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REVIEW ARTICLE/BRIEF REVIEW

Comparing perioperative outcomes between regional anesthesia and general anesthesia in patients undergoing hip fracture surgery: a systematic review and meta-analysis

Comparaison des issues périopératoires entre l'anesthésie régionale et l'anesthésie générale chez la patientèle bénéficiant d'une chirurgie de fracture de la hanche : une revue systématique et une méta-analyse

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Abstract

Purpose *Nearly all patients with hip fractures undergo surgical treatment. The use of different anesthesia techniques during surgery may influence the clinical outcomes. The optimal anesthetic technique for patients undergoing hip fracture surgery is still controversial. We performed this updated systematic review and meta-analysis to compare clinical outcomes of patients undergoing hip fracture surgery with different anesthesia techniques.*

Source *Articles published from 2000 to May 2023 were included from MEDLINE, Embase, Web of Science, and the Cochrane Library. We included randomized controlled trials and observational studies comparing general anesthesia (GA) with regional anesthesia (RA) for the outcomes of 30-day mortality, 90-day mortality, in-hospital mortality, perioperative complications, length of hospital stay, and length of surgery in patients undergoing hip fracture surgery. Subgroup analyses were performed for the outcomes based on study design (randomized controlled trials or observational studies). We used a random-effects model for all analyses.*

Principal findings *In this meta-analysis, we included 12 randomized controlled trials. There was no difference in postoperative 30-day mortality between the two groups (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.44 to 1.74; I^2 = 0%). The incidence of intraoperative hypotension was lower in patients who received RA vs GA (OR, 0.52; 95% CI, 0.38 to 0.72; I^2 = 0%). No significant differences were observed in 90-day mortality, in-hospital mortality, postoperative delirium, pneumonia, myocardial infarction, venous thromboembolism, length of surgery, and length of hospital stay.*

Conclusion *In this updated systematic review and meta-analysis, RA did not reduce postoperative 30-day mortality in hip fracture surgery patients compared to GA. Fewer patients receiving RA had intraoperative hypotension than those receiving GA did. Apart from intraoperative hypotension, the data showed no differences in complications between the two anesthetic techniques.*

Study registration *PROSPERO (CRD42023411854); registered 7 April 2023.*

Song Liu, Jianan Chen, and Huihong Shi have contributed equally to this work and are co-first authors.

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Résumé

Objectif *Presque toutes les personnes ayant subi une fracture de la hanche se font opérer. L'utilisation de différentes techniques d'anesthésie pendant la chirurgie peut influencer les issues cliniques. La technique d'anesthésie optimale pour la patientèle bénéficiant de chirurgie de fracture de la hanche est encore controversée. Nous avons réalisé cette mise à jour par revue systématique et méta-analyse pour comparer les issues cliniques des personnes bénéficiant d'une chirurgie de fracture de la hanche avec différentes techniques d'anesthésie.*

Sources *Les articles publiés de 2000 à mai 2023 ont été inclus à partir des bases de données MEDLINE, Embase, Web of Science et Cochrane Library. Nous avons inclus des études randomisées contrôlées et des études observationnelles comparant l'anesthésie générale (AG) à l'anesthésie régionale (AR) pour les issues de mortalité à 30 jours, de mortalité à 90 jours, de mortalité intrahospitalière, de complications périopératoires, de durée de séjour à l'hôpital et de durée de la chirurgie pour les personnes bénéficiant d'une chirurgie de fracture de la hanche. Des analyses de sous-groupes ont été réalisées pour les issues en fonction de la méthodologie utilisée (étude randomisée contrôlée ou étude observationnelle). Un modèle à effets aléatoires a été utilisé pour toutes les analyses.*

Constatations principales *Dans cette méta-analyse, nous avons inclus 12 études randomisées contrôlées. Il n'y avait pas de différence dans la mortalité postopératoire à 30 jours entre les deux groupes (rapport de cotes [RC], 0,88; intervalle de confiance à 95 % [IC], 0,44 à 1,74;* I^2 *= 0 %). L'incidence d'hypotension peropératoire était plus faible chez les patient·es ayant reçu une AR vs une AG (RC, 0,52; IC 95 %, 0,38 à 0,72;* I^2 *= 0 %). Aucune différence significative n'a été observée dans les issues de mortalité à 90 jours, de mortalité intrahospitalière, de delirium postopératoire, de pneumonie, d'infarctus du myocarde, de thromboembolie veineuse, de durée de la chirurgie, et de durée du séjour à l'hôpital.*

Conclusion *Dans cette revue systématique avec méta-analyse, l'anesthésie régionale n'a pas réduit la mortalité postopératoire à 30 jours chez les personnes ayant bénéficié d'une chirurgie de fracture de la hanche par rapport à l'anesthésie générale. Une proportion moindre de patient·es ayant reçu une AR présentaient une hypotension peropératoire par rapport aux personnes ayant reçu une AG. En dehors de l'hypotension peropératoire, les données n'ont montré aucune différence dans les complications entre les deux techniques anesthésiques.*

Enregistrement de l'étude *PROSPERO (CRD42023411854); enregistrée le 7 avril 2023.*

Keywords hip fracture surgery · general anesthesia · meta-analysis · regional anesthesia

With an aging population, the number of older patients with hip fractures has substantially increased. It is expected that by 2050, about six million older individuals worldwide will experience a hip fracture each year.[1] Hip fractures can cause severe pain and disability and even shorten life expectancy, which places a burden on patients, their families, and the social medical security system.[2] Generally, nearly all patients with hip fractures undergo surgical treatment, which requires general anesthesia (GA) or regional anesthesia (RA), which includes spinal anesthesia, epidural anesthesia, and peripheral nerve blockade. Given the typical patient cohort's prevalent comorbidities, such cardiopulmonary diseases, cerebrovascular diseases, and osteoporosis, surgery is associated with a high risk of developing perioperative complications, potentially culminating in mortality.[3,4] The type of anesthesia may influence outcomes. Some studies have indicated that GA is associated with higher in-hospital mortality than RA is.[5,6] Nevertheless, two recent large randomized controlled trials (RCTs) did not find a difference in 30-day or 60-day mortality between RA and GA.[7,8] Recently, some published meta-analyses have studied postoperative mortality and other perioperative outcomes in patients undergoing hip fracture surgery with different anesthesia techniques. Some only focused on RCTs or limited research articles and showed conflicting conclusions.[9–13] In general, meta-analyses that only look at RCTs may have a stronger certainty of evidence. Nevertheless, considering that RCTs are generally unable to include large numbers of patients as well as the low incidence of postoperative mortality, the results of such meta-analyses should be interpreted with caution. In particular, limited by incomplete follow-up, few comparable studies have examined longer-term mortality, such as 90-day mortality.[14,15] The optimal anesthesia technique for hip fracture surgery is, therefore, still controversial.[16]

In this updated systematic review and meta-analysis, we sought to include sufficient recent data to conduct a comparatively comprehensive and systematic study to assess the short-term to long-term mortality and other perioperative outcomes of RA *vs* GA in patients undergoing hip fracture surgery. We chose 30-day mortality as the primary outcome and 90-day mortality, in-hospital mortality, perioperative complications, length of hospital stay, and length of surgery as the secondary outcomes.

Methods

Search strategy and selection criteria

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[17] The study has been registered in the prospective register of systematic reviews, PROSPERO (CRD42023411854). Two independent authors systematically searched the electronic databases including MEDLINE, Embase, Web of Science and the Cochrane Library for articles published from the construction of the library to 15 May 2023. Search terms were applied to both subject headings and as keywords and the language of publication was restricted to English. Search terms, used both alone and in combination, included but were not limited to "spinal anesthesia" OR "regional anesthesia" OR "general anesthesia" AND "hip fractures" OR "femoral neck fractures" OR "arthroplasty, replacement, hip" OR "intertrochanteric fractures" OR "trochanteric fractures." References to relevant reviews and the identified articles were also manually searched. Two authors independently screened the titles and abstracts after expurgating the duplicates. Subsequently, full texts of the identified studies were screened by the same two reviewers working independently and in duplicate to assess whether the studies met the inclusion criteria, and any disagreements were discussed with a third author.

Both RCTs and observational studies were eligible for this review. We included all studies that reported perioperative outcomes on RA compared with GA in patients undergoing hip fracture surgery. The following outcome measures were included: postoperative 30-day mortality, postoperative in-hospital mortality, postoperative 90-day mortality, perioperative complications (including postoperative delirium, pneumonia, myocardial infarction, intraoperative hypotension, and venous thromboembolism), length of hospital stay, and length of surgery. The following exclusion criteria were used: 1) articles published before 2000; 2) summary studies; 3) case reports or case series reports; 4) meeting summaries; and 5) inability to obtain the relevant information after contacting the author.

Data extraction

A structured table was designed to extract all the relevant data from each study that met the inclusion criteria by two independent reviewers. Extracted data were the first author's name, publication year, country, sample size, age, American Society of Anesthesiologists (ASA) Physical Status, anesthesia technique, and study outcome measures. Any outstanding disagreements were resolved by consensus.

Methodological quality assessment

Two authors independently assessed the methodological quality of included RCTs and observational studies. Any disagreements were discussed with a third author. We used the Cochrane Collaboration risk of bias tool for randomized studies to assess the reporting quality and risk of bias of the included RCTs.[18] This tool evaluates the following seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The methodology for each study was classified into low, unclear, and high risk of bias. The Newcastle–Ottawa Scale (NOS) was used for observational studies to assess the risk of bias in individual studies.[19] Each observational study was judged on three aspects: the selection of the study groups, the comparability of the groups, and the exposure or outcome of interest for the groups. Articles with NOS scores ≥ 6 were regarded as high-quality observational studies.

