Systematic Review and Meta-Analysis

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Effects of sevoflurane inhalation anesthesia versus propofol intravenous anesthesia on postoperative cognitive function in patients with malignant tumors

A meta-analysis

Yuhang Quan, MM[a], Mingxiong Zhang, MM[b], Mengqiu Zheng, MM[c], Min Zhao, MM[a], Zhiyong Lv, MM[a], Guangshun Liu, MM[a,*]

Abstract

Background: Both propofol and sevoflurane, commonly used anesthetics, may cause brain oxygen metabolism abnormalities potentially linked to postoperative cognitive dysfunction (POCD), though their precise relationship with POCD requires further study.

Objective: To systematically evaluate sevoflurane inhalation versus propofol intravenous anesthesia effects on postoperative cognitive function in cancer patients.

Methods: We searched PubMed, EMbase, Cochrane Library, CBM, CNKI, Wanfang, VIP, and Chinese Biomedical Literature databases (from January 10, 2023) using keywords including Anaesthesia, Anesthetic Agents, Neoplasm, Cancer, Cognition, and Cognitive Function. Only human randomized controlled trials (RCTs) and prospective cohort studies were included; no language restrictions applied.

Results: 41 studies met criteria (40 RCTs, 1 cohort), involving 4342 patients (2171 sevoflurane, 2171 propofol). Meta-analysis: Overall POCD incidence showed no significant difference between groups. Subgroup analysis revealed significantly increased POCD with sevoflurane at unspecified postoperative times. No significant differences were found at 6 hours, 7 days, or 3 months. Significantly decreased POCD with sevoflurane was observed at 1 and 3 days postoperatively. Preoperative Mini-Mental State Examination (MMSE) scores showed no significant difference. Overall postoperative MMSE scores also showed no significant difference. However, MMSE scores were significantly lower in the sevoflurane group at 1, 3, 6, and 12 hours postoperatively. No significant differences were found at 1, 2, 3, 5, 7 days, or 1 month.

Conclusion subsections: Sevoflurane and propofol anesthesia may exert differing short-term, but not long-term, negative impacts on cognitive function in cancer patients. Overall, no significant difference exists in their effects on postoperative cognitive function.

Abbreviations: MMSE = Mini-Mental State Examination, POCD = postoperative cognitive dysfunction, RCT = randomized controlled trial.

Keywords: anesthesia, cognitive dysfunction, malignant tumor, meta-analysis, neuropsychological tests, postoperative cognitive complications, propofol, sevoflurane

1. Introduction

As the main treatment of solid malignant tumor, surgery is frequently adopted in clinic. Meanwhile, anesthesia, the important part of surgery, not only determines whether the operation can be performed smoothly, but also plays a critical part in the therapeutic effect. Recently, clinical studies find that patients may suffer from cognitive impairment

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

The article does not cover ethical issues, so it does not require approval from the ethics committee.

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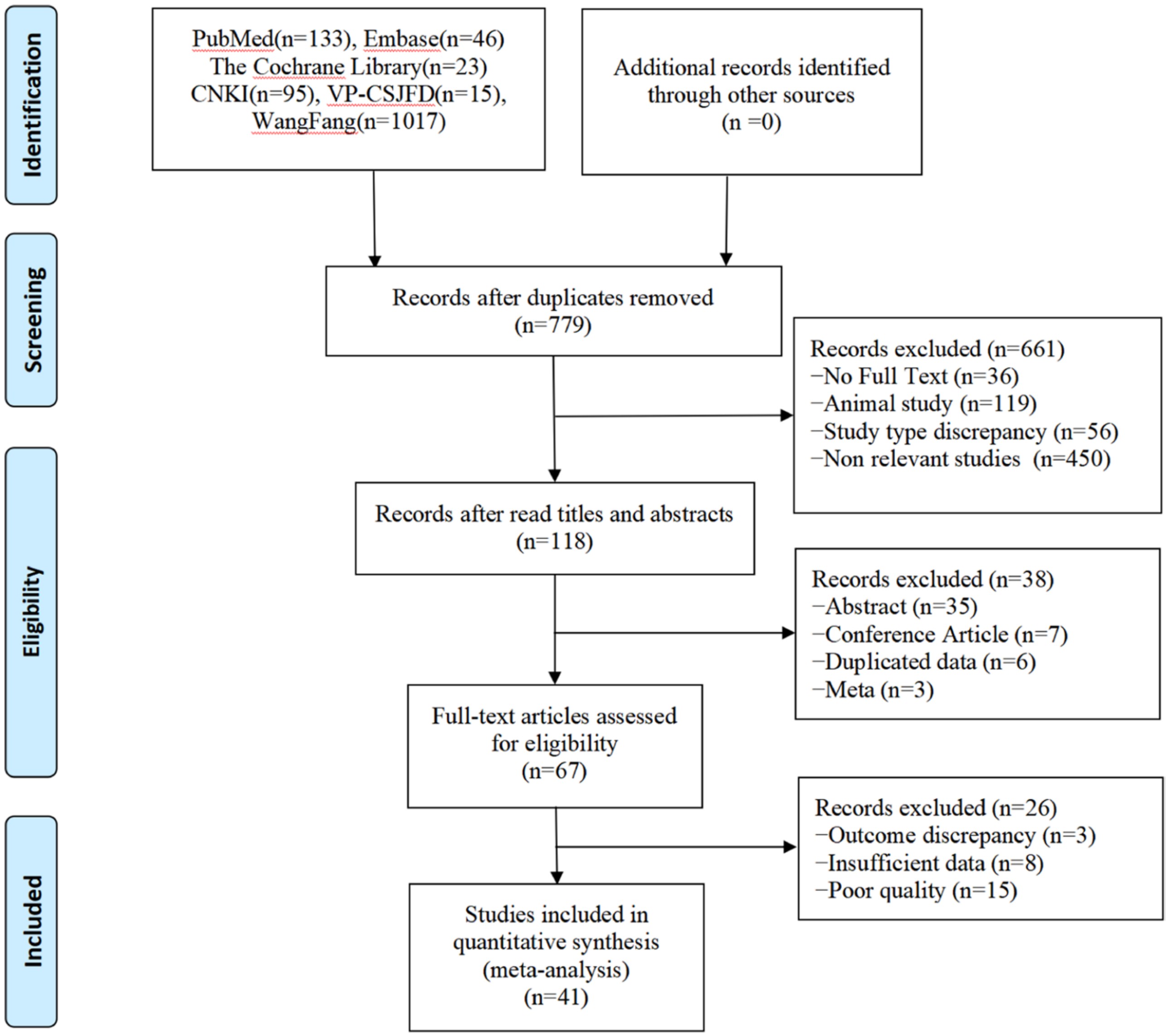

Figure 1. Study selection process.

after anesthesia, and postoperative cognitive dysfunction (POCD) may occur after anesthesia to a certain extent.[1,2] As a common complication after anesthesia, cognitive dysfunction often manifests as memory impairment, cognitive decline, anxiety, personality change, and even dementia. The POCD symptoms may last for several weeks or even months postoperatively, which leads to a longer hospital stay, lower patient life quality, heavier economic burdens on patients, and greater demand for social support, and is also related to higher morbidity and mortality rates.[3] At present, regardless of the largely unclear and multifactorial pathogenic mechanism and etiology of POCD, anesthesia accounts for a key factors affecting the POCD occurrence, while propofol and sevoflurane, the commonly used anesthetics in clinic, can cause abnormal cerebral oxygen metabolism, which in turn leads to POCD. Recent studies by Modolo and Fang showed that inflammatory response induced by surgery is significantly involved in POCD pathogenesis, given that the preoperative administration of corticosteroids ameliorates inflammatory response prompted by surgery and thereby, reduced the severity and incidence of POCD.[4,5]

Sevoflurane is an inhalation anesthetic used to maintain anesthesia, which has been recognized as the risk factor related to cognitive impairment during brain aging, nonetheless, its application remains a source of controversy.[6,7] As shown in certain experimental studies,[8,9] sevoflurane inhalation can cause pathological alterations within the hippocampus of rats and lead to apoptosis, thus leading to the decline of neurocognitive function. Sevoflurane inhalation anesthesia can result in emotional abnormality and cognitive dysfunction in elderly rats undergoing abdominal surgery.[10] Another report[11] points out that sevoflurane does not damage the learning and memory functions of adult rats. Moreover, according to 1 prospective study,[4] sevoflurane general anesthesia is related to cognitive dysfunction among elderly surgical patients suffering from mild cognitive impairment. Nonetheless, the early POCD incidence following general anesthesia was not significantly different between sevoflurane and propofol anesthesia. In 1 RCT, compared with propofol anesthesia, sevoflurane anesthesia has a lower POCD incidence among elderly surgical patients receiving propofol anesthesia 1 and 3 days postoperatively, nevertheless, the RCT is limited since postoperative delirium and POCD are not defined.[12] However, a RCT finds that the POCD incidence is not significantly different between sevoflurane anesthesia and propofol anesthesia 3 months after operation.[13]

Table 1

Baseline study features and quality assessment.

