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Research article

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Risk factors determining bile leakage after multiple liver hydatid cyst surgery

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Abstract

Background/Aim: Biliary leaks are the main source of morbidity after liver hydatid cyst surgery. Many identified factors have been examined in predicting biliary leaks. The aim of this study was to determine the postoperative bile leakage rate and predictive factors affecting bile leakage in multiple liver hydatid cysts.
Method: In our retrospective cohort study, the data of 130 patients who underwent multiple liver hydatid surgery in our clinic between January 2007 and November 2013 were analyzed.
Results: In the 130 patients with multiple cysts, 323 hydatid cysts were detected. The number of cysts was 2 in 65.4% of the patients, and 3 or more in 34.6% of the patients. The postoperative bile leakage rate was 19.2%. According to the univariate analyses, during the preoperative period, the presence of jaundice, fever, leukocytosis, eosinophilia, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, alkaline phosphatase, and direct bilirubin increase, the largest cyst being located in the perihilar region, the mean diameter of the cyst, the diameter of the largest cyst, biliary tract dilatation on the preoperative images, and infection were associated with increased postoperative bile leakage. In the multivariate analyses, eosinophilia and biliary tract dilatation on the preoperative images were found to be independent risk factors for postoperative bile leakage.
Conclusion: In this study, the most determining factors for bile leakage after multiple liver hydatid cyst surgery were a high eosinophil rate and the presence of dilatation in the biliary tract on the preoperative radiological images.

Keywords: Liver, Hydatid cyst, Bile leak

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Introduction

Hydatid cyst is a zoonotic disease caused by infection with the larval form of *Echinococcus granulosus* and can affect almost all organs in the body but usually affects the liver (50–70%) followed by the lungs [1, 2]. Hydatid cyst is, above all, a public health problem and a preventable disease and is among the 17 neglected tropical diseases, according to the World Health Organization (WHO). It reportedly affects more than a million people around the world and results in three billion dollars in medical costs each year. Turkey is among the highly endemic regions where over 50/100,000 individuals develop hydatid cysts annually [3]. It is still a major public health problem in many parts of the world due to infected dogs, unregulated animal slaughter, and hygiene issues. Hydatid disease is endemic in many parts of the world and is quite common in countries engaged in agriculture and animal husbandry.

Currently, the preferred treatment of liver hydatid cysts is surgery. Treatment primarily aims to inactivate the parasite, empty the cystic cavity and prevent contamination, and to obliterate the remaining cavity by eliminating the germinal layer and all living components [4, 5].These principles apply to all types of surgical treatment options.

The most common complication of liver hydatid cysts is cysto-biliary communication (CBC), which was reported at a rate between 13% and 37% in the literature [6]. After the relationship of the cyst cavity with the biliary system, a clinical spectrum of disease can be seen, ranging from biliary symptoms to systemic findings. This relationship can be in the form of a major or minor relationship. A major CBC is usually associated with jaundice and cholangitis, while a minor CBC is usually asymptomatic and presents with postoperative bile leakage and the preoperative diagnosis is difficult. The postoperative biliary complication rate reported in the literature was between 2.6% and 28.6% [7]. The risk factors of this complication, which is the main source of morbidity after liver hydatid cyst surgery, have not been well defined in studies conducted to date. If these risk factors can be determined well, the biliary complication rate can be reduced by additional interventions and treatments during the preoperative and peroperative periods.

In a previous study that included only solitary liver hydatid cysts and excluded multiple cysts, we found that cyst diameter, perihilar localization, ALP elevation, and World Health Organization-International Working Groups of Echinococcosis (WHO-IWGE) stage was associated with postoperative biliary leakage [8].

Multiple cysts make up 29-38% of liver hydatid cysts [9, 10]. Studies reported that the number of cysts did not affect postoperative bile leakage but did not evaluate the differences in the identified risk factors in cases of multiple cysts.

The aim of this study was to determine the rate of biliary leakage in multiple liver hydatid cysts and the risk factors affecting it.

Materials and methods

In our clinic, a total of 370 patients underwent surgical treatment for liver hydatid cyst between January 2007 and November 2013. As per the purpose of this study, 240 patients with radical resection and/or operated for solitary cyst were excluded. Additionally, 130 patients who underwent multiple liver hydatid cyst surgery were included in the study. The data were obtained by retrospective analysis of the prospective patient records.

