

Association between Intraoperative Electroencephalogram Burst Suppression and Postoperative Delirium: A Systematic Review and Meta-analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Multiple studies have suggested that intraoperative burst suppression might be a predictor for postoperative delirium
- However, the evidence regarding an association between burst suppression and the development of postoperative delirium is mixed, with some studies that find an association and others that do not

What This Article Tells Us That Is New

- This systematic review and meta-analysis of 14 studies involving 6,435 patients undergoing cardiac and noncardiac surgery identified that burst suppression was associated with the development of postoperative delirium, although Grading of Recommendations Assessment, Development, and Evaluation (GRADE) quality of the evidence was low

ABSTRACT

Background: Electroencephalogram burst suppression can be associated with postoperative delirium; however, the results of relevant studies are discrepant. This systematic review and meta-analysis aimed to assess the association between intraoperative burst suppression and postoperative delirium in adult surgical patients.

Methods: PubMed, MEDLINE, Embase, Google Scholar, and the Cochrane Central Register of Controlled Trials were systematically searched and updated in May 2023. The authors included cohort studies, case-control studies, and randomized controlled studies reporting on postoperative delirium incidence with documented intraoperative burst suppression in adults receiving general anesthesia for any surgery. The primary outcome was the pooled odds ratio for postoperative delirium in cases with intraoperative burst suppression compared to those without burst suppression, calculated using a random-effects model. Two independent investigators extracted the data. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (registration No. CRD42022326479); the results were reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Results: Fourteen studies (6,435 patients) were included in the analysis. The overall incidence of postoperative delirium was 21.1% (1,358 of 6,435). Patients with intraoperative burst suppression had a higher incidence of postoperative delirium than those without burst suppression (pooled odds ratio, 1.492; 95% CI, 1.022 to 2.178; $I^2 = 44\%$; 95% CI, 0 to 75%; $\tau^2 = 0.110$). The intraoperative duration of burst suppression was significantly longer in patients who developed postoperative delirium (standardized mean difference, 0.462; 95% CI, 0.293 to 0.632; $I^2 = 63\%$; 95% CI, 16 to 84%; $\tau^2 = 0.027$). The burst suppression ratio was significantly higher in the delirium group (standardized mean difference, 0.150; 95% CI, 0.055 to 0.245; $I^2 = 0\%$; 95% CI, 0 to 85%; $\tau^2 = 0.00$).

Conclusions: The meta-analysis suggests an association between intraoperative burst suppression and postoperative delirium; however, the quality of evidence was very low. The limited number of studies and substantial heterogeneity across them emphasize the need for further high-quality studies to establish a more robust conclusion.

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Postoperative delirium is the most common complication after surgery in older patients.^{1–4} It is associated with significant morbidity and mortality.^{1,3,5} The prevention

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of postoperative delirium has been identified as a public health priority by relevant academic societies.² However, delirium remains a neurocognitive syndrome with a multifactorial etiology and poorly understood pathophysiology, making its prevention challenging.^{1,5}

Electroencephalographic burst suppression is defined as a continuous, quasiperiodic alteration between high-amplitude electrical activity and the isoelectric electroencephalogram (EEG).^{1,2} Exposure to excessive anesthetics during surgery can cause burst suppression.^{1,2} Observational studies have suggested that EEG burst suppression during general anesthesia may be a predictor of postoperative delirium.^{1,4,6} However, the results from relevant research have been conflicting.^{2,7} A previous randomized trial did not find a reduction in postoperative delirium by minimizing EEG burst suppression.² Furthermore, conducting interventional studies where patients are randomly assigned to groups with or without burst suppression is not feasible because of ethical concerns. Thus, the overall relationship between intraoperative burst suppression and postoperative delirium is not fully understood.

Therefore, we performed a systematic review and meta-analysis to assess the association between intraoperative burst suppression and postoperative delirium in adult surgical patients.

