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Review Article

Laparoscopic *versus* open surgery for hepatic cystic echinococcosis: a systematic review and meta-analysis

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Abstract: Objective: To systematically evaluate and compare the efficacy and safety of laparoscopic and conventional surgical treatment of hepatic cystic echinococcosis. Methods: Literature research was carried by using databases of PubMed, Medline, Ovid-Embase and the Cochrane Library with searching phrases "hydatid cyst or echinococcosis", "liver or hepatic", "surgery", "conventional or open", "laparoscopic or minimal invasive". After applying the inclusion and exclusion criteria detailed above, 7 articles with 999 patients were selected for final analysis. A meta-analysis of feasibility, safety and efficacy were performed on eligible studies with RevMan 5.2 statistical software. Results: A literature search revealed a total of seven publications (2 prospective and 5 retrospective) that met criteria, reporting data from 999 patients. Patients were categorized into laparoscopic group with 212 patients and conventional open surgery group with 787 patients. Meta-analyses indicated significantly lower perioperative morbidity [OR=0.59, 95% CI (0.39, 0.90), P=0.001] and lesser wound related complications [OR=0.34, 95% CI (0.13, 0.91), P=0.03], as well as shorter hospitalization period [MD=-3.44, 95% CI (-4.85, -2.03), P<0.000001] in the laparoscopic group. With regard to mortality, biliary leakage, residual cavity infection or fluid collection, recurrence rate, both therapeutic methods showed no statistical significance.Conclusions: The laparoscopic approach is safe for selected patients. Clinical outcomes are comparable to open surgery; however, further randomized controlled trials are strongly needed to determine a universally accepted result, because the certainty of the evidence is very low.

Keywords: Echinococcosis, laparoscopy, surgery

Introduction

Cystic ehinococcosis (CE), also named hydatid cyst or hydatidosis, is a parasitic disease caused by metacestodes of tapeworm *Echinococcusgranulosus*. *E. granulosus* infestation occurs in humans when they accidentally ingest tapeworm eggs [1]. It is endemic to regions in Northern China, Mediterranean, Turkey, Australia, North Africa, New Zealand, South America and the Indian subcontinent [2]. The infection is frequently targeting liver, about 75% of the cases [3]. Even though with benign nature, it may lead to lethal disability or come with many serious complications. Therapeutic methods of hepatic CE ranges from surgical intervention (conventional open procedure or laparoscopic approach) to PAIR or medical treatment [4]. Surgical treatment, open and laparoscopic approach are more commenly used all over the world. Open procedure is widely accepted and performed by the surgeons all over the world, and shows a good result. After the first successful laparoscopic surgery reported by Katkhouda in 1992 [5], there has been steady growth presented in the laparoscopic treatment of CE, as reported in our previous work [6]. Although several comparative studies comparing the perioperative outcomes of these two approaches have been reported, however, the feasibility, safety and efficacy of laparoscopy for hepatic CE cases are still controversial. This study is aiming to present a systematic review and meta-analysis based on the available data, then compare, if any, the feasibility, safety and efficacy of open and laparoscopic approaches in patients with hepatic CE.