Preoperative Evaluation

Patients presenting with asymptomatic or different symptoms were recorded. Ultrasonography (USG), computed tomography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography were used as the imaging methods for diagnosis, and the indirect hemagglutination test was used as serological test. The leukocyte count and eosinophil ratio were recorded as the hematological parameters and alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and direct bilirubin were recorded as the biochemical parameters.

Peroperative evaluation

After the general abdominal exploration, preparations were made for the hydatid cyst. In some cysts with difficult localization, peroperative USG was performed and the location of the cyst was determined. Compresses that had been soaked scolicidal agent (combination of 0.5% cetrimide and 0.05% chlorhexidine; Savlex, Drogsan, Ankara, Turkey) were placed around the cyst and then, cyst puncture was performed. Cyst aspiration was continued until the fluid inside of the cyst was had all been removed. If the cyst content was clear, a scolicidal agent was inserted inside of the cyst cavity and left therefor 10min. A scolicidal agent was not given if the cyst content was biliary or purulent. After performing the cystotomy, the cyst contents were removed along with the germinative membrane, very carefully, without contaminating the environment. After the cyst pouch had been rinsed again with scolicidal material, it was washed with 0.9% NaCl. If there was a free cyst wall, it was removed as a partial cystectomy. Continuous 2/0 absorbable sutures were used at the edges of the cyst in the event of hemostasis and bile leakage. When a cystobiliary relationship was detected, it was closed with absorbable sutures. Next, a cavity check was performed, depending on the preference of the surgeon, comprising capitonnage, introflection, or drainage. The operation was ended by placing drains in all of the patients according to the location of the cysts.

Postoperative follow-up

Oral nutrition was given to all of the patients on the first postoperative day. The drain was kept in for at least 3 days, and removed if the drainage amount was less than 30 cc and there was no bile. If the drainage content was biliary, it was considered as a biliary leak. Endoscopic retrograde cholangiopancreatography (ERCP) was performed on patients whose bile leakage lasted for longer than 10 days. Sphincterotomy, nasobiliary drain, or stent placement was performed according to these findings. Percutaneous drainage was performed and antibiotic treatment was initiated in patients with intraabdominal collections or abscesses. Despite all of these attempts, relaparotomy was performed in cases whose intraabdominal sepsis findings could not be controlled. All morbidities (Clavien&Dindo classification) and mortality, if any, that developed in the postoperative period, were recorded.

Identified risk factors

Potential risk factors for the cysts and patients were determined based on the literature information and clinical experience. Accordingly, risk factors for bile leakage after hydatid cyst surgery were determined as: age, gender, presence of recurrence, number of cysts, diameters of cysts, presence of cysts in perihilar or peripheral location, hydatid cyst classification of the WHO-IWGE, surgical procedures performed (omentopexy, introflexion, and external drainage), cyst contents (bile/infected and clear), presence of symptoms (abdominal pain, fever, and jaundice), and laboratory tests (leukocyte count, eosinophil rate, ALT, AST, ALP, GGT, and direct bilirubin). Cyst locations were defined according to preoperative imaging methods and peroperative findings. If the cyst was associated with more than one segment, the segment where it was dominant was considered the segment localization of that cyst. The cyst diameter was recorded based to the preoperative radiological imaging methods used. The nature of the cyst contents was decided according to the first cyst aspiration during surgery. The liver segmental anatomy of Couniad and Bizmuth was used while determining the perihilar and peripherally located cyst groups. Accordingly, in this study: segments I, III, IVb, and V were considered as perihilar segments, while segments II, IVa, VI, VII, and VIII were considered as peripheral segments.

Statistical analysis

All patient data were obtained from the forms prepared for this study. Statistical evaluation of the data obtained was performed using SPSS Statistics for Windows 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were shown as the mean ± standard deviation (minimum-maximum) for continuous variables, and as the number of cases and percentage (%) for the categorical variables. In the evaluations, the chisquare and Fisher exact tests were used for comparisons of the categorical variables related to bile leakage, and the t test was used for the independent samples indicated by measurement. In addition, univariate and multivariate logistic regression analyses were used to determine the factors affecting bile leakage. Statistical significance was accepted as $P<0.05$. For the multivariate logistic regression analysis, the limit for including variables in the model was accepted as 0.10. The odds ratio (OR) and 95% confidence interval (CI) for each variable were calculated.

