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Risk Factors for Postanesthetic Emergence Delirium in Adults: A Systematic Review and Meta-analysis

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Abstract: Emergence delirium (ED) is delirium that occurs during or immediately after emergence from general anesthesia or sedation. Effective pharmacological treatments for ED are lacking, so preventive measures should be taken to minimize the risk of ED. However, the risk factors for ED in adults are unclear. In this systematic review and meta-analysis, we evaluated the evidence for risk factors for ED in adults. The PubMed, Scopus, Cochrane Library, Google Scholar, and Embase databases were searched for observational studies reporting the risk factors for ED in adults from inception to July 31, 2023. Twenty observational studies reporting 19,171 participants were included in this meta-analysis. Among the preoperative factors identified as risk factors for ED were age <40 or $\geq$65 years, male sex, smoking history, substance abuse, cognitive impairment, anxiety, and American Society of Anesthesiologists physical status score III or IV. Intraoperative risk factors for ED were the use of benzodiazepines, inhalational anesthetics, or etomidate, and surgical factors including abdominal surgery, frontal craniotomy (vs. other craniotomy approaches) for cerebral tumors, and the length of surgery. Postoperative risk factors were indwelling urinary catheters, the presence of a tracheal tube in the post-anesthetic care unit or intensive care unit, the presence of a nasogastric tube, and pain. Knowledge of these risk factors may guide the implementation of stratified management and timely interventions for patients at high risk of ED. The majority of studies included in this review investigated only hyperactive ED and further research is required to determine risk factors for hypoactive and mixed ED types.

Key Words: emergence delirium, anesthesia, adults, risk factors, meta-analysis

(*J Neurosurg Anesthesiol* 2024;36:190–200)

Delirium is a common complication after surgery and is characterized by acute and fluctuating alterations in mental state, including reduced awareness and disturbance of attention.[1] Postoperative delirium (POD) can present in the postanesthesia care unit (PACU),[1] up to 1 week postprocedure, or until hospital discharge.[2] The incidence of POD is reported to range from 3.6% to 28.3% in elective surgical patients,[1] in 15% to 53% of older individuals,[2] in 4.0% to 53.3% in patients with hip fractures,[1] and in 3% to 52% of cardiac surgery patients.[3] Emergence delirium (ED) is considered the early stage of POD and occurs during or immediately after emergence from general anesthesia or sedation.[4] Although ED has not been clearly defined, delirium occurring during the anesthesia recovery period is considered ED[5] and may be recognized in the operating room, PACU, or intensive care unit (ICU). Therefore, the timing of ED is considered to be the period between discontinuation of anesthetic or sedative agents and discharge of a patient to a regular ward or to an environment in which they are receiving regular care.

According to the 2017 European Society of Anesthesiology evidence-based and consensus-based guidelines on POD,[1] and the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, delirium can present as hypoactive (decreased alertness and motor activity, and anhedonia), hyperactive (agitated and combative), or mixed types.[1] Accordingly, these 3 types of ED must always be considered in clinical practice or

Received for publication April 18, 2023; accepted September 29, 2023.
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This study was supported by grants from the Chengdu Municipal Health Commission (no. 2020134), the Provincial Project of Sichuan Medical and Health Care Promotion Institute (no. KY2022SJ0044), and from the major project of Affiliated Hospital of Chengdu University (no. Y202203).
M.H. and Z.Z. designed the study. X.L., M.J., and M.H. performed the initial screening of the retrieved titles by using the search strategy. M.H. and R.W. were responsible for the full-text review and data extraction. M.H. and X.C. performed statistical analyses. M.H., Z.Z., and X.C. drafted the initial version of the protocol. M.H., Z.Z., M.J., R.W., X.L., J.Z., X.C., and C.L. contributed to and reviewed the final version of the manuscript.
The authors have no conflicts of interest to declare.
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Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.jnsa.com.

DOI: 10.1097/ANA.0000000000000942

research.[6,7] However, ED was initially referred to as acute agitation and this term is still often misused in the literature and sometimes referred to as "emergence agitation."[8,9] Some scholars also define it as "inadequate emergence," which is classified into emergence agitation and hypoactive emergence.[10–12]

The incidence of ED depends on multiple perioperative predisposing and triggering factors, including individual patient factors, anesthesia, and surgery-related factors. It has been estimated that ED occurs in 14% to 37% of elective noncardiac surgeries among patients older than 18 years.[6,7,13] The adverse effect of ED on outcomes has always been a concern for anesthesiologists, particularly in patients with a hyperactive form which is associated with an increased risk of postoperative hemorrhage, injury, extended PACU and hospital lengths of stay, morbidity, mortality, and resource utilization.[1,10] Hypoactive and mixed ED types have rarely been studied, but their prognosis is likely worse than hyperactive ED because of underdetection by health care teams leading to delayed intervention.[1]

It is widely acknowledged that delirium should be prevented because there are currently no effective pharmacological treatments. Therefore, it would be ideal if high-risk patients could be identified early so that they can receive timely and adequate perioperative care. Unfortunately, the risk factors for ED in adults have not been fully identified. Wei et al[8] summarized the risk factors for hyperactive ED in adults after general anesthesia in 18 original studies, but only 4 risk factors were identified. Moreover, significant heterogeneity existed in 3 of the 4 risk factors identified among these studies, leading to unreliable conclusions.

In this systematic review and meta-analysis, we evaluated the risk factors for all ED types in the immediate postanesthetic period in adult patients. Using a multivariate regression model in each observational study, we exclusively adopted adjusted odds ratio (OR) and 95% CIs rather than using a crude analysis generating ORs without adjusting for confounding factors. This strategy was chosen to eliminate confounding factors and concomitantly determine the independent risk factors for ED in adults. Moreover, sensitivity analysis was applied to reduce heterogeneity to below 75% to provide more robust evidence for clinical practice.