Number	Author	Year	Country	Study	Intervention measures		Sample size		Disease	Jender		Age		Jadad score	Outcome measures
					Observation	Control	Observation	Control		Observation	Control	Observation	Control		
1	Qiu S	2016	China	RCT	Sevoflurane	Propofol	30	30	Lung cancer	20/10	18/12	71.4± ± 6.3	70.5 ± 6.6	4	MMSE, POCD
2	Huang MH	2021	China	RCT	Sevoflurane	Propofol	50	50	Gastric carcinoma	24/26	23/27	68.67 ± 3.45	68.65 ± 3.48	4	MMSE
3	Yang XL	2021	China	RCT	Sevoflurane	Propofol	30	30	Prostate cancer	NA	NA	72.5 ± 8.7	71.0 ± 7.2	4	MMSE
4	Shang YW	2020	China	RCT	Sevoflurane	Propofol	34	34	Gastric carcinoma	17/17	18/16	53.59 ± 5.84	54.28 ± 5.23	3	MMSE
5	Zhang L	2021	China	RCT	Sevoflurane	Propofol	46	47	Gastric carcinoma	24/22	26/21	58.79 ± 8.94	59.03 ± 8.97	4	MMSE
6	Wang W	2020	China	RCT	Sevoflurane	Propofol	47	48	Gastric carcinoma	21/26	18/30	74.38 ± 5.34	73.25 ± 5.81	4	MMSE
7	Zhu TF	2021	China	RCT	Sevoflurane	Propofol	50	50	Esophagus cancer	35/15	36/14	60.08 ± 4.92	60.11 ± 4.91	4	MMSE
8	Jiang XY	2019	China	RCT	Sevoflurane	Propofol	50	50	Gastric carcinoma	29/21	27/23	71.59 ± 10.34	72.54 ± 10.19	4	MMSE
9	Chai H	2021	China	RCT	Sevoflurane	Propofol	40	40	Colorectal cancer	21/19	24/16	66.30 ± 5.71	65.05 ± 4.87	3	MMSE
10	Xiao YR	2014	China	RCT	Sevoflurane	Propofol	32	32	Lung cancer	20/12	18/14	65.57 ± 4.51	65.48 ± 4.59	3	MMSE
11	Tang CJ	2014	China	RCT	Sevoflurane	Propofol	35	35	Lung cancer	20/15	18/17	69.2 ± 12.6	70.5 ± 10.8	4	MMSE, POCD
12	Liu W	2018	China	RCT	Sevoflurane	Propofol	45	45	Gastric carcinoma	23/22	24/21	69.1 ± 9.3	68.4 ± 8.2	4	MMSE
13	Le SY	2019	China	RCT	Sevoflurane	Propofol	46	46	Gastric carcinoma	27/19	26/20	65.5 ± 0.5)	66.5 ± 0.5	4	MMSE
14	Ma GX	2021	China	RCT	Sevoflurane	Propofol	90	90	Lung cancer	59/31	48/42	52.75 ± 9.21	53.68 ± 10.23	4	MMSE
15	Li YA	2017	China	RCT	Sevoflurane	Propofol	45	41	Gastric carcinoma	30/15	28/16	69.1 ± 1.3	68.7 ± 1.5	4	MMSE
16	Wang W	2020	China	RCT	Sevoflurane	Propofol	32	32	Esophagus cancer	17/15	18/14	66.25 ± 2.52	65.47 ± 3.68	5	MMSE
17	Wang YH	2015	China	RCT	Sevoflurane	Propofol	30	30	Gastric carcinoma	21/9	22/8	70.9 ± 2.9	71.8 ± 3.1	4	MMSE
18	Zhang SL	2016	China	RCT	Sevoflurane	Propofol	49	50	Lung cancer	27/22	26/24	66.89 ± 5.82	67.03 ± 6.18	3	MMSE, POCD
19	Zhang SL	2018	China	RCT	Sevoflurane	Propofol	34	34	Gastric carcinoma	21/13	20/14	60.4 ± 2.2	59.2 ± 1.8	4	MMSE
20	Lu JH	2017	China	RCT	Sevoflurane	Propofol	77	77	Lung cancer	52/25	56/21	66.01 ± 8.21	64.78 ± 6.28	4	MMSE
21	Hou HJ	2021	China	RCT	Sevoflurane	Propofol	42	41	Lung cancer	29/13	26/15	67.56 ± 3.29	67.51 ± 3.31	4	MMSE
22	Su J	2015	China	RCT	Sevoflurane	Propofol	41	41	Lung cancer	28/13	30/11	70.53 ± 4.19	70.83 ± 4.11	5	MMSE
23	Zhang AC	2015	China	RCT	Sevoflurane	Propofol	53	53	Lung cancer	37/16	35/18	63.7 ± 3.5	63.8 ± 3.4	4	MMSE
24	Huang DH	2015	China	RCT	Sevoflurane	Propofol	45	45	Lung cancer	25/20	25/20	67.99 ± 1.24	68.59 ± 1.79	4	MMSE
25	Cao L	2013	China	RCT	Sevoflurane	Propofol	63	63	Colorectal cancer	47/20	45/22	43.37 ± 13.38	43.66 ± 12.53	4	MMSE
26	Luo D	2015	China	RCT	Sevoflurane	Propofol	107	107	Esophagus cancer	70/37	67/40	64.7 ± 2.8	65.0 ± 3.1	4	MMSE
27	Yu XC	2012	China	RCT	Sevoflurane	Propofol	40	40	Lung cancer	22/18	22/18	68.53 ± 3.51	69.00 ± 4.14	4	MMSE
28	Liao WN	2018	China	RCT	Sevoflurane	Propofol	45	45	Lung cancer	37/8	38/7	69.9 ± 1.3	70.0 ± 1.3	4	MMSE
29	Chen HM	2018	China	RCT	Sevoflurane	Propofol	62	62	Lung cancer	39/23	41/21	69.64 ± 8.99	71.02 ± 9.31	4	MMSE, POCD
30	Guo L	2020	China	RCT	Sevoflurane	Propofol	117	117	Cancer	76/41	71/46	69.0 (66.0, 74.0)	69.0 (66.0, 72.5)	6	MMSE, POCD
31	Qiao Y	2015	China	RCT	Sevoflurane	Propofol	30	30	Esophagus cancer	22/8	21/9	68 ± 3	68 ± 2	6	MMSE
32	Tang N	2014	China	RCT	Sevoflurane	Propofol	99	101	Rectal cancer	32/67	32/67	70.0 ± 4.3	70.0 ± 4.3	5	POCD
33	Egawa J	2016	Japan	RCT	Sevoflurane	Propofol	72	72	Lung cancer	33/39	23/48	72 (63–72)	69 (63–73)	6	MMSE, POCD
34	Ishii K	2016	Japan	RCT	Sevoflurane	propofol	30	29	Gastrointestinal cancer	20/10	20/9	76.5 ± 4.5	77.3 ± 4.6	6	POCD
35	Zhang Y	2018	China	RCT	Sevoflurane	Propofol	189	190	Cancer	130/59	128/62	72.4 ± 5.6	72.8 ± 5.5	5	MMSE, POCD
36	Yi D	2018	China	RCT	Sevoflurane	Propofol	55	55	Rectal cancer	32/23	29/26	56.10 ± 11.35	58.75 ± 12.98	4	MMSE
37	Gan Y	2011	China	RCT	Sevoflurane	Propofol	30	30	Gastric carcinoma	40/20		65.76 ± 5.82		3	MMSE, POCD
38	Han J	2019	China	RCT	Sevoflurane	Propofol	30	30	Gastric carcinoma	16/14	18/12	69 ± 5	69 ± 5	4	MMSE
39	Guo LL	2016	China	RCT	Sevoflurane	Propofol	45	45	Gastric carcinoma	23/22	24/21	66.5 ± 2.3	66.8 ± 3	4	MMSE
40	Li HJ	2020	China	RCT	Sevoflurane	Propofol	54	54	Cervical carcinoma	NA	NA	45 ± 8.04	49 ± 9.48	4	MMSE
41	Cai MS	2015	China	RCT	Sevoflurane	Propofol	30	30	Lung cancer	NA	NA	69.43 ± 2.17		4	MMSE, POCD

MMSE = Mini-Mental State Examination, POCD = postoperative cognitive dysfunction, RCT = randomized controlled trial.

To sum up, the above data show that more investigations are needed to explore the relationship between sevoflurane versus propofol anesthesia and postoperative cognitive function. Therefore, it is of positive significance to explore the efficacy of propofol versus sevoflurane in postoperative cognitive function of cancer patients. To this end, the present work conducted a meta-analysis to offer some guiding significance for clinical practice.

2. Data and methods

2.1. Inclusion criteria

Research type: clinical randomized controlled trials (RCTs). Objects of study: cancer patients, with no restriction of cancer type. Interventions: sevoflurane/ether was used in observation group, whereas propofol was used in control group. Outcome measures: Mini-mental State Examination (MMSE) score and the POCD incidence.

2.2. Exclusion criteria

Studies satisfying at least one of criteria below were eliminated: studies with unclear research objects; unable to extract data; studies not including research indicators; documents with duplicate data; duplicate publications; summaries and case reports; non-RCTs; documents with inconsistent intervention measures; and pet-name ruby basic experimental research.

2.3. Literature retrieval

RCTs or prospective cohort studies comparing the efficacy of sevoflurane inhalation anesthesia versus propofol intravenous anesthesia in cancer patients were retrieved in PubMed, EMbase, the Cochrane Library, CBM, CNKI, Wanfang Medical Network, VIP, and Chinese Biomedical Literature network database to obtain relevant articles up to January 10, 2023 using the keywords of Anaesthesia, Anesthetic Agents, Anesthetic Drugs, Anesthetic, Neoplasm, Tumor, Neoplasia, Cancer, Malignant Neoplasm, Malignancy, Malignancies, Malignant Neoplasms, Malignant tumor, Cognition, and Cognitive Function. The search was not restricted by language and Human and animal studies are not included.

2.4. Data extraction

All the retrieved documents were screened by 2 independent researchers in the research group in strict accordance

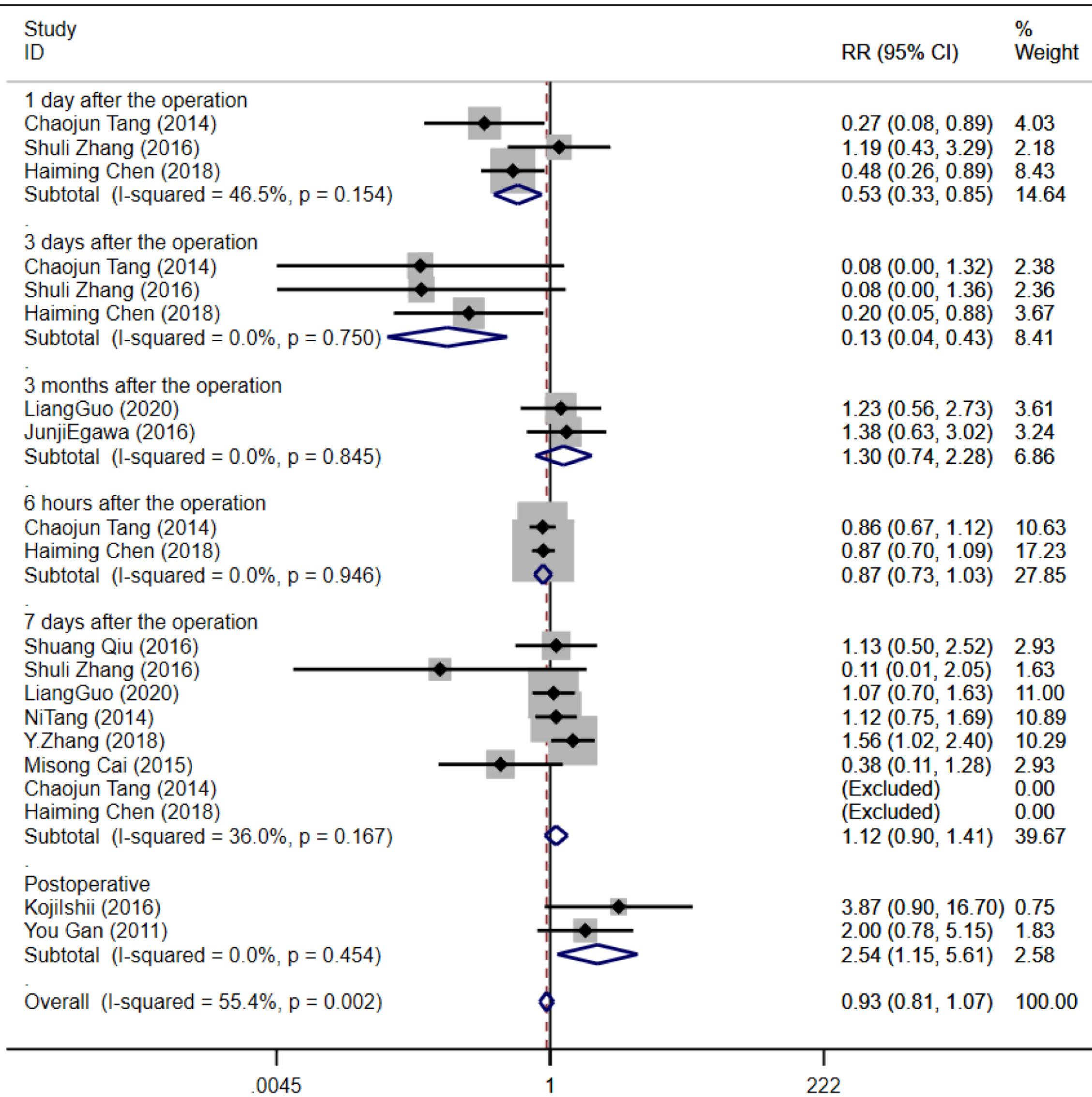

Figure 2. Incidence of POCD. POCD = postoperative cognitive dysfunction.