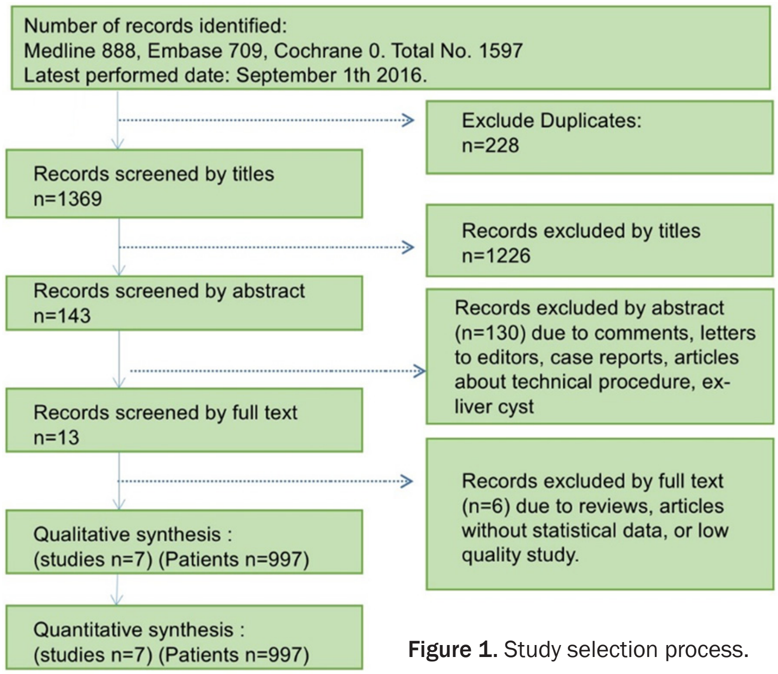

Figure 1. Study selection process.

Materials and methods

Process of study selection and data collection

Research type: The PRISMA statement was strictly followed in producing this systematic review [7]. An extensive electronic search of the relevant literature in English language was carried out using MEDLINE (through PubMed searching engine), Ovid-Embase and the Cochrane Library. Publishing time was set from January 1992 to September of 2016. Last searching time was: 2016-09-01. Searching phrases used are "hydatid cyst or echinococcosis", "liver or hepatic", "surgery", "conventional or open", "laparoscopic or minimal invasive". All relevant comparative studies, retrospective studies, prospective studies, systematic reviews regarding comparison of open and laparoscopic approach were carefully analysed. Characteristics of the study, inclusion and exclusion criteria, intervention type and different results were measured carefully. We followed GRADE approach when analyzing the certainty of the evidence [8]. Disagreements were solved through discussion.

Search strategy

Figure 1 shows the study selection and data collection process. Data collection Excel forms were used to extract data items from each included study.

Inclusion and exclusion criteria

All comparative studies regarding laparoscopic and open surgery for cystic echinococcosis were included.

Data extraction and result measurement

Detailed information on author of publication, gender, number of patients, typ e of the hydatid cyst with Gharbi et al. [9] or WHO/IWGE classification [10], lesion size and site, preoperative examination, operative time, morbidity, mortality, recurrence rate, intervention to postoperative complications and follow-up period were carefully collected and written into an Excel file, then tabulated into several categories. The necessary data from the original publications were thoroughly extracted and processed for further analysis. If the data was not specifically recorded or reported, it was considered as missing or not reported. No assumption was made about the missing data.

Statistical analysis

Statistical analysis was performed in line with recommendations from the PRISMA statement [7] and the Cochrane Handbook [11] for systematic reviews. All references were managed and duplicates were calculated by the software Endnote (X7.2 version). Data was documented in parametric and nonparametric pattern, according to their presentation in the original article. The RevMan (5.2 version) software was performed to generate the meta-analysis and forest plots. Statistical analysis for categorical variables was performed by using the odds ratio (OR) as the summary statistic. This ratio represents the odds of an adverse event occurring in laparoscopic group compared with the conventional surgery group. Mantel-Haenszel methods were used to perform statistical analysis, with confidence interval of 95%. If no significant heterogeneity ($I^2<50\%$) was found among studies, a fixed effects model was used to estimates; otherwise, a random effects model was chosen. The Q and I^2 statistics were

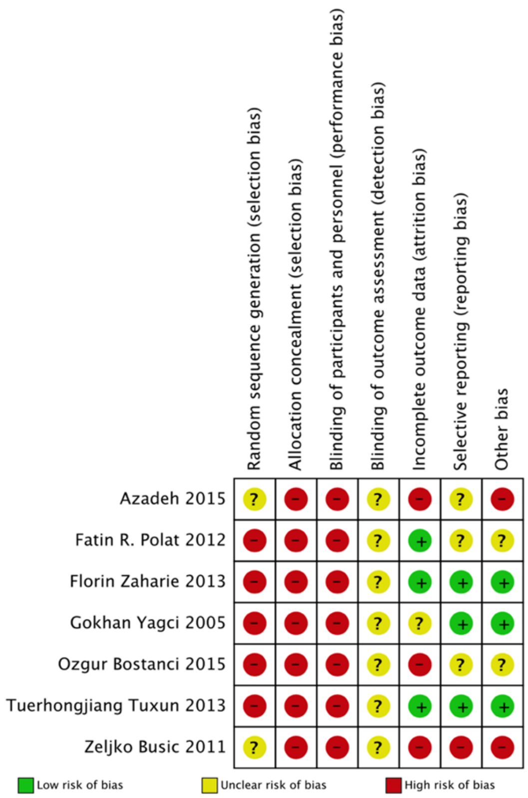

Figure 2. Risk of bias. Authors' judgements about each methodological quality item for each included study.