METHODS

This systematic review followed the meta-analyses of observational studies in epidemiology reporting guidelines and the protocol was registered on PROSPERO (CRD42022315601). The PubMed, Scopus, Cochrane Library, Google Scholar, and Embase databases were searched from inception until July 31, 2023, using the following MeSH terms: ("emergence delirium"[Title/Abstract] OR "acute delirium"[Title/Abstract] OR "acute agitation"[Title/Abstract] OR "emergence agitation"[Title/Abstract] OR "recovery room delirium"[Title/Abstract]) AND ("surgery"[Title/Abstract] OR "surgical"[Title/Abstract] OR "operative"[Title/Abstract] OR "operation"[Title/Abstract] OR "postoperative"[Title/Abstract] OR "post-operation"[Title/Abstract]) NOT ("Pediatric"[Title/Abstract] OR "child"[Title/Abstract] OR "children"[Title/Abstract]) Any potentially relevant studies were manually searched on the basis of the references of identified trials and systematic reviews.

The inclusion criteria were: (i) original research conducted as observational studies; (ii) studies with adult patients who recovered from anesthesia in the PACU, operating room, or ICU after surgery and anesthesia (including general and neuraxial anesthesia, peripheral nerve blocks, and sedation); (iii) studies in which risk factors for delirium were assessed with adjusted ORs with 95% CIs using a generalized linear model in the original articles; and (iv) studies for which the full text was available. The exclusion criteria were: (i) reviews, meta-analyses, study protocols, randomized controlled trials, conference proceedings, comments, case reports, and editorials; (ii) studies with patients who underwent postoperative sedation or postoperative mechanical ventilation in an unarousable state during the first 24 hours after the operation; and (iii) multiple reports on overlapping populations.

Data Extraction and Synthesis

The following data were collected from the included studies: authors, publication year, study design, country of origin, sample size, incidence of ED, diagnosis criteria, subtypes of ED, age, surgery and anesthesia types, location where the study was conducted, and analysis approach. Possible risk factors were selected only if they were identified in at least 2 studies. The ORs with corresponding 95% CIs generated by multivariate linear regression models were extracted for each identified risk factor.

Review Manager (version 5.3) was used for all statistical analyses, and $P < 0.05$ was considered statistically significant. Adjusted ORs from the multivariate linear regression models in each included study were merged into the meta-analysis. If $I^2 < 50\%$ and $P > 0.01$, a fixed-effects model was adopted; otherwise, a random-effects model was used. If there was obvious heterogeneity, which was numerically defined as $I^2 > 75\%$, sensitivity analysis or other methods were performed. Publication bias assessments were performed using Egger test on risk factors with 5 or more pooled studies.

Risk of Bias

Quality assessment was performed using the Newcastle Ottawa Quality Assessment Scale for cohort and case-control studies and the Agency for Healthcare Research and Quality for cross-sectional studies. Two investigators independently searched, assessed, and collected data from the studies. Any discrepancies were adjudicated by a senior investigator.

RESULTS

Twenty studies were identified for inclusion in this meta-analysis.[5–7,9–11,13–26] The selection process is summarized in Supplemental Digital Content 1, http://links.lww.com/JNA/A647 (Flow chart of search history and study selection). The main features of the included studies are summarized in Tables 1 and 2. In summary, 17 cohort studies,[5–7,9–11,13,16,17,19–26] 2 case-control studies,[14,18] and 1 cross-sectional study[15] were included in our analysis. The total sample size was 19,171, and the included studies originated from 10 countries.

The overall incidence of ED ranged from 25.0% to 37.1%.[6,7] The incidence of hyperactive ED ranged from 2.1% to 31.7%,[5,7,9–11,13–17,19–26] the incidence of hypoactive ED ranged from 3.2% to 17.6%,[5,7,10,11,13] and the incidence of mixed ED was 1.64%.[7] Importantly, this finding does not mean that hypoactive/mixed ED was not common, but that these two types of ED were reported less than hyperactive ED. Of the 20 included studies, 16[9–11,14–26] reported risk factors for hyperactive ED. Although 6 studies[5–7,10,11,13] reported on hypoactive ED, only those by Makarem et al[10] and Radtke et al[11] reported risk factors for hypoactive ED. None of the 20 included articles reported the risk factors for mixed ED. Eighteen of the included studies[5–7,9–11,13,14,16,17,19–26] were assessed as being of good quality (Table showing quality assessment of the included studies, Supplemental Digital Content 2, http://links.lww.com/JNA/A648).

Preoperative Risk Factors for ED

In total, 21 risk factors potentially related to ED were identified and analyzed. These included age, sex, smoking history, substance abuse, preoperative cognitive impairment, preoperative anxiety, American Society of Anesthesiologists (ASA) physical status score, anesthetic agents, abdominal surgery, frontal craniotomy for brain tumors, length of surgery, the presence of catheters and tubes, and postoperative pain. The preoperative risk factors for ED are summarized as Forest plots in Figure 1 and discussed below.

Age

Seven studies[5,7,11,14,16,21,23] reported a correlation between ED and patient age (Forest plots of age and ED, Supplemental Digital Content 3, http://links.lww.com/JNA/A649). Five[5,7,11,16,21] of these 7 studies reported no statistical significance in age (per 1 year, OR, 1.02; 95% CI, 0.98-1.06; I^2, 95%). Removing any 1 study did not reduce the heterogeneity and yielded similar results. Using the Galbraith heterogeneity test, the studies by Zhang et al,[7] Gu et al,[5] and Ramroop et al[16] were the major contributors to the heterogeneity (The Galbraith heterogeneity test of age, Supplemental Digital Content 4, http://links.lww.com/JNA/A650). Removing these studies resulted in an OR of 0.98 (95% CI, 0.97-0.99) and no heterogeneity. Two[11,23] of the 7 studies reported that the risk of hyperactive ED in patients aged 18 to 40 years was higher than that in those aged 40 to 65 years (pooled OR, 1.84; 95% CI, 1.32-2.58), and 2[11,14] studies reported that patients aged ≥65 years had a significantly increased incidence of hyperactive ED than those aged 40 to 65 years (synthesized OR, 1.52; 95% CI, 1.18-1.97).

