Endovascular Coiling versus Microsurgical Clipping for Ruptured Intracranial Aneurysms: A Meta-Analysis and Systematic Review.

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Abstract

Objectives: The purpose of this analysis is to evaluate the current evidence with regard to efficiency and safety between coiling and clipping in patients with ruptured intracranial aneurysms (RIAs).

Methods: We performed a meta-analysis that compared clipping with coiling between July 2000 and September 2019. PubMed, EMBASE, and the Cochrane Library were searched for related articles systematically.

Results: We identified three randomized controlled trials and thirteen-six observational studies involving 60217 patients with ruptured cerebral aneurysms. The summary results showed that coiling was related a better quality of life (mRS0-2; OR=1.462; CI=1.2375-1.676; P=0.000), a higher risk of mortality (OR=1.116; CI=1.054-1.180; P=0.000), higher rate of rebleeding (RR=1.410; CI=1.092-1.822; P=0.000), lower incidence of vasospasm (OR=0.787; CI=0.649-0.954; P=0.015), lower risk of hydrocephaly (RR=1.143; CI=1.043-1.252; P=0.004), lower risk of cerebral infarction (RR=0.669; CI=0.596-0.751; P=0.000), lower risk of neuro deficits(RR=0.720; CI=0.582-0.892; P=0.003), lower pulmonary complications(RR=0.456; CI=0.232-0.896; P=0.023), and shorter length of stay in hospital and ICU(WMD=-2.290; CI=-3.423–1.157; P=0.000, SMD=-0.346; CI=-0.459–0.234; P=0.000, respectively), a lower rate of complete occlusion(OR=0.495; CI=0.280-0.876; P=0.016). There were no significant difference with regard to the result of GOS (4-5) and the incidence of seizure, intracranial infection.

Conclusion: Coiling was significantly associated with a better life quality (mRS0-2), a lower incidence of postoperative complications (vasospasm, hydrocephaly, cerebral infarction, neuro deficits, pulmonary complications), and a higher rate of mortality, rebleeding than clipping. What's more, coiling was associated with a lower rate of complete occlusion. There was no significant difference about seizure and intracranial infection and the result of GOS (4-5) between the two groups.

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is account for 80% of cases of nontraumatic subarachnoid hemorrhage (SAH)[1], contributing to significant mortality. There are two procedures for treatment of aSAH: microsurgical clipping and endovascular coiling[2]. The first clipping operation was published by Walter Dandy in 1937[3]. In 1991, the Guglielmi detachable coil for coiling was found, putting a platinum coil into a cerebral aneurysm[4]. The treatment methods are aimed to occlude the aneurysm so that reduce the risk of rebleeding. Given this purpose, clipping and coiling are both effective, although there remain controversial with regard to which treatment strategies is better for patients with aSAH.

Until 2002, the International Subarachnoid Aneurysm Trial (ISAT) demonstrated that individuals underwent coiling were associated with a less morbidity and mortality at 1-year follow-up compared with clipping[5]. This finding contributed to endovascular coiling had been widely accepted becoming the preferred strategy of treatment at many centers[6]. However, results of ISAT also caused some criticism, such as 7416 of the 9559 patients with ruptured intracranial aneurysms (RIAs) were excluded, the location and type of intracranial aneurysms (IAs) as well as types of recruiting centers were widely different, the proficiencies of performer of coiling and clipping were varied[5, 7].

In recent years, some randomized controlled trials (RCTs) and retrospective comparative studies and prospective studies have also been published, some results of these publications were different from ISAT[8]. As a result, there remain some debate about the choice of coiling and clipping for patients with aSAH, while it is the aim of this meta-analysis and systematic review to evaluate the two treatments efficiency, complications, length of stay from a great deal of evidence containing RCTs and observational studies to provide a guiding strategy in selecting which treatment methods to perform in patients with aSAH.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses, PRISMA[9], was used for this Meta-analysis guidelines.

Systematic Literature Search

We searched all literatures with regard to the comparison between coiling and clipping for ruptured intracranial aneurysms (RIAs) through PubMed, Medline, EMBASE, and Cochrane Library databases systematically and comprehensively. The date of these studies was ranged from 2000 to 2019. The search strategies were conducted using "ruptured intracranial aneurysms", "coiling", "clipping", as

our search terms and keywords. A manual search for literatures that referenced by other publications but met our inclusion criteria was conducted as a supplement. We would use the most current literature, when a study produced multiple papers.

Inclusion and Exclusion Criteria

Literatures were included if they met the PICOS criteria: 1. Population: limited the comparison to the RIAs individuals; 2. Intervention: used coiling and clipping; 3. Comparison: compared the results after coiling and clipping; 4. Outcome measures: the results after treatment and the follow-up; 5. an official published RCTs or non-RCT

The exclusion criteria were as follows: 1. Letters to editor and commentary or conference articles and; 2. Animal trials; 3. Unclear patient outcome data; 4. Case reports and case series; 5. Systematic reviews or meta-analyses; 6. Other types of IAs, such as trauma.

Selection and Data Extraction

The data were extracted independently by two observers, C Peng, SF Cai, YH Diao, containing basic data (author, publication time, age), study characteristics (trial type), and outcomes (rebleeding; mortality; complete occlusion, complications of postoperative; length of hospital stay and length of stay in intensive care unit(ICU)) in a table. The senior investigator (YY Yang) would review the data for completeness and accuracy.

Statistical Analyses and Quality Assessment

The results of this study were analyzed by standard software (Stata version 12.0 statistical software). For categorical variable results, risk ration (RR) or odds ratios (ORs) with 95% confidence intervals (CIs) were tested for results assessment. When I^2 50%, the data was treated as obvious heterogeneity; therefore, a meta-analysis was preformed using random effect model. Otherwise, the fixed effect model was conducted. For continuous variable results, standard mean difference (SMD) or weighted mean difference (WMD) with 95% CIs were calculated for assessment. When I^2 50%, the data was treated as obvious heterogeneity, and the data analysis was conducted by random effect model. Otherwise, the fixed effect model was conducted. The quality of the RCTs literatures were assessed by Cochrane Collaboration's tool and the Newcastle-Ottawa scale were used to evaluate the quality of the observational studies.

Result

Search results and study characteristics

Initially, 515 literatures were found by searching electronic database, 17 articles were identified by manual search. And there were 522 articles after duplicates removed. 412 publications were deleted by preliminary screening, Ultimately, 39 articles met the inclusion criteria and were included in this meta analysis. The details were shown in the flow chart (Figure 15). There were 3 RCTs and 36 observational studies[10-36],[7, 37-47]. A total of 60217 patients were included and the size of sample ranged from 32 to 21905, 31462 patients were treated by coiling, 28755 individuals performed by clipping, other information was shown in Table 2.

Quality of Included Studies

The article quality assessment was conducted separately by three reviewers, C Peng, YH Diao, SF Cai. 23 observational studies were assessed by the Newcastle-Ottawa scale, the Cochrane Risk of Bias Tool was used to assess the quality of the 4 RCTs. And the results were showed in Table 1.

Synthesis of Results Table 3

Efficiency of treatment

Modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS)

The GOS and mRS were used in this article to assess the quality of life. There were 10 articles, 4106 patients, included the result of mRS. 10 literatures,1867 patients, included GOS result. 73.6% of patients in coiling group and 66.2% patients in clipping group had quality of life defined as mRS0-2. And there was statistical significance in the results of mRS0-2 (coiling1478 of 2007 (73.6%) VS clipping1390 of 2099 (66.2%); OR=1.462; CI=1.2375-1.676; P=0.000; I^2=0.0%; Figure1). And 74.4% and 67.8% of patients had good

quality of life (GOS4-5) in coiling and clipping group, respectively. However, there was not significantly difference in the two groups (OR=0.700; CI=0.474-1.035; P=0.074; I^2=53.4%; Figure2).

Rebleeding

Fourteen articles included a total of 4659 patients with RIAs provided the rate of rebleeding after clipping or coiling. There was higher postoperative rebleeding in coiling group than clipping group. And it was associated with statistical significance (coiling128 of 2232(5.7%) VS clipping103 of 2427(4.2%); RR=1.410; CI=1.092-1.822; P=0.000; I^2=10.6%; Figure3).

Mortality

Twenty-one literatures encompassing the rate of mortality after coiling or clipping among 44909 patients with RIAs. Coiling had a significant effect on the risk of mortality compared with clipping (coiling3847 of 25268(15.2%) VS clipping2955 of 19641(15.0%); OR=1.116; CI=1.054-1.180; P=0.000; I^2=36.9%; Figure4).

Complete occlusion

Eight studies included the result of complete occlusion among 2730 patients with RIAs. There was a higher rate of occlusion in clipping group than coiling group with a statistical significance (coiling 992 of 1562 (63.5%) VS clipping 898 of 1168 (76.9%); OR=0.495; CI=0.280-0.876; P=0.016; I^2=87.5%; Figure5).

Postoperative complications

Vasospasm

Thirteen publications included a total of 2857 patients with RIAs provided the result of vasospasm after clipping or coiling. There was a less postoperative vasospasm in coiling group than clipping group with a statistical significance (coiling 241 of 1177 (20.5%) VS clipping 416 of 1680 (24.8%); OR=0.787; CI=0.649-0.954; P=0.015; I^2=41.1%; Figure6).

Hydrocephaly

Nine literatures contained the result of hydrocephaly after treatment among 3856 patients with RIAs. Coiling had a significant effect on the postoperative hydrocephaly compared with clipping (coiling 611 of 1819 (50.6%) VS clipping 581 of 2037 (39.9%); RR=1.143; CI=1.043-1.252; P=0.004; I^2=30.7%; Figure7).

Seizure

Eight articles contained the result of seizure after coiling and clipping among 14232 patients with RIAs. Clipping had a significant effect on the postoperative seizure compared with coiling (coiling 502 of 5926 (8.5%) VS clipping 774 of 8306 (9.3%); RR=0.541; CI=0.291-1.006; P=0.052; I^2=64.1%; Figure8).

Cerebral infarction

There sixteen articles concluded the result of ischemic infarct after coiling or clipping among 5423 patients. Coiling had a lower postoperative ischemic infarct than clipping with statistical significance (coiling 375 of 2598 (14.4%) VS clipping 597 of 2825 (21.1%); RR=0.669; CI=0.596-0.751; P=0.000; I^2=18.9%; Figure9).

Postoperative neuro deficits

There five articles concluded the result of Neuro complications (defined as any new weakness, decreased level of consciousness, paresthesia or cranial nerve deficit), after coiling or clipping among 3076 patients. Clipping had a higher rate of postoperative neuro deficits than coiling with statistical significance (coiling 119 of 1530 (7.8%) VS clipping 167 of 1546 (10.8%); RR=0.720; CI=0.582-0.892; P=0.003; I^2=15.3%; Figure10).

Intracranial infection

Five studies included a total of 22608 patients provided the result of intracranial infection after clipping or coiling. Clipping had a higher intracranial infection than coiling. But there was not a statistical significance (coiling 364 of 15674 (2.3%) VS clipping 187 of 6934 (2.7%); RR=0.745; CI=0.422-1.315; P=0.310; I^2=73.9%; Figure11).

Pulmonary complications

Four studies included a total of 22614 patients provided the result of respiratory complications after clipping or coiling. Clipping had a higher respiratory complications than coiling. And there was a statistical significance (coiling 77 of 15701 (0.5%) VS clipping 125 of 6913 (1.8%); RR=0.456; CI=0.232-0.896; P=0.023; I^2=80.3%; Figure12).

Hospital LOS

Fifteen studies included a total of 36791 patients provided the result of hospital LOS after clipping or coiling. Clipping had a longer length of hospital stay than coiling. And there was a statistical significance (WMD=-2.290; CI=-3.423–1.157; P=0.000; I^2=69.4%; Figure13).

ICU LOS

Seven studies included a total of 1573 patients provided the result of LOS in ICU after clipping or coiling. Clipping had a longer LOS in ICU than coiling. And there was a statistical significance (SMD=-0.346; CI=-0.459–0.234; P=0.000; I^2=97.6%; Figure14).

Discussion

This meta-analysis summarized the available data with regard to outcomes of patients with RIAs underwent clipping or coiling procedures systematically. Our meta-analysis included 39 articles involving 60217 patients with RIAs. And we compared fourteen outcomes between coiling and clipping including the efficiency of treatment (mRS(0-2); GOS(4-5); postoperative rebleeding; postoperative mortality; the rate of complete occlusion), the postoperative complications (vasospasm; hydrocephaly; seizure; cerebral infarction; postoperative neuro deficits; intracranial infection; pulmonary complications), and length of hospital stay, length of stay in ICU.

