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COMMUNICATION

CLINICAL ANATOMY WILEY

Comparison of the cystocholedochal angle in patients with choledocholithiasis and only cholelithiasis

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Abstract

This study aims to evaluate the relation between the cystocholedochal angle (SCA) and choledocholithiasis. The data of 3.350 patients were reviewed retrospectively and a total of 628 patients who met the criteria were included in the study. The patients included in the study were divided into three groups as patients with choledocholithiasis (Group I), patients with only cholelithiasis (Group II), and patients without gallstones as control group (Group III). Measurements of SCA, cystic, bile, and common hepatic ducts (CHDs) were made on magnetic resonance cholangiopancreatography (MRCP) images. Laboratory findings and demographic characteristics of the patients were also recorded. Of the patients included in the study 64.2% were female, 35.8% were male, and their age ranged from 18 to 93 (mean 53.37 ± 18.87 years). While the mean SCA values of all patient groups were 35.44° ± 10.44°, the mean length of cystic, bile and CHDs were 28.91 ± 9.30, 40.28 ± 12.91, 27.09 ± 9.68 mm respectively. All measurements were higher in Group I in comparison to other groups, whereas all measurements of Group II were higher than those of Group III (p < 0.001). Statistical analysis suggests that a SCA of 33.5° and above is an important criterion for diagnosis of choledocholithiasis. Increase of SCA raises the likelihood of choledocholithiasis, as it facilitates the passage of stones from gallbladder into the bile ducts. This is the first study to compare SCA in patients with choledocholithiasis and those with only cholelithiasis. Therefore, we think that this study is important and will be a guide for clinical evaluation.

KEYWORDS
choledocholithiasis, cystocholedochal angle, extrahepatic bile ducts, gallbladder, magnetic resonance cholangiopancreatography

1 | INTRODUCTION

Choledocholithiasis means that there is a stone in the Bile Duct (BD). The most common cause is a stone in the gallbladder, which is seen in 1%–15% of patients. Other causes include a primary stone formation in the BD and, rarely, a stone forming in the intrahepatic BDs and entering the BD (McNicoll et al., 2021).

Previous studies reported that when the size of the stone in the gallbladder is ≤8 mm, the probability of the stone entering the BD is high. In ultrasonography (USG) follow-ups, it was detected that these stones fell into the BD in some patients, but did not enter when the size of the stones was ≥8 mm (Frossard et al., 2000). Although the exact cause is not known, anatomical differences can affect this situation. The junction of cystic duct (CD) and BD was first described by

Sipahi et al. as SCA (Sipahi et al., 2015). We think that SCA may be effective in the entry of the stone in the gallbladder into BD. There is a limited number of studies that evaluate SCA in the literature. Keizman et al. reported that increased SCA was associated with choledocholithiasis in T-tube patients (Keizman et al., 2006). Warren et al. showed in their study that the increased angle of the common hepatic duct (CHD), which is in contact with the SCA, with the BD, caused biliary stasis and lead to recurrent choledocholithiasis (Warren, 1987).

Many anatomical variations were described in the intrahepatic and extrahepatic BDs. However, the effect of these structural differences on the formation of cholelithiasis (stones in the gallbladder) and choledocholithiasis is not known clearly (Collins et al., 2004).

In the present study, we thought that SCA might be a predisposing factor for the development of choledocholithiasis in patients with cholelithiasis. The purpose of the present study was to evaluate the patients with cholelithiasis and choledocholithiasis in terms of SCA with the control group without gallstones and to uncover the relationship between SCA and choledocholithiasis.

2 | MATERIALS AND METHODS

The study was conducted in the General Surgery Clinic and Radiology Clinic of a training and research hospital of the University of Health Sciences. The ethics committee approval was obtained from X University Science, Social and Non-Interventional Health Sciences Research Ethics Committee (date: September 2, 2019, number: 2019/09).

In this retrospective study, the data of the patients who applied to the abovementioned training and research hospital between 2017 and 2019 were used. The patients were collected in three groups; Group I patients with choledocholithiasis, Group II patients with cholelithiasis only, and Group III (control group) patients who had an MRCP report and were not diagnosed with choledocholithiasis and/or cholelithiasis. The patients who were older than 18 years were included in the study and those who had a previous cholecystectomy and/or hepatopancreaticobiliary surgery, gastrointestinal tumor findings, and were pregnant were excluded from the study. The distribution of retrospectively analyzed patients is given in Figure 1.

Laboratory findings (ALT, albumin, ALP, AST, direct bilirubin, total bilirubin, CRP, GGT, hemoglobin, leukocytes, INR) and MRCP images were recorded as well as the demographic characteristics of the patients at the time of the first admission to the hospital and SCA was examined on the images. The SCA value was obtained by measuring the angle between the two intersecting lines that extended into the CD and BD (Figure 2). In addition to SCA measurements on coronal cross-section images, CHD length (mm) (Figure 3), CD length (mm) (Figure 4), BD length (mm) (Figure 5), and stone sizes (mm) of patients with stones were measured. The measurements of 15% of randomly selected patients from each group were repeated by a second observer for the reliability of the results.

According to the clinical indications of USG and MRCP, they were generally performed in the hospital where the study was conducted, within a week in outpatient admissions, within the first 24 h in hospitalizations, or one week before the surgery at the latest. All MRI