applied to quantify the between-trial heterogeneity. A *P* value of <0.05 was considered statistically significant.

Assessment of study quality

Quality of the reviewed trials was assessed by a "risk of bias" chart as **Figure 2**, which was constructed with the Review Manager (RevMan) software. The parameters of bias included sequence generation (representing election bias), allocation concealment (representing selection bias), blinding (representing performance bias or detection bias), incomplete data (representing attrition bias), selective reporting (representing reporting bias). Each parameter was graded as 'low', 'high' or 'unclear' to classify its risk of bias.

Results

General information and quality evaluation of included studies

A total of 1597 publications were identified during the primary screening process. Duplicates, review articles, editorials and surgical technique reports were excluded. Non-comparable studies on different treatment modalities or comparable studies without postoperative surgical results were excluded from final analysis [12-18]. Seven independent studies [19-25] with 999 patients, 212 laparoscopic and 787 open, comparing the clinical outcomes of laparoscopic and open surgery of hepatic hydatid cyst were analyzed. Data were assessed in a qualitative and quantitative synthesis [19-25]. The Prisma flow process was shown in **Figure 1**. No RCTs were identified and 2 prospective, 5 retrospective studies comparing laporoscopic approach with conventional open treatment modality were included. General information are shown in **Table 1**. The existence of blinding could not be determined because it was not mentioned in these studies. All seven studies reported relative clinical results and statistics. Five studies clearly described patient selection criteria, however, selection criteria were not given in the rest two studies [20, 21]. The risk of bias assessment of all included studies is described in **Figure 2**.

Postoperative morbidity, hospitalization period, recurrence and meta-analysis

Postoperative morbidity: Postoperative complications (total event *n=225*) were reported in six studies [19, 21-25] and good homogeneity among studies *($P=0.16$, $I^2=37\%$)* was observed. Fixed effect model meta-analysis revealed statistically significant differences between groups *[OR=0.59, 95% CI (0.39, 0.90), P=0.001]*, suggesting that the laparoscopic group showed fewer postoperative complications compared with the open group (**Figure 3**).

Postoperative morbidity of Clavien-Dindo classification IIIa or higher: It is necessary to classify the morbidity and perform more exact comparison in order to eliminate the effect of some slight complications, which occur much more often in open approach. Two studies [24, 25] revealed postoperative morbidities and interventions to them in detail. Clavien-Dindo et al. [26] classification is applied to categorize morbidities into different levels (**Table 2**), and analyzed staged IIIa or higher (total event *n= 24*) complication. It shows good homogeneity among studies *($P=0.20$, $I^2=39\%$)* and fixed effect model meta-analysis presents no statistically significant differences between groups

Table 1. General characteristics of the publication and enrolled patients

	Type	Year	Author	Nationality	Journal	Total No. of patients	Lap*	Open	Male	Female	Age (y)
1	Retrospective	2013	Zaharie Florin	Romania	Surg Endosc	231	59	172	97	134	43.8
2	Retrospective	2013	Tuxun Tuerhongjiang	China	J Gastrointest Surg	353	60	293	207	146	-
3	Retrospective	2005	Yagci Gokhan	Turkey	World J Surg	215	30	185	137	78	10-73 (35.2±13.3)
4	Prospective	2015	Jabbari Nooghabi Azadeh	Iran	Surg Laparosc Endosc Percutan Tech	73	37	36	24	49	38.97±16.48
5	Retrospective	2012	Polat Fatin R.	Turkey	Surg Laparosc Endosc Percutan Tech	19	7	12	7	12	31.7
6	Retrospective	2015	Bostanci O.	Turkey	Ann Ital Chir	83	14	69	47	36	41.6±10.5 (16-67)
7	Prospective	2011	Busic Z.	Croatia	Coll Antropol	25	5	20	11	14	47 (16-78)

*Lap = Laporoscopic.