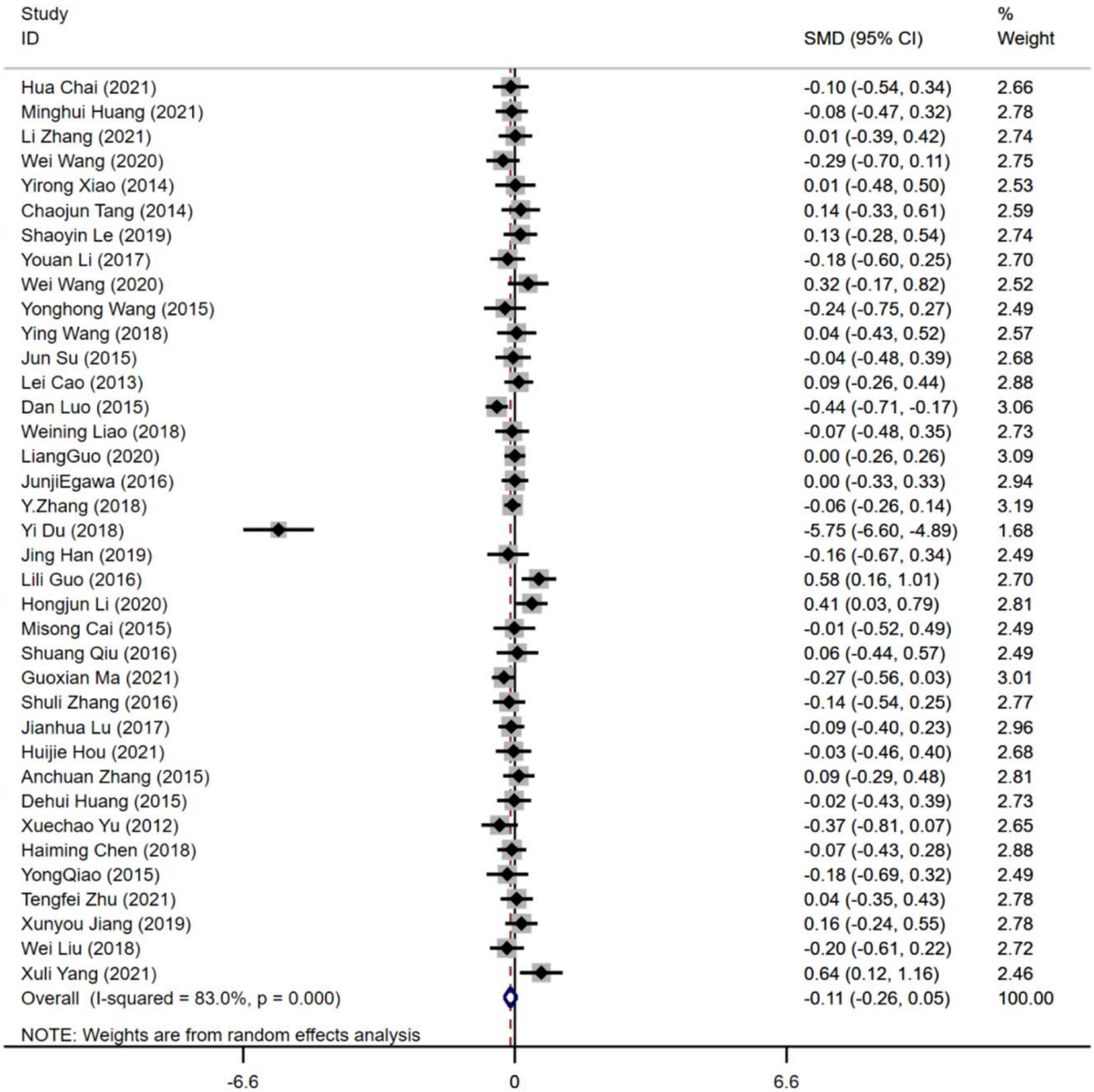

Figure 3. MMSE scores in preoperative patients. MMSE = Mini-Mental State Examination.

with our predetermined eligibility criteria. Any disagreement between them was solved through discussion. The basic information extracted mainly included author and publication year, gender, age, sample size, intervention measures, and treatment duration. Meanwhile, the main outcome measure data extracted were MMSE score and POCD incidence.

2.5. Evaluation of methodological quality in the literature

The Jadad quality scoring method was utilized for evaluating the RCT methodological quality, and the evaluation items included randomization, allocation concealment, blinding method, and withdrawals and dropouts.[14] Studies of 4 to 7 points had high quality, while those of 1 to 3 points had low quality.

2.6. Statistical analysis

Stata17.0 was employed for statistical analysis. Continuous data were expressed by mean differences (MD) and 95% confidence interval (CI), while dichotomous data were analyzed through odds ratio (OR) and 95%CI.

3. Results

3.1. Study retrieval and screening

This work identified altogether 1329 documents from primary literature retrieval, and 779 of them were retained after duplicates were removed. Titles and abstracts were read, as a result, 67 documents were chosen in line with eligibility criteria. Thereafter, full-texts were carefully read, and non-RCTs were eliminated. Finally, 41 studies were included.[15–55] Figure 1 displays the study selection process.

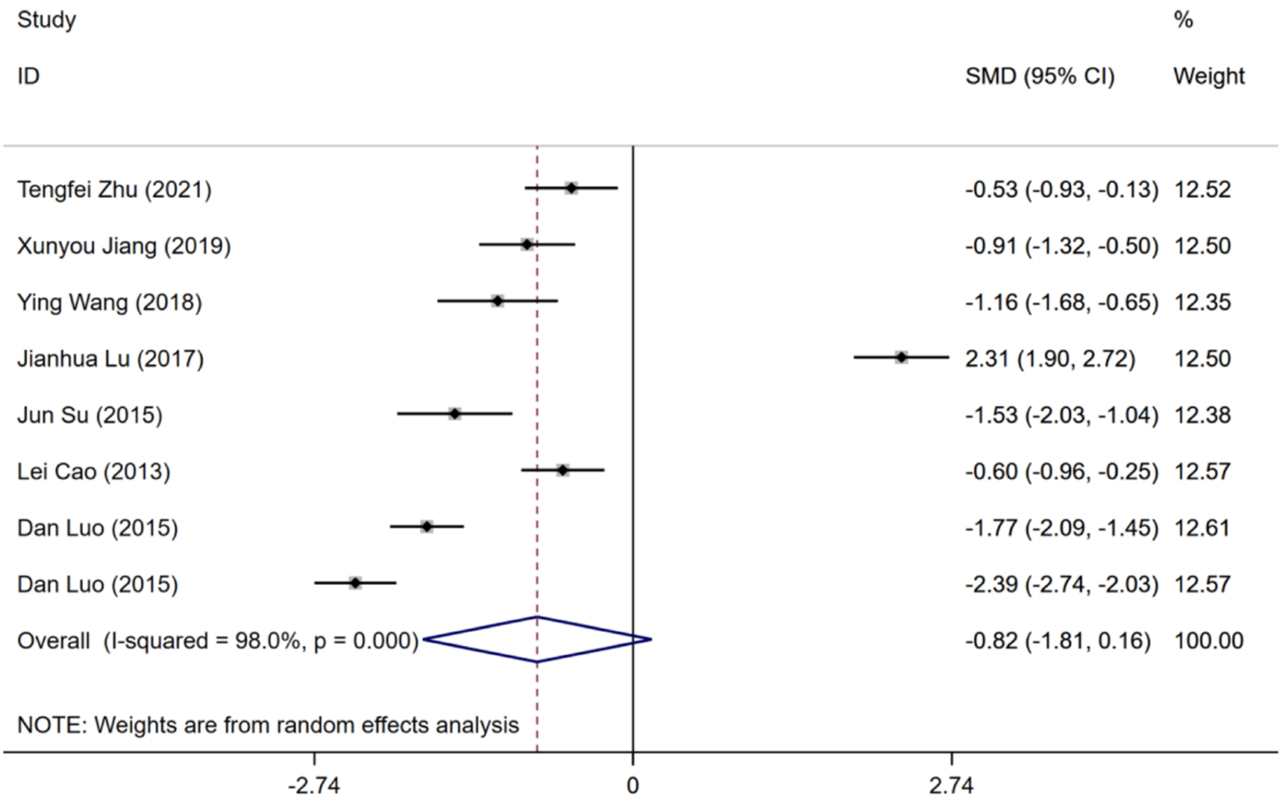

Figure 4. MMSE scores of patients 1 h after operation. MMSE = Mini-Mental State Examination.

