

**Running Head:** laparoscopy in proximal ureteral calculus.

**Comparison of the Safety and Efficacy between Transperitoneal and Retroperitoneal Approach of Laparoscopic Ureterolithotomy for the Treatment of Large (>10mm) and Proximal Ureteral Stones: A Systematic Review and Meta-analysis**

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**Keywords:** laparoscopy; meta-analysis; retroperitoneal; transperitoneal; ureteral calculus; ureterolithotomy

**ABSTRACT**

**Purpose:** We aimed to compare the safety and efficacy between laparoscopic transperitoneal ureterolithotomy (LTU) and laparoscopic retroperitoneal ureterolithotomy (LRU) in the treatment of large (>10mm) and proximal ureteral stones.

**Materials and Methods:** Electronic databases, including PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus searched through December 2019. Comparative studies were comparing two approaches included. The primary outcome was a single-procedure success rate; the secondary outcomes included operative time, hospital duration, and complications (according to the Clavien-Dindo Grade). Newcastle–Ottawa scale (NOS) and the modified Jadad scale was used to evaluate the quality of the included studies. The Egger's test estimated publication bias. The meta-analysis was performed by Review Manager 5.3 and STATA 15.0.

**Results:** 7 studies, involving 125 participants in LTU group and 128 in LRU group, were included in the study. The results suggested that both single-procedure success rate and the rate of postoperative paralytic ileus were significantly higher in LTU group than in LRU group (95.2% vs 87.5%, 95% CI: .00-.16, RD = .08,  $P = .04$ ; 10.4% vs 0, 95% CI: .02-.19, RD = .10,  $P = .02$ , respectively). No publication bias of the primary outcome was observed with the Egger's test ( $P = .117$ ). No significant differences were noted in terms of operative time and hospital duration (95% CI: -18.95-8.80, MD = -5.08,  $P = .47$ ; 95% CI: -.98-.58, MD = -.20,  $P = .61$ , respectively). Additionally, according to Clavien-Dindo Grade, the rates of major complications ( $\geq$  Grade 3a) including open conversion (.8% vs 5.5%, 95% CI: -.11-.01, RD = -.05,  $P = .12$ ), stone migration (8.1% vs 6.7%, 95% CI: -.08-.11, RD = .02,  $P = .76$ ), vascular injury (5.4% vs 0, 95% CI: -.03-.14, RD = .05,  $P = .21$ ) and ureteral stricture (1.3% vs 5.3%, 95% CI: -.11-.02, RD = -.04,  $P = .20$ ), were comparable between two groups.

**Conclusion:** In the treatment of large and proximal ureteral calculi, LTU has a significantly higher single-procedure success rate and a higher rate of postoperative paralytic ileus than LRU. However, the complication was well-tolerated. The small sample size and limited, including studies, were the main limitations.

**Keywords:** laparoscopy; meta-analysis; retroperitoneal; transperitoneal; ureterolithiasis; ureterolithotomy

## INTRODUCTION

The treatment of large proximal ureteral stones is complicated.<sup>(1)</sup> Although ureterorenoscopy (URS) and extracorporeal shockwave lithotripsy (SWL) are the most common procedures. However, multiple sessions are required.<sup>(2)</sup> This drawback promotes the usage of laparoscopic ureterolithotomy (LU) due to its high stone-free rate (SFR). Traditional LU was realized through the retroperitoneal approach. Due to that the laparoscopic retroperitoneal ureterolithotomy (LRU) is still at risk of stone migration to the kidney, the new method of laparoscopic transperitoneal ureterolithotomy (LTU) is attempted<sup>(3)</sup>. However, different opinions have emerged during this exploration of these two approaches. LTU is recommended to the less-experienced surgeons by Abat et al<sup>(4)</sup> for its broader operation field and familiar anatomy. However, another study reported that LTU and LRU were comparable in terms of efficiency and safety and surgeons could perform the procedure depend on personal preference.<sup>(5)</sup> Due to such controversy, A comprehensive study of this issue was needed. Thus, we conducted a meta-analysis with an attempt to understand these two approaches comprehensively.

## MATERIALS AND METHODS

This meta-analysis was performed based on the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.<sup>(6)</sup>

### Search strategy

We conducted a systematic search of electronic databases, including PubMed, EMBASE, Cochrane Library, Web of Science, and Scopus (through December 2019) to identify all relevant studies. The search strategy was combining with following terms without language restriction: ('laparoscopic ureterolithotomy' OR 'LU') AND ('proximal' OR 'upper') AND ('ureteral stone' OR 'ureteral stones' OR 'ureteral calculi' OR 'ureteral calculus' OR 'ureteral lithiasis'). And references of included studies were manually identified for relevant records. The titles and abstracts of identified studies were independently screened by two reviewers (Hualin and Han) following deduplication. Then, full texts or conference abstracts were obtained for further identification of their eligibility.

### Inclusion and Exclusion Criteria

The including trials met the following requirements:

- 1) Study types: randomized controlled trials (RCTs) and non-randomized comparative studies.
- 2) Patients with large (>10mm) and proximal ureteral calculi.
- 3) Comparison between LTU and LRU.
- 4) Report on the primary outcome and at least one of the secondary outcome measures mentioned below.
- 5) Reviews, animal studies, case reports, and non-comparative studies were excluded.

### Data extraction and outcome measures

Two reviewers (Hualin, Han) extracted data from including literature independently, including baseline characteristics and data of outcome measures. 1) baseline characteristics included first author, time of publication, country, recruitment duration, study design, stone characteristics, number of surgeon(s) and patients, gender proportion, body mass index (BMI) and average age, stone size and laterality. 2) Outcome measures were single-procedure success rate (defined below), operative time, length of hospital duration and complications.