TABLE 1. Design, Country of Origin, Sample Size, Diagnostic Standard, ED Subtypes (Incidence), and Population Age of the Included Studies

Study	Study design	Country of origin	Sample size	Diagnostic standard	Subtypes of ED (incidence, %)	Age (y)
Gu et al[5]	Retrospective cohort	China	618	CAM-ICU/RASS	Hyper (3.56) and hypo (17.64)	≥18
Wu et al[6]	Prospective cohort	China	228	CAM-ICU/RASS	Hyper, hypo and mixed (total: 25.00)	≥18
Zhang et al[7]	Retrospective cohort	China	915	CAM-ICU/RASS	Hyper (28.63), hypo (6.78) and mixed (1.64)	65-90
Kang et al[14]	Retrospective case-control	China	1950	SAS	Hyper (14.05)	≥18
Makarem et al*[10]	Prospective cohort	Iran	1136	RASS	Hyper (13.91) and hypo (6.43)	≥18
Assefa and Sahile[15]	Prospective cross-sectional	Ethiopia	306	RASS	Hyper (31.70)	≥18
Ramroop et al[16]	Prospective cohort	Trinidad and Tobago	417	Nu-DESC	Hyper (11.75)	≥18
Wiinholdt et al[17]	Prospective cohort	Denmark	1000	Nu-DESC	Hyper (10.30)	≥12
Fields et al[18]	Retrospective case-control	United States	1020	RASS or use of haloperidol	Hyper (1:1 matched)	≥18
Munjupong et al[13]	Prospective cohort	Thailand	454	CAM-ICU/RASS	Hyper (5.07) and hypo (9.25)	≥18
Munk et al[19]	Prospective cohort	Denmark	1970	RASS	Hyper (3.71)	≥16
Umholtz et al[20]	Retrospective cohort	United States	1763	Nursing notes	Hyper (2.10)	NR
Kim et al (1)[21]	Retrospective cohort	South Korea	792	RASS	Hyper (22.22)	≥18
Kim et al (2)[22]	Retrospective cohort	South Korea	488	SAS	Hyper (9.84)	20-90
Liu[23]	Prospective cohort	China	674	SAS	Hyper (23.15)	≥18
Chen et al[24]	Prospective cohort	China	123	SAS	Hyper (28.46)	≥18
Bao et al[25]	Prospective cohort	China	90	SAS	Hyper (26.67)	14-84
Radtke et al*[11]	Prospective cohort	Germany	1868	RASS	Hyper (4.98) and hypo (3.21)	≥18
Yu et al[26]	Prospective cohort	China	2000	Self-defined	Hyper (21.30)	16-70
Lepousé et al[9]	Prospective cohort	France	1359	SAS	Hyper (4.71)	≥15

*Separately observed risk factors for hyperactive and hypoactive ED.

CAM-ICU indicates Confusion Assessment Method of the Intensive Care Unit; ED, emergence delirium; Hyper, hyperactive ED; Hypo, hypoactive ED; NR, not reported; Nu-DESC, Nursing Delirium Screening Scale; RASS, Richmond Agitation Sedation Scale; SAS, Riker sedation agitation score.

TABLE 2. Identified Risk Factors, Surgery Types, Anesthesia Types, Location, Diagnosis Time Window, and Quality Assessment of the Included Studies

Study	*Risk factors	Surgery types	Anesthesia types	Location	Evaluation time	Quality assessment
Gu et al[5]	2, 7, 11	Elective craniotomy for brain tumor	GA	ICU	ICU admission	9
Wu et al[6]	5, 8	Elective noncardiac surgery	GA	PACU	10 min after PACU admission	8
Zhang et al[7]	2, 11, 14	Elective noncardiac surgery	GA	PACU	10 and 30 min after PACU admission, and before PACU discharge	8
Kang et al[14]	4, 5, 9, 16, 17, 18	Elective thoracoscopic lung surgery	GA	PACU	Every 15 min during PACU	7
Makarem et al[10]	16	Elective surgery	GA	PACU	10 min after PACU admission	7
Assefa and Sahile[15]	10, 12, 13, 19	Not restrictions	NR	PACU	PACU admission	5
Ramroop et al[16]	2, 9	Non-neurological procedures	GA	PACU	10 min after PACU admission	8
Wiinholdt et al[17]	5, 8	Elective or acute orthopedic or abdominal surgery	GA, NA and PNB	PACU	PACU admission and discharge	8
Fields et al[18]	8, 14, 19, 20, 21	Not restrictions	GA	PACU	During the PACU stay	6
Munjupong et al[13]	6, 8, 10	Elective noncardiac surgery	GA and RA	PACU	During the PACU stay	9
Munk et al[19]	17	Elective and non-elective surgery	GA	PACU	Immediately after awakening from GA, and during PACU stay	8
Umholtz et al[20]	6	Major surgery	GA	PACU	During the PACU stay	7
Kim et al(1)[21]	2, 8, 10, 15, 18, 20	Elective nasal surgery	GA	PACU	PACU admission, every 15 min thereafter, and PACU discharge	7
Kim et al(2)[22]	9, 11, 21	Elective urological surgery	GA	PACU	During the PACU stay	8
Liu[23]	3, 8, 10, 12, 13, 15, 17, 20	Nasal surgery	GA	NR	NR	7
Chen et al[24]	7, 15, 17	Elective craniotomy for cerebral tumor	GA	Neurosurgical ICU	Every 1 h during 12 h after surgery	7
Bao et al[25]	8, 12, 20	Elective hepatobiliary surgery	GA	NR	Within 30 min after surgery	7
Radtke et al[11]	1, 2, 3, 4, 6, 9, 10	Elective and non-elective surgery	GA	PACU	10 min after PACU admission	8
Yu et al[26]	8, 10, 15, 17, 20	Elective surgery	GA	PACU	During the PACU stay	8
Lepousé et al[9]	1, 9, 12	Noncardiac surgery	GA	PACU	During the PACU stay	7