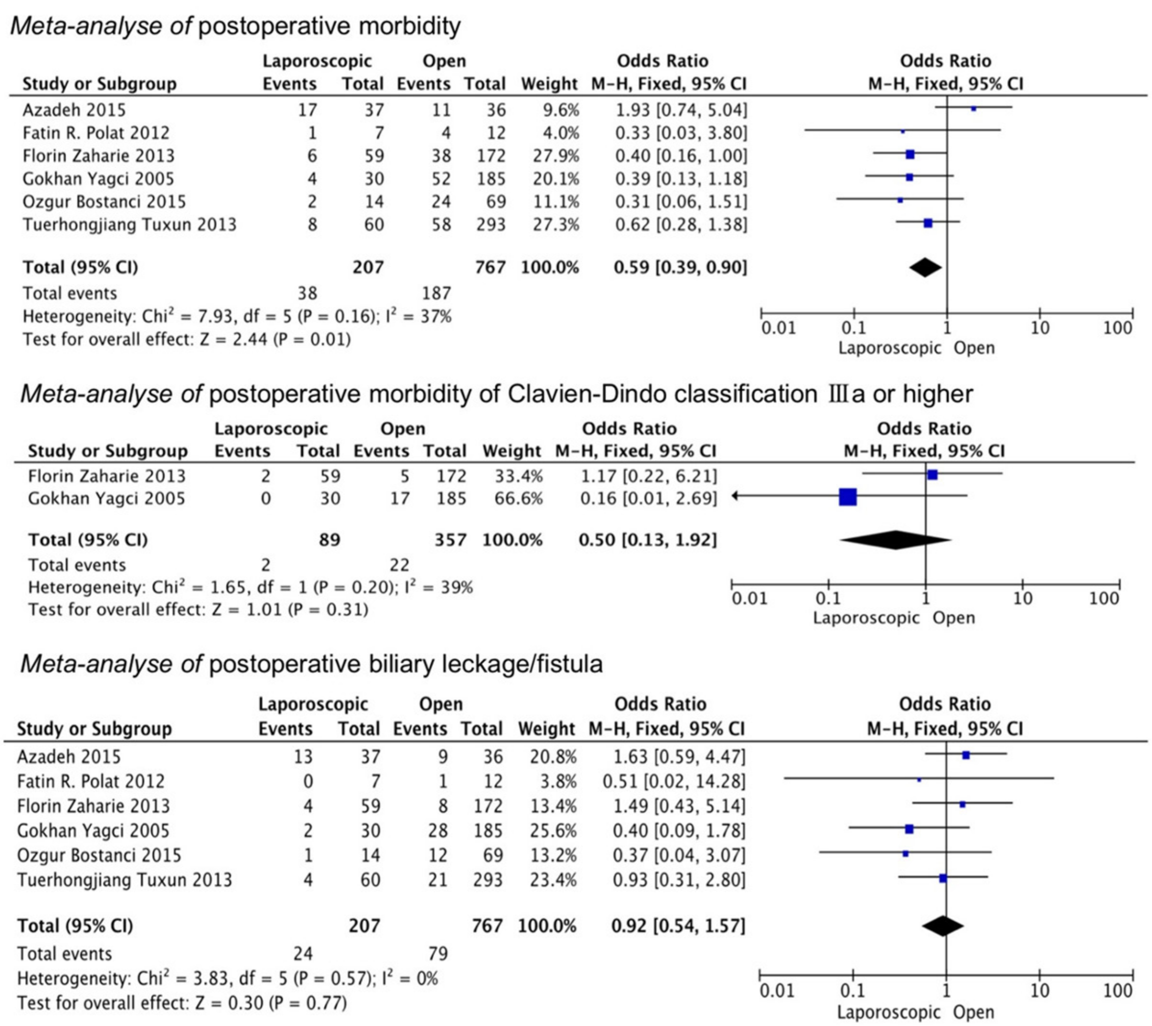

Figure 3. Meta-analysis of mortality and morbidity.