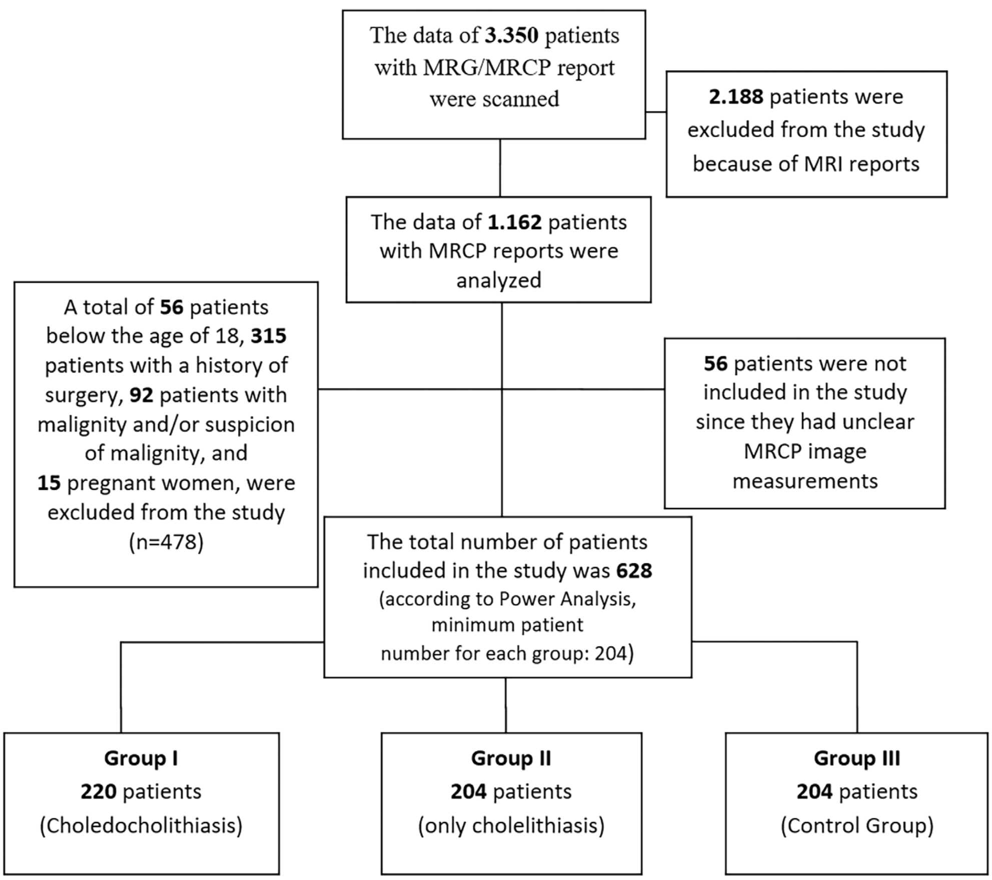
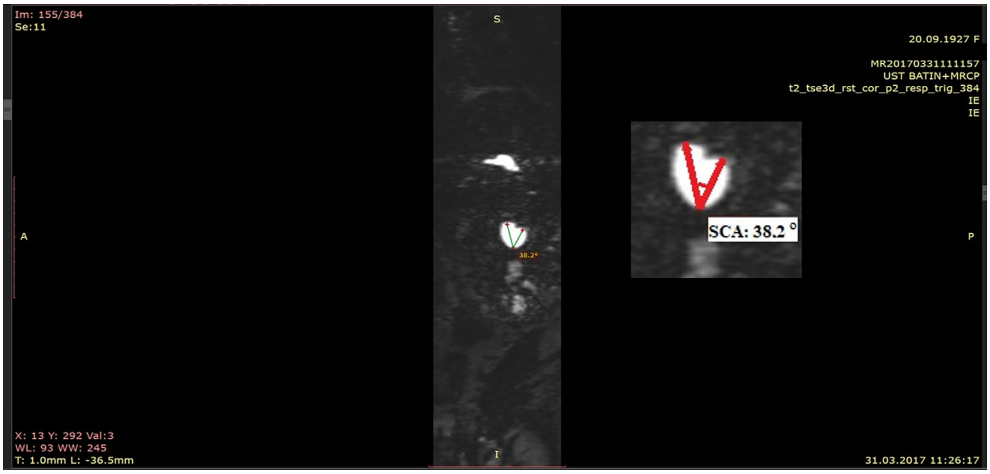


FIGURE 1 The distribution of the retrospectively examined patients.

FIGURE 2 SCA (°) on MRCP image.



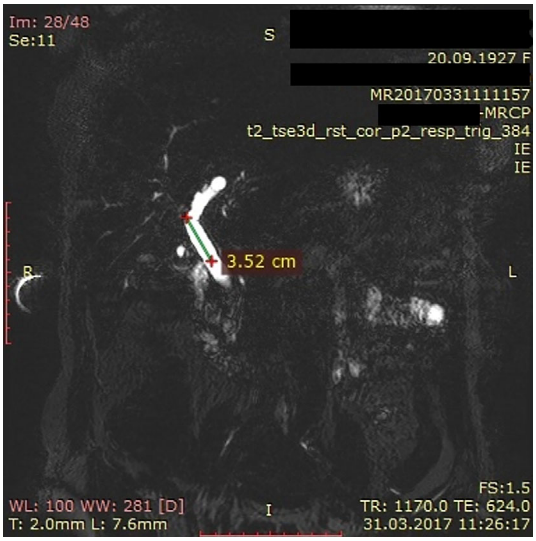


FIGURE 3 CHD length (cm) on MRCP image.

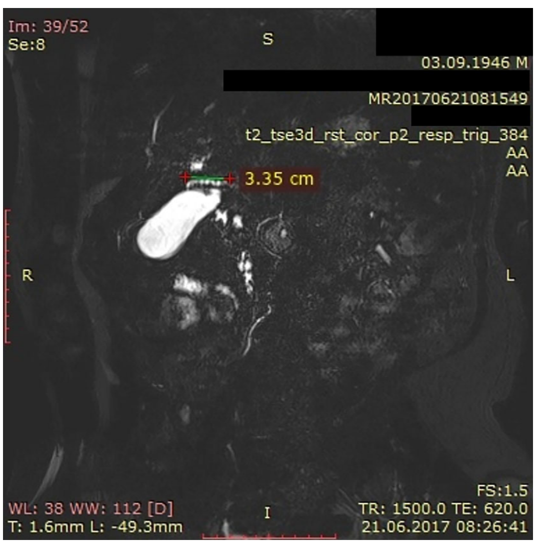


FIGURE 4 CD length (cm) on MRCP image.

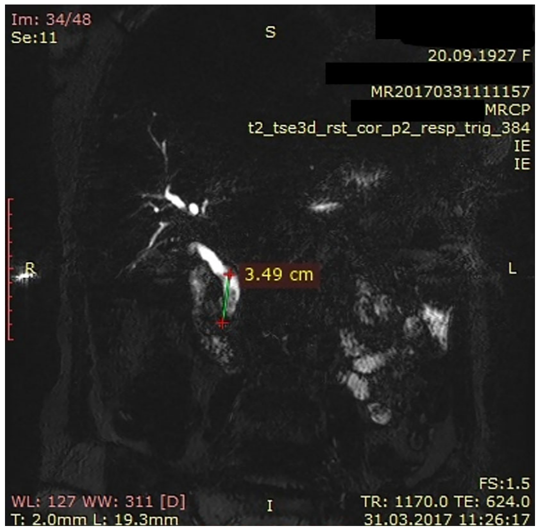


FIGURE 5 BD length (cm) on MRCP image.

examinations are performed with a whole-body Siemens Magnetom Aera Device by using an abdominal coil at 1.5 Tesla units. For T2W-TSE slices, the imaging parameters were set at 1100 ms/620 ms/1 (repetition time [TR]/echo time [TE]/mean number of signals [NSA]). Also, MRCPad and MRCP 3D images were taken and MRCP images were obtained.

