

A comparative study of ultrasonic scalpel (US) versus conventional metal clips for closure of the cystic duct in laparoscopic cholecystectomy (LC)

A meta-analysis

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Abstract

Background: laparoscopic cholecystectomy (LC) has become the gold standard surgery for benign gallbladder diseases. Metal clips are conventionally used to secure the cystic duct and artery, while monopolar electrocautery (ME) predominates during laparoscopic dissection. ultrasonic scalpel (US) has already been explored for sealing the cystic duct and artery as a sole instrument, which has been regarded as a reasonable alternative to clips. The aim of this study was to investigate the safety and effectiveness of US versus clips for securing the cystic duct during LC.

Methods: We identified eligible studies in PubMed, Medline, Cochrane Library, Embase, and SpringerLink up to 1st May 2018, together with the reference lists of original studies. Meta-analysis was conducted using STATA 14.0. Q-based chi-square test and the I^2 statistics were utilized to assess heterogeneity among the included studies. A P -value below .05 was set for statistical significance. Forest plots of combined Hazard ratios (HRs) with 95% confidence intervals (CIs) were also generated.

Results: Eight studies met eligibility criteria in this meta-analysis eventually. A total of 1131 patients were included, of whom 529 were contained in the US group, compared to 602 in the clips group, which showed a significant difference ($P=.025$) without substantial statistical heterogeneity ($I^2=0.0\%$). No statistical significance was revealed regarding age ($I^2=0.0\%$, $P=.957$), and sex ($I^2=0.0\%$, $P=.578$) between both groups. The operative time and hospital stay in the US group were significantly shorter than that in the clips group, with $I^2=95.0\%$, $P=.000$ and $I^2=72.8\%$, $P=.005$, respectively. Concerning conversion ($I^2=48.6\%$, $P=.084$), perforation ($I^2=12.0\%$, $P=.338$), along with bile leakage ($I^2=0.0\%$, $P=.594$), and overall morbidity ($I^2=19.1\%$, $P=.289$), comparison between both groups exhibited no statistical significance.

Conclusions: US enabled shorter operative time and hospital stay during LC, compared with clips. Additionally, US was comparable to clips regarding conversion, perforation, along with bile leakage and overall morbidity. Therefore, our meta-analysis concluded that US is clinically superior to the conventional clips in some aspects, or is at least as safe and effective as them, concerning closure of the cystic duct and artery.

Abbreviations: CIs = confidence intervals, HRs = Hazard ratios, LC = laparoscopic cholecystectomy, LVSS = LigaSure Vessel Sealing System, MDs = mean differences, ME = monopolar electrocautery, non-RCT = non-randomized controlled trials, ORs = odds ratios, RCT = randomized controlled trials, SDs = standard deviations, US = ultrasonic scalpel.

Keywords: clips, cystic duct, laparoscopic cholecystectomy (LC), ultrasonic scalpel (US)

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1. Introduction

Since its first introduction in 1987, Laparoscopic cholecystectomy (LC) has gained worldwide acceptance and rapidly taken the place of traditional open cholecystectomy. It has become the gold standard surgical methodology for benign gallbladder diseases,^[1] due to its well-recognized advantages of minimal invasiveness and fast convalescence.^[2] In general, the standard LC is performed by routinely taking use of metal clips, mostly being the titanium clips, to achieve closure of the cystic duct and artery. Meanwhile, laparoscopic scissors are exploited to cut the cystic duct, and monopolar electrocautery (ME) is employed to divide the cystic artery, cauterize the tissues and dissect the gallbladder from the liver bed. Even if development of thermal energy devices, such as bipolar electrocautery, CO₂ laser, ultrasonic scalpel (US), and LigaSure Vessel Sealing System (LVSS), and so on, has exerted a brilliant effect on hemostatic tissue dissection,^[3] ME still predominates during laparoscopy, representing the preferred method for more than 85% of surgeons.^[13,14]

Conventional metal clips remain to be the basic tool in LC and are commonly considered safe. However, many reports have figured out disadvantages of clips, among which the postopera-

tive bile leakage may be the most serious. Besides, some risks have been addressed to be linked with the use of ME, especially as visceral injuries on thermal basis. Thence, there are still areas for refinement in LC. Various measures including re-absorbable clips, linear stapler, endoloops, or sutures, have been proposed to seal the cystic duct, which, however, have not acquired adequate attention. Consequently and unsurprisingly, those aforementioned energy devices, especially as bipolar electrocautery, as well as US and LVSS, have been explored to secure the cystic duct in recent years.

The US possesses a variety of terminology in worldwide literature, such as ultrasonic shear, ultrasonically (harmonically) activated coagulating scalpel (shear), Harmonic scalpel (HS), and Ultracision. Designed to be a superior alternative to ME for hemostasis, it offers remarkable strengths, particularly as occlusion of vessels up to 5 mm with safety without requirement of clips,^[4] thus leading to its widespread popularity in both laparoscopic and open procedure.

In LC, US was initially looked upon as an advanced energy form for tissue dividing and coagulating, in order to remove the gallbladder from its liver bed.^[5] Then, in 1999, the application of US for both closure and division of the cystic duct and artery was attempted successfully for the first time,^[6] in the absence of clips. Thereafter, several worldwide studies have corroborated the clipless cholecystectomy by taking advantage of US as the sole instrument to completely occlude the cystic duct and artery.^[7,13,17,24] Therefore, the excellent performance of US continually encourages surgeons to broaden its role and accept it as a reasonable alternative to the standard clipping.

However, so far, the hesitancy to utilize US as the single working device for sealing the cystic duct during LC still persists clinically, mainly because of concerns about its insufficiency to withstand the biliary pressure as well as postoperative bile leakage. After all, its role in securing the cystic duct is still under evaluation.

Herein, we carried out a systematic review to investigate the practicality of US versus conventional metal clips for closure of the cystic duct in LC. Interestingly, there has recently published a relevant meta-analysis comparing different methods for securing the cystic duct,^[30] which was however, mainly focused on the outcome of postoperative bile leakage. Furthermore, several techniques were assigned into the same group for the sake of convenience for analysis, and a number of pooled patients receiving metal clips did not directly contrast with those receiving US in their original trails, which would compromise the reliability of the article. Therefore, the aim of our research was to further evaluate the safety and effectiveness of both techniques separately. Although some other energy devices, in particular, LVSS, have been applied to occlude the cystic duct and proven to be as equally safe, it is, however, not the purpose of our study.

2. Patients and methods

2.1. Search strategies

A comprehensive literature search of 5 databases (PubMed, Medline, Cochrane Library, Embase and SpringerLink) was carried out up to May 1st, 2018, for comparing US to clips for closure of the cystic duct in LC. The medical subject headings and keywords searched for in all possible combinations, included: "ultrasonic scalpel", or "harmonic scalpel", or "ultrasonically (harmonically) activated coagulating scalpel", or "Ultracision", or "ultrasonic device", and "clips", or "metal clips", or

"conventional clips", or "traditional clips", or "clipping", and "cholecystectomy", or "laparoscopic cholecystectomy", or "clipless laparoscopic cholecystectomy", or "LC", and "cystic duct", or "biliary duct". Reference lists of relevant articles were further evaluated to seek for missed studies during the electronic search. The last search was conducted on May 1st, 2018.

