

**Akut Biliyer Pankreatit Hastalarında ERCP Gereksinimi Tahmin Edilebilir mi?**

**Can ERCP Requirement be Predictable in Patients with Acute Biliary Pancreatitis ?**

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**Özet**

**Giriş:** Akut biliyer pankreatitin (ABP) en sık nedeni safra kesesi taş hastalığıdır. Hastaların büyük çoğunluğunda taşın düşmesi sonucu spontan iyileşme gözlenirken, düşmediği durumlarda ERCP ve sfinkterotomi işlemi ile taşın çıkartılması gerekebilir. Hangi hastada taşın spontan düşüp-düşmeyeceğini önceden bilmek mümkün değildir. Bu nedenle ERCP kararı medikal tedavi sırasında klinik durum ve laboratuvar değerlerine göre belirlenmektedir. ERCP yapılmasına gerek duyulabilecek hastaların bilinmesi klinisyen açısından öngörü sağlayacağı ve daha planlı bir tedavi sağlayacağı aşikardır. Bu çalışmada ERCP yapılacak hastaları belirleyecek prediktif değerlerin belirlenmesi amacıyla planlanmıştır.

**Gereç ve Yöntem:** ABP nedeniyle tedavi edilen 179 hasta retrospektif olarak değerlendirildi. Hastalar ERCP yapılan (ERCP) ve spontan gerileyen (MEDİKAL) olmak üzere iki gruba ayrıldı. Hastaların demografik verileri, komorbid hastalıkları, biliyer ranson değerleri, biyokimyasal ve hemogram parametreleri ilk başvuru anında ve 48 saat (h) sonra kaydedildi.

**Bulgular:** Grup MEDİKAL 160, grup ERCP ise 19 hastadan oluşmaktaydı. Gruplar arası değerlendirmede yaş ERCP grubunda farklı bulunurken, cinsiyet, biliyer ranson ve komorbid hastalıklarda fark bulunmadı. ROC analizinde amilaz (24h) <104.5, amilaz (48h) < 123.5, total bilirubin (48h) <2.15, direk bilirubin (48h) <1.45, kreatinin (48h) < 0.75 olan hastalarda ERCP yapılmasına gerek olmadığı anlamlı bulundu. 48 h deki lojistik regresyon analizi sonucuna göre amilaz değeri yüksek olan hastada 7.032, direk bilirubin değeri yüksek olan hastada 6.710, beyaz küre değeri yüksek olan hastada 4.287 kat fazla ERCP endikasyonu olduğu gösterildi.

**Sonuç:** ERCP yapılması gereken hastaları belirlemek için ilk 24 h'de amilaz değeri, 48 h'de ise amilaz, direk bilirubin, beyaz küre değerleri prediktif değer olarak kullanılabilir.

**Anahtar Kelimeler:** akut biliyer pankreatit, ERCP, prediktif değer

## Abstract

**Introduction:** Gallstone disease is the most common cause of acute pancreatitis. In many patients, spontaneous recovery is common after dropping of the stones into the common bile duct. Whereas, endoscopic retrograde cholangiopancreatography or sphincterotomy may be necessary to remove the stone in some cases where spontaneous dropping did not occur. It is unpredictable in which situations these gallstones will drop spontaneously. Therefore, the decision to perform an ERCP is generally depended on the clinical course and laboratory work-up. It is obvious that early prediction of the ERCP during admission will provide improvisation of a structured treatment plan. The present study sought to determine whether ERCP requirement might be predicted by some certain parameters in patients with gallstone disease.

**Patients and methods:** Clinical records of a total of 179 patients with acute biliary pancreatitis (ABP) were retrospectively evaluated. Patients were divided into two groups as to receive ERCP (ERCP group – 19 patients) or have spontaneous recovery (Medical Group – 160 patients). Study data included demographics, history of comorbid diseases, biliary Ranson Scale Scores and laboratory findings. Parametric data were recorded on admission into the hospital and the assessments were repeated at 48<sup>th</sup> hour of admission.