[OR=0.50, 95% CI (0.13, 1.92), P=0.31], suggesting that as to serious morbidities, either group has obvious advantages (**Figure 3**).

Postoperative biliary leakage/fistula: Biliary leakage/fistula was reported in 6 studies [19, 21-25] (total event *n=103*). Analysis on these

Table 2. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in the suffix "d"

*Brain hemorrhage, ischemic stroke, and subarrachnoidal bleeding, but excluding transient ischemic attacks.CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

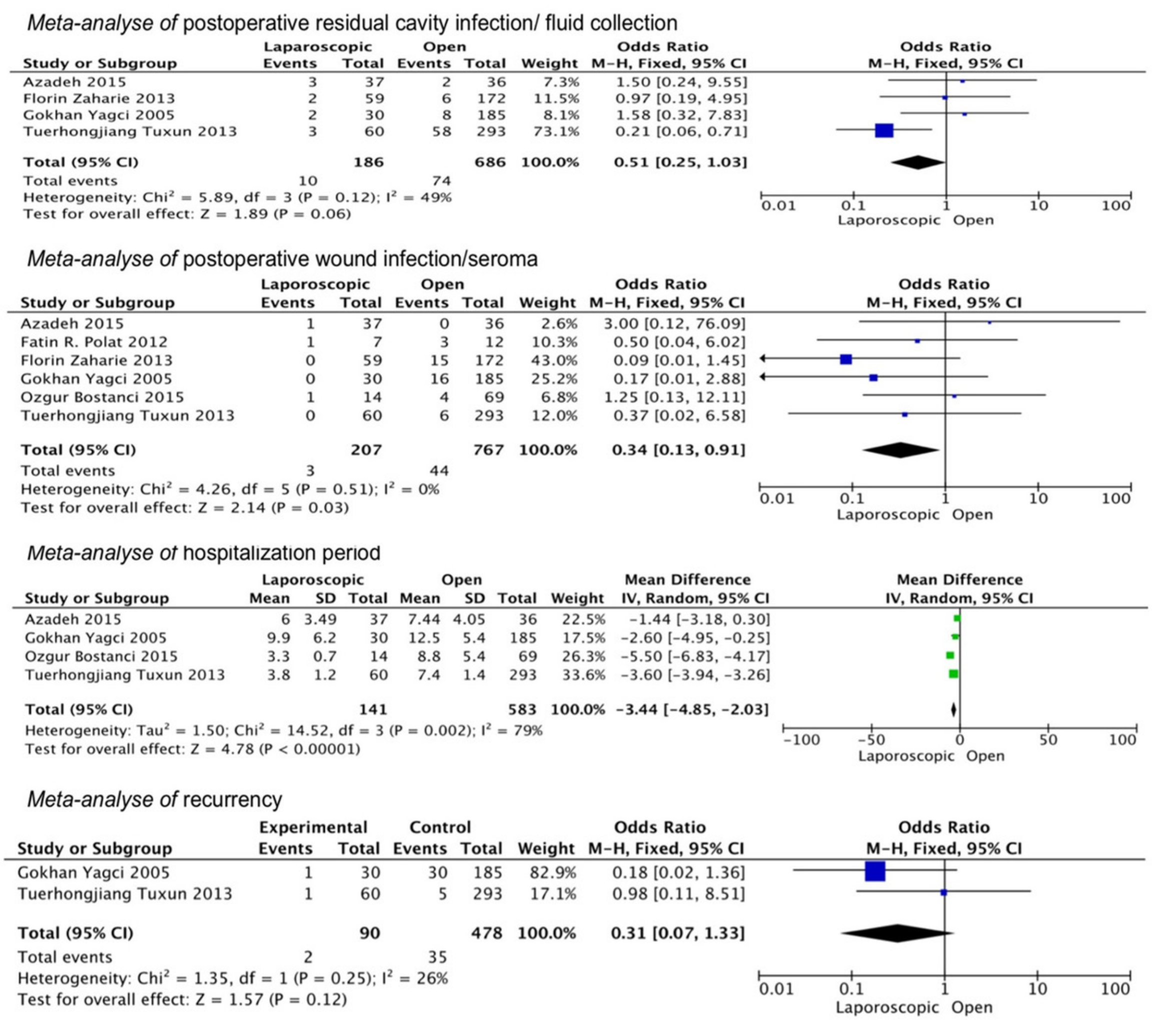

Figure 4. Meta-analysis of morbidity, hospital stay and recurrence.

