A Comparison of Laparoscopic Enucleation with Preoperative Selective Arterial Embolization (SAE) and Non-SAE for Renal Angiomyolipoma: A Meta-Analysis

Jiaqi Kang
Tianjin Medical University General Hospital https://orcid.org/0000-0003-4191-854X
Yuxuan Song
Tianjin Medical University General Hospital
Shangren Wang
Tianjin Medical University General Hospital
Jia Tian
Tianjin Medical University General Hospital
Li Liu
Tianjin Medical University General Hospital
Xiaoqiang Liu (xiaoqiangliu1@163.com)
Tianjin Medical University General Hospital

Research

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Abstract

Background: To compare the outcomes of laparoscopic enucleation with preoperative selective arterial embolization (SAE) and non-SAE for renal angiomyolipoma (RAML), we performed this systematic review and meta-analysis.

Methods: We searched Web of Science, PubMed, EMBASE, the Cochrane Library, the Web of Science Core Collection, ClinicalTrials.gov, and China National Knowledge Infrastructure up to May 2019. Pooled relative ratio (RR) and standardized mean difference (SMD) with their 95% confidence intervals (CIs) were used to estimate the perioperative outcomes assessing the effectiveness and safety of laparoscopic enucleation with SAE and non-SAE.

Results: A total of 4 studies were incorporated. The results showed that SAE group had a shorter operative time (SMD -2.15, 95% CI: -2.85 to -1.46, P < 0.001) , less blood loss (SMD -1.77, 95% CI: -2.06 to -1.47, P < 0.001), shorter warm ischemia time (SMD -2.57, 95% CI: -3.04 to -2.10, P < 0.001), and lower postoperative complication rate (RR 0.29, 95% CI: 0.08 to 0.98, P = 0.047), compared with the Non-SAE group. However, there was no significant difference in length of stay after operation (SMD -0.82, 95% CI: -3.26 to 1.63, P = 0.512), postoperative serum creatinine (SMD -0.59, 95% CI: -1.35 to 0.18, P =0.133), and GFR (SMD 0.59, 95% CI: -0.15 to 1.32, P =0.116) between the two groups. Sensitivity analysis showed that the results of our meta-analysis were robust, and deleting anyone study had no significant effect on the pooled results.

Conclusions: Laparoscopic enucleation with preoperative SAE can shorten the operation time and warm ischemia time, decrease blood loss, preserve the renal function, and reduce the incidence of complications, which is a good option for the treatment of large RAMLs.

Introduction

As the most common benign solid tumor of the kidney, renal angiomyolipoma (RAML) is characterized by special histology, composed of blood vessels, smooth muscle, and adipose tissue [1]. RAML can be sporadic or occur with tuberous sclerosis complex (TSC) or lung lymphangioleiomyomatosis (LAM) [2]. The prevalence of AML is much more common than previously thought, and it is now estimated as being around 13 per 10,000 in the general population, with a female to male ratio of 2–4:1 [3]. The insidious growth of these tumors predisposes patients to some serious complications, such as retroperitoneal hemorrhage due to rupture, which can be life-threatening [2, 4]. The current view is that the criteria for intervention in cases of RAML have been asymptomatic sporadic lesions > 4 cm in size, suspected malignancy, and presence in females of childbearing age [5]. The main treatments for RAML include arterial embolization and surgical excision of the tumor [6].

With the progress made in the field of medical equipment and technology, laparoscopic enucleation has been ever more applied for the treatment of RAMLs. As one way of nephron-sparing surgery (NSS), it can achieve the complete resection of the tumor and saving the renal function to the greatest extent [7]. However, NSS would be challenging for large tumors, because the potential severe intra-operative bleeding could postpone the operation procedure and threaten patients' life. Therefore, some people believe that preoperative selective arterial embolization (SAE) of the large RAMLs should be adopted to avoid excessive bleeding during surgery [8]. Till now, whether laparoscopic tumor enucleation with preoperative SAE has advantages is still controversial.

As far as we know, there is still no systematic review and meta-analysis to make a comparison of laparoscopic enucleation with preoperative SAE and non-SAE for renal angiomyolipoma. Therefore, we conducted a literature search and meta-analysis to provide the best evidence for clinical practice.

Methods

Study Design

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement [9]. And the protocol has been registered in PROSPERO (CRD42019133969).

Search strategy

We searched for relevant clinical studies published before May 2019, in Web of Science, PubMed and EMBASE, the Cochrane Library, the Web of Science Core Collection, ClinicalTrials.gov, and China National Knowledge Infrastructure. The keywords used were as follows: selective arterial embolization, SAE, renal angiomyolipoma, and RAML without restrictions on sample size. The language was restricted to English and Chinese. We also conducted a manual search of the references of the relevant stAudies.

Inclusion and Exclusion Criteria

Eligible studies enrolled in this meta-analysis met the following criteria: (1) participants were diagnosed with sporadic RAML; (2) the study compared perioperative outcomes of preoperative SAE with laparoscopic enucleation; (3) prospective or retrospective cohort study. Exclusion criteria: (1) Studies with insufficient data to calculate the odds ratios (ORs) or weighted mean differences (WMDs) with 95% confidence intervals (CIs); (2) not the original article, such as review, case report, letter, and so on; (3) duplicated results from the same cohort.

Data Extraction and Quality Assessment

The two authors (Kang JQ and Song YX) extracted the data from included studies independently using a standardized form. If any disagreements arose, a third reviewer (Liu XQ) would be consulted to reach a consensus. For each enrolled study, the following items were collected: the first author's name, year of publication, ethnicity, study design, the number of participants, mean age, laparoscopic surgical approach, follow-up period, and related outcome data.

The quality of included studies was evaluated independently by two authors (Kang JQ and Tian J) according to the Newcastle–Ottawa Scale (NOS), which comprised three dimensions including selection, comparability, and outcomes [10]. A total score of 7-9 is defined as high quality, 4-6 is moderate quality, 1-3 is low quality.

