PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Cholangiohydatidosis. Clinical features, postoperative complications and hospital mortality. A systematic review

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Abstract

Background

Cholangiohydatidosis (CH) is an evolutionary complication of hepatic cystic echinococcosis, associated with increased morbidity and mortality. The aim of this study was to describe the available evidence regarding clinical characteristics of CH, postoperative complications and hospital mortality.

Methodology/Principal findings

Systematic review. Studies related to CH with no language or publication restriction were included. Sensitive searches were performed in Trip Database, SciELO, BIREME-BVS, WoS, PubMed, EMBASE and SCOPUS. MeSH and free terms were used, including articles up to April 2023. The main outcome variables were postoperative complications and hospital mortality; the secondary ones were publication year, origin and design of primary studies, main clinical manifestation, anatomical location and type of cysts, hospital stay, surgical procedure performed, reinterventions; and methodological quality of primary studies, which was assessed using MInCir-T and MInCir-P scales. Descriptive statistics, calculation of weighted averages and their comparison by least squares logistic regression were applied. 446 studies were retrieved from the searches performed, 102 of which met the inclusion and exclusion criteria. The studies analyzed represent 1241 patients. The highest proportion of articles was published in the last decade (39.2%). Reports are mainly from Turkey (28.4%), Greece (9.8%), Morocco and Spain (8.8% each). With a weighted mean of 14.3 days of hospital stance; it was verified that 26.2% of patients developed postoperative complications (74,3% Clavien y Dindo III y IV), 6.7% needed re-interventions, and 3.7% died. When comparing the variables age, postoperative complications, hospital mortality, and reinterventions in two periods of time (1982–2006 vs. 2007–2023), no statistically significant differences were found. When applying the MInCir-T and MInCir-P scales, the methodological quality of the primary studies was 9.6±1.1 and 14.5±4.3 points, respectively.

Competing interests: The authors have declared that no competing interests exist.

Conclusion/Significance

CH is associated with severe postoperative complications and significant hospital mortality, independent of the development of therapeutic support associated with the passage of time.

Author summary

Cystic echinococcosis (CE) is a zoonotic neglected tropical disease which predominantly affects poor pastoral communities globally. The parasite cycles between farm dogs and livestock and is associated with livestock farming and feeding of infected offal to dogs. Human morbidity and mortality occur due to cyst formation in body organs, especially in the liver. One of the evolutionary complications of hepatic CE is the passage of parasitic structures, characteristic of CE (germ or pieces thereof, daughter vesicles or both), inside the bile duct, causing total or intermittent biliary obstruction, with or without secondary infection which is known as cholangiohydatidosis (CH), considered the most frequent evolutionary complication of CE, associated with increased morbidity and mortality, and worsened prognosis of the disease. This review aims to describe the available evidence regarding clinical characteristics of CH, postoperative complications and hospital mortality.

Introduction

Echinococcus granulosus and its various genotypes (preferably G1-G3 and G6-G7), is the etiological agent of cystic echinococcosis of the liver (CEL). This infection manifests itself three weeks after ingesting the egg and can reach 2 to 3 cm. in diameter in the liver parenchyma, three months after the infection occurred [1,2].

As CEL progresses, intracystic pressure reaches values of up to 80 cm H_2O, producing atrophy and fibrosis of the liver parenchyma due to compression which eventually leads to biliary tree obstruction. This occurrence happens namely in those cysts located in the center of the liver. Similarly, the increase in intracystic pressure and the fragility of the cyst wall, can generate a rupture of the cyst towards the lumen of the bile ducts, developing a cysto-biliary communication (CBC); However, even if there is no cyst rupture into the bile ducts, it can manifest biochemically and radiologically as an obstructive syndrome of the bile duct, secondary to compression [3].

Consequently, the evidence suggests that the most frequent evolutionary complication of CEL, is CBC development, with a reported incidence of up to 42% [4–6]. These communications, in relation to the diameter, can be classified as minor (or simple) and major (or frank intrabiliary rupture). Minor ones, which affect between 10% and 37% of patients with CEL, are small communications between the cyst wall and the bile ducts, where there is no passage of daughter vesicles or pieces of germinative membrane to the bile ducts. Nevertheless, in these cases fluid, protoscolex, or hydatid grit may enter the bile ducts without causing obstruction. Being asymptomatic, pre-surgical diagnosis is unlikely and minor CBCs are detected during surgery, by visualizing bile leakage or bile fistulas [6].