This meta-analysis showed that patients who underwent coiling had a significantly better (mRS 0-2; P=0.01) (GOS 4-5; P=0.074; I^2=53.4) quality of life than those who underwent clipping at one year after treatment. Liu et al.[36] also reported that coiling patients had more good quality of life outcomes than clipping patients at one year after treatment. And this result was consistent with ISAT data[40, 48]. What's more, there were six articles[19, 23, 28] showed the trend that coiling was related to higher rate of good outcomes (mRS 0-2) than clipping group. Yu et al.[21] reported that the result of GOS (1-3) was lower in endovascular coiling (12/80, 15%) than in microsurgical clipping (30/89, 34%; P=0.005). Zhang et al.[49] had opposite result about the rate of GOS (4-5). Because the admission grade (Hunt-Hess 4 – 5; $p < 0.01$) [27] was associated with poor outcome, it could explain why there were different results.

250 (23·5%) of 1063 individuals underwent coiling treatment were dependent or dead at one year, compared with 326 (30·9%) of 1055 patients with clipping, an absolute risk reduction of 7·4% (95% CI 3·6–11·2, p=0·0001) reported by Molyneux et al.[40], Spetzler et al.[50] also showed coiling was related with a lower rate of mortality. While Shen et al.[18] had a opposite point, their result showed coiling was associated a higher mortality rate than clipping, this result was similar with our meta-analysis. Our result of mortality was different from published studies, the difference of categorical data may be one of the reasons[18].

Several articles[18, 19, 31, 32] demonstrated that a trend toward postoperative rebleeding in coiling group, while other literatures[30, 33, 35] showed clipping group had a higher rate of rebleeding than coiling group, and there was not significant difference in theirs results. In present article, we find a significantly higher risk of rebleeding in endovascular coiling group(P=0.000). Varelas et al.[33] reported that rebleeding was significantly associated with ventriculoperitoneal shunt(P=0.003), and some published articles suggested that rebleeding also depended on the follow up period and on the rate of occlusion after endovascular coiling or microsurgical clipping[5, 40, 51] and this meta-analysis also found that clipping was significantly associated with higher rate of complete occlusion(P=0.016), this result was consistent with published studies[28, 30, 35]. Murayama et al.[52] also reported that rate of complete occlusion was found in 55% of aneurysms and the lesion neck remnant was identified in 35.4% of aneurysms and the rate of recanalization was up to 20.9%, which was associated with the neck of the aneurysm and size of the dome. And coil compaction and/or loosening and high rate of remnant of neck could also cause recanalization[48, 53]

Our articles showed endovascular coiling was associated with significantly lower risk of vasospasm, cerebral infarction, post neuro deficits and pulmonary complications, but with a significantly higher postoperative hydrocephaly than microsurgical clipping. And there were not a significantly difference in seizure and intracranial infection between coiling and clipping group.

Li et al.[35, 54] also showed the lower incidence of vasospasm and cerebral infarction in coiling group. Some other publications[45, 54] were similar to ours about the infarction. The one of vasospasm reasons is that blood degradation products, accumulating in subarachnoid space and reserve as triggers to cause intramural inflammation and endothelial dysfunction[55]. However, there was a argument about vasospasm, someone thought that remove cisternal blood during clipping would reduce the risk of vasospasm[56]. But this effect could be offset by other effects related with clipping[57], such as surgical operations of vessels and craniotomy with brain retraction would aggravate the preexisting cerebral vasospasm[58-61]. And some previous publications suggested that cerebral vasospasm was associated with the incidence of cerebral infarction [62, 63]. There were some other reasons of cerebral infarction: microsurgical clipping blocked some microvascular during surgery, leading to ischemia event. The compression of small vessels that around the lesion clip may lead to local ischemia[18]. These factors may cause a higher risk of infarction in clipping group. What's more, vasospasm related cerebral infarction significantly influence the rate of mortality following aSAH , and cause poor clinical outcomes[64].

The result of postoperative neuro complications was consistent with some published studies[20, 57], Dumont et al. also analyzed the risk factor of neuro deficits, such as clipping, ventriculostomy , thick clot size, history of hypertension , and intracerebral hemorrhage[57]. Pulmonary complications were detected to be more prevalent in clipping group, these pulmonary complications were well known in participants with increased LOS in ICU, prolonged artificial ventilation and bed rest. The different incidence of pulmonary between the two methods may be that coiling would provide quicker mobilization in these patients. Therefore, we could avoid prolonging bed rest and discharge from hospital as early as possible[25]. Accordingly we demonstrated that patients underwent clipping were related to a longer LOS in hospital and ICU (P=0.000). Although there were heterogeneous in our article, the trend that clipping was associated with longer LOS in hospital or ICU was similar with previous studies[24, 27, 32]. We speculated that heterogeneous may be caused by small sample of LOS, different characteristics of patient, and the different analysis methods.

So far, some publications had reviewed the morbidity of hydrocephalus after endovascular coiling and microsurgical clipping systematically, while there was no uniform conclusion[8, 65, 66]. While the result of Shen et al[18] was consistent with this article that coiling was related with higher risk of hydrocephaly. as is known to all, arachnoid granules absorbed cerebrospinal fluid (CSF), and some CSF was absorbed though cerebral capillaries. Blood clots may lead to impairment of CSF absorption by disturbing cerebral capillaries and arachnoid villi, causing cerebral hydrocephaly[65]. While clipping could remove the blood clots, improving circulation of CSF, decreasing the risk of hydrocephaly[18]. And the controversy with regard to the result of hydrocephaly, may be the different diagnosis criteria of cerebral hydrocephalus[19].

Previous studies found the risk of epilepsy was significantly lower in patients with coiling treatment, and it is reasonable for us to believe that aneurysm dissection, the craniotomy, and the use of brain retractors to some extent lead to the incidence of epilepsy.[25, 40]. Some articles[18, 23, 25] reported that clipping treatment was associated with a higher development of cerebral infection. Because exposure of brain tissue during the clipping procedure would increase the risk of infection. However, there were not significantly difference in the two results in present study, the small sample sizes of the two indexes may be caused this difference, and there need more studies with regard to seizure and intracranial infection between the two groups.

This study has several potential limitations: 1. The included literatures were only 4 RCTs and this article was limited to the evaluation of short-term results. 2. The sample of some comparative indicators was relatively small.

Conclusion

Coiling was significantly associated with a better quality of life (mRS0-2), a lower incidence of postoperative complications (vasospasm, hydrocephaly, cerebral infarction, neuro deficits, pulmonary complications), and a higher rate of mortality, rebleeding than clipping. What's more, coiling was associated with a lower rate of complete occlusion. There was no significant difference about seizure and intracranial infection between the two groups.

Declarations

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Declaration of conflicting interests

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Ethical Approval and Consent for publication

This study protocol was examined and approved by the Ethical Committee of Tianjin Medical University, an academic medical center.

Author' contribution

Chao Peng: Writing draft, Editing, data election, quality evaluation of included studies, data analysis

Yu-hang Diao: quality evaluation of included studies, data election, data analysis

Shi-fei Cai: data election, quality evaluation of included studies, data analysis

Xin-yu Yang: Writing - Review & Editing, Supervision, Project administration

References

[1]. Lawton, M.T. and G.E. Vates, Subarachnoid Hemorrhage. N Engl J Med, 2017. 377(3): p. 257-266.

[2]. Solheim, O., et al., Quality of life after treatment for incidental, unruptured intracranial aneurysms. Acta Neurochir (Wien), 2006. 148(8): p. 821-30; discussion 830.

[3]. Dandy, W.E., INTRACRANIAL ANEURYSM OF THE INTERNAL CAROTID ARTERY: CURED BY OPERATION. Ann Surg, 1938. 107(5): p. 654-9.

[4]. Dovey, Z., et al., Guglielmi detachable coiling for intracranial aneurysms: the story so far. Arch Neurol, 2001. 58(4): p. 559-64.

[5]. Molyneux, A., et al., International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet, 2002. 360(9342): p. 1267-74.

[6]. Lin, N., et al., Treatment of ruptured and unruptured cerebral aneurysms in the USA: a paradigm shift. J Neurointerv Surg, 2012. 4(3): p. 182-9.

[7]. McDougall, C.G., et al., The Barrow Ruptured Aneurysm Trial. J Neurosurg, 2012. 116(1): p. 135-44.

[8]. Li, H., et al., Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. Stroke, 2013. 44(1): p. 29-37.

[9]. Akhigbe, T., A. Zolnourian and D. Bulters, Compliance of systematic reviews articles in brain arteriovenous malformation with PRISMA statement guidelines: Review of literature. J Clin Neurosci, 2017. 39: p. 45-48.

[10]. O'Kelly, C.J., et al., The impact of therapeutic modality on outcomes following repair of ruptured intracranial aneurysms: an administrative data analysis. Clinical article. J Neurosurg, 2010. 113(4): p. 795-801.

[11]. Choi, J.H., et al., Aneurysmal Neck Clipping as the Primary Treatment Option for Both Ruptured and Unruptured Middle Cerebral Artery Aneurysms. J Korean Neurosurg Soc, 2016. 59(3): p. 269-75.

[12]. Ayling, O.G., et al., Operative complications and differences in outcome after clipping and coiling of ruptured intracranial aneurysms. J Neurosurg, 2015. 123(3): p. 621-8.

[13]. Berro, D.H., et al., Clip-first policy versus coil-first policy for the exclusion of middle cerebral artery aneurysms. J Neurosurg, 2019: p. 1-8.

[14]. Darsaut, T.E., et al., A randomized trial of endovascular versus surgical management of ruptured intracranial aneurysms: Interim results from ISAT2. Neurochirurgie, 2019. 65(6): p. 370-376.

[15]. Heit, J.J., et al., Patient Outcomes and Cerebral Infarction after Ruptured Anterior Communicating Artery Aneurysm Treatment. AJNR Am J Neuroradiol, 2017. 38(11): p. 2119-2125.

[16]. Scheller, C., et al., Increased rate of ventriculostomy-related hemorrhage following endovascular treatment of ruptured aneurysms compared to clipping. Acta Neurochir (Wien), 2018. 160(3): p. 545-550.

[17]. Koh, K.M., et al., Management of ruptured intracranial aneurysms in the post-ISAT era: outcome of surgical clipping versus endovascular coiling in a Singapore tertiary institution. Singapore Med J, 2013. 54(6): p. 332-8.

[18]. Shen, J., et al., Clinical Efficacy Between Microsurgical Clipping and Endovascular Coiling in the Treatment of Ruptured Poor-Grade Anterior Circulation Aneurysms. World Neurosurg, 2019. 127: p. e321-e329.

[19]. Zhao, B., et al., Endovascular Coiling versus Surgical Clipping for Poor-Grade Ruptured Intracranial Aneurysms: Postoperative Complications and Clinical Outcome in a Multicenter Poor-Grade Aneurysm Study. AJNR Am J Neuroradiol, 2016. 37(5): p. 873-8.

[20]. McDonald, J.S., et al., Comparative effectiveness of ruptured cerebral aneurysm therapies: propensity score analysis of clipping versus coiling. AJNR Am J Neuroradiol, 2014. 35(1): p. 164-9.

[21]. Yu, S.C., et al., Endovascular coiling versus neurosurgical clipping for ruptured intracranial aneurysms: significant benefits in clinical outcome and reduced consumption of hospital resources in Hong Kong Chinese patients. Hong Kong Med J, 2007. 13(4): p. 271-8.

[22]. Bekelis, K., et al., Surgical clipping versus endovascular coiling for elderly patients presenting with subarachnoid hemorrhage. J Neurointerv Surg, 2016. 8(9): p. 913-8.

[23]. Li, J., et al., Endovascular Coiling Versus Microsurgical Clipping for Patients With Ruptured Very Small Intracranial Aneurysms: Management Strategies and Clinical Outcomes of 162 Cases. World Neurosurg, 2017. 99: p. 763-769.

[24]. Deutsch, B.C., S.N. Neifert and J.M. Caridi, No Disparity in Outcomes Between Surgical Clipping and Endovascular Coiling After Aneurysmal Subarachnoid Hemorrhage. World Neurosurg, 2018. 120: p. e318-e325.

[25]. Ryttlefors, M., et al., International subarachnoid aneurysm trial of neurosurgical clipping versus endovascular coiling: subgroup analysis of 278 elderly patients. Stroke, 2008. 39(10): p. 2720-6.

[26]. Hoh, B.L., et al., Length of stay and total hospital charges of clipping versus coiling for ruptured and unruptured adult cerebral aneurysms in the Nationwide Inpatient Sample database 2002 to 2006. Stroke, 2010. 41(2): p. 337-42.

[27]. Brunken, M., et al., [Coiling vs. clipping: hospital stay and procedure time in intracranial aneurysm treatment]. Rofo, 2009. 181(10): p. 989-95.

[28]. Taweesomboonyat, C., et al., Outcome of Ruptured Posterior Communicating Artery Aneurysm Treatment Comparing Between Clipping and Coiling Techniques. World Neurosurg, 2019. 125: p. e183-e188.