Statistical analyses

We performed a meta-analysis for postoperative mortality (including 30-day mortality, in-hospital mortality, and 90-day mortality), perioperative complications (including postoperative delirium, pneumonia, myocardial infarction, intraoperative hypotension, and venous thromboembolism), length of hospital stay, and length of surgery. We used Review Manager version 5.4.1 (The Cochrane Collaboration, London, UK) and Stata version 18 (StataCorp LLC, College Station, TX, USA) to perform the meta-analyses. Dichotomous data were analyzed as odds ratios (ORs) with 95% confidence intervals (CIs), and continuous data are presented as mean differences (MDs) and 95% CIs. For length of hospital stay, some articles provided the median and quartiles or ranges. In these cases, we detected the skewness of data using the method proposed by Shi *et al.*[20] If no skewness was seen in the data, we converted the data into means and standard deviations according to the method proposed by Shi *et al.*,[21,22] Luo *et al.*,[23] and Wan *et al.*[24] For log-normally distributed variables like length of surgery,[25,26] we included only those that reported mean with SD in the meta-analysis. The *P* value with the Cochrane Q test was tested to estimate the extent of statistical heterogeneity among the studies. A random effect model was performed because of differences in patients and interventions.[15] For analyses with few studies (< 10), a DerSimonian–Laird test combined with Knapp–Hartung adjustment was performed.[27,28] Subgroup analysis was conducted according to the study design. We conducted sensitivity analyses by leaving out one study at a time to investigate whether the removal of a particular article had any effect on the overall results to assess the stability.[14]

Results

Study selection

We identified 1,102 studies through the Web of Science, MEDLINE, Embase, and Cochrane Library. After checking for duplicates, 312 studies were excluded. A total of 697 articles were eliminated after screening the titles and abstracts. Ninety-three additional studies were assessed by perusing full texts; however, 61 of these studies were excluded for not meeting the inclusion criteria. A further 23 articles that met the inclusion criteria from references of included articles and other systematic reviews were included. Overall, 55 studies were included in this systematic review (Fig. 1).

Study characteristics

Twelve RCTs and 43 observational studies were included in the systematic review.[5–8,29–79] Ten of the studies included patients of any age, while the majority of the other studies focused on elderly individuals. The largest study included 124,960 patients, and the smallest one included 30 patients. The 30-day mortality was the outcome most frequently evaluated in the included studies. The descriptive characteristics of the included studies are shown in the Table.

Risk of bias assessment

The Cochrane Risk of Bias tool (The Cochrane Collaboration, London, UK) was used to evaluate the quality of RCTs (Fig. 2A and B). Only one trial was considered as a high risk of selection bias, and the others were at low or unclear risk. Considering the blinding of the patients is challenging when comparing RA and GA, we judged performance bias to be at high risk of bias for eight studies and five studies were found to have a high risk of detection bias. For attrition bias, we classified two studies as having a high risk of bias. Two studies were deemed to have a high risk of reporting bias, and three were considered to have a high risk of other bias.

Fig. 1 Flow diagram of study selection

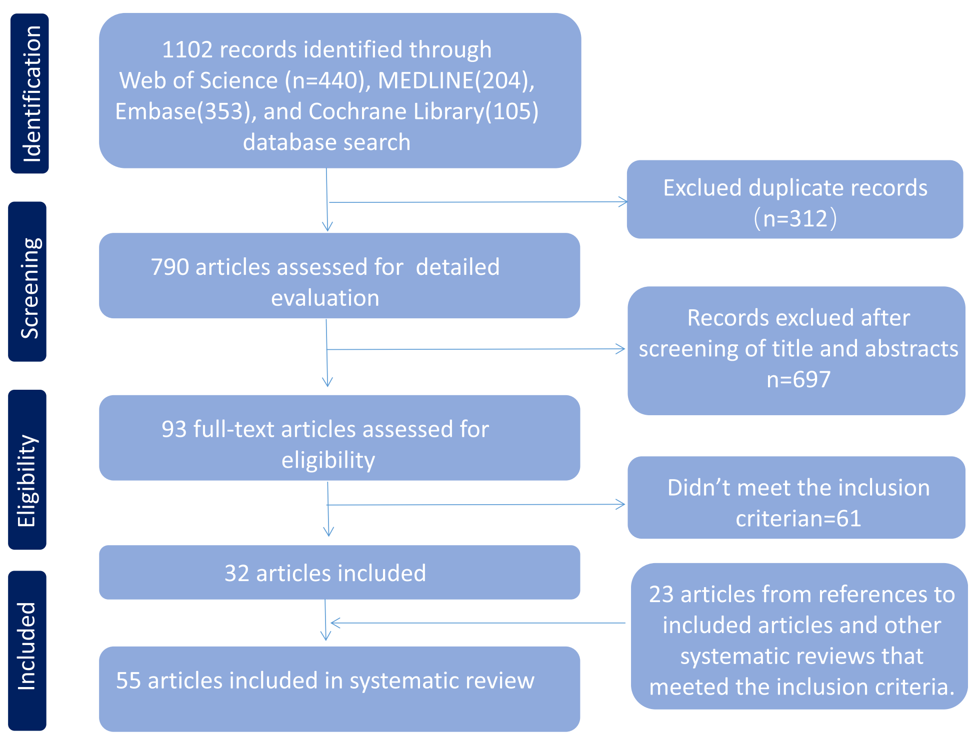


Table Characteristics of included studies

Author, year	Country	Design	Age	Male/female	Anesthetic technique	ASA PS	Outcomes*
O'Hara *et al.* 2000[29]	USA	Retrospective observational study	≥ 60	8,088/1,337	RA (*n* = 3,078) *vs* GA (*n* = 6,206)	I–IV	[2][3][5][6][7]
Heidari *et al.* 2011[30]	Iran	RCT	≥ 30	257/102	RA (*n* = 190) *vs* GA (*n* = 197)	I–III	[2][6][5][8][9][10]
Neuman *et al.* 2012[31]	USA	Retrospective observational study	≥ 50	4,763/13,395	RA (*n* = 5,254) *vs* GA (*n* = 12,904)	—	[2][5][6]
Le-Wendling *et al.* 2012[32]	USA	Retrospective observational study	≥ 65	79/229	RA (*n* = 73) *vs* GA (*n* = 235)	—	[2][9]
Rashid *et al.* 2013[33]	Pakistan	Retrospective observational study	—	98/96	RA (*n* = 87) *vs* GA (*n* = 107)	—	[2][9][10]
Neuman *et al.* 2014[34]	USA	Retrospective observational study	≥ 50	41,984/14,745	RA (*n* = 15,904) *vs* GA (*n* = 40,825)	—	[3][9]
Liu *et al.* 2014[35]	China	Retrospective observational study	≥ 65	66/151	RA (*n* = 145) *vs* GA (*n* = 72)	II–IV	[1][2][3][5][6][8][9][10]
White *et al.* 2014[36]	UK	Retrospective observational study	—	17,637/47,898	RA (*n* = 23,665) *vs* GA (*n* = 31,092)	I–V	[2][3]
Basques *et al.* 2015[37]	USA	Retrospective observational study	≥ 70	2,666/7,176	RA (*n* = 2,589) *vs* GA (*n* = 7,253)	—	[3][5][6][8][9][10]
Chu *et al.* 2015[38]	China	Retrospective observational study	≥ 65	37,713/66,375	RA (*n* = 52,044) *vs* GA (*n* = 52,044)	—	[2][6][9]
Fields *et al.* 2015[39]	USA	Prospective cohort study	—	1,949/4,679	RA (*n* = 1,815) *vs* GA (*n* = 4,813)	I–IV	[3][5][6][8][10]
Parker *et al.* 2015[40]	UK	RCT	> 49	87/235	RA (*n* = 158) *vs* GA (*n* = 164)	I–IV	[1][3][4][5][6][7][8][9]
Brox *et al.* 2016[41]	USA	Retrospective observational study	≥ 55	2,091/5,225	RA (*n* = 3,059) *vs* GA (*n* = 4,257)	I–IV	[3][4]
Ilango *et al.* 2016[42]	Australia	Prospective cohort study	≥ 48	89/229	RA (*n* = 151) *vs* GA (*n* = 167)	—	[1]
Lončarić *et al.* 2017[43]	Croatia	Retrospective observational study	≥ 70	14/101	RA (*n* = 38) *vs* GA (*n* = 77)	II–III	[2][3][7][9]
Qiu *et al.* 2018[5]	USA	Retrospective observational study	≥ 65	4,827/11,398	RA (*n* = 6,597) *vs* GA (*n* = 9,629)	I–V	[2]
Tzimas *et al.* 2018[44]	Greece	RCT	≥ 65	33/37	RA (*n* = 37) *vs* GA (*n* = 33)	I–III	[1][3][6][9][10]
Ahn *et al.* 2019[45]	Korea	Retrospective observational study	≥ 65	13,528/37,658	RA (*n* = 25,593) *vs* GA (*n* = 25,593)	—	[1][3][6]
Nishi *et al.* 2019[46]	Japan	Retrospective observational study	—	1,577/7,839	RA (*n* = 4,708) *vs* GA (*n* = 4,708)	—	[3][4][9]
Morgan *et al.* 2020[47]	UK	Retrospective observational study	—	2,090/6,054	RA (*n* = 3,958) *vs* GA (*n* = 4,186)	—	[6][8]
Shin *et al.* 2020[48]	Korea	RCT	≥ 65	46/130	Desflurane (*n* = 60) *vs* propofol (*n* = 58) *vs* SA (*n* = 58)	—	[1][2][3][4][5][9]
Roghayeh *et al.* 2020[49]	Iran	Single-blind non-RCT	> 50	45/49	RA (*n* = 47) *vs* GA (*n* = 47)	I–III	[1][10]
Mounet *et al.* 2021[50]	France	Retrospective observational study	—	52/77	GA (*n* = 43) *vs* CSA (*n* = 43) *vs* MNB (*n* = 43)	II–IV	[2][3][5][6][7][9][10]
Neuman *et al.* 2021[7]	USA	RCT	≥ 50	528/1,072	RA (*n* = 795) *vs* GA (*n* = 805)	I–IV	[1][2][5][6][9]
Song *et al.* 2021[51]	China	Prospective cohort clinical trial	≥ 65	36/102	RA (*n* = 69) *vs* GA (*n* = 69)	I–III	[5][8][9][10]
Li *et al.* 2022[8]	China	Multicentre RCT	≥ 65	247/695	RA (*n* = 471) *vs* GA (*n* = 471)	I–IV	[1][3][5][6][7][9]
Fukuda *et al.* 2022[52]	Japan	Retrospective observational study	≥ 60	2,984/12,054	RA (*n* = 7,519) *vs* GA (*n* = 7,519)	—	[1][5]

