ISSN 2222-0682 (online)

World Journal of *Methodology*

World J Methodol 2023 September 20; 13(4): 166-372

Published by Baishideng Publishing Group Inc

World Journal of Methodology

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Quarterly Volume 13 Number 4 September 20, 2023

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The *WJM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Methodology

ISSN
ISSN 2222-0682 (online)

LAUNCH DATE
September 26, 2011

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Timotius Ivan Hariyanto

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2222-0682/editorialboard.htm

PUBLICATION DATE
September 20, 2023

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World J Methodol 2023 September 20; 13(4): 272-286

DOI: 10.5662/wjm.v13.i4.272

ISSN 2222-0682 (online)

ORIGINAL ARTICLE

Observational Study

Biliary fistula and late recurrence of liver hydatid cyst: Role of cysto-biliary communication: A prospective multicenter study

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: He YF, China; Koubaa M, Tunisia

Received: March 22, 2023
Peer-review started: March 22, 2023
First decision: June 14, 2023
Revised: June 16, 2023
Accepted: June 27, 2023
Article in press: June 27, 2023
Published online: September 20, 2023

Tamer A A M Habeeb, Mahmoud Abdou Yassin, Abdelshafy Mostafa, Amr Ibrahim, Waleed A-Abdelhady, Tamer Mohamed Elshahidy, Mohamed Ibrahim Mansour, Adel Mahmoud Moursi, Mohamed Abdallah Zaitoun, Ehab Shehata Abd-Allah, Ashraf Abdelmonem Elsayed, Rasha S Elsayed, Ahmed M Yehia, Amr Abdelghani, Mohamed Negm, Heba Alhussein Abo-Alella, Mostafa M Elaidy, Department of General Surgery, Faculty of Medicine Zagazig University, Sharkia 44511, Egypt

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Abstract

BACKGROUND

Hydatid cyst disease (HCD) is common in certain locations. Surgery is associated with postoperative biliary fistula (POBF) and recurrence. The primary aim of this study was to identify whether occult cysto-biliary communication (CBC) can predict recurrent HCD. The secondary aim was to assess the role of cystic fluid bilirubin and alkaline phosphatase (ALP) levels in predicting POBF and recurrent HCD.

AIM

To identify whether occult CBC can predict recurrent HCD. The secondary aim was to assess the role of cystic fluid bilirubin and ALP levels in predicting POBF and recurrent HCD.

METHODS

From September 2010 to September 2016, a prospective multicenter study was undertaken involving 244 patients with solitary primary superficial stage cystic echinococcosis 2 and cystic echinococcosis 3b HCD who underwent laparoscopic partial cystectomy with omentoplasty. Univariable logistic regression analysis assessed independent factors determining biliary complications and recurrence.

RESULTS

There was a highly statistically significant association ($P \leq 0.001$) between cystic fluid biochemical indices and the development of biliary complications (of 16 patients with POBF, 15 patients had high cyst fluid bilirubin and ALP levels), where patients with high bilirubin-ALP levels were 3405 times more likely to have biliary complications. There was a highly statistically significant association ($P \leq 0.001$) between biliary complications, biochemical indices, and the occurrence of recurrent HCD (of 30 patients with recurrent HCD, 15 patients had high cyst fluid bilirubin and ALP; all 16 patients who had POBF later developed recurrent HCD), where patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cysts, respectively.

CONCLUSION

Occult CBC can predict recurrent HCD. Elevated cyst fluid bilirubin and ALP levels predicted POBF and recurrent HCD.

Key Words: Cysto-biliary communication; *Echinococcus granulosus*; Hydatid disease recurrence; Hydatid fluid analysis; Laparoscopy

Core Tip: There has been no research on occult cysto-biliary communication (CBC) prediction for recurrent hydatid cyst disease (HCD) or the role of elevated cyst fluid bilirubin and alkaline phosphatase (ALP) levels in predicting postoperative biliary fistula and recurrent HCD. The main finding of this study was that there was a statistically significant association ($P \leq 0.001$) between biochemical indices and the development of biliary complications, where patients with high bilirubin-ALP levels were 3405 times more likely to have biliary complications. There was a highly statistically significant association between biliary complications, biochemical indices, and the occurrence of recurrent HCD, where patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cysts, respectively.

Citation: Habeeb TAAM, Podda M, Tadic B, Shelat VG, Tokat Y, Abo Alsaad MI, Kalmoush AE, Nassar MS, Mustafa FM, Morsi Badawy MH, Sobhy Shaaban M, Mohamed TZ, El Sayed Henish MI, Elbelkasi H, Abdou Yassin M, Mostafa A, Ibrahim A, A-Abdelhady W, Elshahidy TM, Mansour MI, Moursi AM, Abdallah Zaitoun M, Abd-Allah ES, Abdelmonem Elsayed A, S Elsayed R, M Yehia A, Abdelghani A, Negm M, Abo-Alella HA, Elaidy MM. Biliary fistula and late recurrence of liver hydatid cyst: Role of cysto-biliary communication: A prospective multicenter study. *World J Methodol* 2023; 13(4): 272-286
URL: https://www.wjgnet.com/2222-0682/full/v13/i4/272.htm
DOI: https://dx.doi.org/10.5662/wjm.v13.i4.272

INTRODUCTION

Hydatid cyst disease (HCD) is caused by *Echinococcus granulosus*, which infects humans in many areas worldwide. Different organs may be affected by HCD[1-2]; however, the liver is mainly affected by HCD (50%-70%)[3]. The World Health Organization's Informal Working Group on Echinococcosis (WHO-IWGE) advocated a standardized consensus in diagnosis, treatment, and follow-up[4].