The primary outcome was a single-procedure success rate. It was defined as reaching stone-free status at a single-one procedure without an open conversion requirement or auxiliary procedures requirement due to stone migration. Secondary outcomes included length of hospital stay, operative time, minor and complications. Complications were classified according to the Clavien-Dindo Grade.<sup>(7)</sup> Additionally, complications of more than Grade 3a were regarded as major ones. Prolonged drainage was defined as urine leakage requiring

drainage for more than 72 hours.<sup>(4,5,8,9)</sup> And paralytic ileus was defined as absence of bowel sound lasting for over 36 hours.<sup>(2,4,8)</sup>

Any disagreements were resolved by discussion or consultation with a third reviewer (Gang).

Evaluation of study quality

Comparative studies included RCTs and non-randomized comparative studies. The modified Jadad scale was used to assess the methodological qualities of RCTs, while, Newcastle–Ottawa scale (NOS) was used for non-randomized comparative studies. The results were listed in table 1.

### ***Statistical analysis***

The risk difference (RD) was used for dichotomous variables, while the mean difference (MD) was used for continuous ones. Forest plots were used to present the results of our meta-analysis. The Z test determined all the pooled effects, and  $p < 0.05$  was considered statistically significant. P values of dichotomous and continuous variables were calculated by Mantel–Haenszel (MH) test and Inverse-Variance (IV) weighting, respectively. Chi square-based Q test and  $I^2$  tests were used to assess the quantity of heterogeneity among these studies. When  $I^2 < 50\%$ ,  $p > 0.1$ , the pieces of evidences were thought to be acceptable heterogeneity, we used the fixed-effects model. Otherwise, the random-effects model was applied. Publication bias was evaluated with the Egger's regression asymmetry test. Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) was used to analyze the aggregate data. STATA 15.0 (College Station, Texas, USA) was used to identify publication bias and generate Eggers plot.

## **RESULTS**

### ***Search process and study characteristics***

The systematic search identified 1172 relevant studies. After further screening, seven studies (2 RCTs and five non-randomized comparative studies),<sup>(2,4,5,8-11)</sup> involving 125 participants in LTU group and 128 in LRU group, satisfied our inclusion criteria. The process of study identification as detailed in Figure 1. Except for one conference abstract,<sup>(11)</sup> the full texts of left six studies were obtained. Overall, the quality of non-randomized comparative studies was very high, with only one study<sup>(4)</sup> having a NOS of 6, and two RCTs<sup>(8,10)</sup> had a modified Jadad scale of 5. The characteristics of included studies were listed in Table 1. Demographic and baseline characteristics of enrolled patients were presented in Table 2.

Primary outcome

### ***Single-procedure success rate***

Patients in LTU group had significantly higher single-procedure success rate than those in LRU group (95.2% vs 87.5%, 95% CI: .00-.16, RD = .08,  $P = .04$ , Figure 2). For the primary outcome, the publication bias was not observed with the Egger's test ( $P = .117$ ; Figure 3).

### ***Secondary outcomes***

According to the Clavien-Dindo Grade, complications were listed in Table 3. No significant differences were observed in terms of operative time (95% CI: -18.95-8.80, MD = -5.08,  $P = .47$ , Figure 4) and length of hospital stay (95% CI: -.98- .58, MD = -.20,  $P = .61$ , Figure 4). However, significant heterogeneity was reported ( $I^2 = 87\%$ ,  $I^2 = 90\%$ , respectively, Figure 3 & 4). Additionally, according to the Clavien-Dindo Grade, major complications between two groups were similar in terms of open conversion (.8% vs 5.5%, 95%CI: -.11- .01, RD = -.05,  $P = .12$ , Figure 5), stone migration (8.1% vs 6.7%, 95% CI: -.08- .11, RD = .02,  $P = .76$ , Figure 5), vascular injury (5.4% vs 0, 95%CI: -.03- .14, RD = .05,  $P = .21$ , Figure 5) and ureteral stricture (1.3% vs 5.3%, 95% CI: -.11- .02, RD = -.04,  $P = .20$ , Figure 5). One case in LTU group with Grade 4a complication (pulmonary embolus) was recorded in the study by Abat et al.<sup>(4)</sup> And the patient was admitted to intensive care unit (ICU) for further treatment (Figure 4). Considering minor complications, except for paralytic ileus of which the morbidity

was significantly higher in LTU group (10.4% vs 0, 95% CI: .02- .19, RD = .10,  $P = .02$ , Figure 6), no statistical differences were noted between two groups in terms of urinary tract infection (UTI) (21.8% vs 23.1%, 95% CI: -.17- .14, RD = -.01,  $P = .87$ , Figure 6), transfusion (4.2% vs 1.4%, 95% CI: -.04- .09, RD = .02,  $P = .49$ , Figure 6), prolonged drainage (8% vs 7.3%, 95% CI: -.08- .09, RD = .00,  $P = .95$ , Figure 6) and retroperitoneal hematoma (2.4% vs 3.5%, 95% CI: -.07- .05, RD = -.01,  $P = .74$ , Figure 6).