*Risk factors: (1) abdominal surgery; (2) age (per 1 y); (3) age <40 years old; (4) age ≥ 65 years old; (5) American Society of Anesthesiologists classification; (6) etomidate; (7) frontal approach craniotomy for cerebral tumors; (8) inhalational anesthetics; (9) length of surgery (per 1 min); (10) postoperative complaints of pain; (11) postoperative pain score ([numeric rating scales, NRS], per 1 score); (12) premedication with benzodiazepines; (13) preoperative anxiety; (14) preoperative cognitive impairment; (15) presence of tracheal tubes in PACU or neurosurgical ICU; (16) rescue analgesia in the PACU; (17) sex; (18) smoking history; (19) substance abuse; (20) urinary catheters; and (21) use of nasogastric tubes.

GA indicates general anesthesia; ICU, intensive care unit; NA, neuraxial anesthesia; NR, not reported; PACU, postanesthesia care unit; PNB, peripheral nerve blocks; RA, regional anesthesia.

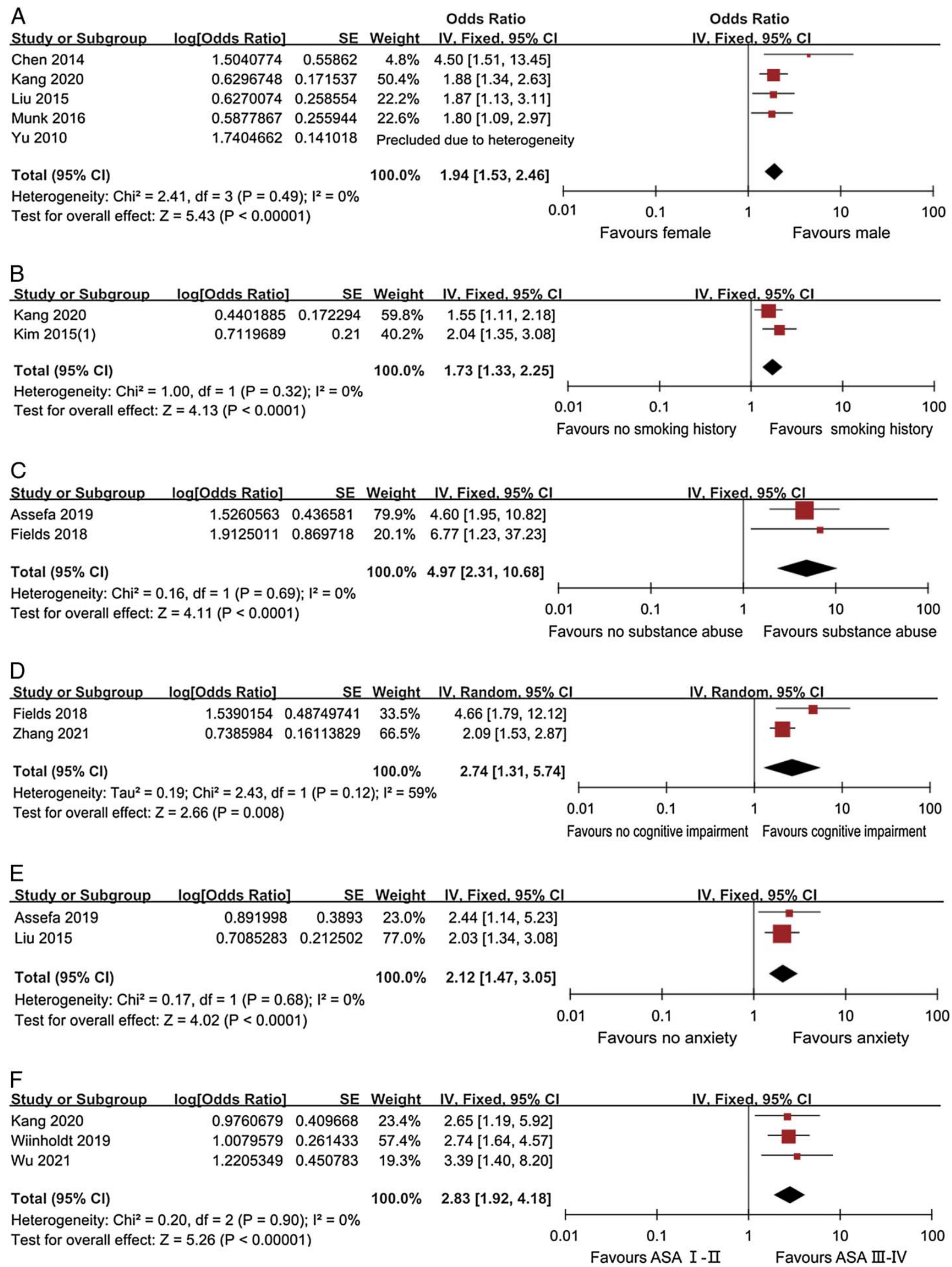

FIGURE 1. Forest plots summarizing preoperative risk factors for emergence delirium. (A) Sex. (B) Smoking history. (C) Substance abuse. (D) Preoperative cognitive impairment. (E) Preoperative anxiety. The data are presented as odds ratios with corresponding 95% CIs. The I^2 statistic was used to assess heterogeneity among studies. ASA indicates American Society of Anesthesiologists; SE, Standard error. full color online

Male Sex

Five studies[14,19,23,24,26] were pooled to investigate the effect of sex on hyperactive ED. The incidence of ED in men was significantly higher than that in women (merged OR, 2.70; 95% CI, 1.48-4.91; I^2, 89%). Sensitivity analysis revealed that the study by Yu et al[26] was a possible outlier. In that study, the diagnostic standard of delirium was derived from self-defined criteria and showed an abnormally higher OR than the other studies. Omitting this study resulted in an OR of 1.94 (95% CI, 1.53-2.46) and no heterogeneity (Fig. 1A).