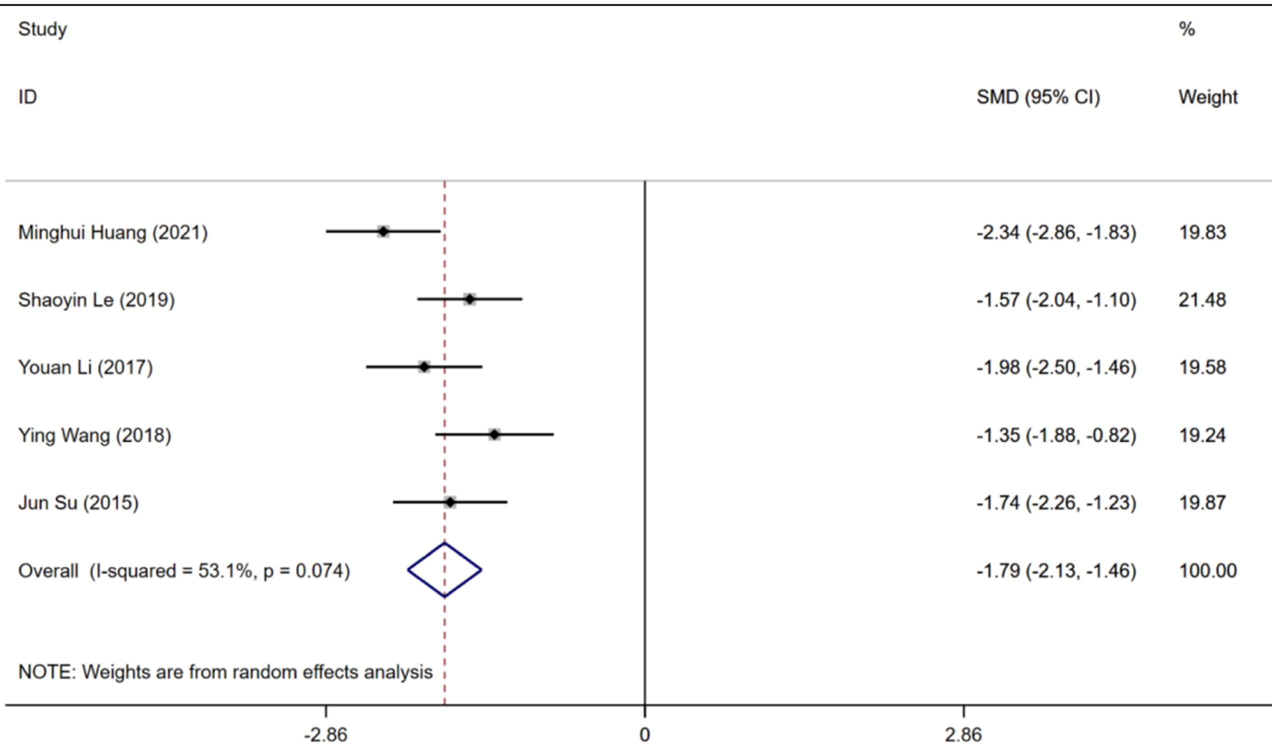

Figure 5. MMSE scores of patients 3 h after operation. MMSE = Mini-Mental State Examination.

3.2. Baseline study features and quality assessment

Table 1 displays baseline study features. Besides, quality of those enrolled articles was evaluated, which suggested that 5 RCTs had the Jadad score of 3 points, and the others had the score of ≥ 4 points, demonstrating high quality of our enrolled studies.

3.3. Meta-analysis results

3.3.1. Incidence of POCD. Due to the inconsistent time points of detecting the incidence of POCD after anesthesia among various studies, including postoperatively (unspecified time), 6 hours, 1, 3, 7 days, and 3 months postoperatively, subgroup

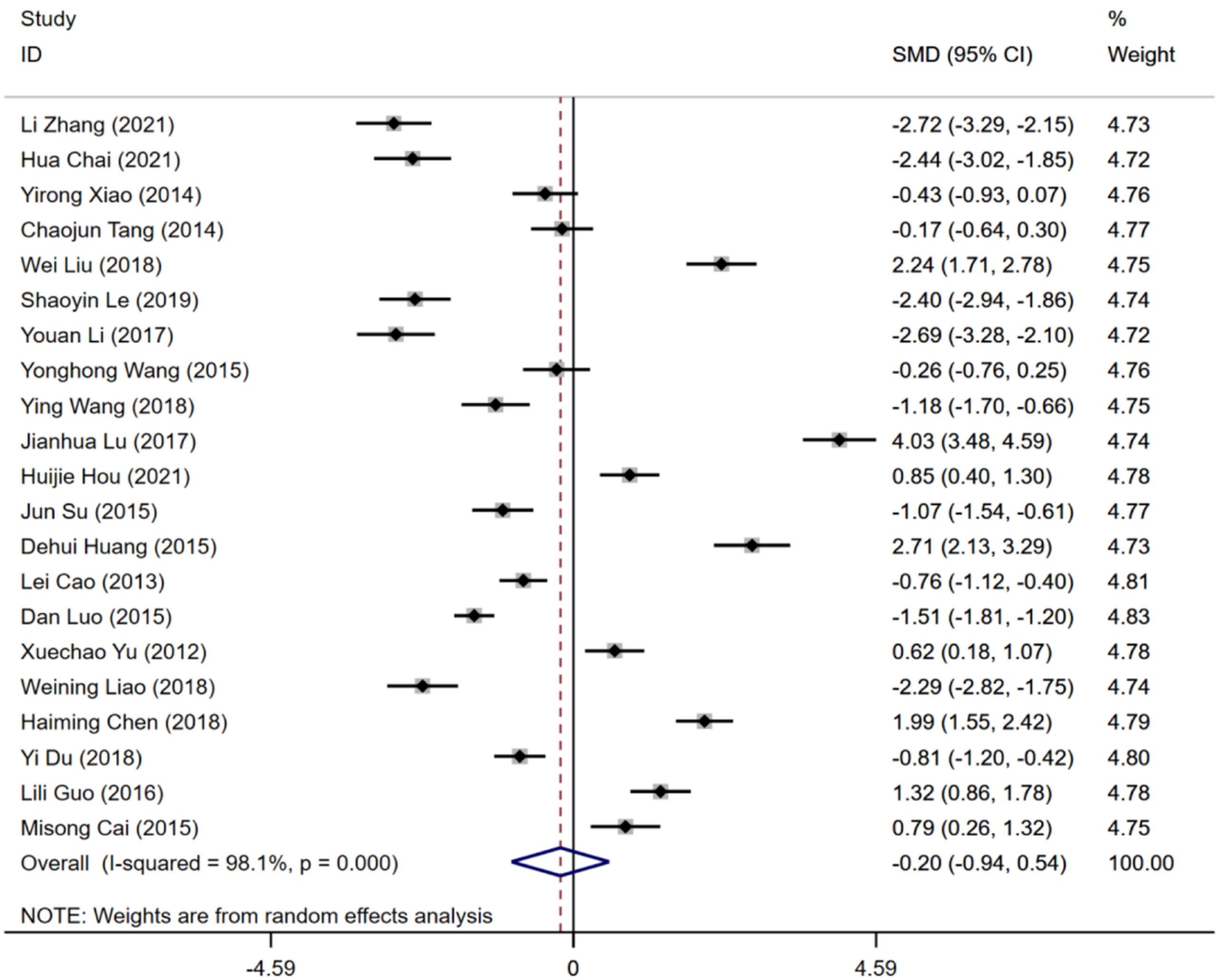

Figure 6. MMSE scores of patients 6 h after operation. MMSE = Mini-Mental State Examination.

analysis was carried out according to the different time points of POCD detection. In the subgroup after operation (unspecified time), 2 studies[48,51] reported the incidence of POCD, and the heterogeneity test ($I^2 = 0.0\%$ and $P > .10$) showed the absence of obvious heterogeneity across those enrolled articles, therefore, a fixed-effect model was adopted for calculating combined effect. As a result, the POCD incidence of sevoflurane group increased relative to control group, with a significant difference [RR = 2]. In the subgroup 6 hours after operation, 2 studies[25,43] mentioned the POCD incidence, and heterogeneity test ($I^2 = 0.0\%$ and $P > .10$) showed no obvious heterogeneity across those enrolled articles; similarly, a fixed-effect model was applied in analyzing combined effect, which demonstrated that the POCD incidence was not significantly different between 2 groups [RR = 0.87, 95% CI]. In the subgroup 1 day postoperatively, 3 studies[25,32,43] reported the incidence of POCD, and the heterogeneity test ($I^2 = 46.5\%$ and $P > .10$) showed little heterogeneity across those enrolled articles, so the fixed-effect model was used for analyzing combined effect. It was found that the POCD incidence of sevoflurane group decreased relative to control group, with a significant difference [RR = 0.50]. Three studies[25,32,43] mentioned the POCD incidence in the subgroup 3 days postoperatively, and the heterogeneity test ($I^2 = 0.0\%$ and $P > .10$) showed the absence of heterogeneity across those enrolled articles, and the fixed-effect model was adopted to examine combined effect. As discovered, the POCD incidence of sevoflurane group decreased relative to control group, with a significant difference [RR = 0.13]. Seven days after operation, 8 studies[15,25,32,43,44,46,49,55] mentioned the POCD incidence, and heterogeneity test ($I^2 = 36.0\%$ and $P > .10$) revealed little heterogeneity across those enrolled articles, so combined effect was analyzed by using the fixed-effect model. Our findings revealed no significant difference between 2 groups of patients. In the subgroup 3 months after operation, 2 studies[44,47] reported the incidence of POCD, and the heterogeneity test ($I^2 = 0.0\%$ and $P > .10$) demonstrated no obvious heterogeneity across those enrolled articles, so the fixed-effect model was utilized to analyze combined effect. We discovered that the POCD incidence was not significantly different between 2 groups (RR = 1.30, 95% CI[0.74, 2.28], $P > .05$) (Fig. 2).

3.3.2. MMSE scores. Because of the different time points of detecting MMSE scores after anesthesia in various studies, including preoperatively (unspecific time), 1, 3, 6, 12 hours, 1, 2, 3, 5, 7 days and 3 months postoperatively, analyses were made according to the different detection time points of detecting MMSE scores.

3.3.2.1. Meta-analysis of MMSE scores in preoperative patients. Thirty-seven studies reported the preoperative MMSE scores of patients, including 1978 patients of sevoflurane group whereas 1977 of propofol group. A large heterogeneity was detected by heterogeneity test ($I^2 = 83.0\%$ and $P < .10$) across diverse enrolled articles, therefore, combined effect was analyzed by using the random-effects model. As a result, MMSE scores were not significantly different between 2 groups (standardized

