

# Major predictors for difficult common bile duct stone

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**Background/aims:** Endoscopic retrograde cholangiopancreatography has become the standard treatment for common bile duct stones worldwide. However, there are only a few reports with small number of patients concerning the factors that contribute to the technical difficulty of endoscopic retrograde cholangiopancreatography in these patients. In this study we aimed to investigate these factors in a large group of patients. **Materials and Methods:** All patients with a naïve papilla (n=1850) who underwent endoscopic retrograde cholangiopancreatography during a study period of 2 years were prospectively evaluated. Of these, 757 patients with common bile duct stones were included in the study. Following successful cannulation, patients who needed either more than one episode for stone extraction or mechanical lithotripsy, extracorporeal shock wave lithotripsy, or patients in whom stone extraction could not be achieved endoscopically and underwent surgery were regarded as having “difficult stones”. Age, sex, laboratory parameters, endoscopic and cholangiographic findings were recorded in all patients. Predictive factors for difficult stones were investigated using univariate and multivariate analysis. **Results:** The study group consisted of 432 women and 325 men with a mean age of 60±16 years (range, 4-96). Of the total 757 patients, 654 (86.4%) had easy and 103 (13.6%) had difficult stones. Endoscopic stone extraction was successful in 98.1% of patients. A stricture distal to the stone (OR: 8.248), smaller common bile duct /stone diameter ratio (OR: 0,348), stone diameter (OR: 1,187) stone impaction (OR: 1,117) and higher bilirubin levels (OR: 1,1) were found to be independent predictors of difficult stone extraction on multivariate analysis. **Conclusion:** Endoscopic retrograde cholangiopancreatography is a very effective method for the treatment of common bile duct stones. Presence of a stricture distal to the stone, smaller common bile duct /stone diameter ratio, stone diameter, impacted stone, and higher bilirubin levels are significant predictors of difficult stone.

**Key words:** Difficult bile duct stone, endoscopic retrograde cholangiopancreatography, biliary stricture, stone diameter

## Zor safra kanalı taşının en önemli belirteçleri

**Giriş ve Amaç:** Safra kanalı taşlarının tedavisinde endoskopik retrograd kolanjiopankreatografi standard tedavi haline gelmiştir. Bu hastalarda endoskopik retrograd kolanjiopankreatografinin teknik güçlüğüne araştıran küçük hasta grupları ile yapılmış az sayıda çalışma vardır. Bu çalışmada biz bu faktörleri geniş bir hasta grubunda araştırmayı amaçladık. **Gereç ve Yöntem:** İki yıllık bir süre içerisinde endoskopik retrograd kolanjiopankreatografi yapılan tüm naive hastalar (n=1850) prospektif olarak değerlendirildi. Taş çıkartmak için birden fazla endoskopik retrograd kolanjiopankreatografi seansı, mekanik litotripsi, ekstra şok dalga litotripsi gerektiren ya da endoskopik olarak çıkarılamayıp cerrahiye giden hastalar zor taşı olan hastalar olarak kabul edildi. Yaş, cinsiyet, laboratuvar parametreler, endoskopik ve kolanjiografik bulgular kayıt edildi. Zor için prediktif faktörler univariate ve multivariate analizlerle araştırıldı. **Bulgular:** Çalışma grubu ortalama 60±16 yaşında (4-96) 431 kadın 325 erkek hastadan oluştu. 757 hastanın 654'ünde (86,4%) kolay taş, 103'ünde (13,6%) zor taş var idi. Hastaların %98,1'inde endoskopik taş çıkarma işlemi başarılı idi. Taşın ötesinde darlık olması (OR: 8,248), küçük ortak safra kanalı /taş çapı oranı (OR: 0,348), taş çapı (OR: 1,187), taşınstone impakte olması (OR: 1,117) ve yüksek bilirubin değerleri (OR: 1,1) zor taş için multivariate analizde bağımsız belirleyici faktörler olarak tespit edildi. **Sonuç:** Ortak safra kanalı taşları tedavisinde endoskopik retrograd kolanjiopankreatografi çok etkili bir yöntemdir. Taşın ilerisinde darlık olmasının yanında küçük safra kanalı /taş çapı oranı, taş çapı, impakte taş ve yüksek bilirubin değerleri zor taş için önemli belirteçlerdir.