studies showed a high level of homogeneity *(P=0.57, I^2=0%)*, so a fixed effect model meta-analysis was performed. The result demonstrated no significant difference between the groups *[OR=0.92, 95% CI (0.54, 1.57), P=0.77]* for postoperative biliary leakage/fistula between laparoscopic and open approaches (**Figure 3**).

Postoperative residual cavity infection/fluid collection: Four studies [21, 23-25] reported postoperative residual cavity infection/fluid collection (total event *n=84*). Heterogeneity analysis showed that *(P=0.12, I^2=49%)*, fixed effect model meta-analysis was performed. The result presented no significant difference between the groups *[OR=0.51, 95% CI (0.25, 1.03), P=0.06]* for postoperative residual cavity infection/fluid collection (**Figure 4**).

Postoperative wound infection/seroma: Wound related complications (infection, abscess, seroma) were reported in six studies [19, 21-25] (total event *n=47*). A high level of homogeneity among these studies was shown *(P=0.51, I^2=0%)*, so fixed effect model meta-analysis was performed. The results indicated that there was significant difference between the groups *[OR=0.34, 95% CI (0.13, 0.91), P=0.03]*. Result indicated that laparoscopy caused less wound related complications than open procedure (**Figure 4**).

Meta-analysis of hospitalization period: Four studies [19, 21, 23, 24] reported detailed postoperative hospitalization days (patient number *n=724*). Poor homogeneity among studies *(P=0.002; I^2=79%)* was observed. A random effect model meta-analysis was performed. It demonstrated significant difference between groups *[MD=-3.44, 95% CI (-4.85, -2.03), P<0.000001]* with regards to length of hospital stay, meaning that laparoscopic group had advantages (**Figure 4**).

Meta-analysis of recurrence: Two studies [23, 24] reported recurrence (total event *n=37*). Heterogeneity analysis showed that *(P=0.25, I^2=26%)*, we performed fixed effect model meta-analysis. The result presented no significant difference between the groups *[OR=0.31, 95% CI (0.07 1.33), P=0.12]* for relapse of hydatid cyst (**Figure 4**).

Discussion

A wide spectrum of modality including chemotherapy, PAIR, and surgery are being considered for the therapeutic method of hydatid cyst. There are studies showed albendazole (ALB) or mebendazole have a better effect on uncomplicated hydatid cysts [27, 28]. However, complete disappearance of cysts was not achieved according to the studies [16]. Percutaneous aspiration injection and re-aspiration (PAIR), is associated with more clinical and anti-parasitic efficacy; lower morbidity, mortality, as well as recurrence [29]. Nevertheless, it requires strict compliance to the cystic type, site and size of the cyst, and may not be suitable to all patients. PAIR with albendazole administration displayed a favorable improvement in highly selected patients[30]. Surgery remains the mainstream modality for echinococcosis albeit increasing number of interventions [4, 31]. The first successful laparoscopic surgery [5] has opened a new era and increasing number of patients have been reported [32, 33]. However, the acceptance of laparoscopic technique was a long journey because of potential intraoperative spillage due to pneumoperitoneum [13]. Later on, the pneumoperitoneum process was proved to be safe and protective [34]. Radical surgery for liver hydatid cyst including pericystectomy and hepatectomy was reported to show significant low rate of morbidity and recurrence rates [35, 36]. With the increasing experience and instrumental innovation, laparoscopic radical resection in selected cases seems to be acceptable [37, 38]. However, it is unsettled whether laparoscopy or open procedure is better.

