Original Article

Radical surgery decreases overall morbidity and recurrence compared with conservative surgery for liver cystic echinococcosis: systematic review with meta-analysis

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Background: This systematic review with meta-analysis aimed to investigate whether radical surgery (RS) for liver cystic echinococcosis (LCE) is superior to conservative surgery (CS) to decrease morbidity, mortality and recurrence.

Methods: MEDLINE, Embase, the Cochrane Library, Scopus, INIST, Ovid, Science Direct, Google Scholar, Springer link, clinical key, and web of science were searched up to April 13th, 2018. Adults of either sex operated on for symptomatic but non-complicated LCE were included. The quality of studies was assessed using the Jadad scoring system or the Methodological Index for Non-Randomized Studies index when appropriate. Meta-analyses were performed with a Mantel-Hansel method for random-effects.

Results: One randomized controlled trial, one retrospective comparative study using propensity-matching analysis for comparison and 14 retrospective comparative studies were included (3,771 patients). This meta-analysis showed that there were statistically significantly fewer biliary leakage +/− fistula [odds ratio (OR) =0.35; 95% CI, 0.21–0.60, P=0.00001], overall morbidity: (OR =0.49; 95% CI, 0.40–0.59, P=0.00001), and recurrence: (OR =0.17; 95% CI, 0.11–0.26; P<0.00001) in RS compared to CS.

Conclusions: This meta-analysis showed that there were statistically significantly fewer biliary leakage +/− fistula, overall morbidity and recurrence in RS compared to CS. In the absence of large-scale RCTs, this meta-analysis suggests that RS is superior to CS in treating hydatid disease of the liver.

Keywords: Liver; echinococcosis; hydatid cyst; surgery; post-operative infection; meta-analysis

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Introduction

Description of the disease

Hydatid disease or cystic echinococcosis (CE), caused by the tapeworm *Echinococcus granulosus (E. granulosus)*, constitutes a serious public health problem in endemic areas (1). According to the World Health Organization (WHO), *E. granulosus* is endemic in areas of South America, Eastern Europe, Russia, Mediterranean countries, and China, where human incidence rates are 50 per 100,000 person-year (2). Grosso *et al.* (3), evaluating the worldwide epidemiology of liver hydatidosis, concluded that infection with *Echinococcus granulosus* remains a major public health issue in several countries, even in areas where it was previously at low levels.

The true prevalence of CE is difficult to evaluate owing to the high proportion of asymptomatic carriers (4). According to a Tunisian survey of 6,249 surgical interventions during the period 2001–2005, the surgical incidence rate per year ranged from 11 to 13.6 per 100,000 (5).

The liver is the predominant site of CE, encountered in 70% of patients (6). Surgery remains the cornerstone of liver cystic echinococcosis (LCE) management. Unroofing or pericystectomy techniques (7) are the most widely performed.

Why it is important to do this review

Currently, liver surgeons tend to prefer radical surgery (RS) such as pericystectomy or hepatic resection, which avoids recurrence from parasite vesiculation and decreases postoperative deep suppuration in the remnant cavity. On the other hand, general surgeons prefer conservative surgery (CS), an easier technique to perform by young general surgeons, associated with less intraoperative bleeding. Additionally, and despite the expertise of liver surgeons, RS remains difficult or impossible to perform when LCE is close to the hepatic veins or the inferior vena cava.

In 2004 a systematic review of the literature stated, "*it is not possible to conclude which treatment, RS or CS, is better because the level of evidence was low*" (8). One randomized trial, published in 2008 (9) including 32 patients, showed that RS had fewer cavity-related complications and early local recurrences than CS. The main critique of this trial is the small number of included patients. In 2015, the first published meta-analysis (10), included only five observational studies. Therefore, there is still limited evidence concerning the long- and short-term outcomes after surgery for LCE.

Aim of the study

This systematic review with meta-analysis aimed to investigate whether RS for LCE is superior to CS to decrease morbidity, mortality, and recurrence.

Methods

Search strategy and criteria for considering studies for this review

Electronic searches

An extensive electronic search of the relevant literature, published in English or French, was performed on April 13th, 2018 using the following databases: MEDLINE, Embase, the Cochrane Library, Scopus, INIST, Ovid, Science Direct, Google Scholar, Springer link, clinical key and the web of science. Keywords used for the final search in all databases were "liver" "hydatid cyst" "cystic echinococcosis" "surgery" "radical surgery" "conservative surgery" "pericystectomy" and "unroofing".