2.2. Inclusion and exclusion criteria

The inclusion criteria for eligible studies were established as follows:

- (1) as an original article,
- (2) including randomized controlled trials (RCT) or non-randomized controlled trials (non-RCT) that compared US with clips during LC,
- (3) focused on closure of the cystic duct,
- (4) providing details for the outcome measures, and
- (5) published in English.

We selected only the most recent or complete study if a study with the same patient cohort was reported in several publications. We attempted to contact the first author of the original study for missing data whenever encountered, by means of emails.

The exclusion criteria consisted of the following:

- (1) case reports or articles without full text,
- (2) non-comparative studies between US and clips,
- (3) not based on occlusion of the cystic duct,
- (4) performed by open operations, not by LC, and
- (5) inability to retrieve the raw data and failure to contact the authors.

2.3. Data extraction

All of the studies retrieved according to the above selection criteria were assessed by two reviewers (Lu-Lu Han, and Jin-Jing Lu) for the quality of their methodology and relevance to the objective of our meta-analysis. Any inconsistencies between the reviewers were resolved by a reevaluation of the original article with a third reviewer (Li-Chen Ho). The required data were predetermined and extracted using a standardized data collection form: the first author's name, publication year, trocar ports, demographic variables, surgical parameters, as well as conversions and postoperative complications.

2.4. Assessment of methodological quality and risk of bias

The checklists for data extraction were taken advantage of to determine the suitability of the included literature. As for RCTs, Cochrane Collaboration tool^[28] was applied to assess the methodological quality and risk of bias. Oppositely, for non-RCTs, the Newcastle–Ottawa Scale (NOS)^[29] was requested, which comprised three major parameters: patient selection, comparability, along with outcome. The total score can range from 0 to 9, while a higher score is awarded with a higher quality level. Generally, studies gaining a score ≥ 6 was deemed methodologically sound, or of high quality.

2.5. Statistical analysis

Meta-analysis was conducted using STATA version 14.0 software (StataCorp LP, College Station, TX, USA). Mean differences (MDs) and standard deviations (SDs) were calculated

for continuous data, while for dichotomous data, pooled odds ratios (ORs) with their 95% confidence intervals (CIs) were used. We applied Q-based chi-square test and the I^2 statistics to test heterogeneity among the included studies. Subsequently, a random- or fixed-effects model was performed as appropriate according to the presence or absence of heterogeneity. If heterogeneity was present, random-effects model was adopted, otherwise, fixed-effects model was utilized. A P -value below .05 was designated to be significant. Forest plots of combined Hazard ratios (HRs) with 95% CIs were accomplished to describe heterogeneity explained by study level parameters.

3. Results

3.1. Study selection

A flow chart for the included and excluded studies was depicted in Figure 1. In total, 248 studies were initially yielded through the database search, and 13 studies were identified additionally through a further evaluation of the reference lists of relevant articles. After duplicates removed, 35 records remained. Among them, 10 studies were identified fulfilling the eligibility criteria. And then, 2 were once again excluded from our research: one was not the interest of ours, which was focused on bursting pressure of the gallbladder,^[8] while the other lack of the required data about the outcome measures for our research.^[7] Ultimately there were 8 studies included in this meta-analysis.^[13,14,17,18,20,21,22,24]

3.2. Study characteristics

Of the 8 included studies, four were conducted in Egypt,^[13,17,18,20] three in Italy,^[14,21,22] and one in India.^[24] They were all published between 2008 and 2014. This meta-

analysis comprised a total of 1131 patients from the selected cohort, of which 529 underwent LC with US and 602 with clips. Herein, 1 study^[20] chose the 2-trocar technique in the US group in contrast to the 3 trocar ports in the clips group, another one did not specify the technique,^[14] whereas the remaining studies designated the conventional 4 trocar ports. Noticeably, in one study,^[18] LC was accomplished basically for cirrhotic patients. In general, all of the selected studies encompassed the qualified comparisons with US and clips in order to achieve closure of the cystic duct upon LC.

3.3. Risk of bias

As shown in Table 1, 6 RCTs^[13,17,18,20,22,24] and 2 non-RCTs^[14,21] were finally covered in our research. All of the 6 RCTs were believed to be rated as low risk of bias in the light of Figure 11, by exploring the Cochrane Collaboration tool. On the other hand, as stated above, the Newcastle–Ottawa Scale (NOS) was applied for the evaluation of the quality for the other 2 non-RCTs,^[14,21] which was summarized in Table 3. Accordingly, both trials received a score of 9^[14] and 8,^[21] respectively, suggestive of high methodological quality.

3.4. Meta-analysis results

Characteristics of the included studies were listed in Table 1. According to our meta-analysis, a total of 529 cases was contained in the US group, in comparison with 602 in the clips group, which showed a significant difference (Fig. 2) ($P = .025$) without substantial statistical heterogeneity ($I^2 = 0.0\%$), indicating these findings to be reliable. Further comparison also revealed no statistical significance in terms of age (Fig. 3) ($I^2 = 0.0\%$,

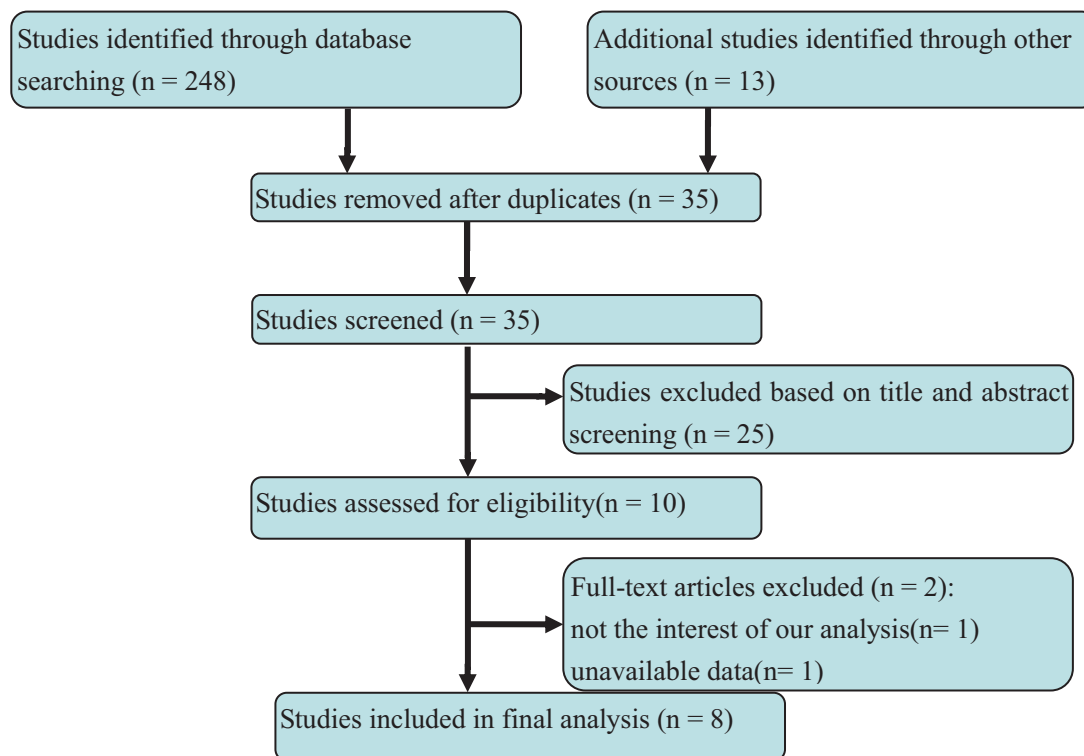


Figure 1. Flow chart depicting the study selection process in the meta-analysis.