**Results:** Baseline characteristics including gender, biliary Ranson Scale Score and

frequency of comorbidities were similar between two groups whereas age was significantly higher in ERCP group. ROC analysis revealed that ERCP was significantly unnecessary in patients with an amylase level <104.5 at 24<sup>th</sup> hour or <123.5 at 48<sup>th</sup> hour, total bilirubin <2.15 at 48<sup>th</sup> hour, conjugated bilirubin <1.45 at 48<sup>th</sup> hour or creatinine <0.75 at 48<sup>th</sup> hour. Logistic regression analysis revealed that risk of ERCP requirement was 7.032 fold higher in patients with high amylase levels, 6.710 fold higher in patients with high bilirubin levels, 4.287 fold higher in patients with high white blood cell count at 48<sup>th</sup> hour.

**Conclusion:** ERCP requirement in gallstone disease may be predicted by amylase levels at 24<sup>th</sup> hour and by amylase, conjugated bilirubin and white blood cell count at 48<sup>th</sup> hour of admission.

**Keywords:** Acute biliary pancreatitis, ERCP, predictive value.

## Introduction

Acute pancreatitis (AP) is an autodigestive, non-bacterial inflammatory process developing as a consequence of activation of the pancreatic enzymes. Annual incidence of AP ranges from 5 to 80 persons per 100,000 population. Although it may be encountered at any age, it is quite more common at 6<sup>th</sup> and 7<sup>th</sup> decade of life [1, 2]. Gallstone disease and alcohol intake are responsible for up to 80 – 90% of AP whilst post-endoscopic retrograde cholangiopancreatography, some medications (corticosteroids, opioids, valproate), hyperlipidemia, biliary abnormalities, idiopathic causes, blunt abdominal trauma, hypercalcemia, viral, bacterial or parasite infections, pancreas divisium and autoimmune

disease are among less common causes of AP (1,2).

According to the Atlanta criteria, diagnosis of AP is made by presence of a three-fold increase in serum amylase and lipase levels. Depending on the clinical presentation, patients with AP are classified as mild, moderate or severe (3). Although majority of patients with AP achieve spontaneous recovery without having any complications, disease course may be severe in up to 10 to 20% of patients. Overall risk of mortality was reported to be ranging from 3-7% whereas it may reach up to 20-30% in patients with severe disease (4, 5).

Biliary or pancreatic duct obstruction with gallbladder stones constitute the most common etiology (35-60%) of acute biliary pancreatitis in Western and Asian populations (6). ABP diagnose is made upon radiographic evidence of presence of stones within the biliary duct in the absence of the other causes of AP. In most cases, the obstructing stone within the common hepatic duct spontaneously drops and clinical symptoms resolve. However, signs of cholestasis and/or a cholangitis attack may occur when the stone did not drop spontaneously. This requires extirpation of the stone through ERCP and sphincterotomy. Presence of acute cholangitis, cholestasis and the duration of biliary and pancreatic duct obstruction were reported to be associated with disease severity, clinical course and prognosis. Therefore, ERCP is recommended for treatment of ACP within first 72 hours of presentation if the patients have cholangitis and cholestasis or if ultrasonography reveals extrahepatic bile duct dilatation (7,8). Moreover, urgent ERCP (<24 hours) was reported to prevent progression of the pancreatitis and it also decrease mortality and morbidity by providing bile duct drainage in patients with cholangitis and biliary obstruction who were unresponsive to medical treatment (9-11). Therefore, ERCP and sphincterotomy have increasingly become an

accepted and effective treatment option in patients with ABP (7,9).

ERCP is an invasive intervention and it was reported to be associated with a 0.02-0.5% mortality and 2-10% morbidity (12,13). Moreover, a prospective randomized study demonstrated that 76% of ERCPs were done unnecessarily (14). Therefore, appropriate timing and decision making for ERCP is of importance not only for relieving the clinical course of the patient but also for preventing its unnecessary use.

A number of studies showed that female gender, age (>50 years), level of alanine aminotransferase (ALT) ( $\geq 150$ ) were independent predictors of presence of gallstone disease in etiology of AP (15-17). In another study, a total bilirubin level of >1.35 mg/dl on 2<sup>nd</sup> day was reported to be the best clinical predictor for presence of gallstone disease as the etiologic factor of AP with 90% sensitivity, 63% specificity, 40% positive predictive value and 96% negative predictive value (18). There have been several studies investigating certain parameters to predict the presence of gallstone disease in etiology of AP whereas, there have been no studies to determine which patients with ABP should receive ERCP. In clinical practice, ERCP is generally indicated in patients unresponsive to medical therapy, which is based on clinical and laboratory findings. However, implementation of some certain parameters that can predict the need for ERCP into the clinical practice may eliminate the uncertainty of the clinical treatment course and may provide guidance for the clinician. Therefore, we sought to determine the clinical parameters which can predict the need for ERCP in patients with ABP.