[29]. Zhao, B., et al., Endovascular Coiling versus Surgical Clipping of Very Small Ruptured Anterior Communicating Artery Aneurysms. World Neurosurg, 2019. 126: p. e1246-e1250.

[30]. Klompenhouwer, E.G., et al., Single-center experience of surgical and endovascular treatment of ruptured intracranial aneurysms. AJNR Am J Neuroradiol, 2011. 32(3): p. 570-5.

[31]. Liao, C.C., et al., Surgical and endovascular treatment for ruptured anterior circulation cerebral aneurysms: a comparison of outcomes--a single centre study from Taiwan. Int J Surg, 2013. 11(9): p. 998-1001.

[32]. Zhang, Q.R., et al., The impact of microsurgical clipping and endovascular coiling on the outcome of cerebral aneurysms in patients over 60 years of age. J Clin Neurosci, 2012. 19(8): p. 1115-8.

[33]. Varelas, P., et al., Clipping or coiling of ruptured cerebral aneurysms and shunt-dependent hydrocephalus. Neurocrit Care, 2006. 4(3): p. 223-8.

[34]. Lusseveld, E., et al., Endovascular coiling versus neurosurgical clipping in patients with a ruptured basilar tip aneurysm. J Neurol Neurosurg Psychiatry, 2002. 73(5): p. 591-3.

[35]. Li, Z.Q., et al., Outcomes of endovascular coiling versus surgical clipping in the treatment of ruptured intracranial aneurysms. J Int Med Res, 2012. 40(6): p. 2145-51.

[36]. Liu, H.M., et al., Taiwan aneurysm registry: multivariate analysis of two-month, one-year, and two-year outcomes after endovascular and microsurgical treatment of ruptured aneurysms. Interv Neuroradiol, 2013. 19(1): p. 35-42.

[37]. Hoh, B.L., et al., Incidence of seizures or epilepsy after clipping or coiling of ruptured and unruptured cerebral aneurysms in the nationwide inpatient sample database: 2002-2007. Neurosurgery, 2011. 69(3): p. 644-50; discussion 650.

[38]. Gross, B.A., et al., Treatment modality and vasospasm after aneurysmal subarachnoid hemorrhage. World Neurosurg, 2014. 82(6): p. e725-30.

[39]. Suzuki, H. and W. Taki, Effect of aneurysm treatment modalities on cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Acta Neurochir Suppl, 2013. 115: p. 99-105.

[40]. Molyneux, A.J., et al., International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet, 2005. 366(9488): p. 809-17.

[41]. Zaidat, O.O., et al., Impact of ruptured cerebral aneurysm coiling and clipping on the incidence of cerebral vasospasm and clinical outcome. J Neuroimaging, 2009. 19(2): p. 144-9.

[42]. Koivisto, T., et al., Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. Stroke, 2000. 31(10): p. 2369-77.

[43]. Niskanen, M., et al., Resource use after subarachnoid hemorrhage: comparison between endovascular and surgical treatment. Neurosurgery, 2004. 54(5): p. 1081-6; discussion 1086-88.

[44]. Rabinstein, A.A., et al., Symptomatic vasospasm and outcomes following aneurysmal subarachnoid hemorrhage: a comparison between surgical repair and endovascular coil occlusion. J Neurosurg, 2003. 98(2): p. 319-25.

[45]. Kim, B.M., et al., Clinical outcome and ischemic complication after treatment of anterior choroidal artery aneurysm: comparison between surgical clipping and endovascular coiling. AJNR Am J Neuroradiol, 2008. 29(2): p. 286-90.

[46]. Wadd, I.H., et al., Aneurysmal Subarachnoid Hemorrhage: Outcome of Aneurysm Clipping Versus Coiling in Anterior Circulation Aneurysm. J Coll Physicians Surg Pak, 2015. 25(11): p. 798-801.

[47]. Zanaty, M., et al., Short-Term Outcome of Clipping Versus Coiling of Ruptured Intracranial Aneurysms Treated by Dual-Trained Cerebrovascular Surgeon: Single-Institution Experience. World Neurosurg, 2016. 95: p. 262-269.

[48]. Molyneux, A., et al., International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet, 2002. 360(9342): p. 1267-74.

[49]. Zhang, Q.R., et al., The impact of microsurgical clipping and endovascular coiling on the outcome of cerebral aneurysms in patients over 60 years of age. J Clin Neurosci, 2012. 19(8): p. 1115-8.

[50]. Spetzler, R.F., et al., The Barrow Ruptured Aneurysm Trial: 6-year results. J Neurosurg, 2015. 123(3): p. 609-17.

[51]. Johnston, S.C., et al., Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. Stroke, 2008. 39(1): p. 120-5.

[52]. Murayama, Y., et al., Guglielmi detachable coil embolization of cerebral aneurysms: 11 years' experience. J Neurosurg, 2003. 98(5): p. 959-66.

[53]. Investigators, C., Rates of delayed rebleeding from intracranial aneurysms are low after surgical and endovascular treatment. Stroke, 2006. 37(6): p. 1437-42.

[54]. de Oliveira, J.G., et al., Comparison between clipping and coiling on the incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. Neurosurg Rev, 2007. 30(1): p. 22-30; discussion 30-1.

[55]. Budohoski, K.P., et al., The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry, 2014. 85(12): p. 1343-53.

[56]. Inagawa, T., M. Yamamoto and K. Kamiya, Effect of clot removal on cerebral vasospasm. J Neurosurg, 1990. 72(2): p. 224-30.

[57]. Dumont, A.S., et al., Endovascular treatment or neurosurgical clipping of ruptured intracranial aneurysms: effect on angiographic vasospasm, delayed ischemic neurological deficit, cerebral infarction, and clinical outcome. Stroke, 2010. 41(11): p. 2519-24.

[58]. Kassell, N.F., et al., The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1: Overall management results. J Neurosurg, 1990. 73(1): p. 18-36.

[59]. Kassell, N.F., et al., The International Cooperative Study on the Timing of Aneurysm Surgery. Part 2: Surgical results. J Neurosurg, 1990. 73(1): p. 37-47.

[60]. Kassell, N.F. and C.G. Drake, Timing of aneurysm surgery. Neurosurgery, 1982. 10(4): p. 514-9.

[61]. Solomon, R.A., S.T. Onesti and L. Klebanoff, Relationship between the timing of aneurysm surgery and the development of delayed cerebral ischemia. J Neurosurg, 1991. 75(1): p. 56-61.

[62]. Leclerc, J.L., et al., Haptoglobin phenotype predicts the development of focal and global cerebral vasospasm and may influence outcomes after aneurysmal subarachnoid hemorrhage. Proc Natl Acad Sci U S A, 2015. 112(4): p. 1155-60.

[63]. Kumar, G., R.B. Shahripour and M.R. Harrigan, Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. J Neurosurg, 2016. 124(5): p. 1257-64.

[64]. Dorsch, N.W. and M.T. King, A review of cerebral vasospasm in aneurysmal subarachnoid haemorrhage Part I: Incidence and effects. J Clin Neurosci, 1994. 1(1): p. 19-26.

[65]. de Oliveira, J.G., et al., Risk of shunt-dependent hydrocephalus after occlusion of ruptured intracranial aneurysms by surgical clipping or endovascular coiling: a single-institution series and meta-analysis. Neurosurgery, 2007. 61(5): p. 924-33; discussion 933-4.

[66]. Xie, Z., et al., Predictors of Shunt-dependent Hydrocephalus After Aneurysmal Subarachnoid Hemorrhage? A Systematic Review and Meta-Analysis. World Neurosurg, 2017. 106: p. 844-860.e6.

Tables

Table 1: the Newcastle-Ottawa scale for quality assessment observational studies.

	Representativeness cohort	Exposure Ascertainment	Comparability	Outcome Assessment	Sufficient Duration	Adequacy of follow up of cohorts
al.	Yes	database	No restricton, Matched in1,2,5,6	record linkage	Yes	Yes
al.	Yes	database	Restricted to MCA, Matched in1,2,5,6	record linkage	Yes	Yes
al.	Yes	database	No restricton, Matched in1,2,4,5,6	record linkage	No	Yes
al.	Yes	medical record	Restricted to MCA, Matched in1,2,4	record linkage	No	Yes
t al.	Yes	database	No restricton	record linkage	Yes	Yes
al.	Yes	database	No restricton, Matched in1,2,4,5,6	record linkage	No	Yes
al.	Yes	medical record	Restricted to ACOA, Matched in1,2,3	record linkage	No	Yes
t al.	Yes	medical record	No restricton, Matched in1,2,3, 6	record linkage	Yes	Yes
al.	Yes	medical record	No restricton, Matched in1,2,6	record linkage	No	Yes
al.	Yes	medical record	Restricted to Anterior Circulation, Matched in1,2,4,5	record linkage	No	Yes
al.	Yes	medical record	No restricton, Matched in1,2,4,5,6	record linkage	Yes	Yes
et al.	Yes	database	No restricton, Matched in1,2	record linkage	unclear	unclear
l.	Yes	medical record	No restricton, Matched in1,2,5	record linkage	Yes	Yes
al.	Yes	database	No restricton, Matched in1,2	record linkage	Yes	Yes
.	Yes	medical record	No restricton, Matched in1,2,3,5,6	record linkage	Yes	Yes
t al.	Yes	database	No restricton, Matched in1,2	record linkage	Yes	Yes
et al.	Yes	medical record	Restricted to≥65 years, Matched in1,2,4,5,6	record linkage	Yes	NO
al.	Yes	medical record	Restricted to ACOA, Matched in1,2,4	record linkage	Yes	Yes
al.	Yes	database	Restricted to≥18 years, Matched in1,2	record linkage	unclear	unclear
t al.	Yes	medical record	No restricton, Matched in1,2,3,6	record linkage	NO	Yes
onyat	Yes	medical record	Restricted to PCOA, Matched in1,2,3,4,5,6	record linkage	Yes	Yes
	Yes	medical record	Restricted to ACOA, Matched in1,2,4,5	record linkage	Yes	Yes
wer	Yes	medical record	No restricton, Matched in1,2,3,5,6	record linkage	Yes	Yes
	Yes	medical record	Restricted to Anterior Circulation, Matched in1,2,3,4	record linkage	Yes	Yes
	Yes	medical record	Restricted to 60years, Matched in1,2,3,6	record linkage	Yes	Yes
al.	Yes	medical record	Restricted to basilar tip aneurysm, Matched in1,2,4,5	record linkage	No	Yes
.	Yes	medical record	No restricton, Matched in1,2,3,6	record linkage	Yes	Yes
	Yes	medical record	Restricted to age older than 18	record linkage	Unclear	Unclear
	Yes	medical record	No restricton	record linkage	Yes	Yes
	Yes	medical record	No restricton, Matched in1,2,3,5	record linkage	Yes	Yes
	Yes	medical record	No restricton, Matched in1,2,3,6	record linkage	Unclear	Unclear
	Yes	medical record	No restricton, Matched in1,2,4,5,6	record linkage	Yes	Unclear
	Yes	medical record	No restricton, Matched in1,2,3,6	record linkage	Unclear	Unclear
al.	Yes	medical record	No restricton, Matched in1,2,3,5,6	record linkage	Yes	Yes
t al.	Yes	medical record	No restricton, Matched in1,2,4,6	record linkage	Yes	Yes
	Yes	medical record	Restricted to anterior choroidal artery aneurysms, Matched in1,2,3,5	record linkage	Yes	Yes

Note: 1=Age; 2=Sex; 3=Hunt and Hess Grade; 4 = World Federation of Neurological Societies Scale; 5=Aneurism size; 6=Aneurism location.

Table 2. Overview of Included Studies.

Note. NA= not available; RCT= randomized controlled trial; RCS= Retrospective comparative study; FM= female.