Medical treatment alone is ineffective, whereas laparoscopic or open surgical management of HCD is an integral treatment component[5-6]. With advances in minimal access surgery, laparoscopic HCD surgery is increasingly being performed, varying from the more conservative choice of partial cystectomy and omentoplasty to the more radical choice of pericystectomy or hepatic resection determined by cyst location, cyst size, risk of complications, and surgical expertise [7]. As HCD is benign, liver resections are avoided as much as possible to reduce perioperative morbidity, such as liver failure[8]. Although a case report used the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy procedure, it has not yet been demonstrated[9].

Cysto-biliary communication (CBC), which presents as a postoperative biliary fistula (POBF), is a common postoperative complication of hepatic HCD, with an incidence of 37%. CBC may be occult or manifest with various clinical symptoms. In occult CBC, cyst fluid, scolices, small daughter cysts, and laminated and germinal layer fragments migrate into the biliary tract and remain asymptomatic or undetectable on imaging. If an occult CBC is missed during surgery, POBF manifests as an external biliary fistula, biliary peritonitis, or intra-abdominal abscess[10-11]. Another concern with HCD surgery is recurrent HCD, which occurs in 11% of cases[12]. The primary aim of this study was to determine whether occult CBC, expressed as POBF, is associated with recurrent HCD. The secondary aim was to determine whether elevated cyst fluid bilirubin and alkaline phosphatase (ALP) levels predict occult CBC and, thus, POBF and recurrent HCD.

MATERIALS AND METHODS

Study design and participants

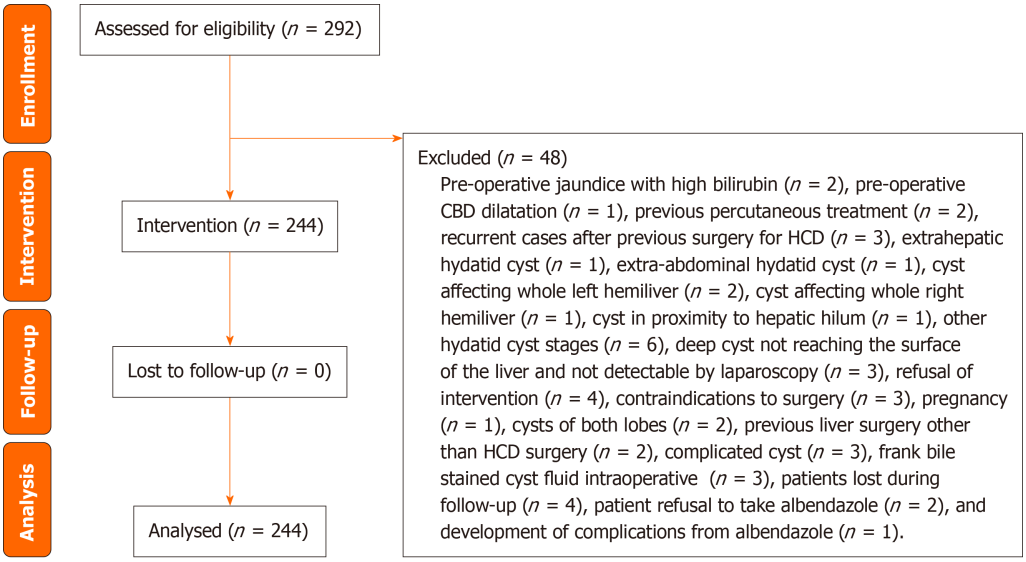
From September 2010 to September 2016, a prospective observational multicenter study was carried out at our university hospitals involving 244 patients with stages cystic echinococcosis 2 (CE2) and cystic echinococcosis 3b (CE3b) according to the WHO-IWGE classification. Patients with large, solitary, symptomatic, or asymptomatic superficial cysts abutting critical vascular and biliary structures were included in this study. Exclusion criteria were: (1) Stage CE1, CE3a, and CE4 HCD patients (WHO- IWGE recommendation); (2) preoperative factors: Total bilirubin > 2.0 mg/dL and direct bilirubin > 1.5 mg/dL; (3) prior liver interventions: Previous percutaneous treatment, recurrence of HCD, previous liver surgery; (4) radiological factors: Common bile duct (CBD) dilatation > 10 mm, extrahepatic cysts affecting an entire hemiliver, complicated (ruptured) or deep location that cannot be accessed by laparoscopy and hydatid cysts in both lobes of the liver; (5) patient factors: Referenceused intervention, surgical contraindication, pregnancy, lost to follow-up, refused to take albendazole, or patients who had albendazole-related complications (deranged liver function); and (6) intraoperative factors: Manifest CBC. This study was approved by the Institutional Review Board committees and registered as a clinical trial (ClinicalTrials.gov ID: NCT05116735) and was conducted following the Helsinki Declaration and STROBE[13].

Definitions of outcomes and measurements

POBF was defined as a bilirubin concentration in the drain fluid at least three times higher than the serum bilirubin concentration on or after postoperative day three[14]. Hydatid recurrence was defined as the appearance of new active cysts after surgery[15]. Postoperative residual fluid cavities were not classified as recurrent HCD[12]. Postoperative morbidity was assessed using the Clavien-Dindo classification[16]. Hydatid cyst fluid bilirubin and ALP levels were measured using an automatic biochemical analyzer (AU-400, Olympus)[17]. All hospitals used the same instrument to measure bilirubin and ALP levels in the cyst fluid. All the machines were calibrated at each institution to ensure consistent reporting. The time from surgery to disease relapse at any site was described as recurrence-free survival.