## Patients and methods

Clinical records of patients who received treatment between 2008 and 2015 for ABP in department of general surgery were prospectively collected and the data were retrospectively analyzed. Patients were included if they were diagnosed to have ABP based on physical examination, laboratory data and radiographic work-up. Patients were divided into two groups as to whether they received ERCP (ERCP Group) or medical treatment (Medical Group). In ERCP group, patients were excluded if they did not have any bile duct stone that could be visualized in radiographic studies or if cholestasis enzymes decreased before ERCP. Archive records were screened for demographics, comorbidities and laboratory findings. Biliary Ranson Scale score was used on admission and at 48<sup>th</sup> hour of admission (19). Also, laboratory data were collected on admission and at 48<sup>th</sup> hour of admission and included, complete blood count, amylase, aspartate aminotransferase (AST), ALT, blood urea, creatinine, total bilirubin and conjugated bilirubin, calcium, gamma glutamil transferase (GGT), alkaline phosphatase (ALP) and white blood cell count. The study was conducted in accordance with Helsinki Declaration for human studies and was reported in line with the STARD (Standards for the Reporting of Diagnostic accuracy studies) criteria.

## Statistical Analysis

Statistical analyses were performed by using SPSS software package (Version 22.0, SPSS Inc., Chicago, IL, USA). Normality distributions of the groups were evaluated with Kolmogorov–Smirnov and Shapiro-Wilk normality tests. Descriptive statistics with a normal distribution were presented as mean  $\pm$  standard deviation and as median values in case of a non-normal distribution and nominal variables were presented as number of cases and percentage (%) for definition of clinical

and social demographic variables. The significances of the difference between two independent groups were evaluated by using independent samples T-test in case of normally distributed data for means and Mann-Whitney U Test in case of data were not normally distributed for medians. Pearson's Chi-square or Fisher's exact test was used to investigate the association between two categorical variables.

Receiver operating characteristics (ROC) curve analysis was performed to identify the optimal cut off value for candidate variables (at which sensitivity and specificity would be maximal) to the prediction of ERCP or medical method. Sensitivity, specificity, positive and negative predictive values were calculated for this variables respectively. The optimal cut-off values that maximizes (sensitivity + specificity) determined by using Youden's index within ROC analyse. After ROC analysis we transformed the statistically significant continuous variables in categorical ones and eventually created fivecategorical variables. Although amilaz (24 hours), amilaz (48hours), T.bil (48 hours), D.bil (48hours), creatin (48 hours) was a continuous variable, five dichotomous variable was created such that patients scoring at the cut off of 104.5 or higher were considered as being high amilaz value, while those with a score of less than 16 were not high amilaz value. Binary logistic regression analysis was used to assess factors associated with ERCP or MEDICAL method. The dichotomous five variable was entered into binary logistic regression models as the primary independent variables. Also age, gender/sex, application type (urgent/electively) and USG result were entered into the model as independent variables with primary independent variables. Initially all variables were included in the models because each one could be related to the ERCP method. Then potential variables for logistic regression models were selected based on forward selection and backward elimination variable selection methods. Then final model was built

by using enter method in logistic regression. A two-sided p value < 0.05 was considered statistically significant.

## Results

There were a total of 179 patients with ABP. There were 160 patients in Medical Group and 19 patients in ERCP Group. Table 1

shows the gender and age distribution of patients between two groups. Age was significantly higher in ERCP group (p=0.043) whereas gender was not significantly different (p=0.072).

**Table1.** Gender-age cross tabulation between groups

	Gender		Total	Age		Total
	Female	Male		Female	Male	
<b>ERCP</b>	6 (31.6%)	13 (68.4%)	19	74.83 ± 12.95	71.46 ± 16.44	72.53 ± 15.15
<b>Medical</b>	90 (56.2%)	70 (43.8%)	160	60.54 ± 18.30	68.93 ± 14.19	64.23 ± 17.09
<b>Total</b>	96 (53.6%)	83 (46.4%)	179	61.44 ± 18.29	69.33 ± 14.49	

(p<sub>Gender</sub>=0,043, p<sub>Age</sub>=0.072)

No significant difference was found between two groups in regard to Biliary Ranson criteria (Table 2).