Statistical Analysis

Relative ratio (RR) and standardized mean difference (SMD) with their 95% confidence intervals (CIs) were calculated for the related outcomes. The heterogeneity among the included studies was tested using the Higgins' I^2 statistic. A value of $I^2 < 50\%$ indicated a lack of heterogeneity. According to the results of the heterogeneity test, the random and the fixed effects model were performed when the heterogeneity was significant or not, respectively. Furthermore, a sensitivity analysis was carried out to determine the stability and effects of the pooled results by consecutively deleting one study at a time. In addition, Begg's funnel plots and Egger's test were used to assess the publication bias, and a significant bias was deemed to be present if the *P*-value is less than 0.05. All statistical tests for the meta-analysis were performed by Stata version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Literature search and Characteristics of studies

A total of 79 related articles were identified after database searching. And 46 articles were remained after excluding duplicated records. Of these, 18 were excluded by reading the title and abstract, and 28 studies were considered for full-text review. Since there were 15 case-only studies, 8 case reports, and 1 review excluded, 4 articles were finally included in the meta-analysis [11-14]. The selection process for studies was shown in Figure 1. The four studies were published recently (2016-2019) by Asian researchers. The sample size ranged from 36 to 163. And all included studies were cohort studies. The characteristics of the studies were summarized in Table 1. And all the included studies were high quality with NOS scores ranging from 8 to 9, which were shown in Table 2.

Perioperative outcomes

Operation time

The four studies compared the operation time between SAE and Non-SAE. We used the random-effects model due to a high heterogeneity (I^2 = 77.4%). The analysis result showed that the SAE group incurred a shorter operative time than the Non-SAE group (SMD -2.15, 95% CI: -2.85 to -1.46, $P < 0.001$) (Figure 2, and Table 3).

Blood loss

Similarly, four studies evaluated the blood loss of SAE and Non-SAE. We chose the fixed effects model because of an insignificant heterogeneity (I^2 =0.0%). The pooled result demonstrated that the SAE group had less blood loss than the Non-SAE group (SMD -1.77, 95% CI: -2.06 to -1.47, $P < 0.001$) (Figure 3, and Table 3).

Warm ischemia time

Only three studies were measuring the warm ischemia time of SAE and Non-SAE. The fixed-effects model was conducted because heterogeneity was not significant among the studies (I^2 =0.0%). Meta-analysis indicated that a significant decrease in the warm ischemia time in the SAE group compared with the Non-SAE group (SMD -2.57, 95% CI: -3.04 to -2.10, $P < 0.001$) (Figure 4, and Table 3).

Postoperative hospitalization

We examined the postoperative hospitalization from four studies. A random-effects model was adopted, as significant heterogeneity was observed (I^2 = 98.3%). However, there was no significant difference in length of stay after operation between the two groups (SMD -0.82, 95% CI: -3.26 to 1.63, $P = 0.512$) (Figure 5, and Table 3).

Serum creatinine and GFR

Only three studies reported the effects of two types of surgical methods on renal function. Unfortunately, no significant difference was observed between the two groups, neither serum creatinine (SMD -0.59, 95% CI: -1.35 to 0.18, P =0.133) nor GFR (SMD 0.59, 95% CI: -0.15 to 1.32, P =0.116) (Figure 6, and Table 3).

Postoperative complications

All four studies reported postoperative complications. We performed a meta-analysis using a fixed-effects model and found the SAE group had a lower incidence of postoperative complications compared to the Non-SAE group (RR 0.29, 95% CI: 0.08 to 0.98, $P = 0.047$) (Figure 7, and Table 3). In addition, there was no significant difference between the two groups in some of the specific complications, such as pleural injury, retroperitoneal hematoma, hematuria, urine leakage, incision infection, and embolization again to stop bleeding (Table 4).

Sensitivity analysis

We conducted a sensitivity analysis for outcomes with high heterogeneity, including operation time, postoperative hospitalization, serum creatinine, and GFR. Sensitivity analysis showed that the results of our meta-analysis were robust, and deleting any study had no significant effect on the pooled results (Figure 8).

Discussion

The overall goal of a meta-analysis is to combine the results of previous studies to draw a summary conclusion about a subject of research. In this study, we analyzed the outcomes of laparoscopic enucleation with preoperative SAE and non-SAE for RAML using a meta-analysis to obtain a powerful conclusion. The findings of our meta-analysis demonstrated that preoperative SAE can shorten operation time (SMD − 2.15, 95% CI: -2.85 to -1.46, $P < 0.001$) and warm ischemia time (SMD − 2.57, 95% CI: -3.04 to -2.10, $P < 0.001$), and reduce blood loss (SMD − 1.77, 95% CI: -2.06 to -1.47, $P < 0.001$) and postoperative complication (RR 0.29, 95% CI: 0.08 to 0.98, $P = 0.047$) in laparoscopic enucleation for RAML, compared with Non-SAE group. However, SAE didn't shorten postoperative hospitalization (SMD − 0.82, 95% CI: -3.26 to 1.63, $P = 0.512$), and improve renal function, including serum creatinine (SMD − 0.59, 95% CI: -1.35 to 0.18, $P = 0.133$) and GFR (SMD 0.59, 95% CI: -0.15 to 1.32, $P = 0.116$). As far as we know, this is the first meta-analysis providing comprehensive insights into the effects of the preoperative SAE on perioperative outcomes of laparoscopic nephron-sparing surgery for renal angiomyolipoma.

As a first-line management option for RAMLs, SAE was recommended in cases of acute hemorrhage and refractory hemodynamic instability. In 2015, Murray et al performed a systematic review of trans-arterial embolization for RAMLs and reported a high technical success of 93.3% and a mean reduction in tumor size of 3.4 cm [15]. Lin et al reported SAE of RAMLs affected renal function preservation, and had a low complication rate, with a mean reduction in the size of 2.09 cm after meta-analyzing 30 studies [16]. Sun et al conducted a real-world study to compare embolization and nephrectomy for renal RAMLs associated with TSC, and embolization was effective, with a reduction in gross hematuria (− 27.7%), retroperitoneal hemorrhage (− 8.4%), and abdominal mass (− 6.9%) [17]. Anis et al assessed long-term outcomes after SAE as first-line treatment for large or symptomatic AML and found SAE was a safe procedure that was associated with freedom from surgery and CKD of 94% and 92.4%, respectively at 10 years post-procedure [3]. However, as reported by most studies, SAE's role in reducing tumor volume is limited. Most RAMLs have shrunk by only 20%-30% after successful embolization[18–20], and showed a high re-embolization rate (41.1%) [3]. Embolization is effective in controlling severe spontaneous hemorrhage in the acute phase, but be of limited value in treating large RAMLs in the long run [21].