2.1 | Statistical analysis

Power analysis was performed by taking a similar study by Sipahi et al. as an example (3). The number of samples was determined as 612, with a minimum of 204 for each group. The IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis in evaluating the findings obtained in the study. The conformity of the variables to the normal distribution was evaluated with the Shapiro-Wilks test, Q-Q graphs, and histograms. The Spearman-rho correlation analysis was used to evaluate the relationship between descriptive

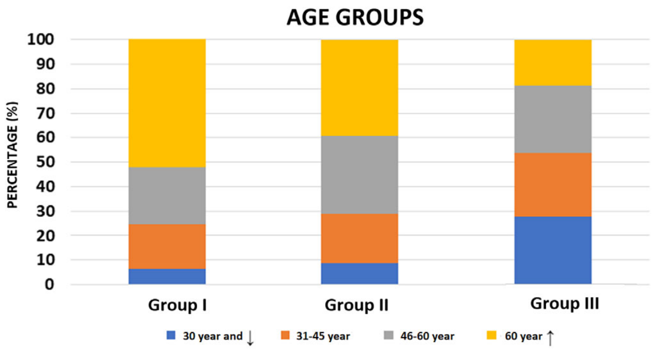


FIGURE 6 The age group distribution of the patients according to groups.

statistical methods (i.e., mean, standard deviation, median, frequency, percentage) as well as quantitative data that did not show normal distribution. The Kruskal Wallis test was used to evaluate the quantitative data, and the Mann–Whitney U test with Bonferroni correction was used to determine the group that caused the difference. The Pearson chi-square test was used in the evaluation of qualitative data. The ROC analysis was used in the diagnostic performance evaluation of the radiological findings. The logistic regression analysis was used to evaluate the risk of choledocholithiasis. Significance was taken as $p < 0.05$.

3 | RESULTS

The study was conducted with a total of 628 patients, 64.2% ($n = 403$) female and 35.8% ($n = 225$) male. The ages of the female patients ranged between 18 and 93, with a mean of 52.07 ± 19.37 years. The ages of male patients ranged between 18 and 90, with a mean of 55.80 ± 17.54 years. The ages of all patients ranged between 18 and 93, with a mean of 53.37 ± 18.87 years. A total of 35% ($n = 220$) of the patients had choledocholithiasis (Group I), 32.5% ($n = 204$) had only cholelithiasis (Group II), and 32.5% ($n = 204$) had BD. The patients in the control group (Group III) who did not have any stones in either the gallbladder formed the control group.

The patients included in the study were divided into age groups considering the age distribution of the patients in all groups (minimum, maximum, mean, median, and quartile values). In this respect, 14.2% of the patients ($n = 89$) were 30 years old or younger, 21.3% ($n = 134$) were between 31 and 45 years old, 27.4% ($n = 172$) were 46–60 years old, and 37.1% ($n = 233$) were over 60 years old (Figure 6).

The incidence of patients aged 30 years and younger in Group III (27.9%) was higher than in Group I (6.4%) and Group II (8.8%) ($p < 0.05$). Also, 42.3% of the patients were male in Group I, 31.4% in Group II were male, and 33.3% in Group III were male (Figure 6, Table 1).

The CD, BD, and CHD lengths of the patients were found to be statistically significantly higher in Group I than in the patients in Group II and Group III ($p < 0.05$) (Figure 7, Table 1).

Statistically significant differences were detected between the groups in terms of SCA averages ($p < 0.001$; $p < 0.01$). The mean SCA of the patients was found to be significantly higher in Group I than the patients in Group II and Group III ($p < 0.01$). No significant differences were detected between the mean SCA scores of the patients in Group II and Group III ($p > 0.05$) (Figure 8, Table 1).

The total bilirubin levels of the patients in Group I were significantly higher than the patients in Group II and Group III ($p < 0.05$). Statistically significant differences were detected between the groups in terms of ALT, ALP, AST, direct bilirubin, CRP, GGT, and leukocyte values of the patients ($p < 0.01$). In this regard, the above-mentioned laboratory values of the patients were found to be significantly higher in Group I than the patients in Group II and Group III. The albumin levels of the patients were found to be significantly higher in Group III than the patients in Group I and Group II ($p < 0.05$). Although the INR levels of the patients were found to be significantly higher in Group I than the patients in Group II and Group III, the INR values of the patients were found to be significantly higher in Group III than in the patients in Group II ($p < 0.05$) (Table 1).

The mean SCA values of the male patients in Group I were found to be statistically and significantly higher than female patients ($p = 0.013$; $p < 0.05$) (Table 2).

In the diagnostic performance test, according to the detection of choledocholithiasis;

The cut-off point for the length of the CD was determined to be 26.5. The sensitivity was 71.57%, the specificity was 55.36%, and the Youden Index was 0.289 for this point. The obtained area under the receiver operating characteristics (ROC) curve was 69.3% and the area under the curve was statistically significant (area under curve (AUC) score = 0.693, 95% confidence interval (CI): 0.646–0.739, $p < 0.05$) (Table 3).

The cut-off point for the length of the CHD was determined to be 24.5. The sensitivity was 76.47%, specificity was 56.62%, and Youden's Index was 0.331 for this point. The obtained area under the ROC curve was 71% and the area under the curve was statistically significant (AUC score = 0.710, 95% CI: 0.664–0.755, $p < 0.05$) (Table 3).

The cut-off point for the BD length was determined to be 35.5. The sensitivity was 71.57%, the specificity was 43.87%, and the Youden Index was 0.154 for this point. The obtained area under the ROC curve was 64.1% and the area under the curve was statistically significant (AUC score = 0.641, 95% CI: 0.592–0.689, $p < 0.05$) (Table 3).

The cut-off point for the cystocholedocal angle was determined to be 33.5. The sensitivity was 65.2%, the specificity was 48.65%, and Youden Index was 0.139 for this point. The obtained area under the ROC curve was 63.4% and the area under the curve was statistically significant (AUC score = 0.634, 95% CI: 0.583–0.686, $p < 0.05$) (Table 3, Figure 9).

TABLE 1 Demographic characteristics of patients, laboratory, and measurement findings.