Table continued

Author, year	Country	Design	Age	Male/ female	Anesthetic technique	ASA PS	Outcomes*
Guo *et al.* 2022[53]	China	Retrospective observational study	≥ 65	70/239	RA (*n* = 206) *vs* GA (*n* = 103)	I–V	[1][5][8] [10]
Matharu *et al.* 2022[54]	UK	Prospective cohort study	≥ 60	36,524/ 88,436	RA (*n* = 56,109) *vs* GA (*n* = 68,851)	I–V	[1][3][9]
Mohammad *et al.* 2022[55]	USA	Prospective cohort study	≥ 18	796/ 1,641	RA (*n* = 1,463) *vs* GA (*n* = 974)	I–IV	[1][3][4][5][9][10]
Rodkey *et al.* 2022[56]	USA	Retrospective observational study	≥ 65, ≤ 90	6,888/ 16,761	RA (*n* = 7,883) *vs* GA (*n* = 15,766)	I–V	[3][5][6][8]
Simonin *et al.* 2022[57]	France	RCT	≥ 70	31/115	SA (*n* = 82) *vs* GA (*n* = 64)	I–III	[7][9]
Vaz *et al.* 2022[58]	Portugal	Prospective cohort study	—	147/415	RA (*n* = 201) *vs* GA (*n* = 361)	I–IV	[2][3][9]
Casati *et al.* 2003[59]	Italy	Prospective randomized study	> 65	2/28	SA (*n* = 15) *vs* SEVO (*n* = 15)	II–III	[9][10]
David *et al.* 2004[60]	USA	Prospective observational study	≥ 65	192/729	SA (*n* = 435) *vs* GA (*n* = 429)	I–IV	[1]
Hoppenstein *et al.* 2005[61]	Israel	Prospective, randomized, open-label study	≥ 60	—	SA (*n* = 30) *vs* GA (*n* = 30)	I–III	[10]
Radcliff *et al.* 2008[62]	USA	Retrospective observational study	≥ 65	—	SA (*n* = 2,330) *vs* GA (*n* = 3,353)	I–V	[3]
Shih *et al.* 2010[63]	Taiwan-China	Retrospective observational study	80–99	189/146	SA (*n* = 168) *vs* GA (*n* = 167)	II–IV	[1][2][5][9][10]
Wood *et al.* 2011[64]	UK	Retrospective observational study	19–105	—	SA (*n* = 578) *vs* GA (*n* = 489) *vs* combined (*n* = 64)	I–IV	[3][7][9]
Sahin *et al.* 2012[65]	Turkey	Retrospective observational study	≥ 60	66/68	SA (*n* = 67) *vs* GA (*n* = 67)	I–V	[2][3][5][6][9][10]
Biboulet *et al.* 2012[66]	France	RCT	> 75	12/31	SA (*n* = 15) *vs* TCI (*n* = 14) *vs* SEVO (*n* = 14)	III–IV	[3][6][10]
Karaca *et al.* 2012[67]	Turkey	Retrospective observational study	≥ 65	80/177	NB (*n* = 50) *vs* GA (*n* = 115) *vs* CPNB (*n* = 92)	I–IV	[3]
Seung *et al.* 2013[68]	Korea	Retrospective observational study	≥ 60	140/366	RA (*n* = 259) *vs* GA (*n* = 245)	I–III	[1][3][5][6]
Elisabetta *et al.* 2014[69]	USA	Retrospective observational study	≥ 18	19,903/ 48,590	RA (*n* = 6,939) *vs* GA (*n* = 61,544)	—	[2]
Seitz *et al.* 2014[70]	Canada	Retrospective observational study	—	2,388/ 9,918	RA (*n* = 6,135) *vs* GA (*n* = 6,135)	III–V	[3][5][6][8][9]
Karaman *et al.* 2015[71]	Turkey	Retrospective observational study	≥ 65	89/219	RA (*n* = 203) *vs* GA (*n* = 105)	I–IV	[3]
Whiting *et al.* 2015[72]	USA	Retrospective observational study	—	—	RA (*n* = 1,924) *vs* GA (*n* = 5,840)	—	
Iftikhar *et al.* 2015[73]	UK	Retrospective observational study	77–88	179/539	CNB (*n* = 452) *vs* GA (*n* = 264)	I–IV	[9]
White *et al.* 2016[74]	UK	Prospective observational study	—	—	RA (*n* = 4,740) *vs* GA (*n* = 5,807)	—	[3][9]
Tung *et al.* 2016[75]	Taiwan-China	Retrospective observational study	≥ 18	6,982/ 10,207	RA (*n* = 11,153) *vs* GA (*n* = 6,036)	—	[3][5][6][8]
Haghighi *et al.* 2017[76]	Iran	RCT	≥ 60	80/20	RA (*n* = 50) *vs* GA (*n* = 50)	I–III	[10]
Gremillet *et al.* 2018[77]	Sweden	Retrospective observational study	≥ 50	4,515/ 8,932	RA (*n* = 11,257) *vs* GA (*n* = 2,190)	I–V	[3]
Meuret *et al.* 2018[78]	France	RCT	≥ 70	8/32	HUSA (*n* = 19) *vs* GA (*n* = 21)	I–III	[3][7]

Table continued

Author, year	Country	Design	Age	Male/ female	Anesthetic technique	ASA PS	Outcomes*
Desai *et al.* 2018[6]	USA	Retrospective observational study	≥ 65	4,827/ 11,398	RA (*n* = 6,597) *vs* GA (*n* = 9,629)	I–V	[2][4][5][6][8]
Weinstein *et al.* 2023[79]	USA	Retrospective observational study	≥ 50	4,245/ 10,471	RA (*n* = 7,358) *vs* GA (*n* = 7,358)	I–V	[1][3][6][8][9][10]

*[1] Delirium, [2] in-hospital mortality, [3] 30-day mortality, [4] 90-day mortality, [5] pneumonia, [6] myocardial infarction, [7] intraoperative hypotension, [8] venous thromboembolism, [9] length of hospital stay, [10] length of surgery

ASA PS = American Society of Anesthesiologists Physical Status; CNB = central neuraxial blocks; CPNB = combined peripheral nerve block; CSA = continuous spinal anesthesia; GA = general anesthesia; HUSA = hypobaric unilateral spinal anesthesia; MNB = multiple nerve blocks; NB = neuraxial block; RA = regional anesthesia; RCT = randomized controlled trial; SA = spinal anesthesia; SEVO = sevoflurane group; TCI = target-controlled infusion group

Observational studies with NOS scores ≥ 6 were regarded as high quality and all studies that we selected met the criteria for high quality (Electronic Supplementary Material [ESM] eAppendix 1). Publication bias of the outcomes was visualized by a funnel plot (ESM eAppendix 2).

Primary outcome

30-day mortality

Thirty-one studies, six of which were RCTs[8,40,44,48,57,66] and 26 of which were observational studies[29,34–37,39,41,43,45,46,50,54–56,58,62,64,65,67,68,70,71,74,75,77,79] compared the 30-day mortality between the RA and GA groups. One hundred and eighty-nine thousand, nine hundred and twenty-three patients were included in the RA group, and 242,206 patients were included in the GA group (Fig. 3A). After Knapp–Hartung adjustment, meta-analysis showed no significant difference between the RA and GA groups in six RCTs (OR, 0.88; 95% CI, 0.44 to 1.74; I^2 = 0%). Twenty-six observational studies also reported no significant difference (OR, 0.95; 95% CI, 0.88 to 1.03; I^2 = 63%).

Secondary outcomes

In-hospital mortality

Eighteen studies reported different in-hospital mortality rates in the RA group and GA group. Three RCTs[7,30,48] and 15 observational studies[5,6,29,31–33,35,36,38,43,50,58,63,65,69] were included. One hundred and six thousand, one hundred and twenty patients in the RA group and 185,292 patients in the GA group were involved (Fig. 3B). Because of the small sample size, the RCT results showed a wide CI (OR, 1.96; 95% CI, 0.02 to 171.66; I^2 = 71%). Fifteen observational studies showed a lower in-hospital mortality in the RA group (OR, 0.84; 95% CI, 0.77 to 0.91; I^2 = 17%).

90-day mortality

The 90-day mortality was examined by six studies, two of which were RCTs[40,48] and four of which were observational studies[6,41,46,55] (Fig. 3C). A total of 16,043 patients received RA and 19,850 patients received GA. After Knapp–Hartung adjustment, a meta-analysis of RCTs indicated a wide CI in 90-day mortality between the RA group and GA group (OR, 1.08; 95% CI, 0.43 to 2.72; I^2 = 0%). Observational studies also reported no significant difference (OR, 0.99; 95% CI, 0.77 to 1.28; I^2 = 69%).