Therefore, surgical treatment is an essential option for RAML. And NSS is advocated as preferred management in patients with symptomatic or large tumors due to a high risk of hemorrhage [5, 22, 23]. However, partial nephrectomy may be dangerous when the tumor is too large. Therefore, some people began to explore the feasibility of SAE used before partial nephrectomy to improve perioperative outcomes. Yeniyol reported a patient with life-threatening hamartoma [24]. They successfully performed nephrectomy five days after selective arterial embolization and no complications were observed. Although the author finally removed the entire kidney, preoperative embolization played a role in reducing the difficulty of the operation. Hoshii reported a 38-year-old female without TSC was diagnosed with a right RAML of 10 cm in diameter [25]. She experienced laparoscopic retroperitoneal NSS without renal artery clamping with preoperative SAE to avoid a significant risk of hemorrhage and the damage of the renal function during NSS. The time taken to accomplish the procedure was 4 hours 11 minutes, with 780mL blood loss. Taiwanese scholars conducted a comparative study of large RAML with or without SAE before partial nephrectomy and found TAE before partial nephrectomy had shorter WIT, decreased intra-operation blood loss, shorter length of stay, and fewer residual tumor than those did not performed TAE [26]. However, it was not included in our meta-analysis, because it was a meeting abstract. Combined with the results of our meta-analysis, it was not difficult to admit that preoperative SAE can shorten the operation time and reduce the amount of intraoperative blood loss, thereby making the operation easier to succeed for large RAMLs. However, Coskuner reported on a patient with a 24 cm AML of the right kidney who successfully underwent nephrectomy without arterial embolization [27]. Warm ischemia time was 35 min and intraoperative bleeding volume was 200cc. Most studies on this topic are case reports, which affect the level of evidence. Multi-center research can expand the sample size and obtain more reliable results, which is worthy of recommendation.

Warm ischemia time was recognized as a crucial factor governing early renal function after partial nephrectomy. Thompson et al reported > 20 min of warm ischemia was an important predictor of adverse renal outcomes, and each additional minute was associated with a 5% and 6% increased odds of developing acute renal failure (ARF) or a GFR < 15 ml/min per 1.73 m^2 in the postoperative period, respectively, and was associated with a 6% increased risk of new-onset stage IV chronic kidney disease during follow-up [28]. With the help of SAE, the clear operative vision enables the surgeon to finish the operation in a shorter time. Surgery could be completed without clamping the renal artery if the tumor's blood supply was blocked by SAE. Thus, our study found the preoperative SAE reduced the warm ischemia time of the operation, but no difference was observed in the postoperative renal function. A review of the literature suggests there is little or no significant deterioration in the mean GFR after selective embolization is performed [29]. Another point to consider is that the studies included in this meta-analysis all observed the renal function of patients in the relatively early postoperative period (6 months after surgery). Numerous factors can influence renal function after surgery, and long-term observation is needed to get more reliable conclusions.

In terms of surgical complications, this analysis demonstrated that preoperative SAE combined with laparoscopic partial nephrectomy reduced the surgical complication rate. While, some of the specific complications such as pleural injury, retroperitoneal hematoma, hematuria, urine leakage, incision infection, and re-embolization to stop bleeding were not significantly different between the two groups. The lack of statistical significance might be explained by the low sample size. For example, only two patients developed hematuria, urine leakage, and incision infection in the Non-SAE group, but none in the SAE group. Urine leakage is a serious complication after partial nephrectomy, which can be caused by unclear boundaries and excessive resection of the renal parenchyma. Preoperative SAE can reduce blood loss and make the surgical field clear, which enables the surgeon to separate the tumor from normal renal parenchyma and avoid damaging the renal parenchyma. Due to the limitation in sample size, larger sample cohorts are still needed to observe surgical safety.

However, some limitations in the present meta-analysis should be mentioned. The major limitation is the small number of eligible studies and sample size. We only enrolled in four observational studies. In addition, heterogeneities existed in some outcomes of our study, and the reasons for heterogeneities were complicated. Heterogeneity may be attributed to different patient characteristics, study designs, and sample sizes. Furthermore, all four studies were from Asia, which might bring a certain selection bias to our meta-analysis.

Conclusions

Based on the present study, laparoscopic enucleation combined with preoperative SAE can shorten the operation time and warm ischemia time, decrease blood loss, preserve the renal function, and reduce the incidence of complications, which is a good option for the treatment of large RAMLs. Additional studies with larger sample sizes are needed to confirm these findings.

Abbreviations

RAML: renal angiomyolipoma; TSC: tuberous sclerosis complex; LAM: lymphangioleiomyomatosis; NSS: nephron-sparing surgery; SAE: selective arterial embolization; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis; PROSPERO: International Prospective Register of Systematic Reviews; ORs: odds ratios; WMDs: weighted mean differences; CIs: confidence intervals; NOS: Newcastle–Ottawa Scale; RR: Relative ratio; SMD: standardized mean difference; GFR: Glomerular filtration rate; CKD: chronic kidney disease; ARF: acute renal failure.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

JQK, YXS, and XQL conceived and designed the project. JQK, YXS, and YL analyzed and interpreted the data. JQK, YXS, and JT wrote the paper. All the authors have read and approved the final version of the manuscript and participated in acquiring the data.

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Tables

Table 1 Characteristics of studies included in the meta-analysis.

Author	Year	Ethnicity	Study Design	Sample size	SAE group			Non-SAE group		
					No. Case	Age	Tumor size	No. Case	Age	Tumor size
Chao Qin	2017	Asian	retrospective cohort study	36	16	42.1±6.69	8.49±0.95	20	42.4±9.08	8.54±1.25
Dong Wang	2017	Asian	prospective cohort study	43	19	38.4±12.3	5.4(4.3-7.1)	24	43.1±13.7	5.7(4.1-7.7)
Yihang Luo	2019	Asian	prospective cohort study	163	33	44±16	4.8±1.1	130	47±15	6.1±2.3
Mingen Lin	2016	Asian	retrospective cohort study	52	22	46.35±4.56	5.56±0.53	30	48.02±5.21)	5.71±0.45

Table 2 The Newcastle-Ottawa Scale scores for cohort studies

Author	Year	Selection				Comparability	Outcomes			Total scores
		Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study		Assessment of outcome	Follow-up long enough	Adequacy of follow-up	
Chao Qin	2017	1	1	1	0	2	1	1	1	8
Dong Wang	2017	1	1	1	1	2	1	1	1	9
Yihang Luo	2019	1	1	1	1	2	1	1	1	9
Mingen Lin	2016	1	1	1	0	2	1	1	1	8