Results

In the 130 patients with multiple cysts,323 hydatid cysts were detected. The postoperative bile leakage rate was 19.2%. Of the patients,61.5% were male and 38.5% were female. The rate of bile leakage was found to be higher in the males than in the females, but it was not statistically significant ($P= 0.275$). The mean age was 47.2 (17.7)years in the group with bile leakage and 42.5 (.1)years in the group without. The difference was not statistically significant ($P=0.224$). The rate of bile leakage was higher in the symptomatic patients than in the asymptomatic patients (20% vs. 10%,$P=0.390$). When evaluated according to the laboratory results, the leukocyte count and eosinophil rates were found to be significantly higher in the patients with bile leakage ($P=0.011$ and$P<0.001$, respectively). ALT, AST, ALP, GGT and direct bilirubin levels were also found to be statistically significantly higher in the patients with bile leakage ($P=0.002$, $P=0.017$, $P=0.03$, $P<0.001$, and $P<0.001$, respectively). With regards to the ALP level, when it is between 1 and 2 times that of the normal level, bile leakage increases by 1.2 times; when it is between 2 and 3 times, the leakage rate increases by 4.6 times; and when it is 5 times or more, the risk of bile leakage increases by 7.4 times. With each 1 mg/dL increase in the direct bilirubin level, bile leakage rate increases by 3.2 times. In the current study, bile leakage was detected as 7 times more than normal in patients with increased direct bilirubin levels. With regards to the GGT level, when it is between 1 and 2 times that of the normal level, the bile leakage rate increases by 3.7 times; when it is between 2 and 3 times, the leakage rate increases by 4.9 times; and when it is 3 or more, the risk of bile leakage increases by 15.7 times.

The number of cysts was 2in 65.4% of the patients and3or more in 34.6% of the patients. The bile leakage rate was found as 18.8% in the patients with 2cysts, and 20% in the patients with 3or more cysts, but the difference was not statistically significant ($P=0.871$). When all of the cysts were taken into account, the mean cyst diameter was 6.9 (3.2) cm. The mean diameter of the cysts was 7.9 (3.7) cm in the group with bile leakage, while it was 6.7 (3.04) cm in the group without. The difference was found to be statistically significant ($P=0.008$). When calculated only for the diameter of the largest cyst, the mean diameter of the cysts was 10.4 (3.5) cm in the group with bile leakage, while it was 8.6 (3.1) cm in the group without, and the difference was statistically significant again ($P=0.012$). Moreover, 56.9% of the patients had perihilar cysts, while 43.1% had peripheral localized cysts. While the bile leakage rate was 23% in the group with perihilar cysts, it was 14.3% in the group with peripherally located cysts. The bile leakage rate was found to be higher in the group with perihilar cysts, but it was not statistically significant ($P=0.213$). However, the bile leakage rate was found as 35.7% in patients where the largest cyst was located in the perihilar region, while it was 14.7% where the largest cyst was found to be in the peripheral location. The difference was statistically significant. ($P=0.012$). The location of the largest cyst according to the segment level and bile leakage rates are given in Table 1.

Table 1: Bile leakage rates by segment location of the largest cyst

Location	With bile leak	Without bile leak	Total
Segment I	1 (100%)	0 (0%)	1 (0.8%)
Segment II	0 (0%)	13 (100%)	13 (10%)
Segment III	1 (14.3%)	6 (85.7%)	7 (5.4%)
Segment IVa	1 (20%)	4 (80%)	5 (3.8%)
Segment IVb	4 (50%)	4 (50%)	8 (6.2%)
Segment V	4 (33.3%)	8 (66.7%)	12 (9.2%)
Segment VI	5 (27.8%)	13 (77.2%)	18 (13.8%)
Segment VII	3 (8.1%)	34 (91.9%)	37(28.5%)
Segment VIII	6 (20.7%)	23 (79.3%)	29 (22.3%)
Total	25 (19.2%)	105 (80.8%)	130 (100%)

In the patient group with bile or infected cyst contents, postoperative bile leakage rate was found to be higher (40%) than the clear group (8.2%), and the difference was statistically significant ($P<0.001$).When the bile ducts were evaluated based on the preoperative images, the bile leakage rates were 7.4% in the patients without biliary duct dilatation (BDD), 34.8% in the patients with localized bile duct dilatation, 77.8% in patients with left or right intrahepatic biliary duct (IHBD) dilatation, and 100% in the patients with diffuse IHBD and extrahepatic BDD (EHBD). When the groups were compared, as the bile duct

dilatation increased, the rate of biliary leakage increased (P<0.001).