**Table 2.** Biliyer Ranson Values.

Ranson Count (Percentage %)	24 hours		p	48 hours		p
	ERCP	Medical		ERCP	Medical	
0	4 (7.1)	52(92.9)	<b>0.538</b>	12 (9.1)	120 (90.9)	<b>0.384</b>
1	10 (13.7)	63 (86.3)		6 (14.6)	35 (85.4)	
2	3 (8.1)	34 (91.9)		1 (20.0)	4 (80.0)	
3	2 (15.4)	11 (84.6)		0 (0.0)	1 (100.0)	
Total	19 (10.6)	160 (89.4)		19 (10.6)	160 (89.4)	

Mean difference is significant p<0.05\*, p<0.001\*\*

No significant difference was found between ERCP and Medical groups in regard to the presence of comorbidities including diabetes; 1 (3.2%) vs. 30 (96.8%), hypertension; 6 (24%) vs 19 (76%), lung disease; 1 (14.3%) vs 6 (85.7%) and heart disease 1 (14.3%) vs. 6 (85.7%) (p=0.137).

Table 3 shows laboratory data and complete blood count values of the patients. In ERCP group, amylase, AST, urea, creatinine, total bilirubin and conjugated bilirubin levels were significantly higher at 24<sup>th</sup> hour whereas amylase, AST, ALT, urea, creatinine, total bilirubin, conjugated bilirubin, white blood cell

count levels were significantly higher at 48<sup>th</sup>

hour than those in Medical Group.

**Table 3.** Laboratory and total blood count during the first 24 and 48 hours periods

	Groups	Mean ± Std. Deviation (24h)	Median (24h)	P values	Mean ± Std. Deviation (48h)	Median (48h)	P values
Amylase (U/L)	ERCP	615.52 ± 748.18	256.00	p<0.001**	282.93±489.81	159.50	p=0.002*
	MEDICAL	389.84 ± 973.64	60.00		122.67±176.81	57.00	
AST (U/L)	ERCP	268.00±262.66	207.00	p=0.029*	124.72±99.74	105.50	p=0.009*
	MEDICAL	228.37±347.57	85.00		91.41±118.76	52.00	
ALT (U/L)	ERCP	216.73±151.39	179.00	p=0.222	145.22±84.10	145.00	p=0.049*
	MEDICAL	211.66±224.54	112.00		122.43±125.31	77.00	
ALP (U/L)	ERCP	150.75±67.23	160.50	p=0.295	456.57±632.84	181.00	p=0.377
	MEDICAL	252.62±191.79	221.00		225.58±174.48	176.00	
Urea (mg/dL)	ERCP	46.63±24.01	42.00	p=0.030*	48.66±30.60	39.00	p=0.034*
	MEDICAL	38.56±22.01	31.00		39.21±40.27	29.50	
Creatinine (mg/dL)	ERCP	1.13±0.51	1.10	p=0.010*	1.21±0.65	0.95	p=0.006*
	MEDICAL	0.91±0.51	0.80		0.96±1.12	0.75	
T. Bil (mg/dL)	ERCP	4.14±4.08	2.90	p=0.017*	4.74±4.54	3.40	p<0.001**
	MEDICAL	2.58±2.44	1.90		1.74±1.62	1.10	
	<b>D.Bil (mg/dL)</b>	ERCP	2.68±3.10		1.79		p=0.028* 3.27±3.34
	MEDICAL	1.67±1.97	0.70	1.06±1.32	0.48		
Calcium (mg/dL)	ERCP	8.89±0.48	8.85	p=0.734	8.32±0.84	8.25	p=0.121
	MEDICAL	8.92±0.80	9.00		8.60±0.80	8.70	
GGT (U/L)	ERCP	184.00±100.31	210.00	p=0.427	191.57±91.58	163.00	p=0.647
	MEDICAL	311.77±254.39	279.00		275.81±244.84	186.00	
WBC (K/mm <sup>3</sup> )	ERCP	11.99±5.28	12.80	p=0.094	12.26±5.44	11.07	p=0.022*
	MEDICAL	9.96 ±4.95	8.50		9.53±4.38	8.60	

Mean difference is significant p<0.05\*, p<0.001\*\*

Area Under ROC curve with 95% confidence interval for 24th hour ALT, calcium, GGT, ALP, WBC was found insignificant (p>0.05). Area Under ROC curve with 95% confidence interval for 48th hour; calcium, GGT, ALP was found insignificant (p>0.05). Area under ROC curve with 95% confidence interval for 24th hour was at the limit of statistical significance; 0.653 (0.543-0.762) for urea, 0.680 (0.546-0.814) for creatinine, 0.653 (0.554-0.752) for AST, 0.668 (0.558-0.778) for total bilirubin, 0.655 (0.543-0.766) for conjugated bilirubin, (p<0.05, 600<AUC<0.700).