Perioperative procedure and follow-up

A multidisciplinary team, including surgical, radiological, and anesthetic specialists, preoperatively evaluated all patients. Abdominal ultrasound, contrast-enhanced computed tomography (CT), and magnetic resonance cholangiopancreatography were performed at the discretion of the leading surgeon[6]. The protocol therapy in our hospitals for



DOI: 10.5662/wjm.v13.i4.272

Figure 1 Flow diagram of the inclusion and exclusion criteria. CBD: Common bile duct; HCD: Hydatid cyst disease.

albendazole was 10 mg/kg ten days before surgery and continued for six months following surgery with a two-week interval between each month. Complete blood counts and liver function monitoring were routinely performed. The surgical technique has been previously reported in detail[18]. In short, pneumoperitoneum with an intra-abdominal pressure of 14 mmHg was established. Fine needle aspiration of the cystic fluid was performed to rule out manifest CBC. The aspirated cyst fluid was analyzed for fluid bilirubin and ALP levels before injection of hypertonic saline, and the bilirubin and ALP levels were determined after surgery. The cystic wall was partially removed using a harmonic scalpel. To detect occult CBC, after the cystic cavity was fully evacuated and complete hemostasis was achieved, the intra-abdominal pressure was lowered to 10 mmHg. Visible orifices of the CBC were searched by thorough laparoscopic exploration of the cyst cavity; 20% hypertonic saline-soaked gauze was placed in the cystic cavity to observe the presence of bile while compressing either the gallbladder or CBD to stimulate bile backflow through the CBC (if present, the CBC was sutured).

Furthermore, we injected air, saline, or methylene blue dye in succession in all patients *via* cystic duct cannulation with CBD occlusion, hoping to increase CBC detection rates (three cases changed from occult CBC to manifest CBC intraoperatively and were excluded from the study). Omentoplasty was performed by inserting a right gastroepiploic-based omental flap into the cavity. A drain was placed in the subhepatic area. After three days, the drain was removed if there was no evidence of bile leakage. The patients were discharged on the fifth postoperative day. Follow-up visits were scheduled after one month, three months, six months, one year, and then every six months for the next four years. The drainage tube was left longer until fistula resolution was achieved in patients with bile leaks. After surgery, an ultrasound scan was used to check the cyst cavity at one, three, six months, one year, and then every six months until completion of the follow-up period (5 years). If the ultrasound results were inconclusive, a CT scan was performed. No mortality was observed in this study.

Statistical analysis

Statistical Package for Social Science software was used to analyze the collected data (version 20.0. IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution were reported as mean and SD, while data with a non-normal distribution were presented as medians and ranges. Absolute and relative frequencies were used to summarize categorical variables. The Chi-square test (χ^2) or Fisher's exact test was used to examine categorical variables. Independent factors determining biliary complications and recurrence were analyzed using univariate logistic regression analysis. The odds ratio (OR) was calculated to compare the relative odds of biliary complications and recurrence of HCD. The 95%CI was used to estimate OR precision. The hydatid cyst-recurrence-free time was determined using the Kaplan–Meier method. Statistically significant and highly statistically significant variables were defined as P values < 0.05 and < 0.001, respectively.

RESULTS

A flowchart of the eligibility criteria is presented in Figure 1. A total of 292 patients with hepatic HCD were referred to our clinics based on abdominal ultrasound results. Forty-eight patients were excluded: Pre-operative jaundice with high bilirubin (n = 2), pre-operative CBD dilatation (n = 1), previous percutaneous treatment (n = 2), recurrent cases after previous surgery for HCD (n = 3), extrahepatic hydatid cyst (n = 1), extra-abdominal hydatid cyst (n = 1), cyst affecting whole left hemiliver (n = 2), cyst affecting whole right hemiliver (n = 1), cyst in proximity to hepatic hilum (n = 1), other

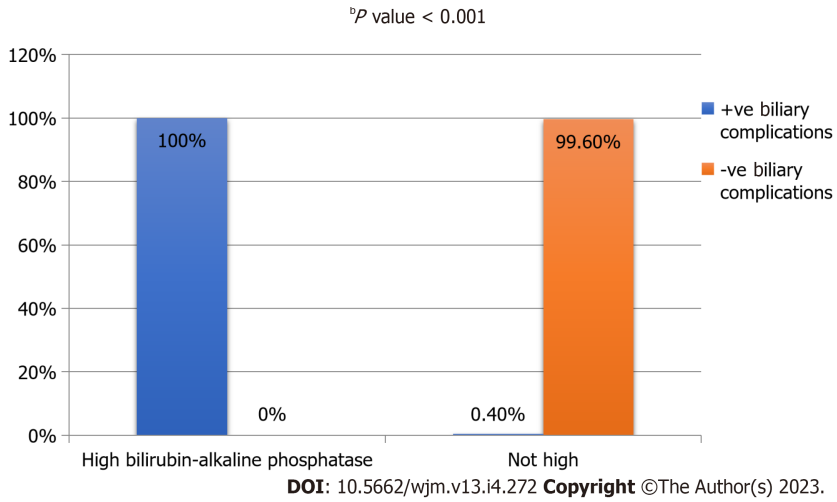


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Figure 2 Relation between the biochemical indices and development of biliary complications among the studied patients (*n* = 244). ^{b}P < 0.01. + ve: Presence of biliary complications; - ve: Absence of biliary complications.