Variables		Group I choledocholithiasis ($n = 220$) Median (IQR)	Group II cholecystolithiasis ($n = 204$) Median (IQR)	Group III healthy control ($n = 204$) Median (IQR)	*p*-value
Age group, *n* (%)	≤30	14 (15.7)	18 (20.2)	57 (64)	<0.001[a,*]
	31–45	40 (29.9)	41 (30.6)	53 (39.6)	
	46–60	51 (29.7)	65 (37.8)	56 (32.6)	
	>60	115 (49.4)	80 (34.3)	38 (16.3)	
Sex, *n* (%)	Female	127 (57.7)	140 (68.6)	136 (66.7)	0.043[a,*]
	Male	93 (42.3)	64 (31.4)	68 (33.3)	
CD length (mm)		32.50 (16.50)	28.00 (9.00)	24.00 (7.75)	<0.001[b,*]
CHD length (mm)		43.00 (17.80)	38.50 (13.75)	36.00 (12.00)	<0.001[b,*]
BD length (mm)		30.00 (14.00)	27.00 (11.00)	21.00 (6.00)	<0.001[b,*]
SCA (°)		37.00 (17.00)	33.00 (10.00)	34.50 (9.75)	<0.001[b,*]
ALT (U/L)		145.50 (207)	31.00 (96.75)	16.00 (7.00)	<0.001[b,*]
Albumin (g/L)		36.75 (9.43)	40.00 (7.00)	42.00 (6.00)	<0.001[b,*]
ALP (U/L)		232.50 (211.00)	110.50 (117.50)	62.00 (26.25)	<0.001[b,*]
AST (U/L)		104.50 (130.75)	28.00 (62.75)	18.00 (9.00)	<0.001[b,*]
D. Bilirubin (mg/dL)		3.37 (3.60)	0.30 (0.655)	0.20 (0.10)	<0.001[b,*]
T. Bilirubin (mg/dL)		3.76 (3.91275)	0.675 (1.21)	0.70 (0.30)	<0.001[b,*]
CRP (mg/dL)		57.07 (102.40)	9.55 (45.50)	2.00 (1.00)	<0.001[b,*]
GGT (U/L)		298.50 (338.00)	65.00 (219.25)	30.00 (5.75)	<0.001[b,*]
Hemoglobin (g/dL)		12.00 (3.08)	12.50 (2.60)	12.00 (1.00)	0.239[b]
Leukocyte (10^3/μL)		10,190 (6465)	7805 (4495)	6850 (2280)	<0.001[b,*]
INR		1.06 (0.18)	1.00 (0.13)	1.00 (0.10)	<0.001[b,*]

Note: Qualitative data were expressed as n (%) and quantitative data as median (IQR).
Abbreviation: IQR, interquartile change.
[a]Pearson chi-square test.
[b]Kruskal Wallis test.
*p < 0.05.

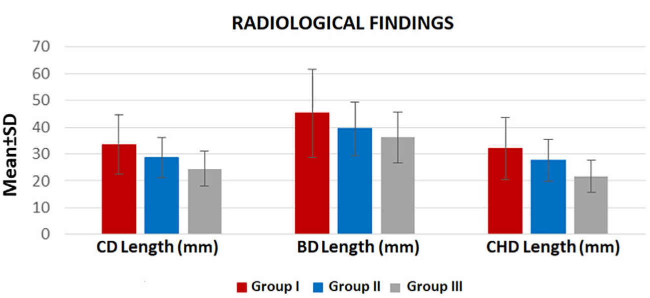


FIGURE 7 Radiological findings of the patients according to the groups.

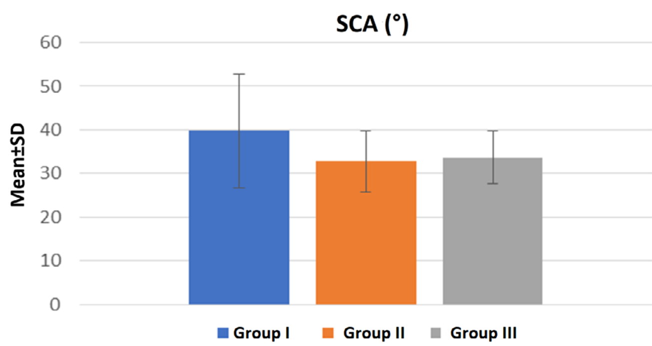


FIGURE 8 The mean SCA values of the patients according to the groups.

3.1 | In Group I

Statistically significant and positive correlations were detected between CD and CHD lengths at 45.4% ($r = 0.454$, $p < 0.001$; $p < 0.05$). Statistically significant and negative correlations were detected between CHD and BD lengths at 17.6% (r: -0.176, $p = 0.012$; $p < 0.05$) (Table 4).

3.2 | In Group II

Statistically significant and positive correlations were detected between CD and CHD lengths at the level of 40.5% ($r = 0.405$, $p < 0.001$; $p < 0.05$). Statistically significant and negative correlations were detected between CHD and BD lengths at the level of 17.3% (r: -0.173, $p = 0.014$; $p < 0.05$) (Table 4).

TABLE 2 Intragroup evaluation of the radiological findings of the patients according to sex.

Clinical findings	Groups	Female (*n* = 403)	Male (*n* = 225)	Test value	*p* value
DC (mm)	Group I	11–65 (32)	11–70 (33)	−0.044	0.965
		33.44 ± 10.77	33.46 ± 11.39		
	Group II	14–53 (28)	17–53 (27.5)	−0.284	0.776
		28.84 ± 7.63	28.61 ± 7.22		
	Group III	13–46 (24)	13–46 (23.5)	−0.069	0.945
		24.57 ± 6.86	24.43 ± 5.88		
DCH (mm)	Group I	14–112 (42)	9.8–97 (43)	−0.494	0.621
		44.79 ± 16.31	44.74 ± 16.17		
	Group II	21–61 (38)	24–75 (39)	−0.217	0.828
		38.93 ± 9.04	40.39 ± 11.74		
	Group III	18–65 (36)	15–65 (34.5)	−1.173	0.241
		36.96 ± 10.00	34.82 ± 8.29		
CHD (mm)	Group I	5–67 (30.5)	6.1–60 (30)	−0.141	0.888
		31.92 ± 11.11	32.22 ± 11.9		
	Group II	12–50 (26)	10–48 (27)	−1.346	0.178
		27.12 ± 7.76	28.66 ± 8.07		
	Group III	6–41 (20.5)	9–34 (21)	−0.667	0.505
		21.51 ± 6.02	21.82 ± 5.57		
SCA (°)	Group I	18–82 (36)	18–98 (41)	**−2.484**	**0.013***
		37.77 ± 13.22	42.57 ± 14.50		
	Group II	19–61 (33)	19–54 (32)	−0.732	0.464
		33.02 ± 7.41	32.44 ± 7.94		
	Group III	21–57 (35)	20–48 (33)	−1.079	0.281
		34.08 ± 6.85	32.85 ± 6.83		

Note: The variables are expressed as minimum–maximum (median) and mean ± standard deviation. Mann Whitney U test *$p < 0.05$.

TABLE 3 ROC curve analysis of patient's measurements in predicting choledocholithiasis.