**Anahtar kelimeler:** Zor taş, endoskopik retrograd kolanjiopankreatografi, bilier darlık, taş çapı

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## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) and/or balloon dilation and stone extraction is the most common therapeutic procedure used for the treatment of common bile duct (CBD) stones. However, in approximately 10% to 15% of patients, removal of bile duct stones during the first attempt can be challenging (1-5).

Stones requiring interventions other than the standard ERCP, ES, balloon and/or basket for extraction, or those requiring a second or third ERCP were named as “difficult stones”. Larger stones, intrahepatic stones, impacted stones in the bile duct or cystic duct, stones in patients with periampullary diverticulum, Billroth II anatomy, Roux-en-Y gastrojejunostomy were observationally defined as difficult stones (1-3, 6, 7). To our knowledge, there are only a few reports with limited number of patients in the existing literature that investigate the factors contributing to the technical difficulty of endoscopic clearance of CBD stones (7-9).

Herein we conducted a prospective study to determine the factors that contribute to the technical difficulty of endoscopic clearance of CBD stones. To our knowledge, this is the largest study investigating predictive factors for difficult stones.

## PATIENTS and METHODS

We prospectively evaluated all patients with a naïve papilla (n=1850) who underwent ERCP between October 2005 and August 2007. Of 1850 patients, 757 (%40.9) had bile duct stones, and all patients with a diagnosis of stone with a naïve pa-

pilla were included in the study. Patients with a prior endoscopic sphincterotomy, Mirizzi’s syndrome and intrahepatic bile duct stones were excluded. The diagnosis of a bile duct stone was based on radiologic and endoscopic visualization. Patient management was as follows: ES was performed after cannulation. If ES was not sufficient for stone extraction, balloon dilation with a 12 mm, 15 mm or 18 mm balloon according to the size of the common bile duct was performed. If a stricture was noted distal to the stone, balloon dilation according to the size of adjacent dilated bile duct was performed. Stones were extracted either with an extraction balloon or a stone extraction basket. Mechanical lithotripsy was performed if necessary. If the stone was too large for basket grabbing, then either a naso-biliary drain was inserted for extracorporeal shock wave lithotripsy (ESWL) (Figure 1 A,B,C), or a 10 Fr plastic stent was inserted and the definitive procedure was postponed for 3 months (Figure 2 A,B,C), or the patient was referred to surgery. If a stent was inserted, the patient was treated with ursodeoxycholic acid. The patient underwent surgery if the stone was too large, if the patient had a previous Billroth II operation, or if an ectopic opening in the common bile duct in the duodenal bulb (EO-CBD-DB) was noted with a non-extractable stone or if the patient preferred surgery. Age, sex, laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, international normalized ratio (INR), platelets, and white blood cell count, characteristics and location of papilla and cholangiographic findings such as common bile duct diame-