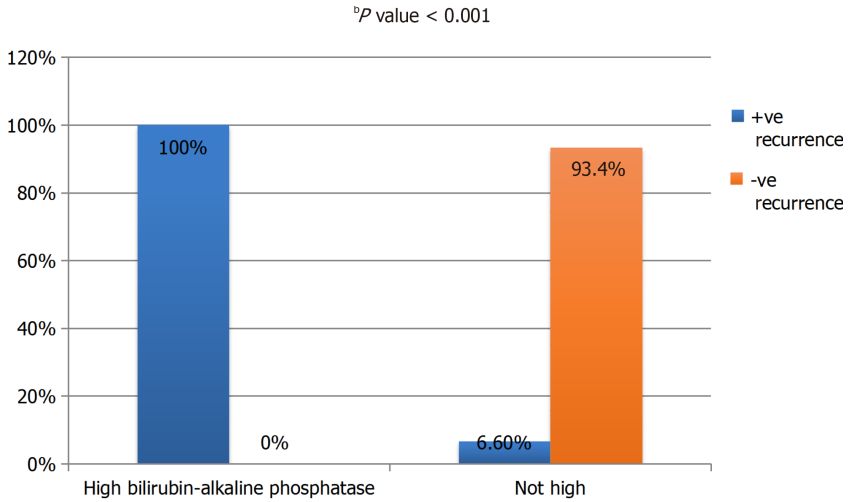

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Figure 3 Relation between the biochemical indices and recurrence of hydatid cyst among the studied patients (*n* = 244). ^{b}P < 0.01. + ve: Occurrence of recurrence; - ve: No recurrence.

hydatid cyst stages (*n* = 6), deep cyst not reaching the surface of the liver and could not be detected by laparoscopy (*n* = 3), refused intervention (*n* = 4), contraindications to surgery (*n* = 3), pregnancy (*n* = 1), cysts of both lobes (*n* = 2), previous liver surgery other than HCD surgery (*n* = 2), complicated cyst (*n* = 3), intraoperative frank bile stained cyst fluid (*n* = 3), patients lost during follow-up (*n* = 4), patient refusal to take albendazole (*n* = 2), and development of complications due to albendazole (*n* = 1). Following the exclusion of 48 patients, a total of 244 patients were enrolled in this study.

The patients' demographic and preoperative characteristics are summarized in Table 1. This study included 244 patients with a mean age of 42.67 ± 9.97 years. The mean cyst diameter was 9.49 ± 3.54 cm, and the most common symptom was abdominal pain (*n* = 125, 51.2%). Most patients had a cyst classification of CE3b (*n* = 183, 75%) with a predominant right hemiliver location (*n* = 184, 75.4%).

Table 2, Figures 2 and 3 show the intraoperative and postoperative findings, respectively. The mean operative time was 107.32 ± 6.92 min, with cystic fluid spilling (4.9%) and high bilirubin-high ALP in cyst fluid (6.1%). Biliary complications occurred in 16 patients (6.6%), and recurrent HCD occurred in 30 patients (12.3%).

Table 3 shows that the mean time to biliary fistula detection was 3.13 ± 1.78 d, and the resolution of bile leak was 14.38 ± 6.12 d. Patients with POBF (*n* = 16/244, 6.6%) had mainly external biliary fistula (*n* = 9/16, 56.2%). Most cases were grade B (7/16, 43.7%). The mean time to recurrent HCD was 2.48 ± 0.98 years with a cyst size of 4.93 ± 2.72 cm. Recurrent HCD was most common in the right hemiliver (18/30, 60%) and with CE2 as the cyst stage (25/30, 83.3%). There was no mortality in our study. A highly statistically significant association ($P \leq 0.001$) was observed between biochemical indices and the development of biliary complications, where patients with high bilirubin-ALP were 3405 times more likely to have biliary complications (Table 4). There was a highly statistically significant association ($P \leq 0.001$) between biliary complications, biochemical indices, and the occurrence of recurrence HCD where patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cyst, respectively

Table 1 Demographic and preoperative characteristics of the patients (*n* = 244), *n* (%)

Characteristics	*n* = 244
Age (year) mean ± SD	42.67 ± 9.97
≤ Median (43)	136 (55.7)
> Median (43)	108 (44.3)
Sex	
Male	163 (66.8)
Female	81 (33.2)
ASA	
I	176 (72.1)
II	47 (19.3)
III	21 (8.6)
Positive family history	15 (6.1)
Clinical presentation	
Asymptomatic	19 (7.8)
Pain	125 (51.2)
Mass	48 (19.7)
Nausea & vomiting	32 (13.1)
Dyspepsia	20 (8.2)
Cyst size (cm) mean ± SD	9.49 ± 3.54
≤ Median (9)	130 (53.3)
> Median (9)	114 (46.7)
Cyst site	
Right lobe	184 (75.4)
Left lobe	60 (24.6)
Cyst stage	
CE2	61 (25)
CE3b	183 (75)

ASA: American Society of Anesthesiologists; CE: Cystic echinococcosis.

(Table 5, Figure 4).