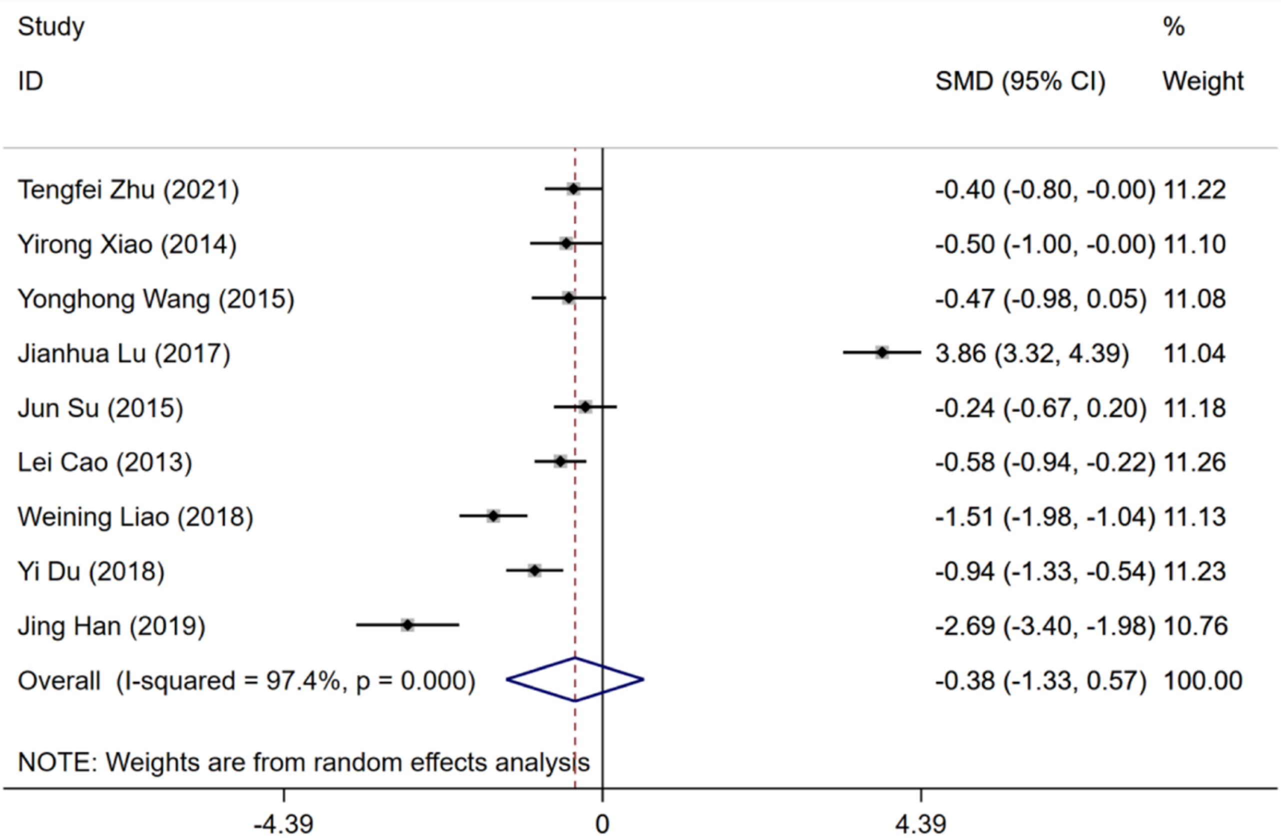

Figure 7. MMSE scores in patients 12 h postoperatively. MMSE = Mini-Mental State Examination.

mean difference [SMD] = −0.11, 95% CI: [−0.26, 0.05], $P > .05$). Moreover, given the high heterogeneity across enrolled articles, sensitivity analysis was carried out by eliminating 1 article each time. It was found that the study conducted by Yi Du[50] was the main source leading to the increase in heterogeneity. After eliminating this study, the results still showed no significant difference in preoperative MMSE scores between 2 groups, so these results were relatively stable and reliable (Fig. 3).

3.3.2.2. Meta-analysis of MMSE scores of patients 1 hour after operation. Eight articles reported the MMSE scores of patients 1 hour postoperatively, including 529 cases of sevoflurane group while 529 of propofol group. A large heterogeneity was detected upon heterogeneity test ($I^2 = 98.0\%$ and $P < .10$) across those enrolled articles, so combined effect was quantified by using the random-effects model. According to our findings, MMSE score was not significantly different between 2 groups 1 hour postoperatively (SMD = −0.82, 95% CI: [−1.81, 0.16], $P > .05$). Considering the high degree of heterogeneity across those enrolled articles, we conducted sensitivity analysis through eliminating 1 article each time, and found that the study performed by Lu[34] accounted for the major source of heterogeneity. When this study was excluded, the results obtained still suggested that MMSE score in sevoflurane group decreased relative to propofol group 1 hour postoperatively, with a significant difference. Therefore, the result was unstable and not reliable, which should be interpreted with caution (Fig. 4).

3.3.2.3. Meta-analysis of MMSE scores of patients 3 hours after operation. Five articles mentioned the MMSE scores of patients 3 hours postoperatively, including 216 cases from sevoflurane group while 212 from propofol group. As suggested by heterogeneity test ($I^2 = 53.1\%$ and $P < .10$), a great heterogeneity was detected across those enrolled articles, and combined effect was analyzed by the random-effects model. It was discovered that, MMSE score of sevoflurane group decreased relative to propofol group 3 hours postoperatively, with a significant difference (SMD = −1.79, 95% CI: [−2.13, −1.46]). Because of the large heterogeneity detected across those enrolled articles, sensitivity analysis was performed through eliminating 1 article each time, but the major source of heterogeneity was not detected. After excluding any literature, the results obtained still demonstrated the decreased MMSE score in sevoflurane group relative to propofol group 3 hours after operation, so the results were relatively stable and reliable (Fig. 5).

3.3.2.4. Meta-analysis of MMSE scores of patients 6 hours after operation. There were 21 articles reporting MMSE scores of patients 6 hours postoperatively, including 1005 cases from sevoflurane group while 1001 from propofol group. As suggested by heterogeneity test ($I^2 = 98.1\%$ and $P < .10$), a large heterogeneity was detected across those enrolled articles, so combined effect was analyzed using the random-effects model. According to our findings, MMSE scores were not significantly different between 2 groups 6 hours postoperatively (SMD = −0.20, 95% CI: [−0.94, 0.54], $P > .05$). Because of the large heterogeneity across those enrolled articles, sensitivity analysis was conducted through excluding 1 study each time, but the major source of heterogeneity was not detected. After excluding any study, MMSE score in sevoflurane group always decreased compared with propofol group 6 hours after operation, so the results were relatively stable and reliable (Fig. 6).

3.3.2.5. Meta-analysis of MMSE scores in patients 12 hours postoperatively. Nine articles mentioned the MMSE scores in patients 12 hours postoperatively, including 1978 cases from sevoflurane group while 1977 from propofol group. A large heterogeneity was detected upon heterogeneity test ($I^2 = 97.4\%$ and $P < .10$) across those enrolled articles, so the combined effect was analyzed using the random-effects model.

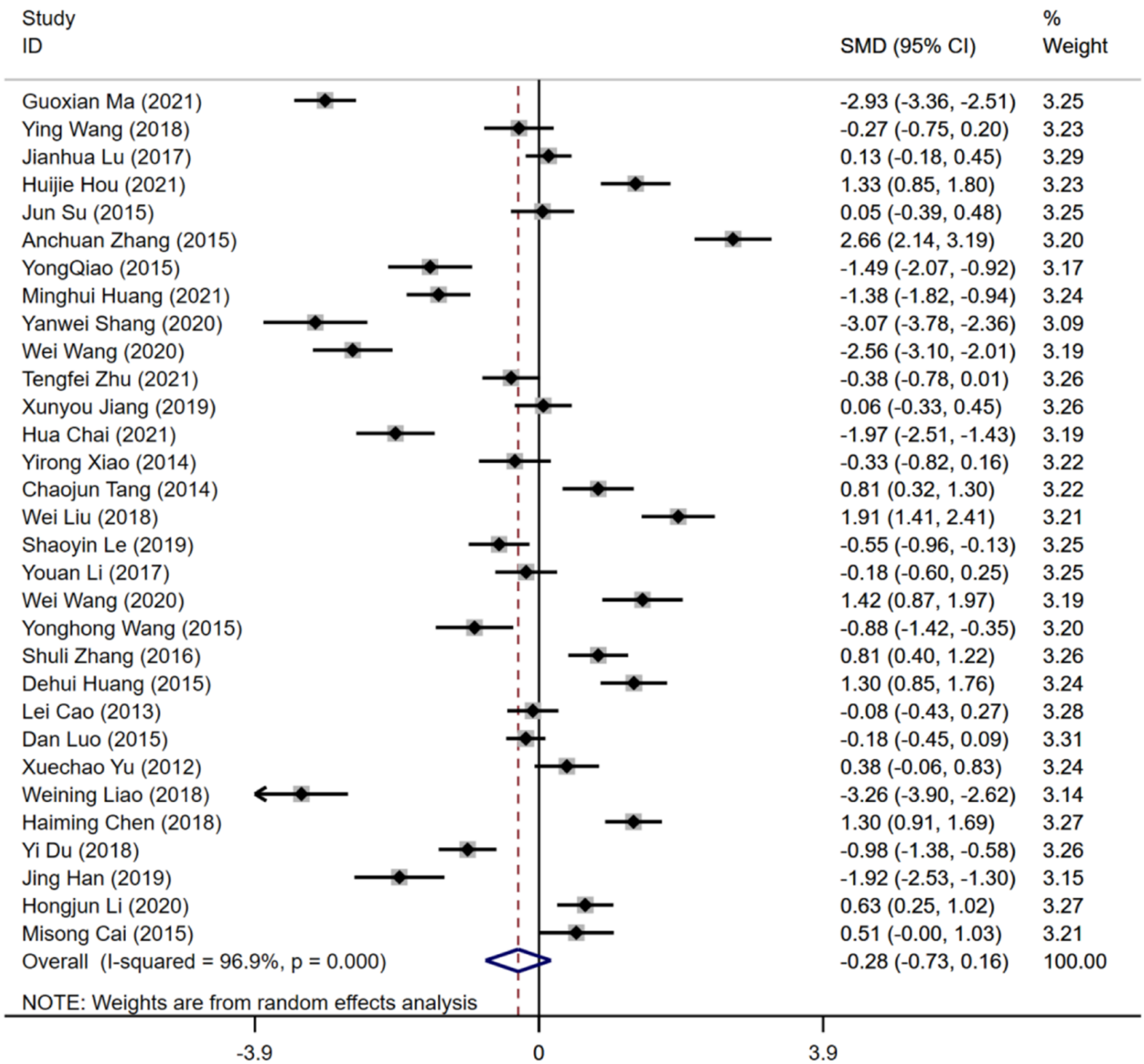

Figure 8. MMSE scores in patients 1 d after operation. MMSE = Mini-Mental State Examination.

It was found that MMSE scores were not significantly different between 2 groups 12 hours postoperatively (SMD = −0.38, 95% CI: [−1.33, 0.57], $P > .05$). Because of the high degree of heterogeneity across our enrolled articles, we conducted sensitivity analysis through excluding 1 article each time and discovered that the study carried out by Lu[34] accounted for the major source of heterogeneity. When this article was excluded, our findings indicated the decreased MMSE score in sevoflurane group relative to propofol group 12 hours after operation, with a significant difference. Therefore, our result was unstable and not reliable, which required careful interpretation (Fig. 7).