Few comparative review articles on the laparoscopic and open surgery of liver hydatid cyst have been published [12, 15, 16, 18], however, systematic and more detailed information on the comparison between laparoscopic and open surgery are still missing. It is obvious that conventional surgery is still the most widely used in endemic and non-endemic areas. Laparoscopy is proving its advantages with less pain, good cosmetic results, shorter hospital stay, less or no blood transfusion requirement, and less postoperative adhesion [6].

In this study, the results of the meta-analyses indicated significantly lower perioperative morbidity *[OR=0.59, 95% CI (0.39, 0.90), P=0.001]* and lesser wound related complications *[OR=0.34, 95% CI (0.13, 0.91), P=0.03]*, as well as shorter hospitalization period *[MD=*

Table 3. Analysis of 5 studies with 907 patients

Group	Radical procedure (229 patients)	Conservative procedure (678 patients)	*P* value
Laparoscopic	44	124	P=0.8312
Open	185	554	

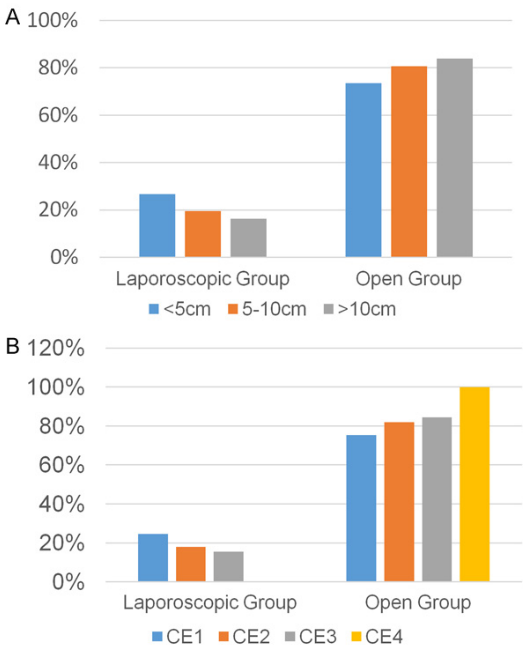

Figure 5. A. Percentage of patients of each size group. B. Percentage of patients of each type group.

-3.44, 95% CI (-4.85, -2.03), P<0.000001] in laparoscopic group. With regard to mortality, biliary leakage, residual cavity infection or fluid collection, recurrence rate, both therapeutic methods showed no statistical significance (**Figures 3**, **4**). But it is important to point out that when classifying postoperative morbidity into different level, as we used Clavien-Dindo classification in this study, postoperative morbidity of IIIa or higher showed no statistical significance *[OR=0.50, 95% CI (0.13, 1.92), P=0.31]* (**Figure 3**). It means that both methods show no advantages at result if ignoring the slight but frequently-suffered complications such as wound infection, medical controlled pulmonary inflammation (infection).

The overall morbidity in laparoscopic group was *17.9% (38/212)* compared to the conventional group *23.8% (187/787)*. Several studies reports, perioperative morbidity varies from *12%* to *63%* in open series and from *8%* to *25%* for laparoscopic series, based on several factors including age, size of cyst, preoperative comorbidities especially biliary-cyst communication [39, 40]. Residual cavity infection and biliary leakage were the main complications according to our analysis of total 974 and 872 patients respectively. Residual cavity infection occurred in 84 patients, 10 in laparoscopic group, *5.4% (10/186)*; 74 in open surgery group, *10.9% (74/686)*. Most of the patients were cured with conservative treatment such as antibiotics therapy and prolonged drainage, except for 3 patients who undergone percutaneous drainage and 5 laparotomy including one left hepatectomy according to 3 studies with detailed information [23-25]. Postoperative biliary leakage occurred in 103 patients, 24 in the laparoscopic group, *11.6% (24/207)*; 79 in the open surgery group, *10.3% (79/767)*. All 103 patients were mentioned detailed interventions. Biliary leakage was cured spontaneously with conservative procedure such as prolonged drainage in 71 cases, 31 patients needed endoscopic retrograde cholangiopancreatography (ERCP) sphincterotomy or endobiliary stenting which is proved effective by other study [41].