Inclusion and exclusion criteria of studies

All relevant studies reporting a comparison between RS and CS to treat LCE, published in a peer-reviewed journal were considered for analysis. Data from non-comparative, editorials, letters to editors, review articles, and case series (fewer than ten cases) were excluded from the analysis.

Participants

Adults (age over 18 years) of either sex operated on for symptomatic but non-complicated LCE were included. We considered complicated LCE as (I) LCE ruptured into the biliary tract, (II) LCE involving the thorax, (III) LCE ruptured into the peritoneum.

Interventions

We studied two groups of surgical procedures: (I) RS, which included pericystectomy techniques (7), and hepatic resection; (II) CS, which corresponds to unroofing procedures, associated or not with other techniques, to manage the remnant cavity (7).

This meta-analysis was conducted according to the PRISMA 2009 checklist (11).

Outcome measures

Primary outcomes

The main outcome measure was overall postoperative morbidity. Overall postoperative morbidity was defined according to the Centers for Disease Control and Prevention classification (12): (I) extra surgical site (ESS) morbidity; (II) incisional surgical site (ISS) morbidity; (III) organ/space surgical site morbidity called "deep organ/space surgical site infection" which included the following: deep abdominal complications, deep abscess, cavity abscess, remnant cavity abscess, perihepatic collection, subhepatic abscess, and intra-abdominal abscess.

Secondary outcomes

(I) Postoperative mortality, defined as any and all deaths occurring during the hospital stay or within 30 days after discharge (13);

(II) Postoperative biliary leakage with or without biliary fistula: patients with bile draining through abdominal drains were classified as having biliary leakage. The biliary fistula was defined as drainage over 250 mL of bile daily for at least 3 days;

(III) Recurrence: recurrent hepatic hydatid disease was defined as the appearance of new active cysts after treatment of intrahepatic or extrahepatic disease (14).

Data collection and analysis

Selection of studies

Three authors (W Dougaz, I Samaali and M Khalfallah) independently retrieved full-texts of all studies that potentially met the inclusion criteria. If these three authors agreed that a study did not meet the eligibility criteria, other co-authors (W Dougaz, I Samaali, M Khalfallah and C Dziri) excluded it. If they disagreed, the conflict was resolved by discussion and consensus or by consulting two other members of the review team (C Dziri, A Fingerhut).

Extraction of data

Each author extracted the data independently from each study and performed the comparisons; all disparities were settled after a discussion with the senior authors (C Dziri, A Fingerhut).

Validity assessment of included studies

All studies that met the selection criteria were assessed for methodological quality by three authors (W Dougaz, I Samaali and M Khalfallah). The quality of the only randomized controlled trial (RCT) was assessed using the Jadad scoring system (15). Five was considered the best global score for RCTs. The Methodological Index for Non-Randomized Studies (MINORS) index was used to assess the quality of non-randomized trials (16). Twenty-four was considered the best global score for comparative studies.

Subgroup analysis and assessment of heterogeneity

Three subgroups were analyzed separately: (I) RCTs, (II) retrospective comparative studies using propensity-matching analysis and (III) retrospective comparative studies.

We used the Cochrane Chi² test (Q-test) to assess heterogeneity. Significant heterogeneity was defined when the test showed a $P<0.05$. The I^2 inconsistency test was used to estimate the degree of heterogeneity (17): an I^2 between 0% and 50% was considered as probably not having substantial heterogeneity, whereas an I^2, between 51% and 100% was considered as substantial heterogeneity.

Data synthesis and statistical analysis

Overall estimates of surgical procedure effect using odds ratios (OR) with their 95% confidence intervals (CIs) were calculated using the Mantel-Hansel method for random-effects. Results were presented in forest plots. All calculations were carried out using Review Manager 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) freeware package.

Results

Retrieved reports

Overall, we identified 3,098 articles. After verification of inclusion and exclusion criteria, we retained 16 studies for final analysis: one RCT (9), one retrospective comparative study using propensity-matching analysis for comparison and 14 retrospective comparative studies (18-32) (PRISMA flow chart - *Figure 1*). *Table 1* summarizes the results of the JADAD and MINORS score assessments.

Results of the search

Overall postoperative morbidity

Twelve studies reported overall postoperative morbidity [251/1,309 (RS) and 565/1,670 (CS), respectively] (*Figure 2*); there was less overall postoperative morbidity in RS; (OR =0.49; 95% CI, 0.40–0.59, P=0.00001) with no substantial between-study heterogeneity (I^2=4%, P=0.40).