Author	Country	Years	Type of Study	Recruitment period	Participants (n)		Gender (FM)		Age (mean ± standard)	
					Coil	Clip	Coil(%)	Clip(%)	Coil	Clip
Kelly et al.	Canada	2010	RCS	1995-2004	778	2342	67	65.5	54.4	53.7
Choi et al.	Korea	2016	RCS	2008-2012	8	30	62.5	60	64.75±11.47	53.17±11.96
Ayling et al.	Canada	2015	RCS	2005-2006	212	181	NA	NA	NA	NA
Berro et al.	France	2019	RCS	2012-2015	48	42	68.8	81	52 ± 10.8	52.6 ± 11.7
Darsaut et al.	Canada	2019	RCS	2012-2017	48	55	65	67	56.5	58.5
Zanaty et al.	USA	2016	RCS	2010-2015	182	70	73.6	67.1	56.6±12.4	55.9±12.7
Heit et al.	USA	2017	RCS	2010-2014	50	50	62	52	55±11.67	50±12.59
Scheller et al.	Germany	2018	RCS	2010-2015	45	54	55.8	75.9	60±13.75	57±13.75
Koh et al.	Singapore	2013	RCS	2005-2009	23	33	65.2	54.5	52.8 ± 11.6	54.1 ± 13.9
Shen et al.	China	2019	RCS	2013-2018	29	65	62	69	65.86±11.597	59.92±10.603
Zhao et al.	China	2016	prospective	2010-2012	133	129	46.6	53.5	54.5 ±11.8	54.4±10.9
McDonald et al.	USA	2014	RCS	2006-2011	1227	1227	65	66	53±13.33	53±12.59
Yu et al.	China	2007	RCS	1995-2001	80	89	60	62.9	56±13	57±13
Bekelis et al.	Lebanon	2016	RCS	2007-2012	2004	1206	73.4	77.2	75.3±6.8	73.5±6.2
Li et al.	China	2017	RCS	2002-2010	77	85	59.7	54.1	47.5±10.3	48.1±11.6
Deutsch et al.	USA	2018	RCS	2013-2014	15350	6555	65.9	69..0	55.3±33.45	54.1±31.58
Ryttlefors et al.	UK	2008	RCS	NA	138	140	68.8	74.3	NA	NA
Wadd et al.	Pakistan	2015	RCS	2010-2013	70	70	60	60	52.5±10	51±10
Hoh et al.	USA	2010	RCS	2002-2016	3564	5783	68	69	55.0±14.0	53.1±13.0
Brunken et al.	Germany	2009	RCS	1990-2004	145	370	NA	NA	53.7±15.5	50.7±16
Taweesomboonyat et al.	Thailand	2019	RCS	2002-2018	84	105	81	74.3	64.3±13.9	56.5±11.4
Zhao et al.	China	2019	RCS	2008-2015	46	65	52.2	55.4	54.5±11.2	55.5±11.1
Klompenhouwer et al.	Netherlands	2011	RCS	2000-2008	230	173	70.4	69.9	53.6	53.1
Liao et al.	China	2013	RCS	2008-2009	56	44	68	61	57.91±11.89	56.93±13.75
Zhang et al.	China	2012	RCS	2005-2009	76	122	64.5	72.95	51.7±13.0	52.8±10.4
Lusseveld et al.	Netherlands	2002	RCS	1983-1999	44	44	66	59	47.0	44.2
Varelas et al.	USA	2006	RCS	2000-2004	48	135	45	66	51±15	53±14
Hoh et al.	USA	2011	RCS	2002-2007	4306	6593	NA	NA	NA	NA
Li et al.	China	2012	RCS	2005-2009	94	92	27.7	32.6	54.7±14.2	53.7±13.8
Liu et al.	China	2013	RCS	2001-2005	281	361	60.5	66.8	55.6±15.21	56.90±13.36
Gross et al.	USA	2014	RCS	2007-2013	52	203	75	75	NA	NA
Suzuki et al.	Japan	2013	Prospective	2006-2007	297	282	65.7	69.9	62.4 ± 14.6	60.2 ± 12.5
Zaidat et al.	USA	2009	RCS	1999-2005	98	118	72	72	58 ±1.5	52 ±1.25
McDougall et al.	USA	2012	RCT	2003-2007	233	238	71	70	54.3 ± 12.0	53.1 ± 12.8
Molyneux et al	Europe	2005	RCT	1994-2002	1073	1070	63	63	52	52
Koivisto et al.	Finland	2000	RCT	1995-1997	52	57	46.1	59.6	49±14.25	50±15.25
Niskanen et al.	Finland	2004	RCS	1997-2000	68	103	52.9	57.3	54 ±13	54±13
Rabinstein et al.	USA	2003	RCS	1990-2000	76	339	62	65	56	53
Kim et al.	Korea	2008	RCS	1999-2006	37	35	62.2	57.1	54±13	45±12

Table 3. Meta-analysis results

Outcomes		Studies	Groups		Overall effect			Heterogeneity	
			Coil	Clip	Effect estimate	95% CI	p-Value	I^2(%)	p-Value
Efficiency	mRs(0-2)	10	2007	2099	1.462	1.2375-1.676	**0.000**	0.0	0.941
	GOS(4-5)	10	616	1251	0.700	0.474-1.035	0.074	53.4	0.023
	Rebleeding rate	14	2232	2427	1.410	1.092-1.822	**0.000**	10.6	0.337
	Mortality	21	25268	19641	1.116	1.054-1.180	**0.000**	36.9	0.047
	Complete occlusion	8	1562	1168	0.495	0.280-0.876	**0.016**	87.5	0.000
Complications	Vasospasm	13	1177	1680	0.787	0.649-0.954	**0.015**	41.1	0.060
	Hydrocephaly	9	1819	2037	1.143	1.043-1.252	**0.004**	30.7	0.173
	Seizure	8	5926	8306	0.541	0.291-1.006	0.052	64.1	0.011
	Cerebral infarction	16	2598	2825	0.669	0.596-0.751	**0.000**	18.9	0.238
	Neuro deficits	5	1530	1546	0.720	0.582-0.892	**0.003**	15.3	0.317
	Intracranial infection	5	15674	6934	0.745	0.422-1.315	0.310	73.9	0.004
	Pulmonary complications	4	15701	6913	0.456	0.232-0.896	**0.023**	80.3	0.002
Hospital LOS		15	21925	14866	-2.290	-3.423--1.157	**0.000**	69.4	0.000
ICU LOS		7	620	953	-0.346	-0.459--0.234	**0.000**	97.6	0.000

Note: mRS= Modified Rankin Scale; GOS= Glasgow Outcome Scale; LOS=Length of Stay.

Figures

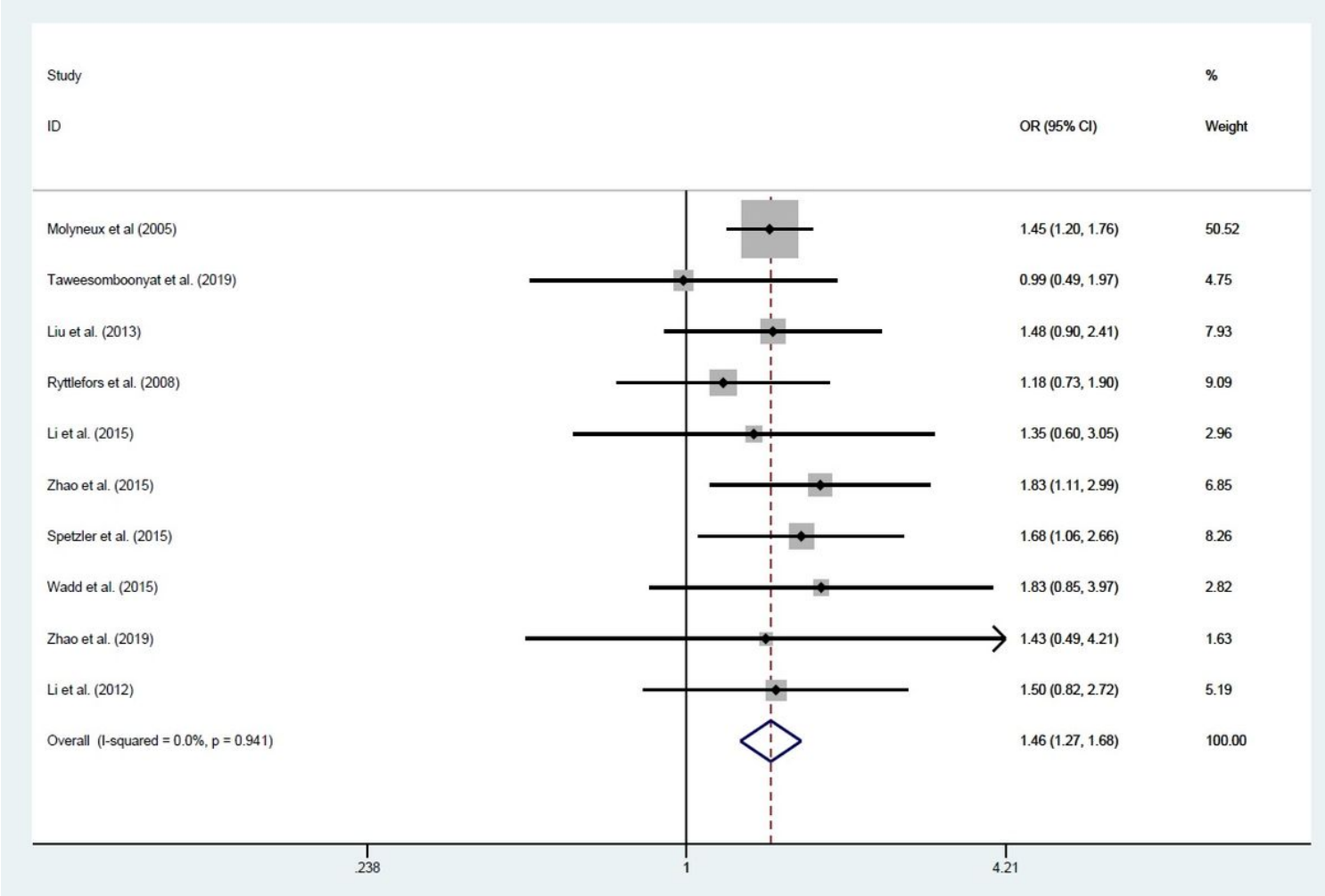

Figure 1

there was statistical significance in the results of mRS0-2 (coiling1478 of 2007 (73.6%) VS clipping1390 of 2099 (66.2%); OR=1.462; CI=1.2375-1.676; P=0.000; I2=0.0%)

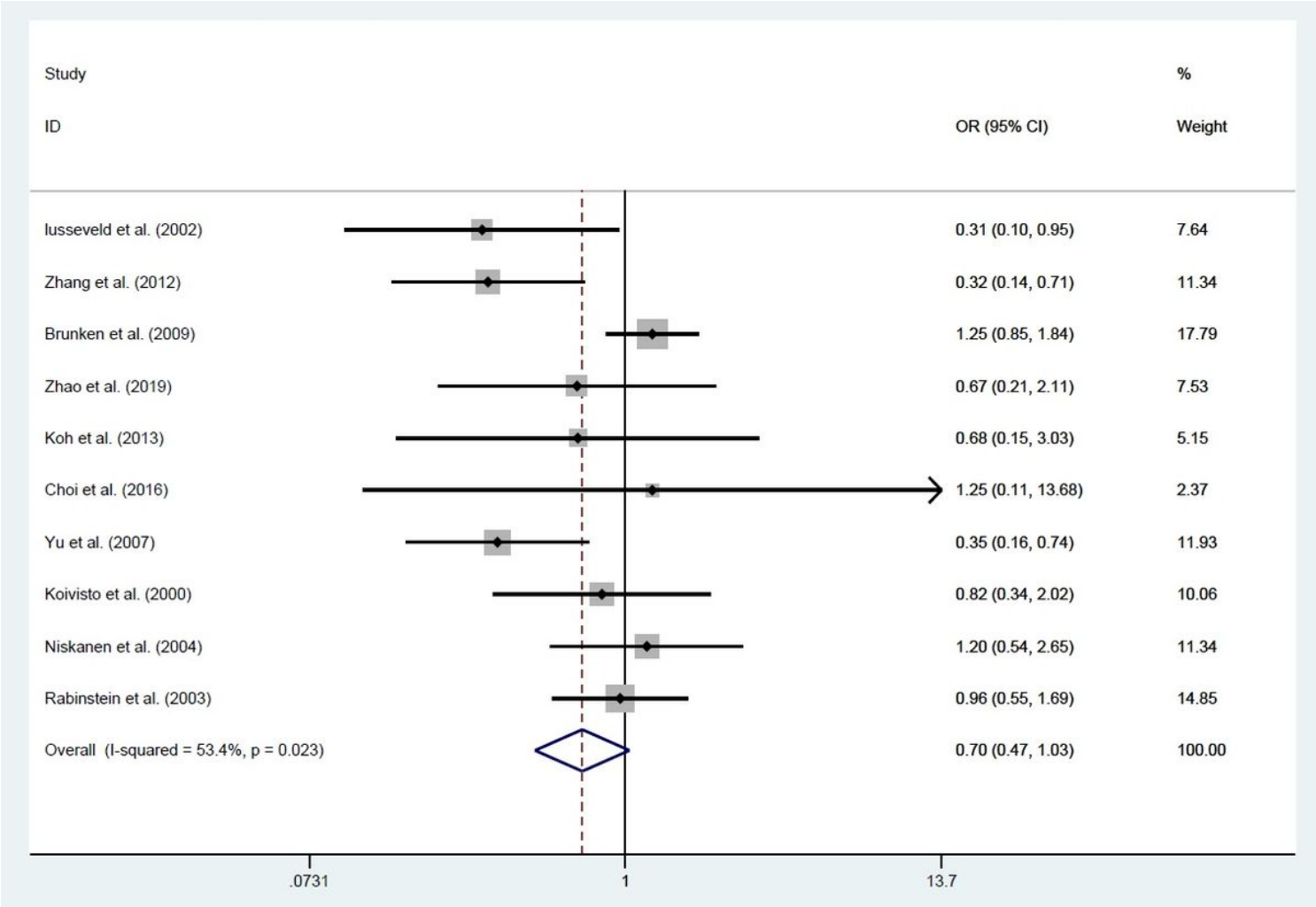

Figure 2

74.4% and 67.8% of patients had good quality of life (GOS4-5) in coiling and clipping group, respectively. However, there was not significantly difference in the two groups (OR=0.700; CI=0.474-1.035; P=0.074; I2=53.4%)