DISCUSSION

This study evaluated the association between occult CBC, POBF, and recurrent HCD. The study results further highlight the importance of hydatid cyst fluid analysis in detecting occult CBC. To the best of our knowledge, no research published in the literature has addressed the relationship between occult CBC and the development of recurrent HCD or the relationship between elevated cyst fluid bilirubin and ALP and the development of POBF and recurrent HCD. This study showed that occult CBC occurred in 6.6% of patients and recurrent HCD occurred in 12.3% of patients. Of the 16 patients with POBF, 15 had high cyst fluid bilirubin and ALP levels, and patients with high bilirubin-ALP were 3405 times more likely to have biliary complications. Of the 30 patients with recurrent HCD, 15 patients had high cyst fluid bilirubin and ALP levels; all 16 patients with POBF later developed recurrent HCD, and patients who developed biliary complications and high bilirubin-ALP were 244.6 and 214 times more likely to have recurrent hydatid cysts, respectively. The detection of occult CBC is essential. In our study, occult CBC and the subsequent development of postoperative biliary leak occurred in 16 patients (6.6%), which was lower than that in the two studies (27% and 16%, respectively)[19-20]. The low incidence of POBF in our study may be due to variations in sample size, different surgical approaches, and inclusion criteria, especially deep/centrally located cysts, such as those in medial segments such as IVa, V, and VIII, extended deep into the liver parenchyma and was closely related to major biliovascular structures with a higher incidence

Table 2 Intraoperative and postoperative outcomes (*n* = 244), *n* (%)

Intraoperative outcome	*n* = 244
Operative time (min) (mean ± SD)	107.32 ± 6.92
≤ Median (106)	126 (51.6)
> Median (106)	118 (48.4)
Blood transfusion	
1 unit	4 (1.6)
2 units	2 (0.8)
Cystic fluid spillage	12 (4.9)
Conversion	7 (2.9)
Causes of conversion	
Extensive adhesion	5 (2.1)
Organ injury	1 (0.4)
Difficult cyst detection	1 (0.4)
Anaphylaxis	2 (0.8)
Cyst fluid biochemical indices	
High both bilirubin-high alkaline phosphatase	15 (6.1)
Postoperative outcomes	*n* = 244
Postoperative hospital stay (days) mean ± SD	3.44 ± 2.51, 3 (2-20)
ICU admission	9 (3.7)
Early postoperative complications	28 (11.5)
Type of early postoperative complications	
Wound infection	7 (2.9)
Cyst cavity bile collection	6 (2.5)
Ileus	2 (0.8)
Subphrenic abscess	4 (1.6)
Subphrenic hematoma	3 (1.2)
Cholangitis	4 (1.6)
Pneumonia	1 (0.4)
Atelectasis	1 (0.4)
None	215 (88.1)
Clavien-Dindo classification	
0	213 (87.3)
I	8 (3.3)
II	11 (4.5)
III	12 (4.9)
Biliary complications	16 (6.6)
Late postoperative complications	
Port/incisional site hernia	7 (2.9)
Recurrence	30 (12.3)

ICU: Intensive care unit.

Table 3 Characteristics of biliary complications and recurrence (*N* = 16), *n* (%)

Biliary complications	*n* = 16
Type	
External biliary fistula	9 (56.2)
Cyst cavity biliary abscess	4 (25)
Biliary peritonitis	3 (18.8)
Grade	
Grade A	6 (37.5)
Grade B	7 (43.7)
Grade C	3 (18.8)
Time of development (days) mean ± SD	3.13 ± 1.78
Treatment	
Conservative	6 (37.5)
Ultrasound guided percutaneous drainage	7 (43.7)
Reoperation	3 (18.8)
Time to leakage cessation (days) mean ± SD	14.38 ± 6.12
Recurrence	*n* = 30
Site	
Right lobe	18 (60)
Left lobe	6 (20)
Peritoneum	4 (13.3)
Spleen	2 (6.7)
Clinical presentation	
Asymptomatic	7 (23.3)
Pain	13 (43.3)
Mass	4 (13.3)
Nausea & vomiting	2 (6.7)
Infection	2 (6.7)
Rupture	1 (3.3)
Jaundice	1 (3.3)
Time to diagnosis (yr) mean ± SD	2.48 ± 0.98
Size (cm) mean ± SD	4.93 ± 2.72
Stage	
CE2	25 (83.3)
CE3b	5 (16.7)
Treatment	
Pericystectomy	17 (56.7)
Left hepatectomy	6 (20)
Abdominal exploration and excision of recurrent abdominal HCD	4 (13.3)
Splenectomy (for recurrent splenic HCD)	2 (6.7)
CBD stent + pericystectomy	1 (3.3)

CE: Cystic echinococcosis; CBD: Common bile duct; HCD: Hydatid cyst disease.

Table 4 Relation between the independent factors and development of biliary complications among the studied patients by univariate analysis (*n* = 244)

Factors	Biliary complications (*n* = 16)		No biliary complications (*n* = 228)		*P* value	Univariate OR (95%CI)
	n	%	*n*	%		
Sex						
Male (*n* = 163)	9	5.5	154	94.5	0.354[1]	Reference
female (*n* = 81)	7	8.6	74	91.4		1.62 (0.58-4.52)
ASA						
I (*n* = 176)	9	5.1	167	94.9	0.160[1]	1.08 (0.12-8.96)
II (*n* = 47)	6	12.8	41	87.2		2.93 (0.33-25.98)
III (*n* = 21)	1	4.8	20	95.2		Reference
Family history						
+ ve (*n* = 15)	8	53.3	7	46.7	< 0.001[2,b]	31.6 (9.18-108.6)
- ve (*n* = 229)	8	3.5	221	96.5		Reference
Cyst size (cm)						
≤ 9 cm (*n* = 130)	3	2.3	127	97.9	0.004[1,a]	Reference
> 9 cm (*n* = 114)	13	11.4	101	88.6		5.45 (1.51-19.64)
Cyst site						
Right lobe (*n* = 184)	13	7.1	171	92.9	0.575[2]	1.44 (0.39-5.25)
Left lobe (*n* = 60)	3	5	57	95		Reference
Cyst stage						
CE2 (*n* = 61)	15	24.6	46	75.4	< 0.001[2,b]	59.3 (7.64-460.9)
CE3b (*n* = 183)	1	0.5	182	99.5		Reference
Operative time (min)						
≤ 106 min (*n* = 126)	9	7.1	117	92.9	0.703[1]	1.22 (0.44-3.39)
> 106 min (*n* = 118)	7	5.9	111	94.1		Reference
Blood transfusion						
Yes (*n* = 6)	4	66.7	2	33.3	< 0.001[2,b]	37.7 (2.26-226.5)
No (*n* = 238)	12	5	226	95		Reference
Cystic fluid spillage						
Yes (*n* = 12)	2	16.7	10	83.3	0.147[2]	3.11 (0.62-15.60)
No (*n* = 232)	14	6	218	94		Reference
Conversion						
Yes (*n* = 7)	5	71.4	2	28.6	< 0.001[2,b]	51.4 (8.94-294.9)
No (*n* = 237)	11	4.6	226	95.4		Reference
Anaphylaxis						
Yes (*n* = 2)	0	0	2	100	0.707[1]	Reference
No (*n* = 244)	16	6.6	226	93.4		0.14 (0.01-1.65)
Cyst fluid biochemical indices						
High bilirubin-alkaline phosphatase (*n* = 15)	15	100	0	0.0	< 0.001[2,b]	3405 (202-57164)
Not high (*n* = 229)	1	0.4	228	99.6		Reference
Hospital stay (days)						