Table3 Meta-analysis results of laparoscopic enucleation with preoperative SAE and Non-SAE for renal angiomyolipoma

Outcones	No. Study	Effects model	SMD or RR(95% CI)	*P*(z test)	Heterogeneity (*I*2, %)	*P*(Begg's test)
Operation time	4	Random model	-2.15(-2.85,-1.46)	0.000	77.4	0.812
Blood loss	4	Fixed model	-1.77(-2.06,-1.47)	0.000	0.0	0.025
Warm ischemia time	3	Fixed model	-2.57(-3.04,-2.10)	0.000	0.0	0.644
Postoperative hospitalization	4	Random model	-0.82(-3.26,1.63)	0.512	98.3	0.823
Serum creatinine	3	Random model	-0.59(-1.35,0.18)	0.133	84.2	0.060
GFR	3	Random model	0.59(-0.15,1.32)	0.116	75.5	0.050
Postoperative complication	4	Fixed model	0.29(0.08,0.98)	0.047	0.0	0.080

Table 4 Comparison of the specific complications between SAE and Non-SAE group.

Complications	No. Study	Sample size		RR (95%CI)	P	I^2(%)
		SAE	Non-SAE			
Pleural injury	2	41	54	3.89(0.42-36.11)	0.232	0
Retroperitoneal hematoma	4	90	204	0.35(0.07-1.65)	0.185	0
Hematuria	1	16	20	0.25(0.01-4.81)	0.356	-
Urine leakage	2	38	50	0.43(0.05-3.97)	0.457	0
Incision infection	2	38	50	0.43(0.05-3.97)	0.457	0
Embolization again to stop bleeding	1	33	130	0.55(0.03-10.40)	0.691	-