Smoking History

Two studies[14,21] evaluated the effect of smoking history on hyperactive ED. The synthesized OR was 1.73 (95% CI, 1.33-2.25) and there was no heterogeneity (Fig. 1B).

Substance Abuse

Two studies[15,18] reported substance abuse as a risk factor for hyperactive ED with a merged OR of 4.97 (95% CI, 2.31-10.68) and no heterogeneity (Fig. 1C).

Preoperative Cognitive Impairment

Bases on 2 studies,[7,18] there was an association between preoperative cognitive impairment and ED with a synthesized OR of 2.74 (95% CI, 1.31-5.74) and no remarkable heterogeneity (Fig. 1D).

Preoperative Anxiety

Preoperative anxiety was significantly correlated with the hyperactive form in 2 studies[15,23] (pooled OR, 2.12; 95% CI, 1.47-3.05) with no heterogeneity (Fig. 1E).

ASA Physical Status Classification

Three[6,14,17] of the included studies reported a higher incidence of ED in patients with ASA physical status scores III or IV compared with I or II. The pooled OR was 2.83 (95% CI, 1.92-4.18) with no heterogeneity (Fig. 1F).

Intraoperative Risk Factors for ED

The intraoperative risk factors for ED are summarized as Forest plots in Figure 2 and discussed below.

Anesthetic Drugs

Pooled data from 4 studies[9,15,23,25] found that benzodiazepine premedication was associated with hyperactive ED (pooled OR, 2.08; 95% CI, 0.47-9.32; I^2, 94%). Sensitivity analysis revealed that the study by Liu,[23] which showed that premedication with benzodiazepines was a protective factor for ED in patients undergoing nasal surgery, was an outlier. Removing this study resulted in an OR of 3.92 (95% CI, 1.41-10.93; I^2, 69%) (Fig. 2A).

Eight studies[6,13,17,18,21,23,25,26] reported an association between inhalational anesthetics and ED (synthesized OR, 2.54; 95% CI, 1.67-3.86; I^2, 80%). Sensitivity analysis again revealed that the study by Yu et al[26] was the cause of significant heterogeneity. Omitting this study resulted in an OR of 2.65 (95% CI, 2.12-3.32; I^2, 24%) (Fig. 2B).

Three studies[11,13,20] reported the effect of etomidate on ED (pooled OR, 4.44; 95% CI, 2.30-8.59) with no heterogeneity (Fig. 2C).

Surgery Types

Two of the included studies[9,11] found that patients undergoing abdominal surgeries had a higher risk of ED than those undergoing other noncardiac surgeries (pooled OR, 2.79; 95% CI, 1.70-4.58) with no heterogeneity (Fig. 2D). Two other studies[5,24] reported a higher incidence of ED in patients undergoing frontal craniotomy than in those undergoing other craniotomy approaches for brain tumors (synthesized OR, 2.49; 95% CI, 1.52-4.06), with no heterogeneity (Fig. 2E).

Length of Surgery

Five studies[9,11,14,16,22] were pooled to investigate the effect of the length of surgery (per 1 minute) on ED. The pooled OR was 1.01 (95% CI, 1.00-1.01; I^2, 56%) (Fig. 2E).

Postoperative Risk Factors for ED

The postoperative risk factors for ED are summarized as Forest plots in Figure 3 and discussed below.

Catheters and Tubes

Five studies[18,21,23,25,26] reported that the presence of an indwelling urinary catheter was associated with a high incidence of hyperactive ED (pooled OR, 3.93; 95% CI, 2.27-6.79; I^2, 69%). Sensitivity analysis revealed that the study by Fields et al[18] was a source of the heterogeneity; it was designed as a case-control study whereas the others were cohort studies. When this study[18] was excluded, the heterogeneity was reduced (OR, 2.87; 95% CI, 2.11-3.90; I^2, 25%) (Fig. 3A).

Four studies[21,23,24,26] reported that the presence of a tracheal tube in the PACU or ICU was associated with a high incidence of hyperactive ED (pooled OR, 5.42; 95% CI, 3.28-8.97; I^2, 61%). The study by Liu[23] was a possible cause of this significant heterogeneity, and the omission of this study resulted in an increased OR to 7.05 (95% CI, 5.13-9.70) with no heterogeneity (Fig. 3B).

Two studies[18,22] were pooled to investigate the effect of nasogastric tubes on hyperactive form, showing an OR of 3.39 (95% CI, 1.69-6.80; $P=0.0006$) and no heterogeneity (Fig. 3C).

Postoperative Pain

Postoperative pain was reported as a risk factor for ED in 11 of the included studies.[5,7,10,11,13–15,21–23,26] Six[11,13,15,21,23,26] of these 11 studies were pooled to investigate the effect of postoperative pain on ED, with a pooled OR of 2.72 (95% CI, 1.68-4.41; I^2, 78%). The study by Yu et al[26] was a possible outlier for the third time, reporting higher ORs than the other studies. Omission of this study resulted in an OR of 1.98 (95% CI, 1.58-2.49; I^2, 42%) (Fig. 3D). Three[5,7,22] of the 11 studies reported that the postoperative pain score (numeric rating scales, per 1 score) was associated with ED (pooled OR, 1.27; 95% CI,