Materials and Methods

The study protocol adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) guidelines⁸ and was prospectively registered at the International Prospective Register of Systematic Reviews (registration No. CRD42022326479). Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁹

Search Strategy and Selection Criteria

Eligible studies included cohort studies, case-control studies, cross-sectional studies, or randomized controlled studies (study design) that reported the incidence of postoperative delirium assessed using validated tools (outcome) with the documentation of intraoperative burst suppression (exposure) in adult patients undergoing general anesthesia for any type of surgery (population). No language or publication year restrictions were applied. Two independent researchers (S.-K.P. and H.K.) systematically searched the OVID-MEDLINE, EMBASE, Google Scholar, and Cochrane Central Register of Controlled Trials (CENTRAL) electronic databases for relevant studies from inception to May 29, 2023. The search terms are provided in Supplementary Material 1 (<https://links.lww.com/ALN/D718>). We also manually scanned the bibliographies of searched articles to identify further relevant studies. Two authors (S.-K.P. and Y.S.) reviewed the titles and abstracts of the searched articles independently. The

full-text article was retrieved and reviewed for potential eligible studies. Any disagreements between the two investigators were resolved through discussion with a third investigator (D.W.H.), and inclusion or exclusion decisions were made after reaching a consensus.

Data Analysis

Data Extraction. Two independent investigators (S.-K.P. and Y.S.) extracted the following data using a standardized extraction form: title, first author, publication year, name of the journal, country, trial period, study design, surgery type, number of participants age, sex, baseline delirium or cognitive function assessment, EEG monitoring device used, the incidence of postoperative delirium, the diagnostic tool for postoperative delirium, the follow-up period for postoperative delirium, the severity of postoperative delirium, presence or absence of intraoperative burst suppression, duration of burst suppression, burst suppression ratio, burst suppression duty cycle, burst suppression probability, American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status, duration of surgery, mean processed EEG values, EEG monitoring period, anesthetic agents used, hospital stay, and postoperative cognitive decline. If data were missing or insufficient, attempts were made to contact the corresponding authors for relevant data. If data were presented solely in graphical format, they were digitized into numerical form using the open-source software Plot Digitizer (version 2.6.8; <https://plotdigitizer.sourceforge.net/>).¹⁰

The primary outcome was the incidence of postoperative delirium in the “burst suppression present” group compared to that in the “burst suppression absent” group. Secondary outcomes included the following: duration of burst suppression, burst suppression ratio, burst suppression duty cycle, burst suppression probability, and processed EEG index values in the “delirium” group compared to that in the “no delirium” group; severity of postoperative delirium; duration of postoperative delirium; incidence of postoperative cognitive dysfunction; and length of hospital stay in the burst suppression present group compared to that in the burst suppression absent group.

Study Quality Assessment. Two independent investigators (S.-K.P. and H.K.) assessed the bias of randomized trials using the Cochrane Risk of Bias 2 (RoB 2.0) tool (Cochrane Collaboration, United Kingdom).¹¹ Each trial was categorized as low-risk, some concerns, or high-risk across five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results.¹¹ The overall risk of bias was judged as low when the bias for all domains was low, or high when the bias for at least one domain was high or if the bias for multiple domains was of some concern. If the overall judgment was neither low nor high, the overall bias was considered as having some concern.

The quality of the nonrandomized trials was independently assessed by two investigators (S.-K.P. and H.K.) using the Newcastle–Ottawa Scale, which evaluates selection, comparability, and exposure assessment.¹² The Newcastle–Ottawa Scale assigns a maximum score of 4 for selection, 2 for comparability, and 3 for exposure, for a maximum total score of 9. Any discrepancies were resolved through discussions, or with the help of a third investigator (Y.S.) if needed.

Statistical Analysis. Meta-analysis was conducted using Comprehensive Meta-Analysis version 4.0 (Biostat, Inc., USA) and Stata version 17.0 (StataCorp, USA). The pooled odds ratio for binary variables or standardized mean difference for quantitative data and their 95% CIs were calculated for each outcome. Statistical heterogeneity was assessed using the chi-squared and I^2 tests. A level of 10% significance ($P < 0.1$) for the χ^2 statistic or an I^2 greater than 50% was considered to indicate considerable heterogeneity. A fixed-effects model was selected if the P value for the chi-squared test was greater than 0.10 and I^2 was less than 50%. If I^2 was greater than 50%, a random effects model was used.^{13,14}

To explore heterogeneity, we performed a sensitivity analysis by removing one study each time and determined whether it altered our results. For combined studies showing substantial heterogeneity with fewer than 10 studies, we additionally applied t -statistics (Hartung–Knapp–Sidik–Jonkman method) instead of Z -test to lower the error rate.¹⁵ The Hartung–Knapp–Sidik–Jonkman model was chosen as a secondary analysis to reduce potential type I error rates compared to the DerSimonian and Laird random effects model, particularly in situations where the number of studies is small and substantial heterogeneity exists.^{15,16}