Area under ROC curve with 95% confidence interval for 24th hour was at the

limit of significance; 0.654 (0.523-0.785) for urea, 0.642 (0.535-0.750) for ALT, (0.690 (0.576-0.805) for AST, 0.670 (0.545-0.796) for WBC (p<0.05, 600<AUC<0.700).

Area under ROC curve was significant for amylase (24th and 48th hour), Total bilirubin (48th hour), conjugated bilirubin (48th hour), creatinine (48th hour) (p<0.05, 700<AUC) and NPV values were found extremely high. It was found that ERCP was significantly unnecessary in patients with an amylase level <104.5 at 24th hour and < 123.5 at 48th hour, total bilirubin <2.15 at 48th hour, conjugated bilirubin <1.45 at 48th hour, creatinine < 0.75 at 48th hour (Table 4). ROC curves were shown at Figure 1, 2, 3, 4 and 5.

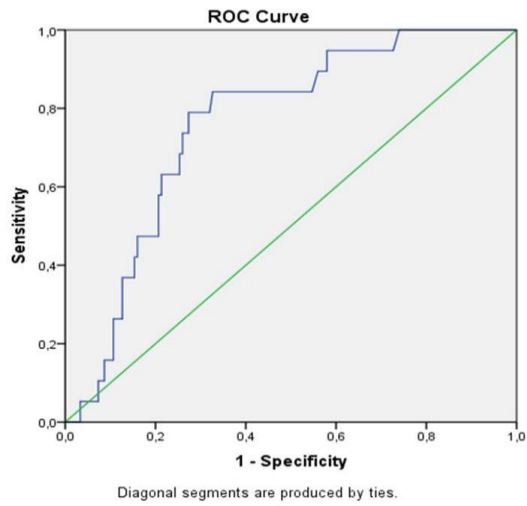


Figure 1 ROC curve of the Amilaz (24h) score predicting the ERCP

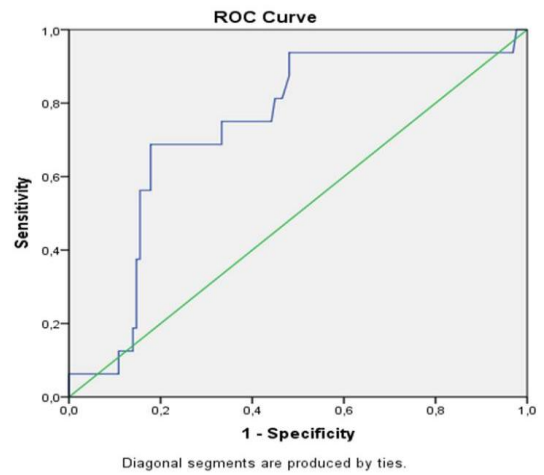


Figure 2 ROC curve of the Amilaz (48h) score predicting the ERCP

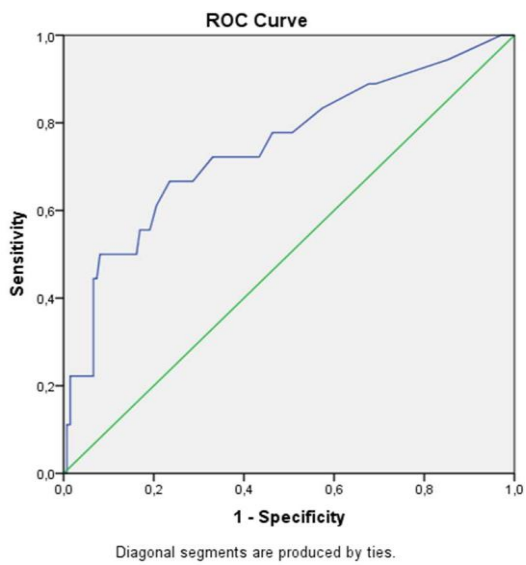


Figure 3 ROC curve of the tbil (48h) score predicting the ERCP

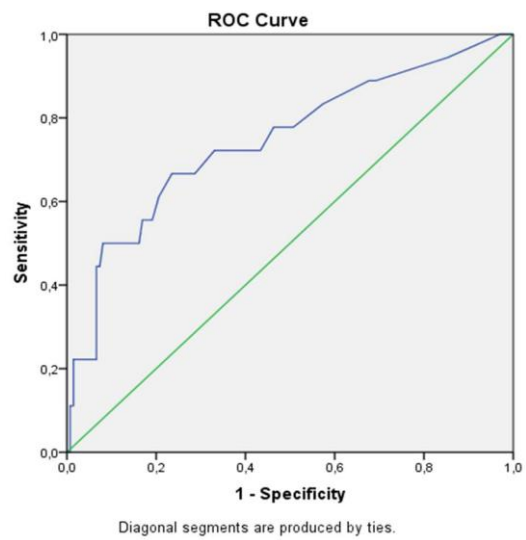


Figure 4 ROC curve of the dbil (48h) score predicting the ERCP

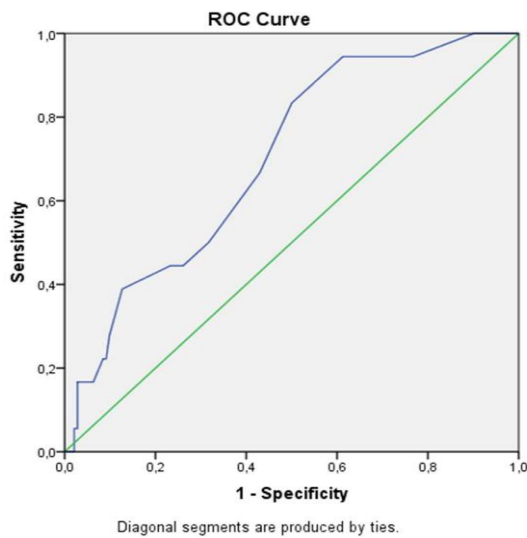


Figure 5 ROC curve of the Creatin (48h) score predicting the ERCP