Delirium

Sixteen studies, including seven RCTs[7,8,40,44,48,49,51] and ten observational studies,[35,42,45,53–55,60,63,68,79] analyzed the incidence of delirium after GA and RA in patients with hip fracture (Fig. 4). There were 99,647 patients in the GA group and 89,171 patients in the RA group. After Knapp–Hartung adjustment, a meta-analysis of seven RCTs could not find a difference (OR, 0.87; 95% CI, 0.36 to 2.12; I^2 = 67%). Ten observational studies indicated that RA significantly reduced postoperative delirium (OR, 0.89; 95% CI, 0.76 to 1.03; I^2 = 82%).

Pneumonia

Pneumonia incidence was assessed by 22 studies with 56,197 patients in the RA group and 79,744 patients in the GA group (Fig. 5). From the merging data of RCTs,[7,8,30,40,48,51] no significant difference between the

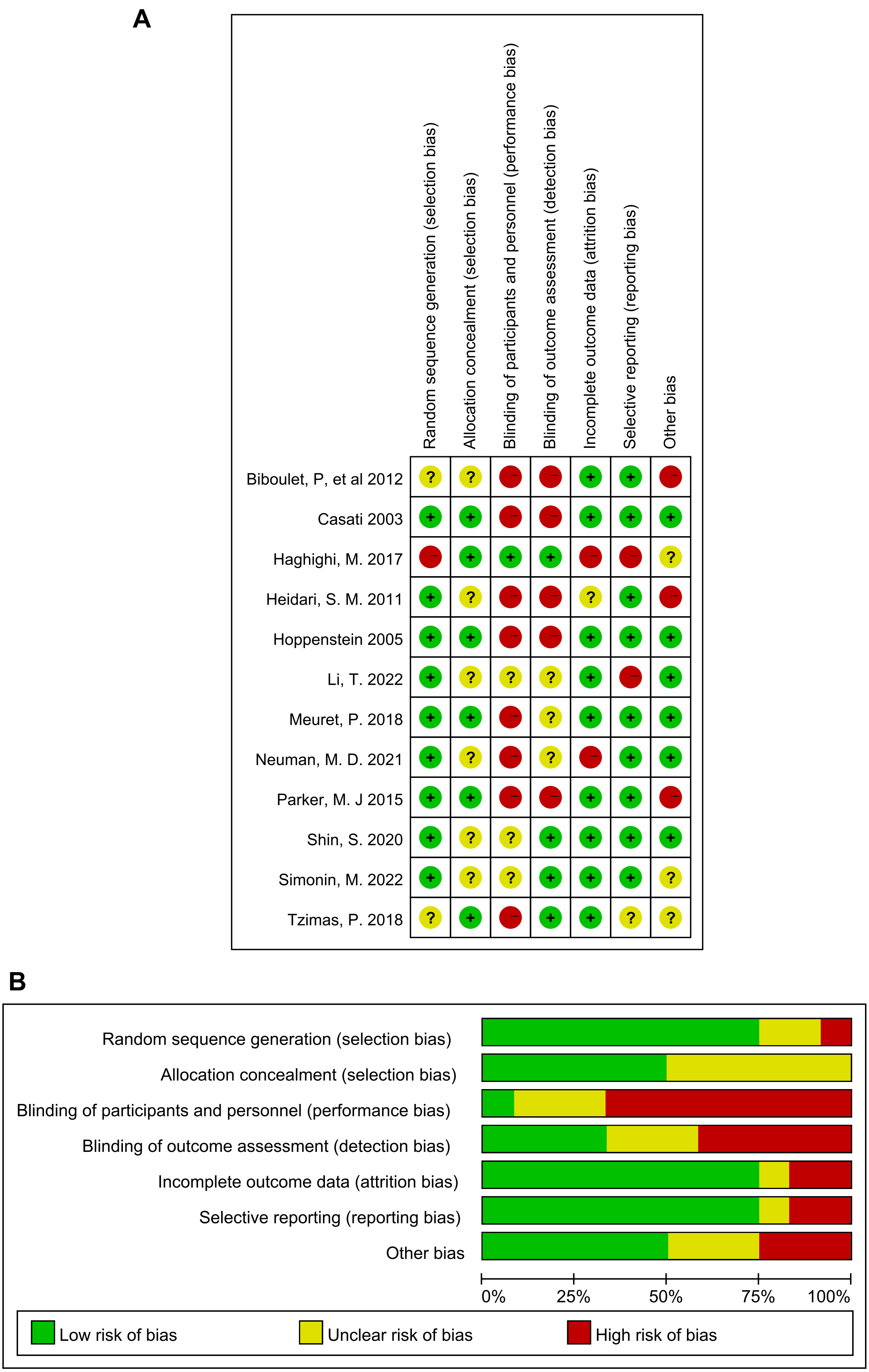


Fig. 2 (A) Risk of bias summary; (B) risk of bias graph

Fig. 3 Meta-analysis of 30-day mortality (A), in-hospital mortality (B), and 90-day mortality (C) in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

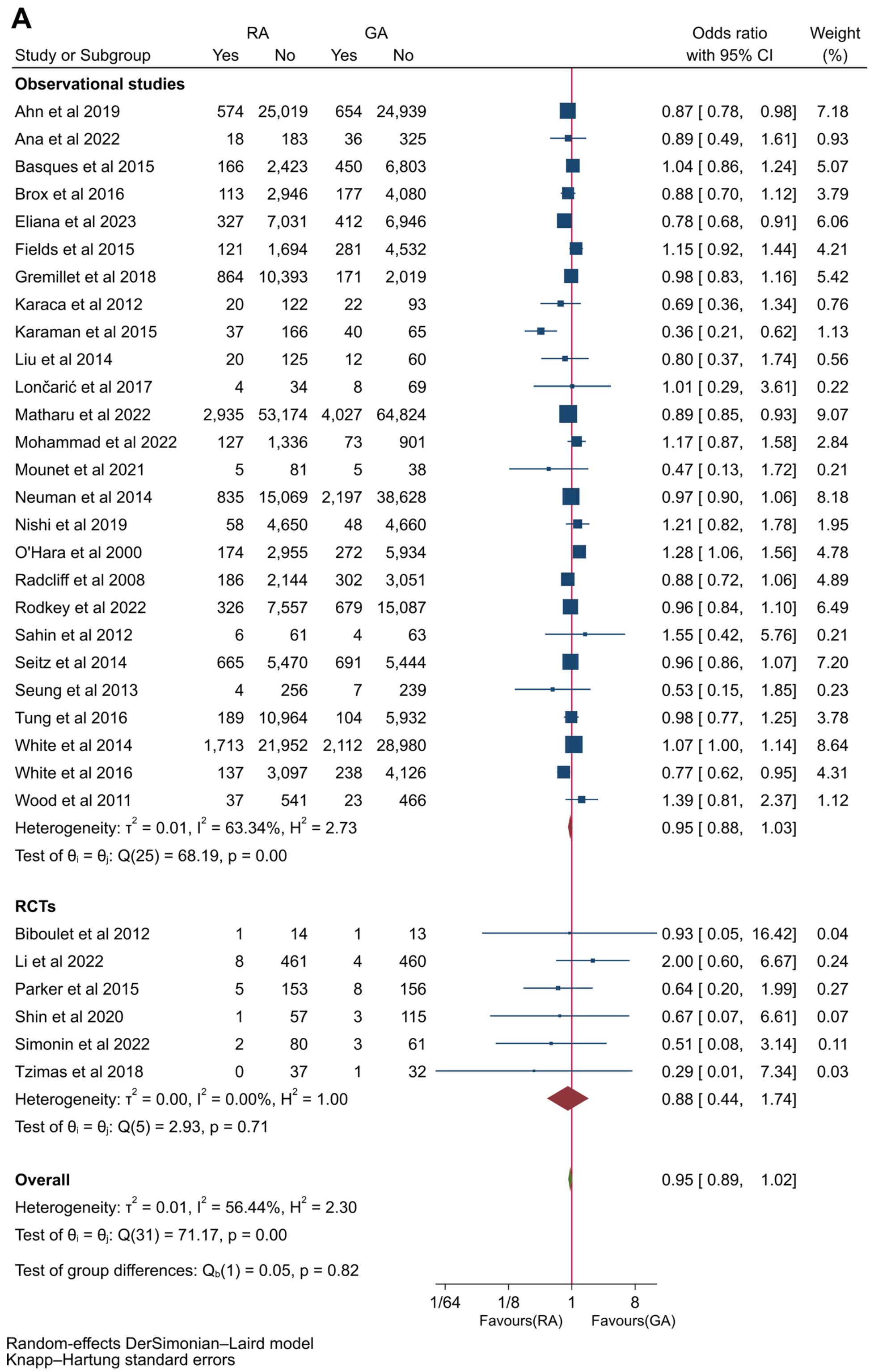
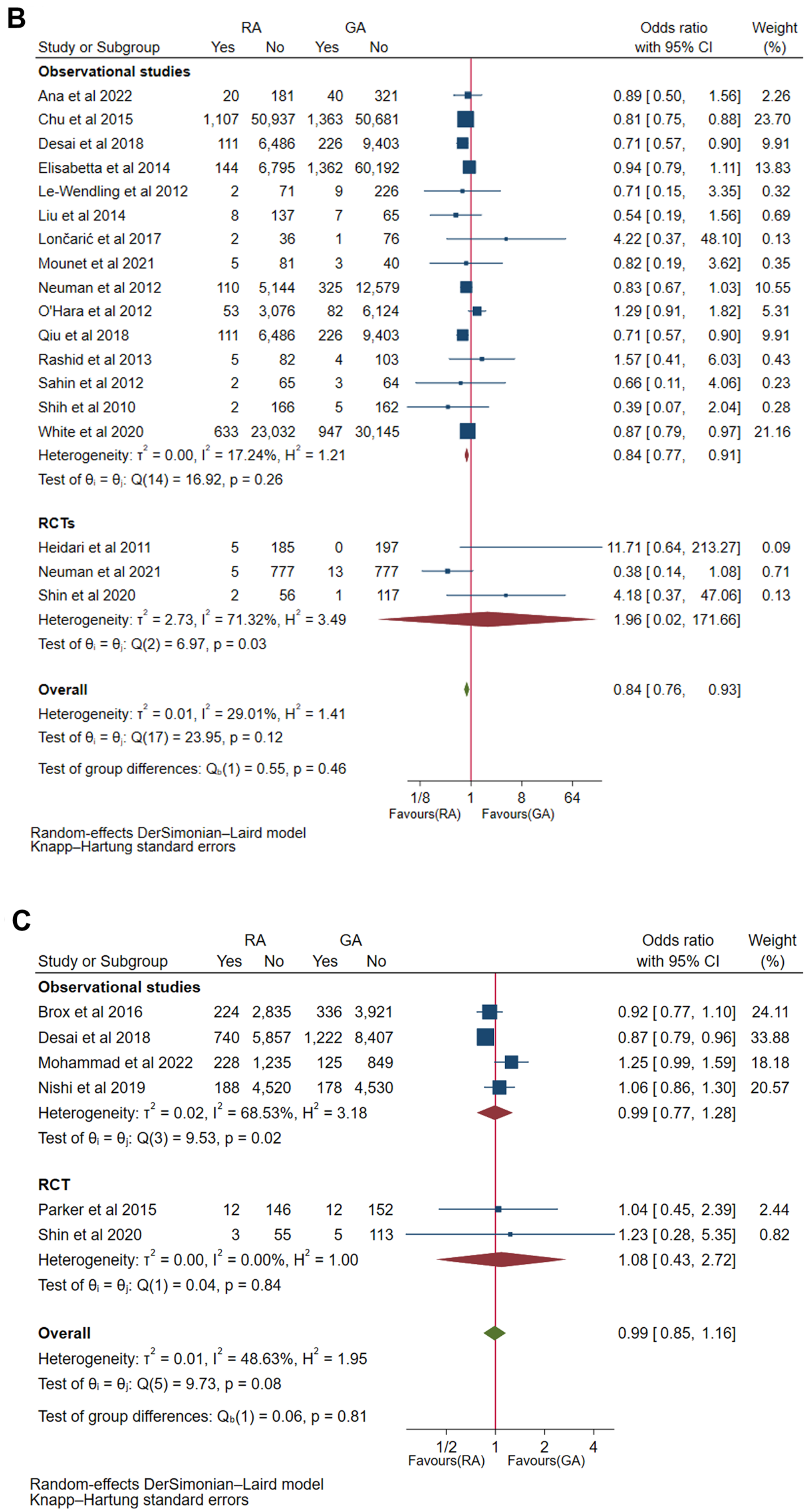