In contrast, major CBCs, with an incidence of 3% to 17% of patients with CEL, are characterized by broad communication between the cyst wall and biliary tree. They are frequently detected preoperatively and typically during surgery. In these cases, the contents of the cyst can spontaneously drain into the bile duct, causing total or intermittent biliary obstruction [7],

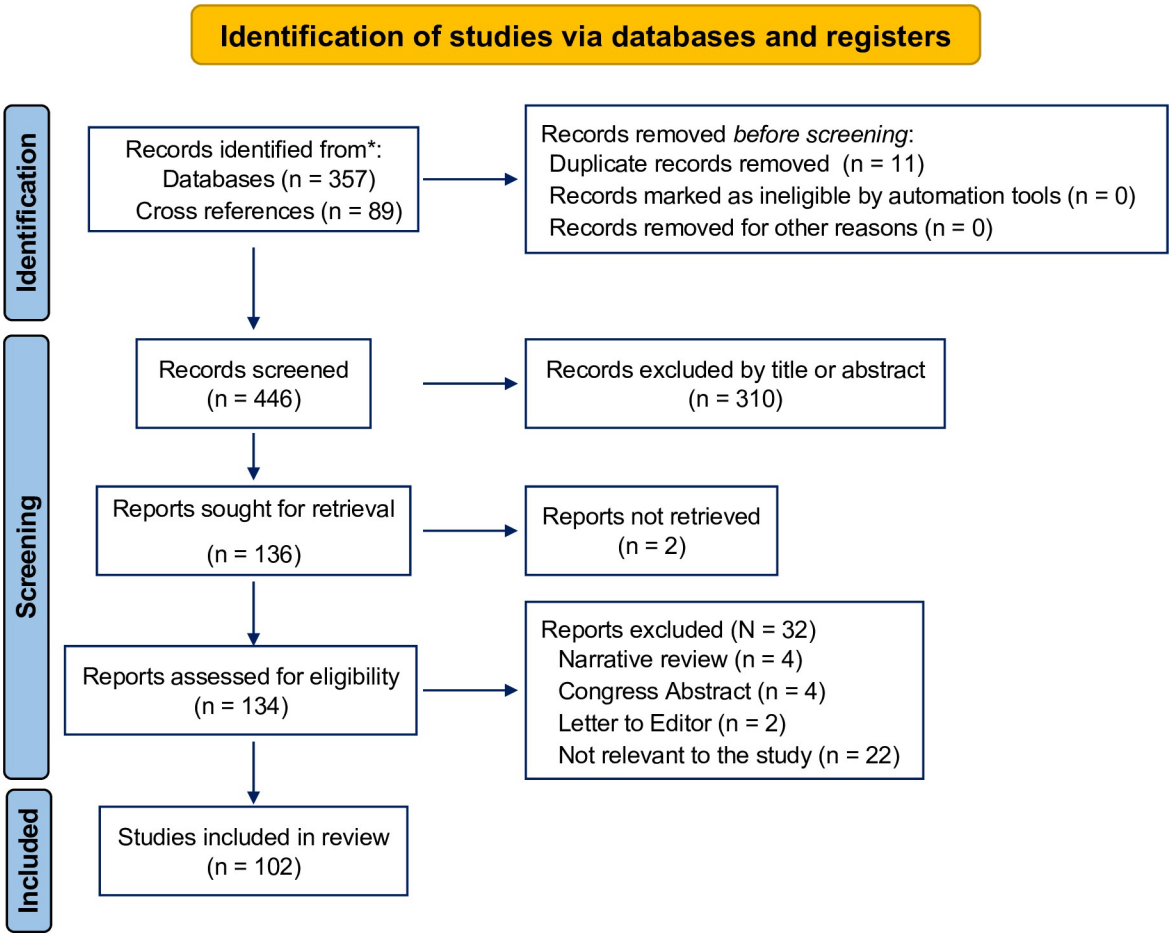

Fig 1. Diagram of pathogenic stages of cholangiohydatidosis. a) Hepatic cystic echinococcosis open into a bile duct. b) Incomplete cystic evacuation into the bile duct. c) Complete cystic evacuation into the bile duct.

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expressing itself clinically as biliary colic, obstructive jaundice and cholangitis [8]; (Fig 1). Such events can progress to sepsis, liver abscess formation, acute cholecystitis and even acute pancreatitis [9–14]. All of the above are situations that significantly increase the probability of developing postoperative complications [15].