3.3.2.6. Meta-analysis of MMSE scores in patients 1 day after operation. There were 31 articles mentioning the MMSE scores in patients 1 day postoperatively, including 1066 cases of sevoflurane group while 1064 of propofol group. A large heterogeneity was detected across our enrolled articles through heterogeneity test ($I^2 = 96.9\%$ and $P < .10$), and combined effect was analyzed using the random-effects model. Our findings revealed that MMSE scores were not significantly different between 2 groups 1 day postoperatively (SMD = −0.28, 95% CI: [−0.73, 0.16], $P > .05$). Because of the large heterogeneity across our chosen articles, sensitivity analysis was conducted through eliminating 1 article each time, but the main source of heterogeneity was not detected. After excluding any study, the results still exhibited no significant difference in MMSE scores between 2 groups 1 day postoperatively, so these results were relatively stable and reliable (Fig. 8).

3.3.2.7. Meta-analysis of MMSE scores in patients 2 days after operation. There were 5 studies reporting MMSE scores in patients 2 days postoperatively, including 210 cases from sevoflurane group whereas 210 from propofol group. Upon heterogeneity test ($I^2 = 96.2\%$ and $P < .10$), a large heterogeneity was detected across the selected articles, so the combined effect was analyzed by the random-effects model. As a result, MMSE scores were not significantly different between 2 groups 2 days postoperatively (SMD = −0.20, 95% CI: [−0.88, 1.28], $P > .05$). Because of the large heterogeneity detected across our chosen articles, we conducted sensitivity analysis through eliminating 1 article each time, but failed to find the main source of

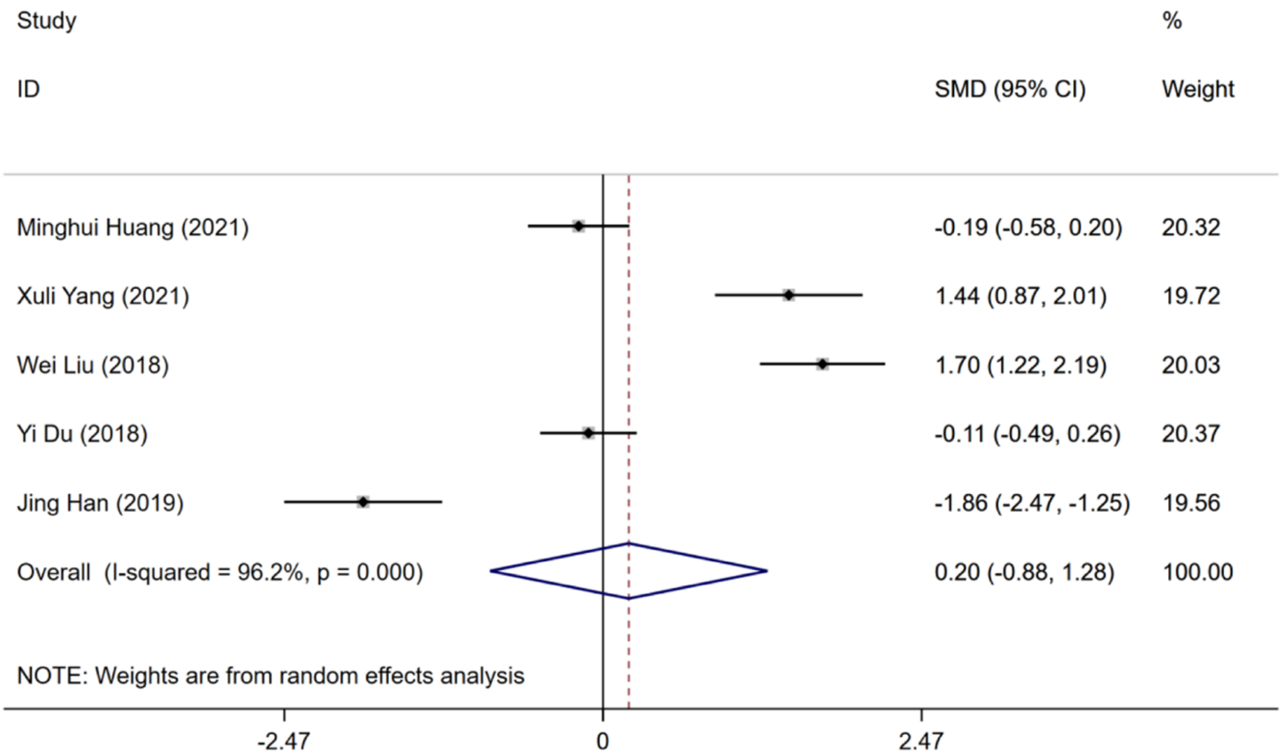

Figure 9. MMSE scores in patients 2 d after operation. MMSE = Mini-Mental State Examination.

heterogeneity. After excluding any article, the results still suggested no statistical difference in MMSE scores between 2 groups 2 days postoperatively, so these results were relatively stable and reliable (Fig. 9).

3.3.2.8. Meta-analysis of MMSE scores in patients 3 days after operation. There were 37 articles reporting the MMSE scores of patients 3 days after operation, including 984 and 981 from sevoflurane and propofol groups separately. Heterogeneity test (I^2 = 91.1% and $P < .10$) detected a large heterogeneity across those selected articles, so the combined effects were analyzed with the random-effects model. It was found that MMSE scores were not significantly different between 2 groups 3 days postoperatively (SMD = −0.25, 95% CI: [−0.06, 0.56], $P > .05$). Because of the large heterogeneity across those enrolled articles, sensitivity analysis was performed through eliminating 1 article each time, but the main source of heterogeneity was not discovered. When any literature was excluded, the results still demonstrated no significant difference in MMSE scores between 2 groups 3 days postoperatively, indicating the relative stability and reliability of our results (Fig. 10).

3.3.2.9. Meta-analysis of MMSE scores in patients 5 days after operation. There were 3 studies mentioning the MMSE scores in patients 5 days postoperatively, including respective 156 from sevoflurane and propofol groups. A large heterogeneity was detected upon heterogeneity test (I^2 = 95.1% and $P < .10$) across those enrolled articles, so we utilized the random-effects model to analyze combined effect. As a result, MMSE scores were not significantly different between 2 groups 5 days postoperatively (SMD = −0.77, 95% CI: [−0.35, 1.88], $P > .05$). Because of the large heterogeneity detected in our enrolled articles, we conducted sensitivity analysis through eliminating 1 study each time, but could not find the main source of heterogeneity. After excluding any literature, the results still revealed no significant difference in MMSE scores between 2 groups 5 days postoperatively, therefore, these results were relatively stable and reliable (Fig. 11).

3.3.2.10. Meta-analysis of MMSE scores in patients 7 days after operation. There were 14 studies reporting the postoperative MMSE scores of patients, including 763 and 764 from sevoflurane and propofol groups separately. Heterogeneity test (I^2 = 78.5% and $P < .10$) detected a large heterogeneity across those enrolled articles, so we utilized the random-effects model to analyze combined effect. It was discovered that MMSE scores were not significantly different between 2 groups 7 days postoperatively (SMD = −0.01, 95% CI: [−0.24, 0.22], $P > .05$). Because of the large heterogeneity detected across diverse articles, sensitivity analysis was carried out through eliminating 1 article each time, which did not find the main source of heterogeneity. After excluding any literature, the results still suggested no significant difference in MMSE scores between 2 groups 7 days postoperatively, demonstrating the relative stability and reliability of these results (Fig. 12).

3.3.2.11. Meta-analysis of MMSE scores in patients 3 months after operation. There were 2 studies mentioning MMSE scores in patients 3 months postoperatively, involving 189 cases from sevoflurane group while 189 from propofol group. Heterogeneity test (I^2 = 0.0% and $P > .10$) showed the absence of obvious heterogeneity across those enrolled articles, therefore, combined effect was analyzed using the fixed-effects model. Based on our findings, MMSE scores were not significantly different between 2 groups 3 months postoperatively (SMD = −0.00, 95% CI: [−0.20, 0.20]) (Fig. 13).

3.3.3. Publication bias. When 2 to 10 articles were enrolled in outcome indicators, publication bias was assessed by Egger test. As a result, publication bias was not detected in outcome indicators such as the POCD incidence 1, 3 and 12 hours, as well as 1, 2, 3, 5 and 7 days postoperatively.

When over 10 articles were included in outcome indicators, publication bias was assessed using the visual funnel diagram.

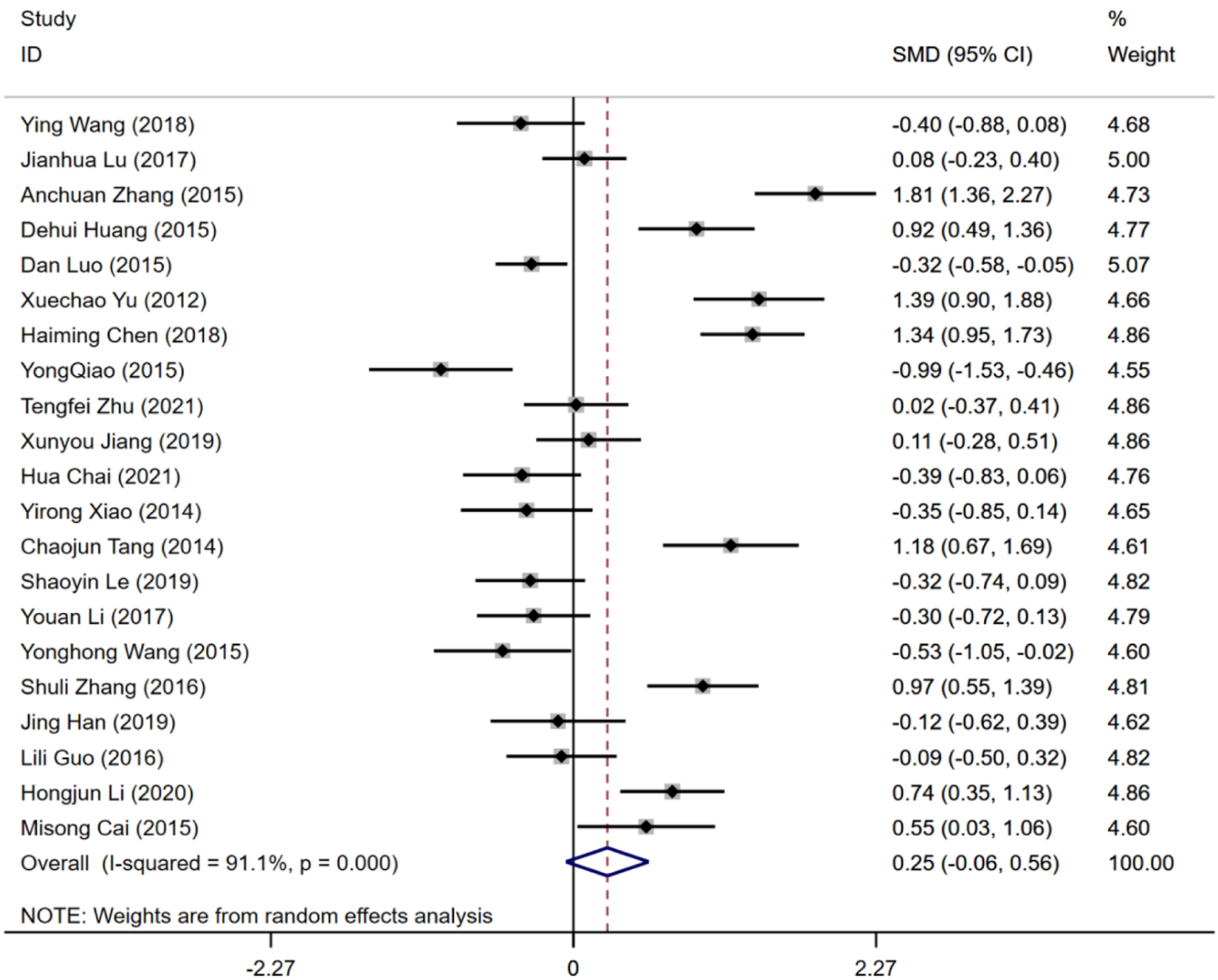

Figure 10. MMSE scores in patients 3 d after operation. MMSE = Mini-Mental State Examination.