Logistic regression analysis was done only for parameters obtained at 48<sup>th</sup> hour. Since ROC analysis at 24<sup>th</sup> hour was found significant only for amylase levels, a multivariable logistic regression analysis could not be instituted (Table 4).

Logistic regression analysis revealed that success of model classification of MEDICAL AND ERCP groups was 89.7%.

The probability of undergoing an ERCP for an individual patient was 4.287 fold higher if the patient had high WBC level at 48<sup>th</sup> hour (>9.55, ROC Cut off value), it was 6.710 fold higher if the patient had high total bilirubin level (>1.45, ROC Cut off value) and 7.032 fold higher if the patient had high amylase levels (>123.5, ROC Cut off value) compared to any patient with normal levels (Table 5).

**Table4.** Area under curve (AUC) and summary statistics of significant variables in ROC analysis.

	<b>Amilaz(U/L) (24h)</b>	<b>Amilaz (U/L) (48h)</b>	<b>T.Bil (mg/dL) (48 h)</b>	<b>D.bil (mg/dL) (48h)</b>	<b>Creatinine (mg/dL) ((48h)</b>
<b>AUC* (95% CI)</b>	0.759 (0.663-0.855)	0.736 (0.613-0.860)	0.756 (0.631-0.882)	0.746 (0.612-0.879)	0.700 (0.584-0.816)
<b>Sensitivity</b>	0.789	0.688	0.722	0.667	0.833
<b>Specificity</b>	0.727	0.822	0.703	0.765	0.500
<b>Positive predictive value (PPV)</b>	0.268	0.324	0.241	0.272	0.174
<b>Negative predictive value (NPV)</b>	0.965	0.955	0.951	0.945	0.959
<b>Cut-off value</b>	<b>104.5</b>	<b>123.5</b>	<b>2.15</b>	<b>1.45</b>	<b>0.75</b>

\*Area under curve 0.70 <AUC<0.80 Moderate, 0.80<AUC<0.90 high 0.90<AUC<1 very high