Based on the pathogenic phenomena previously described, cholangiohydatidosis (CH) is defined as the presence of parasitic structures, characteristic of CEL (germ or pieces thereof, daughter vesicles or both), inside the bile duct, causing total or intermittent biliary obstruction, with or without secondary infection [8,16].

As such, it is an evolutionary complication of CEL, with a wide range of clinical manifestations that make preoperative diagnosis difficult at best. The reported prevalence is between 15.1% and 55.6%; and a cumulative incidence estimated at 0.07 cases in 5 years. It is furthermore associated with postoperative complications and in-hospital mortality of 23% and 7% respectively [15–18].

The aim of this study was to describe the available evidence regarding the clinical features of cholangiohydatidosis, postoperative complications, and hospital mortality.

Methods

This manuscript was written following the PRISMA guideline statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Study protocol

PROSPERO (International prospective register of systematic reviews, NIHR) ID: CRD42023406867.

Study design

A systematic review was conducted following the Updated guideline PRISMA statement [19].

Eligibility criteria

Primary studies related to cholangiohydatidosis were included; without language restriction or year of publication. Editorials, letters to the editor, narrative reviews, consensus documents and discussions, and articles contaminated with patients infected with *E. multilocularis*, *E. vogelii*, or other parasites were excluded.

Information sources

The following metasearch engines, libraries, and databases were reviewed: Trip Database, SciELO, BIREME-BVS, Web of Science (WoS), PubMed, EMBASE, and SCOPUS. The search and recruitment of articles closed on April 25, 2023.

Search criteria

This was carried out using the PECO components (population study [P], exposure [E], comparator [C], and result [O]). Studies related to hepatic echinococcosis (P), with cholangiohydatidosis (E), without comparator (C), postoperative complications and hospital mortality (O). Sensitive searches were carried out using MeSH, DeCS and free terms (Echinococcosis; Cystic Echinococcosis; hydatidosis; echinococcus granulosus infection; Hepatic Hydatid Cyst; Liver Hydatid Cyst; Liver Hydatidosis; Hepatic hydatidosis; Cholangitis; cholangiohydatidosis; Hospital Mortality; mortality and Postoperative Complications); and boolean connectors (AND and OR), with strategies adapted to each database (Table 1). A manual and cross-reference search was also carried out.

Study selection

Identified documents in each information source were filtered by duplication between databases. They were subsequently examined by title and abstract, applying eligibility criteria. The articles were then extensively analyzed by 3 reviewers (CM, JR and CR), all experienced in searching and analyzing biomedical studies. Discrepancy situations were resolved by consensus.

Data collection

Critical review of each selected article, as well as the data extraction and its subsequent verification, was carried out by 3 researchers (CM, JR, and CR). Then, data was collected in an Excel spreadsheet (Mac Excel, version 15.24; 2016 Microsoft Corporation).

Outcomes

Primary outcome variables were "postoperative complications", dichotomized in yes or no, classifying its according to Clavien & Dindo's proposal [20], and "hospital mortality", dichotomized in yes or no. Secondary outcome variables were year of publication, geographical origin of the studies, designs of primary studies, number of patients considered in each study, main

Table 1. Search strategies and results obtained for each source of information used (N = 357).