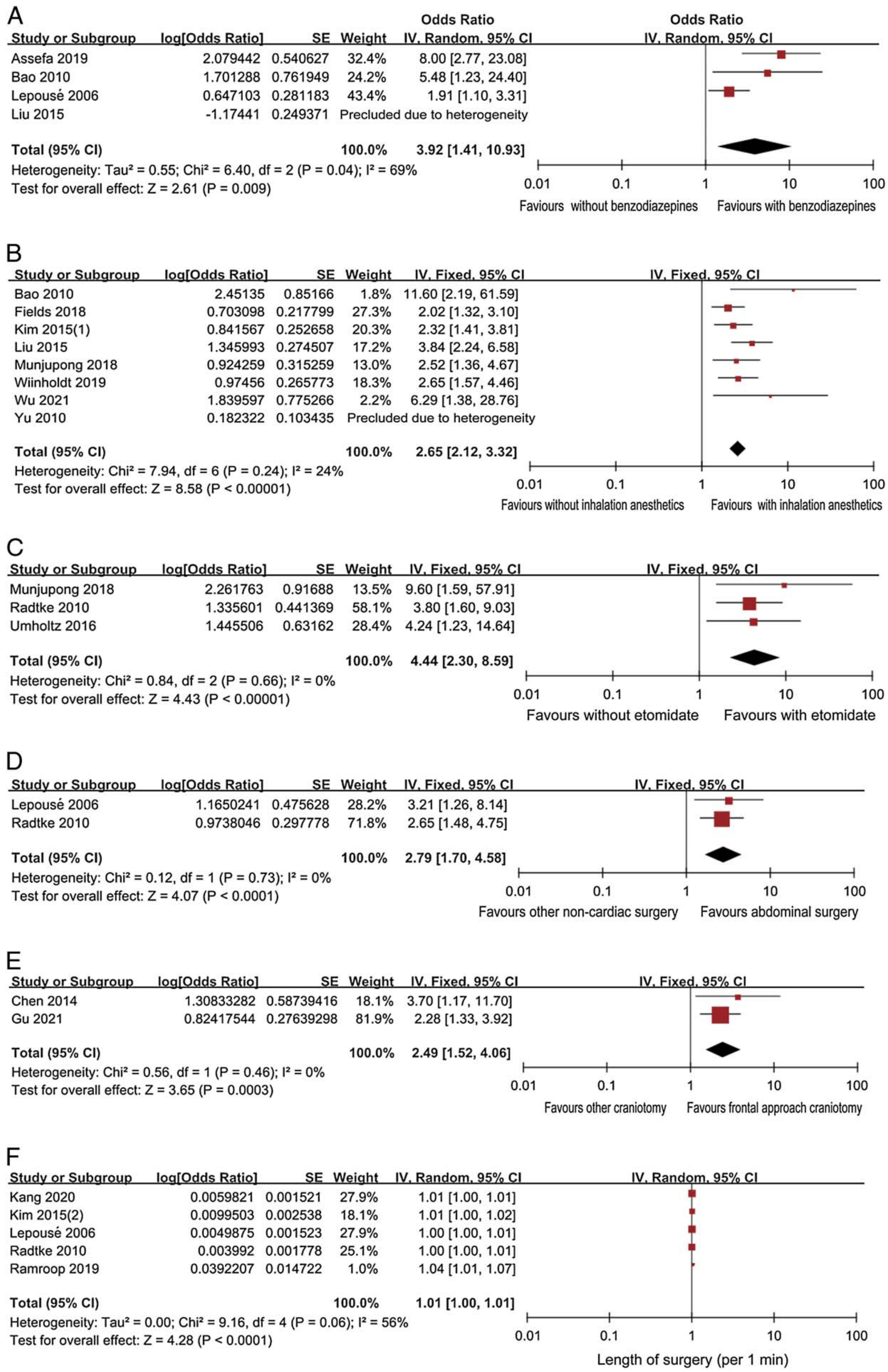

FIGURE 2. Forest plots summarizing intraoperative risk factors for emergence delirium. (A) Premedication with benzodiazepines. (B) Inhalational anesthetics. (C) Etomidate. (D) Abdominal surgery versus other noncardiac surgeries. (E) Frontal craniotomy versus other craniotomy approaches for cerebral tumor. (F) Length of surgery (per 1 minute). The data are presented as odds ratios with corresponding 95% CIs. The I^2 statistic was used to assess heterogeneity among studies. full color online