Mortality

Thirteen studies contained data on mortality [35/1,549 (RS) and 54/1,884 (CS), respectively (P=0.91)]. There was no statistically significant difference found between the two groups RS and CS as shown in the forest plot (*Figure 3*).

Biliary leakage+/– fistula

Twelve studies had exploitable data for biliary leakage+/– fistula (36/700 RS *vs.* 136/927 CS, respectively). As seen in *Figure 4*, there were fewer biliary leakage+/– fistula with RS (OR =0.35; 95% CI, 0.21–0.60, P=0.00001) than with CS with I^2=24%.

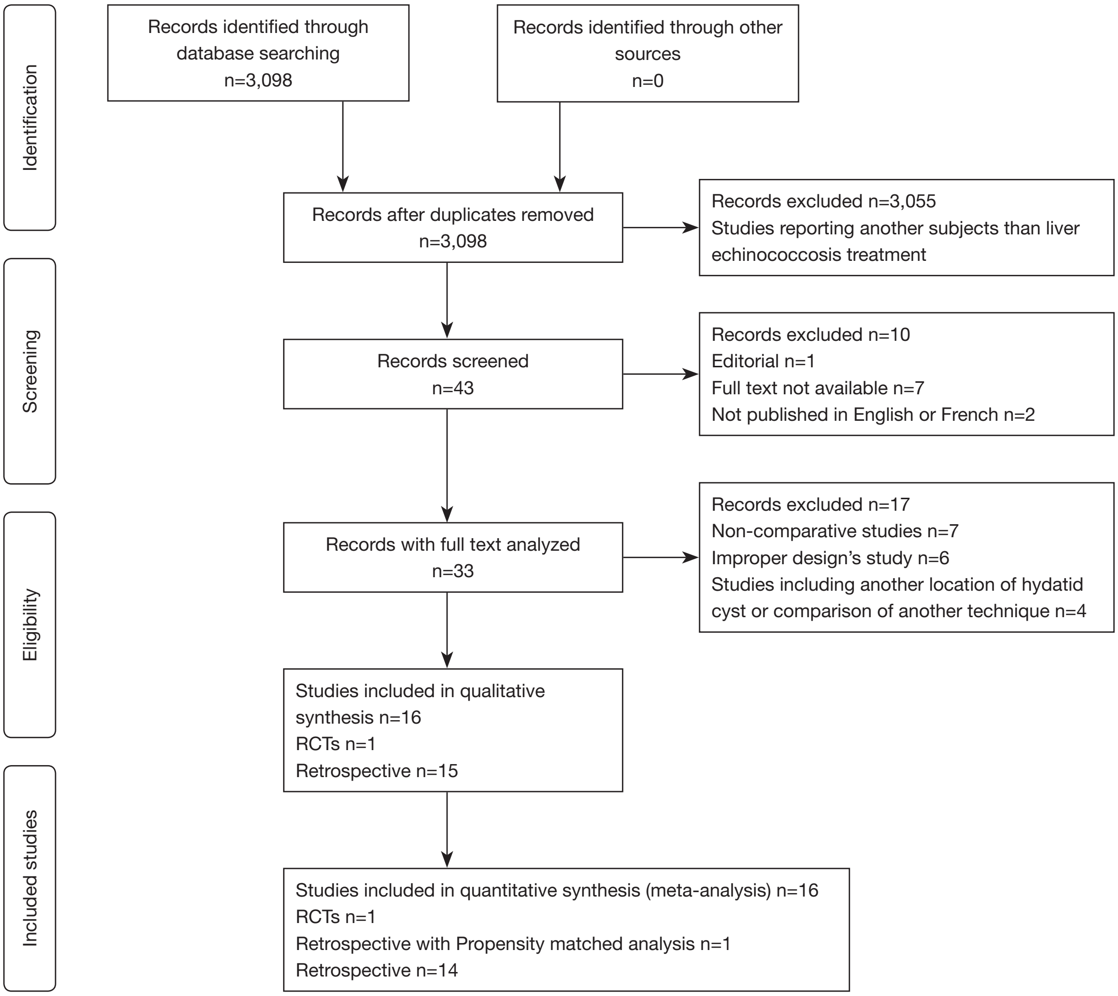

Figure 1 PRISMA diagram showing selection of articles for review.