Meta search engines, libraries, and databases	*Search strategies*
Trip Database (n = 4)	(echinococcosis OR "cystic echinococcosis" OR hydatidos* OR "echinococcus granulosus infection*" OR "infection*, echinococcus granulosus" OR "hepatic hydatid cyst" OR "liver hydatid cyst" OR "liver hydatidosis" OR "hepatic hydatidosis"), (cholangit* OR cholangiohydatidosis), ("hospital mortality" OR mortality OR "postoperative complications")
SciELO (n = 3)	(echinococcosis OR "Cystic Echinococcosis" OR hydatidos* OR "Echinococcus Granulosus Infection*" OR "Infection*, Echinococcus Granulosus" OR "Hepatic Hydatid Cyst" OR "Liver Hydatid Cyst" OR "Liver Hydatidosis" OR "Hepatic hydatidosis") AND (cholangit* OR cholangiohydatidosis)
WoS (n = 24)	(TS = (Echinococcosis OR "Cystic Echinococcosis" OR Hydatidos* OR "Echinococcus Granulosus Infection*" OR "Infection*, Echinococcus Granulosus" OR "Hepatic Hydatid Cyst" OR "Liver Hydatid Cyst" OR "Liver Hydatidosis" OR "Hepatic hydatidosis")) AND (TS = (Cholangit* OR Cholangiohydatidosis)) AND (TS = ("Hospital Mortality" OR Mortality OR "Postoperative Complications"))
PubMed (n = 44)	("Echinococcosis"[MeSH Terms] OR "Echinococcosis"[All Fields] OR "Cystic Echinococcosis"[All Fields] OR "hydatidos*"[All Fields] OR "echinococcus granulosus infection*"[All Fields] OR "infection echinococcus granulosus"[All Fields] OR "Hepatic Hydatid Cyst"[All Fields] OR "Liver Hydatid Cyst"[All Fields] OR "Liver Hydatidosis"[All Fields] OR "Hepatic hydatidosis"[All Fields]) AND ("Cholangitis"[MeSH Terms] OR "cholangit*"[All Fields] OR "cholangiohydatidosis"[All Fields]) AND ("Hospital Mortality"[MeSH Terms] OR "mortality"[MeSH Terms] OR "Postoperative Complications"[MeSH Terms])
EMBASE (n = 95)	('liver hydatid cyst'/exp OR 'echinococcosis'/exp) AND 'cholangitis'/exp AND ('mortality'/exp OR 'hospital mortality'/exp OR 'postoperative complication'/exp)
SCOPUS (n = 117)	(TITLE-ABS-KEY(Echinococcosis OR "Cystic Echinococcosis" OR Hydatidos* OR "Echinococcus Granulosus Infection*" OR "Infection*, Echinococcus Granulosus" OR "Hepatic Hydatid Cyst" OR "Liver Hydatid Cyst" OR "Liver Hydatidosis" OR "Hepatic hydatidosis")) AND (TITLE-ABS-KEY(Cholangit* OR cholangiohydatidosis)) AND (TITLE-ABS-KEY("Hospital Mortality" OR Mortality OR "Postoperative Complications"))
Bireme BVS (n = 70)	((echinococcosis OR "Cystic Echinococcosis" OR hydatidos* OR "Echinococcus Granulosus Infection*" OR "Infection*, Echinococcus Granulosus" OR "Hepatic Hydatid Cyst" OR "Liver Hydatid Cyst" OR "Liver Hydatidosis" OR "Hepatic hydatidosis") AND ("Hospital Mortality" OR mortality OR "Postoperative Complications"))

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clinical manifestation, anatomical location and type of cyst, hospital stay, a surgical procedure performed, reinterventions, and a different kind of associated therapeutics.

Statistics

Descriptive statistics was applied with calculation of frequencies, averages, standard deviations and weighted averages.

Additional analyses

Meta-analysis was performed comparing the behavior of the variables under study in two periods of time (1982–2006, period A vs. 2007–2023, period B), applying a weighted least squares regression model (the weights were the number of patients of each scientific article). Methodological quality of primary studies was determined applying MInCir scales for therapeutic procedures and prognosis [21,22]. Dichotomization was decided because during the exploratory analysis of the data, we verified that this point divided the sample under study into two equal parts. Both used scales for determine methodologic quality (MQ), are valid (face and content validity, and construct validity for extreme groups) and reliable (interobserver reliability).

A)

Domains and items of the scale		Score
Domain 1: Research design		
Concurrent or prospective cohort	Controlled, double-blind, randomised, clinical trial	15
Historical or retrospective cohort	Non-randomised clinical trial	10
Case control study		8
Cross-sectional study		6
Case report or case series		3
DOMAIN 2: Studied population X Justification factor		
> 501		7 or 15
201 - 500		6 or 12
151 – 200		5 or 10
101 - 199		4 or 8
51 - 100		3 or 6
31 - 50		2 or 4
≤30		1 or 2
Domain 3: Methodology		
Objective		
Clear and concrete objectives		3
Vague objectives		2
No objectives		1
Design		
Clearly identified the design		3
Unknown design		1
Variables (definition of outcome, exposure and confounding variables)		
Outcome variables adequately defined		1 or 0
Exposure variables adequately defined		1 or 0
Confounding variables adequately defined		1 or 0
Sample size		
Includes sample size calculation/estimation		3
Does not include sample size calculation/estimation		1
Follow-up		
Mentioned the losses/follow-up percentage		1 or 0
The follow-up was greater than 80%		1 or 0
Cause of losses explained		1 or 0
Domain 4: Analysis and conclusions		
Risk measures		
Included a calculation of the risk measures		5 or 0
Reported data allowed the calculation of risk measures		2 or 0
Association models		
Included predictive or association models		5 or 0
Consistency between objective, methodology and results		
Showed consistent objective-methodology-results		3 or 0
Total Σ (domains 1 + 2 + 3 + 4)		**7–60**