Measurements	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	Youden index	*p*-value
CD length (mm)	0.693	0.646–0.739	26.5	71.57	57.36	0.289	<0.001*
CHD length (mm)	0.710	0.664–0.755	24.5	76.47	56.62	0.331	<0.001*
BD length (mm)	0.641	0.592–0.689	35.5	71.57	43.87	0.154	<0.001*
SCA (°)	0.634	0.583–0.686	33.5	65.20	48.65	0.139	<0.001*

Abbreviations: AUC, area of under the curve. CI, confidence interval.
*$p < 0.05$.

3.3 | In Group III

Statistically significant and positive correlations were detected between CD and CHD lengths at 52.1% ($r = 0.521$, $p < 0.001$; $p < 0.05$). Statistically significant and positive correlations were detected between CHD and BD lengths at 15.8% (r: 0.158, $p = 0.024$; $p < 0.05$). Statistically significant and negative correlations were detected between CHD length and cystocholedocal angle at 20.3% (r: −0.203; $p = 0.004$; $p < 0.05$). Statistically significant and positive correlations were detected between BD length and cystocholedocal angle at 17% (r: 0.170; $p = 0.015$; $p < 0.05$) (Table 4).

3.4 | In all patients

Statistically significant and positive correlations were detected between CD and CHD lengths at the level of 55.1% ($r = 0.551$, $p < 0.001$; $p < 0.05$). Statistically significant and positive correlations were detected between BD length and cystocholedocal angle at 13.9% (r: 0.139; $p < 0.001$; $p < 0.05$) (Table 4).

Statistically significant correlations were detected between the stone sizes and BD lengths of 26.2% in Group II patients between the ages of 46 and 60 ($p = 0.035$; $p < 0.05$). Statistically significant correlations were detected between stone sizes and BD length of 23.4% in patients over 60 years of age in the same group ($p = 0.036$; $p < 0.05$). In Group II, statistically significant correlations were detected between stone sizes and CD length at the level of 22.5% in patients over 60 years of age ($p = 0.045$; $p < 0.05$) (Table 5).

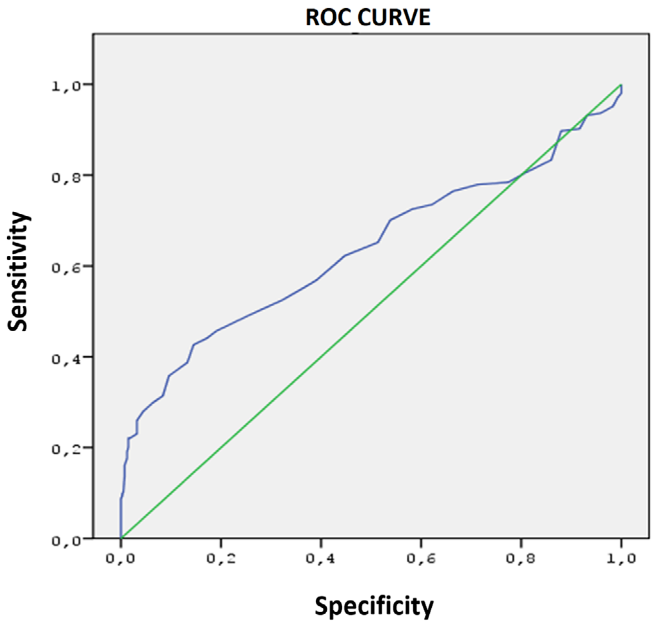


FIGURE 9 The evaluation of the SCA changes with ROC Curve in differentiating patients with choledocholithiasis.

As a result of the univariate evaluations, all variables that were found to be significant were included in the logistic regression analysis. As a result of the logistic regression analysis applied with the backward variable selection method, ALT, albumin, direct bilirubin, CRP, leukocytes, INR, CD, BD, and CHD lengths, and SCA variables were found in the model (Table 6).

Likelihood ratios and Wald tests were used for general model evaluation. According to both tests, the model was found to be statistically significant ($p < 0.001$; $p < 0.05$).

The Hosmer and Lemeshow fit test was used to evaluate the fit of the model. According to this test, it should not be statistically significant for the model to have a good fit. This test was not statistically significant for our model ($p > 0.05$) for this reason, it can be argued that our model had a good goodness-of-fit.

It was found that a one-unit increase in ALT level increased the risk of choledocholithiasis 1.005-fold ($p < 0.001$; $p < 0.05$) and a one-unit increase in albumin level decreased the risk of choledocholithiasis 0.934-fold ($p = 0.004$; $p < 0.05$). It was also determined that a one-unit increase in D. bilirubin level increased the risk of choledocholithiasis 1.595-fold ($p < 0.001$; $p < 0.05$) and a one-unit increase in CRP level increased the risk of choledocholithiasis by 1.004-fold ($p = 0.026$; $p < 0.05$). Also, a one-unit increase in leukocyte level increased the risk of choledocholithiasis 1.000-fold ($p = 0.027$; $p < 0.05$), and a one-unit increase in INR level decreased the risk of choledocholithiasis by 0.278-fold ($p = 0.023$; $p < 0.05$). The risk of choledocholithiasis in patients with cystocholedocal angles of 33.5°

TABLE 4 Correlation analysis between patient's measurements.

	CD length (mm)		CHD length (mm)		BD length (mm)	
Measurements	***r***	***p***	***r***	***p***	***r***	***p***
Group I choledocholithiasis (n = 220)						
CD length (mm)	-	-				
CHD length (mm)	**0.454**	**<0.001***	-	-		
BD length (mm)	−0.034	0.626	**−0.176**	**0.012***	-	-
SCA (°)	0.094	0.183	−0.122	0.082	−0.106	0.131
Group II cholecystolithiasis (n = 204)						
CD length (mm)	-	-				
CHD length (mm)	**0.405**	**<0.001***	-	-		
BD length (mm)	−0.106	0.131	**−0.173**	**0.014***	-	-
SCA (°)	0.011	0.881	0.011	0.874	0.025	0.723
Group III healthy control (n = 204)						
CD length (mm)	-	-				
CHD length (mm)	**0.521**	**<0.001***	-	-		
BD length (mm)	0.108	0.123	**0.158**	**0.024***	-	-
SCA (°)	0.017	0.813	**−0.203**	**0.004***	**0.170**	**0.015***
Total (N = 628)						
CD length (mm)	-	-				
CHD length (mm)	**0.551**	**<0.001***	-	-		
BD length (mm)	0.070	0.083	0.029	0.473	-	-
SCA (°)	**0.096**	0.057	−0.019	0.635	**0.139**	**<0.001***

Abbreviation: r, Spearman's rho correlation coefficient.
*$p < 0.05$.

TABLE 5 The evaluation of the correlation between the stone sizes and radiological findings of the patients according to the age groups.

