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META-ANALYSIS

Laparoscopic *VS* open hepatectomy for hepatolithiasis: An updated systematic review and meta-analysis

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Author contributions: Yang Y and Wang GS takes responsibility for the integrity of the data and the accuracy of the data analysis. Li H, Yang Y and Wang GS designed the study, drafted the manuscript and provided administrative support and supervision; Zheng J, Cai JY and Li SH acquired the data; Li H, Zheng J and Cai JY analyzed and interpreted the data; Wang XM, Chen GH, Yang Y and Wang GS corrected the manuscript for controversial content; Zhang JB performed statistical analysis. Li H, Zheng J and Cai JY contributed equally to this work.

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Abstract

AIM
To perform a meta-analysis on laparoscopic hepatectomy *VS* conventional liver resection for treating hepatolithiasis.

METHODS
We conducted a systematic literature search on PubMed, Embase, Web of Science and Cochrane Library, and undertook a meta-analysis to compare

the efficacy and safety of laparoscopic hepatectomy *VS* conventional open liver resection for local hepatolithiasis in the left or right lobe. Intraoperative and postoperative outcomes (time, estimated blood loss, blood transfusion rate, postoperative intestinal function recovery time, length of hospital stay, postoperative complication rate, initial residual stone, final residual stone and stone recurrence) were analyzed systematically.

RESULTS

A comprehensive literature search retrieved 16 publications with a total of 1329 cases. Meta-analysis of these studies showed that the laparoscopic approach for hepatolithiasis was associated with significantly less intraoperative estimated blood loss [weighted mean difference (WMD): 61.56, 95% confidence interval (CI): 14.91-108.20, P = 0.01], lower blood transfusion rate [odds ratio (OR): 0.41, 95%CI: 0.22-0.79, P = 0.008], shorter intestinal function recovery time (WMD: 0.98, 95%CI: 0.47-1.48, P = 0.01), lower total postoperative complication rate (OR: 0.52, 95%CI: 0.39-0.70, P < 0.0001) and shorter stay in hospital (WMD: 3.32, 95%CI: 2.32-4.32, P < 0.00001). In addition, our results showed no significant differences between the two groups in operative time (WMD: 21.49, 95%CI: 0.27-43.24, P = 0.05), residual stones (OR: 0.79, 95%CI: 0.50-1.25, P = 0.31) and stone recurrence (OR: 0.34, 95%CI: 0.11-1.08, P = 0.07). Furthermore, with subgroups analysis, our results proved that the laparoscopic approach for hepatolithiasis in the left lateral lobe and left side could achieve satisfactory therapeutic effects.

CONCLUSION

The laparoscopic approach is safe and effective, with less intraoperative estimated blood loss, fewer postoperative complications, reduced length of hospital stay and shorter intestinal function recovery time than with conventional approaches.

Key words: Hepatolithiasis; Laparoscopic hepatectomy; Conventional liver resection; Systematic review; Meta-analysis

Core tip: Application of the laparoscopic approach in symptomatic hepatolithiasis has gradually attracted more attention. However, its advantages over the open approach are still unclear. We analyzed 16 articles, comprising 1329 patients, to compare the two techniques for treating hepatolithiasis. We concluded that the laparoscopic approach is safe, effective and feasible for liver resection, with less intraoperative estimated blood loss, fewer postoperative complications, reduced length of hospital stay and shorter intestinal function recovery time than with conventional approaches.

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INTRODUCTION

Hepatolithiasis is a gallstone disorder that involves the intrahepatic biliary duct (IHD), which may occur alone or accompanying extrahepatic gallstones. IHD stones may occur in any segments of the liver, and are particularly prevalent in the left lateral segment[1]. A recent report has shown that only 0.6%-1.3% of patients have intrahepatic stones in western countries, being more prevalent in eastern countries, especially Southeast Asia[2]. Hepatolithiasis over a long period of time may cause secondary cholangitis-originated cirrhosis and even cholangiocarcinoma[1,3], which can seriously affect the health and quality of life of patients.

There are many approaches to treat this disease, including percutaneous transhepatic cholangioscopic lithotripsy, IHD exploration and hepatectomy[4-7]. Among these treatment methods, hepatectomy is considered the most radical option for hepatolithiasis. In the past, open hepatectomy was preferred, with bile duct exploration and stone removal[8,9]. In recent years, with the development of laparoscopic technology and refinement of laparoscopic instruments, laparoscopic hepatectomy is now identified as a safe and flexible technique for hepatolithiasis.

However, few meta-analyses have evaluated the efficacy and safety of the laparoscopic approaches and open surgery that are routinely used in hepatolithiasis. It is unclear whether laparoscopic hepatectomy can be performed as effectively and safely as conventional hepatectomy or is superior to it in treating hepatolithiasis in the left or right hepatic lobes. Here, we performed a meta-analysis to assess the safety and efficacy of laparoscopic hepatectomy for treating intrahepatic bile duct stones. Furthermore, we evaluated left lateral sectionectomy and left hemihepatectomy by performing subgroups analysis.

MATERIALS AND METHODS

Search strategy and criteria

This meta-analysis was performed to compare laparoscopic hepatectomy and conventional open hepatectomy for hepatolithiasis. In January 2017, PubMed, Embase, Web of Science and Cochrane Library were searched for studies comparing laparoscopic hepatectomy with open liver resection for hepatolithiasis. There were no restrictions on publication date, type or language. Search terms were confined to Title/Abstract: "hepatolithiasis" OR "intrahepatic stone" AND "laparoscopic" OR "laparoendoscopic". The reference lists of all selected articles were manually searched to determine if they should be included. Two reviewers browsed the titles and abstracts independently. Articles were included if they: (1) compared the outcomes of laparoscopic and open approaches for hepatolithiasis; and (2) reported at least some of the outcomes that we were interested in. Articles were excluded if they were submitted by the same authors or they reported duplicate data, to avoid duplication of patient populations. Editorials, case reports, conference abstracts and animal studies were excluded.

Data management

Data from the included studies were summarized by two of the authors independently. They were blinded to journals of publication, authors and study institutions of all available articles. Any disagreements between the reviewers were settled by the senior author. Perioperative outcomes were compared, including operative time, estimated blood loss (EBL), intraoperative transfusion, length of hospital stay (LOS), time to oral intake and postoperative complications. Outcomes regarding residual rate of intrahepatic stones containing initial residual, final residual and stone recurrence were also analyzed.

Quality assessment and statistical analysis

The level of evidence of these articles was estimated using the UK Cochrane Centre of Evidence (2009)[10]. The methodological quality of randomized controlled trials (RCTs) was assessed by the Cochrane Risk of Bias Tool[11]. The modified Newcastle-Ottawa scale was used to assess the quality of retrospective studies, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome[12-14]. The maximum total score on this scale was 9, and studies with scores ≥ 7 were defined as high quality[12].

All data were pooled with the Cochrane Collaboration's Review Manager 5.3 (Cochrane Collaboration, Oxford, United Kingdom). Mean differences and 95% confidence intervals (CIs) were calculated to pool functional outcomes. Statistical heterogeneity among studies was assessed using the χ^2 test with significance set at $P < 0.1$, and heterogeneity was quantified using the I^2 statistic. A fixed-effects model was used routinely only if there was obvious heterogeneity among the included literature[15].

Subgroups and publication bias

Intrahepatic duct stones were located in different liver segments. Patients were subgrouped by type of operation, including left lateral sectionectomy (LLS), left hemihepatectomy (LH) and right hepatectomy (RH). Subgroup analysis was performed to compare outcomes resulting from different excision extension. Funnel plots were used to signify the publication bias. If outcomes were associated with significant heterogeneity, a random-effects model was used to minimize bias.

RESULTS

Characteristics of selected articles

The literature search identified 515 articles, 115 from PubMed, 187 from Embase and 213 from Web of Science; no studies were available in Cochrane Library (Figure 1). Of the 515 identified articles, 203 were duplications, 194 did not focus on hepatolithiasis, 40 were not comparative studies, 35 were case reports, 4 were conference abstracts and 2 were editorials. The full text of the remaining 36 articles was carefully reviewed. Twenty more were excluded, including 2 case reports, 5 that were not comparative studies and 13 that had no data of interest. Finally, 16 articles were included in our meta-analysis[16-31]. The characteristics of the selected articles are shown in Table 1.

Of the 1329 patients included in the 16 articles, 624 were treated with the laparoscopic approach and 705 with the open approach (Table 2). All 16 studies were retrospective except for 1 RCT (level of evidence: 2b)[17]. Among the remaining 15 studies, 3 compared contemporary series of patients (level of evidence: 3a)[20,25,30], 11 were retrospective case-control studies (level of evidence: 3b)[16,19,21-24,26-29,31], and 1 was a retrospective study using historical series as controls (level of evidence: 4)[18] (Table 3).