Recurrence

In the forest plot (*Figure 5*), of 14 studies [27/1,555 (RS) and 194/1,813 (CS), respectively, there was fewer recurrence found in RS; (OR =0.17; 95% CI, 0.11–0.26, P<0.00001).

Discussion

This meta-analysis showed that there were statistically significantly fewer overall morbidity, biliary leakage +/− fistula and recurrence in RS compared to CS. On the other hand, there was no statistically significant difference found concerning mortality between these two groups.

Meta-analyses were originally designed to include only data from RCTs (33). Shrier *et al.* (34) argued that systematic reviews and meta-analyses of interventional studies should include only RCTs because the RCTs are more valid for causal inference compared with the observational study design. However, as underlined by Cameron *et al.* (33), incorporating randomized studies with non-randomized studies in the same meta-analysis may be of interest in specific settings: (I) non-randomized studies can complement RCTs or address some of their limitations, such as short follow-up time, small sample size [as was the case concerning Yüksel *et al.*'s RCT (9) for this meta-analysis], highly selected population, high cost, and ethical restrictions; (II) simultaneous assessment of multiple treatments, including treatments that may not have been studied in RCTs is possible; (III) larger sample size and more diverse populations may improve the generalizability of the findings (33).

Moreover, while these two types of designs have their strengths and weaknesses (34), a review of empirical studies

Table 1 Methodological assessment of included studies

Authors (reference)	Year of publication	Design	JADAD	MINORS	No. of patients R/C	Albendazole
Akbulut (18)	2010	Retrospective	–	14/24	18/41	Yes
Aydin (19)	2008	Retrospective	–	13/24	92/129	Yes
Birnbaum (20)	2012	Retrospective	–	12/24	85/12	No
Chautems (21)	2003	Retrospective	–	12/24	57/21	No
Cirenei (22)	2001	Retrospective	–	14/24	164/134	NR
El Malki (23)	2014	RPMA	–	18/24	85/85	Yes
Georgiou (24)	2015	Retrospective	–	11/24	73/145	Yes
Magistrelli (25)	1991	Retrospective	–	14/24	64/71	No
Mohkam (26)	2014	Retrospective	–	16/24	52/27	NR
Motie (27)	2010	Retrospective	–	15/24	64/71	Yes
Priego (28)	2008	Retrospective	–	9/24	162/210	No
Secchi (29)	2009	Retrospective	–	13/24	396/748	NR
Tagliacozzo (30)	2011	Retrospective	–	14/24	240/214	NR
Yüksel (9)	2008	RCT	3/5	–	15/17	Yes
Gupta (31)	2011	Retrospective	–	14/24	61/33	Yes
Yagci (32)	2005	Retrospective	–	13/24	14/171	Yes

MINORS, Methodological Index of Non-Randomized Studies; JADAD, scale for assessing the quality of reports of randomized clinical trials; RPMA, retrospective with propensity-matched analysis; RCT, randomized controlled trial; NR, not reported.

suggests that meta-analyses based on observational studies can produce estimates of effect similar to those from meta-analyses based on RCTs only (34). In addition, Hannan *et al.* (35) stated that the design and ultimate conduct of the study is the principal criterion to consider, not the type of study. However, it must be emphasized that causality cannot be inferred with the same strength as if all studies were randomized.

Agreements and disagreements with other studies or reviews

The meta-analysis, published in 2015 (10), including five observational studies, concluded that RS, especially total pericystectomy, had fewer complications, lower postoperative recurrence, and a lower incidence of biliary fistula and infection, as compared with CS. However, there are several statistical flaws in this meta-analysis as some relevant articles were lacking (20-26,28,30). Furthermore: (I) for "biliary leakage and fistula", the authors did not extract data exactly as mentioned in the articles of Akbulut *et al.* (18), Aydin *et al.* (19) and Motie *et al.* (27); (II) for "mortality" and "overall morbidity", Akbulut *et al.*'s article (18) was not concerned by these two criteria and the authors reported that the mortality and overall morbidity were nil; (III) for "length of hospital stay", the forest plot showed no statistical difference with a high heterogeneity and the authors did not explain this heterogeneity. In addition, as concerns, the outcome "postoperative biliary leakage", their conclusion (10) was a lower incidence of biliary fistula and infection in favor of RS but in the text, it was mentioned that there was no statistical significance found between the two groups.