Stone size		Age groups: 30 years and ↓ Group I	31–45 years Group II	Group I	46–60 years Group II	Group I	60 years and ↑ Group II	Group I	Group II
DC (mm)	*r*	−0.492	−0.038	0.267	−0.184	0.006	0.062	0.078	**0.225**
	p	0.148	0.882	0.139	0.249	0.972	0.621	0.480	**0.045***
DCH (mm)	*r*	−0.160	0.292	−0.126	0.016	0.241	**0.262**	0.062	**0.234**
	p	0.658	0.240	0.491	0.919	0.135	**0.035***	0.575	**0.036***
CHD (mm)	*r*	0.350	0.729	0.136	−0.057	−0.256	0.029	−0.063	0.065
	p	0.322	0.001	0.456	0.724	0.111	0.817	0.569	0.566
SCA (°)	*r*	−0.276	−0.389	−0.115	0.001	0.168	−0.087	0.185	0.114
	p	0.440	0.110	0.531	0.993	0.299	0.066	0.089	0.312

Note: Spearman rho correlation analysis.
p* < 0.05.*p* < 0.01.

TABLE 6 The logistic regression analysis for risk assessment of choledocholithiasis.

Predictor	*β*	SE (*β*)	Wald's χ^2	df	*p*	Odds ratio	95% CI for odds ratio Lower	Upper
Constant	0.023	1.218	0.001	1	0.985	1.023	NA	NA
ALT (U/L)	0.005	0.001	23.735	1	<0.001*	1.005	1.003	1.006
Albumin (g/L)	−0.069	0.024	8.512	1	0.004*	0.934	0.892	0.978
D. Bilirubin (mg/dL)	0.467	0.077	36.363	1	<0.001	1.595	1.370	1.856
CRP	0.004	0.002	4.966	1	0.026*	1.004	1.000	1.007
Leukocyte (10^3/μL)	0.000	0.000	4.887	1	0.027*	1.000	1.000	1.000
INR	−1.281	0.565	5.132	1	0.023*	0.278	0.092	0.841
CD length ≥ 26.5 mm	0.408	0.281	2.113	1	0.146	1.503	0.868	2.605
BD length ≥ 35.5 mm	0.427	0.266	2.577	1	0.108	1.533	0.910	2.584
CHD length ≥ 24.5 mm	0.539	0.285	3.577	1	0.059	1.715	0.981	2.999
SCA ≥ 33.5° mm	0.528	0.254	4.332	1	0.037*	1.696	1.031	2.790
Test			χ^2	df	*p*			
Overall model evaluation								
Likelihood ratio test			343.114	10	<0.001*			
Wald test			65.342	1	<0.001*			
Goodness-of-fit test								
Hosmer and Lemeshow			12,055	8	0.149			

Note: Cox and Snell $R^2 = 0.429$. Nagelkerke R^2 (Max reSCAled R^2) = 0.596.
Abbreviations: CI, confidence interval; NA, not applicable; SE, standard error.
**p* < 0.05.

and above was 1.696-fold higher than those with an angle of less than 33.5° ($p = 0.037$; $p < 0.05$) (Table 6).

4 | DISCUSSION

Bile is a secretion that consists of water, cholesterol, lecithin, bile pigments (bilirubin and biliverdin), and bile salts (sodium glycocholate and sodium taurocholate) (Önür & Beyler, 2001). Choleliths (gallstones) are crystal structures formed in the body by the growth or fusion of normal or abnormal bile components (Dickson, 2019). The presence of one or more stones in the gallbladder is called cholelithiasis, which is a gastrointestinal system disease with the most common surgical indication today. Patients with cholecystectomy operation within the indication might face various preoperative and postoperative complications. For this reason, it is very important to know the etiologies causing cholelithiasis (Venneman & van Erpecum, 2010).

Choledocholithiasis, which develops because of cholelithiasis, is the state of stone formation in the biliary tract, in which the bile produced in the liver is transmitted to the gallbladder. The resulting cholangitis might cause serious life-threatening clinical pictures. For this reason, studies conducted on the etiology and treatment of the disease are important. Choledocholithiasis might develop primarily in the form of new stone formation (Denova) in the biliary tract, or it may occur secondarily when stones in the gallbladder enter the duct. There are many anatomical variations in both intra- and extrahepatic BDs (Collins et al., 2004). However, the significance of these variations and the anatomical characteristics of the biliary tract on the motility of bile fluid and the occurrence of cholelithiasis/ choledocholithiasis is unknown. It has been reported in recent studies that structural differences in the biliary tract may cause resistance to bile flow and cause gallstone formation. It was observed that the bile and biliary tract were examined in many studies, but the angle between cystic duct and BD was examined in a limited number of studies. This angle was first reported by Sipahi et al., who defined it as the SCA SCA, and argued that as SCA increased, it might be effective in the formation of cholelithiasis by changing the bile flow (Sipahi et al., 2015). In his study, Medisoglu named the angle between BD and CD as the DCH-DCY junction angle and argued that the presence of stones in these anatomical structures had no effect on the angle (Medişoğlu, 2019).

In this study, as in the study of Sipahi et al., the junction angle of CD and BD was named SCA. In the present study, the primary purpose was to compare SCA in two different patient groups with choledocholithiasis and those with only cholelithiasis, and uncover whether the angle is important in the passage of stones into the extrahepatic BDs. It was also aimed to standardize the data obtained by examining SCA in the control group patients without stones in the Turkish population and to uncover the effects of the presence of stones on this angle. As well as these, CD, BD, and CHD lengths and stone sizes in the patient groups with gallstones were also measured and a comparison was made in this respect. As well as the radiological measurements of the patients, their clinical findings and demographic characteristics were also compared.

There are various invasive and non-invasive techniques enabling the evaluation of the BDs. In cases of obstruction of the biliary system, it is an important factor in the preference of the MRCP Method and provides information on the state of the biliary tract both proximal and distal to the obstruction. However, it is also important in the evaluation of simultaneous choledocholithiasis in patients with acute cholecystitis (in the presence of elevated liver transaminase values and total bilirubin values, and/or in the presence of anatomical changes in the BD on USI). For all these reasons, MRCP is the most preferred imaging method in the evaluation of similar clinical manifestations (Fulcher & Turner, 2002; Sipahi et al., 2015; Taourel et al., 1996). In the present study, the images of 628 patients who had MRCP images were used because of their superiority in showing the biliary tract in detail. The mean SCA scores of the patients who were included in the study were between 18° and 98°, and statistically significant differences were detected between the groups in this regard ($p < 0.001$). The mean SCA of the patients with choledocholithiasis was found to be significantly higher than the patients in the patient group with only cholelithiasis and the control group. However, no significant differences were detected between the patients with only cholelithiasis and the control group. The cut-off value was determined to be 33.5° in the diagnostic performance test performed to determine from which degree SCA can be distinguished for the presence of choledocholithiasis. The data obtained here show us that the SCA value above this value strengthens the presence of choledocholithiasis in the patient. In the logistic regression analysis based on this idea, it was found that SCA is an important variable in determining the presence of stones in the common BD, and it was determined that a one-unit increase in SCA increased the probability of choledocholithiasis by 1.696-fold.