Duration of operation in the 15 studies[16-21,23-31] was similar between the two groups [weighted mean difference (WMD): 21.49, 95%CI: -0.27 to 43.24, P = 0.05] (Figure 2A). EBL was analyzed among 1221 patients from 13 studies[16-20,23-26,28-31], and less EBL was found in the laparoscopic group (WMD: -61.56, 95% CI: -108.2 to -14.91, P = 0.01) (Figure 2B). Intraoperative transfusion was analyzed in 9 articles[19,21,24-26,28-31], showing lower transfusion rate in the laparoscopic group [odds ratio (OR): 0.41, 95%CI: 0.22-0.79, P = 0.008) (Figure 2C). All 16 articles[16-31] were analyzed for postoperative complications, indicating that the rate was significantly lower in the laparoscopic group (OR: 0.52, 95%CI: 0.39-0.70, P < 0.001) (Figure 2D). Seven articles[16,22-25,27,31] reported time to oral intake, with a significantly shorter time for recovery of bowel movement in the laparoscopic group (WMD: -0.98, 95%CI: -1.48 to -0.47, P < 0.001) (Figure 3A). Fifteen studies[16,17,19-31], including 1294 patients, evaluated LOS, which was significantly shorter in the laparoscopic group (WMD: -3.32, 95% CI: -4.32 to -2.32, P < 0.001) (Figure 3B). No significant difference was found in initial and final

Table 1 Characteristics of included studies

Ref.	Level of evidence	Design	Patient No.		Location of stone	F/U, mo	Matching	Quality score
			LH	OH		LH/OH		
Cai *et al*[16], 2007	3b	Re	29	22	L+R	16.1/16.1	1,2,3,4,5	7
Ding *et al*[17], 2015	2b	RCT	49	49	L	Perioperative	1,2,3,5	RCT
Li, H *et al*[18], 2008	4	Re	14	20	L+R	Perioperative	1,2	5
Jin *et al*[19], 2015	3b	Re	96	105	L	18-90	1,2,3,6,7	5
Kim *et al*[20], 2015	3a	Re	17	17	R	35/35	1,3,4,5	7
Lee *et al*[21], 2014	3b	Re	7	9	L	12.1/11.1	1,2,4,6	6
Li, J *et al*[22], 2014	3b	Re	35	40	L+R	41/41	1,2,3	6
Li, Y *et al*[23], 2015	3b	Re	23	22	L+R	15-51	1,2,3,6	5
Namgoong *et al*[24], 2014	3b	Re	37	112	L	NA	1,2,3,4	7
Peng *et al*[25], 2016	3a	Re	36	39	L	18.9/20	1,2,3,4	7
Shin *et al*[26], 2015	3b	Re	40	54	L	46.8/75.7	1,2,6	5
Song *et al*[27], 2010	3b	Re	7	10	L	Perioperative	1,2,3,4,5	7
Tian *et al*[28], 2013	3b	Re	116	78	L+R	29/29	1,2,4	6
Tu *et al*[29], 2010	3b	Re	28	33	L	17/17	1,2,3,4	7
Ye *et al*[30], 2015	3a	Re	46	51	L	33/33	1,2,3,4	7
Zhou *et al*[31], 2013	3b	Re	44	44	L+R	24/24	1,2,3,4,5,6,7	7

1: Age; 2: Sex; 3: Liver function; 4: Previous upper surgery history; 5: Surgeon experience; 6: Body mass index; 7: American Society of Anesthesiologists score. F/U: Follow-up, mean or median or range, month; L: Left intrahepatic; LH: Laparoscopic hepatectomy; NA: Not available; OH: Open hepatectomy; R: Right intrahepatic; RCT: Randomized controlled trail; Re: Retrospective.

Table 2 Results of meta-analysis in laparoscopic hepatectomy *vs* open hepatectomy

Outcomes of interest	Study, *n*	LH, *n*	OH, *n*	WMD/OR (95%CI)	*P*	Study heterogeneity			*P*
						χ^2	df	I^2, %	
Operative time, min	15	589	665	21.49 (-0.27, 43.24)	0.05	227.54	14	94	< 0.001
Estimated blood loss, mL	13	575	646	-61.56 (-108.2, -14.91)	0.01	124.6	12	90	< 0.001
Intraoperative transfusion	9	450	525	0.41 (0.22, 0.79)	0.008	13.36	8	40	0.10
Length of hospital stay, d	15	609	685	-3.32 (-4.32, -2.32)	< 0.001	75.37	14	81	< 0.001
Postoperative complications	16	624	705	0.52 (0.39, 0.70)	< 0.001	10.10	15	0	0.81
Time to oral intake, d	7	210	289	-0.98 (-1.48, -0.47)	< 0.001	188.28	6	97	< 0.001
Initial residual stone	12	517	604	0.79 (0.50, 1.25)	0.31	3.96	11	0	0.97
Final residual stone	5	136	146	0.34 (0.11, 1.08)	0,07	2.92	4	0	0.57
Stone recurrence	12	530	604	0.63 (0.34, 1.16)	0.14	4.08	11	0	0.97

df: Degrees of freedom; LH: Laparoscopic hepatectomy; OH: Open hepatectomy; WMD/OR: Weight mean difference/odds ratio.

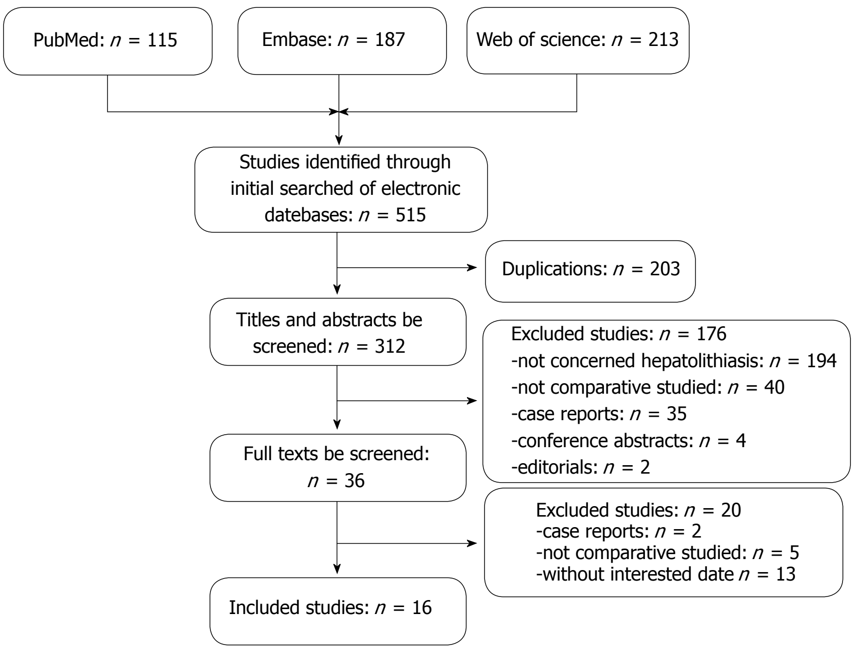


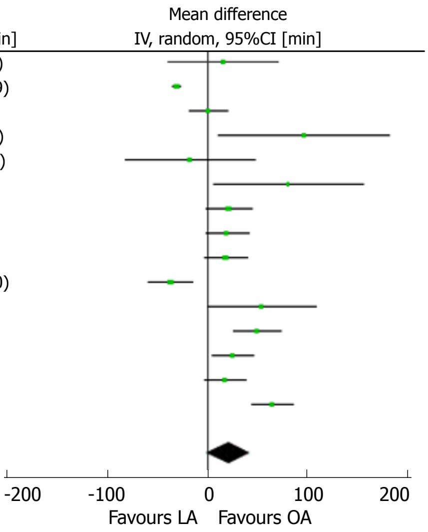
Figure 1 Flow chart showing study retrieval and selection process.

A

Study or subgroup	LA Mean [min]	LA SD [min]	LA Total	OA Mean [min]	OA SD [min]	OA Total	Weight	Mean difference IV, random, 95%CI [min]
Cai 2007	236	135	29	220	61	22	5.4%	16.00 (-39.65, 71.35)
Ding 2015	67.1	8.36	49	97.1	9.82	49	8.2%	-30.00 (-33.61, -26.39)
Jin 2015	207	81	96	206	53	105	7.7%	1.00 (-18.11, 20.11)
Kim 2015	432	158	17	335	85	17	3.6%	97.00 (11.71, 182.29)
Lee 2014	212	66	7	229	66	9	4.7%	-17.00 (-82.19, 48.19)
Li 2008	259	134	14	178	58	20	4.2%	81.00 (6.35, 155.65)
Li 2015	171.3	42.46	23	149.55	35.89	22	7.5%	21.75 (-1.19, 44.69)
Namgoong 2014	257	50.4	37	237	75.5	112	7.6%	20.00 (-1.43, 41.43)
Peng 2016	206.3	52.1	36	187.6	40.6	39	7.6%	18.70 (-2.56, 39.96)
Shin 2015	174.2	56.6	40	210.4	51.6	54	7.6%	-36.20 (-58.50, -13.90)
Song 2009	316.43	64.47	7	262	42.11	10	5.4%	54.43 (0.00, 108.86)
Tian 2013	323.3	103	116	272.8	66.8	78	7.5%	50.50 (26.60, 74.40)
Tu 2010	158	43	28	132	39	33	7.6%	26.00 (5.25, 46.75)
Ye 2015	254	52	46	236	50.75	51	7.7%	18.00 (-2.49, 38.49)
Zhou 2013	277.5	55	44	212.5	43.75	44	7.6%	65.00 (44.23, 85.77)
Total (95%CI)			589			665	100.0%	21.49 (-0.27, 43.24)

Heterogeneity: Tau^2 = 1499.21; Chi^2 = 227.54, df = 14 (P < 0.00001); I^2 = 94%

Test for overall effect: Z = 1.94 (P = 0.05)