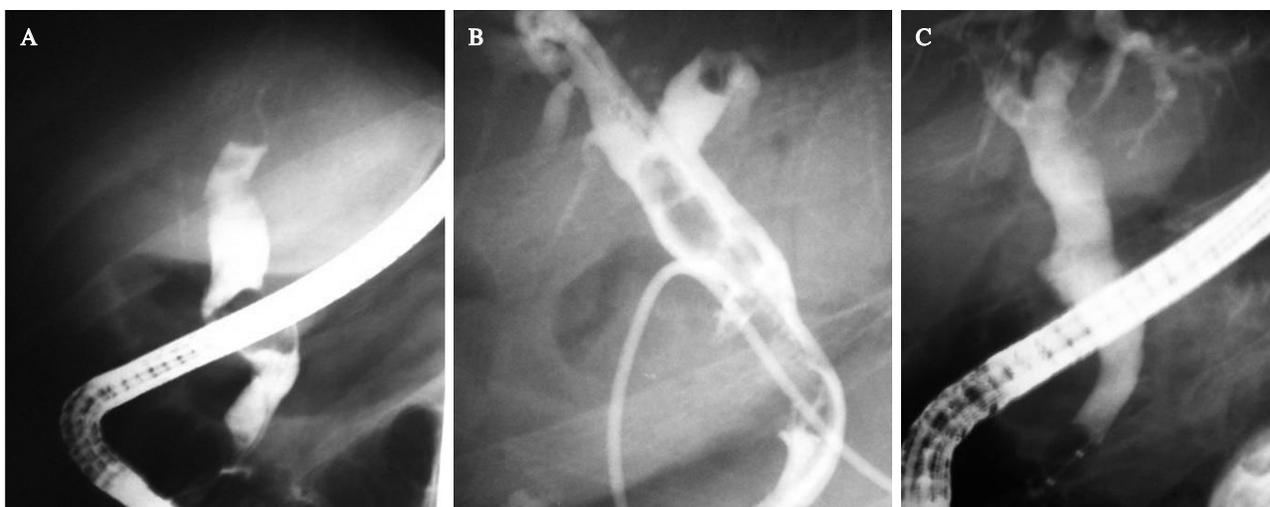
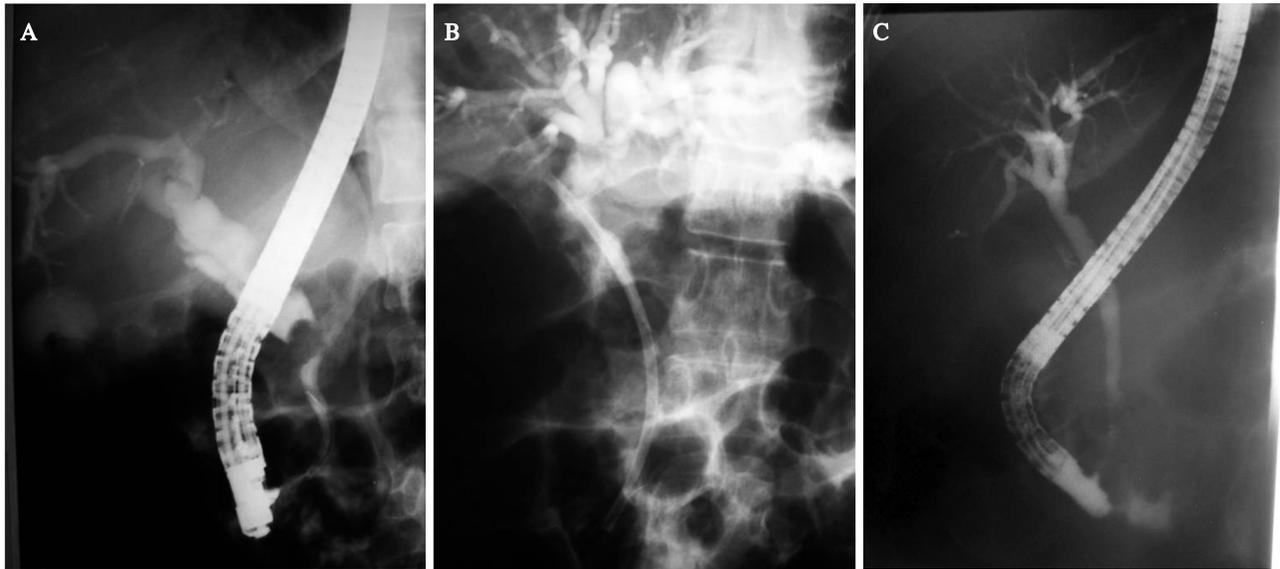


Figure 1. A, B, C: Management of a huge stone with naso-biliary drain insertion and extracorporeal shock wave lithotripsy (ESWL).



**Figure 2. A, B, C:** Management of a stone with a stricture distal to the stone with 10 f plastic stent insertion and definite procedure was postponed for 3 months.

ter, stone diameter, presence of stricture distal to the stone and impacted stone were recorded in all patients. Diameter of the common bile duct and stone size were measured by a ruler on radiologic imaging. A stone was defined as being impacted in the bile duct if it was immobile and hampered passage of the catheter. ERCP was performed by experienced endoscopists with a side-viewing duodenoscope (Olympus TJF 240, Japan) under conscious sedation with midazolam and meperidine. Following successful cannulation, stones which required more than one session of ERCP, mechanical lithotripsy or extracorporeal shock wave lithotripsy (ESWL) for extraction or which could not be extracted by ERCP and necessitated surgery, were regarded as “difficult stones”. Demographic data, laboratory parameters and endoscopic findings mentioned above were evaluated in order to determine predictive factors for difficult stones. A written informed consent was obtained from all patients included in the study. The study was approved by the local ethics committee.