## DISCUSSION

For large(>10mm) and proximal ureteral stones, LU shows significantly higher SFR than URS.<sup>(8)</sup> It is still unclear which approach, transperitoneal or retro-peritoneal, is better in terms of efficacy and safety. Our results revealed that patients in LTU group had a significantly higher single-procedure success rate than those in LRU group. But they also suffered from a substantially higher proportion of postoperative paralytic ileus. However, it had to be admitted that the overall sample size and number of included studies were small, which was the main drawback of the study. Thus, theoretical significance may be clinically insignificant. Considering the significantly higher single-procedure success rate in LTU group, it may be explained by the advantages of transperitoneal approach and drawbacks of retro-peritoneal approach, as well as open conversion rate. As we know, LTU owns advantages including wider operating field, clear anatomical landmarks and easy identification of the ureter. Contrarily, LRU has drawbacks including limited working space, lacking anatomic landmarks and difficulty in suture the ureter. Moreover, periureteral inflammatory adhesions because of long impaction time by large stones could contribute to relative difficult identification of ureter in retroperitoneal approach.<sup>(8,10)</sup> Thus, open conversion rate was relatively higher in LRU group (5.5% VS 0.8%) due to these drawbacks, although the difference was not significant. Moreover, Şahin et al<sup>(12)</sup> also reported one case in LRU group converted to open surgery.

With respect to postoperative complications, the rate of paralytic ileus was significantly higher in LTU group. Surprisingly, only patients receiving LTU suffered from the complication.<sup>(2,4,8)</sup> The result was consistent with that of the study of Şahin et al.<sup>(12)</sup> Moreover, Khalil et al<sup>(10)</sup> described in their report that the average time to oral intake was significantly longer in LTU group than in LRU group ( $15.5 \pm 2.8\text{h}$  VS  $21.2 \pm 4.9\text{h}$ ,  $P = .002$ ). This could be explained by the fact that LTU has disadvantages including intestine mobilization, peritoneal contamination with blood or urine leakage and dissection or retraction of viscera. While in LRU, lost blood does not come into the bowel and urine leakage would be contained within the retroperitoneal space and for cases with previous abdominal surgery, bowel injury could be prevented.<sup>(4)</sup> However, the complication was well-tolerated, and did not need any further or surgical intervention.

It seemed that vascular injury only developed in LTU group (Table 3). The outcome, however, revealed no significant difference between two groups. In fact, patients in LRU group still had possibility to suffer from the complication.<sup>(12)</sup> Among patients with vascular injury, two suffered from inferior vena cava injuries, who were managed by laparoscopy and open access,<sup>(2,4)</sup> respectively. Of note, surgeons in each study had limited laparoscopic experience. They just completed a laparoscopic training programme or were during their learning curve in laparoscopy. Besides, Pierluigi et al<sup>(2)</sup> reported 10 cases in LRU group developed peritoneal tearing when the surgeon tried to make pneumoperitoneum, resulting in prolonged operative time. We also noticed that the outcomes of operative time and hospital duration revealed significant heterogeneity ( $I^2 = 87\%$ ,  $I^2 = 90\%$ , respectively, Figure 3 & 4). The experience of surgeon, which differed in studies included, may explained for it. Because surgeon who has initial experience in laparoscopy is unfamiliar with surgical procedure and the anatomy around ureter, resulting in slow, careful and more dissection and prolonged operative time. However, more analysis can increase postoperative pain and dose of analgesic prescribed.

Therefore, longer hospital stay is required due to pain management.<sup>(10)</sup> In brief, it was noteworthy that experience in laparoscopy mattered with respect to operative time and hospital stay, as well as morbidity of complications.

Three included studies reported their experience in the management of migrated stones.<sup>(4,8,10)</sup> URS, percutaneous nephrolithotomy (PCNL) and LU were adopted and these patients achieved complete SFR. Total 5 stone migrations were reported in the study by Şahin et al<sup>(12)</sup> and were managed by SWL and ureteroscope successfully. For migrated stones, combination of LU with endourologic lithotripsy through the laparoscopic ports (URS) may be better for that URS took advantages of the laparoscopic ports<sup>(13)</sup>, indicating that no more puncture was needed.

In the study, the incidences of prolonged drainage and ureteral stricture were similar between two groups. Portion of urologists believed that ureteral stent placement following LU could prevent urine leakage and stricture, while others opposed the opinion because stenting may add cost and discomfort to the patient.<sup>(8)</sup> One meta<sup>(14)</sup> in 2017 concluded that no significant difference was found in the rate of prolonged drainage between stented and stentless LU. However, ureteral stricture was not pooled analyzed for limited data. Future studies are needed to address this topic. Other minor complications including UTI and retroperitoneal hematoma were well-tolerated and were managed without non-conservative treatment. Although blood transfusion was needed for some cases, the overall rate (2.8%) was low.

Overall, both two approaches were safe and efficient in the management of large and proximal ureteral stones. Interestingly, Nouralizadeh et al<sup>(13)</sup> reported their experience in synchronous or metachronous bilateral laparoscopic stone surgery and the result revealed that this procedure was feasible for laparoscopic expertise. And O'Kelly and colleagues<sup>(15)</sup> found that LU was safe in the management of partial duplex ureteric collecting system.

Even though this is the first meta-analysis to evaluate the efficacy and safety of two approaches in the management of large and proximal ureteral calculi, some limitations should be clarified. Firstly, the number of including studies and the sample sizes was relatively small, indicating that theoretical significance may be not be significant in practice. Secondly, number and experience of surgeons varied among these studies, in addition to different study designs, contributing to certain biases. Thirdly, subgroup analysis was not applied due to limited data. However, the outcomes may be referred by surgeons in making decision during future clinical practice.

## CONCLUSIONS

LTU has significantly higher single-procedure success rate and paralytic ileus rate than LRU, but the complication is well-tolerated. Due to the study limitations, further well-designed studies are needed to validate our findings.

## ACKNOWLEDGMENT

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## CONFLICTS OF INTEREST

The authors report no conflicts of interest

## AUTHOR CONTRIBUTIONS

Gang Chen was the senior arbiter reviewed and revised the paper.

Hualin Chen wrote drafts of the paper.

Hualin Chen and Han Chen collected and analyzed the data.