B)

Domains and items of the scale	Score
Domain 1: Study design	
Multicenter double blinding RCT	12
Individual double blinding RCT	9
CT without or simple blinding, without randomization	6
Concurrent Cohort	4
Case Controls and Historical Cohort Studies	3
Cross Sectional Studies	3
Series of Cases	1
Domain 2: Population studied x justification factor	
> 201	6 or 12
151 - 200	5 or 10
101 - 150	4 or 8
61 - 100	3 or 6
31 - 60	2 or 4
≤30	1 or 2
Domain 3: Methodology	
Objective	
A clear and specific objective is set out	3
Vague objective is set out	2
No objective is set out	1
Design	
The design used is clearly mentioned	3
The design used is not mentioned	1
Selection criteria	
Inclusion and exclusion criteria are described	3
Inclusion or exclusion criteria are described	2
Selection criteria are not described	1
Sample size	
Sample size used is justified	3
Sample size used is not justified	1
Final score (Domain 1 + Domain 2 + Domain 3)	**6 - 36**

C)

$$WA = \frac{\Sigma Xi\ ei}{\Sigma ei}$$

Xi: Variable value in study i
ei : Score obtained by the study i

Fig 2. MInCir-T (A), MInCir-P (B), and weighted average formula (C), to determine methodological quality.

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MInCir-T scale, composed of 3 domains and 6 items: the first related to the study design; the second to the population sample size, and the third related to the methodology used; according to which, a score which represents the sum of the 3 domains is generated, with a final score that can vary between 6 and 36 points (6 points being the worst MQ study and 36 being the best), with a cut-off point to define the construct of 18 points [21]. And MInCir-P scale, composed of 4 domains and 11 items (study design, population sample size, methodology used, analysis and conclusions); according to which, a score which represents the sum of the 4 domains is generated, with a final score that can vary between 7 and 60 points (7 points being the worst MQ study and 60 being the best), with a cut-off point to define the construct of 33 points [22]. Then data were entered to a spreadsheet and calculation of weighted means was applied, and its comparison applying a weighted least squares regression model (Fig 2).

Risk of bias in individual studies

The likelihood of inaccuracy in the estimate of causal effect in primary studies was assess applying MInCir scales [21,22], in both time periods.

Ethics

In order to reduce selection and analysis biases masking of authors and study centers was implemented.

Results

Study selection

357 studies were retrieved from the search, and 89 were obtained from cross-searches. Of these, 446 articles, 201 were eliminated due to duplication of information sources. 245 were