≤ 3 d (*n* = 184)	0	0.0	184	100	< 0.001[2,b]	Reference
> 3 d (*n* = 60)	16	26.7	44	73.3		67 (8.64-518.15)
ICU admission						
Yes (*n* = 9)	5	55.6	4	44.4	< 0.001[2,b]	25.5 (5.99-108.24)
No (*n* = 235)	11	4.7	224	95.3		Reference
Early postoperative complications						
Yes (*n* = 28)	13	46.4	15	53.6	< 0.001[2,b]	61.5 (15.8-239.8)
No (*n* = 216)	3	1.4	213	98.6		Reference

[1]Chi square test (χ^2).
[2]Fisher's exact test.
[a]*P* ≤ 0.05: Statistically significant.
[b]*P* ≤ 0.001: Highly statistically significant.
OR: Odds Ratio; ICU: Intensive care unit, ASA: American Society of Anesthesiologists; CE: Cystic echinococcosis; + ve: Positive family history; - ve: Negative family history.

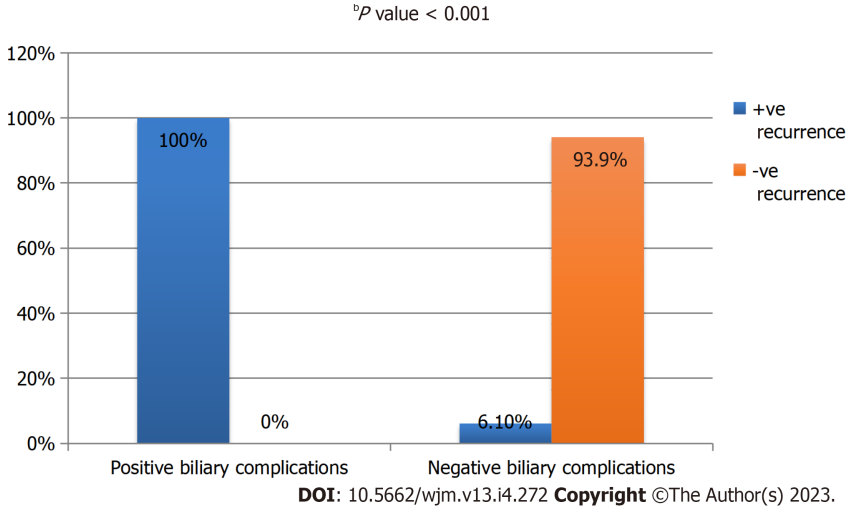

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Figure 4 Relation between the biliary complications and recurrence of hydatid cyst among the studied patients (*n* = 244). [b]*P* < 0.01. + ve: Occurrence of recurrence; - ve: Absence of recurrence.

of CBC in these studies. Furthermore, we meticulously searched for tiny CBC using various techniques. Another challenge during the laparoscopic surgical approach for liver HCD is that pneumoperitoneum increases intra-abdominal pressure and may prevent bile leakage into the cyst. We faced this challenge through adequate laparoscopic exploration of the cyst cavity after cyst deroofing, intraoperative dye injection, and white gauze left inside the residual cavity for a few minutes and lowering the intra-abdominal pressure to 10 mmHg, which could facilitate CBC detection. Ultimately, this helped decrease the incidence of POBF. Of the 16 patients who developed POBF, 15 (15/16) had high cyst fluid bilirubin and ALP levels. CBC is the cause of high levels of these biochemicals in cyst fluid. The high level of cyst fluid in the postoperative period led us to suspect the development of POBF in these patients. Another point of contention is the relationship between cyst size and the development of CBC. The relationship between cyst size and CBC varies between studies, with numerous studies reporting a cyst size cut-off of 10 cm for CBC[21-24]. We found a significant correlation between cyst size and POBF, with cysts larger than the median 9 cm being 5.45 times more likely to develop POBF. A larger cyst is more likely to deform the biliary pedicle anatomy owing to the greater exposed surface area, thus predisposing the patient to CBC. Therefore, size has a direct relationship with the CBC. Furthermore, it has been reported that intracystic pressure increases with the diameter of the hepatic cyst, increasing the likelihood of CBC[25]. In our experience, POBF occurred on the third postoperative day, mainly as an external biliary fistula (9/16, 56.2%). Most patients had grade B disease (7/16, 43.7%). Most POBFs were treated conservatively or with ultrasound-guided percutaneous drainage, and all patients demonstrated clinical resolution within two weeks. In our study, endoscopic biliary stenting was unnecessary except in patients with persistent bile leaks.