Table 1
Demographic characteristics of the studies included in the meta-analysis.

author	year	group	trocator ports	number of cases	age (years)	sex: male (female)	study type
Bessa et al ^[17]	2008	US	4	60	22–68 (41.5 ± 10.3)	13 (47)	prospective RCT
		clips	4	60	19–74 (42.5 ± 11.4)	12 (48)	
El et al ^[18]	2010	US	4	60	24–65 (41.42 ± 10.36)	42 (18)	prospective RCT
		clips	4	60	20–74 (39.93 ± 13.82)	35 (25)	
Kandil et al ^[13]	2010	US	4	70	18–66 (40.97 ± 11.56)	29 (41)	prospective RCT
		clips	4	70	18–66 (41.38 ± 11.91)	30 (40)	
Gelmini et al ^[14]	2010	US	NA	95	52.05 ± 18.13	37 (58)	retrospective Non-RCT
		clips	NA	90	51.08 ± 16.41	37 (53)	
Redwan ^[20]	2010	US	2	80	NA	27 (53)	prospective RCT
		clips	3	80	NA	33 (47)	
Jain ^[24]	2011	US	4	100	22–83 (39.55 ± 11.12)	6 (90)	prospective RCT
		clips	4	100	18–65 (38.67 ± 11.87)	11 (85)	
Catena ^[22]	2014	US	4	21	71.2 ± 7.1	11 (10)	prospective RCT
		clips	4	21	71.6 ± 6.2	10 (11)	
Zanghi et al ^[21]	2014	US	4	43	18–80 (50.9)	68 (96)	retrospective Non-RCT
		clips	4	121			

US = ultrasonic scalpel.

$P = .957$), as well as sex (Fig. 4) ($I^2 = 0.0\%$, $P = .578$) between both groups, which declared their comparability, without nonuniformity.

Main outcomes of the included studies were illustrated in Table 2. In view of our meta-analysis, the operative time in the US group was shorter than that in the clips group (Fig. 5) ($I^2 = 95.0\%$, $P = .000$), with a statistical significance. Similarly, the length of hospital stay was significantly more reduced in the US group (Fig. 6) ($I^2 = 72.8\%$, $P = .005$). On the contrary, conversion to open cholecystectomy occurred in 9 cases in the US group, exhibiting no statistical significance (Fig. 7) ($I^2 = 48.6\%$, $P = .084$), compared to 20 in the clips group. Meanwhile, further comparison with respect to perforation (Fig. 8) ($I^2 = 12.0\%$, $P = .338$), along with overall morbidity (Fig. 10) ($I^2 = 19.1\%$, $P = .289$), demonstrated non-significant results between both groups. Importantly, although 3 cases of bile leakage occurred in the US group in contrast to 6 in the clips group, comparative analysis did not reach a statistical significance (Fig. 9) ($I^2 = 0.0\%$, $P = .594$).

3.5. Sensitivity analyses

Sensitivity analyses were conducted to examine the robustness of this research. By withdrawing each study in turn, the main pooled results were recalculated repeatedly, and invariably exhibited no outstanding changes, in favor of good robustness of the findings (Fig. 12A). Similarly, omitting the 2 non-RCTs^[14,21] exerted little influence on the combined outcomes of the remaining RCT studies, indicating stability of our results (Fig. 12B).

3.6. Publication bias

The funnel plots were not suitable to delineate the publication bias in our research, as the number of the final selected studies was actually less than 10.

4. Discussion

A great deal of studies has confirmed the efficacy and feasibility of US since its introduction in LC, and at the same time some reports

Table 2
Main outcomes of the studies included in the meta-analysis.

author	group	operative time (min)	hospital stay	conversion: n	gallbladder perforation: n	bile leakage: n	overall morbidity: n
Bessa et al ^[17]	US	18–75 (32)	NA	0	6	0	3
	clips	21–85 (40)	NA	0	20	0	4
El et al ^[18]	US	30–70 (45.17 ± 10.54)	18–36 (21.87 ± 4.34) h	2	6	1	5
	clips	30–90 (69.71 ± 13.01)	18–96 (34.54 ± 16.99) h	3	11	2	9
Kandil et al ^[13]	US	33.21 ± 9.62	23.44 ± 2.29h	0	5	0	3
	clips	51.7 ± 13.79	26.95 ± 8.94h	2	13	2	11
Gelmini et al ^[14]	US	20–140 (60)	2 (1–16) d	1	NA	0	2
	clips	45–130 (80)	2 (1–12) d	0	NA	0	2
Redwan ^[20]	US	9–30 (16.8 ± 6.8)	1 (1.00 ± 0.00) d	0	8	1	NA
	clips	35–55 (44.01 ± 6.47)	1–2 (1.53 ± 0.51) d	0	11	0	NA
Jain et al ^[24]	US	31–72 (50.00 ± 9.35)	1–3 (1.89 ± 0.56) d	4	9	0	NA
	clips	42–102 (64.70 ± 13.74)	2–7 (2.52 ± 0.75) d	4	18	0	NA
Catena et al ^[22]	US	101.3 ± 10.1	5.2 ± 0.9 d	1	NA	1	5
	clips	106.4 ± 11.3	5.4 ± 1.1 d	7	NA	0	4
Zanghi et al ^[21]	US	35.36 ± 10.15	48.15 ± 4.29 h	1	3	1	5
	clips	55.6 ± 12.10	49.06 ± 2.94 h	4	25	2	16

US = ultrasonic scalpel.

Table 3
The NOS for evaluating the quality of the 2 nonrandomized studies.

Non-RCT studies	Selection			Comparability		Assessment of Outcome				
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure to cohorts	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design- main factor	Comparability of cohorts on the basis of the design- secondary factor	Assessment of outcome with independence	Adequacy of Follow up length (to assess outcome)	Adequacy of follow up of cohorts	Total Quality score
Gelmini et al ^[14]	*	*	*	*	*	*	*	*	*	9
Zanghiat al ^[21]	*	*	*	*	*	*	*	*	*	8

Non-RCT = non-randomized controlled trials, NOS = Newcastle-Ottawa Scale.

have already conducted a comparative investigation on US over ME, but most of them were basically concentrated on sealing of the cystic artery and tissue division, demanding the help of conventional clips to ligate the cystic duct. Needless to say, clips have been coupled with thermal devices from the start on, preponderantly being laparoscopic scissors and ME.