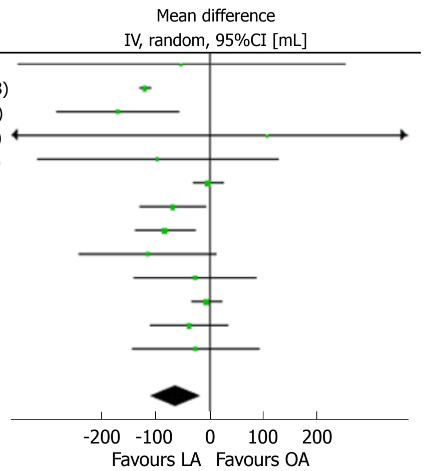


B

Study or subgroup	LA Mean [mL]	LA SD [mL]	LA Total	OA Mean [mL]	OA SD [mL]	OA Total	Weight	Mean difference IV, random, 95%CI [mL]
Cai 2007	603	525	29	655	569	22	2.0%	-52.00 (-357.03, 253.03)
Ding 2015	380	24.7	49	500	22.3	49	12.4%	-120.00 (-129.32, -110.68)
Jin 2015	383	281	96	554	517	105	7.1%	-171.00 (-284.75, -57.25)
Kim 2015	988	929	17	879	942	17	0.5%	109.00 (-519.92, 737.92)
Li 2008	454.5	314.2	14	550.9	348.1	20	3.2%	-96.40 (-320.82, 128.02)
Li 2015	214.57	42.58	23	216.36	50.74	22	11.9%	-1.79 (-29.22, 25.64)
Namgoong 2014	280	96.9	37	347	285.5	112	10.2%	-67.00 (-128.40, -5.60)
Peng 2016	215.8	75.8	36	298.7	158.9	39	10.6%	-82.90 (-138.58, -27.22)
Shin 2015	263.3	166.3	40	378.4	432.9	54	6.5%	-115.10 (-241.54, 11.34)
Tian 2013	479.2	402.1	116	505.8	396.9	78	7.1%	-26.60 (-141.11, 87.91)
Tu 2010	180	56	28	184	50	33	11.9%	-4.00 (-30.86, 22.86)
Ye 2015	332	166.75	46	369	193.75	51	9.6%	-37.00 (-108.76, 34.76)
Zhou 2013	367.5	262.5	44	392.5	300	44	6.9%	-25.00 (-142.79, 92.79)
Total (95%CI)			575			646	100.0%	-61.56 (-108.20, -14.91)

Heterogeneity: Tau^2 = 4557.70; Chi^2 = 124.60, df = 12 (P < 0.00001); I^2 = 90%

Test for overall effect: Z = 2.59 (P = 0.010)

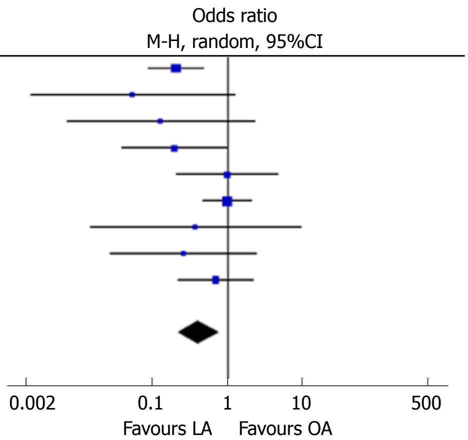


C

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, random, 95%CI
Jin 2015	8	96	32	105	21.0%	0.21 (0.09, 0.48)
Lee 2014	0	7	5	9	3.8%	0.05 (0.00, 1.24)
Namgoong 2014	0	37	10	112	4.4%	0.13 (0.01, 2.28)
Peng 2016	2	36	9	39	10.8%	0.20 (0.04, 0.98)
Shin 2015	3	40	4	54	11.3%	1.01 (0.21, 4.80)
Tian 2013	21	116	14	78	22.6%	1.01 (0.48, 2.13)
Tu 2010	0	28	1	33	3.6%	0.38 (0.01, 9.70)
Ye 2015	1	46	4	51	6.7%	0.26 (0.03, 2.43)
Zhou 2013	6	44	8	44	15.9%	0.71 (0.22, 2.25)
Total (95%CI)		450		525	100.0%	0.41 (0.22, 0.79)
Total events	41		87			

Heterogeneity: Tau^2 = 0.34; Chi^2 = 13.36, df = 8 (P = 0.10); I^2 = 40%

Test for overall effect: Z = 2.67 (P = 0.008)



D

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, fixed, 95%CI
Cai 2007	2	29	4	22	3.4%	0.33 (0.06, 2.01)
Ding 2015	3	49	2	49	1.5%	1.53 (0.24, 9.60)
Jin 2015	16	96	26	105	16.4%	0.61 (0.30, 1.22)
Kim 2015	5	17	11	17	6.2%	0.23 (0.05, 0.96)
Lee 2014	1	7	3	9	1.8%	0.33 (0.03, 4.19)
Li 2008	1	14	4	20	2.4%	0.31 (0.03, 3.10)
Li 2014	1	35	6	40	4.3%	0.17 (0.02, 1.46)
Li 2015	1	23	1	22	0.8%	0.95 (0.06, 16.27)
Namgoong 2014	4	37	20	112	7.0%	0.56 (0.18, 1.75)
Peng 2016	5	36	14	39	9.2%	0.29 (0.09,0.91)
Shin 2015	7	40	22	54	12.3%	0.31 (0.12, 0.82)
Song 2009	2	7	6	10	2.8%	0.27 (0.03, 2.12)
Tian 2013	23	116	17	78	13.0%	0.89 (0.44, 1.80)
Tu 2010	4	28	5	33	3.1%	0.93 (0.22, 3.87)
Ye 2015	6	46	11	51	7.2%	0.55 (0.18, 1.62)
Zhou 2013	10	44	14	44	8.6%	0.63 (0.24, 1.63)
Total (95%CI)		624		705	100.0%	0.52 (0.39, 0.70)
Total events	91		166			

Heterogeneity: Chi^2 = 10.10, df = 15 (P = 0.81); I^2 = 0%

Test for overall effect: Z = 4.30 (P < 0.001)

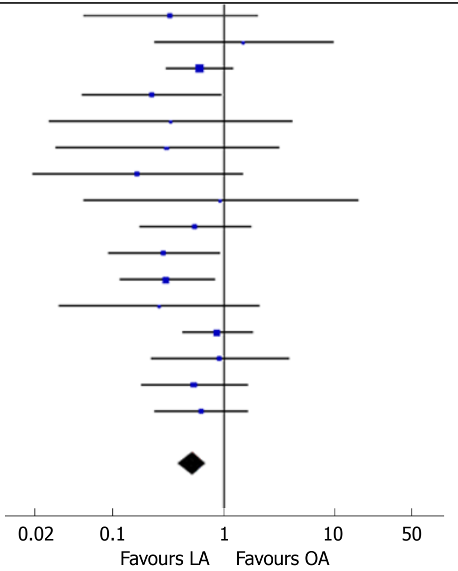


Figure 2 Forest plots comparing operative outcomes between laparoscopic and open liver resection for hepatolithiasis. A: Operative time; B: Intraoperative blood loss; C: Intraoperative transfusion; D: Postoperative complications.

residual rate (P = 0.31 and 0.07, respectively) (Figure 3C and D). Twelve studies[16,19-22,24-26,28-31] reported stone recurrence rate, with no significant difference between the two groups (OR: 0.63, 95%CI: 0.34-1.16, P = 0.14) (Figure 3E).

Subgroup analysis

Operative time, EBL, LOS, intraoperative transfusion, postoperative complications, initial residual stone and stone recurrence were included in subgroup analysis. In the subgroup assessment of operative time, 8 studies[17,19,20,23-26,30] with 793 patients were included. Pooled data of 5 studies[17,19,23,25,26] showed no significant difference in operating time in patients who underwent LLS by laparoscopic and open approach (WMD: -3.04, 95%CI: -28.19 to 22.11, P = 0.81) (Figure 4A). Pooled analysis of 4 studies[24-26,30] evaluating patients who underwent left hemihepatectomy showed no significant difference between the two groups (WMD: 6.72, 95% CI: -14.64 to 28.09, P = 0.54). In contrast, patients who underwent right hepatectomy tended to have a shorter operating time in the laparoscopic group (WMD: 97.00, 95%CI: 11.71-182.29, P = 0.03)[20].

Five studies[17,19,23,25,26] compared estimated blood loss for LLS, and showed significantly less blood loss for laparoscopic hepatectomy compared to open liver resection (WMD: -76.30, 95%CI: -144.45 to -8.15, P = 0.03) (Figure 4B). Four studies[24-26,30] comparing EBL for left hemihepatectomy found significantly less blood loss in the laparoscopic group (WMD: -72.86, 95%CI: -116.03 to -28.69, P = 0.001). One study[20] analyzed EBL for right hepatectomy, and indicated no significant difference between the two groups (WMD: 109.0, 95%CI: -519.92 to 737.92, P = 0.73).

Intraoperative transfusion was analyzed in 3 studies[19,25,26] of left lateral sectionectomy, and showed a lower transfusion rate for the laparoscopic approach (OR: 0.25, 95%CI: 0.12-0.52, P < 0.001) (Figure 4C). Similarly, 4 studies[24-26,30] comparing left hemihepatectomy indicated a lower transfusion rate for the laparoscopic approach (OR: 0.28, 95%CI: 0.08-0.90, P = 0.03).

Postoperative complication rate was analyzed in 8 studies[17,19,20,23-26,30], of which 5 involved LLS, 4 left hemihepatectomy[24-26,30] and 1 right liver resection[20] (Figure 4D). It revealed that the laparoscopic approach resulted in fewer postoperative complications than LLS and RH (P = 0.02 and 0.04, respectively). However, it suggested no significant difference between the two groups for left hemihepatectomy (OR: 0.55, 95%CI: 0.29-1.06, P = 0.07).

Eight studies[17,19,20,23-26,30] were included in the subgroup analysis of LOS. Five[17,19,23,25,26] evaluated LLS, showing shorter LOS in the laparoscopic group (WMD: -2.03, 95%CI: -2.44 to -1.62, P < 0.001) (Figure 4E). Four studies[24-26, 30] revealed that patients in the laparoscopic left hemihepatectomy group spent less time in hospital (WMD: -3.47, 95%CI: -4.33 to -2.61, P < 0.001). One article[20] suggested no significant difference between the two operative approaches for right hepatectomy (WMD: 4.0, 95%CI: -8.40 to 16.40, P = 0.53).