Figure 14 exhibits the funnel diagram of outcome indicators such as preoperative MMSE score, MMSE scores 6 hours, 1, 3 and 7 days postoperatively. The points on the funnel diagram were scattered and not completely symmetrical, suggesting that there was a certain publication bias (Figure 14A–E).

4. Discussion

POCD, the frequent complication after general anesthesia and major surgery, has the typical features of difficulty in memory and recall, mental decline, being unable to accomplish tasks, inattention, language understanding impairment and social integration problems.[3] The course of POCD ranges from short to lasting and permanent. Because of the unobvious early symptoms, POCD can hardly be found by clinicians and family members and is thereby neglected. According to Bedford research in 1955,[56] about 10% of surgical cases suffered from long-time or persistent neurocognitive function decline after general anesthesia and surgery. However, their work was limited at that time since the decline of cognitive function was determined only by the self-expression of patients and the description of their families, not by neuropsychological test results. After research for decades, cognitive decline after general anesthesia and major surgery, selection of general anesthesia and its relationship with POCD are still controversial.

Sevoflurane and propofol represent 2 frequently applied general anesthesia agents, and their anesthesia methods and mechanisms are different.[57] Sevoflurane exerts its anesthetic effect mainly by inhibiting N-methyl-D aspartate (NMDA) receptor. NMDA serves as the natural amino acid derivative in animals and a critical excitatory neurotransmitter L-glutamic acid homologue within the mammalian central nervous system. After inhibiting the activity of NMDA, the synaptic transmission of cholinergic neurons and synaptic enhancement in hippocampus are inhibited.[58,59] Propofol is a short-acting intravenous anesthetic of alkyl acids, which takes effect quickly, can achieve the ideal anesthetic effect within 40 seconds, and its efficacy is relatively stable. This anesthetic mainly exerts its anesthetic effect by enhancing the function of γ-aminobutyric acid (GABA) receptor, thus inhibiting the increased expression of hippocampal synapses.[60] When dealing with the body internal and external environments, synaptic plasticity lays the basis for synapses to cope with the external environment.[61] Enhancement and inhibition are both normal neural responses of synapses to external environment, and their coordination together establishes the basis of learning and memory.[62] Obviously, both anesthetics affect the neurological function of patients and play an anesthetic role. As reported in several clinical trials,[63,64] the selection of general anesthesia agents does not negatively affect the early postoperative recovery quality, but these trials are limited by the small sample size and/or minor surgical research. Guo research[44] found that sevoflurane and propofol anesthesia had negative effects on early postoperative cognitive dysfunction among the old cancer patients, but there was no significant difference

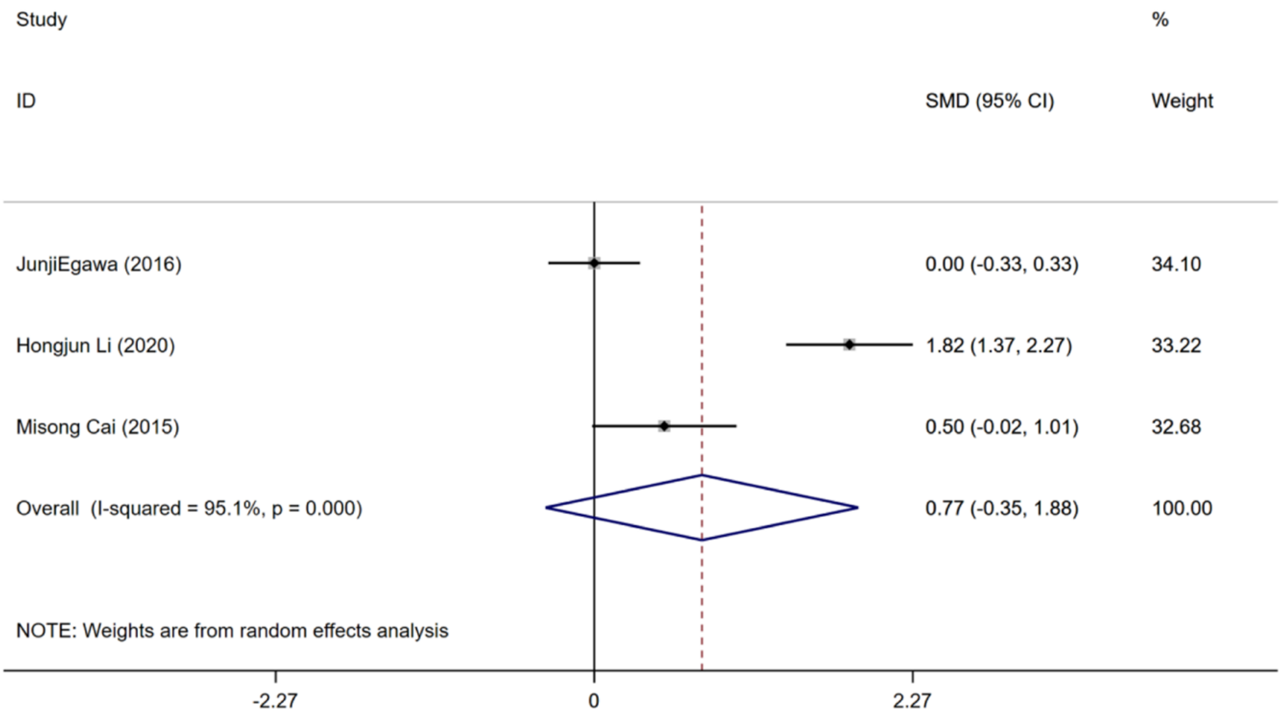

Figure 11. MMSE scores in patients 5 d after operation. MMSE = Mini-Mental State Examination.

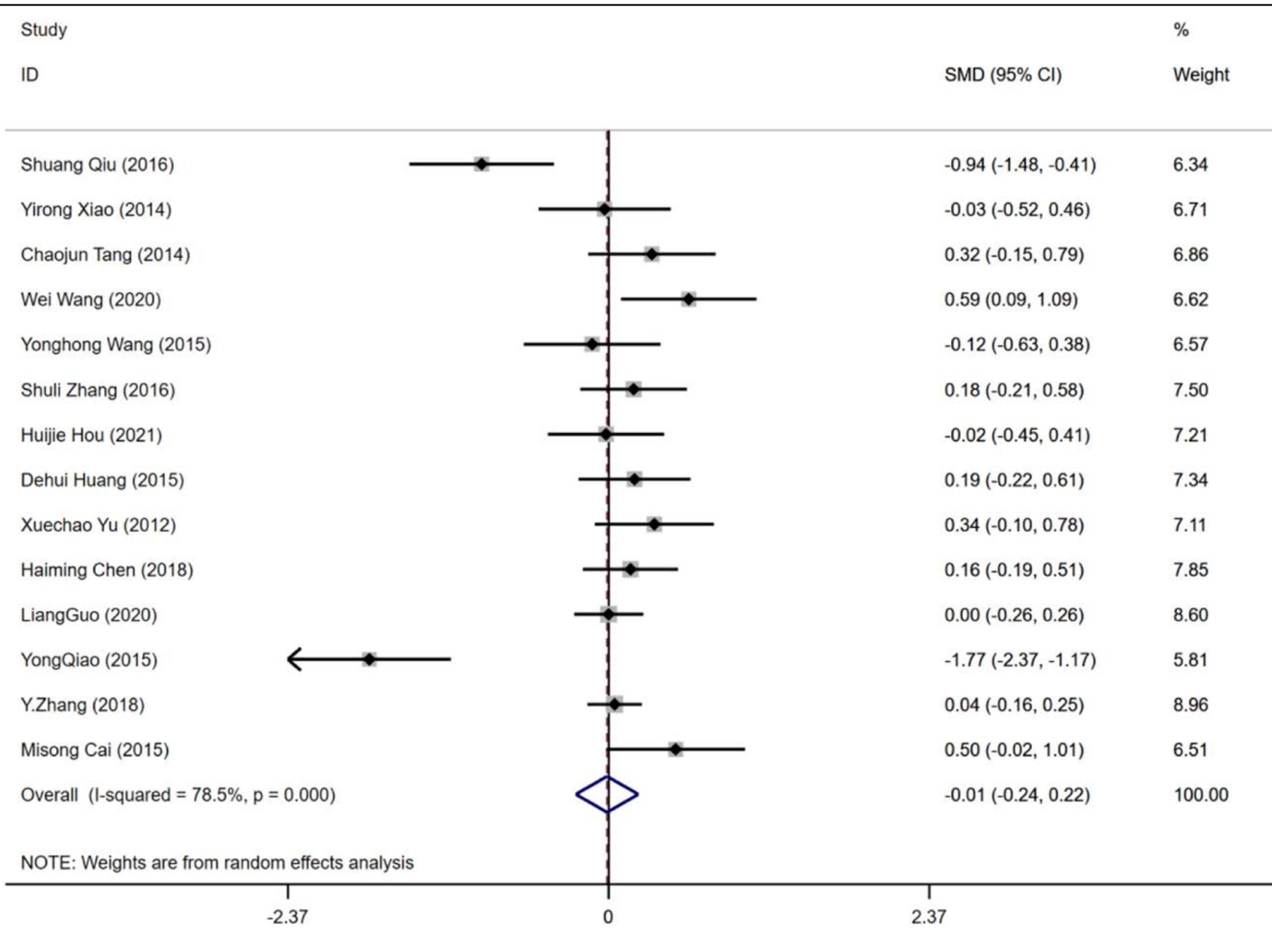

Figure 12. MMSE scores in patients 7 d after operation. MMSE = Mini-Mental State Examination.