Figures

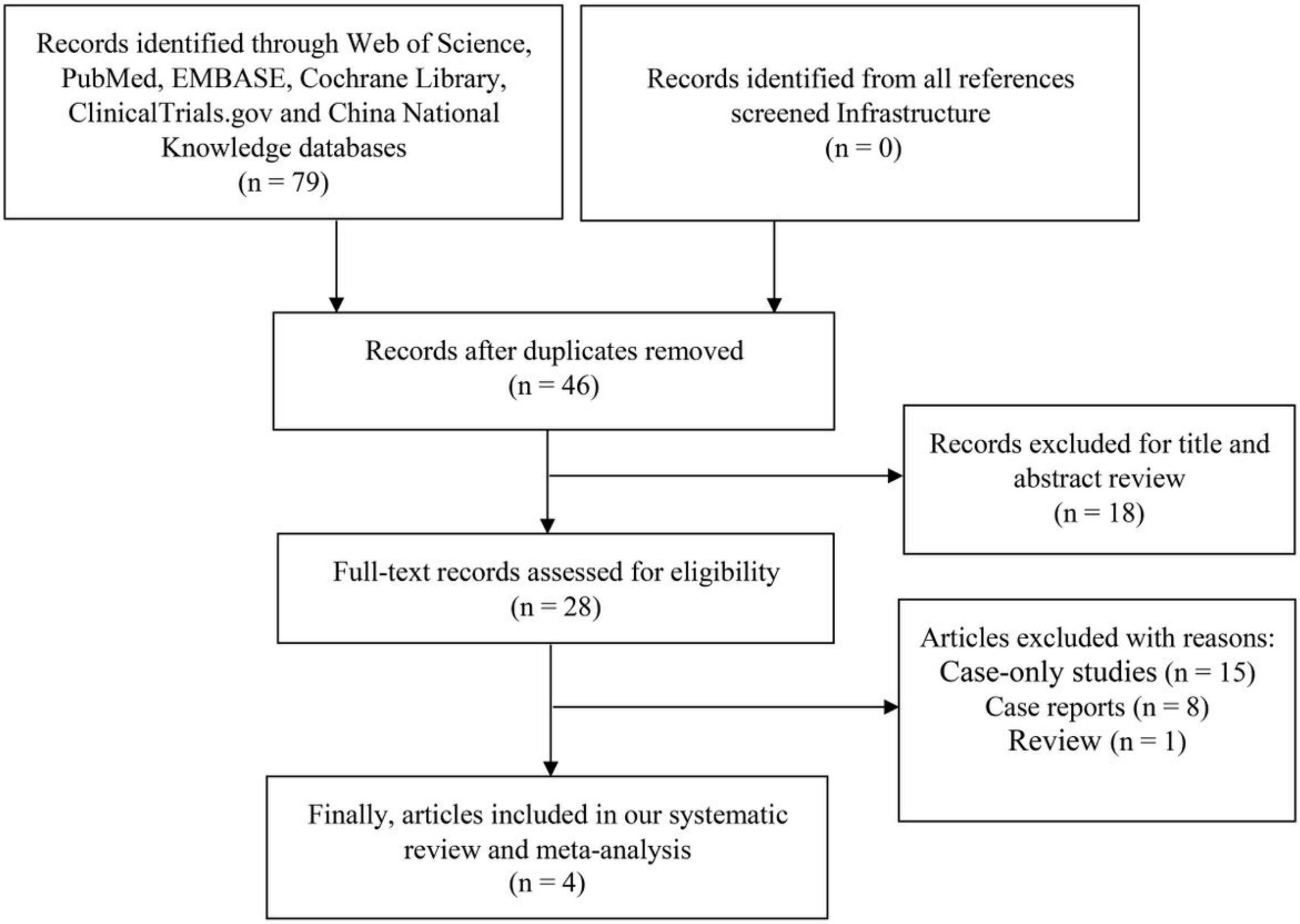


Figure 1

Flow chart of literature selection

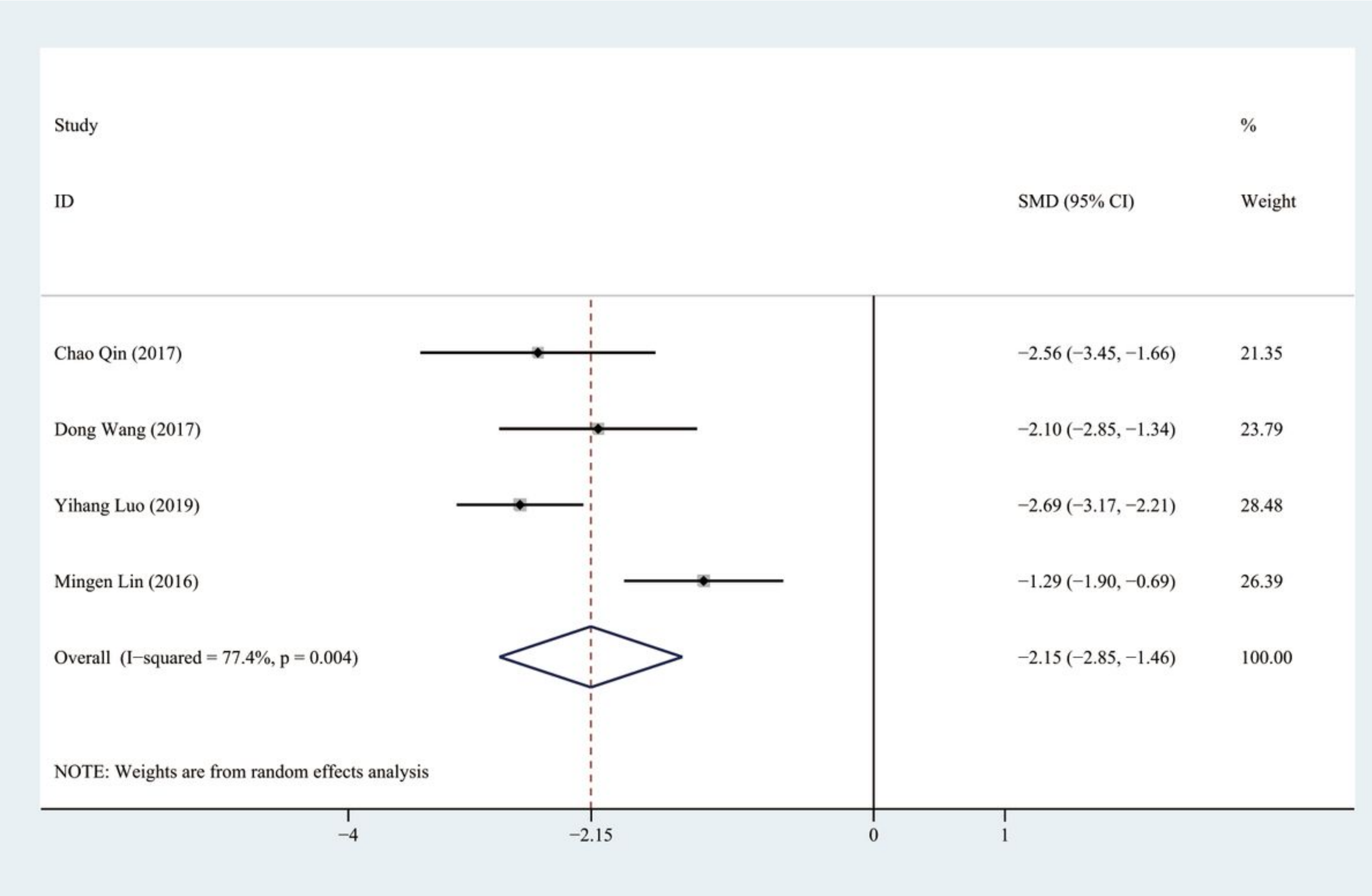


Figure 2

Forest plot comparing Operation time for SAE versus Non-SAE