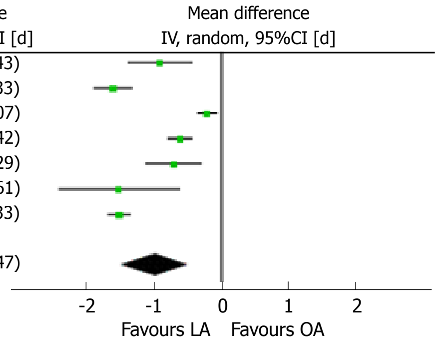
As for initial residual stone and stone recurrence, subgroup analysis suggested no significant difference

A

	LA			OA				Mean difference
Study or subgroup	Mean [d]	SD [d]	Total	Mean [d]	SD [d]	Total	Weight	IV, random, 95%CI [d]
Cai 2007	1.1	0.6	29	2	1	22	13.8%	-0.90 (-1.37, -0.43)
Li 2014	2.4	0.5	35	4	0.7	40	15.0%	-1.60 (-1.87, -1.33)
Li 2015	0.8	0.18	23	1	0.26	22	15.5%	-0.20 (-0.33, -0.07)
Namgoong 2014	2.2	0.48	37	2.8	0.46	112	15.4%	-0.60 (-0.78, -0.42)
Peng 2016	2.3	0.8	36	3	1	39	14.2%	-0.70 (-1.11, -0.29)
Song 2009	3.29	0.49	7	4.8	1.32	10	10.5%	-1.51 (-2.41, -0.61)
Zhou 2013	2.5	0.5	43	4	0.25	44	15.4%	-1.50 (-1.67, -1.33)
Total (95%CI)			210			289	100.0%	-0.98 (-1.48, -0.47)

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 188.28$, df = 6 ($P < 0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 3.79 ($P = 0.0001$)

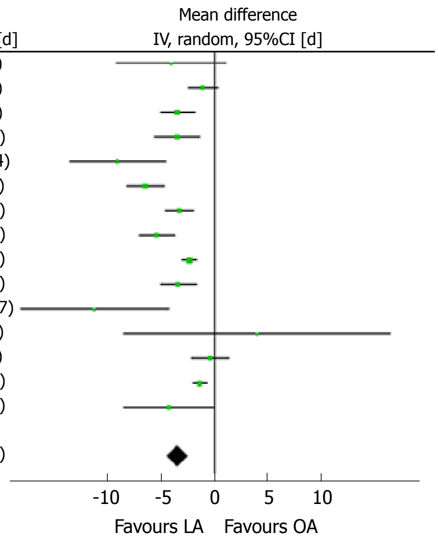


B

	LA			OA				Mean difference
Study or subgroup	Mean [d]	SD [d]	Total	Mean [d]	SD [d]	Total	Weight	IV, random, 95%CI [d]
Zhou 2013	9.5	10.75	43	13.5	13.25	44	2.8%	-4.00 (-9.06, 1.06)
Ye 2015	11	3.25	46	12	3.75	51	8.9%	-1.00 (-2.39, 0.39)
Tu 2010	6.8	2.8	28	10.2	3.4	33	8.5%	-3.40 (-4.96,-1.84)
Tian 2013	13.1	5.6	116	16.5	8.3	78	7.3%	-3.40 (-5.51, -1.29)
Song 2009	10.14	2.41	7	19.1	6.52	10	3.5%	-8.96 (-13.38, -4.54)
Shin 2015	7.9	2.6	40	14.3	5.5	54	8.2%	-6.40 (-8.07, -4.73)
Peng 2016	7.7	2.2	36	10.9	3.3	39	9.2%	-3.20 (-4.46, -1.94)
Namgoong 2014	8.8	4.1	37	14.1	4.98	112	8.4%	-5.30 (-6.91, -3.69)
Li 2015	10.7	0.82	23	13	1.2	22	10.3%	-2.30 (-2.90, -1.70)
Li 2014	12.3	2.6	35	15.6	4.3	40	8.4%	-3.30 (-4.89, -1.71)
Lee 2014	10.9	4.7	7	22	9	9	1.8%	-11.10 (-17.93, -4.27)
Kim 2015	16	22	17	12	14	17	0.6%	4.00 (-8.40, 16.40)
Jin 2015	10.8	5.3	96	11.1	7.1	105	8.1%	-0.30 (-2.02, 1.42)
Ding 2015	4.5	2	49	5.8	1.5	49	10.2%	-1.30 (-2.00, -0.60)
Cai 2007	8.8	4.4	29	13	9.2	22	3.7%	-4.20 (-8.36, -0.04)
Total (95%CI)			609			685	100.0%	-3.32 (-4.32, -2.32)

Heterogeneity: $Tau^2 = 2.41$; $Chi^2 = 75.37$, df = 14 ($P < 0.00001$); $I^2 = 81\%$

Test for overall effect: Z = 6.52 ($P < 0.00001$)

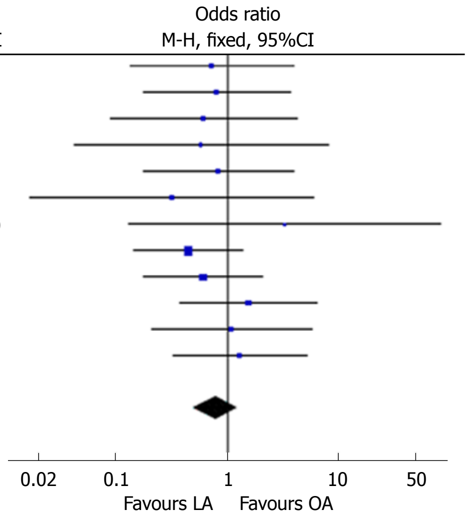


C

	LA		OA			Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95%CI
Cai 2007	3	29	3	22	7.2%	0.73 (0.13, 4.02)
Jin 2015	3	96	4	105	8.7%	0.81 (0.18, 3.74)
Kim 2015	2	17	3	17	6.2%	0.62 (0.09, 4.29)
Lee 2014	1	7	2	9	3.5%	0.58 (0.04, 8.15)
Li 2014	3	35	4	40	8.1%	0.84 (0.18, 4.06)
Namgoong 2014	0	37	4	112	5.3%	0.32 (0.02, 6.11)
Peng 2016	1	36	0	39	1.1%	3.34 (0.13, 84.60)
Shin 2015	5	40	13	54	22.9%	0.45 (0.15, 1.39)
Tian 2013	5	103	6	78	15.3%	0.61 (0.18, 2.08)
Tu 2010	5	28	4	33	7.1%	1.58 (0.38, 6.55)
Ye 2015	3	46	3	51	6.3%	1.12 (0.21, 5.83)
Zhou 2013	5	43	4	44	8.2%	1.32 (0.33, 5.27)
Total (95%CI)		517		604	100.0%	0.79 (0.50, 1.25)
Total events	36		50			

Heterogeneity: $Chi^2 = 3.96$, df = 11 ($P = 0.97$); $I^2 = 0\%$

Test for overall effect: Z = 1.01 ($P = 0.31$)

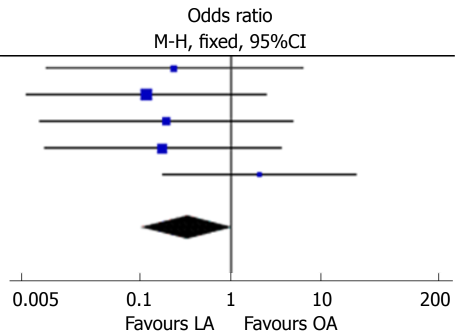


D

	LA		OA			Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, fixed, 95%CI
Cai 2007	0	29	1	22	15.1%	0.24 (0.01 6.26)
Kim 2015	0	17	3	17	30.8%	0.12 (0.01, 2.48)
Lee 2014	0	7	2	9	18.9%	0.20 (0.01, 4.91)
Shin 2015	0	40	3	54	26.7%	0.18 (0.01, 3.62)
Zhou 2013	2	43	1	44	8.5%	2.10 (0.18, 24.02)
Total (95%CI)		136		146	100.0%	0.34 (0.11, 1.08)
Total events	2		10			

Heterogeneity: $Chi^2 = 2.92$, df = 4 ($P = 0.57$); $I^2 = 0\%$

Test for overall effect: Z = 1.83 ($P = 0.07$)



E

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, fixed, 95%CI
Cai 2007	0	29	1	22	6.3%	0.24 (0.01, 6.26)
Jin 2015	1	96	0	105	1.8%	3.31 (0.13, 82.33)
Kim 2015	0	17	4	17	16.5%	0.09 (0.00, 1.73)
Lee 2014	0	7	1	9	4.7%	0.38 (0.01, 10.74)
Li 2014	2	35	2	40	6.6%	1.15 (0.15, 8.63)
Namgoong 2014	0	37	2	112	4.7%	0.59 (0.03, 12.55)
Peng 2016	2	36	3	39	10.3%	0.71 (0.11, 4.49)
Shin 2015	1	40	3	54	9.4%	0.44 (0.04, 4.35)
Tian 2013	3	116	2	78	8.8%	1.01 (0.16, 6.18)
Tu 2010	1	28	1	33	3.3%	1.19 (0.07, 19.86)
Ye 2015	2	46	3	51	10.3%	0.73 (0.12 4.56)
Zhou 2013	3	43	5	44	17.3%	0.58 (0.13, 2.62)
Total (95%CI)		530		604	100.0%	0.63 (0.34, 1.16)
Total events	15		27			

Heterogeneity: Chi^2 = 4.08, df = 11 (P = 0.97); I^2 = 0%

Test for overall effect: Z = 1.49 (P = 0.14)

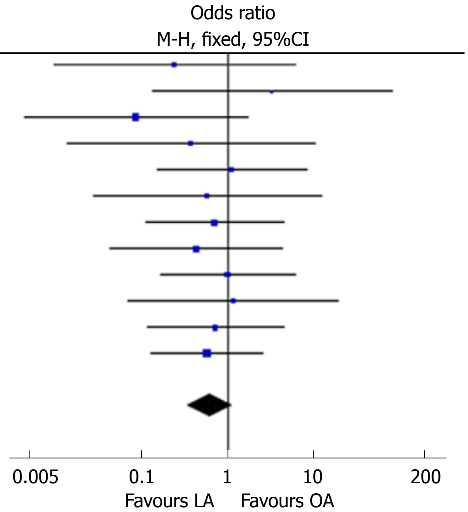


Figure 3 Forest plots comparing postoperative outcomes between laparoscopic and open liver resection for hepatolithiasis. A: Time to oral intake; B: Length of postoperative hospital stay.