Recurrence of HCD is the second most common complication for both surgeons and patients. Failure to remove all viable cysts and protoscolices, particularly long-standing cysts with host tissue adventitial layer (pericyst) branching into the surrounding tissue, may be responsible for recurrence. Although the laparoscopic approach has many advantages during HCD surgery, drawbacks include difficulty in accessing a cyst, difficult aspiration with a fine needle that may be

Table 5 Relation between the independent factors and recurrence of hydatid cyst by univariate analysis (*n* = 244)

Factors	Recurrence (*n* = 30)		No recurrence (*n* = 214)		*P* value	Univariate OR (95%CI)
	n	%	*n*	%		
Sex						
Male (*n* = 163)	18	0.11	145	0.89	0.398[1]	Reference
Female (*n* = 81)	12	0.148	69	0.852		1.40 (0.62-3.07)
ASA						
I (*n* = 176)	21	0.119	155	0.881	0.792[1]	1.29 (0.28-5.924)
II (*n* = 47)	7	0.149	40	0.851		1.66 (0.31-8.78)
III (*n* = 21)	2	0.095	19	0.905		Reference
Family history						
+ve (*n* = 15)	15	1	0	0	< 0.001[2,b]	214 (26.45-1731.7)
-ve (*n* = 229)	15	0.066	214	0.934		Reference
Cyst size (cm)						
≤ 9 cm (*n* = 130)	7	0.054	123	0.946	< 0.001[1,b]	Reference
> 9 cm (*n* = 114)	23	0.202	91	0.798		4.44 (1.83-10.80)
Cyst site						
Right lobe (*n* = 184)	23	0.125	161	0.875	0.864[1]	1.08 (0.44-2.66)
Left lobe (*n* = 60)	7	0.117	53	0.883		Reference
Cyst stage						
CE2 (*n* = 61)	27	0.443	34	0.557	< 0.001[1,b]	47.7 (13.7-165.95)
CE3b (*n* = 183)	3	0.016	180	0.984		Reference
Operative time (min)						
≤ 106 min (*n* = 126)	16	0.127	110	0.873	0.843[1]	1.08 (0.50-2.324)
> 106 min (*n* = 118)	14	0.119	104	0.881		Reference
Blood transfusion						
Yes (*n* = 6)	5	0.833	1	0.167	< 0.001[2,b]	42.6 (4.78-397.4)
No (*n* = 238)	25	0.105	213	0.895		Reference
Cystic fluid spillage						
Yes (*n* = 12)	12	1	0	0	< 0.001[2,b]	142 (17.5-1160.4)
No (*n* = 232)	18	0.078	214	0.922		Reference
Conversion						
Yes (*n* = 7)	6	0.857	1	0.143	< 0.001[2,b]	53.3 (6.15-461.2)
No (*n* = 237)	24	0.101	213	0.899		Reference
Anaphylaxis						
Yes (*n* = 2)	2	1	0	0	< 0.001[2,b]	15.3 (1.34-174.1)
No (*n* = 244)	28	0.116	214	0.884		Reference
Cyst fluid biochemical indices						
High bilirubin-alkaline phosphatase (*n* = 15)	15	1	0	0	< 0.001[2,b]	214 (26.45-1731.7)
Not high (*n* = 229)	15	0.066	214	0.934		Reference
Hospital stay (days)						
≤ 3 d (*n* = 184)	10	0.054	174	0.946	< 0.001[1,b]	Reference
> 3 d (*n* = 60)	20	0.333	40	0.667		8.7 (3.78-20.02)

ICU admission						
Yes (n = 9)	8	0.889	1	0.111	< 0.001[2,b]	77.5 (9.25-648.4)
No (n = 235)	22	0.094	213	0.906		Reference
Early postoperative complications						
Yes (n = 28)	22	0.786	6	0.214	< 0.001[2,b]	95.33 (30.3-299.9)
No (n = 216)	8	0.037	208	0.963		Reference
Biliary complications						
Yes (n = 16)	16	1	0	0	< 0.001[2,b]	244.6 (30.21-1981)
No (n = 228)	14	0.061	214	0.939		Reference
Port/incisional site hernia						
Yes (n = 7)	7	1	0	0	< 0.001[2,b]	65.13 (7.67-553.1)
No (n = 237)	23	0.097	214	0.903		Reference

[1]Chi square test (χ^2).
[2]Fisher's exact test.
[a]$P \leq 0.05$: Statistically significant.
[b]$P \leq 0.001$: Highly statistically significant.
OR: Odds Ratio; ICU: Intensive care unit; ASA: American Society of Anesthesiologists; CE: Cystic echinococcosis; + ve: Positive family history; - ve: Negative family history.

obstructed by fragments of the laminated and germinal layers, and puncture of the cyst under pressure with an associated risk of intraoperative spillage and thus recurrence that may reach up to 22%[26-27]. According to our results, 12.3% of the patients developed recurrent HCD, which was lower than in two previous reports. This was due to differences in technique, cyst size, or follow-up duration. We routinely release the pneumoperitoneum to reduce intra-abdominal pressure during puncture and aspiration of the cyst, aiming to decrease intra-abdominal spillage. However, unrecognized spillage of cyst contents due to multiple cyst punctures by fine needles could contribute to spillage and dissemination, which may contribute to recurrence. In our opinion, the larger sample size, intense and longer follow-up protocol in our study is a true reflection of the real recurrence risk. The proposed solutions to these recurrence challenges have been developed by Bickel *et al*[28] and Palanivelu *et al*[29]. These two previous studies did not report recurrence, as both provided contamination-free management of HCD with a large-diameter suction needle and suction apparatus that allowed cyst aspiration without multiple punctures.