The US is well known as an advanced, minimally invasive surgical instrument for tissue cutting and coagulation. As an alternative to traditional diathermy, US can securely seal the vessels with a diameter of up to 5 mm without vessel clipping,^[4] and usually enables better management of hemorrhage during dissection upon LC than clips combined with laparoscopic scissors and ME, thus making postoperative bleeding controllable,^[4] although bleeding was not referred to in our analysis.

US fulfils synchronous functions of cutting, coagulation, and cavitation while tissue dissecting by transforming the electric energy into a high-frequency (55,500Hz) vibration,^[10] which is most often referred to as 3 main "C" effects. The very high-frequency vibration, specific to US, is intended to produce heat which is localized and ranged from 60 to 100 °C, but this heat is far lower than that generated during electrosurgery (150 °C) or laser surgery (200 °C).^[8] Thence, US affords minimal collateral energy into the adjacent tissue^[11] as well as the resultant diminished thermal damage,^[10] thus facilitating tissue separation, in contrast to clips in traditional LC. Of note, the collateral damage from ME, mostly being the small intestine and common bile duct,^[11,12] which still remains problematic clinically, could turn seldom encountered with the assistance of US.^[15]

The major advantage of US over clips has been documented to be shortening of the operative time,^[11] which was consistent with our results (Fig. 5) ($I^2=95.0\%$, $P=.000$). Apart from the aforementioned intrinsic virtues, it might be also on account of some other important factors. To begin with, US is capable of implementing the procedure with a sole instrument, avoiding the frequent exchange of a number of tools during conventional LC, which then brings about a substantial time saving.^[3,4,16] Furthermore, it produces mist, instead of smoke formed by ME, which not only affects the operative vision and prolongs the surgery course,^[3,16,19] but also is poisonous to the patient, together with the surgeons and the environment.^[23]

Likewise, a variety of influential elements, like minimal invasiveness of US over a combination of clips as well as scissors and ME, the outstanding potential to improve the quality of surgery, a shorter operative time, in addition to its intrinsic excellent function of dissection and coagulation, could altogether make contribution to another impressive result of our analysis, which was just the significant reduction in length of hospital stay taking advantage of US (Fig. 6) ($I^2=72.8\%$, $P=.005$).

According to literature, the utility of US in closure of the cystic duct was associated with a reduced risk of conversion to open procedure and overall complications.^[11] Nevertheless, it was not the case in our study. Although there were exactly less cases of conversion utilizing US versus clips (9 vs 20), the comparison did not differ to a significant extent (Fig. 7) ($I^2=48.6\%$, $P=.084$). As for gallbladder perforation (Fig. 8) ($I^2=12.0\%$, $P=.338$) and overall morbidity (Fig. 10) ($I^2=19.1\%$, $P=.289$), no significant differences were observed once again, which was inconsistent with other reports in the literature.

Multiple reasons should be taken into consideration. Above all, we should acknowledge that US is not absolutely insulated, it can still pose the additional thermal injuries,^[25] regardless of its superiority over clips affiliated with scissors and ME. Secondly, some of the studies were based on patients with acute

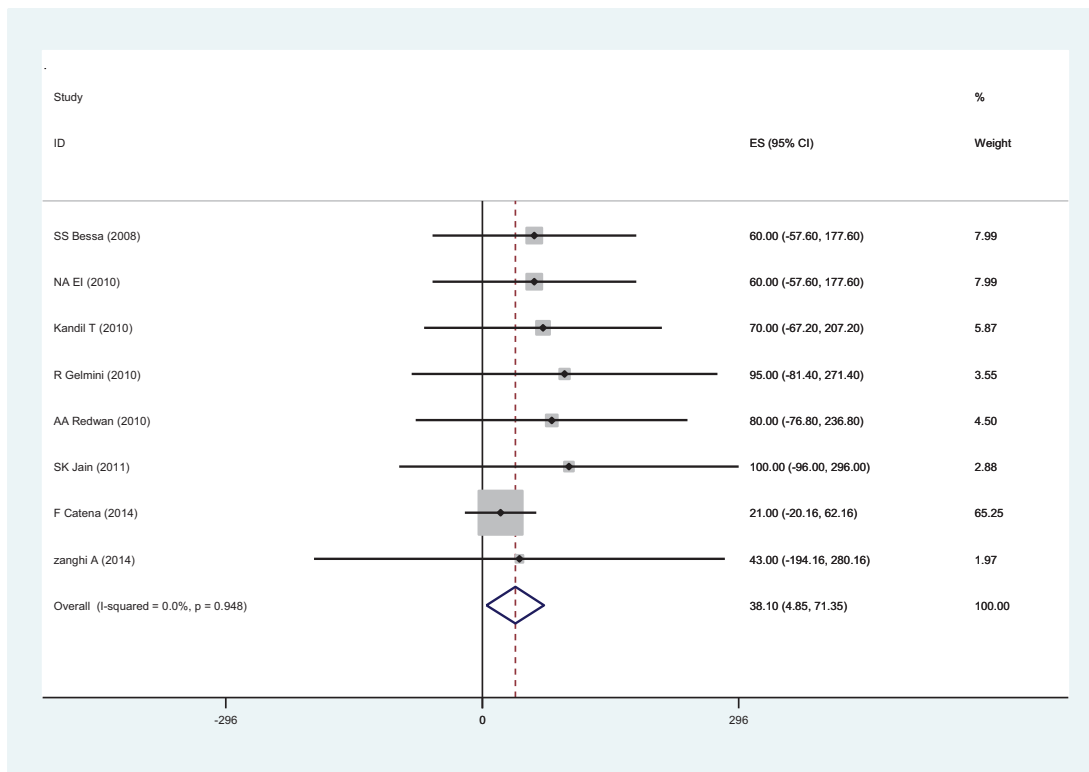


Figure 2. Forest plot of comparison of US versus clips in the included studies with respect of number of cases. US=ultrasonic scalpel.