Table 3 Quality of cohort studies evaluated by modified Newcastle-Ottawa scale

Ref.	Selection				Comparability		Outcomes		Quality score
	Definition of cases	Representativeness	Selection of controls	Definition of controls	Comparable for 1, 2, 3, 4	Comparable for 5, 6, 7	Assessment of outcomes	Integrity of follow-up	
Cai *et al*[16], 2007	Yes	No	No	Yes	Yes	5	Yes	Yes	7
Li, H *et al*[18], 2008	Yes	No	No	Yes	1, 2	5	Yes	Yes	5
Jin *et al*[19], 2015	Yes	No	No	Yes	1, 2, 3	No	Yes	Yes	5
Kim *et al*[20], 2015	Yes	Yes	No	Yes	1, 3, 4	6, 7	Yes	Yes	7
Lee *et al*[21], 2014	Yes	No	No	Yes	1, 2, 4	5	Yes	Yes	6
Li, J *et al*[22], 2014	Yes	No	No	Yes	1, 2, 3	6	Yes	Yes	6
Li, Y *et al*[23], 2015	Yes	No	No	Yes	1, 2, 3	No	Yes	Yes	5
Namgoong *et al*[24], 2014	Yes	No	No	Yes	Yes	6	Yes	Yes	7
Peng *et al*[25], 2016	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
Shin *et al*[26], 2015	Yes	No	No	Yes	1, 2	No	Yes	Yes	5
Song *et al*[27], 2010	Yes	No	No	Yes	Yes	6	Yes	Yes	7
Tian *et al*[28], 2013	Yes	No	No	Yes	1, 2, 4	5	Yes	Yes	6
Tu *et al*[29], 2010	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7
Ye *et al*[30], 2015	Yes	Yes	No	Yes	Yes	No	Yes	Yes	7

1: Age; 2: Sex; 3: Liver function; 4: Previous upper surgery history; 5: Surgeon experience; 6: Body mass index; 7: American Society of Anesthesiologists score.

between the two approaches. *P* value for initial residual rate in the different subgroups was 0.09, 0.99 and 0.63, respectively (Figure 5). *P* value for postoperative stone recurrence rate in the different subgroups was 0.99, 0.53 and 0.11, respectively.

Sensitivity analysis and publication bias

The RCT and 8 retrospective studies that scored seven stars or more on the modified Newcastle-Ottawa scale were included in sensitivity analysis (Table 4). No significant changes were found in any of the outcomes. The degree of between-study heterogeneity decreased for operative time, EBL, intraoperative transfusion, LOS and time to oral intake. The degree of between-study heterogeneity remained significant for operating time, EBL, LOS and time to oral intake.

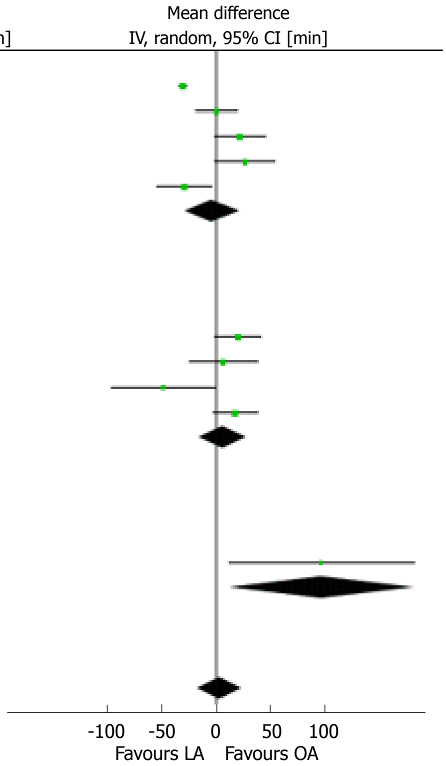
The funnel plot of postoperative complications showed that all articles included in this meta-analysis lay inside the 95% CIs and were symmetrically distributed around the center line, indicating a lack of obvious publication bias (Figure 6).

DISCUSSION

Treatment for symptomatic hepatolithiasis is still an intractable clinical problem. With appropriate therapy, a variety of complications would be avoided, including cholangitis, biliary stricture, recurrent stones, cirrhosis and even cholangiocarcinoma[32]. Traditionally, open hepatectomy was identified as the best method for this disease[33,34]. However, as laparoscopic approaches have been increasingly used in abdominal surgery

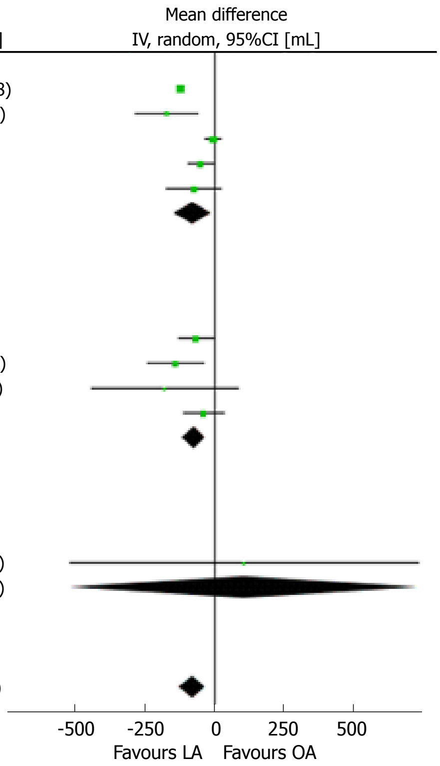
A

Study or subgroup	LA Mean [min]	LA SD [min]	LA Total	OA Mean [min]	OA SD [min]	OA Total	Weight	Mean difference IV, random, 95% CI [min]
2.1.1 LLS								
Ding 2015	67.1	8.36	49	97.1	9.82	49	12.7%	-30.00 (-33.61, -26.39)
Jin 2015	207	81	96	206	53	105	11.5%	1.00 (-18.11, 20.11)
Li 2015	171.3	42.46	23	149.55	35.89	22	11.0%	21.75 (-1.19, 44.69)
Peng 2016	199	56	21	172.2	32.6	23	10.4%	26.80 (-0.61, 54.21)
Shin 2015	175.1	57.2	33	203.8	43	30	10.7%	-28.70 (-53.55, -3.85)
Subtotal (95%CI)			222			229	56.2%	-3.04 (-28.19, 22.11)
Heterogeneity: Tau^2 = 710.69; Chi^2 = 43.07, df = 4 (P < 0.00001); I^2 = 91%								
Test for overall effect: Z = 0.24 (P = 0.81)								
2.1.2 LH								
Namgoong 2014	257	50.4	37	237	75.5	112	11.2%	20.00 (-1.43, 41.43)
Peng 2016	216.5	45.9	15	209.9	41.4	16	9.9%	6.60 (-24.24, 37.44)
Shin 2015	170.1	58.1	7	218.5	50.7	24	7.5%	-48.40 (-95.98, -0.82)
Ye 2015	254	52	46	236	50.75	51	11.3%	18.00 (-2.49, 38.49)
Subtotal (95%CI)			105			203	39.8%	6.72 (-14.64, 28.09)
Heterogeneity: Tau^2 = 263.83; Chi^2 = 7.17, df = 3 (P = 0.07); I^2 = 58%								
Test for overall effect: Z = 0.62 (P = 0.54)								
2.1.3 RH								
Kim 2015	432	158	17	335	85	17	3.9%	97.00 (11.71, 182.29)
Subtotal (95%CI)			17			17	3.9%	97.00 (11.71, 182.29)
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.23 (P = 0.03)								
Total (95%CI)			344			449	100.0%	3.49 (-16.86, 23.84)
Heterogeneity: Tau^2 = 844.88; Chi^2 = 90.65, df = 9 (P < 0.00001); I^2 = 90%								
Test for overall effect: Z = 0.34 (P = 0.74)								
Test for subaroup difference: Chi^2 = 4.87, df = 2 (P = 0.09); I^2 = 59.0%								