According to our results, 12.3% of patients developed recurrent HCD, higher than in two previous reports. This was due to differences in technique, cyst size, or follow-up duration. The follow-up period for Bickel *et al*[28] was 4.1 years, and for Palanivelu *et al*[29], was 5.8 years. In our study, the mean duration to diagnosis of recurrent HCD was 2.48 ± 0.98 years, and the mean cyst size at recurrence was 4.93 ± 2.72 cm. The recurrent cyst size was less than the original preoperative cyst size, most likely due to regular follow-up, and thus cysts were detected earlier before becoming symptomatic. Ultrasound scans were primarily used to detect recurrent HCD during the follow-up period. CT was performed in patients with inconclusive ultrasound results. The diagnostic accuracies of ultrasonography and CT scans were 90% and 100%, respectively, and we did not rely on routine serological testing owing to its low specificity[30-31]. Occult CBC with POBF indicates cyst invasion and, consequently, recurrence. Our data showed that POBF was strongly associated with recurrence (all patients with POBF later developed recurrent HCD), possibly due to the laminated layer and germinal layer invasion into the surrounding liver tissue or biliary tree. Hydatid cyst generally is an "expansive" disease, not "infiltrative." However, with growth in size, distorted anatomy, and elevated intracystic pressure, the adjacent liver parenchyma may develop pressure necrosis. CBC can lead to POBF, which, if persistent, can cause the formation of cystic recurrence, particularly starting from the fragment of cyst lying on the biliary and vascular structure that was not removed during the operation. We equate the management of HCD with oncologic principles: (1) Multidisciplinary management; (2) treatment with intent to cure; (3) active monitoring for recurrence; and (4) long duration of follow-up beyond five years.

Regarding recurrent HCD treatment, there is consensus that non-surgical treatment is preferable for small asymptomatic cysts in elderly patients with comorbidities. The surgical approach is preferred for patients with large, symptomatic, and complicated cysts[32]. However, in our study, radical surgery was recommended unless contraindicated. In our experience, a patient with a predicted life expectancy of 5-10 years should be offered surgery. Informed decision-making is essential because once a decision is made for nonoperative watchful waiting, the clock does not stop. There is a possibility that the cyst may expand, leading to complications, and surgery may become more complicated with an increased risk of morbidity. Thus, early and timely surgery in patients with recurrent small HCD may be advantageous. The most common re-operative procedures in our experience were open pericystectomy (56.7%) and open left hepatectomy (20%). Laparoscopic splenectomy was performed for recurrent HCD of the spleen. Laparoscopic excision was performed in patients with recurrent intraperitoneal HCD.

The limitation of this study is that we omitted patients with multiple or recurrent HCD and those managed with open surgery. In addition, we did not perform a multivariate analysis due to the small number of patients with CBC and recurrent HCD. The low incidence of complications namely POBF and recurrence constitutes a limitation for conducting a reliable regression analysis to predict these outcomes. It may compromise the statistical power and validity of the model, impeding the identification of significant predictors and the generalization of the results to larger populations. Despite these limitations, the information presented in this study adds to the current body of scientific evidence, and the study has the merits of large sample size and multicenter collaboration.

CONCLUSION

Occult CBC can predict recurrent HCD. Elevated cyst fluid bilirubin and ALP levels predicted POBF and recurrent HCD.

ARTICLE HIGHLIGHTS

Research background

Different methods have been used to treat hydatid cyst of the liver but there are no conclusive results. The two most common complications are postoperative biliary fistula and recurrent hydatid cyst disease (HCD).

Research motivation

We were motivated to conduct this study to evaluate the incidence of occult cysto-biliary communication (CBC) and HCD recurrence after laparoscopic partial resection and omentoplasty.

Research objectives

The objectives of the study were to determine the incidence of occult CBC and HCD recurrence rate with the aim of reducing these two complications. The second objective was to detect an association between high cystic fluid biochemical indices and the incidence of developing postoperative biliary fistula and HCD recurrence.

Research methods

A prospective observational study was conducted involving 244 patients with stage cystic echinococcosis 2 and cystic echinococcosis 3b according to the World Health Organization's Informal Working Group on Echinococcosis classification who underwent laparoscopic partial cystectomy with omentoplasty.

Research results

There was a highly statistically significant association between cystic fluid biochemical indices and the development of biliary complications. There was a highly statistically significant association between biliary complications, biochemical indices, and the occurrence of recurrent HCD.

Research conclusions

This study is the first to propose that occult CBC can predict recurrent HCD. Elevated cyst fluid bilirubin and alkaline phosphatase levels predicted POBF and recurrent HCD. These findings will encourage surgeons to detect occult CBCs to avoid morbidity and mortality due to POBF and recurrent HCD.

Research perspectives

Future studies should focus on the detection of CBCs to decrease the incidence and morbidity of POBF and HCD recurrence.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design, material preparation, data collection, and analysis; All authors commented on the previous versions of the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Institutional Review Board Committees, No. IRB10032.

Clinical trial registration statement: This study is registered at https://clinicaltrials.gov/. The registration identification number is ID: NCT05116735.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Data are available from the corresponding author on reasonable request at tameralnaimy@hotmail.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Li L
L-Editor: Webster JR
P-Editor: Xu ZH

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