#### Statistical analysis

The distribution of continuous variables was assessed with the Shapiro Wilks’ test. Categorical variables (gender, characteristics of the papilla, cholangiographic findings) were compared using chi-square test, or Fisher’s exact test. Continuous variables (age, laboratory results, stone and bile duct diameter) were analyzed using the Mann–Whitney U test. Significant predictors for “difficult stone” ( $p < 0.05$ ) identified by univariate

analysis were included in a multiple logistic regression analysis to determine the most significant risk factors for difficult stones. An odds ratio for every risk factor was calculated at a 95% confidence interval, and  $p < 0.05$  was considered as significant. Statistical analysis was performed with the SPSS package 11.5 (SPSS Inc. Chicago, IL, USA).

#### RESULTS

Of 1850 patients with a naïve papilla, 757 (40.9%, 432 women, 325 men) had CBD stones. Mean age of the patients was  $60 \pm 16$  years (Range:4-96). Stone extraction with standard ERCP, ES, balloon or basket extraction was successfully achieved in 654 (86.4%) patients on the first attempt, whereas additional attempts or procedures were necessary for the remaining 103 (13.6%) patients, and they were regarded as having “difficult stones”. Fifty-four patients needed more than one procedure. While 34 of them were stented 2,3 (2-4) times before bile duct clearance, 20 of them were treated during the same admission. Thirty-nine patients needed mechanical lithotripsy, 13 patients had ESWL and 15 patients had surgery for stone clearance. Endoscopic stone extraction was successful in 98,1% of patients. Endoscopic interventions failed in 15 (14,6% of difficult stones, 1,9% of overall) patients with difficult stones, and they underwent surgery. Results of univariate analysis of possible predictive factors for difficult stones are presented in Table 1 and 2. There was no significant difference between the easy and difficult stone groups with re-

**Table 1.** Demographic data and laboratory parameters predicting difficult stones on univariate analysis

Factors	Easy stone (n: 654)	Difficult stone (n: 103)	P value
Age (years)	60,3±16,6	63,3±14,8	,180
Sex (%)			,258
Male	286 (43,8)	39 (37,9)	
Female	368 (56,2)	64 (62,1)	
ALT (median±SD, U/L)	139,5±134,1	103,3 ± 103,4	,026
AST (median±SD, U/L)	103,9±116,1	89,6±136,8	,193
GGT (median±SD, U/L)	372,9±342,6	324,3±267,1	,449
ALP (median±SD, U/L)	585,6±486,4	607,2±437,1	,271
Total bilirubin (median±SD, mg/dl)	3,9±2,3	5,2±7,5	,011
Direct bilirubin (median±SD, mg/dl)	1,8±2,7	3,2±5,1	,007
INR	0,9±0,1	1,0±0,1	,020
Platelet (median±SD, billion/L)	312,6±93,2	314,6±121,8	,545
WBC (median±SD, billion/L)	9423±1523	8435±3517	,454

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. GGT: Gamma glutamyl transferase.

ALP: Alkaline phosphatase. INR: International normalized ratio. WBC: White blood cell. SD: Standart deviation.