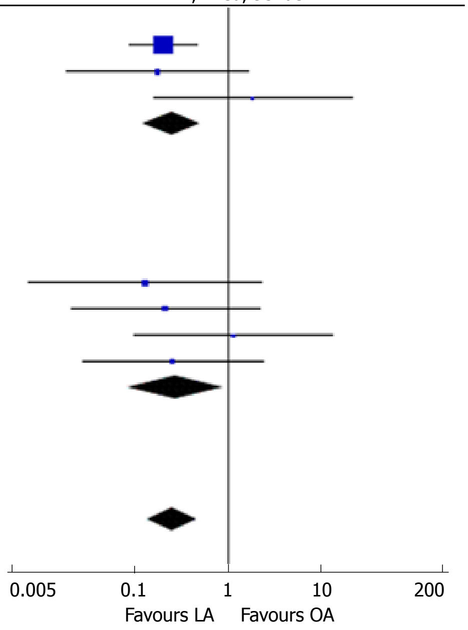
B

Study or subgroup	LA Mean [mL]	LA SD [mL]	LA Total	OA Mean [mL]	OA SD [mL]	OA Total	Weight	Mean difference IV, random, 95%CI [mL]
2.3.1 LLS								
Ding 2015	380	24.7	49	500	22.3	49	15.7%	-120.00 (-129.32, -110.68)
Jin 2015	383	281	96	554	517	105	8.5%	-171.00 (-284.75, -57.25)
Li 2015	214.57	42.58	23	216.36	50.74	22	15.0%	-1.79 (-29.22, 25.64)
Peng 2016	186.7	54.2	21	235.2	94.7	23	13.9%	-48.50 (-93.61, -3.39)
Shin 2016	268.5	170.8	33	340	221.6	30	9.6%	-71.50 (-169.91, 26.91)
Subtotal (95%CI)			222			229	62.7%	-76.30 (-144.45, -8.15)
Heterogeneity: Tau^2 = 4983.84; Chi^2 = 72.08, df = 4 (P < 0.00001); I^2 = 94%								
Test for overall effect: Z = 2.19 (P = 0.03)								
2.3.2 LH								
Namgoong 2014	280	96.9	37	347	285.5	112	12.6%	-67.00 (-128.40, -5.60)
Peng 2016	256.7	84.5	15	394.7	185.2	18	9.5%	-138.00 (-238.32, -37.68)
Shin 2015	244.3	159.4	7	421.7	591	24	2.8%	-177.40 (-441.69, 86.89)
Ye 2015	332	166.75	46	369	193.75	51	11.8%	-37.00 (-108.76, 34.76)
Subtotal (95%CI)			105			203	36.7%	-72.86 (-117.03, -28.69)
Heterogeneity: Tau^2 = 151.10; Chi^2 = 3.21, df = 3 (P = 0.36); I^2 = 7%								
Test for overall effect: Z = 3.23 (P = 0.001)								
2.3.3 RH								
Kim 2015	988	929	17	879	942	17	0.6%	109.00 (-519.92, 737.29)
Subtotal (95%CI)			17			17	0.6%	109.00 (-519.92, 737.29)
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
Total (95%CI)			344			449	100.0%	-77.53 (-126.55, -28.51)
Heterogeneity: Tau^2 = 3973.52; Chi^2 = 78.15, df = 9 (P < 0.00001); I^2 = 88%								
Test for overall effect: Z = 3.10 (P = 0.002)								
Test for subaroup difference: Chi^2 = 0.33, df = 2 (P = 0.85); I^2 = 0%								



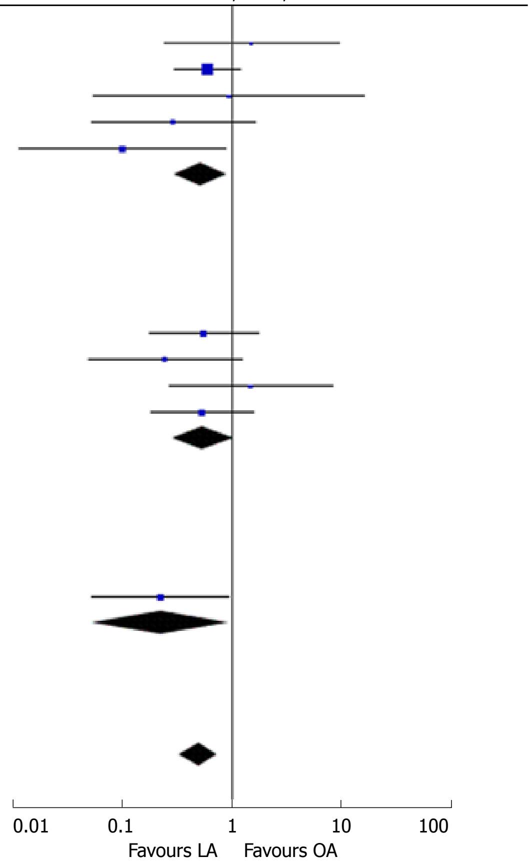
C

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, fixed, 95%CI
2.5.1 LLS						
Jin 2015	8	96	32	105	59.3%	0.21 (0.09, 0.48)
Peng 2016	1	21	5	23	9.6%	0.18 (0.02, 1.69)
Shin 2015	2	33	1	30	2.1%	1.87 (0.16, 21.75)
Subtotal (95%CI)		150		158	71.0%	0.25 (0.12, 0.52)
Total events	11		38			
Heterogeneity: Chi^2 = 2.86, df = 2 (P = 0.24); I^2 = 30%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
2.5.2 LH						
Namgoong 2014	0	37	10	112	11.0%	0.13 (0.01, 2.28)
Peng 2016	1	15	4	16	7.6%	0.21 (0.02, 2.19)
Shin 2015	1	7	3	24	2.5%	1.17 (0.10, 13.36)
Ye 2015	1	46	4	51	7.9%	0.26 (0.03, 2.43)
Subtotal (95%CI)		105		203	29.0%	0.28 (0.08, 0.90)
Total events	3		21			
Heterogeneity: Chi^2 = 1.66, df = 3 (P = 0.65); I^2 = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
Total (95%CI)		225		361	100.0%	0.26 (0.14, 0.48)
Total events	14		59			
Heterogeneity: Chi^2 = 4.58, df = 6 (P = 0.60); I^2 = 0%						
Test for overall effect: Z = 4.30 (P < 0.0001)						
Test for subaroup difference: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 = 0%						



D

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, fixed, 95%CI
2.4.1 LLS						
Ding 2015	3	49	2	49	2.7%	1.53 (0.24, 9.60)
Jin 2015	16	96	26	105	29.7%	0.61 (0.30, 1.22)
Li 2015	1	23	1	22	1.4%	0.95 (0.06, 16.27)
Peng 2016	2	21	6	23	7.4%	0.30 (0.05, 1.68)
Shin 2015	1	33	7	30	10.2%	0.10 (0.01, 0.89)
Subtotal (95%CI)		222		229	51.4%	0.52 (0.30, 0.90)
Total events	23		42			
Heterogeneity: Chi^2 = 4.26, df = 4 (P = 0.37); I^2 = 6%						
Test for overall effect: Z = 2.31 (P = 0.02)						
2.4.2 LH						
Namgoong 2014	4	37	20	112	12.7%	0.56 (0.18, 1.75)
Peng 2016	3	15	8	16	8.9%	0.25 (0.05, 1.24)
Shin 2015	3	7	8	24	3.0%	1.50 (0.27, 8.38)
Ye 2015	6	46	11	51	13.0%	0.55 (0.18, 1.62)
Subtotal (95%CI)		105		203	37.5%	0.55 (0.29, 1.06)
Total events	16		47			
Heterogeneity: Chi^2 = 2.24, df = 3 (P = 0.52); I^2 = 0%						
Test for overall effect: Z = 1.78 (P = 0.07)						
2.4.3 RH						
Kim 2015	5	17	11	17	11.1%	0.23 (0.05, 0.96)
Subtotal (95%CI)		17		17	11.1%	0.23 (0.05, 0.96)
Total events	5		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
Total (95%CI)		344		449	100.0%	0.50 (0.33, 0.75)
Total events	44		100			
Heterogeneity: Chi^2 = 7.83 df = 9 (P = 0.55); I^2 = 0%						
Test for overall effect: Z = 0.36 (P = 0.0008)						
Test for subaroup difference: Chi^2 = 1.27, df = 2 (P = 0.53); I^2 = 0%						



E

Study or subgroup	LA Mean [d]	LA SD [d]	LA Total	OA Mean [d]	OA SD [d]	OA Total	Weight	Mean difference IV, random, 95%CI [days]
2.2.1 LLS								
Ding 2015	4.5	2	49	5.8	1.5	49	28.2%	-1.30 (-2.00, -0.60)
Jin 2015	10.8	5.3	96	11.1	7.1	105	4.6%	-0.30 (-2.02, 1.42)
Li 2015	10.7	0.82	23	13	1.2	22	37.9%	-2.30 (-2.90, -1.70)
Peng 2016	6.8	1.4	21	9.6	2.9	23	7.8%	-2.80 (-4.13, -1.47)
Shin 2015	8	2.7	33	14.7	5.8	38	2.7%	-6.70 (-8.97, -4.43)
Subtotal (95%CI)			222			229	81.2%	-2.03 (-2.44, -1.62)
Heterogeneity: Chi^2 = 26.36, df = 4 (P < 0.0001); I^2 = 85%								
Test for overall effect: Z = 9.66 (P < 0.00001)								
2.2.2 LH								
Namgoong 2014	8.8	4.1	37	14.1	4.98	112	5.3%	-5.30 (-6.91, -3.69)
Peng 2016	8.9	2.4	15	12.8	2.9	16	3.9%	-3.90 (-5.77, -2.03)
Shin 2015	7.6	1.9	7	13.7	5	24	2.3%	-6.10 (-8.55, -3.85)
Ye 2015	11	3.25	46	12	3.75	51	7.1%	-1.00 (-2.39, 0.39)
Subtotal (95%CI)			105			203	18.7%	-3.47 (-4.33, -2.61)
Heterogeneity: Chi^2 = 21.67, df = 3 (P < 0.0001); I^2 = 86%								
Test for overall effect: Z = 7.90 (P < 0.00001)								
2.2.3 RH								
Kim 2015	16	22	17	12	14	17	0.1%	4.00 (-8.40, 16.40)
Subtotal (95%CI)			17			17	0.1%	4.00 (-8.40, 16.40)
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.63 (P = 0.53)								
Total (95%CI)			344			449	100.0%	-2.29 (-2.67, -1.92)
Heterogeneity: Chi^2 = 57.73 df = 9 (P < 0.00001); I^2 = 84%								
Test for overall effect: Z = 12.11 (P < 0.00001)								
Test for subgroup difference: Chi^2 = 9.69, df = 2 (P = 0.008); I^2 = 79.4%								