No other studies were found in the literature comparing SCA between patients with choledocholithiasis, those with only cholelithiasis, and those without stones. Although studies that examined SCA are limited, Sipahi et al. examined SCA and its relationship with cholelithiasis on MRCP images of 38 patients with cholelithiasis and 88 patients without cholelithiasis and reported that similar to the results of the present study, the drainage of bile fluid would be impaired and cholelithiasis formation would increase as SCA increased (Sipahi et al., 2015). Medisoglu detected cholelithiasis in 28 of 79 cases (41 males and 38 females) and choledocholithiasis in 27 of them. In this regard, although the mean BD-CD junction angle was 41.05°, it was reported as 33.9° in women and 48.6° in men (Medişoğlu, 2019). In the present study, when the comparison of SCA was made with sex between groups, it was found to be 37.77° in women for Group I and 42.57° in men, and there was a statistically significant difference between the sexes ($p < 0.001$). Although the mean SCA value was 33.02° in women for Group II, 32.44° in men, and 34.08° in women for Group III, it was 32.85° in men (Table 2). However, no statistically significant differences were detected in SCA values between the sexes for both Group II and Group III ($p > 0.05$). Although the mean angles in women were similar to our study, it was observed that the mean SCA scores of men were higher than in our study. Medisoglu also reported that there were no significant relationships between SCA, sex, and age (Medişoğlu, 2019). Similarly, in the present study, when SCA was compared with age, no statistically significant differences were detected between the age groups and the mean SCA values of the patients in all three groups ($p > 0.05$). This result showed that the joining angles in anatomical structures are genetically-based and will not change with age unless there is an external intervention. When the relationship between the sex and SCA was evaluated, no significant relationship was found in Group II and Group III, but SCA values of male patients in the patient group with choledocholithiasis were found to be significantly higher than in females ($p = 0.013$; $p < 0.05$). Also, a statistically positive and significant correlation was detected between the stone sizes of male patients with choledocholithiasis ($p < 0.05$). We think that our study is important because the SCA value between patient groups was compared separately for the sex and age groups.

Various studies investigated the effects of anatomical variations of the biliary tract on the occurrence of cholelithiasis. In his study, Medisoglu classified the BD variations according to the Huang calcification method and reported that the variations had no effects on the formation of cholelithiasis/choledocholithiasis and SCA. As well as the biliary tract variations, it was reported that the variations of the CD are quite high (Medişoğlu, 2019). CD has 3 different opening variances as angular, parallel, and spiral. Among these, the most common is the angular type joint with a rate of 75% (Fong & Blumgart, 2000). Since the opening variants of the CD were not the subject of the present study, the frequency of variance and angulation changes were not evaluated. However, these different variants can cause angulation changes, resulting in changes in SCA. We believe that it would be appropriate to address this issue in another study.

In his study, Warren BL. reported that the stone in the gallbladder passes more easily to the extrahepatic BDs with the increased SCA, which causes angulation in the BD and may cause the formation of choledocholithiasis (Warren BL. Association between Cholangiographic Angulation of the Common BD and Choledocholithiasis, 1987). In the present study, it could not be evaluated whether the change in SCA caused choledocholithiasis or choledocholithiasis caused the change in SCA. The reason for this was that the patients followed and measured in such a study should include the period before, during, and after the formation of gallstones, when the stone enters the CD. This makes it impossible to conduct such a study. However, it is possible to argue that the SCA changes with the increased CD length and/or BD length and causes elbows in the BD, which may cause choledocholithiasis similar to the literature, and that the increased BD length also increases the SCA value (Table 3). In the diagnostic performance test (ROC analysis) made to uncover the effects of the anatomical structures of the extrahepatic BDs on the presence of choledocholithiasis, it was determined that CD length over 26.5 mm, CHD length over 24.5 mm and BD length over 35.5 mm increased the risk of choledocholithiasis (Table 3). Also, it was found in the logistic regression analysis that a one-unit increase in these lengths increased the probability of choledocholithiasis 1.50, 1.71, and 1.53-fold, respectively (Table 6).

Various etiological factors are involved in the formation of gallstones. The main ones are environmental and genetic factors. Also, increased cholesterol synthesis, decreased bile salt secretion, decreased absorption of bile salts in the intestines, and motility disorders of the gallbladder are among the most common etiological factors (Venneman & van Erpecum, 2010). When the literature was reviewed in this respect, studies were found revealing the effects of age and sex along with these factors in stone formation. Age and sex are variables that cause anatomical differences in the BDs in humans. Previous studies show that the prevalence of cholelithiasis is higher in women than men in all age groups (Aerts & Penninckx, 2003; Everhart et al., 1999; Medişoğlu, 2019). It was reported that this difference may be because of genetic structure and hormonal reasons, as well as the difference in body mass index and the higher waist-hip ratio in women (Festi et al., 2008; Palermo et al., 2013; Yildirim et al., 2008). Similar to the literature data, statistically significant differences were found in the present study between the presence of cholelithiasis and sex groups ($p < 0.05$). The incidence of both cholelithiasis and choledocholithiasis in women was found to be significantly higher than in men in the present study, which shows us that not only the formation of gallstones but also the anatomical structures in which the stone is located are different between the sexes. Another situation is that the incidence of cholelithiasis increases with age. Similar to the literature data, it was found in the present study that the incidence of cholelithiasis increased with age, which also included choledocholithiasis (Table 1). When the results of our study were evaluated, it is possible to argue that the probability of choledocholithiasis and/or cholelithiasis increases with age after the age of 30. While the incidence of being 30 years old or younger in the patient groups was 27.9% in Group III, this rate was 6.4% in Group I and 8.8% in Group II. Medisoglu reported in his study that, contrary to the literature data and the results of our study, the incidence of cholelithiasis did not have a significant relationship with age groups ($p > 0.05$). He supported both the literature and the results of our study by stating that the incidence of choledocholithiasis increased in people over the age of 45 ($p < 0.05$) (Medişoğlu, 2019). Attili et al. reported that the prevalence of cholelithiasis was two-three-fold higher in women than in men under 50 years of age, but less than twice in men over 50 years of age, in large cohort studies of 46.139 people, 29.739 of whom had abdominal USG results (Attili et al., 1995). Previous studies also showed that these prevalence differences between women and men differed according to age, and this difference was more significant in young people compared to older adults (Maurer et al., 1989; The Rome Group for Epidemiology and Prevention of Cholelithiasis (GREPCO), 1988; Sampliner et al., 1970). Although sex and age are important variables in detecting the presence of choledocholithiasis, it was not included as a significant variable among the risk factors with priority compared to other parameters in the logistic regression analysis made in the present study (Table 6).