Fig. 3 continued



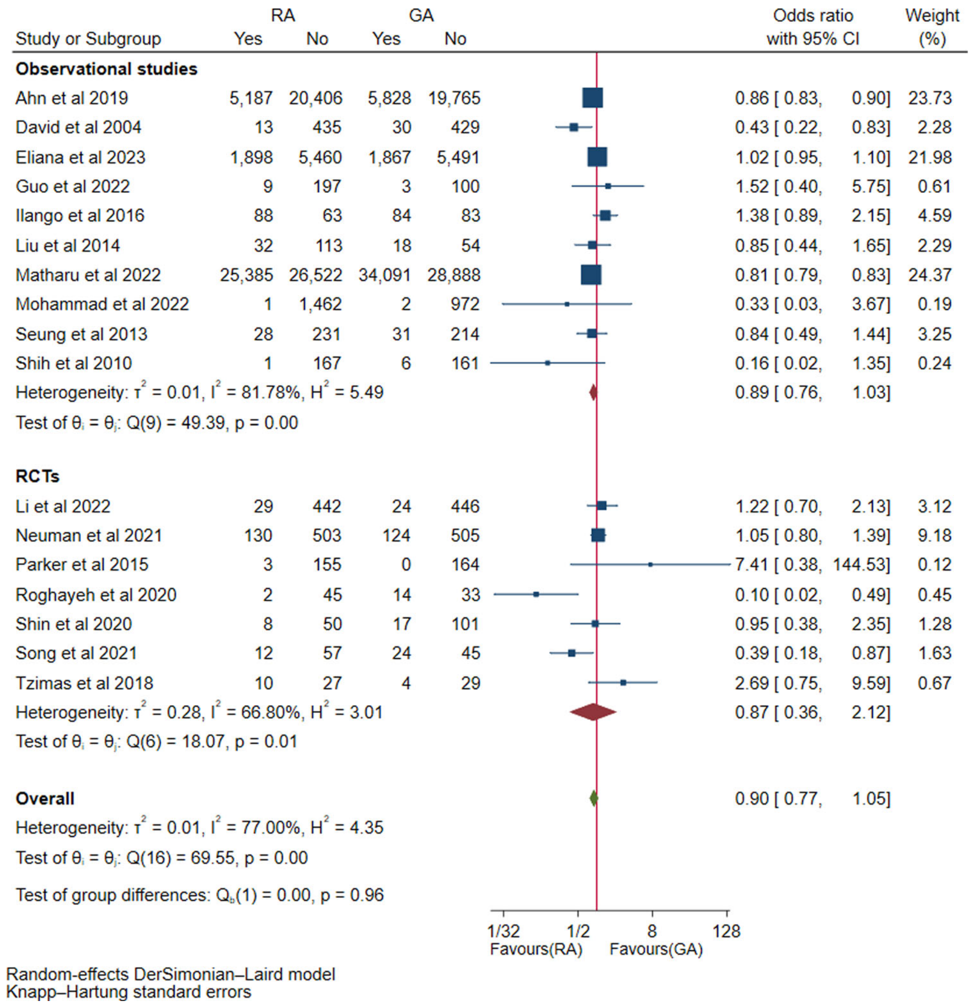


Fig. 4 Meta-analysis of postoperative delirium in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

two groups was found in the incidence of pneumonia after Knapp–Hartung adjustment (OR, 0.65; 95% CI, 0.42 to 1.03; I^2 = 0%). Sixteen observational studies[6,29,31,35,37,39,50,52,53,55,56,63,65,68,70,75] revealed no significant difference between the RA group and GA group (OR, 1.03; 95% CI, 0.93 to 1.15; I^2 = 40%).

Myocardial infarction

Five RCTs[7,8,30,40,66] and 16 observational studies[6,29,31,35,37–39,45,47,50,56,65,68,70,75,79] assessed the incidence of myocardial infarction (Fig. 6). This analysis contained 135,682 patients in the RA group and 159,989 patients in the GA group. After Knapp–Hartung adjustment, meta-analysis of RCTs indicated no significant difference in myocardial infarction between the two groups (OR, 0.83; 95% CI, 0.47 to 1.44; I^2 = 0%). Observational studies also showed no statistically significant difference between the two groups (OR, 0.95; 95% CI, 0.89 to 1.02; I^2 = 0%).

Intraoperative hypotension

Nine studies provided the outcome of intraoperative hypotension rate, including four RCTs[8,40,57,78] and five observational studies[29,43,50,59,64] (Fig. 7). Four thousand, five hundred and seventy-six patients were included in the RA group and 7,550 patients in the GA group. After Knapp–Hartung adjustment, the meta-analysis of RCTs showed a significant reduction in intraoperative hypotension with RA (OR, 0.52; 95% CI, 0.38 to 0.72; I^2 = 0%). Nevertheless, five observational studies indicated no significant difference between the two groups (OR, 0.87; 95% CI, 0.41 to 1.84; I^2 = 88%).

Venous thromboembolism

Fourteen studies that examined the incidence of deep venous thromboembolism and/or pulmonary thromboembolism were included in this meta-analysis (Fig. 8), including three RCTs[30,40,51] and 12 observational studies.[6,33,35,37,39,47,53,56,69,70,75,79] Seventy-