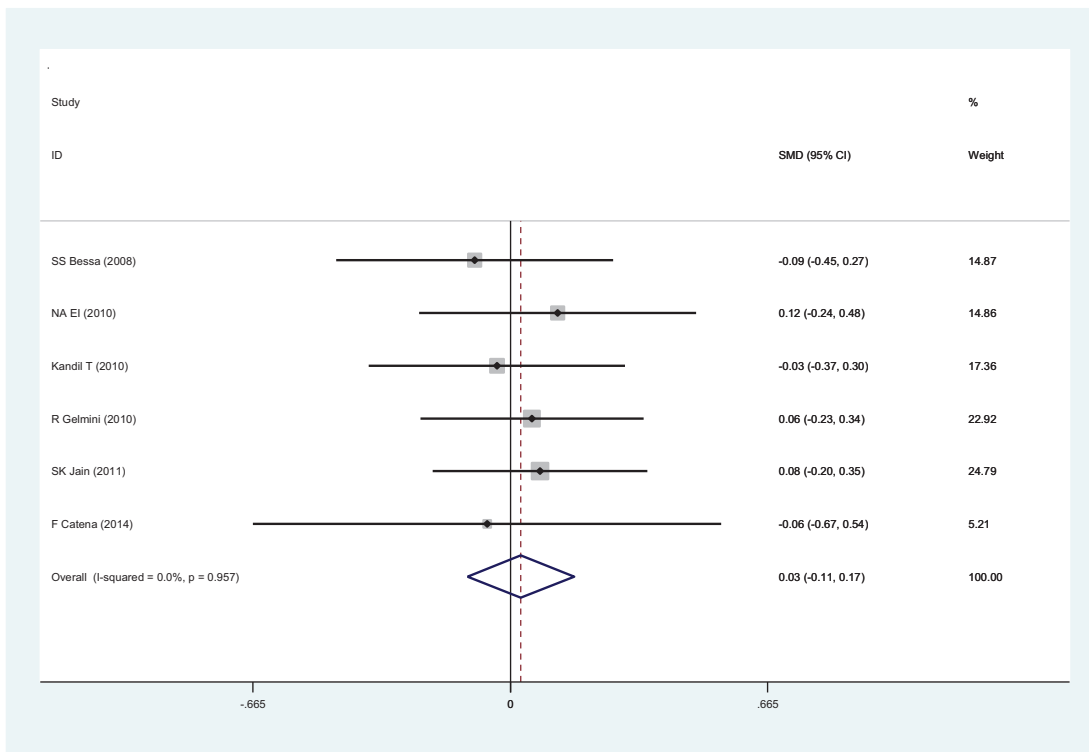


Figure 3. Forest plot of comparison of US versus clips as for age. US=ultrasonic scalpel.

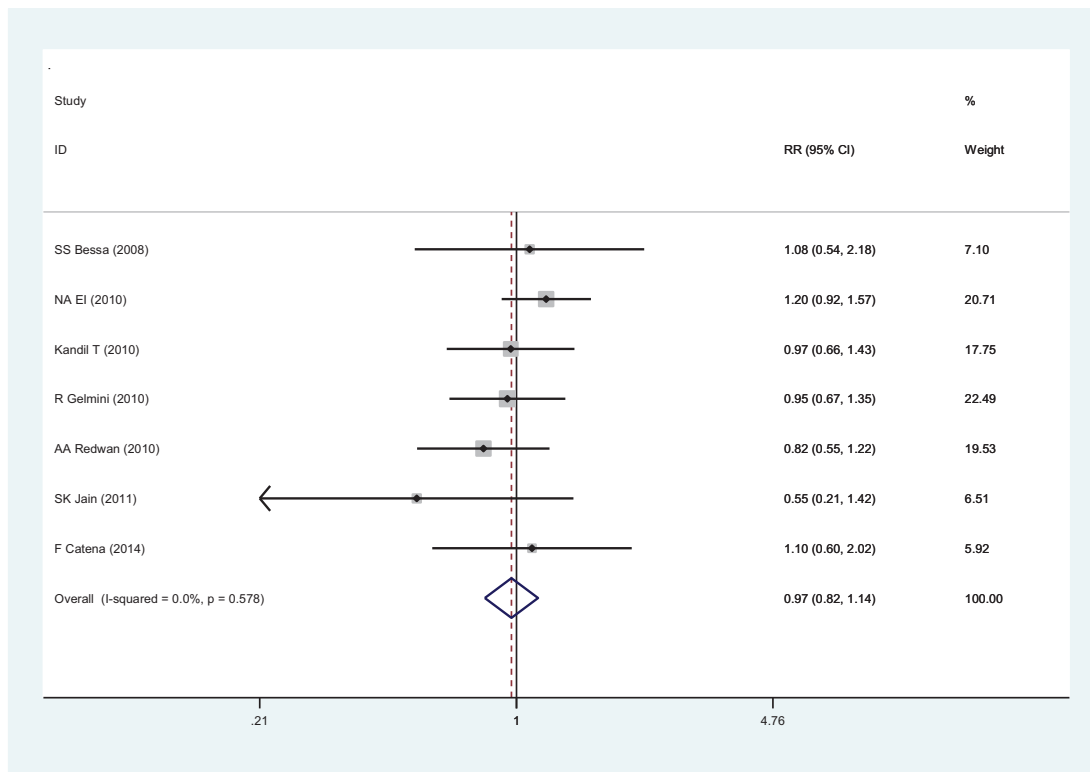


Figure 4. Forest plot of comparison of US versus clips with regard to sex. US=ultrasonic scalpel.

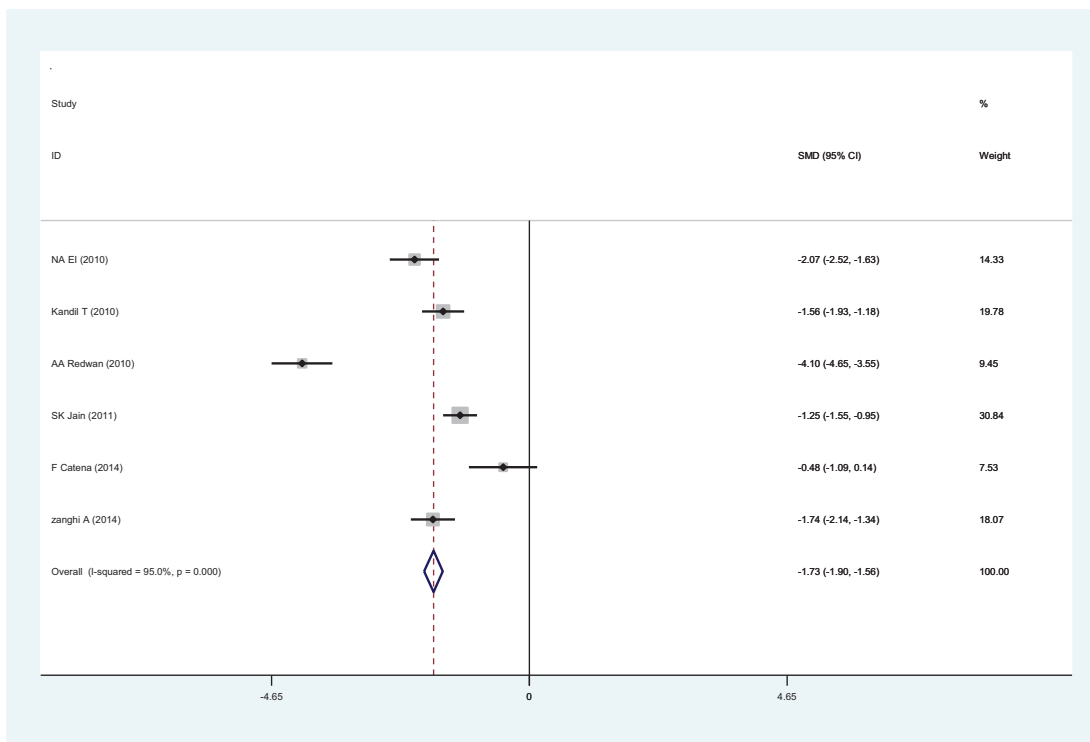


Figure 5. Forest plot of comparison of US versus clips in terms of operative time. US=ultrasonic scalpel.