Yunxiao Zhu, Yang Pan, Fei Gao and Jinxiao Xiang provided access to the electrical library and the analysis tool.

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Tables and Legends to figures

**Table 1.** Characteristics and quality evaluation of including studies.

Study ID	Preop- imagin g	Postop- imagin g	Countr y	Study Period	Stud y Type	Stone Characteristics	No. Surgeon(s )	Surgical Experience	F/u (mon)	Qualit y Score
Abat 2016	KUB, US IVU, NCCT	NA	Turkey	Nov. 2011 to Mar. 2013	Retro -	Proximal	2	Limited	14.84±7.46 / 35.56±9.11	6
Almeida 2009	KUB, US IVU, CT	KUB	Brazil	Jan. 2004 to Nov. 2007	Pro-	Large(>10mm),proximal	1	Limited	1	8
Pierluigi 2009	US, IVU CT	NA	Italy	2004 to 2006	Pro-	Large(>10mm),proximal , impacted	2	Limited	12	8
Khalil 2015	CT	NA	Egypt	Jan. 2012 to Sep. 2013	RCT	Large(>15mm),proximal , impacted	NA	NA	NA	5 <sup>a</sup>
Wisoot 2010	KUB	NA	Thailan d	Jul. 1997 to Dec. 2007	Retro -	Large(>15mm), impacted	3	NA	18	7
Vishwajee t 2013	KUB, US IVU	KUB, IVU US	India	Jan. 2009 to May 2012	RCT	Proximal	1	NA	14/15	5 <sup>a</sup>
Chiu 2015	NA	NA	China	Dec. 2009 to Sep. 2014	Retro -	Large(>15mm),proximal , impacted	1	Experience d	3	8

**Abbreviations:** Preop- imaging, preoperative imaging examinations; postop- imaging, postoperative imaging examinations; KUB, Kidney; Ureter; and Bladder X-ray; US, ultrasound; IVU, intravenous urogram; NCCT, non-contrast computed tomography; NA, not available; retro-, retrospective comparative study; pro-, prospective comparative study; F/u, follow up.

<sup>a</sup> Quality evaluated by the modified Jadad scale, the others were evaluated by NOS.

**Table 2.** Demographic and baseline characteristics of including patients.

Study ID	Sample Size(n)	Age(years)	BMI(kg/m2)	Stone Size(mm)	Stone Side(R:L)	Gender(M:F)	Single-procedure Success Rate	Operative Time(mins)	Hospital Duration(days)
Abat 2016	25/25	38.96±17.01/ 47.8±14.1	NA	16.62±4.78/ 20.12±5.18	6:19/ 11:14	6:19/ 15:10	21/20	147±36.54/ 106.4±38	2.94±1.69/ 7.12±4.47
Almeida 2009	15/19	43.2±16.7/ 43.8±15.7	NA	12.5±2.6/ 13.6±3.8	10:6/ 8:10	8:7/ 12:7	15/15	100(70-180)/ 105(90-120)	3(2-3)/ 2(2-3)
Pierluigi 2009	18/17	42(25-60)/ 40(28-61)	22.3(20.6-35.7)/ 21.6(20.2-31.8)	23(15-45)/ 22(13-35)	NA	NA	17/17	68(48-130)/ 103(69-147)	4(2-7)/ 5(2-10)
Khalil 2015	13/11	37.6±13.2/ 44.6±7.9	25.9±2.8/ 28.09±4.4	15.5±3.7/ 15.8±3.02	5:8/ 5:6	9:4/ 8:3	13/7	116.2±21.8/ 137.3±17.9	5.4±1.2/ 5±0.8
Wisoot 2010	11/28	42.1/ 44.2	NA	17.8/ 18.2	NA	NA	11/27	128.3(75-180)/ 125.9(75-270)	8.8/ 4.1
Vishwajeet 2013	24/24	37.75±10.61/ 39.16±11.49	NA	18±3.6/ 17±3.8	14:10/ 8:16	14:10/ 13:11	23/22	83.12±8.3/ 84.1±6.4	3.125±0.74/ 2.67±0.63
Chiu 2015	19/4	54.47±10.75/ 51.5±17.91	25.31±2.82/ 28.2±4.19	20.2±6.4/ 18±2.2	NA	15:4/ 3:1	19/4	102.3±33.9/ 111.25±8.3	5±1.76/ 5.25±1.26

Data was presented as “LTU/LRU”

**Abbreviations:** R, right; L, left; M, male; F, female; NA, not available.

**Table 3.** Intra- or postoperative complications classified by the modified Clavien-Dindo Grade (P value was calculated by using MH test).

Grade	No. Complications (%)		P Value
	LTU	LRU	
Grade 1	8 (6.4%)	9 (7.03%)	
Prolonged drainage	6 (4.8%)	7 (5.47%)	.95
Retroperitoneal hematoma	2 (1.6%)	2 (1.56%)	.74
Grade 2	22 (17.6%)	13 (10.16%)	



UTI	12 (9.6%)	12 (9.38%)	.87
Transfusion	3 (2.4%)	1 (.78%)	.49
Paralytic ileus	7 (5.6%)	0	.02
Grade 3a	-	-	
Grade 3b	10 (8%)	16 (12.5%)	
Open conversion	1 (.8%)	7 (5.47%)	.12
Stone migration	5 (4%)	4 (3.13%)	.76
Vascular injury	3 (2.4%)	0	.21
Ureteral stricture	1 (.8%)	5 (3.91%)	.20
Grade 4a	1 (.8%)	0	
Pulmonary embolus	1 (.8%)	0	.45
Total complications	41 (32.8%)	39 (30.47%)	