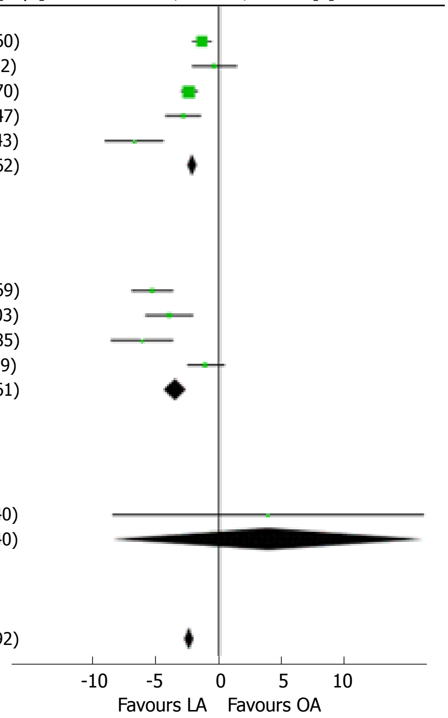


Figure 4 Forest plots and subgroup meta-analysis of operative time (A), blood loss during operation (B), intraoperative transfusion rate (C), postoperative complication rate (D) and length of hospital stay (E). IV: Inverse variance method; LA: Laparoscopic approach; LH: Left hemihepatectomy; LLS: Left lateral sectionectomy; OA: Open approach; RH: Right hemihepatectomy; SD: Standard deviation.

Table 4 Sensitivity analysis in laparoscopic hepatectomy *vs* open hepatectomy

Outcomes of interest	Study, *n*	LH, *n*	OH, *n*	WMD/OR (95%CI)	*P*	Study heterogeneity			*P*
						χ^2	df	I^2, %	
Operative time, min	11	416	464	26.58 (-1.78, 54.94)	0.07	201.48	10	95	< 0.001
Estimated blood loss, mL	9	402	445	-56.21 (-108.00, -4.43)	0.03	73.92	9	88	< 0.001
Intraoperative transfusion	7	314	366	0.47 (0.23, 0.97)	0.04	8.03	6	25	0.24
Length of hospital stay, d	12	450	504	-3.47 (-4.67, -2.27)	< 0.001	47.8	11	77	< 0.001
Postoperative complications	12	451	504	0.55 (0.38, 0.78)	< 0.001	8.33	11	0	0.68
Time to oral intake, d	6	187	267	-1.12 (-1.56, -0.68)	< 0.001	70.78	5	93	< 0.001
Initial residual stone	10	381	445	0.90 (0.53, 1.53)	0.71	2.74	9	0	0.97
Final residual stone	5	136	146	0.34 (0.11, 1.08)	0,07	2.92	4	0	0.57
Stone recurrence	10	394	445	0.59 (0.31, 1.15)	0.12	3.01	9	0	0.96

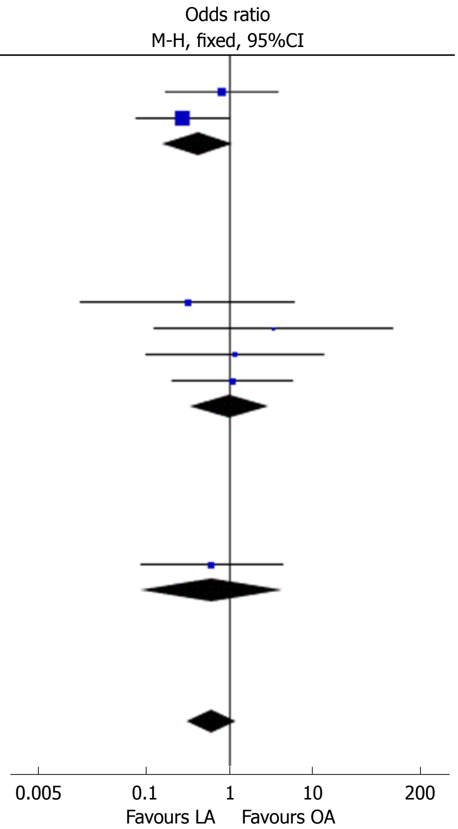
df: Degrees of freedom; LH: Laparoscopic hepatectomy; OH: Open hepatectomy; WMD/OR: Weight mean difference/odds ratio.

over the past two decades, laparoscopic hepatectomy for hepatolithiasis has been considered as standard practice for appropriate cases. Yet, laparoscopic hepatectomy for hepatolithiasis still has not been widely accepted, mainly due to the lack of convincing evidence by adequate comparison of surgical outcomes and long-term quality of life. Nevertheless, numerous studies[16,35] have reported the efficacy, safety and flexibility of laparoscopic hepatectomy for hepatolithiasis. In the current study, we aimed to conduct an extensive worldwide review and meta-analysis to evaluate whether laparoscopic liver surgery can replace open traditional approaches for symptomatic hepatolithiasis.

An earlier meta-analysis performed by Peng *et al*[36] in 2016 focused on left-sided hepatectomy for hepatolithiasis. It included studies of patients with hepatolithiasis in the left lobe and left lateral lobe that underwent laparoscopic or open hepatectomy. It included 8 studies, 1 RCT and 7 non-randomized trials. The conclusion was that the laparoscopic approach was a safe procedure for patients with hepatolithiasis. However, there were several limitations to that study. First, only 8 studies were included, comparing surgical outcomes between the two methods. Second, the

A

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, fixed, 95%CI
2.6.1 LLS						
Jin 2015	3	96	4	105	16.8%	0.81 (0.18, 3.74)
Shin 2015	4	33	10	30	41.8%	0.28 (0.08, 1.00)
Subtotal (95%CI)		129		135	58.5%	0.43 (0.16, 1.13)
Total events	7		14			
Heterogeneity: Chi^2 = 1.13, df = 1 (*P* = 0.29); I^2 = 11%						
Test for overall effect: Z = 1.70 (*P* = 0.09)						
2.6.2 LH						
Namgoong 2014	0	37	4	112	10.1%	0.32 (0.02, 6.11)
Peng 2016	1	15	0	16	2.0%	3.41 (0.13, 90.49)
Shin 2015	1	7	3	24	5.3%	1.17 (0.10, 13.36)
Ye 2015	3	46	3	51	12.1%	1.12 (0.21, 5.83)
Subtotal (95%CI)		105		203	29.5%	1.01 (0.34, 2.98)
Total events	5		10			
Heterogeneity: Chi^2 = 1.14, df = 3 (*P* = 0.77); I^2 = 0%						
Test for overall effect: Z = 0.01 (*P* = 0.99)						
2.6.3 RH						
Kim 2015	2	17	3	17	12.0%	0.62 (0.09, 4.29)
Subtotal (95%CI)		17		17	12.0%	0.62 (0.09, 4.29)
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (*P* = 0.63)						
Total (95%CI)		251		355	100.0%	0.62 (0.32, 1.22)
Total events	14		27			
Heterogeneity: Chi^2 = 3.61, df = 6 (*P* = 0.73); I^2 = 0%						
Test for overall effect: Z = 1.37 (*P* = 0.17)						
Test for subaroup difference: Chi^2 = 1.31, df = 2 (*P* = 0.52); I^2 = 0%						



B

Study or subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Odds ratio M-H, fixed, 95%CI
2.7.1 LLS						
Jin 2015	1	96	0	105	3.3%	3.31 (0.13, 82.33)
Peng 2016	1	21	1	23	6.4%	1.10 (0.06, 18.77)
Shin 2015	1	33	2	30	14.3%	0.44 (0.04, 5.09)
Subtotal (95%CI)		150		158	24.0%	1.01 (0.23, 4.52)
Total events	3		3			
Heterogeneity: Chi^2 = 0.98, df = 2 (*P* = 0.61); I^2 = 0%						
Test for overall effect: Z = 0.01 (*P* = 0.99)						
2.7.2 LH						
Namgoong 2014	0	37	2	112	8.7%	0.59 (0.03, 12.55)
Peng 2016	1	15	2	16	12.7%	0.50 (0.04, 6.17)
Shin 2015	0	7	1	24	4.8%	1.04 (0.04, 28.44)
Ye 2015	2	46	3	51	19.1%	0.73 (0.12, 4.56)
Subtotal (95%CI)		105		203	45.3%	0.67 (0.19, 2.31)
Total events	3		8			
Heterogeneity: Chi^2 = 0.14, df = 3 (*P* = 0.99); I^2 = 0%						
Test for overall effect: Z = 0.63 (*P* = 0.53)						
2.7.3 RH						
Kim 2015	0	17	4	17	30.7%	0.09 (0.00, 1.73)
Subtotal (95%CI)		17		17	30.7%	0.09 (0.00, 1.73)
Total events	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (*P* = 0.11)						
Total (95%CI)		272		378	100.0%	0.57 (0.24, 1.36)
Total events	6		15			
Heterogeneity: Chi^2 = 3.13, df = 7 (*P* = 0.87); I^2 = 0%						
Test for overall effect: Z = 1.26 (*P* = 0.21)						
Test for subaroup difference: Chi^2 = 2.08, df = 2 (*P* = 0.35); I^2 = 3.9%						