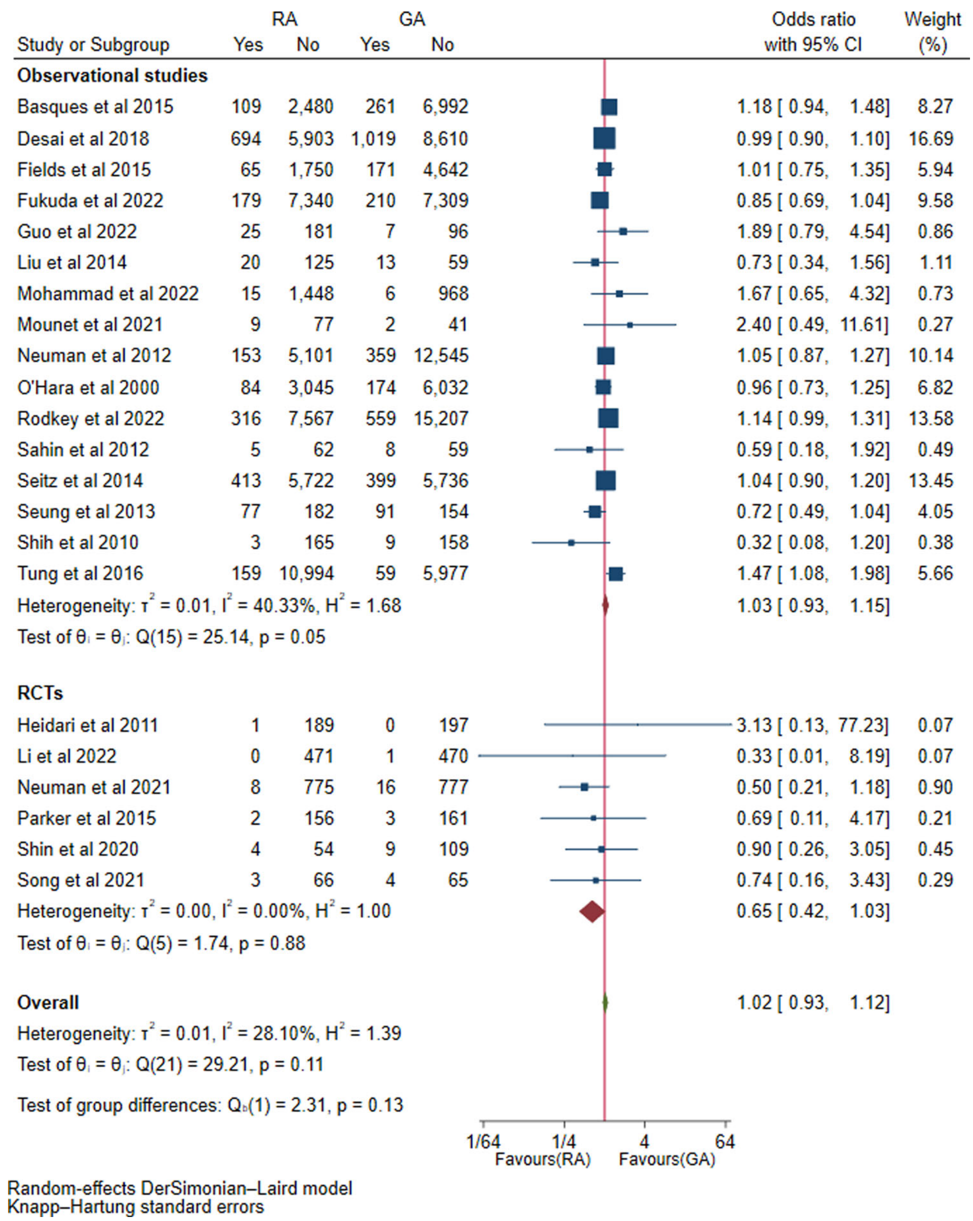


Fig. 5 Meta-analysis of pneumonia in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

three thousand, nine hundred and thirty-six patients belonged to the RA group, and 87,481 patients belonged to GA group. After Knapp–Hartung adjustment, the pooled analysis of RCTs revealed a wide CI between two groups in postoperative venous thromboembolism (OR, 1.19; 95% CI, 0.18 to 8.03; I^2 = 0%). For observational studies, no significant difference was found between the two groups (OR, 0.77; 95% CI, 0.58 to 1.02; I^2 = 51%).

Length of hospital stay (in days)

The length of hospital stay was recorded in 26 studies, seven of which were RCTs[8,30,40,44,48,51,57] and 20 of which were observational studies[32–35,37,38,43,45,46,50,54,55,59,63–65,70,73,74,79] (Fig. 9). There were 152,476 in the RA group and 195,467 participants in the GA group. No significant difference was found between two groups of RCTs (MD, 0.22 days; 95% CI, −0.22 to 0.66; I^2 = 54%). For observational studies, there was no significant difference between the RA and GA groups (MD, −0.36 day; 95% CI, −0.87 to 0.14; I^2 = 100%).

Duration of surgery (in minutes)

A total of four RCTs[30,44,49,76] and eight observational studies[33,35,37,39,53,61,65,79] were included in the analysis of length of surgery (Fig. 10). After Knapp–Hartung adjustment, there was no significant difference in the

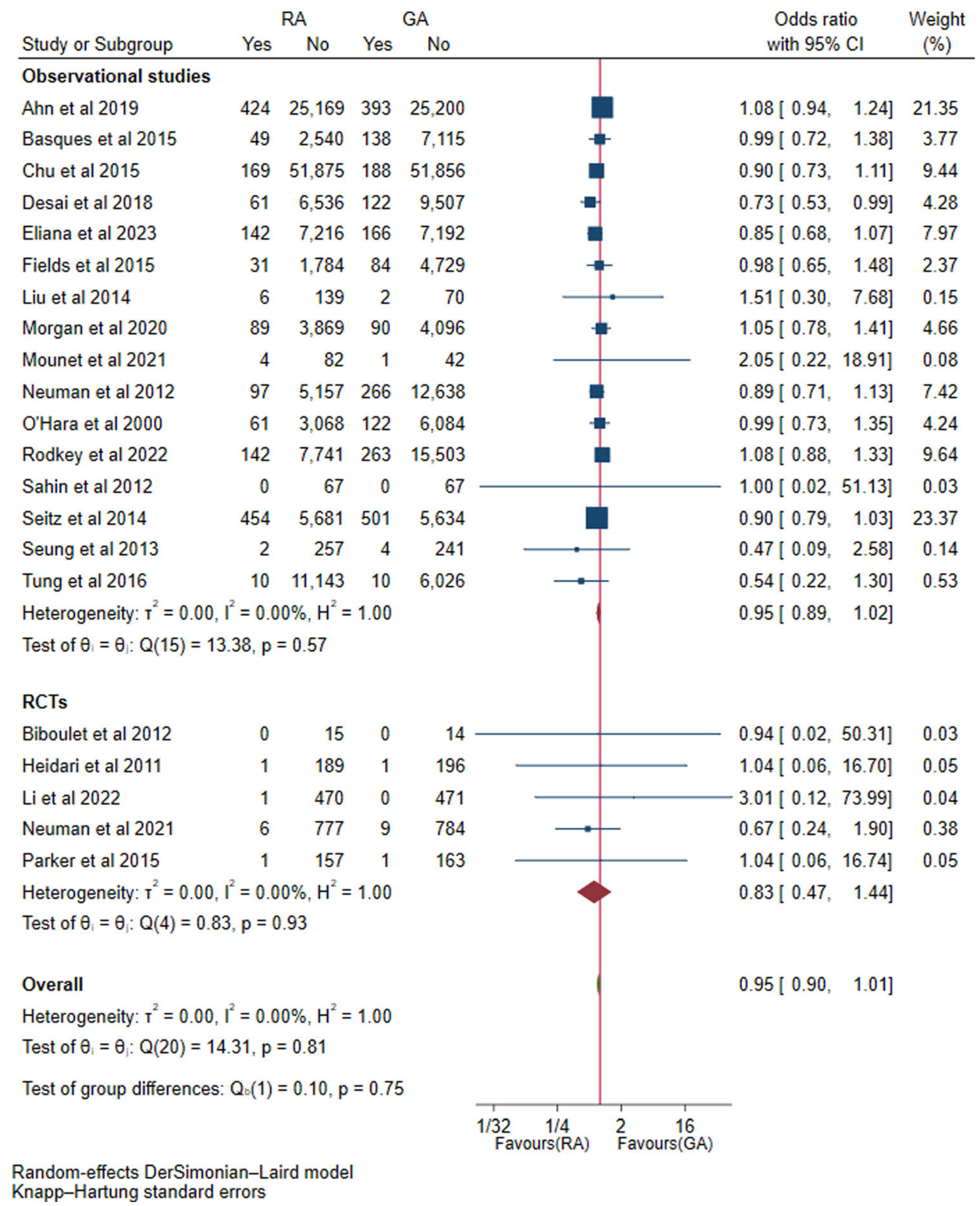


Fig. 6 Meta-analysis of myocardial infarction in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

duration of surgery between the two groups reported in RCTs (MD, −8.60 min; 95% CI, −20.48 to 3.28; I^2 = 54%). The observational studies showed a slight reduction in the length of surgery in the RA group (MD, −6.68 min; 95% CI, −11.30, −2.06; I^2 = 77%).

Sensitivity analysis

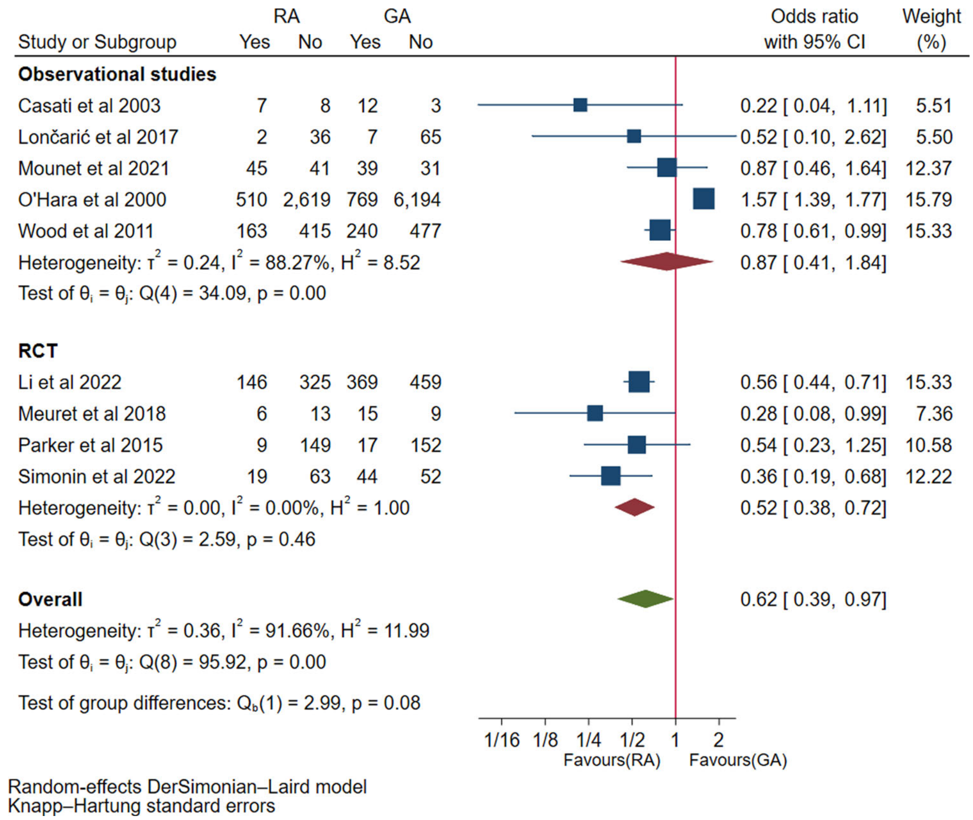
Sensitivity analyses showed that most results were stable and consistent with the main analysis. Nevertheless, when we removed the study of Morgan *et al*.[47] from the analysis of venous thromboembolism, the OR value changed distinctly (Fig. 11). Therefore, the results of venous thromboembolism were unstable.