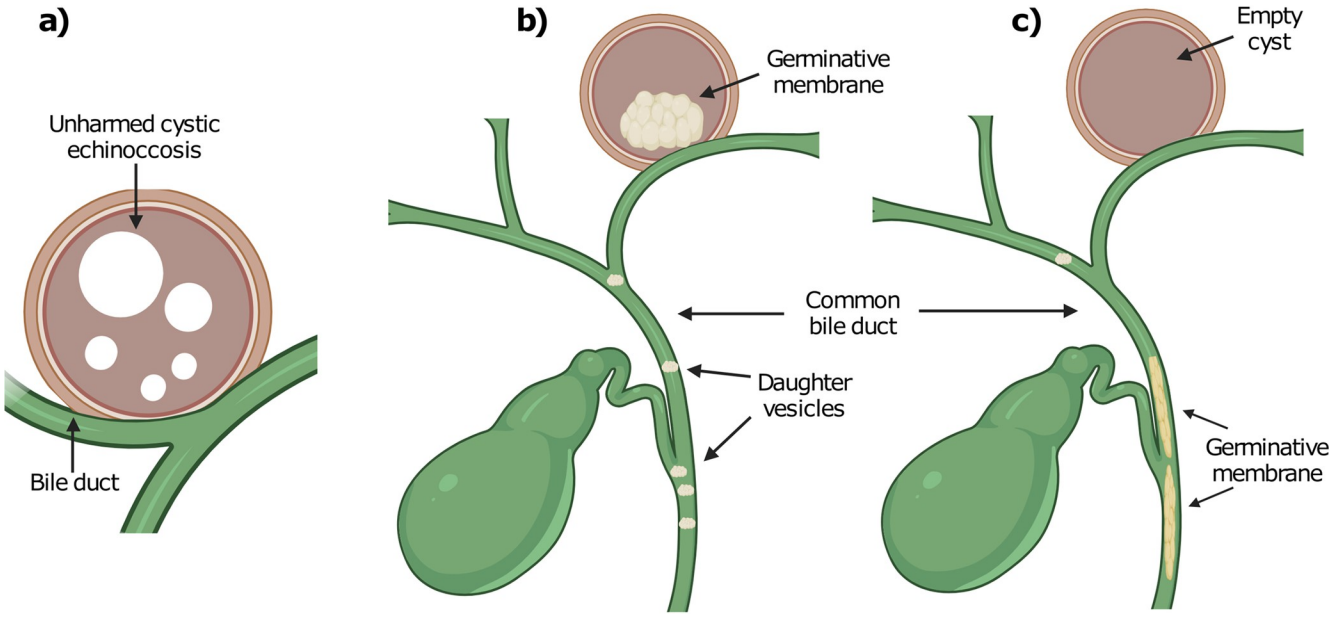

Fig 3. Flowchart of participating studies. Figure created with BIORENDER.COM, accessed on 30 November 2022.

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examined by title and abstract, 109 of which were discarded because they were considered "not related" to the research; leaving 136 articles to evaluate eligibility by reading the full text (2 were not retrieved). An in-depth analysis of the selected studies was then performed, excluding 32 studies based on the review criteria. Finally, 102 studies correspond to the study sample of this review (Fig 3) [4,7,8,10,12,16,17,23,25–118].

Study characteristics

39.2% of the included studies were published in the last decade (Table 2). Turkey had the highest number of publications (n = 29, 28.4%; Table 3). Most included studies were case reports and case series (64.7% and 33.3% respectively [Table 4]), representing 1241 patients, with a weighted mean age of 43.7 years, 50.6% male (Table 5).

Synthesis of results

Weighted means of the common bile duct and cyst diameter were 16.3 mm and 12.9 cm, respectively (Table 5). Clinical presentation was obstructive jaundice, acute suppurative

Table 2. Year of publication of the included studies (N = 102).

Year of publication	*N° studies*	*%*
2018–2023	17	16.7
2013–2017	4	3.9
2012–2016	19	18.6
2007–2011	12	11.8
2002–2006	17	16.7
1997–2001	15	14.7
1992–1996	6	5.9
1987–1991	7	6.9
1982–1986	5	4.9
T o t a l	**102**	**100**

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Table 3. Origen of included studies (N = 102).

Study origin	*N° studies*	*%*
Turkey	29	28.4
Greece	10	9.8
Spain	9	8.8
Morocco	9	8.8
Tunisia	7	6.9
India	6	5.9
Italy	5	4.9
Germany	3	2.9
Chile	3	2.9
Iran	3	2.9
Saudi Arabia	2	2.0
Israel	2	2.0
Pakistan	2	2.0
U.S.A	2	2.0
Others *	10	9.8
T o t a l	**102**	**100**

*: Belgium, China, Croatia, Netherlands, England, Libya, Moldova, Peru, Portugal, and Romania; one of each.

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cholangitis, acute pancreatitis and a mixture of cholangitis with acute pancreatitis. In the common bile duct, daughter vesicles and germinative membrane were found. CE2 and CE3B were the most frequent types founded (Table 4). CH most frequent treatment was choledocostomy with a Kehr tube, and hydatid cyst's most common treatment was partial cystectomy. Associated pharmacotherapy with benzimidazoles and antibiotics was utilized (Tables 5 and 6).

With a weighted mean of 14.4 days of hospital stance, it was verified that 26.2% of patients developed postoperative complications (74.3% Clavien and Dindo III and IV), 6.7% needed re-interventions, and 3.7% died (Table 5). The etiology and Clavien & Dindo distribution of postoperative complications is summarized in Table 6.

MQ of primary studies was 9.6±1.1 applying MInCir-Therapy scale (minimum 8 and maximum 15 points), and 14.5±4.3 applying MInCir-Prognosis scale (minimum 13 and maximum 53 points). When measuring methodological quality in the time periods under study, no statistical differences were observed (Table 5). Thus, the likelihood of inaccuracy in the estimate of causal effect in primary studies is high.

Finally, when comparing different in-study variables in two different time-periods, statistical difference in total leukocytes ($p = 0.0163$) and common bile duct diameter ($p = 0.001$) was observed. However, no differences were verified in postoperative complications, re-interventions or hospital mortality (Table 5).

Possible biases in the review process

Additional information was requested from the authors to expand or verify some study data, unfortunately there was no response. Therefore, missing data may introduce bias in this review. The risk of missing studies was reduced by searching for cross references.