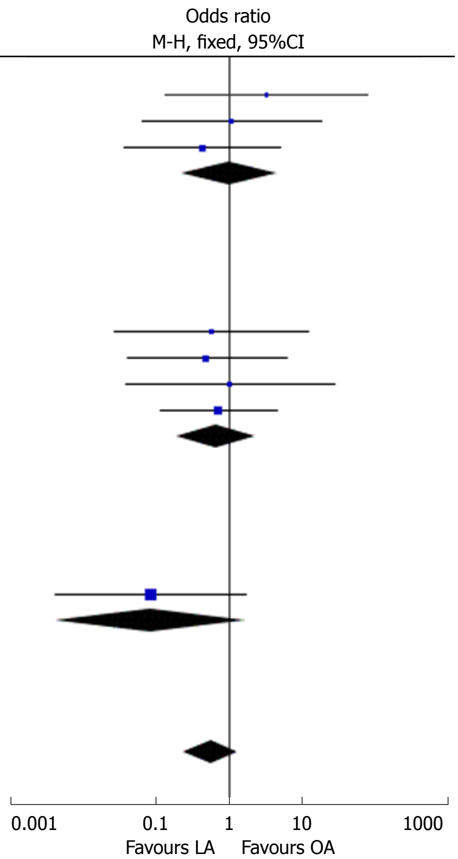


Figure 5 Forest plots and subgroup meta-analysis of initial residual stone rate (A) and stone recurrence rate (B). IV: Inverse variance method; LA: Laparoscopic approach; LH: Left hemihepatectomy; LLS: Left lateral sectionectomy; OA: Open approach; RH: Right hemihepatectomy; SD: Standard deviation.

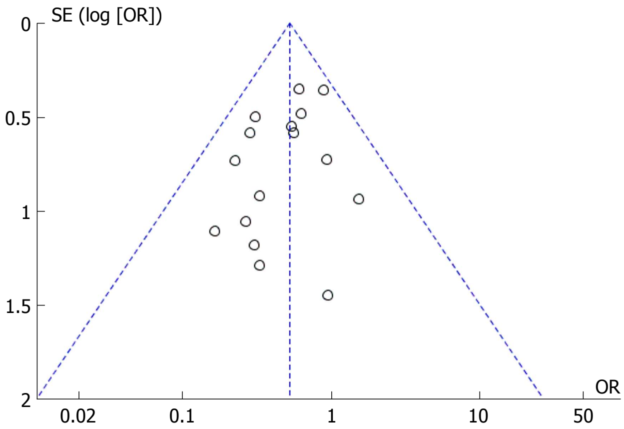


Figure 6 Funnel plot presenting meta-analysis of postoperative complication rate.

authors concluded the advantages of laparoscopic surgery for patients without any subgroup analysis. Furthermore, although hepatolithiasis is prevalent in the left-sided liver, stones may occur in any segment of the liver. The study only included studies that compared the safety and efficacy of laparoscopic and open approaches in left hemihepatectomy and left lateral segmentectomy for hepatolithiasis.

Our meta-analysis of an RCT and 15 retrospective studies, including 1329 patients, compared the efficacy and flexibility of two methods for hepatolithiasis. We showed that the laparoscopic approach was better than the open approach for both right and left sides of the liver, with significantly lower intraoperative blood loss and blood transfusion rate, shorter intestinal function recovery time, shorter LOS, and lower postoperative complication rate. However, no significant differences in operation time, residual stone and stone recurrence were found.

With respect to surgical outcomes, patient safety should be determined first in the application of any procedure. From the pooled data of postoperative complication rate, EBL and intraoperative blood transfusion, our results indicated that patients who underwent laparoscopic liver resection had better perioperative outcomes than those treated with the open approach.

In term of intraoperative outcomes, our study demonstrated that, compared with the open approach, laparoscopic hepatectomy for patients with hepatolithiasis had advantages of lower blood loss and less transfusion. Laparoscopic parenchymal dissection and the high intra-abdominal pressure during laparoscopic hepatectomy attained by pneumoperitoneum result in lower intraoperative blood loss[37]. Moreover, laparoscopy provided a magnified view of the liver, which contributed to bleeding control. Therefore, fewer patients undergoing laparoscopic surgery were in need of intraoperative transfusion. However, operating time did not differ significantly between the two approaches. This suggests that laparoscopic techniques are still a challenge for hepatic surgeons. The surgeons' experience had an impact on hepatic lobe dissection under laparoscopy, which contributed significantly to operating time[38,39]. The laparoscopic approach required frequent installation and removal of laparoscopic devices, resulted in additional operative time. In addition, the dissimilarity of the operating procedures in different institutions would have affected the result.

As for postoperative outcomes, the pooled outcomes of 16 studies with 1329 patients revealed that few patients experienced postoperative complications, including wound-related, vascular and biliary complications. Furthermore, fewer postoperative complications appeared in patients who underwent laparoscopic hepatectomy. In laparoscopic liver resection, the vessels and hepatic bile duct could be identified more precisely with the amplification effect of laparoscopy, and the probability of bile duct injury was reduced. Preoperative magnetic resonance cholangiopancreatography would help to reduce postoperative bile leak. With respect to postoperative recovery, the pooled outcomes of 7 studies suggested that the laparoscopic approach was associated with shorter time to oral intake and intestinal function recovery. Minimal incision, better intraoperative outcomes, and faster intestinal function recovery were confirmed to be in favor of shorter hospital stay in patients undergoing laparoscopic hepatectomy. Future well-designed studies should be performed to confirm these potential benefits.

Long-term outcomes after any procedure should also be taken into account. Our meta-analysis and subgroup analysis both showed that, compared with open surgery, there were no significant differences in residual stone rate and hepatolithiasis recurrence rate between the laparoscopic and open approaches. On the one hand, it means that there is no correlation between selection of the surgical procedure and stone residual/recurrent rate. Indeed, the generation and development of hepatolithiasis may have mainly been caused by anatomical variation and dietary habits in different regions[40,41]. Hepatolithiasis is likely to recur even if no residual stones exist after radical hepatectomy. On the other hand, it is known that the severity of abdominal adhesion after laparoscopic liver resection is significantly less than after open surgery[42]. Even though the patients have recurrence of intrahepatic bile duct stones, it would be easier for them to receive effective and safe treatment.

We conducted subgroup analysis, including left lateral hepatectomy, left hemihepatectomy and right hepatectomy for hepatolithiasis, to avoid the influence of heterogeneity. Similar outcomes were found for postoperative complication rate, blood loss and intraoperative blood transfusion, whereas EBL in the subgroup of right hepatectomy did not differ between the two surgical approaches. Sensitivity analysis was also performed to assess the impact of study quality on the estimates. A meta-analysis of RCTs would be ideal. However, with ethical concerns and patient expectations, this kind of study is difficult to conduct. This situation highlights the importance of the present meta-analysis. Although only 1 RCT was included in the present study, most of the other studies were of high quality, and the results could be considered credible and evidential.

The present study confirmed that the laparoscopic approach was better than the open approach for hepatolithiasis. However, our meta-analysis had several limitations that should be taken into account. First, although there was no evidence of publication bias, all the included studies were retrospective studies, except for one RCT. This increased the risk of bias for inadequate random sequencing and blinding. Second, the different levels of surgical expertise would have affected the final outcomes, and multicenter studies with large patient samples are required. Third, the included studies were in English, Chinese and Korean, which could have caused language selection bias. Finally, only studies performed in eastern countries were included in our meta-analysis, which could have resulted in regional selection bias. Further studies are needed to overcome the above-mentioned limitations and confirm our findings.

Nevertheless, the results of this meta-analysis are encouraging, as laparoscopic surgical techniques are frequently applied in abdominal surgery. Moreover, sufficient data on a large patient cohort that underwent liver resection for treatment of hepatolithiasis have been accumulated, allowing evaluation by meta-analysis. Multiple strategies were used to identify applicable studies, with strict criteria used for study inclusion and evaluation. Subgroup analysis was performed to minimize heterogeneity. Future studies comparing laparoscopic and open approaches for treatment of intrahepatic bile duct stones should include larger numbers of patients, with a longer follow-up period.

In summary, this meta-analysis demonstrated that laparoscopic surgery was technically feasible and safe, and superior to open surgery for treatment of hepatolithiasis. Subgroups analysis showed consistent results, except for EBL during right hepatectomy. The laparoscopic approach provides a favorable option for patients seeking curative treatment for hepatolithiasis.

COMMENTS

Background

Hepatectomy has become an established treatment modality for patients with hepatolithiasis. With laparoscopic approach widely used in hepatic surgery in recent years, laparoscopic hepatectomy for treating symptomatic hepatolithiasis attracted more and more attention. Despite this, no consensus is available in the literature about which of these two approaches is more beneficial to the patient.

Research frontiers

Laparoscopy is applied in hepatic surgery more and more frequently. It has been reported about no less safety and efficacy of laparoscopic hepatectomy for liver cancer compared to the conventional approach. The worldwide research is directed towards a type of technique to guaranteeing the safety of patients with benign liver disease.

Innovations and breakthroughs

In this study, the authors investigate the perioperative outcomes of laparoscopic hepatectomy and conventional liver resection by pooling data from the literature. This is the first report of a meta-analysis comparing these two kinds of surgical approaches with large sample size comprehensively.

Applications

This work allows understanding the role of two surgical techniques for treating hepatolithiasis.

Peer-review

This systematic review and meta-analysis adds useful information for practice and research, and probably for policy.

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