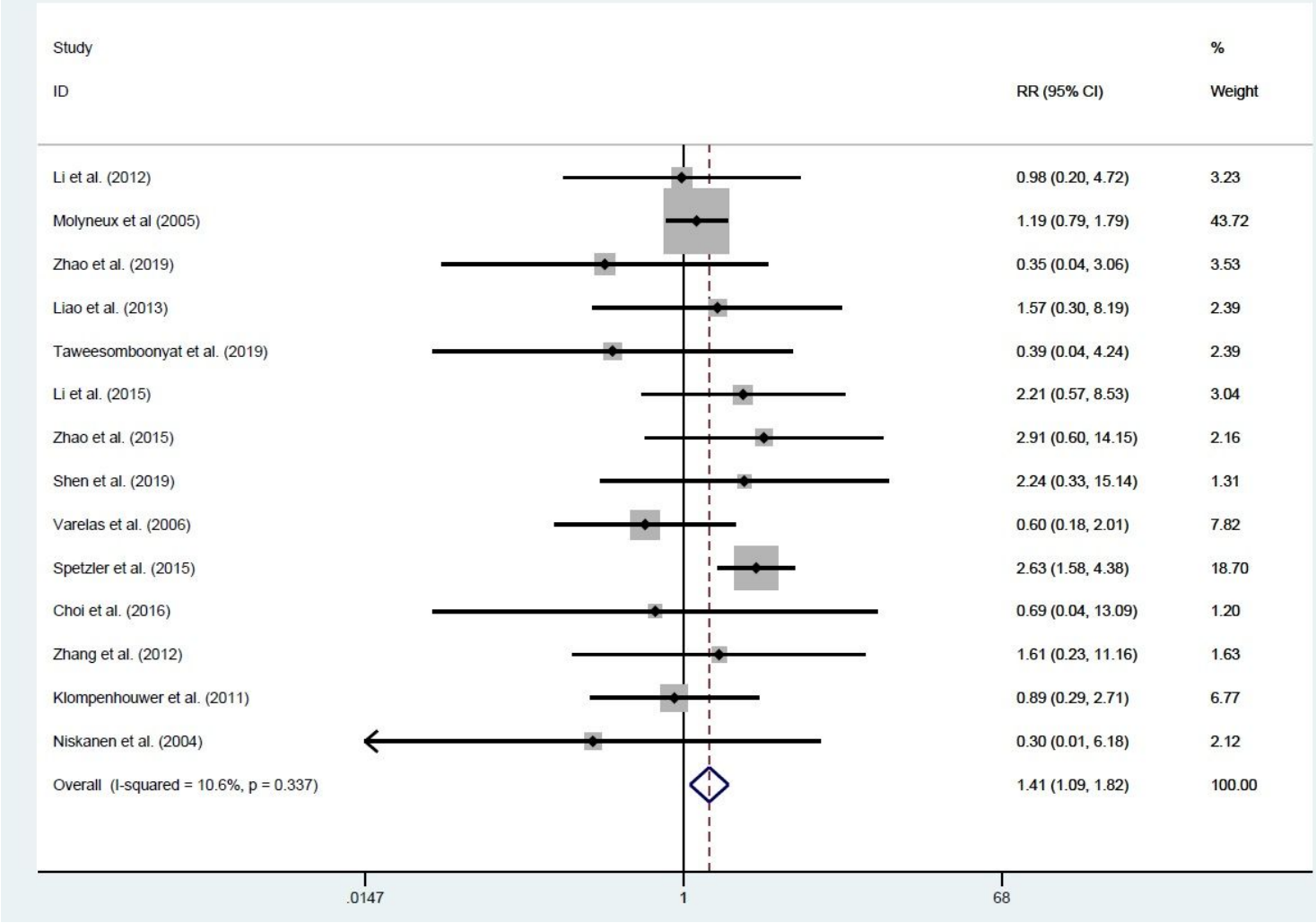

Figure 3

There was higher postoperative rebleeding in coiling group than clipping group. And it was associated with statistical significance (coiling128 of 2232(5.7%) VS clipping103 of 2427(4.2%); RR=1.410; CI=1.092-1.822; P=0.000; I2=10.6%;)

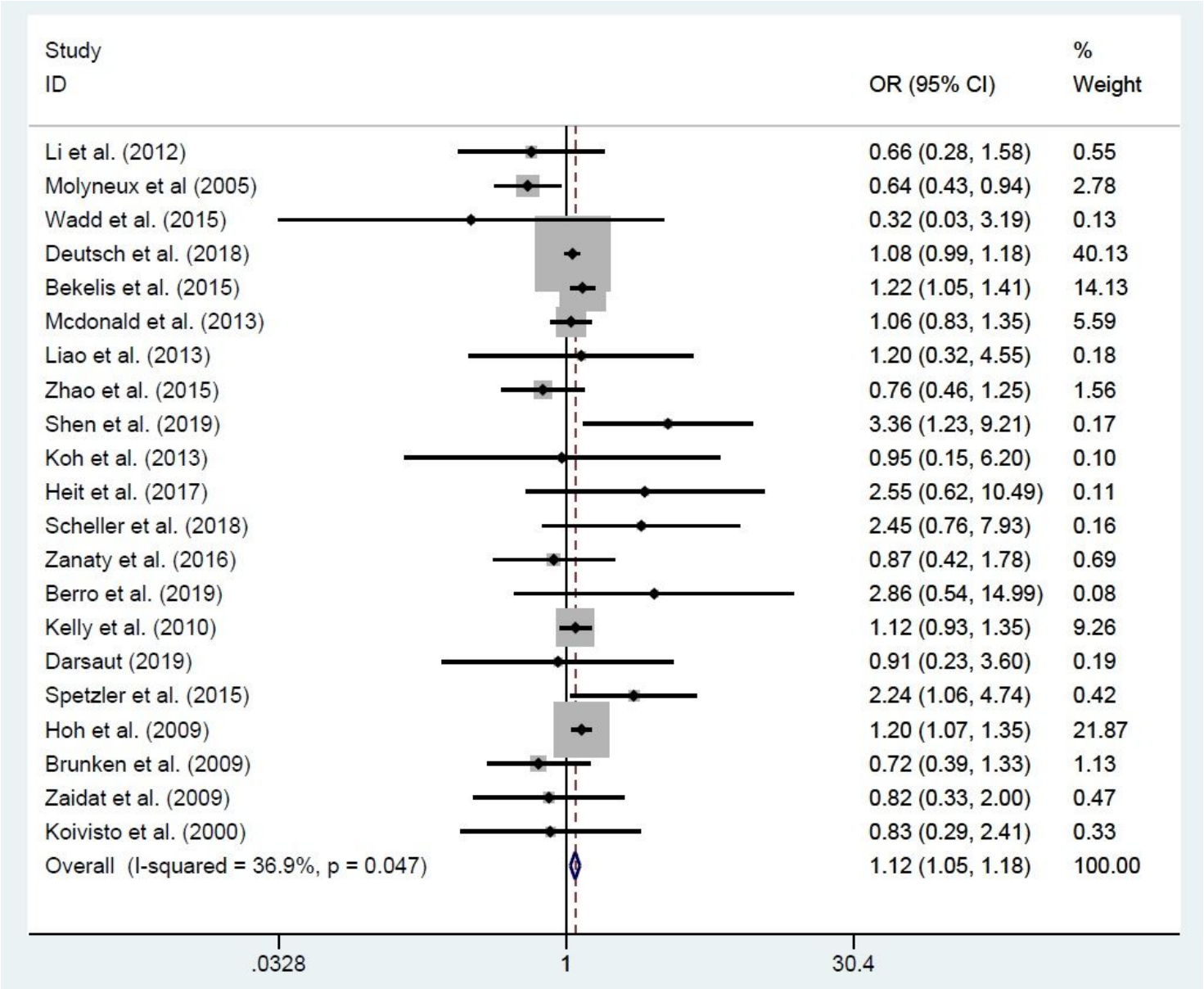

Figure 4

Coiling had a significant effect on the risk of mortality compared with clipping (coiling3847 of 25268(15.2%) VS clipping2955 of 19641(15.0%); OR=1.116; CI=1.054-1.180; P=0.000; I2=36.9%;).

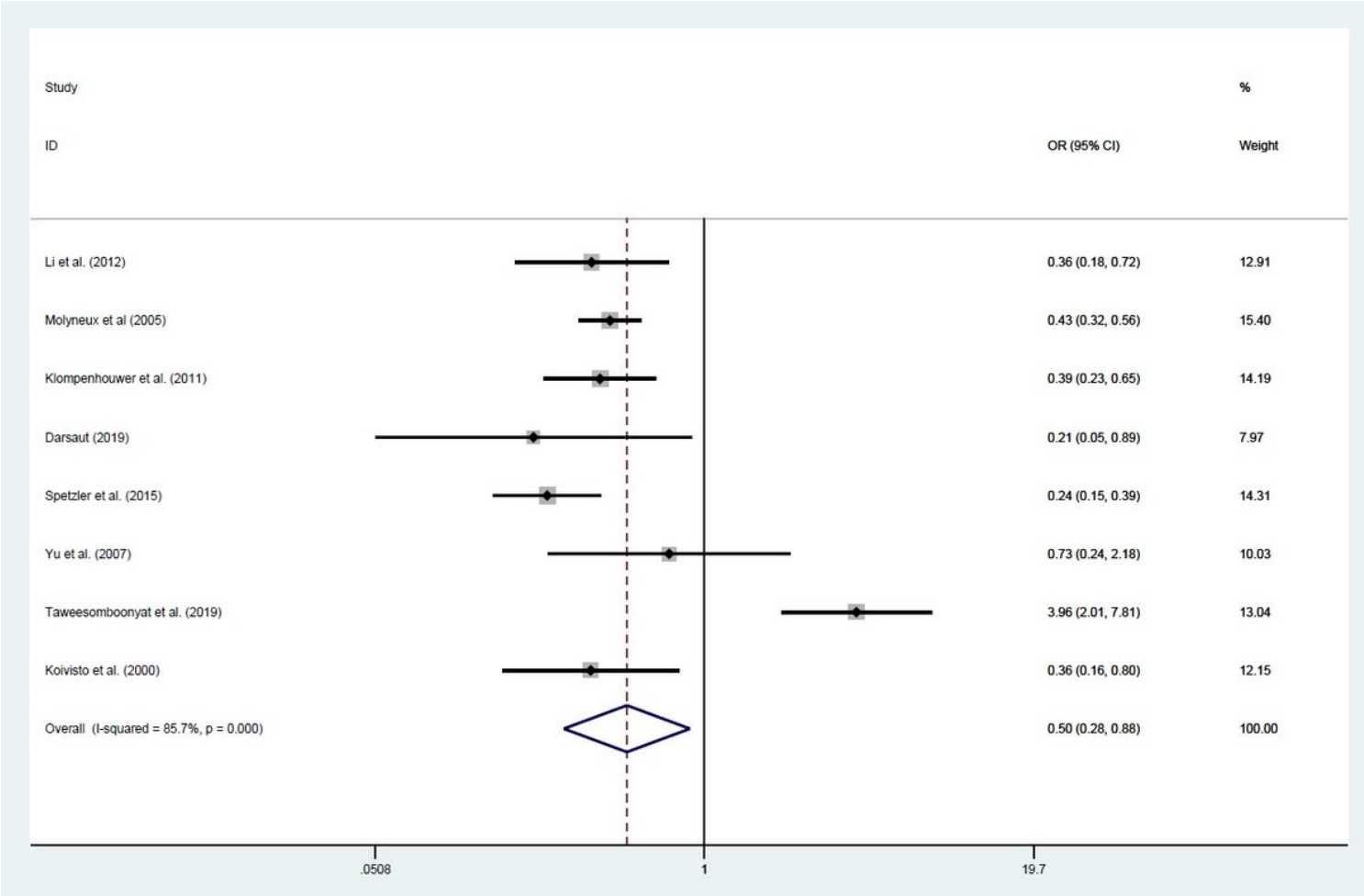

Figure 5

There was a higher rate of occlusion in clipping group than coiling group with a statistical significance (coiling 992 of 1562 (63.5%) VS clipping 898 of 1168 (76.9%); OR=0.495; CI=0.280-0.876; P=0.016; I2=87.5%;)