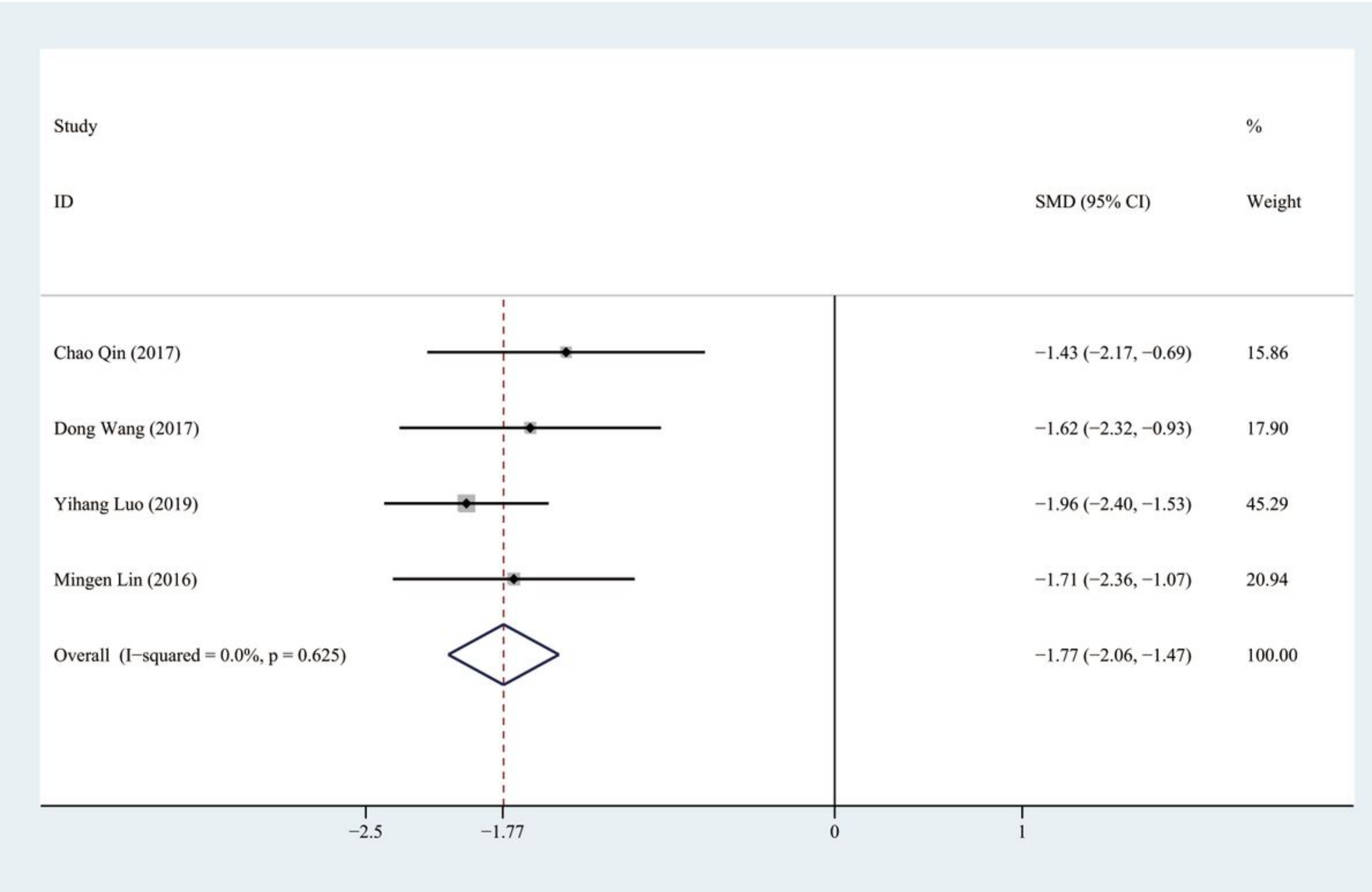


Figure 3

Forest plot comparing Blood loss for SAE versus Non-SAE

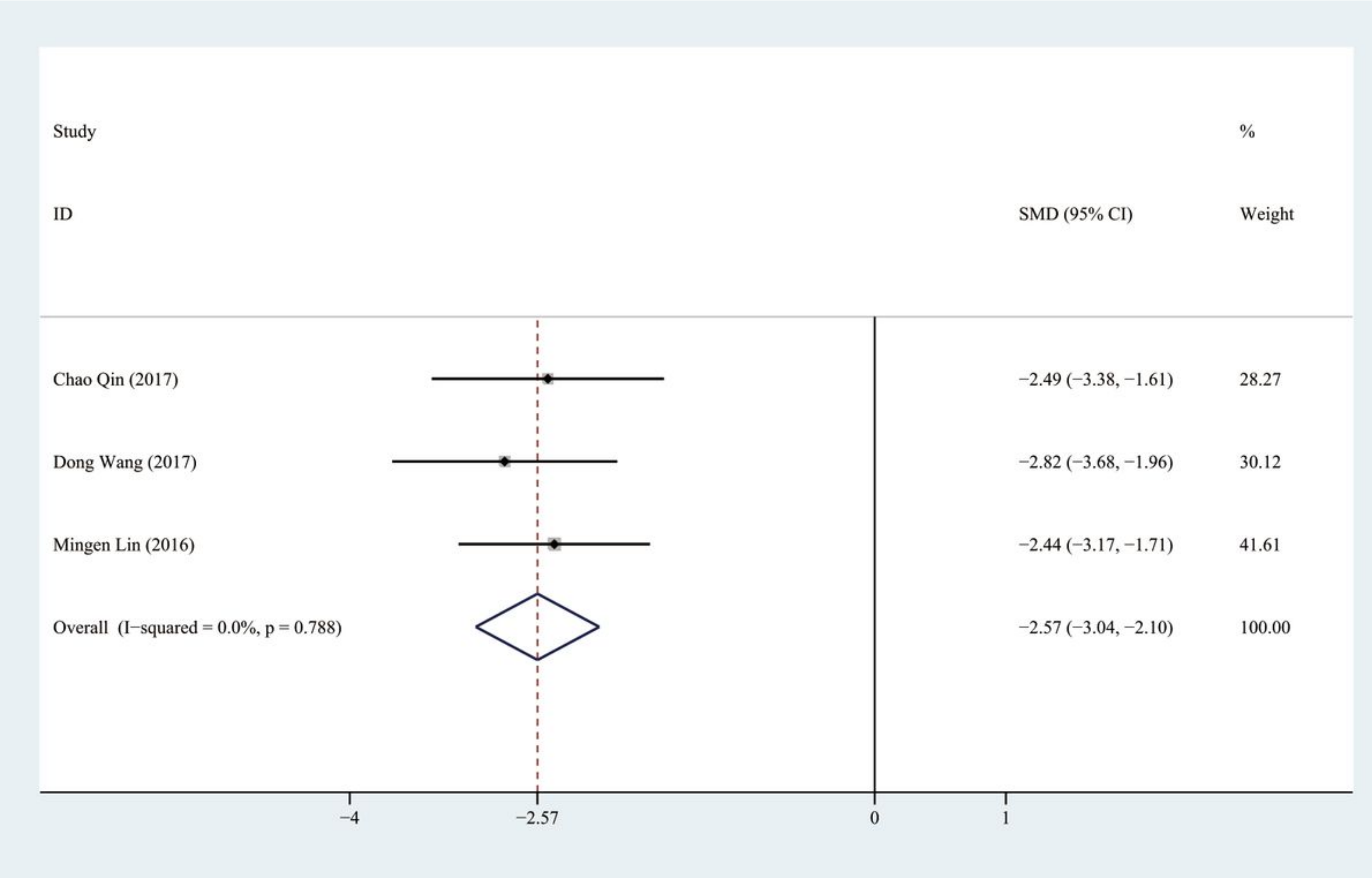


Figure 4

Forest plot comparing warm ischemia time for SAE versus Non-SAE