Accepted

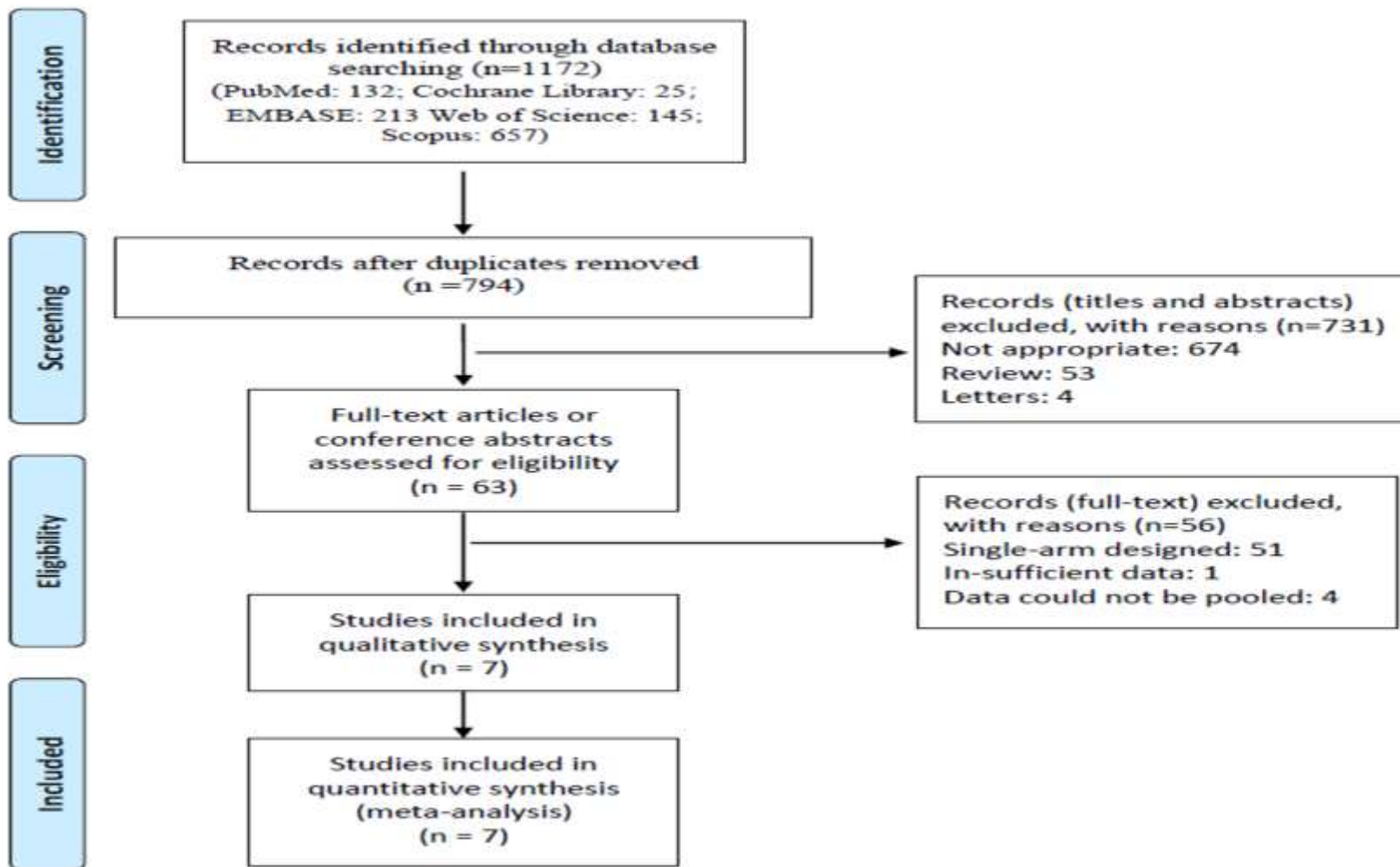


Figure 1. Flow diagram of identification process (PRISMA flow diagram).

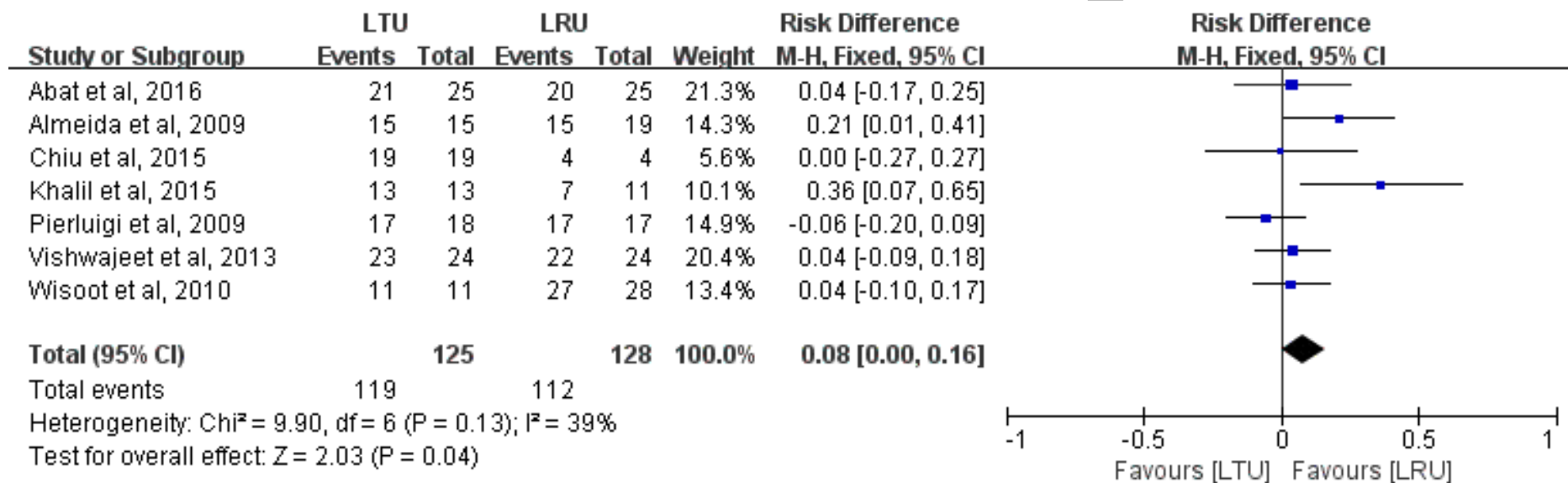


Figure 2. Forest plot of comparison: single-one procedure success rate.