Herein, the rate of CBC was 36.9%. In patients with CBC, the opening was closed by primary suturing. Postoperative bile leakage developed in 41.7% of these patients. However, postoperative bile leakage was prevented in 58.3% with the repair. The postoperative bile leakage rate was found as 6.1% in patients without peroperative CBC.

According to the univariate analysis, age, gender, and number of cysts were not associated with bile leakage. In the preoperative period, the presence of jaundice or fever, leukocytosis, eosinophilia, increase in AST, ALT, GGT, ALP, and direct bilirubin levels, the largest cyst being located in the perihilar region, mean cyst diameter, the largest cyst diameter, BDD on the preoperative images, and infected or bile contents of the cyst were associated with increased postoperative bile leakage. The univariate statistical analysis results of the patient risk factors determined for bile leakage after multiple liver hydatid cyst surgery are given in Table 2, and the factors for cysts are given in Table 3. In the multivariate analyses, eosinophilia and BDD on the preoperative images were found to be independent risk factors for postoperative bile leakage (Table 4).

Table 2: Univariate statistical analysis results of patient risk factors

Risk Factors	Leakage (–) n (%)		Leakage (+) n (%)		Total n	*P*-value
Age (year), mean	42.5 (15.1)		47.2 (17.7)			0.224
	105	(80.8%)	25	(19.2%)	130	
Gender						
Male	38	(76.0%)	12	(24.0%)	50	0.275
Female	67	(83.8%)	13	(16.2%)	80	
Symptom						
Yes	96	(80.0%)	24	(20.0%)	120	0.390
No	9	(90.0%)	1	(10.0%)	10	
Pain						
Yes	94	(80.3%)	23	(19.7%)	117	0.526
No	11	(84.6%)	2	(15.4%)	13	
Jaundice						
Yes	1	(10.0%)	9	(90.0)	10	<0.001
No	104	(86.7%)	16	(13.3%)	120	
Fever						
Yes	4	(33.3%)	8	(66.7%)	12	<0.001
No	100	(85.5%)	17	(14.5%)	117	
Eosinophilia						
Yes	18	(54.5%)	15	(45.5%)		<0.001
No	87	(89.7%)	10	(10.3%)		
AST level(U/L)						
Normal	90	(84.9%)	16	(15.1%)	106	0.017
High	15	(62.5%)	9	(37.5%)	24	
ALT level (U/L)						
Normal	86	(86.9%)	13	(13.1%)	99	0.002
High	19	(61.3%)	12	(38.7%)	31	
GGT value (U/L)						
Normal (≤61)	77	(91.7%)	7	(8.3%)	84	<0.001
Up to 2 times(62–122)	12	(75.0%)	4	(25.0%)	16	
More than 2times (>122)	16	(53.3%)	14	(46.7%)	30	
ALP values(U/L)						
Normal (0-40)	52	(88.1%)	7	(11.9%)	59	0.030
Up to 2 times (41–80)	31	(86.1%)	5	(13.9%)	36	
2–3 times (81–120)	13	(61.9%)	8	(38.1%)	21	
3–5 times (121–200)	7	(70.0%)	3	(30.0%)	10	
More than 5 times (≥201)	2	(50%)	2	(50%)	4	
Direct bilirubin						
Normal	89	(98.0%)	11	(11.0%)	100	<0.001
High	16	(53.3%)	14	(46.7%)	30	

Table 3: Univariate analysis results of factors related to cysts

Factors	Leakage (–) n (%)		Leakage(+) n (%)		Total n	*P*-value
Number of cysts						
2	69	(81.2%)	16	(18.8%)	85	0.871
3 or more	36	(80.0%)	9	(20.0%)	45	
Perihilar location (any of the cysts)						
Yes	57	(77.0%)	17	(23.0%)	74	0.213
No	48	(85.7%)	8	(14.3%)	56	
Diameter of the largest cyst (mean)	105	8.6 (3.1) (80.8%)	25	10.4 (3.5) (19.2%)	130	0.012
Location of largest cyst						
Perihilar	18	(64.3%)	10	(35.7%)	28	0.012
Peripheral	87	(85.3%)	15	(14.7%)	102	
Cyst content						<0.001
Bile/infected	27	(60.0%)	18	(40.0%)	45	
Clear	78	(91.8%)	7	(8.2%)	85	
BDD on imaging						
No BDD	88	(92.6%)	7	(7.4%)	95	<0.001
Localized BDD	15	(65.2%)	8	(34.8%)	23	
Right or left IHBD dilatation	2	(22.2%)	7	(77.8%)	9	
IHBD + EHBD dilatation	0	(0%)	3	(100%)	3	

BDD: bile duct dilatation, IHBD: intra hepatic bile duct, EHBD: extra hepatic bile duct.