**Table5.** Binary logistic regression analysis final results for predicting ERCP method.

	<b>P values</b>	<b>Odds Ratio (OR)</b>	<b>95% CI for OR</b>	
			<b>Lower</b>	<b>Upper</b>
<b>WBC (K/mm3) (48h)</b>	<b>0.033*</b>	<b>4.287</b>	1.121	16.386
<b>Conjugated bilirubin (mg/dL) (48h)</b>	<b>0.005*</b>	<b>6.710</b>	1.797	25.054
<b>Amylase (U/L) (48h)</b>	<b>0.002*</b>	<b>7.032</b>	2.002	24.699

## Discussion

Acute pancreatitis is an acute inflammatory process that may affect multiple organs. Gallstone disease has been known to be the most common underlying etiology although several other etiologic factors may play a role in its development (6). In general,

acute biliary pancreatitis limits itself when the stone stacked within the common bile duct drops as the edema at the pancreatic head resolves. However, the stone should be removed with ERCP and sphincterotomy if it does not drop spontaneously. Clinical course worsens with time as the stone remains longer within the bile duct. Therefore, optimum



timing for ERCP is crucially important in patients with acute biliary pancreatitis.

Increasing age (>50) was reported to be an independent predictor for determination of the underlying pathogenesis in patients with acute biliary pancreatitis (15-17). In line with this, in our study, mean age was significantly higher in ERCP Group compared to Medical Group (p=0.043). We think that previous acute cholecystitis episodes or increasing age may decrease the elasticity of the tissue preventing these stones drop spontaneously and thus resulting more common use of ERCP in patients with advanced age.

In previous studies, acute biliary pancreatitis was demonstrated to be more common in women compared to men, which may be attributed to the higher incidence of gallstone disease in women (15). Moreover, female gender was shown to be an independent predictor in determination of biliary etiology in patients with acute biliary pancreatitis (15-17). In our study, it was notable that male gender was slightly more common in ERCP group although there was no significant difference. We found that male gender is unlikely to be predictive for ERCP requirement although men are more tend to have ERCP. We also found that comorbid diseases have no predictive values in determination of acute biliary pancreatitis etiology.

Although there were no differences between two groups in regard to biliary Ranson criteria, beginning from the admission to the hospital, patients in ERCP group had higher amylase, AST, ALT, urea, creatinine, total bilirubin, conjugated bilirubin and white blood cell count values than those in Medical Group. In Medical group, none of the parameters showed significant increase whilst laboratory parameters returned to normal as the clinical course resolved spontaneously. However, laboratory parameters and complete blood count parameters have remained high in ERCP group.

In our study, ROC analysis demonstrated that NPV value was extremely higher in patients with an amylase level <104.5 at 24<sup>th</sup> hour or <123.5 at 48<sup>th</sup> hour, a total bilirubin level <2.15 at 48<sup>th</sup> hour, conjugated bilirubin <1.45 at 48<sup>th</sup> hour and creatinine <0.75 at 48<sup>th</sup>. In these patients, acute biliary pancreatitis resolved spontaneously without any need for ERCP.

The logistic regression analysis which was performed on the data obtained at 48<sup>th</sup> hour demonstrated that the probability of undergoing an ERCP was 7.032 fold higher in patients with high amylase levels, 6.710 fold higher in patients with high conjugated bilirubin levels and 4.287 fold higher in patients with high white blood cell count.

In conclusion, amylase level at 48<sup>th</sup> hour and amylase, conjugated bilirubin and white blood cell count levels can be used to predict patients who need ERCP for management of acute biliary pancreatitis. We think that, use of these parameters will provide an important insight to the clinician to decide whether an individual patient with acute biliary pancreatitis will require ERCP or will have spontaneous resolution from the beginning of the admission. This aspect may also decline the number of unnecessary ERCPs performed.

Since no other studies on predictive value of ERCP could be found in the literature, we were unable to make a direct comparison of our results with those of others. In addition, higher number of patients in the ERCP group is mandatory to make a reliable estimation of the positive predictive value. Further prospective randomized studies involving acute phase proteins, comprehensive biochemical and laboratory tests are warranted to make a reliable determination of the predictive value of ERCP. Despite its retrospective design, the present study seems to put forward an alternative aspect and provide baseline information for future studies.

**Declaration of interest:** The authors of the present study declare that they do not have any potential conflict of interest including any financial relationships.

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