Discussion

The present systematic review and meta-analysis aimed to compare the postoperative 30-day mortality and other perioperative outcomes of RA *vs* GA in patients undergoing surgery for hip fracture. Our study was a large systematic review with 55 studies. Nevertheless, some observational studies we included only reported unadjusted data. Pooling all studies without consideration of adjustment was not considered methodologically appropriate. Therefore, we considered the results of the meta-analyses of RCTs to be reliable. The findings of this study suggested that RA might have advantages over GA in terms of intraoperative hypotension. Nevertheless, intraoperative hypotension *per se* is a surrogate outcome,

Fig. 7 Meta-analysis of intraoperative hypotension in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia



and there were no significant differences between the two groups regarding 30-day mortality, 90-day mortality, in-hospital mortality, postoperative delirium, pneumonia, myocardial infarction, venous thromboembolism, or length of hospital stay.

At present, there is no consensus in the literature regarding whether RA can reduce mortality in patients after hip fracture surgery. Our meta-analysis showed no significant difference in 30-day mortality between the RA and GA groups. These findings are consistent with previous studies that have reported similar outcomes between the two groups.[9–15,80–82] Recently, the REGAIN and RAGA trials also indicated that RA did not reduce 30-day or 60-day mortality in patients after hip fracture surgery.[7,8] Due to the small sample size and wide CI, our current data are insufficient to know the effect of RA *vs* GA on in-hospital mortality (OR, 1.96; 95% CI, 0.02 to 171.66; I^2 = 72%) and 90-day mortality (OR, 1.08; 95% CI, 0.43 to 2.72; I^2 = 0%). Previous meta-analyses have found differences in in-hospital mortality between the RA and GA groups.[9,14,82] A large propensity score-matched study that evaluated 52,044 paired patients indicated that those undergoing RA had a significantly lower incidence of in-hospital mortality.[38] A meta-analysis including only two RCTs could not find a significant difference between the two groups.[13] The sample size in RCTs may not be large enough to show a difference in mortality endpoints between GA and RA.

Several previous meta-analyses reported 30-day mortality, but few reported 90-day mortality. Nevertheless, as reported, the mortality after hip fractures remained high for several months and up to a year.[83] In our meta-analysis, we did not find a difference in 90-day mortality between the RA and GA groups. A meta-analysis included only three articles and suggested that those receiving RA had a lower 90-day mortality.[82] Desai *et al.* retrospectively identified 16,695 patients, indicating that RA was associated with a lower likelihood of overall 90-day mortality.[6] Nevertheless, the difference was not significant from hospital discharge to 90 days postoperatively. In a large propensity score-matched cohort, researchers found no significant difference in 90-day mortality between RA and GA groups after adjusting for confounding factors.[46]

In the context of patients undergoing surgical intervention for hip fractures, no significant association was found between the use of RA and short- and long-term mortality. The recent RAGA trial[8] and previous meta-analyses deemed no significant difference in terms of postoperative delirium between the two groups.[11,12,14,15] In our meta-analysis, we found similar results. It is possible that the sample size of RCTs was not large enough to detect a significant difference in this outcome. The mechanism

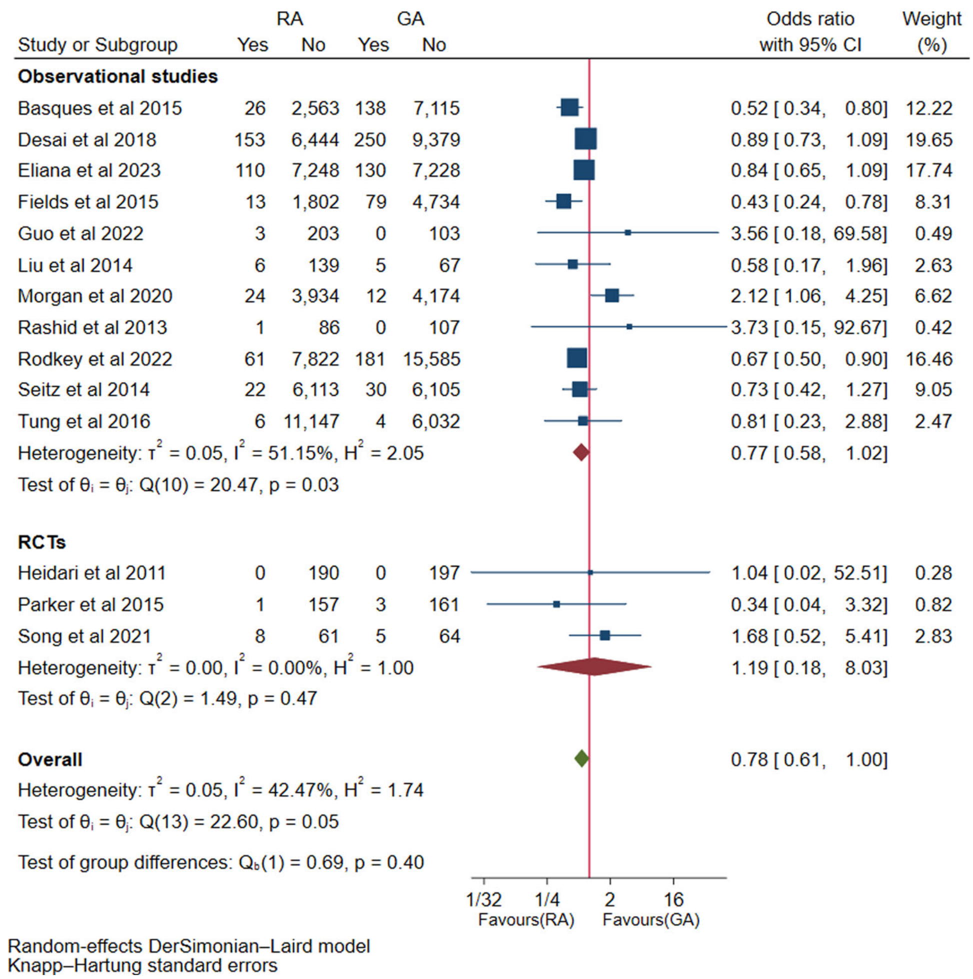


Fig. 8 Meta-analysis of venous thromboembolism in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

behind postoperative delirium is complex and multifactorial, and age, sex, medical illness, and biochemical abnormalities are considered to be the risk factors for postoperative delirium.[84] The choice of anesthesia may play a role in its development, and this finding supports the use of RA in patients undergoing hip fracture surgery to reduce the risk of postoperative delirium. The confusion assessment method (CAM) and confusion assessment method for the intensive care unit (CAM-ICU) were the most common tools used to diagnose delirium.[85] There is no consensus between the studies regarding which tool should be the gold standard.[86] Among the included studies, different methods were used to evaluate delirium, which may have led to the heterogeneity of the results.

We also investigated the incidence of pneumonia, myocardial infarction, intraoperative hypotension, and venous thromboembolism between the GA and RA groups. We found that there was no significant difference between the two groups in the incidence of postoperative pneumonia, myocardial infarction, and venous thromboembolism. This is consistent with the conclusions of two recent meta-analyses, which only included RCTs.[13,87]

The present meta-analysis revealed a significantly higher incidence of intraoperative hypotension in the GA group. This was similar to the results of most included studies.[8,50,57,78] Recently, two reviews that included only RCTs suggested no significant difference in the incidence of intraoperative hypotension between the two anesthesia techniques.[12,13] This might be related to the fact that the two reviews analyzed limited research.

The meta-analysis of the incidence of venous thromboembolism indicated a significant difference between the two groups. Nevertheless, the CI was too wide to know the effect of RA *vs* GA on the outcome. The sensitivity analysis also showed that the meta-analysis results were not robust and must be interpreted cautiously.