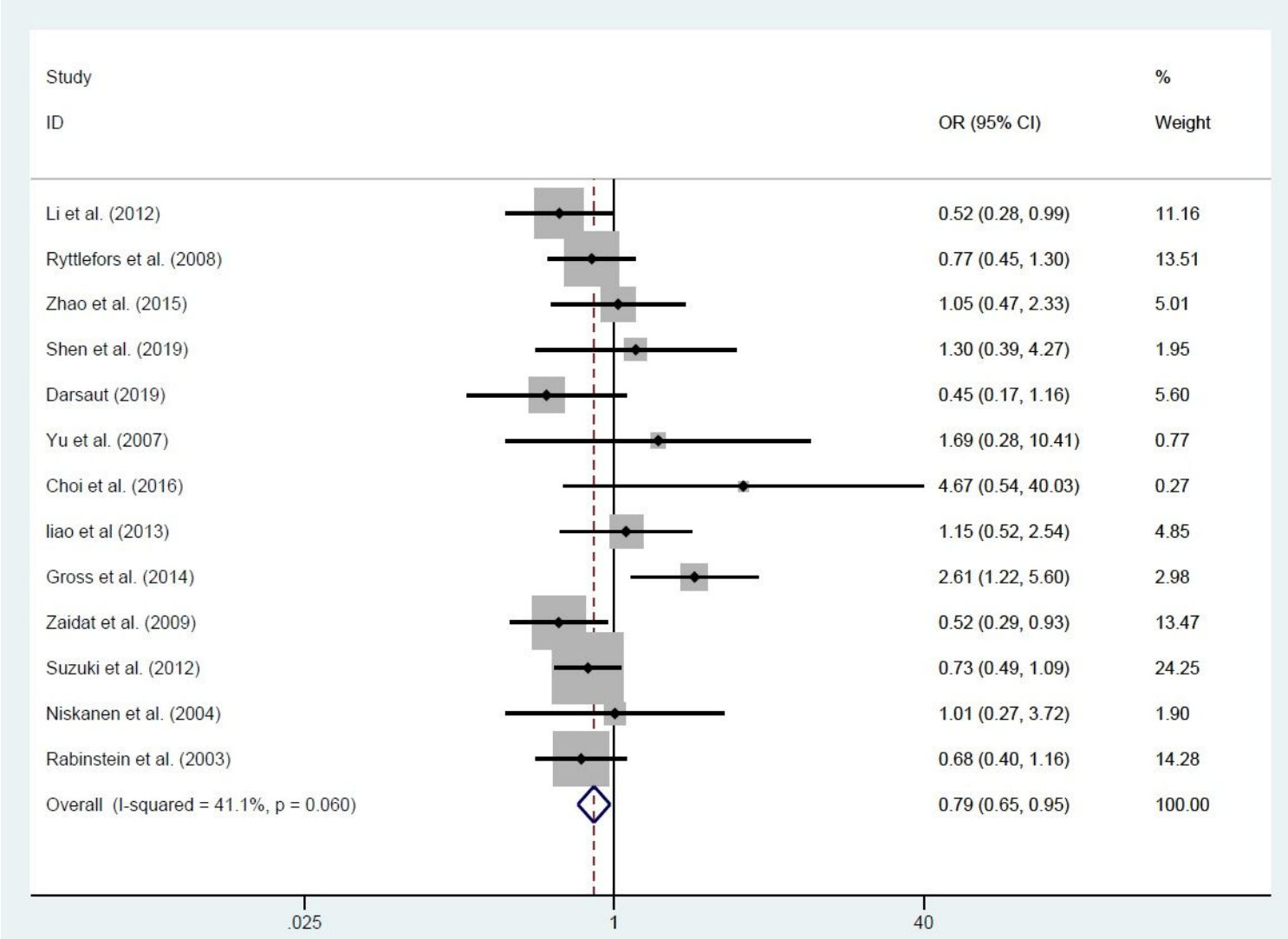

Figure 6

There was a less postoperative vasospasm in coiling group than clipping group with a statistical significance (coiling 241 of 1177 (20.5%) VS clipping 416 of 1680 (24.8%); OR=0.787; CI=0.649-0.954; P=0.015; I2=41.1%;)

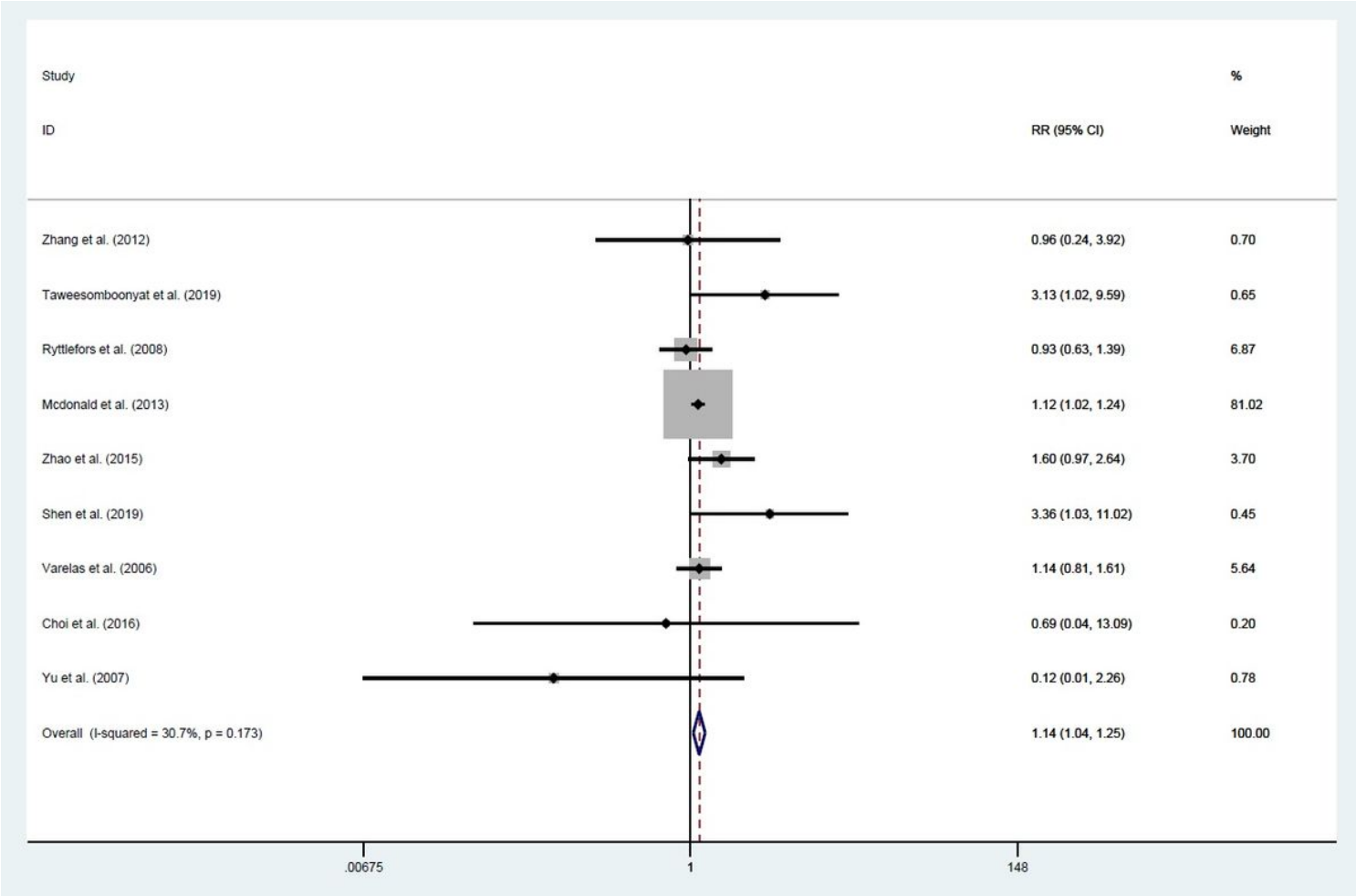

Figure 7

Coiling had a significant effect on the postoperative hydrocephaly compared with clipping (coiling 611 of 1819 (50.6%) VS clipping 581 of 2037 (39.9%); RR=1.143; CI=1.043-1.252; P=0.004; I2=30.7%)

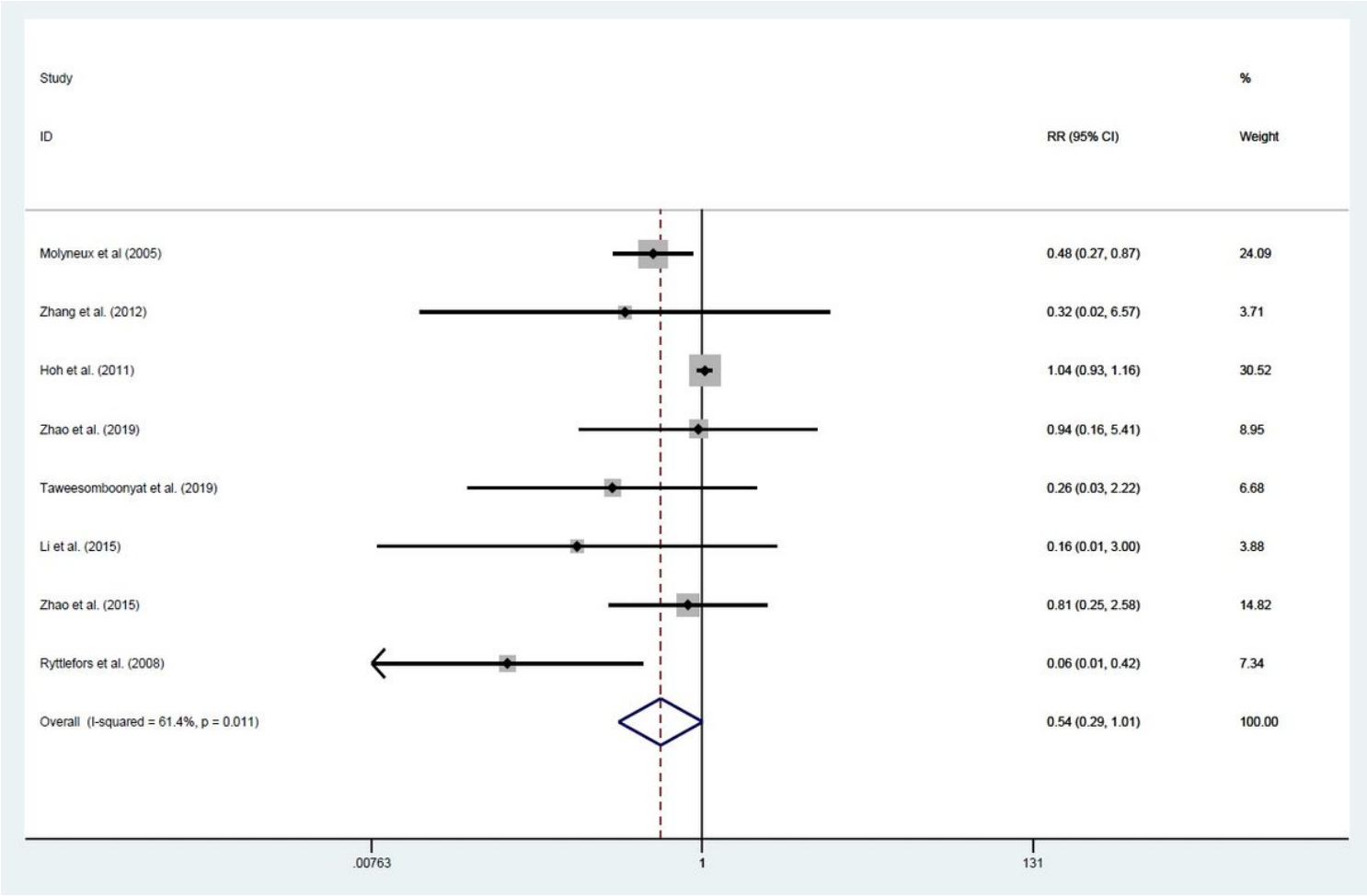

Figure 8

Clipping had a significant effect on the postoperative seizure compared with coiling (coiling 502 of 5926 (8.5%) VS clipping 774 of 8306 (9.3%); RR=0.541; CI=0.291-1.006; P=0.052; I2=64.1%).