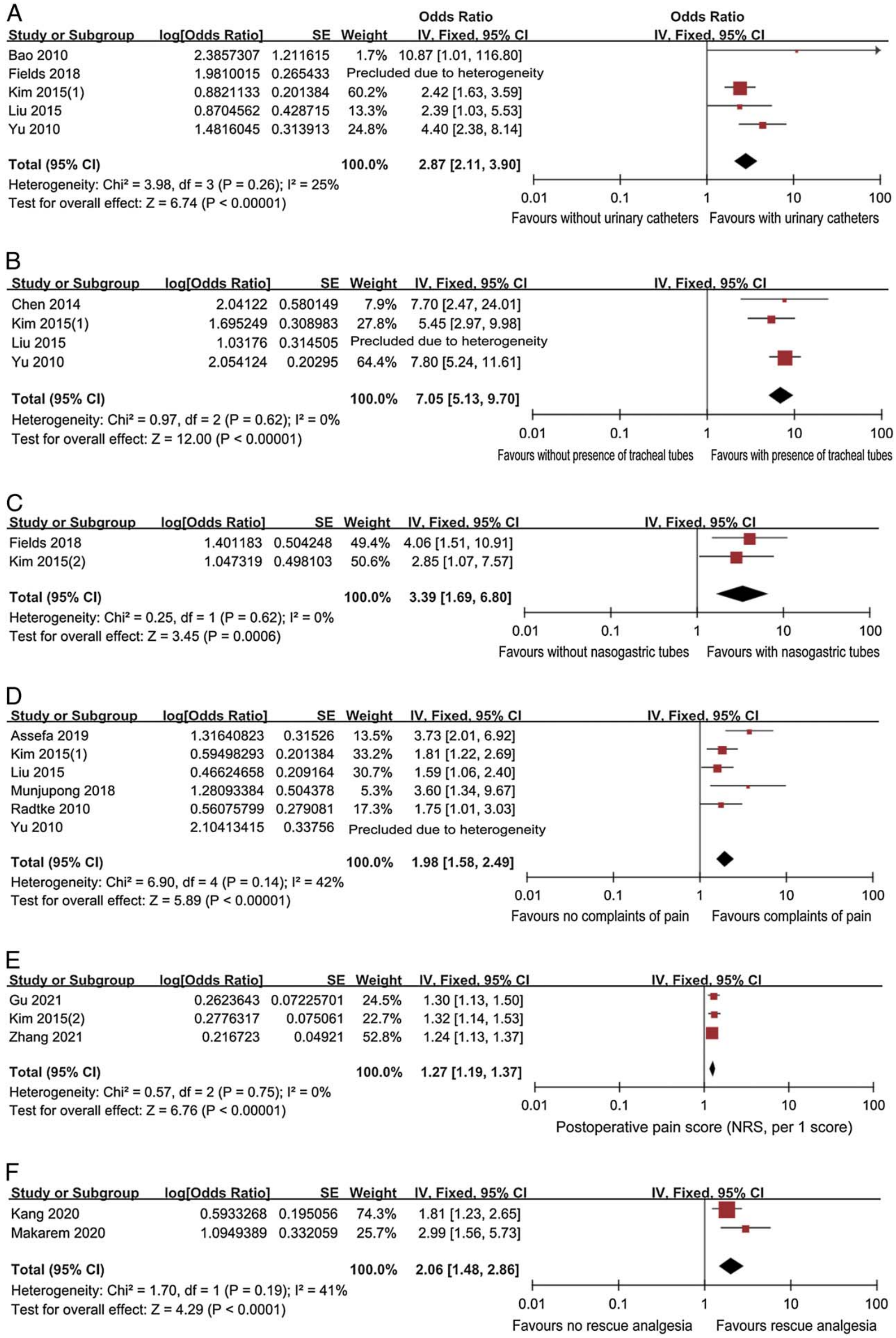

FIGURE 3. Forest plots summarizing postoperative risk factors for emergence delirium. (A) Presence of a urinary catheter. (B) Presence of a tracheal tube in PACU or intensive care unit. (C) Pressence of a nasogastric tube. (D) Complaint of pain. (E) Postoperative pain score (NRS, per 1 score). (F) Rescue analgesia in PACU. The data are presented as odds ratios with corresponding 95% CIs. The I^2 statistic was used to assess heterogeneity among studies. NRS indicates numerical rating scale; PACU, postanesthesia care unit. full color online

1.19-1.37), with no heterogeneity (Fig. 3E). Two studies[10,14] reported the relationship between rescue analgesia in the PACU and hyperactive ED, with a pooled OR of 2.06 (95% CI, 1.48-2.86; I^2, 41%) (Fig. 3F).

Publication Bias

Publication bias assessments were performed on studies that examined inhalational anesthetics and complaints of pain. Egger tests showed no quantitative evidence of publication bias in complaints of pain ($P = 0.133$), but there was a publication bias in the studies on inhalational anesthetics ($P = 0.027$).

DISCUSSION

This systematic review and meta-analysis evaluated the risk factors for ED in adult patients. Pooled ORs from multivariate regression models were used to preclude confounding factors in each of the studies included in the review. We identified multiple perioperative risk factors for ED in adults, including male sex, ASA physical status III or IV, intraoperative use of inhalational anesthetics or etomidate, a long operation time, indwelling catheters or tubes, and postoperative pain.

ED has a complex pathophysiology and multiple risk factors. Currently, there is no unifying hypothesis to elucidate the complexity and phenotypic diversity of delirium.[27] Furthermore, there is a large variation in the clinical assessment of ED for many reasons. The nomenclature regarding POD was not standardized before 2018,[2] there are no unified diagnostic criteria for ED,[6] few noninvasive modalities exist to test the mechanisms of delirium in humans,[27] and there is no generally recognized animal model of delirium, resulting in a lack of biomarker identification and prevention of the development of additional theoretical hypotheses.[27] Therefore, identifying perioperative risk factors is essential not only for the prevention and management of ED but also for future investigations into the underlying mechanism(s) of delirium. This review found that the majority of published studies (70% of those included in this review) were focused on hyperactive ED, with a lack of studies investigating hypoactive or mixed ED types. Despite this limitation, our systematic review and meta-analysis provides reliable, evidence-based guidance for the prevention and management of ED. It also highlights the need for more attention from clinicians and investigators to hypoactive and mixed forms of ED.

ED is generally regarded as a provisional neuropsychiatric disorder that can occur in individuals of any age.[4,28] Clinically, children and older adults have a higher incidence of delirium. This meta-analysis of studies that included only adult patients found that hyperactive ED tended to occur in those aged <40 years or ≥65 years, leading to speculation that there is a U-shaped relationship between age and hyperactive ED in adults. In addition, younger patient age was associated with a higher incidence of ED. However, as only 2 studies[11,21] investigated the relationship between ED and age, the relationship between age and ED warrants further investigation.

Other patient-related factors were also associated with ED, including sex, smoking history, substance abuse, preoperative cognitive impairment, preoperative anxiety, and ASA physical status. The risk of ED in men was approximately twice that in women in 4 studies reporting this relationship,[14,19,23,24] and this may be due to a higher proportion of men who are smokers or who have a history of alcohol or drug abuse. The ASA physical status classification categorizes patients into 6 grades based on the patient's physical condition and surgical risk with postoperative complications and mortality increasing with higher ASA grades.[29] Therefore, patients with ASA physical status grades III or IV would be expected to be at an increased risk for ED compared to those with ASA physical status grades I or II. Although a smoking history, substance abuse, preoperative cognitive impairment, and anxiety are all considered risk factors for ED, on the basis of this meta-analysis, more research is needed to confirm their risk actual prediction value given the limited number of studies investigating these issues.