Similar to the results of some meta-analyses,[10–12] our meta-analysis found no significant difference in the length of hospital and length of surgery between the two groups. Two previous reviews considered a longer hospital stay in the GA group than in the RA anesthesia group.[14,15] In our

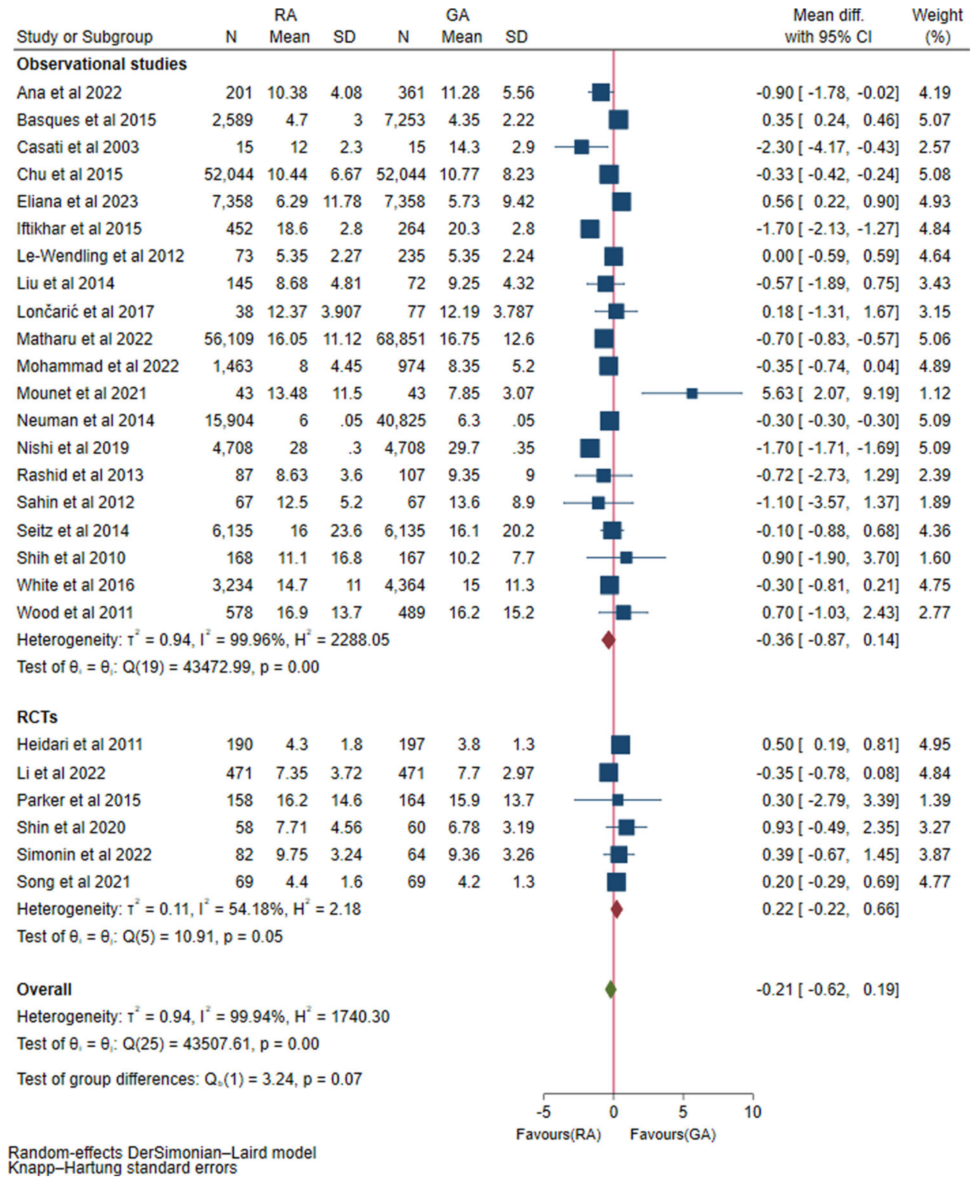


Fig. 9 Meta-analysis of length of hospital stay in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

review, we included more studies to analyze length of hospital stay, making it more representative.

Strengths and limitations

We systematically analyzed short-term and long-term mortality after hip fracture surgery under two different anesthesia techniques. In addition, we included several new RCTs in our meta-analysis.

Our current study also has the following potential limitations, which were primarily inherent: 1) among eligible studies, some outcome definitions and time points are not precisely the same; 2) the small sample size and wide CI make it insufficient to know the effect of RA *vs* GA on some outcomes; 3) the sample size of the included studies varied widely; 4) like in all meta-analyses, publication bias was an inevitable flaw; 5) the inclusion of both RCTs and observational studies may have led to confounding and other bias, and may have magnified the problems seen in observational studies; 6) subgroup analysis by ASA Physical Status classifications or age of patients could not be performed to make the results more reliable because data acquisition was challenging; and 7) research[88] has indicated that the surgeon may be an important covariate for observational studies, but this was not studied as a covariate in the included studies. Greater attention should be paid to the role of surgeons as covariates affecting outcomes in future studies.

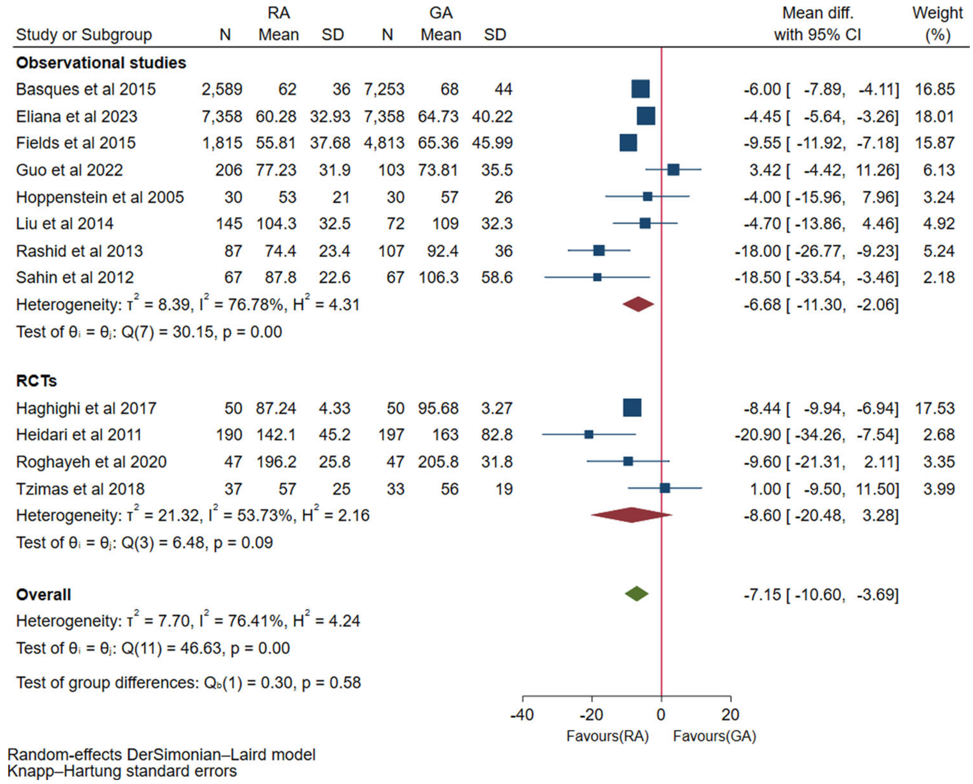


Fig. 10 Meta-analysis of length of surgery in patients receiving general anesthesia *versus* regional anesthesia

CI = confidence interval; GA = general anesthesia; RA = regional anesthesia

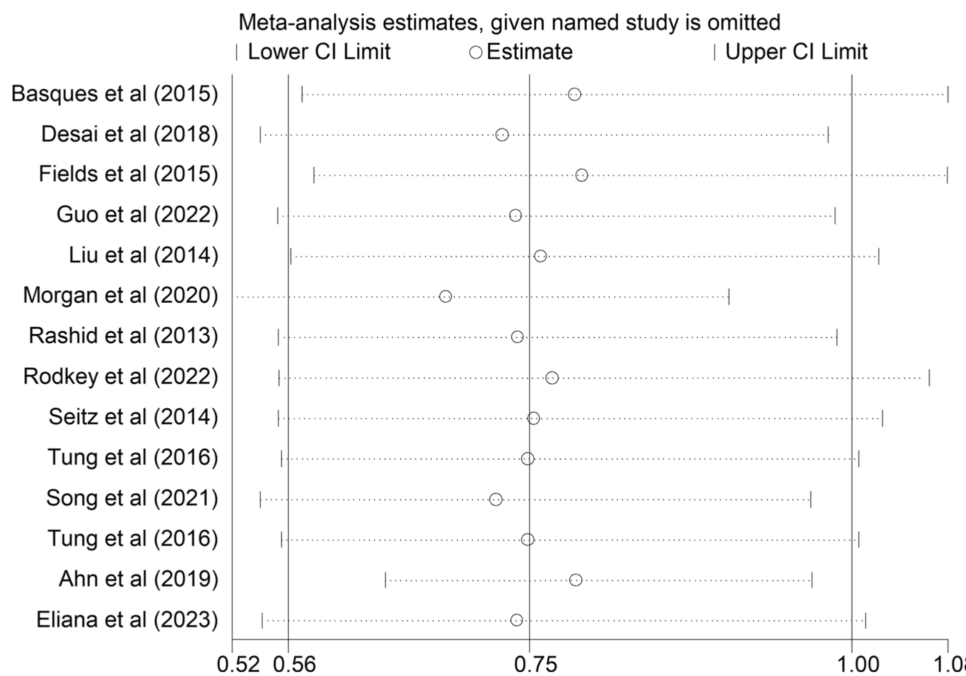


Fig. 11 Sensitivity analysis of venous thromboembolism

CI = confidence interval

Conclusion

In conclusion, RA may have advantages over GA in reducing intraoperative hypotension. Our findings indicate no difference in in-hospital mortality, 30-day mortality, 90-day mortality, postoperative delirium, pneumonia, myocardial infarction, venous thromboembolism, length of hospital stay, and length of surgery between RA and GA for hip fracture surgery.

Author contributions All authors participated in designing and conceiving the study. *Song Liu* and *Jianan Chen* performed the literature search. *Wenjun Hu* and *Gang Zeng* extracted information from the literature, which was independently checked by *Wenzhou Liu*, *Jianhong Li*. *Song Liu*, *Jianan Chen*, and *Huihong Shi* contributed to data analysis. All authors contributed to data interpretation. *Song Liu*, *Jianan Chen*, and *Huihong Shi* contributed to drafting the manuscript, and *Yanbo Chen*, *Wenjie Gao*, *Anjing Liang*, and *Weidong Song* contributed to critically reviewing and editing it.

Disclosures None.

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