Accepted

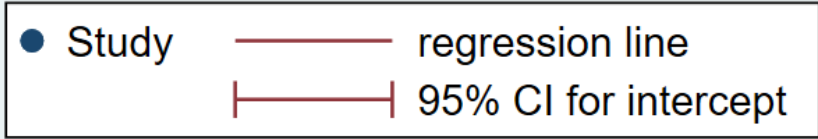
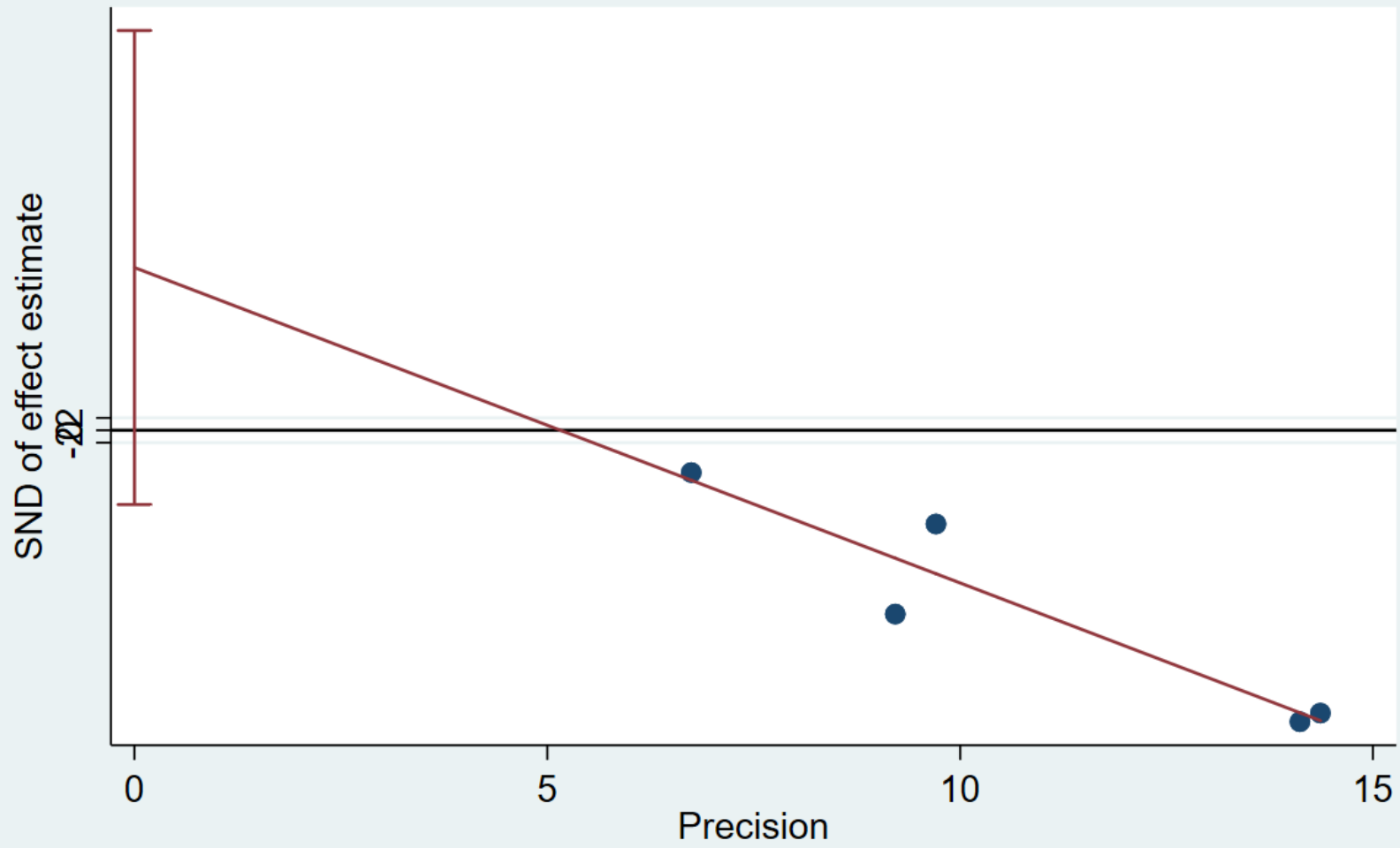


Figure 3. Eggers plot for the single-one procedure success rate.