Table 4: Risk factors detected for bile leakage in the multivariate logistic regression model

Variables	Odds ratio	*P*-value	95% CI	
			Lower limit	Upper limit
Eosinophilia	4.935	0.006	1.577	15.440
BDD on imaging				
Localized BDD	5.546	0.006	1.629	18.889
IHBD ± EHBD dilatation	48.735	0.001	8.269	287.217

The rate of intraoperative complications was 4.6%, including diaphragm injury (n=3), small intestine injury (n=1), hepatic vein injury (n=1), and hemorrhage (n=1).

Postoperative complication rate was 33.1%, the most common being bile leakage (19.2%).The remaining postoperative other complications are presented in Table 5 according to Clavien&Dindo classification.

Table 5: Clavien&Dindo classification of other complications following hydatid cyst surgery

Clavien&Dindo category *	n	%
Grade I	10	7,7
Grade II	17	13,1
Grade III	7	5,4
Grade IV	2	1,5
Grade V	2	1,5

*Some patients developed multiple complications.

Bile leakage stopped within 10 days in 7 patients and lasted more than 10 days in 18 patients. The mean duration of bile leakage was17.4 (9.9) days (range 5–45).Bile leakage was managed with medical therapy in 44% of the patients and with additional intervention in 56%.2 patients with postoperative bile leakage underwent relaparotomy due to uncontrolled biliary peritonitis. Treatments applied to patients with bile leakage are presented in Table 6.

Table 6: Treatment methods for bile leakage

Treatment of complication	n	%
Only medical follow-up	11	44
Only ERCP	7	28
Only intervention	1	4
ERCP+intervention	4	16
ERCP+intervention+surgery	2	8
Total	25	100

Mean length of hospital stay was 20.2 (9.2) days and 6.6 (5.8) days for patients with and without bile leakage, respectively.

Mortality rate was 1.5%. One patient was re-operated due to postoperative bile leakage and uncontrolled biliary peritonitis. This patient developed Budd-Chiari syndrome following reoperation and died during follow-up due to sepsis. Another patient was reoperated due to postoperative intraabdominal abscess and peritonitis and died following reoperation due to pneumonia and sepsis.

Discussion

Hydatid cyst disease is mostly located in the liver, and can be seen as a single cyst or as multiple cysts. The incidence of multiple liver hydatid cysts was reported in the literature as between 29% and 38% [10]. In the current study, 35.1% of the hydatid cyst patients treated in our clinic had multiple cysts, which was found to be compatible with the literature. Bile leakage after liver hydatid cyst surgery is one of the most important factors affecting postoperative morbidity. In the literature, the incidence ranges from 2.6% to 28.6% [7, 11]. The postoperative morbidity rate is between 12% and 63%, and most of it is due to biliary leakage [12]. Therefore, it is important to determine and prevent possible risk factors of a complication that can develop at such high rates after hydatid cyst surgery. Possible risk factors have been identified in studies conducted previously. Unlike other studies, the current study was performed only for multiple liver hydatid cysts. In the other studies performed, single and multiple cysts were evaluated together and it was reported that the number of cysts did not affect bile leakage [7]. In the current study, the rate of biliary leakage was compatible with that in the literature and was found at a rate of 19.2%. In the present study, 7.7% of the patients were asymptomatic and 92.3% were symptomatic. While the rate of bile leakage was 10% in the asymptomatic patients, it was 20% in the symptomatic patients, and the difference was not statistically significant. Some studies have reported the history of preoperative cholangitis as one of the clinical indicators of CBC. These patients should undergo preoperative ERCP, sphincterotomy should be performed according to the findings, and a nasobiliary drain should be placed if necessary [13]. In the current study, the presence of jaundice and fever in the preoperative period was associated with a significant increase in the rate of postoperative bile leakage. These patients should be evaluated in terms of CBC during the preoperative and peroperative period.

