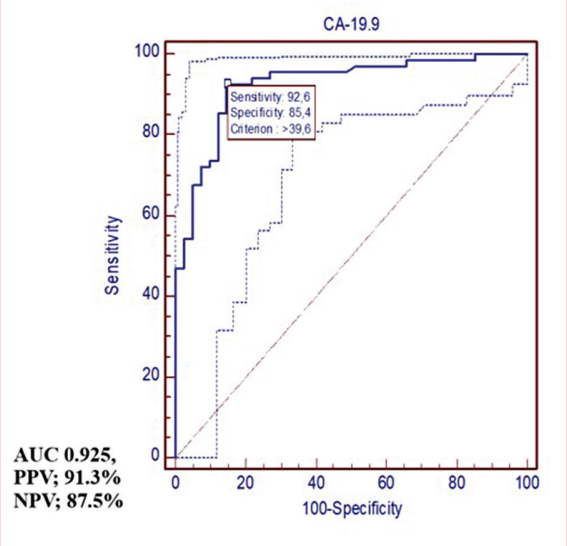

Figure 2. ROC curve for carbohydrate antigen 19-9 sensitivity and specificity (cut-off value: 39.6).

DISCUSSION

BAP are the most common causes of acute pancreatitis in our country (1-3). When we examined the etiologies of 421 patients with mild and moderate pancreatitis admitted to our center in the last two years, 53% of the patients had gallstones, 11% had a history of alcohol consumption, and 36% had idiopathic and other causes. There is no single biochemical marker for the detection of gallstones in the common bile duct, which is the most common cause of acute mechanical pancreatitis. Alkaline phosphatase (ALP), direct bilirubin, gamma-glutamyl transferase levels are the reliable markers for common bile duct stones; however, it is still possible to obtain false positive and negative results with them. A prospective study by Al-Jiffry et al. (4) concluded that ALP >200 IU, ALT >220 IU, bilirubin above the normal range, suggest common bile duct stones in 69.7%, 62%, and 63% of the cases, respectively. Another prospective study by Videhult et al. (23) demonstrated that gallstone was found in the common bile duct of less than half of the patients who underwent cholecystectomy with ALP and bilirubin elevation, and who had intraoperative cholangiography. Al-Jeffrey, Sherman, et al. (4,5) have also developed scoring systems to predict the presence of gallstones in the common bile duct; however, these scoring systems are complex because they use many laboratory data and imaging methods.

CA 19-9 has a sensitivity of 70-80% and a specificity of 80-90% in the diagnosis of pancreatic cancer in various studies (24,25). CA 19-9 is a commonly used tumor marker in clinical practice. Its primary role is in the follow-up of palliative chemotherapy and curative surgery in hepatobiliary and pancreatic cancers. However, CA 19-9 levels increase in various benign events, which limit their sensitivity. In addition to pancreaticobiliary cancers, high CA 19-9 levels can be detected in the cancers of esophagus, stomach, and colorectal system (26-29). There are some studies about CA 19-9 levels in patients who develop stasis in the bile ducts due to benign and malignant events and provided drainage (6-8,10,30). Marrelli et al. (7) investigated 128 patients admitted with obstructive jaundice (87 pancreaticobiliary malignancy and 41 benign events) and concluded that CA 19-9 level was higher in 61% of benign cases, and 86% of malignant cases. Furthermore, CA 19-9 levels decreased in all benign cases

and 50% of malignant cases after biliary drainage. Also, the value of more than 90 U/ml of CA 19-9 levels after drainage mostly indicated malignant events (7). Another study by Kim et al. (6) showed that CA 19-9 levels of more than 37 U/mL was detected in 90% of malignant and 59% of benign diseases. The mean CA 19-9 level was 442.4 U/mL in malign cases and 67.4 U/mL in benign cases. These data indicate that CA 19-9 level is a predictive marker in the clinical events with stasis in bile ducts.