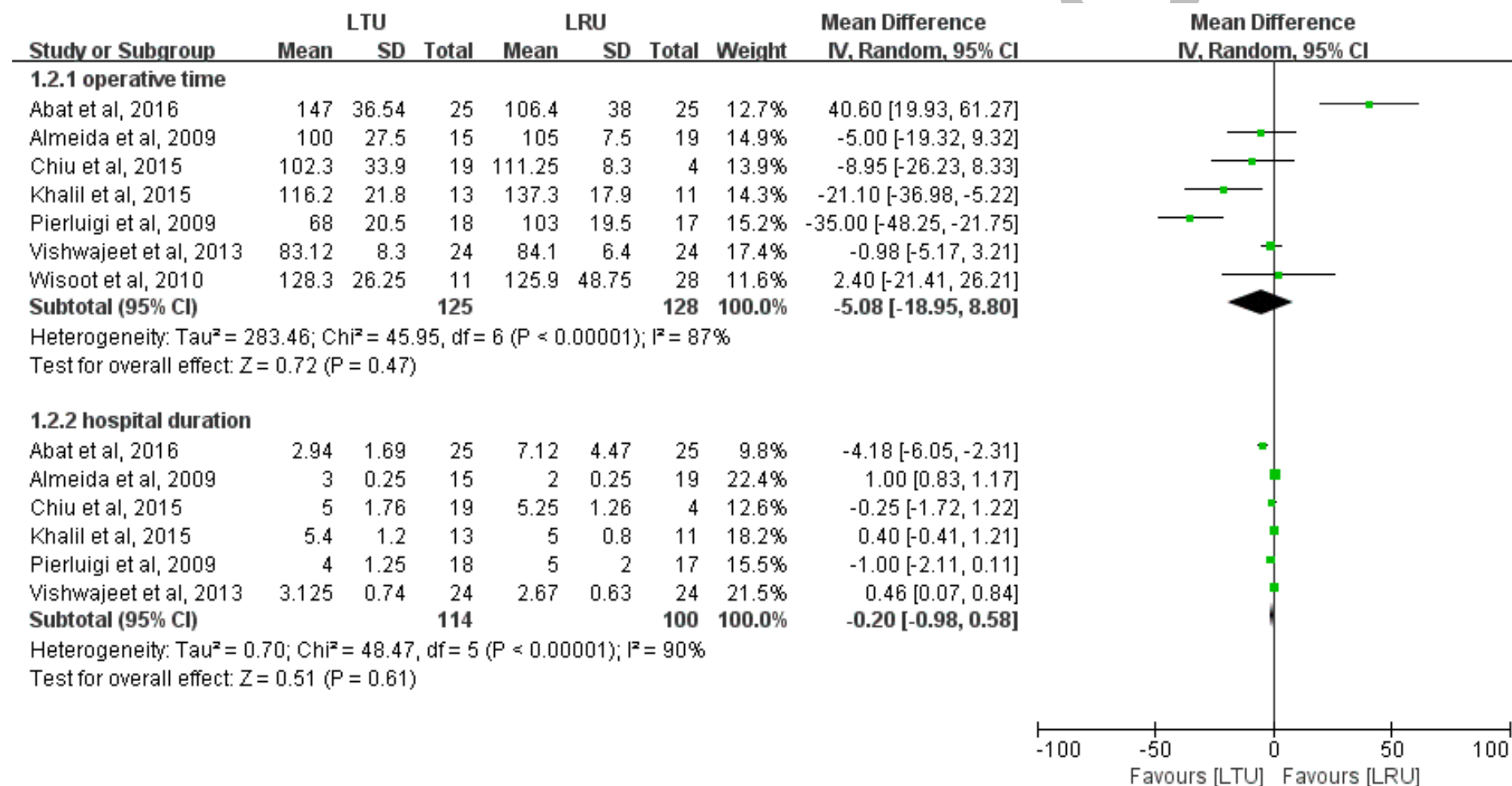


Figure 4. Forest plot of comparison: operative time and hospital duration.

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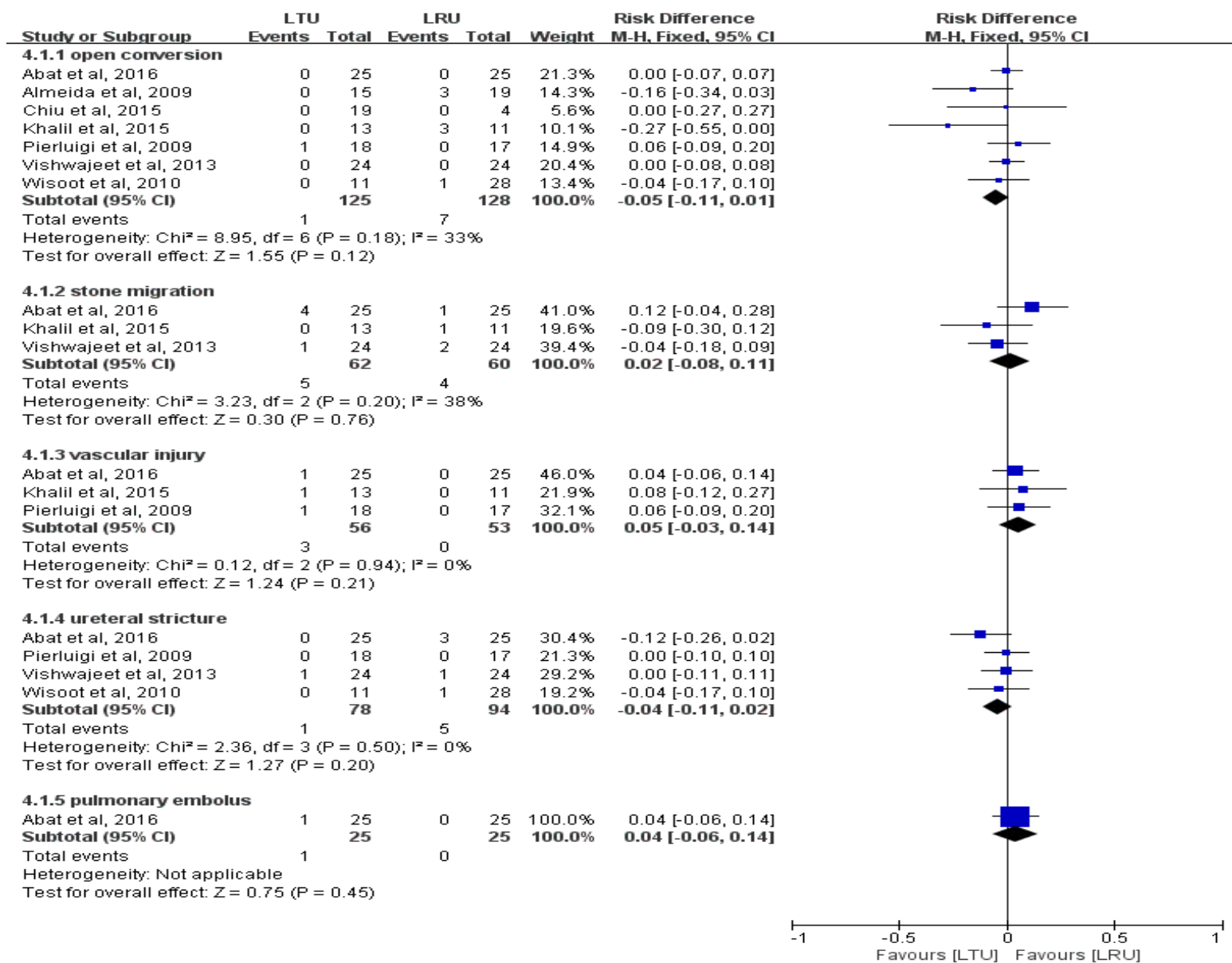