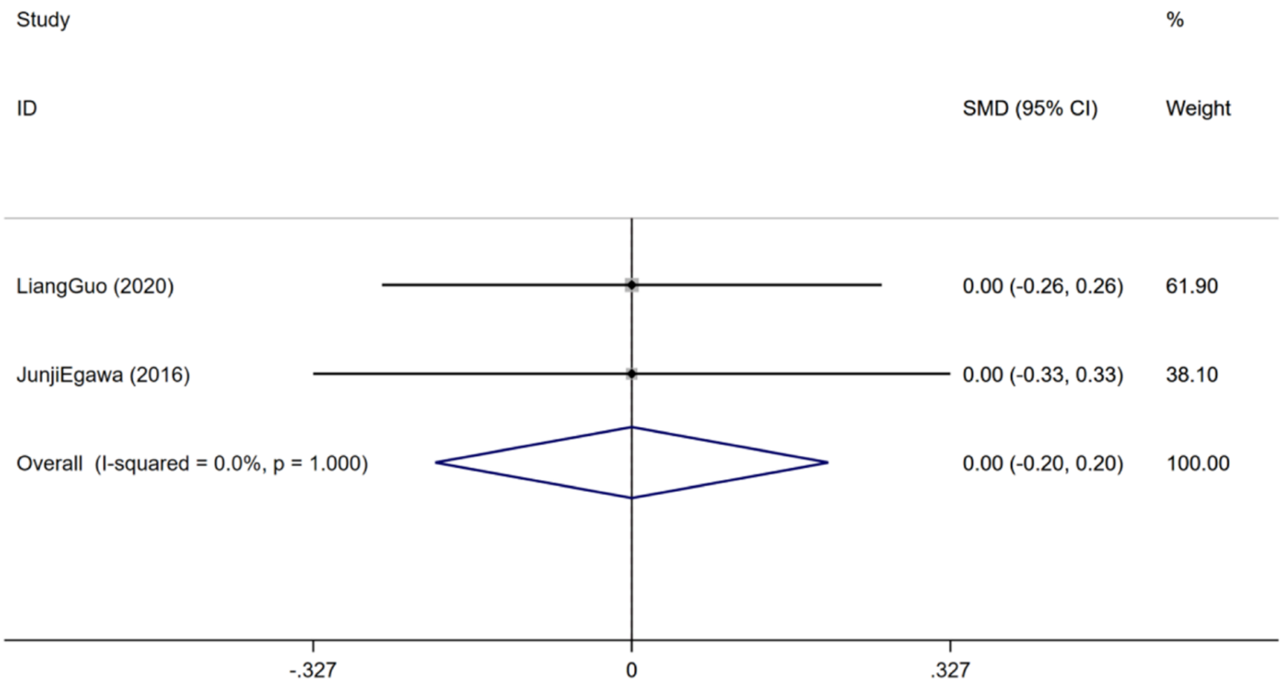

Figure 13. MMSE scores in patients 3 mo after operation. MMSE = Mini-Mental State Examination.

between them, and there was no negative impact on patient life quality or prognostic outcome 3 months postoperatively. Egawa research[47] also found that the POCD incidence was not significantly different between sevoflurane and propofol anesthesia after lung surgery. Tang research[46] discovered that patients with rectal cancer achieved good neurological recovery after sevoflurane or propofol anesthesia, but it seemed that patients who received propofol anesthesia had better cognition, yet the difference did not reach statistical significance. Qiao[45] suggested that the esophageal cancer patients who received major surgery with sevoflurane inhalation anesthesia had the increased POCD incidence relative to those undergoing intravenous propofol anesthesia. Ishii research[48] also found that the POCD incidence after propofol anesthesia (6.9%) markedly decreased relative to that after sevoflurane anesthesia (26.7%). According to Zhang research,[49] compared with sevoflurane general anesthesia, propofol general anesthesia might reduce the postponed neurocognitive recovery among the elderly following large cancer surgery.

The 41 studies selected in the present work were all RCTs, with high meta-analysis quality and reliable results. Publication bias was assessed by Egger test for outcome indicators, which revealed the absence of obvious publication bias in outcome indicators, such as the POCD incidence 1, 3, 12 hours, and 1, 2, 3, 5 and 7 days postoperatively. In addition, we used visual funnel chart for evaluating publication bias for outcome indicators. The points on the funnel chart were scattered and showed incomplete symmetry, revealing the presence of some publication bias. Our enrolled studies included sevoflurane/ether inhalation anesthesia for lung, esophageal, gastric, colorectal, prostate, cervical and unclassified cancers, and the neurological status after propofol intravenous anesthesia. The results showed that sevoflurane/ether inhalation anesthesia and propofol intravenous anesthesia reduced the postoperative cognitive function of patients with malignant tumors to varying degrees. Moreover, several studies[22,42,45,50,52] show that severe MMSE scores can be moderately reduced and the effect of sevoflurane is more obvious, but the MMSE scores are basically evaluated within 3 days after operation, and can basically return to normal levels after 5 days. A study[44] reported that the patients still had a slight decrease in MMSE scores 3 months after operation, but the hospital stay of patients in this study was not prolonged and patients were not hospitalized again because of neurological adverse events, meanwhile, the neurological function status was not evaluated 3 months postoperatively. Generally speaking, these 2 anesthetics are not significantly different. According to our results, the POCD incidence was not significantly different between 2 groups. As revealed by subgroup analysis, the functions of sevoflurane/ether inhalation anesthesia and propofol intravenous anesthesia in postoperative cognitive function of cancer patients were not significantly related to the cancer types.

Certain limitations should be noted in this meta-analysis: firstly, MMSE score is simple and convenient to operate, and the score result is recognized by neurology and psychiatry, but there are subjective differences. Affected by age and education, patients receiving higher education probably have false negatives, while patients receiving lower education can have false positives, and there are many items measured by this score, which is mainly sensitive to left hemisphere lesions-induced cognitive impairment, rather than to frontal lobe and right hemisphere lesions-induced one. Additionally, its effectiveness on evaluating cognitive function of frontotemporal lobe is weak, and the score is poor in identifying mild cognitive impairment. Therefore, there may be some information bias in the results included in the study, which affects the reliability of the results in this meta-analysis to some extent. Secondly, in the process of anesthesia operation, different medical institutions and different doctors will use different doses of narcotic drugs, and there are also differences in the use methods. For example, propofol can be administered through ordinary intravenous pumping and target-controlled infusion, besides, the anesthesia operation time of patients is different, and the postoperative recovery of patients is also different. Moreover, epidural anesthesia/peripheral nerve blocks is most probably added to general anesthesia in some cases. These factors will affect postoperative clinical outcome of patients to varying degrees.

To sum up, sevoflurane/ether inhalation anesthesia and propofol intravenous anesthesia may have different degrees

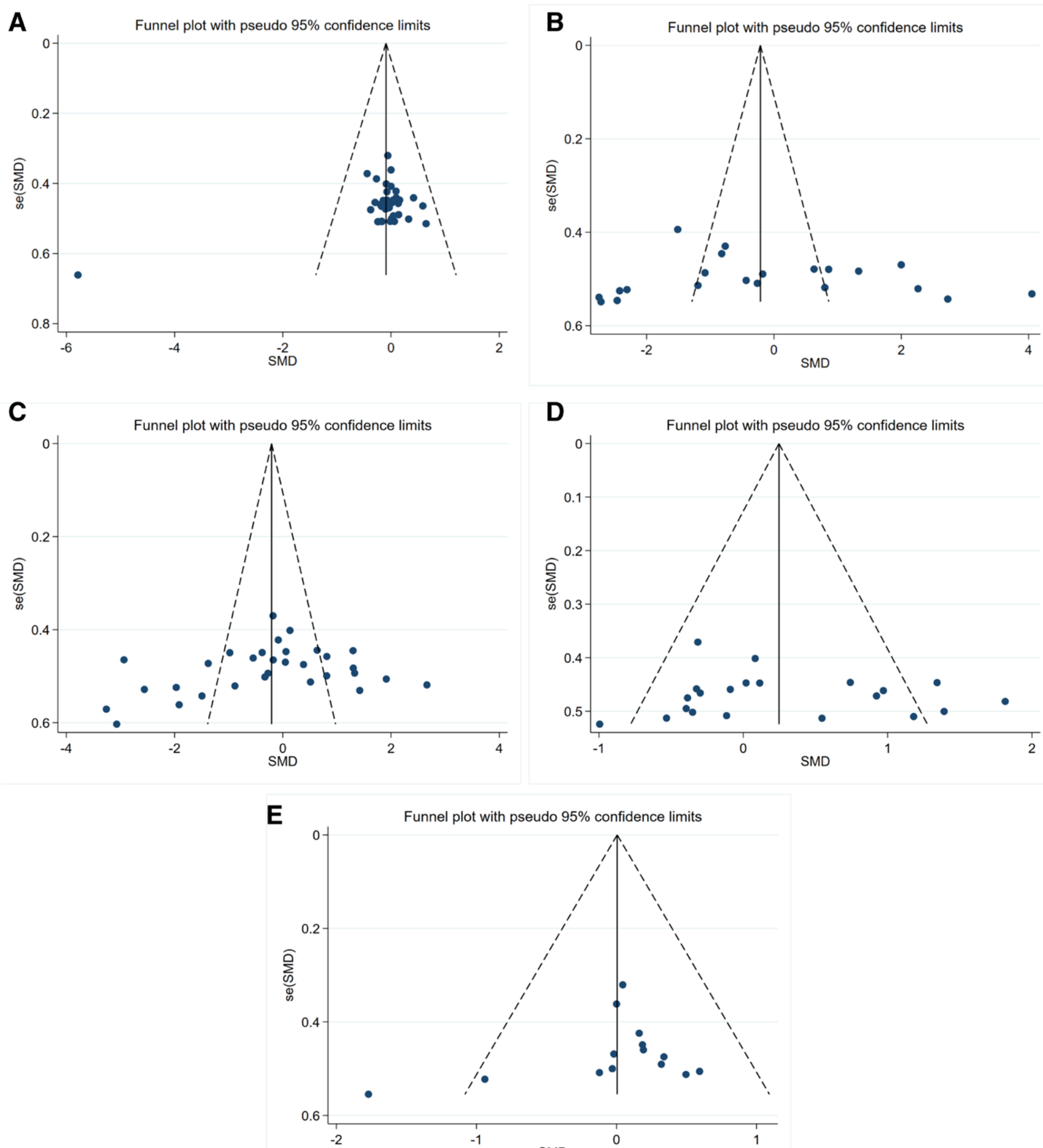

Figure 14. Publication bias. (A–E) The funnel diagram of outcome indicators such as preoperative MMSE score, MMSE scores 6 hours, 1, 3, and 7 days post-operatively. MMSE = Mini-Mental State Examination, SMD = standardized mean difference.

of negative effects on postoperative cognitive function among cancer patients, but there is no obvious long-term effect, and there is no obvious difference between the 2 anesthetics in their effects on postoperative cognitive function. However, our results should be further validated through large-scale, multi-center RCTs.

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Writing – original draft: Yuhang Quan.
Writing – review & editing: Mingxiong Zhang.

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