**Table 2.** ERCP findings predicting difficult stones on univariate analysis

Factors	Easy stone	Difficult stone	p value
Papilla in bulbus n (%)	11 (1,7)	7 (6,8)	,007
Papilla in 3 <sup>rd</sup> portion, n (%)	5 (0,7)	0 (0)	1,000
Fibrotic papilla, n (%)	3 (0,5)	4 (3,9)	,008
Juxtadiverticular papilla, n (%)	171 (26,1)	27 (26,2)	,989
BII anastomosis, n (%)	10 (1,5)	6 (5,8)	,015
Impacted stone, n (%)	2 (0,3)	18 (17,5)	< ,001
Stricture distal to the stone, n (%)	7 (1,1)	14 (13,6)	< ,001
BD, median±SD, mm	13,6±4,5	16,9±6,6	< ,001
ST, median±SD, mm	8,8±4,4	15,0±6,0	< ,001
BD/S ratio, median±SD	1,8±0,9	1,2±0,5	< ,001

BII: Billroth II. BD: Bile duct size. ST: Stone size.

gard to age, gender, AST, ALP, GGT, platelet and white blood cell count. Although patients with a juxtapapillary diverticulum had a higher stone diameter (median 11 mm vs 8 mm), it was not a risk factor for difficult stones. Higher total and direct bilirubin, higher INR, location of papilla in the bulb of duodenum, the presence of a fibrotic papilla, an impacted stone, stricture distal to the stone, more dilated bile duct and past history of a Billroth II operation were found to be predictive for difficult stones. The mean diameter of stones was significantly bigger in the difficult stone group compared to easy group (15,0±6,0 mm vs 8,8±4,4 mm). Bile duct/stone ratio was significantly lower in the difficult stone group (1,2±0,5 vs 1,8±0,9). On multivariate analysis, presence of a stricture distal to the stone was the most important predictor for difficult stone with an odds ratio of 8,248. Bile duct/stone ratio was the second most significant predictor with an odds ratio of 0,348. Results of multivariate analysis are presented in Table 3.

## DISCUSSION

Our study included 757 patients with CBD stones, making it the largest study investigating predictive factors for difficult stones in the literature. The success rate of stone extraction with standard ERCP, ES, balloon or basket extraction was 86,4% during the first attempt, and 98,1% of overall. This rate was reported as 87% by Cotton and 87,3% by Vaira (1, 4) This high rate of success may be related to the experience at our center performing a high volume of procedures. There is no standard definition of a difficult stone in the literature. Here a new definition of a difficult stone is presented, including patients who needed more than one episode of ERCP with basket/balloon sweeping or mechanical lithotripsy or ESWL for stone extraction or patients in whom stone extraction could not be achieved endoscopically and underwent surgery. Presence of a stricture distal to the stone, smaller common bile duct/ stone diameter ratio, stone diameter, stone impaction and high-

**Table 3.** Factors predicting difficult stone on multivariate analysis

Predictive factors	P value	Odds ratio	95% CI
High direct bilirubin	,012	1,100	1,021-1,184
Stone size	,000	1,187	1,114-1,265
Stone size/Bile duct size	,010	0,348	0,156-0,776
Impacted stone	,001	1,117	2,156-6,312
Stricture distal to the stone	,000	8,248	3,419-19,897

CI: Confidence interval.

her bilirubin levels were found to be independent predictors of difficult stone on multivariate analysis.

There are only a few reports investigating the factors that affect the success of endoscopic clearance of CBD stones. Some of them emphasized the importance of stone size. Lauri in 1993 studied 100 patients and found that there was a significant difference in the success rate of stone extraction with regard to size of stone (7). In this first study on difficult stones, stone extraction and clearance of the common bile duct was achieved in 59% of the 75 patients in whom endoscopic sphincterotomy was performed. Duct clearance was achieved in 30 patients at the first session, 13 at a second and one at a third session. Although all stones <10 mm were successfully removed by endoscopic sphincterotomy, only 3 of 25 stones (12%) over 15 mm could be removed successfully by endoscopic sphincterotomy. This very low rate may be related to the time of the study since it may represent the learning era of safety margins of ES and stone extraction. Wan studied 216 patients with CBD stones (9) in patients with stones >2 cm, more ERCP procedures per patient (mean: 1,5/patient) were performed than in patients with stones <2 cm (mean: 1,1/patient). The overall success rate and the success rate on the first ERCP session in the >2 cm group was significantly lower than that in the <2 cm group (77.8% vs 91.7% and 58.3% vs 83.3% respectively). Our finding that stone size is an independent predictor of a difficult stone is inconsistent with the findings of Lauri and Wan.