After surgery, the major problem is the recurrence rate which accounts for *2.2% (2/90)* and *7.3% (35/478)* respectivelyin laparoscopic group and open group with follow-up period ranges from 12 to 63 months. In situ recurrence mainly due to the intraoperative spillage and incomplete removal of cyst content from the residual cavity [42]. Potential intraoperative spillage impeded laparoscopic hydatid cyst resection from obtaining general acceptation. In fact, the real risk of spillage is lower than might be expected [43], and the short-term recurrence rate varies between *0* and *9%* after laparoscopy, whereas in open cases, it is higher *(0-30%)* [44, 45]. Radical resection including the closed cystectomy and hepatectomy for liver hydatid cyst associated with significantly lower recurrence rate [46] and improved by experts [47].

Conversion to open is another aspect that should be seriously taken into consideration. Nine conversions were reported in the laparoscopic group *(4.5%, 9/212)*. Inadequate exposure was the main reason (six cases), following by bleeding (two cases) and risk of spillage (one case). The conversion from laparoscopic to an open resection should not be considered a failure. Rather, the safety of the patient and cystic integrity for preventing the spillage should be of the utmost importance.

Though, four cases in two studies [24, 25] reported postoperative mortality in conventional open group, but two of them had severe concurrent comorbidities, a 71 years old woman with chronic obstructive lung disease and positive serology for hepatitis C virus, who died of pulmonary failure, and another one patient with cirrhosis diagnosed with perioperative liver biopsy. So, the event is incomparable with that small amount.

On the other side, laparoscopic surgery needs special instruments, which could be expensive and unavailable for the centers of endemic regions with large number of population suffering from hydatid cyst, such as Northern China, Mediterranean, North Africa, South America and the India. So, most of the researches were conducted by well-resourced centers, that may not be widely applied in poor-resourced area.

Furthermore, we found no randomized controlled trials on this subject, neither any confirmed blinding trials. There are two prospective studies [20, 22] without detailed methodology described, will lead to low quality of evidence. Other studies were retrospective, also couldn't be regarded as high quality evidence [8]. Unified indication for laparoscopic surgery has not yield yet, various standard has been using depending on time, area, instrument development level, experience of surgeons. Lack of detailed report in studies, insufficient classified postoperative complications reminds suspicious that more complicated cases were performed by open procedure. In previous review, two studies [23, 25] set criteria for enrolled patients in both comparative groups. Zaharie *et al*. [25] draw a selection criteria for laparoscopic surgery: cysts located surface of liver, not in segment 1 or 7, and no evidence of intrabiliary rupture. In our previous study [23] we excluded patients with previous upper abdominal surgery, intrabiliary ruptured cyst, intraparenchymal located cyst, recurrent cyst, multiorgan cyst, cyst located in segments 1 and 7, and cyst larger than 15 cm. Five studies [19, 20, 23-25] with 907 patients described radical and conservative procedure. Among 229 cases who underwent radical hydatid cyst resection, *19.2% (44/229)* cases received laparoscopic approach and *18.3% (124/678)* in conservative procedure, no statistical significance between them *(P>0.05)* (**Table 3**). We conduct an analysis on cystic size and type from two studies with 584 patients [23, 25]. Laparoscopic surgery seems to be not suitable in patients with larger cysts (**Figure 5A**). Ranging from type CE1 to CE4 (WHO classification) [10], the number of the patients who underwent laparoscopic surgery showed a decrease (**Figure 5B**). Therefore, any conclusions drawn from these comparative literatures would be scientifically weak because the higher rate of various morbidity which tends to happen in the open group could be associated with the higher comorbidities and more complicated cases undergone radical surgical procedures in open group. Evidence-based surgery is hard to achieve because surgical studies were rarely randomized [48].

Conclusion

Different therapeutic method should be performed according to the type, size and location of the cystic echinococcosis. Laparoscopic approach for hepatic hydatid disease is safe and effective in properly selected patients with its advantages. Due to low quality of the evidence, it is unclear that either group has definite advantages on morbidity, mortality, and recurrence rate. Large, prospective, and randomized trials are strongly recommended to determine a universally accepted standard technique.

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Disclosure of conflict of interest

None.

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