Frossard et al. reported in their study that stones that had a size of ≤8 mm in the vesica biliaris fell into the BD in a short time in some patients, and they did not cause any complaints for a long time in others (Frossard et al., 2000). Although the reason for this was not elucidated fully, the stone sizes of Group I and Group II patients were compared in the present study to determine the relationship between choledocholithiasis and stone sizes. Stone sizes of patients with choledocholithiasis were found to be statistically larger than those with only cholelithiasis ($p < 0.001$; $p < 0.01$). Although it is expected that the stone sizes of patients with cholelithiasis are larger because of the volumetric size of the gallbladder, the fact that the stones are usually at subcentimetric level and the diameter of the BD is narrower indicates that small stones are more likely to enter or remain in the gallbladder, and large stones increase the probability of remaining in the BD. For this reason, we think that the stone sizes of patients with choledocholithiasis were found to be larger. It was also observed that the stone sizes of patients with choledocholithiasis increased with age over the age of 30 ($p < 0.05$). Similar to the results of the present study, Medisoglu reported in his study that there was a positive correlation between stone size and the age of patients with choledocholithiasis (Medişoğlu, 2019). He also reported that there is a positive relationship between the diameter of the BD and age, which is because of the increased elasticity of the diameter of the BD with age (Medişoğlu, 2019). We also think that the increasing stone size in patients with choledocholithiasis with age is because of the same reason (Table 5). When the correlation between stone sizes and radiological findings was examined, a positive and significant correlation was detected between the mean BD length and stone sizes of only patients with cholelithiasis ($p < 0.01$). Based on this result, we think that the increased length of the BD also increases the possibility of stone formation in the gallbladder by making it difficult for the bile to reach the duodenum, which may enlarge the existing stone and cause new stone formation. New studies are needed to evaluate this aspect. We intend to address this hypothesis in another study.

Significant changes in the configuration of the extrahepatic BDs also increase the risk of choledocholithiasis. In a study that included 259 patients published in 2011 conducted by Seo et al., it was shown that performing T-tube drainage in the extrahepatic biliary tract and elbowing in the BD may increase stone formation in these tracts (Seo et al., 2011). In this respect, pregnancy can be given as an example. It was reported that gallstone formation increases during pregnancy and as a result, biliary diseases increase. The primary reason for this is the changes in hormones (Pitchumoni & Yegneswaran, 2009). Laboratory findings are also important in the diagnosis of cholelithiasis and choledocholithiasis in addition to anamnesis and physical examination. Laboratory findings of patients with cholelithiasis include leukocytosis and a left shift in the form of bands. Bilirubin and alkaline phosphatase elevations are not seen in non-complicated acute cholecystitis because the obstruction is limited only to the gallbladder. However, mild elevations in bilirubin, aminotransferases, and amylase were also reported in the literature. It is considered that this may be because of the passage of mud and pus (Kurzweil et al., 1994). Elevated bilirubin also causes liver dysfunction. In cases with a functional deterioration in the liver, the coagulation factors synthesized from the liver also deteriorate leading to prolonged laboratory values of Pt, aPTT, and for this reason, an increase in the INR value (Fargo et al., 2017). Also, elevated bilirubin is one of the important symptoms of choledocholithiasis. When the results of the present study were evaluated, it was found that a one-unit increase in the direct bilirubin level of the patients increased the risk of choledocholithiasis 1.595-fold ($p < 0.001$; $p < 0.01$). Right upper quadrant or epigastric pain and elevation of cholestasis enzymes (elevated ALP, GGT, and bilirubin) make the clinician suspect choledocholithiasis in patients admitted to the hospital with mostly symptomatic complaints and an ALT/ALP ratio of two or fewer is an indication of extrahepatic cholestasis in patients with clinically elevated bilirubin (Chalasani et al., 2014). Liver enzyme tests resulting in normal values are very important in excluding the diagnosis of choledocholithiasis. The return of liver enzyme tests to normal values with the resolution of symptoms indicates that the patient has spontaneously excreted gallstones (Stender et al., 2013). In the present study, ALT, ALP, AST, direct bilirubin, CRP, GGT, and leukocyte levels of the patients were found to be significantly higher in Group I than the patients in Group II and Group III ($p < 0.001$). Since albumin is a negative acute phase reactant, it is expected to be low in case of inflammation in the body (Peters Jr., 1995; Sirico et al., 2012). Protein, albumin, and prothrombin time, or INR, are associated with liver synthesis function. Low protein and albumin, or prolonged prothrombin time or INR level, show decreased synthetic function because of hepatic decompensation (Fargo et al., 2017). Also, it was found that the albumin values of the patients were higher in Group III than the patients in Groups I and II, and the albumin values of the patients were higher in Group II than the patients in Group I. Our results were consistent with the literature data. In the logistic regression analysis made to determine the parameters that pose a risk for the presence of choletocholithiasis in the present study, it was found that a one-unit increase in ALT, albumin, direct bilirubin, CRP, leukocytes, and INR levels, which were among the laboratory findings of the patients, affected the risk of choledocholithiasis significantly (Table 6).

In conclusion, it was found that CD, BD and CHD lengths and SCA averages were higher in patients with choledocholithiasis in the present study. As the SCA increases (over 33.5°), the probability of choledocholithiasis increases because it will become easy for the stone in the gallbladder to enter the biliary tract.

The present study was the first to compare patients with choledocholithiasis and patients with cholelithiasis in terms of SCA; uncover a certain standardization with the measurements of these anatomical structures in the stone-free control group; compare radiological measurements with laboratory values and demographic characteristics among patient groups; compare the size of existing stones with radiological measurements and demographic characteristics in patients with choledocholithiasis and cholelithiasis because the number of the patients who were included was higher than previous studies. Because of all these reasons and the results obtained, we think that our data are important and that they can create a roadmap and guide clinicians in the diagnosis and treatment approach.

However, there were also limitations in the present study. The data of the patients in the control group were collected from patients who had pancreatitis, who were examined for various lesions of the liver or pancreas, instead of normal healthy individuals, two people made measurements in the evaluation of the data (a radiologist and an anatomist), and functional disorders were not evaluated in terms of stone formation. Also, our results might differ in genetically different societies because they contained certain social data. However, the data of a single high-volume tertiary center were shared in the study, and we think that the results will be more meaningful with prospective multicentric studies.

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