Any relationship between anesthesia and neurocognitive disorders has always been a controversial topic, and there is no strong clinical evidence to show a causal relationship between anesthesia and cognitive dysfunction. This meta-analysis provided clinical evidence for a relationship between anesthetics, including inhalational anesthetics and etomidate, and ED. Following Bedford's[30] report in 1955 of cognitive dysfunction in older patients undergoing general anesthesia, which was termed "less degrees of dementia" at that time, many preclinical studies investigating the effects of various general anesthetic agents on neurotoxicity and cognitive dysfunction began to emerge. Notably, inhalation anesthetics were regarded as a risk factor for pediatric ED, as summarized by the European Society of Anesthesiology evidence-based and consensus-based guidelines on POD.[1] The current meta-analysis identified inhalational anesthetics as a risk factor for ED in adults on the basis of data from 7 studies,[6,13,17,18,21,23,25]. However, an additional study investigating the association between inhalational anesthetics and ED[26] introduced substantial heterogeneity highlighting that further research is rquired to confirm a relationship between inhalational anesthesia and ED. In addition, the induction of anesthesia with etomidate was associated with a high incidence of ED (pooled OR, 4.44).[11,13,20] On the basis of pooled data from 4 studies, benzodiazepine premedication was also associated with hyperactive ED.[9,15,23,25] However, 1 study was an outlier, finding that premedication with benzodiazepines was a protective factor for ED in patients undergoing nasal surgery,[23] a study population that was different to those included in the other 3 studies.[9,15,25] Therefore, benzodiazepines represent a controversial risk factor for ED. Importantly, γ-aminobutyric acid type A ($GABA_A$) receptor agonists or positive allosteric modulators are associated with addiction-related behavioral and neuropsychiatric disorders,[31,32] involving GABA withdrawal mechanism.[33] Even a single brief exposure to a commonly used general anesthetic drug can trigger a sustained increase in cell-surface expression and the function of extrasynaptic $GABA_A$ receptors.[34] Coincidentally, the above three anesthetics investigated in the studies included in this review are $GABA_A$ receptor agonists and/or positive allosteric modulators.

Surgical factors are known to be related to postoperative neurocognitive changes. A high rate of POD has previously been reported in cardiac, thoracic, orthopedic, urological, and abdominal surgeries, and, based on 2 studies, this meta-analysis found that abdominal surgery was associated with a higher risk of ED than other noncardiac surgeries.[9,11] However, this does not mean that there is a low risk of ED in other surgeries, as noncardiac surgeries that may be associated with a high risk of ED, including thoracic and orthopedic surgeries, have not been fully investigated. Frontal craniotomy may be associated with a higher incidence of ED than other craniotomy approaches for cerebral tumors.[5,24] Based on 5 studies,[9,11,14,16,22] this meta-analysis found that the length of surgery was associated with ED, with the risk of ED increasing by 1.82 times for each additional hour of surgery.

According to previous clinical studies, postoperative noxious stimuli from indwelling catheters/tubes and pain are associated with hyperactive ED. The presence of a urinary catheter, nasogastric tube, or endotracheal tube was associated with hyperactive ED in this meta-analysis. In particular, patients with endotracheal tubes in place while in the PACU or ICU had a high incidence of hyperactive ED (pooled OR, 7.05).[21,23,24,26] Postoperative pain was also associated with ED based on data from 11 studies.[5,7,10,11,13–15,21–23,26] Patients experiencing postoperative pain were twice as likely to develop ED than those without pain complaints, and the risk of ED increased with higher levels of pain. Accordingly, early removal of catheters and tubes and improvement in postoperative pain management may reduce the risk of ED.

This meta-analysis has several limitations. First, no stratified analysis was performed according to ED subtypes. Only 2 studies reported risk factors for hypoactive ED, and they did not report the same risk factors making it impossible to pool data. Furthermore, none of the 20 included studies reported risk factors for mixed ED. Second, a subgroup analysis was not performed according to different diagnostic criteria because there was no or low heterogeneity in the included studies for most of the risk factors. Third, few cardiac surgery patients were included in this meta-analysis; therefore, the results are more generally applicable to patients undergoing noncardiac surgery. Fourth, the definition of "adult" varied across studies and countries, ranging from older than 15 years to older than 21 years. For example, the study by Wiinholdt et al[17] included patients older than 12 years whereas the study by Bao et al[25] included patients aged from 14 to 84 years. Fifth, some of the included studies did not rigorously describe certain risk factors. For example, smoking history was not clearly defined as past or current, substance abuse did not report which substance, and the scale(s) used to define preoperative cognitive impairment was not always reported. Finally, certain outcomes were based on data from only 2 studies. However, even with the limited number of studies, we were able to identify clinical clues for the recognition of patients at high risk for ED.

CONCLUSIONS

This systematic review and meta-analysis identified multiple perioperative risk factors for ED in adults. The independent risk factors included male sex, ASA physical status score III or IV, intraoperative use of inhalational anesthetics or etomidate, long operation time, indwelling catheters or tubes, and postoperative pain. Probable risk factors were smoking history, substance abuse, preoperative cognitive impairment, preoperative anxiety, abdominal surgery, and frontal craniotomy for cerebral tumors. Age was also a risk factor, with ED tending to occur in patients aged <40 years or ≥ 65 years. Though there was an association between benzodiazepine premedication and ED, further research is needed to confirm this relationship. Finally, the majority of data relates to hyperactive ED, with limited investigation of hypoactive and mixed ED types.

ACKNOWLEDGMENT

The authors acknowledge the Translational Neurology Laboratory, Affiliated Hospital of ZunYi Medical University, for the expertise and help in study design.

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