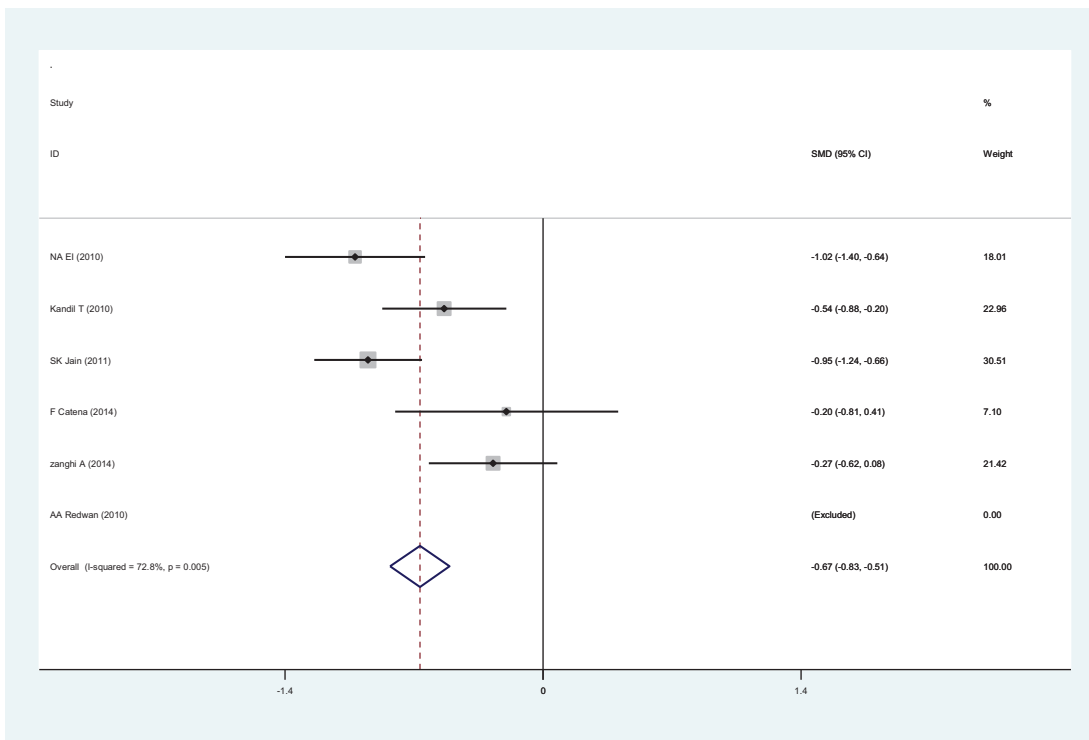


Figure 6. Forest plot of comparison of US versus clips regarding length of hospital stay. US=ultrasonic scalpel.

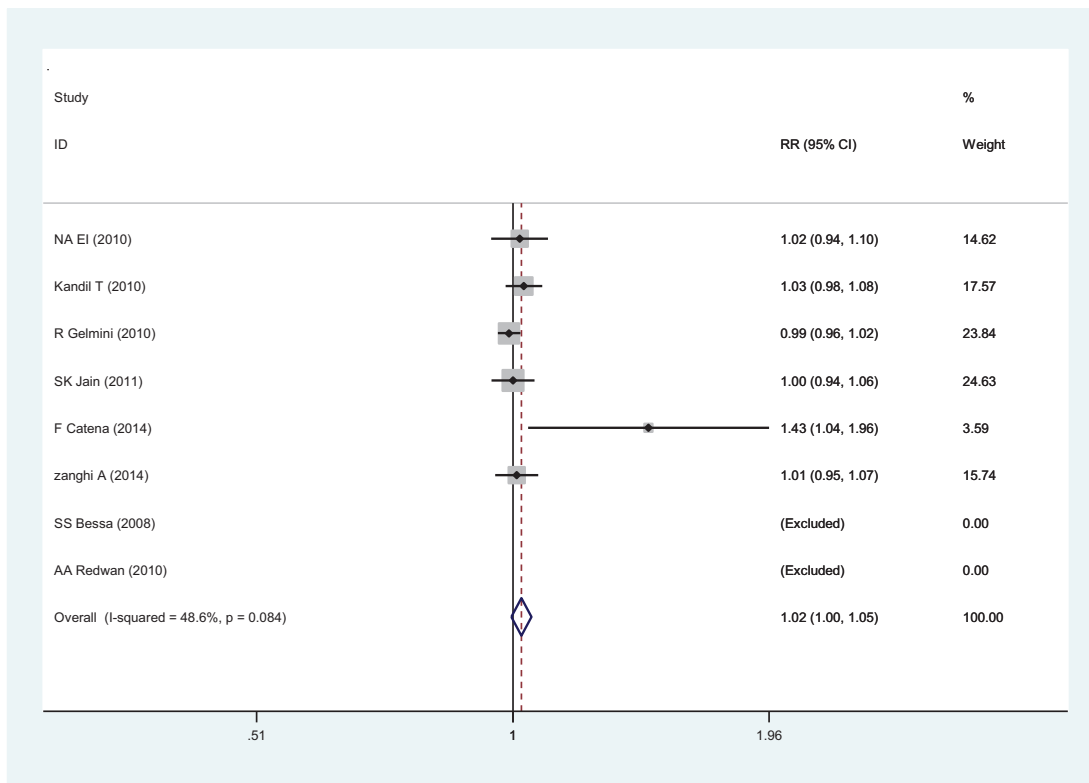


Figure 7. Forest plot of comparison of US versus clips with respect of conversion. US=ultrasonic scalpel.