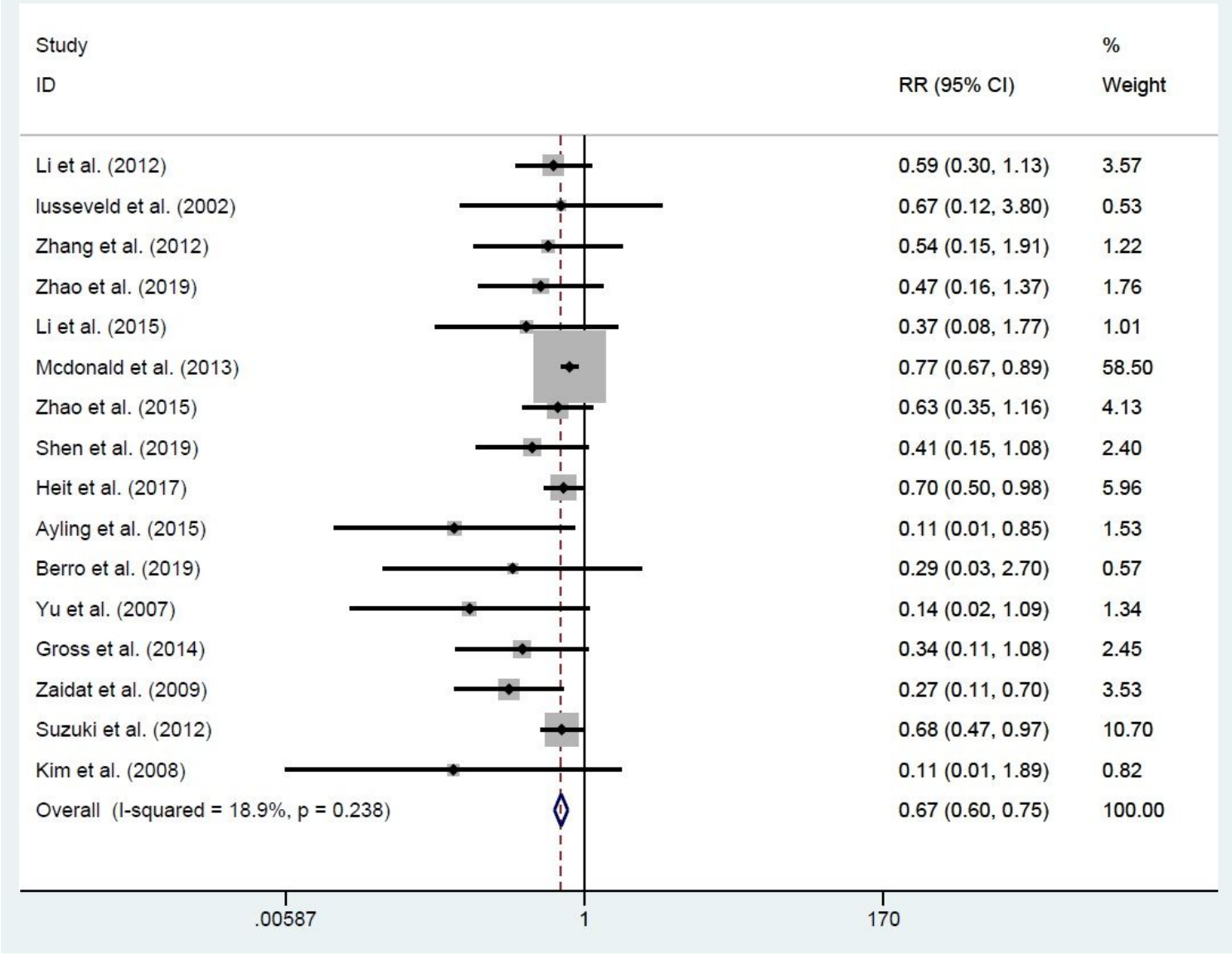

Figure 9

Coiling had a lower postoperative ischemic infarct than clipping with statistical significance (coiling 375 of 2598 (14.4%) VS clipping 597 of 2825 (21.1%); RR=0.669; CI=0.596-0.751; P=0.000; I2=18.9%;)

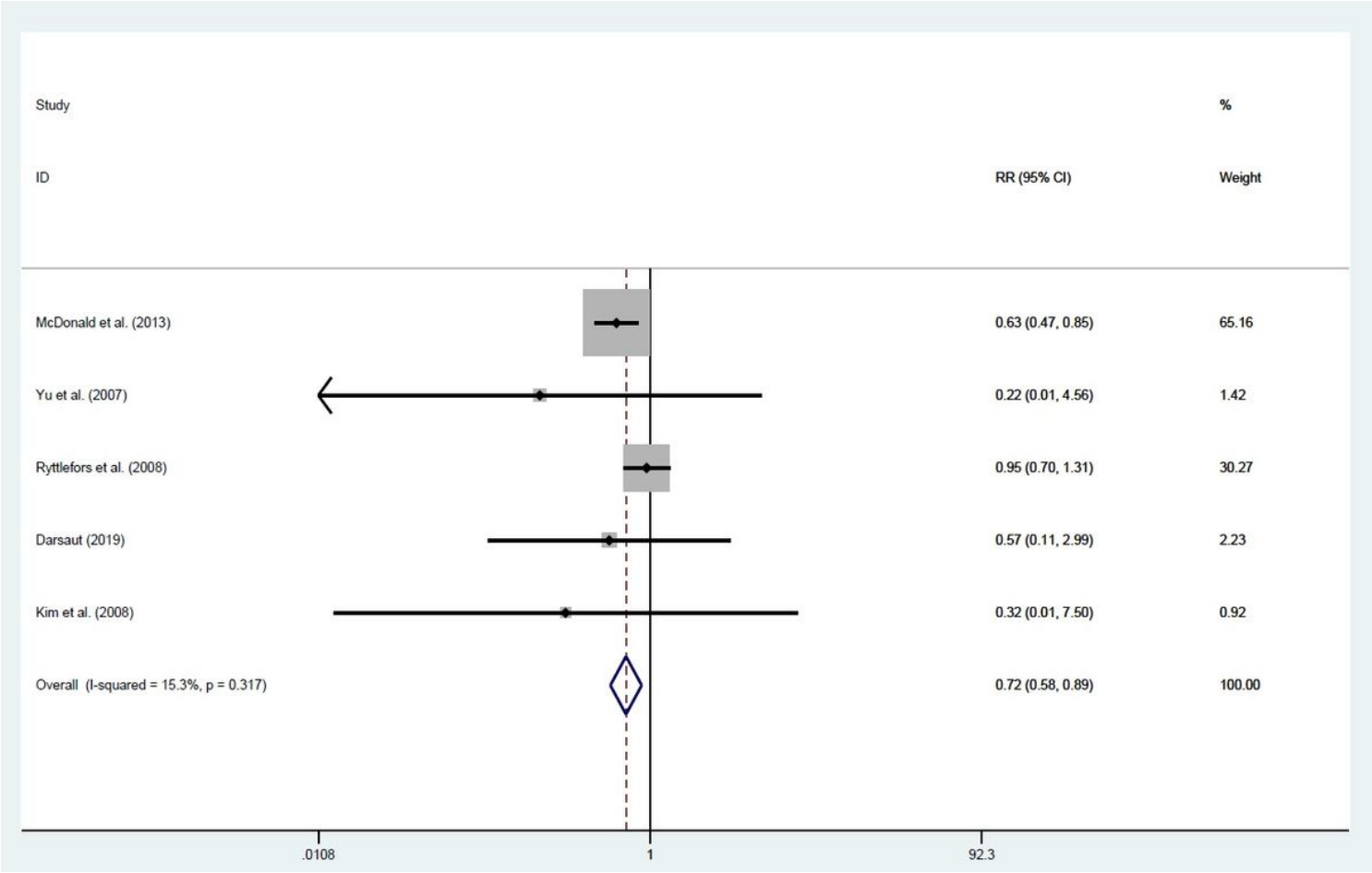

Figure 10

Clipping had a higher rate of postoperative neuro deficits than coiling with statistical significance (coiling 119 of 1530 (7.8%) VS clipping 167 of 1546 (10.8%); RR=0.720; CI=0.582-0.892; P=0.003; I2=15.3%;)

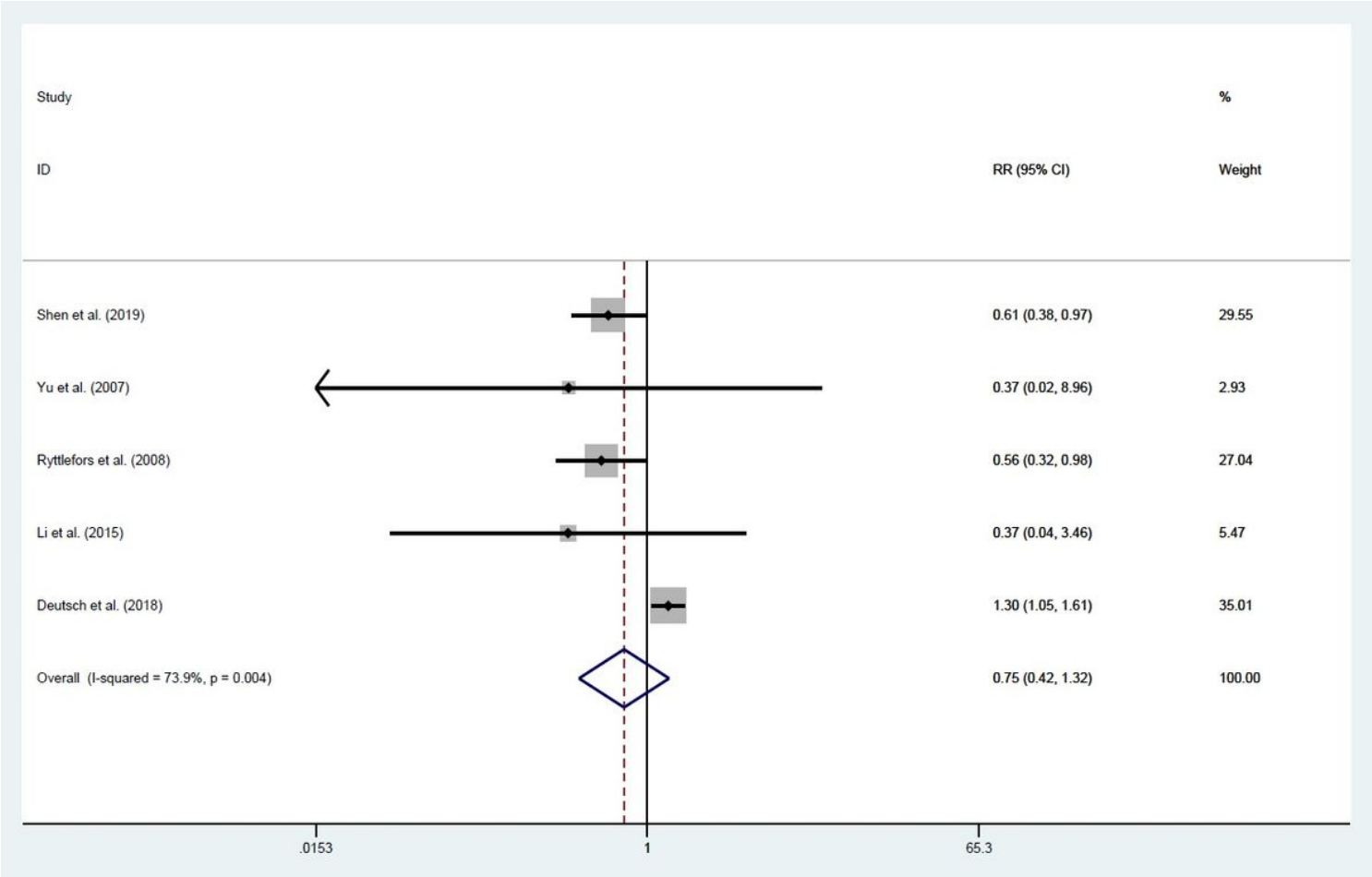

Figure 11

Clipping had a higher intracranial infection than coiling. But there was not a statistical significance (coiling 364 of 15674 (2.3%) VS clipping 187 of 6934 (2.7%); RR=0.745; CI=0.422-1.315; P=0.310; I2=73.9%)