A group from Korea investigated the effects of additional factors on the success of CBD stone extraction in 102 patients (8). Patients with stenosis (benign or malignant) of the CBD were excluded from the study. In this study the technical difficulty of CBD stone removal was graded as easy, moderately difficult and very difficult according to the number of attempts of basket grasping or balloon sweeping for stone extraction. Procedure failure was defined as incomplete CBD clearance

during that session of ERCP. Complete bile duct clearance was achieved after one session of ERCP in 96 (94,1%) patients. The remaining 6 patients underwent additional ERCP sessions or percutaneous approaches and all of them achieved complete bile duct clearance. Older age ( $\geq 65$  years), previous gastrojejunostomy, larger CBD stone ( $\geq 15$  mm), presence of impacted CBD stone, use of mechanical lithotripsy, shorter length of the distal CBD arm ( $\leq 36$  mm), and more acute distal CBD angulation ( $\leq 135$  degrees) were all found to be significant contributing factors to the technical difficulty of endoscopic clearance of CBD stone(s) in exploratory univariate testing. However, only more acute distal CBD angulations ( $\leq 135$  degrees) and a shorter length of the distal CBD arm ( $\leq 36$  mm) were found as independent contributors to technical difficulty according to multivariate analysis. Exclusion of patients with a stricture distal the stone may have caused a bias. In our study we did not include distal angulations or length of distal arm of CBD and we have no comment on these factors. Features of three previous studies and of our current study on difficult stones are presented in Table 4.

Although Cotton outlined the importance of a stricture distal to the stone and duct/stone ratio and concluded that stones are more difficult to extract when there is relative narrowing below the stone, this statement was based on only clinical observation (1). There is no study investigating the importance of a stricture distal to the stone for stone clearance from the bile duct in the literature. To our knowledge, this is the first study which has statistically proven that these two parameters are significant predictors of technical difficulty in removing CBD stones. A stricture distal to the stone was described for the first time in the literature in this study as the most important predictor for difficult stone (OR: 8,2). Bile duct/stone ratio was the second most significant predictor with an odds ratio of 0,348 and also was described for the first time in the literature in this study.

**Table 4.** Features of 3 previous studies and the current study about difficult stones

Author	Year of publication	Number of patients	Definition of difficulty	Significant factors of difficult stone	First/overall success
Lauri A (7)	1993	100	Failed complete CBD clearance	Stone size	73.3%/Na
Kim HJ (8)	2007	102	Number of attempts of basket grasping or balloon sweeping or failed	Distal CBD arm $\leq$ 36 mm, CBD angulation $\leq$ 135 degrees	94.1%/100%
Wan XJ (9)	2011	216	Failed complete CBD clearance	Stone size	75%/87%
Our study		757	Need of more than one ERCP session, mechanical lithotripsy, ESWL or failed complete CBD clearance	Stricture distal to the stone, CBD/stone ratio, stone size, stone impaction, higher bilirubin levels	86,4%/98,1%

NA: Not available. CBD: Common bile duct. ERCP: Endoscopic retrograde cholangiopancreatography. ESWL: Extracorporeal shock wave lithotripsy.

A study from India including 401 patients reported the impaction of the stone or presence of stones in the bile duct as a significant predictor of failure of mechanical lithotripsy and consequently, the failure of bile duct clearance (10). The end point of the study was total clearance of the bile duct stone either in one or more sessions, and mechanical lithotripsy was decided when the stone size exceeded 15 mm. Although the aim of this study was to evaluate the factors that interfere with mechanical lithotripsy, stone impaction was found to be significant also for bile duct clearance. This was consistent with our finding on stone impaction.

High INR is found to be a statistically significant

predictor for difficult stone on univariate analysis but this was probably the result of a bias. Patients were usually managed with a small ES and stenting for large stones in case of a high INR.

In conclusion, ERCP is a very effective procedure for the treatment of common bile duct stones. Presence of strictures distal to the stone, smaller common bile duct/ stone diameter ratio, larger stone size, impacted stone, and higher bilirubin levels are predictors for difficult stones. Knowledge about which stones are difficult may enable physicians to consider the next step, and prevent procedural and therapeutic delays due to the aforementioned factors.

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