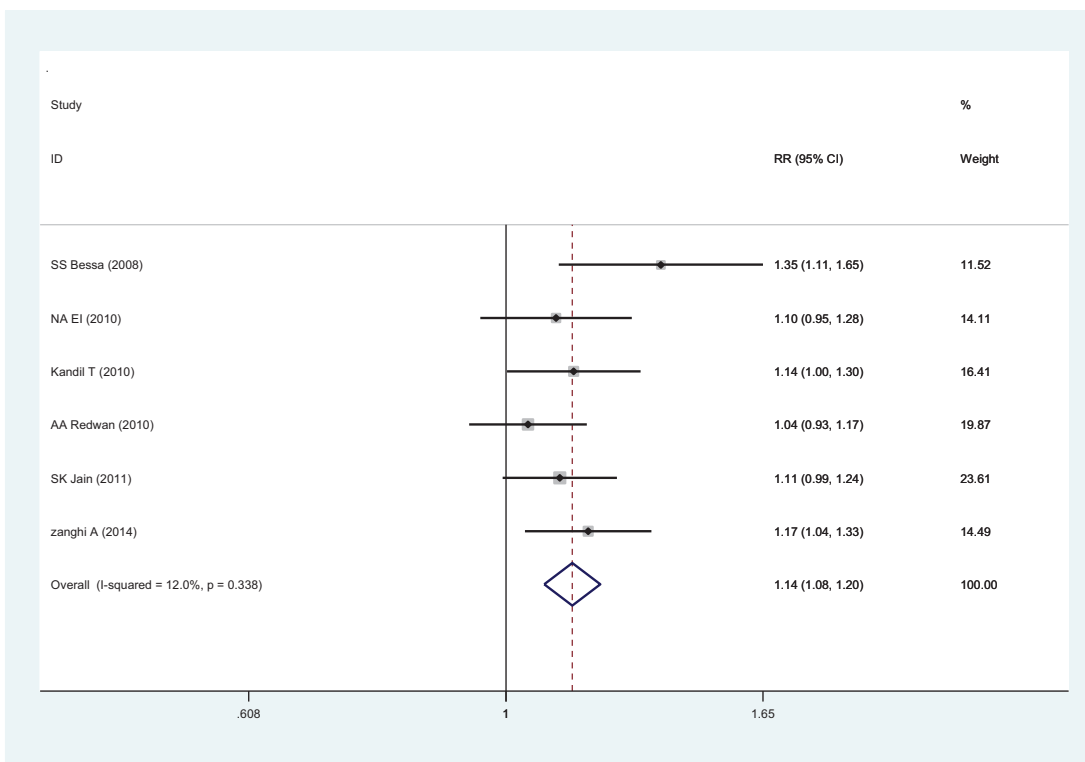


Figure 8. Forest plot of comparison of US versus clips as for perforation. US=ultrasonic scalpel.

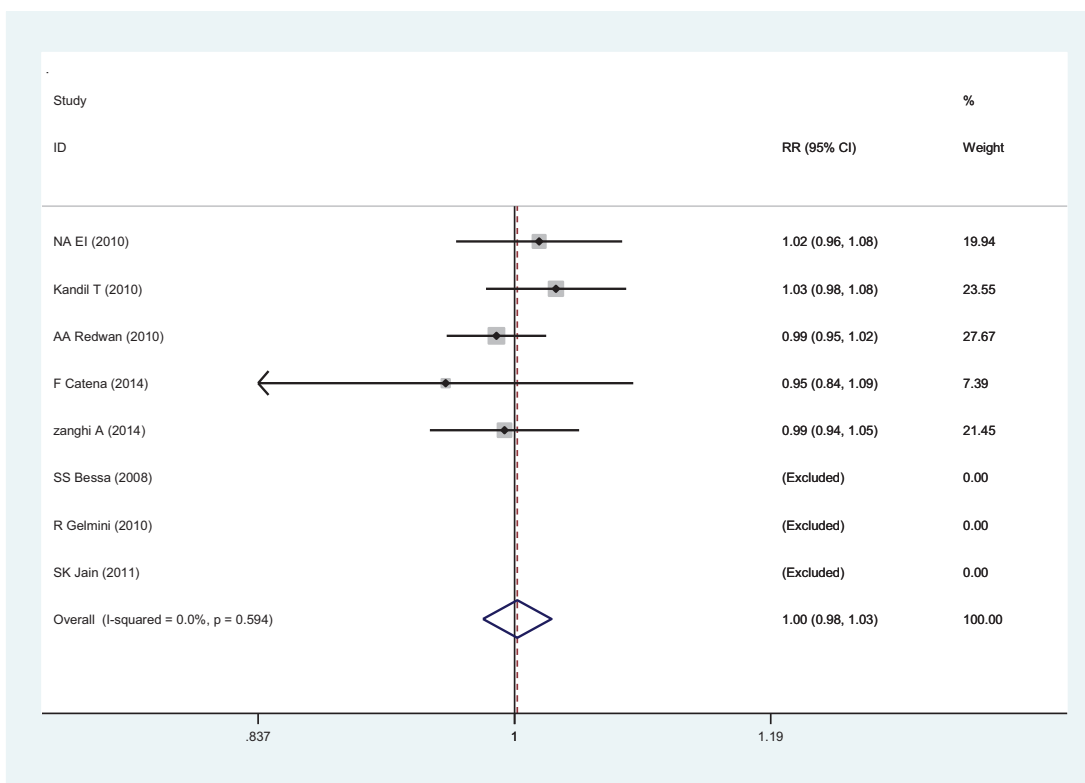


Figure 9. Forest plot of comparison of US versus clips in terms of postoperative bile leakage. US=ultrasonic scalpel.

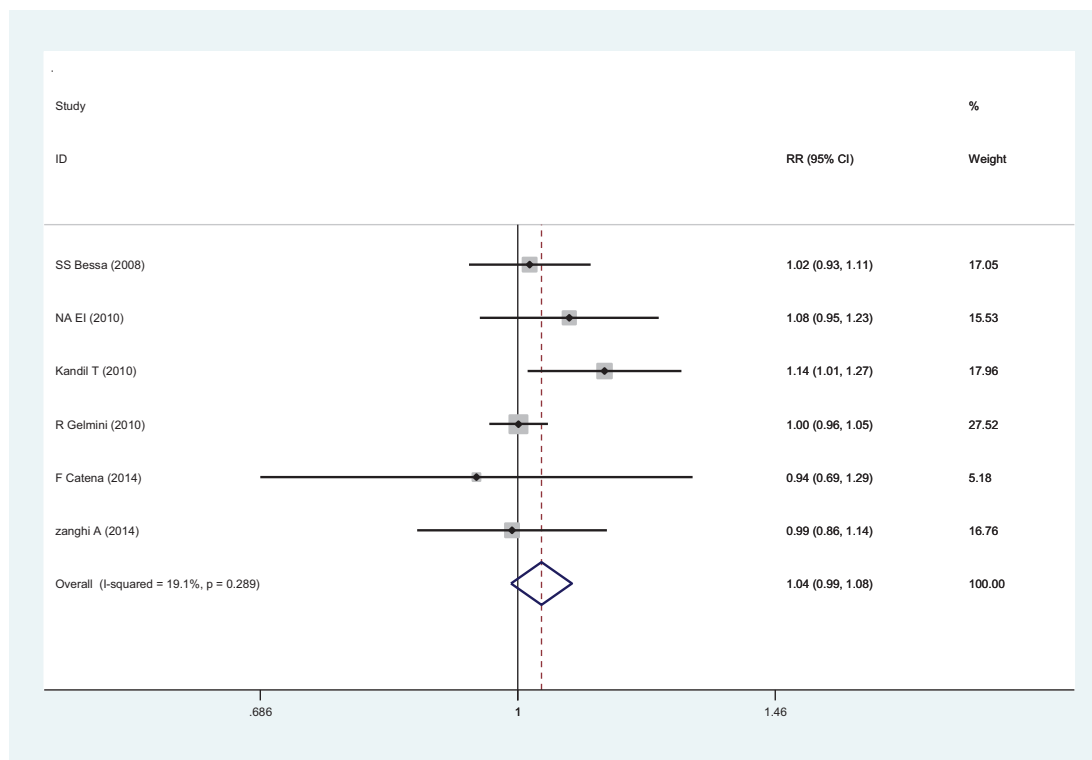


Figure 10. Forest plot of comparison of US versus clips as regards overall morbidity. US=ultrasonic scalpel.

inflammation, even severe individually, which could be susceptible to complications. Additionally, complex comorbidities,^[1,25] such as cirrhosis, diabetes mellitus, extreme obesity, heart diseases, pulmonary infection and so on, could also affect outcomes adversely. Last but not least, the surgical technique was not investigated as an independent factor in our analysis. Certain surgeons were willing to adopt the 2- or 3- trocar ports to accomplish LC in their studies, who themselves could add up to the surgical difficulty and impose increased risks, apart from the variations in their surgical approaches and experiences.