A recent systematic review with meta-analysis in "Frontiers in medicine" (36), including 19 studies, concluded that RS may reduce the risk of postoperative complications and recurrence. Heterogeneity between included studies was considerable in this review and the authors were forced to withdraw several studies to solve this problem. Among studies included in this review, two did not meet the selection criteria that we consider in our meta-analysis (37,38).

Study or Subgroup	Radical surgery Events	Radical surgery Total	Conservative surgery Events	Conservative surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 Randomized trial						
Yüksel 2008	3	15	4	17	1.4%	0.81 [0.15, 4.40]
Subtotal (95% CI)		**15**		**17**	**1.4%**	**0.81 [0.15, 4.40]**
Total events	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.4.2 Retrospective with propensity matched analysis						
ElMalki 2014	16	85	13	85	5.9%	1.28 [0.58, 2.87]
Subtotal (95% CI)		**85**		**85**	**5.9%**	**1.28 [0.58, 2.87]**
Total events	16		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
1.4.3 Retrospective studies						
Aydin 2008	3	92	15	129	2.4%	0.26 [0.07, 0.91]
Birnbaum 2012	16	85	3	12	1.9%	0.70 [0.17, 2.86]
Chautems 2003	18	57	10	21	3.7%	0.51 [0.18, 1.41]
Cirenei 2001	9	164	17	134	5.4%	0.40 [0.17, 0.93]
Georgiou 2015	17	73	44	145	8.9%	0.70 [0.36, 1.33]
Magistrelli 1991	12	64	20	71	5.8%	0.59 [0.26, 1.33]
Mohkam 2014	19	52	16	27	4.2%	0.40 [0.15, 1.03]
Motie 2010	12	64	20	71	5.8%	0.59 [0.26, 1.33]
Priego 2008	22	162	66	210	12.7%	0.34 [0.20, 0.59]
Secchi 2009	104	396	337	748	41.9%	0.43 [0.33, 0.57]
Subtotal (95% CI)		**1209**		**1568**	**92.7%**	**0.45 [0.37, 0.55]**
Total events	232		548			
Heterogeneity: Tau² = 0.00; Chi² = 4.97, df = 9 (P = 0.84); I² = 0%						
Test for overall effect: Z = 8.19 (P < 0.00001)						
Total (95% CI)		**1309**		**1670**	**100.0%**	**0.49 [0.40, 0.59]**
Total events	251		565			
Heterogeneity: Tau² = 0.01; Chi² = 11.51, df = 11 (P = 0.40); I² = 4%						
Test for overall effect: Z = 7.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.55, df = 2 (P = 0.04), I² = 69.5%						

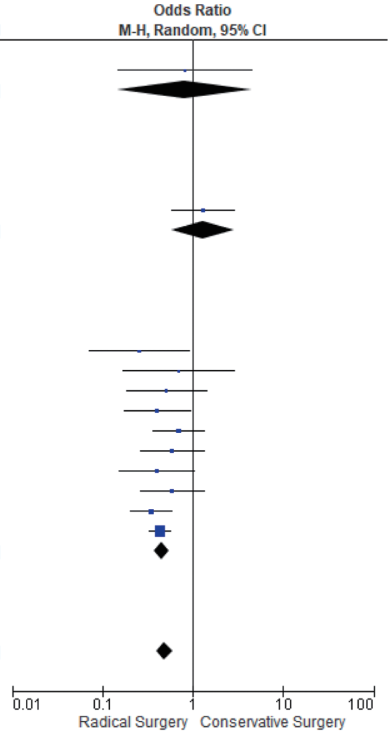

Figure 2 Forest plot: radical surgery *vs.* conservative surgery, outcome: overall morbidity.