Figure 5. Forest plot of comparison: major complications.

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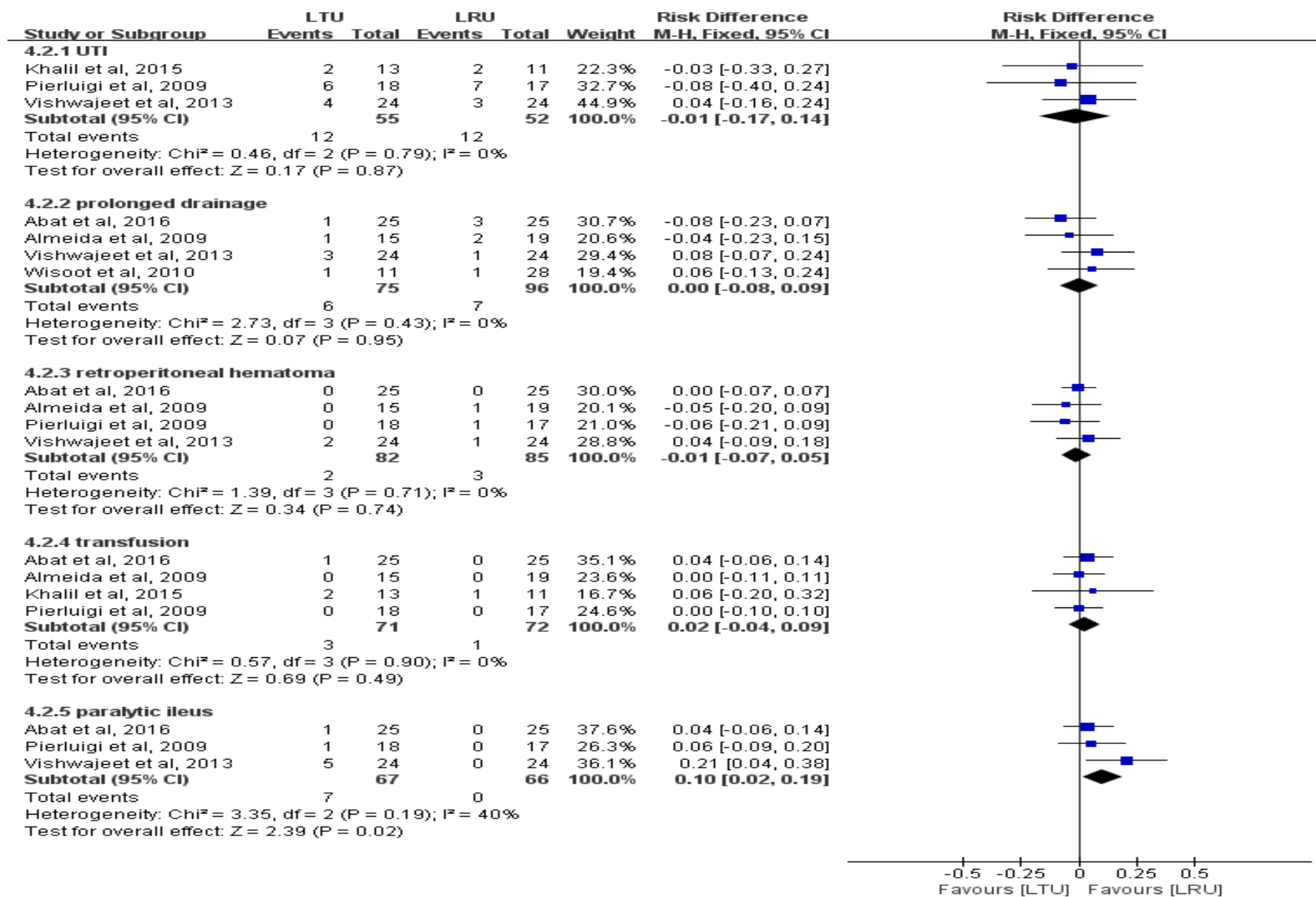


Figure 6. Forest plot of comparison: minor complications.

Accepted