In some studies, high blood bilirubin, ALP, and GGT levels, and the presence of bile duct dilatation on the preoperative images were reported in patients with CBC [14, 15]. Demircan et al. [16] stated ALT, AST, ALP, total bilirubin, direct bilirubin and GGT elevation as predictive factors for the existence of a cystobiliary relationship. In the present study, increased ALP, AST, ALT, GGT, and direct bilirubin were found to be predictive factors for postoperative bile leakage in the univariate analysis. However, these parameters were not found as effective factors in the multivariate logistic regression model.

There are few studies in the literature investigating the relationship between leukocytosis and eosinophilia with biliary leakage. While no significant relationship was found between them in some studies, there are studies reporting otherwise. In the study of Atahan et al. [17], no relationship was found between leukocytosis and eosinophilia with occult CBC. In the study of Demircan et al. [16], leukocytosis and eosinophils over 0.09 were reported as a predictive factor for cystobiliary fistula. In the current study, the high rate of leukocytosis and eosinophils was found to be associated with postoperative bile leakage in the univariate analyses. In the multivariate analyses, the high rate of eosinophils was found to be an independent risk factor for bile leakage. Eosinophilia is not an increasing parameter secondary to cholestasis. As is known, the cyst content is a fluid with antigenic properties and it is a known complication that anaphylaxis develops as a result of hydatid cyst perforation [18]. It is our belief that in patients with cystobiliary fistula, some of the cyst fluid passes into the systemic circulation and the rate of eosinophils in the blood increases secondary to this. Therefore, when the eosinophil rate is found to be high in patients with hydatid cysts, it should be evaluated thoroughly peroperatively, considering the risk of postoperative bile leakage.

Studies have shown that the relationship between the cyst diameter and bile leakage was controversial. Some studies have emphasized that there was no relationship between the cyst diameter and biliary leakage [7, 19]. However, there are studies reporting the opposite. Recently, in the study of Zeybek et al. [13], the maximum cyst diameter was reported as 10.5 cm and was found to be associated with postoperative biliary fistula. In a study on solitary hepatic hydatid cysts, the diameter of the cyst, perihilar location of the cyst, elevation of ALP, and WHO-IWGE stage were found to be associated with postoperative biliary leakage [8]. In the current study, the mean diameter of the cysts was determined as 10.4 (3.5) cm in the patients with bile leakage, while it was 8.6 (3.1) cm in the patients without, in the evaluation performed by taking the diameter of the largest cyst, and the difference was found to be significant according the bile leakage in the univariate analyses. However, it was not found to be significant in the multivariate analyses. In the univariate logistic regression analyses, the bile leakage risk increased by 1.2 times for every 1 cm increase in cyst diameter. The risk of bile leakage in patients with the largest cyst being than 10 cm was detected as 2.25 times more than those with a cyst smaller than 10 cm. When all of the cysts were evaluated, the mean diameter was 6.7 (3.04) cm in the group without bile leakage, while it was 7.9 (3.7) cm in the group with it, and the difference was statistically significant. These results showed that although the cyst diameter was not significant in the multivariate analyses, it was an important factor in the development of postoperative bile leakage.

In this study, the detection of intrahepatic localized dilatation and/or dilatation in IHBD and EHBD on the preoperative images was found to be associated with postoperative bile leakage in both the univariate and multivariate analyses. Dilatation in the bile ducts develops secondary to the existing cyst compression or cyst material opened in the bile ducts. Herein, only intrahepatic localized biliary dilatation increased the postoperative bile leakage by 5.5 times, and dilatation in the IHBD and/or EHBD increased by 48.7 times. In these patients, ERCP should be considered during the preoperative period, and a detailed CBC investigation should be performed during the peroperative period.

CBC can develop from any cyst located in the liver. Studies have argued that cysts close to the liver hilum are more likely to rupture into the bile ducts. However, there are few studies about this issue. In addition, which segments should be considered as perihilar (central)is controversial. Dziri et al. [20] divided the liver segments into 2groups, as posterosuperior segments (II, VII, and VIII) and anterior segments (III, IV, V, and VI), according to their projections based on the diaphragm,