The literature does not have enough studies regarding the relationship between CA 19-9 levels and acute pancreatitis. Teng et al. (31) evaluated CA 19-9 levels in 693 of 1609 patients with acute pancreatitis, and they detected CA 19-9 levels above 37 U/mL in 186 (26.8%) patients. They also noted that CA 19-9 levels were not correlated with the severity of pancreatitis. In this study, CA 19-9 level was found to be higher in 53.8% of patients with gallstone-induced acute pancreatitis, in 11.3% of patients with alcohol-induced acute pancreatitis, and in 7.5% of patients with hypertriglyceridemia-induced acute pancreatitis. However, it was not stated when CA 19-9 level assessments were performed in the respective study. In our study, we divided the patients into two groups. The first group included patients with pancreatitis due to any mechanical obstruction (BAP) in the biliary tract, whereas the second group included patients with nonmechanical or idiopathic pancreatitis (NBAP). In addition to AST, ALT, and bilirubin values, CA 19-9 levels were found to be significantly higher in the BAP group (164.5 vs. 24.1 U/mL, respectively; $p < 0.05$). We found that 92% of the patients in the BAP group and 19% of the patients in the NBAP group had CA 19-9 levels greater than 37 U/mL. Also, according to the ROC curve analysis, when the cut-off value of CA 19-9 is 39.6 U/mL, it is possible to say that pancreatitis is related with a mechanical cause (BAP) with sensitivity and specificity of 92.65% and 85.37%, respectively.

Despite the advances in technology and laboratory techniques, idiopathic pancreatitis cases still occur at high rates in acute pancreatitis (32). In our study, 12 (11%) of the cases were diagnosed with idiopathic acute pancreatitis. The CA 19-9 levels of eight of the 41 patients in the NBAP group were more than 37 U/ml. Most of these patients were diagnosed with idiopathic acute pancreatitis. We conducted MRCP in all the patients with idiopathic acute pancreatitis, but did not detect any pathology. We did not perform EUS because these patients did not have a history of recurrent pancreatitis. Patients with high levels of CA 19-9 were diagnosed with idiopathic pancreatitis; however, their imaging modalities were normal. While treating patients with high levels of CA 19-9, we must question whether the high levels are caused by mechanical causes such as microlithiasis, diverticulum at the papilla level, or stricture of common bile duct.

Although the relationship between cholestasis and levels of CA 19-9 cannot be fully explained, the hypothesis states that the epithelial cells in the bile ducts in the cholestatic events involve an excessive mucin secretion and secretion includes CA 19-9 epitopes. This situation can be explained by a dramatic decrease in CA 19-9 after drainage in the benign events. In malignant events, proliferating cells of the tumor play an essential role, and CA 19-9 levels are high due to excessive production (10).

There are some limitations in our study. Our study is a retrospective study and we excluded the cases if their medical records were absent. Of the 421 patients with mild and moderate acute pancreatitis, only 121 patients had records of CA 19-9 levels in 24 hours after admission to the hospital. After following exclusion criteria, we included 109 patients in the study. We found that ERCP, percutaneous drainage, or surgery were performed in all the patients who were included in the study and diagnosed with BAP. However, because most of the patients did not have higher CA 19-9 values after the regression of pancreatitis or procedures, no comparison was made according to the baseline values.

In conclusion, in patients with acute pancreatitis with high levels of CA 19-9 (especially above 39.6 U/mL), it is possible to say that it is highly related to BAP. Especially in patients with idiopathic pancreatitis, it is appropriate to evaluate ERCP or EUS even if ultrasonography, CT, or MRCP is normal. In cases with normal CA 19-9 levels, we may say that we are confronted with a non-mechanical (NBAP) clinical event. We think that non-biliary causes such as hyperlipidemia, alcohol usage, drug use, toxin, and infectious diseases should be investigated firstly in these patients. Finally, prospective studies are needed to evaluate higher CA 19-9 levels after the drainage of biliary tract and after management of pancreatitis.

"The authors declared that there is no conflict of interest regarding the publication of this article."

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