If reported data are median (interquartile range), median (range), or mean $\pm$ SEM, the means and SDs were calculated from these values.¹⁷ Publication bias was assessed using Begg’s funnel plots, and each dataset’s funnel plots were visually inspected for asymmetry.¹⁸ We calculated the number needed to treat using a 95% CI based on the absolute risk reduction to estimate the overall clinical impact of the intervention.¹⁹

Subgroup analyses were planned according to type of surgery (cardiac *vs.* noncardiac surgery), patient age (age greater than 60 yr *vs.* 60 yr or younger), type of anesthetic agents (intravenous *vs.* volatile agents), and type of EEG monitors.

Quality of the Evidence. The evidence was graded as high, moderate, low, and very low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. This system sequentially assesses the quality of the evidence, risk-benefit balance, and the strength of recommendations.²⁰ We used GRADE software for this evaluation (<https://gdt.gradepro.org>).

Results

Study Selection

A total of 2,346 records were searched on the electronic database, and an additional four articles were identified through manual search (fig. 1). After removing 343 duplicates, the title and abstract review excluded 1,860 irrelevant articles. After the review of full-text articles, we identified 16 relevant articles. Among these, the studies conducted by Fritz *et al.* (2018)²¹ and Fritz *et al.* (2016)⁶ were based on the data from identical cohorts. We excluded the study by Fritz *et al.* (2018)²¹ because the study conducted by Fritz *et al.* (2016)⁶ reported our primary outcome. The study conducted by Fritz *et al.* (2020)²² involved a secondary analysis of the randomized trial conducted by Wildes *et al.*² We included the study by Wildes *et al.*² in our analysis to utilize primary data from the original study, thus excluding the study by Fritz *et al.* (2020)²² due to data overlap. Finally, 14 studies involving 6,435 patients were included in this systematic review and meta-analysis.

Study Characteristics

The characteristics of the included studies are presented in table 1. One study was a randomized trial,² eight were case-control studies,^{23–26,28–31} and five were cohort studies.^{4,6,27,32,33} Two of the studies involved secondary analyses of data from randomized controlled trials.^{4,27} Substantial variation was observed across the studies in patient demographics, type of surgery, anesthetic agents, and assessment tools for postoperative delirium. Three studies involved cardiac surgery,^{23,26,27} and seven involved noncardiac surgery.^{24,25,29–30,32,33} Four studies involved both cardiac and noncardiac surgery.^{2,4,6,31} Various types of EEG monitors were used to measure burst suppression, including Bispectral Index (BIS) in five studies,^{2,4,6,23,33} SedLine brain monitor in three studies,^{24,27,29} BIS or SedLine in one study,²⁵ NeuroSENSE in one study,²⁶ Narcotrend in one study,²⁸ Entropy in one study,³² and other monitors in two studies.^{30,31}

Risk of Bias Assessment

The risk of bias assessments of the included studies are presented in Supplemental Table S1 (<https://links.lww.com/ALN/D718>).

Postoperative Delirium: Burst Suppression Present versus Burst Suppression Absent Groups

The overall incidence of postoperative delirium was 21.1% (1,358 of 6,435) among the included populations. The incidence of postoperative delirium was significantly higher in the burst suppression present group than in the burst suppression absent group (pooled odds ratio, 1.492; 95% CI, 1.022 to 2.178; $I^2 = 44\%$; 95% CI, 0 to 75%; $\tau^2 = 0.110$; eight studies; $n = 2,473$; fig. 2).^{4,6,25,27,29–32}