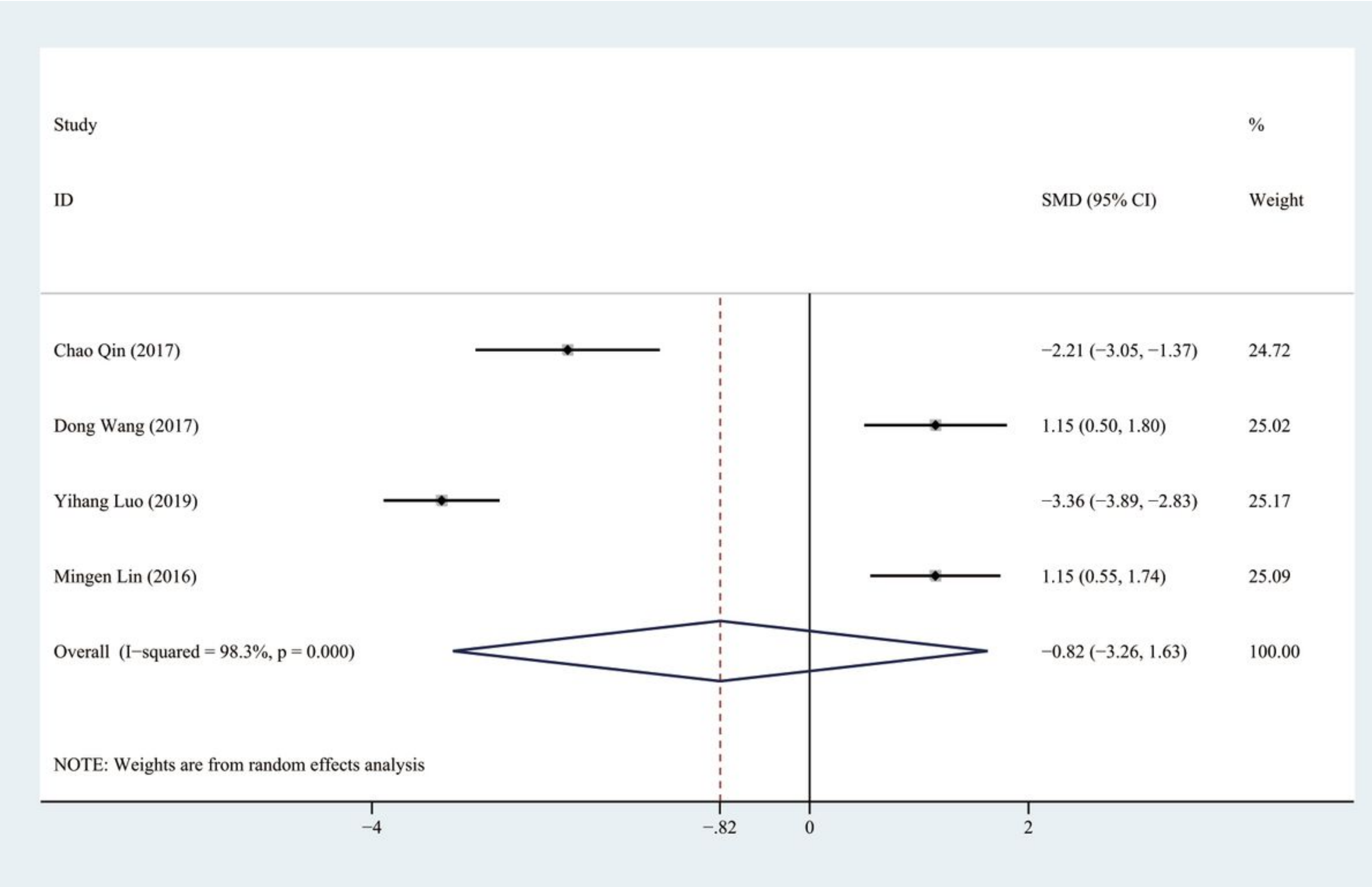
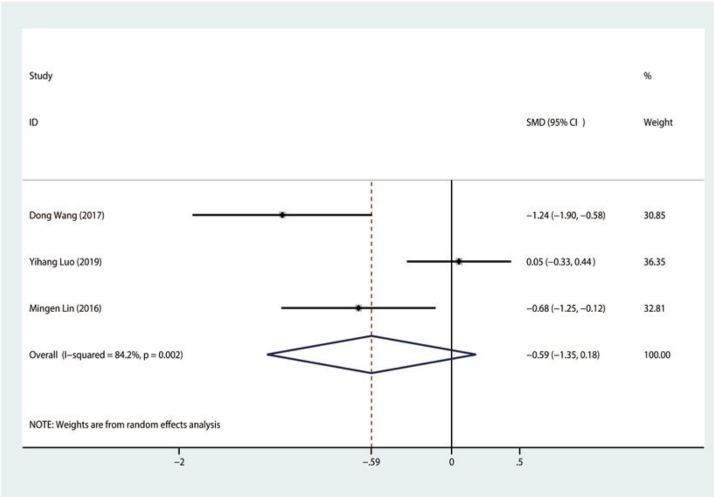


Figure 5

Forest plot comparing Postoperative hospitalization for SAE versus Non-SAE

(a)



(b)