and no difference was found between the 2groups in terms of CBC. However, in this study, segment IV was evaluated without splitting it into its subsegments, namely segments IVa and IVb. In the current study, postoperative bile leakage was detected as 50% in segment IVb, which is a perihilar subsegment, and 20% in segment IVa, which is a peripheral subsegment. In the study of Kayaalp et al. [21], by modifying the classification of Dziri et al., it was determined that the perihilar location of the cyst is a risk factor for CBC and postoperative bile leakage. According to their study, segments I, III, IVb, V, and VI were evaluated as perihilar localized, and segments II, IVa, VII, and VIII were evaluated as peripherally localized. In this study, segment VI was accepted as a perihilar segment, but when Couniaud's liver segmental anatomy was considered, segment VI was seen to be peripherally located [22]. In the current study, the perihilar segment group (segments I, III, IVb, and V) was accepted as the peripheral segment group (segments II, IVa, VI, VII, and VIII). Herein, for solitary cysts, the perihilar location of the cyst was found to be associated with bile leakage[8].Moreover, the postoperative bile leakage rate was found as 23% in patients with at least one perihilar localized cyst, and 14.3% in patients with peripherally located cysts, and the difference was not statistically significant. However, when the location of the largest cyst was evaluated, if the largest cyst was located in the perihilar region, it was found that the bile leakage rate increased to 35.7% and was statistically significant. In light of these findings, it can be considered that with the presence of denser and wider bile ducts in the perihilar region, the possibility of contact with the bile ducts of the cysts developing there would be higher, and this possibility would increase as the diameter of the cyst increases; hence, the rate of postoperative bile leakage may be higher.

The contents of cysts with bile and/or infection are an important risk factor for bile leakage. In some studies, this has been defined as an independent risk factor for biliary fistula and high postoperative morbidity has been reported [7, 23**].** In the current study, the biliary or infected cyst contents were found to be associated with postoperative bile leakage in the univariate analysis. It was found that it increased the risk of postoperative bile leakage by 6.6 times. A detailed cystobiliary relationship should be investigated and repaired in these patients during surgery [12].

Herein, the rate of CBC was 36.9%. In patients with CBC, the opening was closed by primary suturing. Postoperative bile leakage developed in 41.7% of these patients. However, postoperative bile leakage was prevented in 58.3% with the repair. The postoperative bile leakage rate was found as 6.1% in patients without peroperative CBC. Therefore, peroperative CBC should be investigated and treated in detail. Because major CBC is usually associated with cholangitis, it is easy to diagnose during the preoperative period. However, it is difficult to show minor (occult) CBC during the preoperative period, and it is usually detected peroperatively or manifested by postoperative bile leakage, abscess, and peritonitis. Detection and treatment of occult CBC reduces the postoperative biliary leakage rate [11, 24]. Risk factors should be determined well, especially in this patient group.

Since this study was conducted with multiple cysts, the effect of the surgical procedures and cavity obliteration techniques, as well as the WHO-IWGE phase of cysts on bile leakage could not be evaluated. Because cysts at different stages could be found in a patient, it seemed impossible to obtain an objective result, because different surgical interventions and obliteration techniques were applied to each cyst in the same patient.

Strengths and limitations

Our study is strong in that the number of patients with multiple cysts is high and also our study shows that eosinophilia can be used as a marker in predicting bile leakage. Since there is more than one cyst in each patient in our study, the fact that when bile leakage develops, it cannot be determined from which cyst the leakage develops. This is one of the limitations in our study. Also the retrospective nature of our study is another limitation.

Conclusion

In conclusion, the bile leakage rate after multiple liver hydatid cyst surgery was found to be 19.2% in this study, and it was found to be consistent with the literature. The most decisive factors for this complication were a high eosinophil rate and the presence of dilatation in the biliary ducts on the preoperative radiological images. In addition, the average cyst diameter, diameter of the largest cyst, perihilar location of the largest cyst, high level of the leukocyte count, AST, ALT, GGT, ALP, and direct bilirubin, and bile and/or infection of the cyst contents were found to be associated with postoperative bile leakage in the univariate analyses. In this study, the opening was treated in patients with peroperative cystobiliary fistula, and postoperative bile leakage was prevented in 58.3% of these patients. Therefore, in patients with the risk factors identified above, ERCP should be considered during the preoperative period, and intraoperative cystobiliary fistula research should be performed and treated.