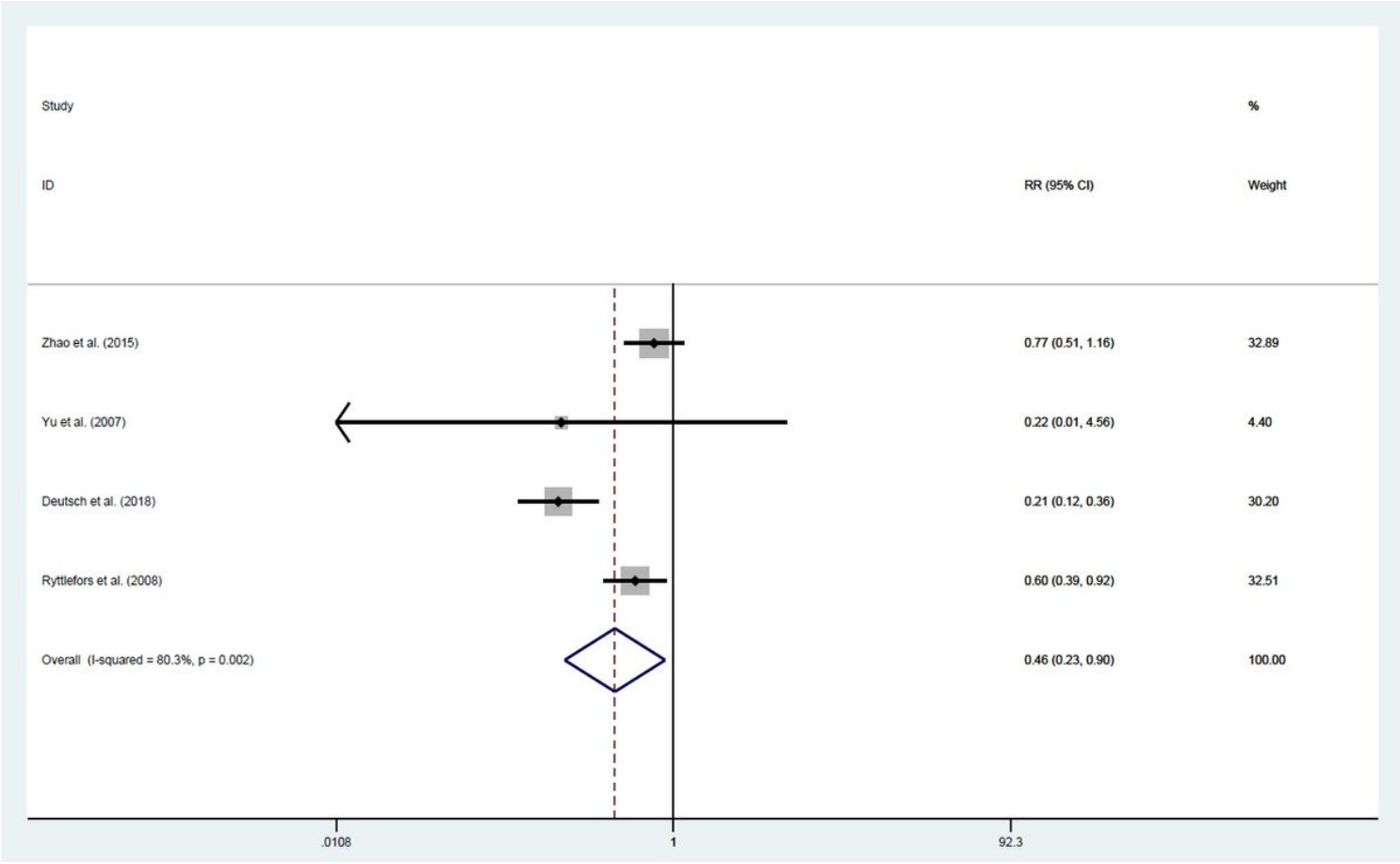

Figure 12

Clipping had a higher respiratory complications than coiling. And there was a statistical significance (coiling 77 of 15701 (0.5%) VS clipping 125 of 6913 (1.8%); RR=0.456; CI=0.232-0.896; P=0.023; I2=80.3%;)

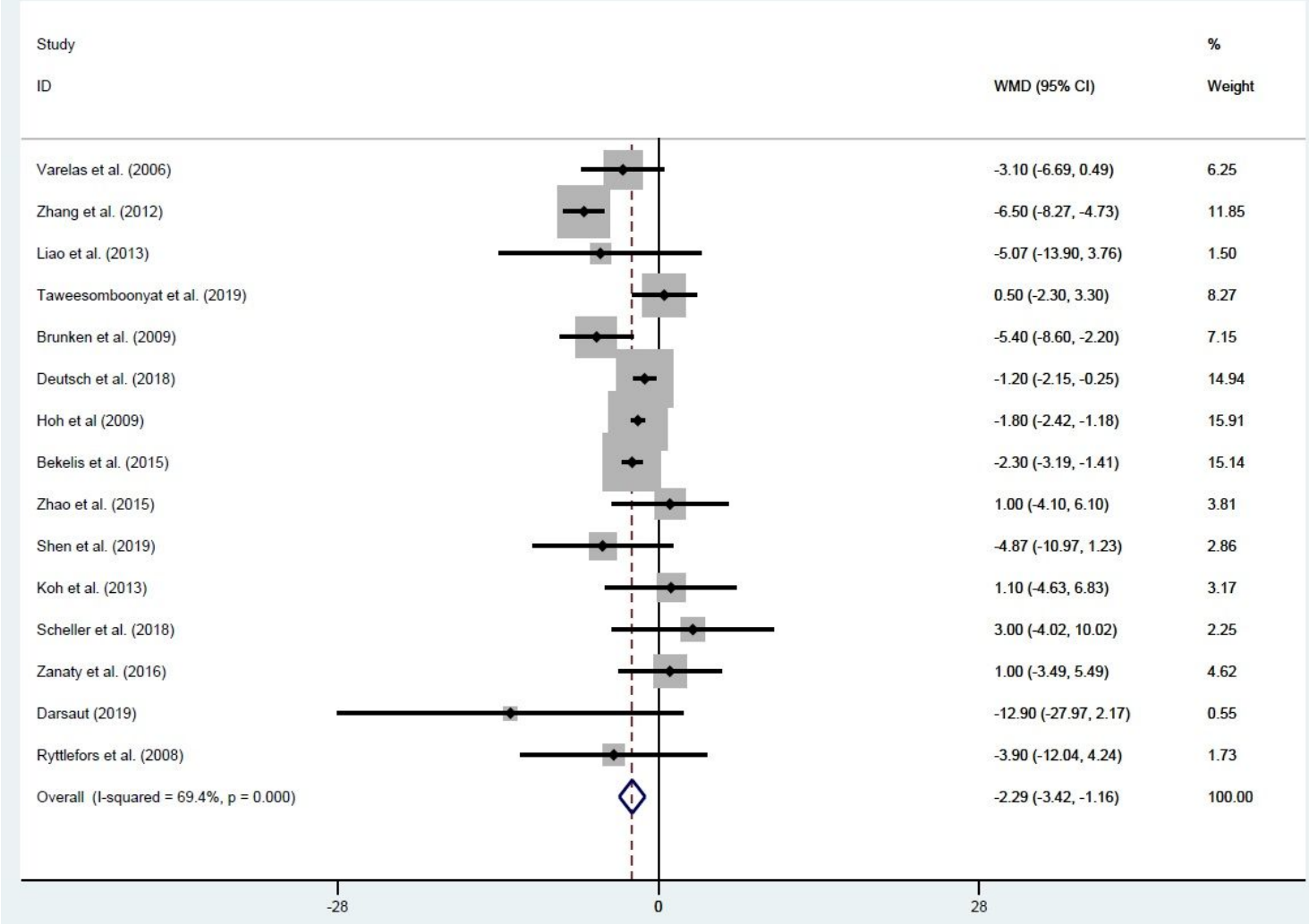

Figure 13

Clipping had a longer length of hospital stay than coiling. And there was a statistical significance (WMD=-2.290; CI=-3.423–1.157; P=0.000; I2=69.4%;)

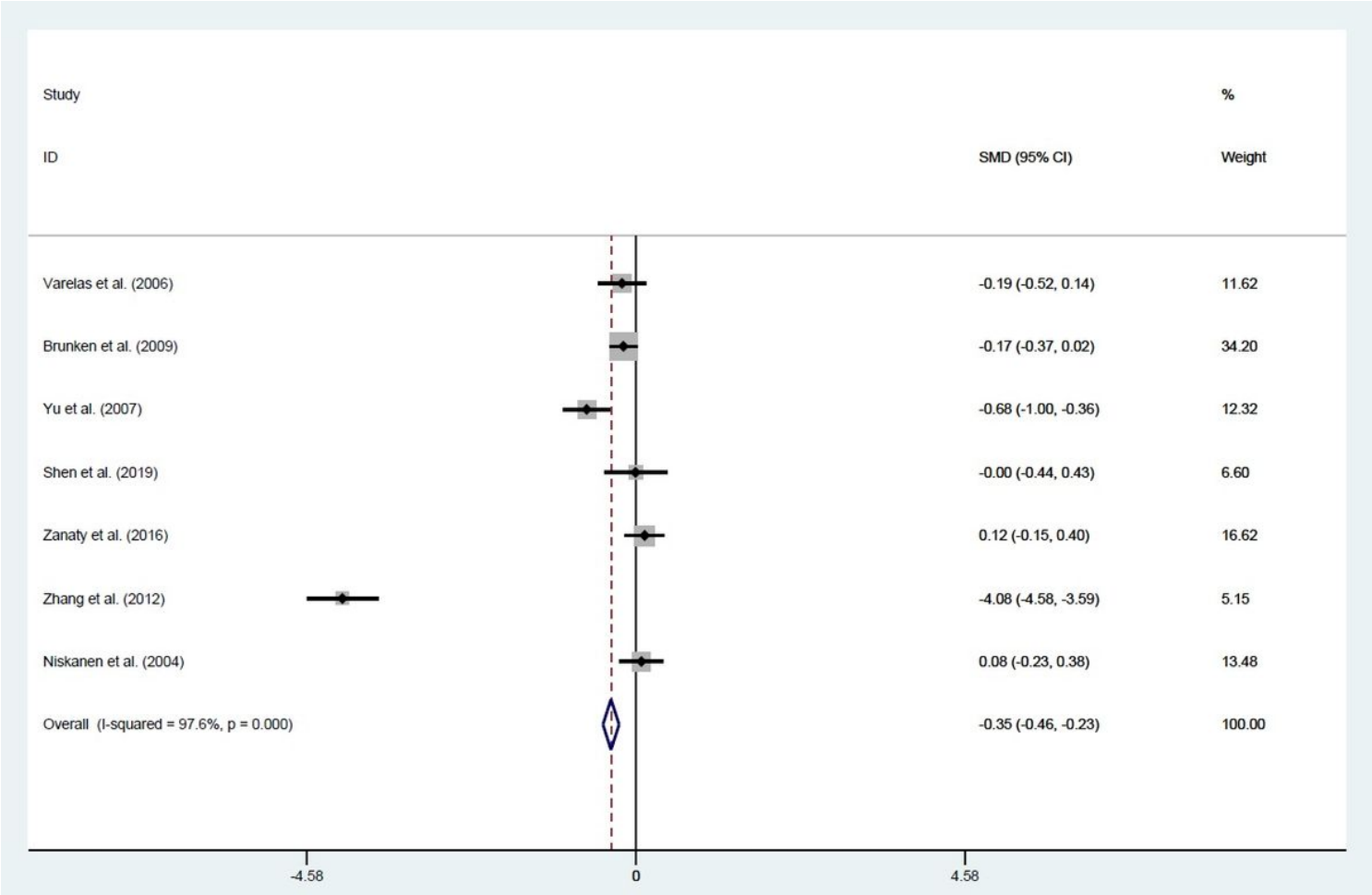

Figure 14

Clipping had a longer LOS in ICU than coiling. And there was a statistical significance (SMD=-0.346; CI=-0.459–0.234; P=0.000; I2=97.6%)

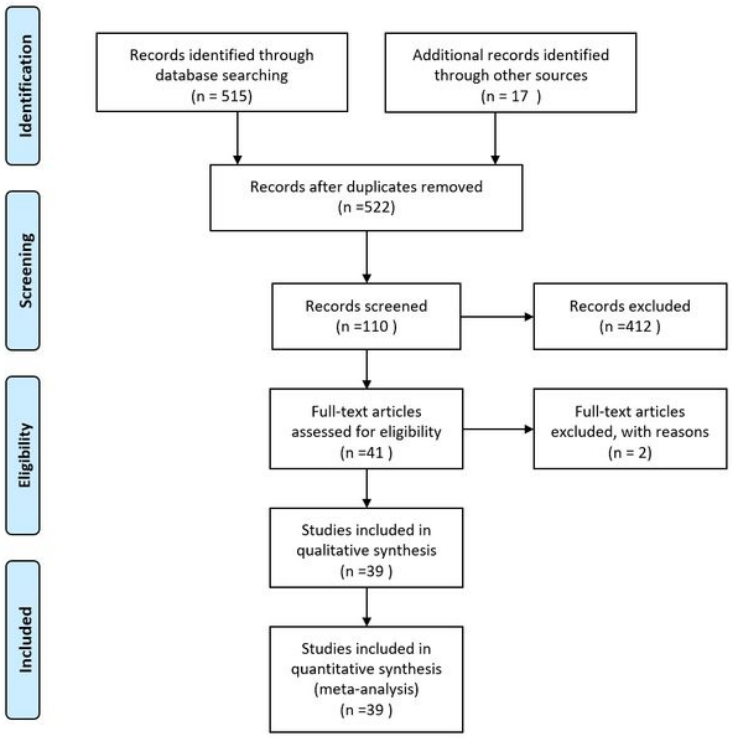

Figure 15

Flowchart

Supplementary Files

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