Study or Subgroup	Radical surgery Events	Radical surgery Total	Conservative surgery Events	Conservative surgery Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 Randomized trial						
Yüksel 2008	0	15	0	17		Not estimable
Subtotal (95% CI)		**15**		**17**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.2 Retrospective with propensity score						
ElMalki 2014	0	85	1	85	3.9%	0.33 [0.01, 8.20]
Subtotal (95% CI)		**85**		**85**	**3.9%**	**0.33 [0.01, 8.20]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.5.3 Retrospective studies						
Aydin 2008	1	92	3	129	7.1%	0.46 [0.05, 4.51]
Birnbaum 2012	0	85	0	12		Not estimable
Chautems 2003	0	57	0	21		Not estimable
Cirenei 2001	3	164	8	134	15.6%	0.29 [0.08, 1.13]
Georgiou 2015	0	73	4	145	4.6%	0.21 [0.01, 4.03]
Magistrelli 1991	0	64	3	71	4.5%	0.15 [0.01, 2.99]
Mohkam 2014	0	52	0	27		Not estimable
Motie 2010	1	64	2	71	6.4%	0.55 [0.05, 6.19]
Priego 2008	0	162	8	210	4.8%	0.07 [0.00, 1.28]
Secchi 2009	8	396	12	748	23.9%	1.26 [0.51, 3.12]
Tagliacozzo 2011	22	240	14	214	29.1%	1.44 [0.72, 2.89]
Subtotal (95% CI)		**1449**		**1782**	**96.1%**	**0.63 [0.31, 1.29]**
Total events	35		54			
Heterogeneity: Tau² = 0.34; Chi² = 11.13, df = 7 (P = 0.13); I² = 37%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)		**1549**		**1884**	**100.0%**	**0.64 [0.33, 1.25]**
Total events	35		55			
Heterogeneity: Tau² = 0.27; Chi² = 11.47, df = 8 (P = 0.18); I² = 30%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						

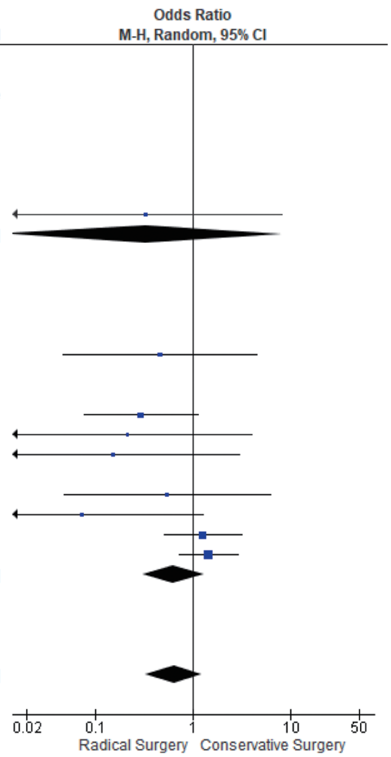

Figure 3 Forest plot: radical surgery *vs.* conservative surgery, outcome: mortality.

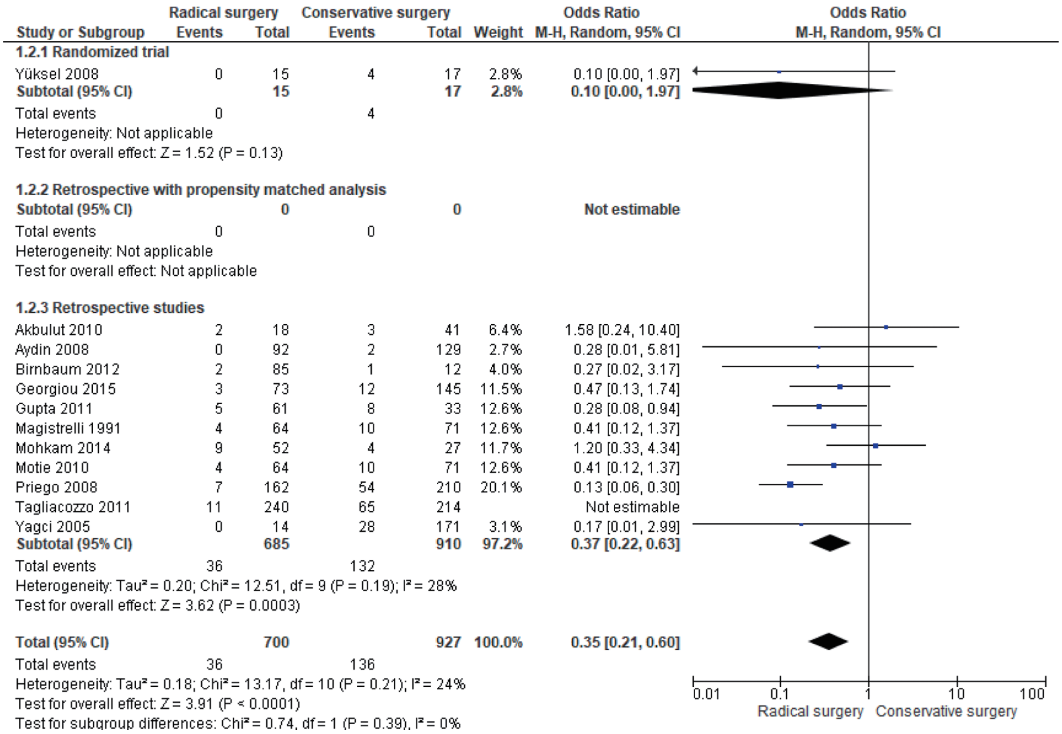

Figure 4 Forest plot: radical surgery *vs.* conservative surgery, outcome: biliary leakage +/– fistula.