References

1. Wen H, Vuitton L, Tuxun T, et al. Echinococcosis: Advances in the 21st Century. Clin Microbiol Rev. 2019;32(2).
2. Keong B, Wilkie B, Sutherland T, Fox A. Hepatic cystic echinococcosis in Australia: an update on diagnosis and management. ANZ J Surg. 2018;88:26-31.
3. WHO. Echinococcosis, Epidemiology 2019. Available from: URL: https:// www.who.int/echinococcosis/epidemiology/en
4. Gupta N, Javed A, Puri S, Jain S, Singh S, Agarwal AK. Hepatic Hydatid: PAIR, Drain or Resect? J Gastrointestinal Surg. 2011;9 Aug 2011
5. Giorgio A, deStefano G, Esposito V, et al. Long-term results of percutaneous treatment of hydatid liver cysts: a single center 17 years experience. Infection. 2008;36:256-61.
6. Saylam B, Coşkun F, Demiriz B, Vural V, Comçali B, Tez M. A new and simple score for predicting cystobiliary fistula in patients with hepatic hydatid cysts. Surgery. 2013;153:699-704.
7. Kayaalp C, Bzeizi K, Demirbag AE, Akoglu M. Biliary complications after hydatid liver surgery: incidence and risk factors. J Gastrointest Surg. 2002;6:706-12.
8. Surmelioglu A, Ozer İ, Reyhan E, Dalgic T, Ozdemir Y, Ulas M, et al. Risk Factors for Development of Biliary Complications after Surgery for Solitary Liver Hydatid Cyst. Am Surg. 2017;1:83(1):30-5.
9. Demirci S, Eraslan S, Anadol E. Comparison of the results of different surgical techniques in the management of hydatid cyst of the liver. World J Surg. 1989;13:88–90.
10. Safioleas M, Misiakos E, Manti C, Katsikas D, Skalkeas G. Diagnostic evaluation and surgical management of hydatid disease of the liver. World J Surg. 1994;18:859–65.
11. Kayaalp C, Aydın C, Olmez A, Isik S, Yılmaz S. Leakage tests reduce the frequency of biliary fistulas following hydatid liver cyst surgery. Clinics. 2011;66(3):421-4.
12. Dziri C, Haouet K, Fingerhut A, Zaouche A. Management of Cystic Echinococcosis Complications and Dissemination: Where is the Evidence? World J Surg. 2009;33:1266–73.
13. Zeybek N, Dede H, Balci D, Coskun AK, Ozerhan IH, Peker S, et al. Biliary fistula after treatment for hydatid disease of the liver: When to intervene. World J Gastroenterol. 2013;19:355-61.
14. Kornaros SE, Aboul-Nour TA. Frank intrabiliary rupture of hydatid hepatic cyst: diagnosis and treatment. J Am Coll Surg. 1996;183:466-70.
15. Alper A, Ariogul O, Emre A, Uras A, Okten A. Choledochoduodenostomy for intrabiliary rupture of hydatid cysts of liver. Br J Surg. 1987;74:243-5.
16. Demircan O, Baymus M, Seydaoglu G, Akinoglu A, Sakman G. Occult cystobiliary communication presenting as postoperative biliary leakage after hydatid liver surgery: Are there significant preoperative clinical predictors? Can J Surg. June 2006;49:177-84.
17. Atahan K, Kupeli H, Deniz M, Gür S, Çökmez A, Tarcan E. Can occult cystobiliary fistulas in hepatic hydatid disease be predicted before surgery? Int J Med Sci. 2011;8:315-20.
18. Ozturk G, Aydınlı B, Yıldırgan MI, Basoglu M, Atamanalp SS, Polat KY, et al. Posttraumatic free intraperitoneal rupture of liver cystic echinococcosis: a case series and review of literature. Am J Surg. 2007;194:313-6.
19. Bedirli A, Sakrak O, Sozuer ME, Kerek M, Ince O. Surgical management of spontaneous intrabiliary rupture of hydatid liver cysts. Surg Today. 2002;32:594-7.

20. Dziri C, Paquet JC, Hay JM, Fingerhut A, Msika S, Zeitoun G, et al. Omentoplasty in the prevention of deep abdominal complications after surgery for hydatid disease of the liver: a multicenter, prospective, randomized trial. J Am Coll Surg. 1999:188:281–9.
21. Kayaalp C, Bostancı B, Yol S, Akoglu M. Distribution of hydatid cysts into liver with reference to cystobiliary communications and cavity-related complications. The American Journal of Surgery. 2003;185:175-9.
22. Couinaud C. Le foie. Etudes anatomiques et chirurgicales. Masson, Paris, 1957.
23. Kayaalp C, Sengul N, Akoglu M. Importance of cyst content in hydatid liver surgery. Arch Surg. 2002;137:159-63.
24. Kılıç M, Yoldaş O, Koç M, Keskek M, Karakose N, Ertan T, et al. Can biliary-cyst communication be predicted before surgery for hepatic hydatid disease: does it matter? Am J Surg. 2008;196:732.

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