Risk of bias between studies

There may be publication bias, given the concentration of studies from a few countries, and the paucity of studies from other geographic areas, places, and countries (Table 3).

Table 4. Characteristics of the included studies and patients.

Variables	N° cases	%
Study design (n = 102)		
Case report	66	64.7
Case series	34	33.3
Historic cohort	2	2.0
Clinical presentation (n = 1244)		
Obstructive jaundice	639	51.4
Acute suppurative cholangitis	530	42.6
Acute pancreatitis	73	5.9
Cholangitis and acute pancreatitis	2	0.2
Findings in the bile duct (n = 102)		
Daughter vesicle	40	39.2
Germinative membrane	30	29.4
Both	32	31.4
Type of cysts, WHO classification (n = 102)		
CE2	31	30.4
CE3A	13	12.7
CE3B	41	40.3
CE4A	9	8.8
CE4B	8	7.8
Cholangiohydatidosis treatment (n = 1088)		
Choledocostomy with Kehr tube	669	61.5
Endoscopic surgery	292	26.8
Choledochoduodenum anastomosis	83	7.6
Suture of CQB	36	3.3
Percutaneous drainage	8	0.7
Cyst treatment (n = 1156)		
Partial cystectomy	713	61.7
Pericystectomy	216	18.7
Nothing	123	10.6
Liver resection	86	7.4
Cystostomy	18	1.6
Associated pharmacotherapy (n = 639)		
Albendazole	290	45.4
Antibiotics	272	42.6
Antibiotics + Albendazole	58	9.1
Mebendazole	16	2.5
Antibiotics + Mebendazole	3	0.5

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Discussion

Summary of the evidence

This is the first SR that summarizes the available evidence concerning CH. There are one SR refers to gallbladder echinococcosis, based on 20 studies that include 22 cases [119].

The information of this SR was recovered from systematic searches carried out in 7 information sources (metasearch engines, libraries, and databases), including information of the last 40 years, and represents a compilation of 102 primary articles that represent 1241 patients treated in different countries, but preferably in Turkey, Greece, Morocco, and Spain.

Table 5. Clinical characteristics of patients and studies, and behavior of some variables in the two evaluated periods of time.

Variables	Weighted mean (N° studies = 102) (N° cases = 1241)	1982–2006 (N° studies = 52) (N° cases = 592)	2007–2023 (N° studies = 50) (N° cases = 649)	*p*
Age (years)	43.7±7.4	44.3±27.6	43.2±23.5	0.380
Postoperative complications (%)	26.2±19.1	25.6±63.1	27.0±81.2	0.732
Hospital mortality (%)	3.7±5.1	3.7±18.8	3.7±17.3	0.942
Re-interventions (%)	6.7±9.5	8.4±33.4	6.4±66.8	0.704
Total leukocytes ($10e^3$/uL)	13208±4405	11407±14470	14540±7837	**0.016**
Total bilirubin (mg/dL)	5.5±3.5	5.1±9.6	5.9±7.1	0.403
Gamma-glutamyl transferase (U/L)	455±179	368±190	464±390	0.449
Alkaline phosphatase (U/L)	698±343	651±1060	743±669	0.406
ASAT (U/L)	263±232	295±811	241±197	0.420
ALAT (U/L)	301±170	270±613	328±253	0.271
Hospital stance (days)	14.4±6.3	13.5±20.1	16.1±24.6	0.107
Common bile duct diameter (mm)	16.3±6.7	20.3±15.8	13.8±15.3	**0.001**
Cysto-biliary communications (N°)	26.0±46.5	25.1±44.8	30.8±48.4	0.181
Cyst diameter (cm)	12.9±3.3	13.2±7.9	12.7±12.8	0.544
Follow-up (months)	67.9±51.0	70.6±154.8	66.2±141.9	0.791
MQ applying MInCir-T scale (points)	9.6±1.1	9.6±1.0	9.6±1.2	0.961
MQ applying MInCir-P scale (points)	12.9±3.3	14.2±2.3	14.8±5.7	0.918

ASAT: aspartate aminotransferase

ALAT: alanine aminotransferase

MQ: Methodological quality

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The first drawback of the selection of MeSH terms and free words in order to define the search strategies, was the need to highlight that the CH concept is either unclear or is generally not well-known given that the number of publications found where CH appears in the title or abstract, is extremely limited (only 5 primary studies in this SR).