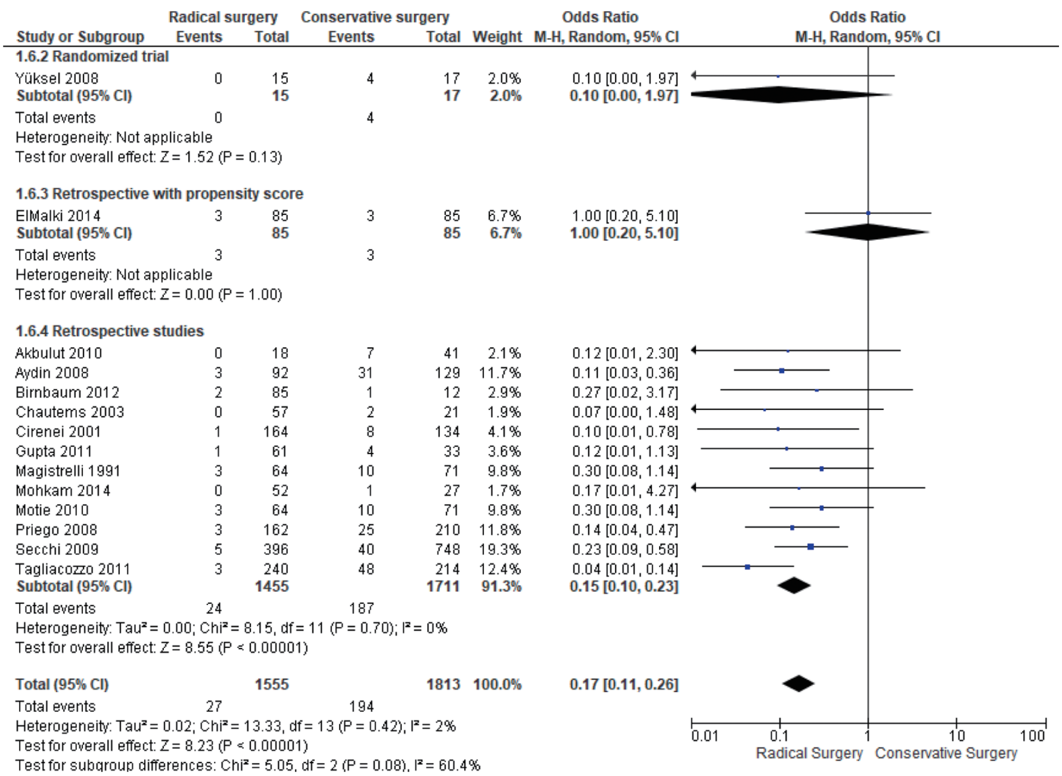

Figure 5 Forest plot: radical surgery *vs.* conservative surgery, outcome: recurrence.

Potential weaknesses in our study

Our meta-analysis included one RCT, one observational study with propensity matching and 14 retrospective comparative studies. Cameron *et al.* (33) also emphasized that "*Including low-quality, non-randomized comparative cohort studies, could perpetuate the biases that are unknown, unmeasured, or uncontrolled.*"

Even if the sample size of the only RCT included herein was 32, 0.51% of the total, we cannot eliminate unknown confounders that might have skewed the results of mixing randomized with observational propensity-matched or retrospective unmatched comparative studies in our analysis, therefore no causality can be inferred. Moreover, three potentially relevant articles were not available with full texts and therefore were not analyzed: one in Chinese (39) and two in English (40,41).

In conclusion, in the absence of multicenter RCTs, this comprehensive meta-analysis of the available evidence suggests that RS is superior to CS in treating hydatid disease of the liver.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ales.2019.08.01). AF served as the unpaid Guest Editor of the series and serves as the Editor-in-Chief of *Annals of Laparoscopic and Endoscopic Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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