Among the postoperative complications, bile leakage is always the most severe concern, most commonly originated from the cystic duct stump.^[19] Conventionally, the chief cause may be ascribed to the use of clips,^[1] alongside with the unrecognized thermal injury from ME. In our article, definitely 3 cases of leakage took place in the US group in contrast to 6 in the clips group, which however, did not reach a statistical significance (Fig. 9) ($I^2=0.0\%$ $P=.594$). This very achievement proved that US is capable of attaining complete hemo-biliary stasis as a single working device.^[6,7]

When US is applied to the cystic duct, it causes collagen shrinkage and degeneration in the wall and sealing of the lumen, as well as coagulative necrosis, the same mechanisms as coagulation of vessels,^[26] irrespective of the main anatomic and structural difference between the vessels and cystic duct. Valid occlusion of the cystic duct by US alone and the distinctive feature of collagen degeneration have already been testified histologically.^[6] An additional benefit of US is the more effective closure of the ducts of Luschka^[27] during division of the liver bed, which is extremely troublesome in clinical practice and predisposed to postoperative bile leakage.

As regards manometric research, the airtight bursting pressure of the cystic duct sealed by US was estimated to amount to

"higher than 320 mm Hg",^[6] which was much more elevated than either the basal or maximal pressure of the sphincter of Oddi.^[9,26] It is another nonnegligible proof contributing to resistance of leakage.

On the basis of our results, operative time and length of hospital stay were obviously more decreased with US than that with clips, whereas no statistical significance was shown between both groups in terms of conversion, perforation, along with postoperative bile leakage and overall morbidity. It could be interpreted that US is superior to clips coupled with scissors and ME in some aspects, or at least is comparable to them. It is equally safe and effective for US to occlude the cystic duct in LC, thus is capable of replacing the conventional clips.

It is noteworthy to mention that US is exclusively suitable for occluding biliary ducts and vessels whose diameter is within 5 mm.^[13,14] It is preferably recommended for benign gallbladder diseases, not involved in a severely acute inflammatory condition. If the cystic duct is ≥ 6 mm in diameter, an additional ligature is designated,^[14] owing to its inherent limitations. However, the total US for sealing the cystic duct during LC is frequently described in the European literature, but is only anecdotal in other countries.

On the other hand, certain underlying limitations were attached to our research. First of all, the number of the included studies together with the involved case volume was relatively small, which was susceptible to potential bias. Thence, more similar, multicenter randomized trials with larger cohort population are still in need. Next to it, a major shortcoming in these studies was that data for outcome measures in some of the original articles were unavailable, which might probably discount the results. Another issue is that some additional parameters, such as comorbidities, hemorrhage, in conjunction with bile duct and other organ injuries, and mortality, should also

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AA Redwan 2010	?	?	+	+	+	+	?
F Catena 2014	+	+	+	+	+	+	+
Kandil T 2010	+	+	+	?	+	+	+
NA El 2010	+	+	+	+	+	+	?
SK Jain 2011	+	+	?	+	+	+	?
SS Bessa 2008	+	+	+	?	+	+	+

Figure 11. Quality assessment of the eligible randomized controlled trials based on the Cochrane risk of bias tool.

be investigated as independent factors, as an overall evaluation of US versus clips. Moreover, there were 2 other non-RCTs besides the 6 RCTs involved in our analysis, which potentially played an indelible impact on interpretation of the outcome. Finally, the role of US might be underestimated because literature in other languages was ruled out in our research.

5. Conclusion

This study demonstrated that to take advantage of US could bring about more reduced operative time as well as hospital stay during LC, compared with conventional clips. Meanwhile, US was as well comparable to clips with respect to conversion, perforation, along with bile leakage and overall morbidity.

Therefore, our meta-analysis led us to draw a conclusion that US is in fact superior to clips coupled with laparoscopic scissors and ME in some aspects, or is at least as safe and effective as them, in terms of closure of the cystic duct and artery. It is worthy of the acceptance as an alternative to the standard clipping. Whereas, more randomized trials with larger cohort population are still required. The implication of our research may lie in that the complete LC could be performed with US in future, leaving no metal objects in the body and minimizing the risk of damage of the adjacent structures.

Author contributions

Xiao-Ming Ai, Li-Chen Ho, and Nian-Yin Yang have contributed equally to this article. Xiao-Ming Ai and Li-Chen Ho were devoted to the conception and design of the study. Lu-Lu Han and Jin-Jing Lu carried out the electronic searches. Li-Chen Ho and Xiong Yue performed the statistic analysis. Xiao-Ming Ai and Nian-Yin Yang wrote the main manuscript. Nian-Yin Yang revised the manuscript for important intellectual content. All authors read the manuscript and gave their final approval for publication.

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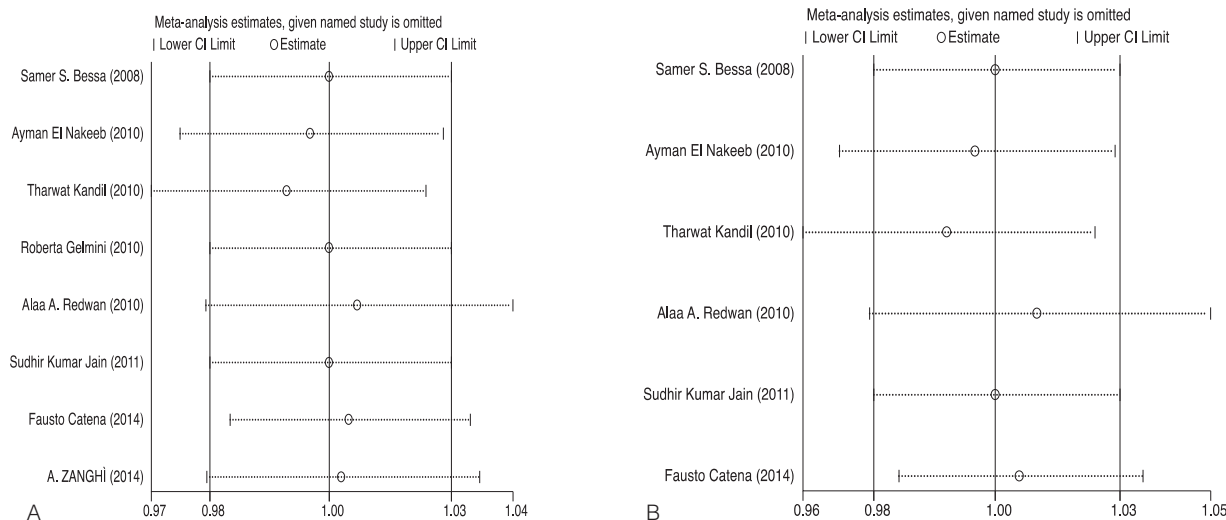


Figure 12. Sensitivity analysis (A) by removing each study sequentially, (B) by omitting the 2 non-RCTs. non-RCT=non-randomized controlled trials.

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