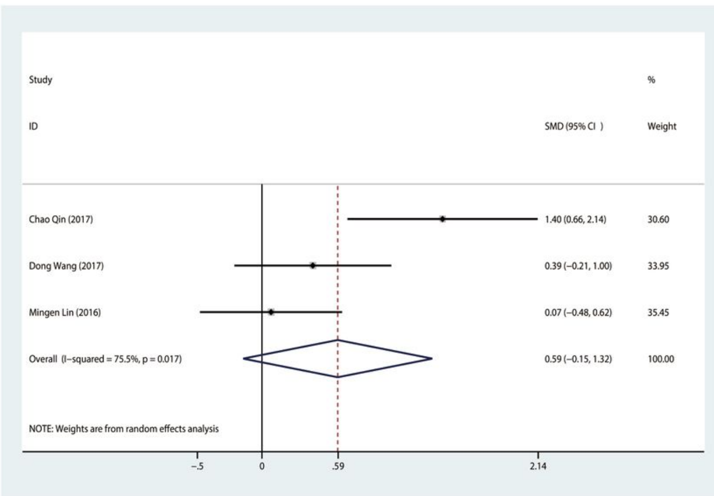


Figure 6

Forest plot comparing serum creatinine (a) and GFR (b) for SAE versus Non-SAE

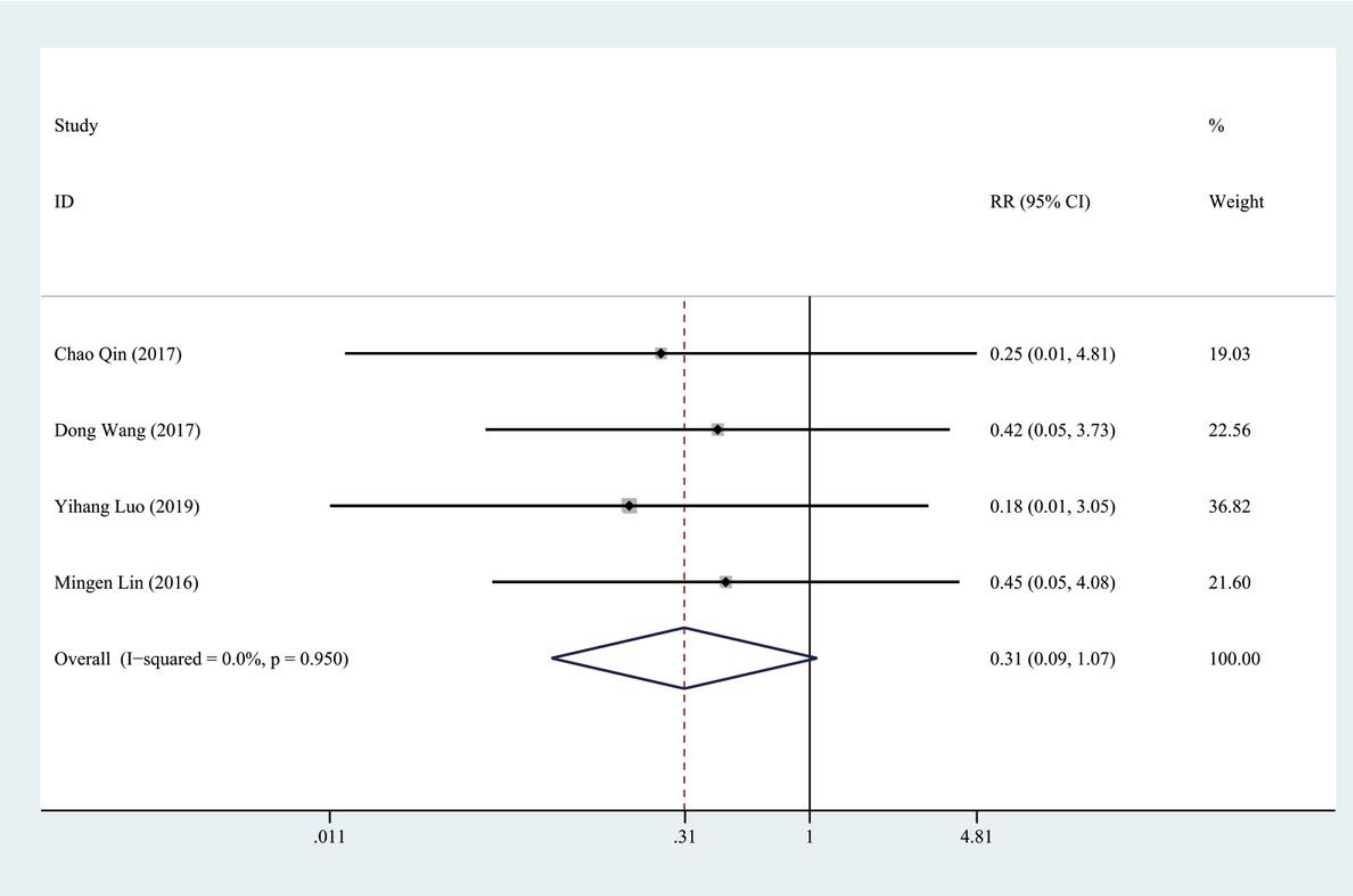


Figure 7

Forest plot comparing Postoperative complication for SAE versus Non-SAE

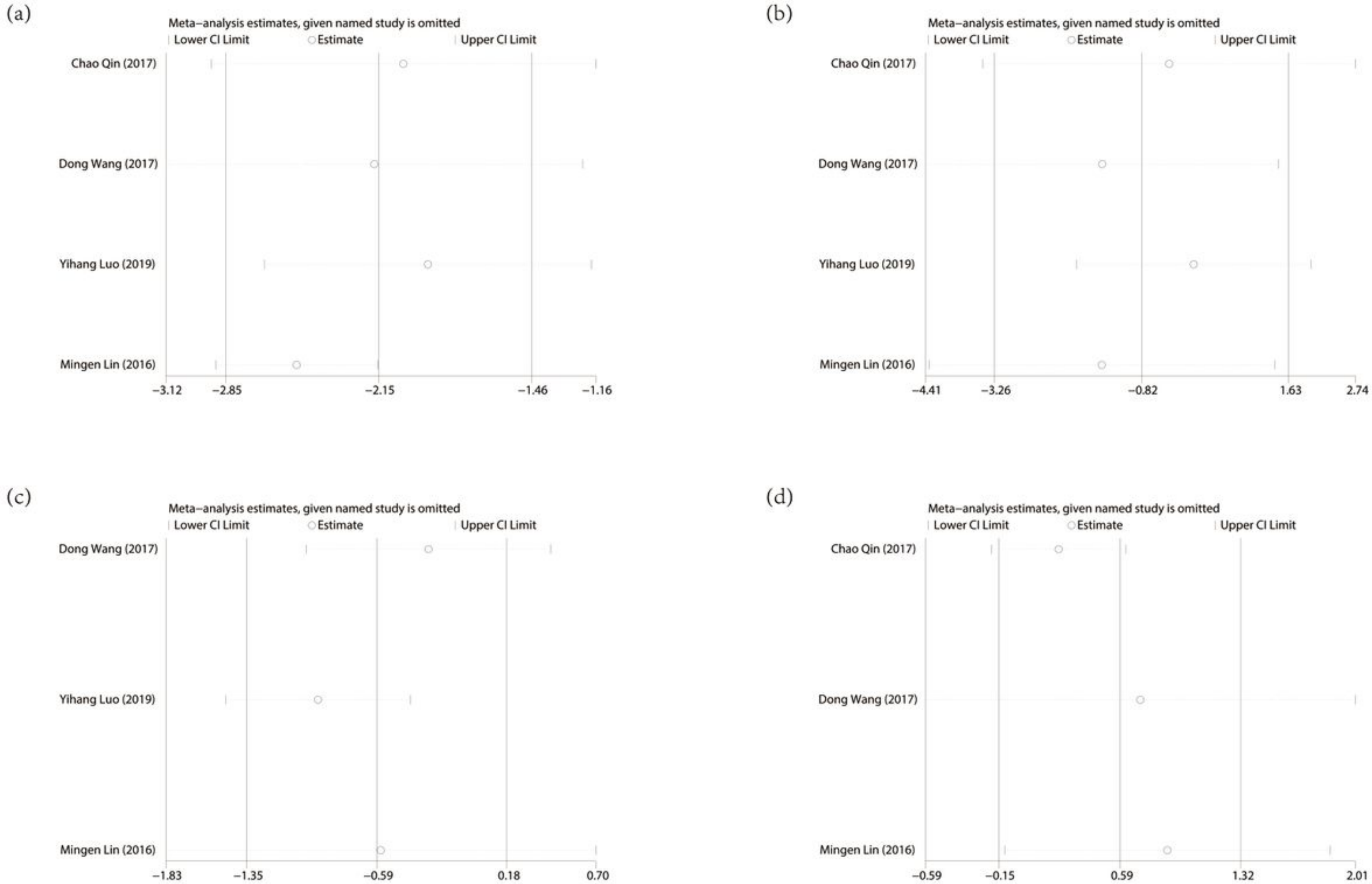


Figure 8

Sensitivity analysis for including operation time (a), postoperative hospitalization (b), serum creatinine (c), and GFR (d)