Most primary articles with which we worked had other types of denominations, such as "*frank biliary communication*", "*frank intrabiliary rupture*", "*frank cysto-biliary communication*", "*ruptured liver hydatid cyst*", "*opening in the biliary tract*", "*complicated hepatic hydatid disease*", etc., articulated with the concept "role of ERCP". Considering such, it is important to note that all these concepts, only define the existence of communications between a hydatid cyst and the bile duct, but do not consider necessarily the presence of hydatid material (daughter vesicles, germinal membrane, or a part thereof), inside the biliary tree. On the other hand, the use of different definitions for the same concept may represent a source of selection and information biases.

It was very interesting to note that in two different time periods, the variables of postoperative complications, re-interventions and hospital mortality showed very similar behavior, though without statistically significant differences. Consequently, it could be purported that the need for re-interventions, the morbidity and mortality associated with CH have not changed despite continuous advancements in technology, suggesting that CH is an aggressive disease itself.

In patients with sepsis due to cholangitis secondary to CH, who require emergency surgery, taking the patient directly to the operating room would seem indicated to repair the cysto-biliary communication, without previous ERCP, given that ERCP is an invasive procedure that should be performed by an experienced team, which is not always on site or available in emergency centers around the world [23].

Table 6. Postoperative complications (n = 191).

Postoperative complication	*Clavien & Dindo*	*N° patients*	*%*
Surgical wound infection	I	32	16.8
Biliary fistula	IIIa	30	15.7
Biliary fistula	IIIb	21	11.0
Subphrenic abscess	IIIb	15	7.9
Atelectasis	II	14	7.3
Intra-abdominal abscess	IIIb	9	4.7
Infected residual cavity	IIIa	8	4.2
Pneumonia	IVa	8	4.2
Metabolic decompensation	IVa	6	3.1
Pleural empyema	IIIa	6	3.1
Sepsis	IVb	6	3.1
Bile duct stricture	IIIb	6	3.1
Bilioma formation	IIIb	5	2.6
Intestinal occlusion	IIIb	4	2.1
Evisceration	IIIb	4	2.1
Acute pancreatitis	IIIb	3	1.6
Cholangitis	IIIb	3	1.6
Atrial fibrillation	IIIa	3	1.6
Upper gastrointestinal bleeding	II	3	1.6
Infected residual cavity	IIIb	2	1.0
Anaphylaxis	IVb	2	1.0
Cyst rupture	IVa	1	0.5
T o t a l		**191**	**100**

Clavien I: 16.8%

Clavien II: 8.9%

Clavien III: 62.3% (IIIa: 24.6% and IIIb: 37.7%)

Clavien IV: 12.0% (IVa: 7.8% and IVb: 4.1%)

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On the other hand, is possible that type of cyst and or size has impact on the development of CH. For example, CE2 or CE3B type, has a higher rate of CH based on findings in bile duct (daughter vesicle and germinate membrane + daughter vesicle, reach 70.6%, because daughter cysts were present only in CE2 and CE3B). So, I it is possible could be a relationship between cyst size and/or type of cyst with CH.

Moreover, the variables that were found to be associated with the development of postoperative complications were as follows: common bile duct diameter (weighted average of 16.6 mm), main cyst diameter (weighted average of 13.2 cm), leukocytosis (weighted average of 13,469 10e3/uL), total bilirubin (weighted average of 5.5 mg/dL), alkaline phosphatase (weighted average of 799 U/L), and transaminases (weighted averages of 296 and 335 U/L).

In addition, the variables that were found to be associated with mortality were: common bile duct diameter (weighted average of 18.7 mm), main cyst diameter (weighted average of 13.8 cm), leukocytosis (weighted average of 14,546 10e3/uL), total bilirubin (weighted average of 4.8 mg/dL), alkaline phosphatase (weighted average of 621 U/L), and transaminases (weighted averages of 200 and 255 U/L).

We devised an alternative methodology for meta-analyzing data derived from studies of different design studies (especially in systematic reviews in which series of cases are the most frequent design founded in the searches). This approach involves the utilization of weighted

averages, with weights assigned based on the methodological quality of the studies contributing to each datum [24].

Limitations

The available evidence on CH was obtained only from level 4 studies (case reports, retrospective case series and historical cohorts, with reduced casuistry). On the other hand, methodological quality of primary studies was low: 9.6±1.1 for MInCir-Therapy and 14.5±4.3 for MInCir-Prognosis scales, which cutoff-points are 18 and 33 respectively [21,22].

Conclusion

The available evidence related with CH is indicative that this evolutionary complication of EHQ is prone to severe postoperative complications, the need of reinterventions, and high hospital mortality rates, despite the passage of time.

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