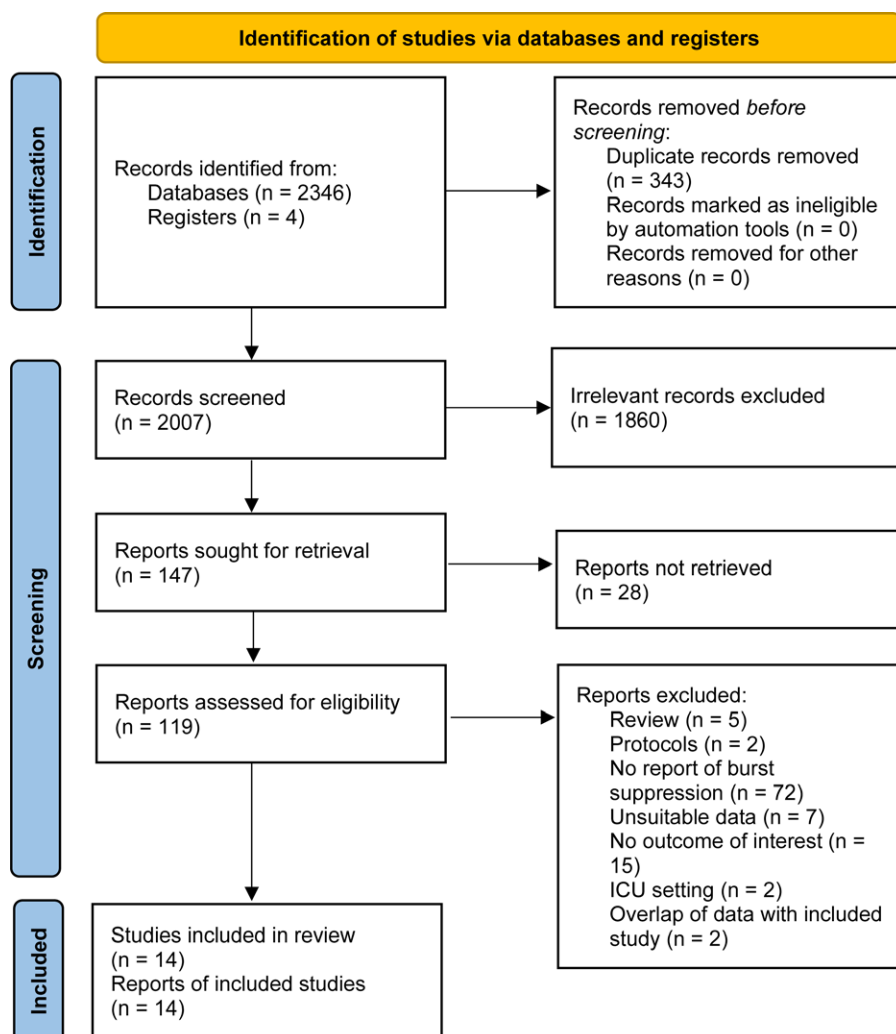


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the review process and screening articles. ICU, intensive care unit.

However, a preplanned secondary analysis for the primary outcome using the Hartung–Knapp–Sidik–Jonkman model showed no statistical significance, presumably due to the conservative nature of the Hartung–Knapp–Sidik–Jonkman model (odds ratio, 1.492; 95% CI, 0.913 to 2.439). Nonetheless, there was a statistically significant difference with respect to the number needed to treat benefit (19.0; 95% CI, 11.8 to 48.9). We conducted a sensitivity analysis by systematically removing one study at a time. Upon excluding the studies conducted by Pedemonte *et al.*,²⁷ Fritz *et al.* (2016),⁶ Hesse *et al.*,²⁵ Lele *et al.*,³⁰ or Linassi *et al.*,³² the overall significance of the results was changed to insignificance, and the heterogeneity was eliminated (Supplemental Figure S1, <https://links.lww.com/ALN/D718>). The study conducted by Pedemonte *et al.*²⁷ reported the presence of

burst suppression during cardiopulmonary bypass (CPB), and other studies reported the occurrence of burst suppression during surgery.^{6,25,29–32} Two studies separately reported the occurrence of burst suppression during the peri-induction and maintenance periods.^{25,31} Both studies showed that burst suppression during the maintenance periods was significantly associated with postoperative delirium (Supplemental Figure S2, <https://links.lww.com/ALN/D718>).^{25,31}

Duration of Burst Suppression: Delirium versus No Delirium Groups

The duration of burst suppression was significantly longer in the delirium group (standardized mean difference, 0.462; 95% CI, 0.293 to 0.632; $I^2 = 63\%$; 95% CI, 16 to 84%; τ^2

Table 1. Characteristics of the Included Studies in Systematic Review and Meta-analysis

First Author, Year	Country	Study Design	Number of Patients	Age, yr	ASA Physical Status Criteria	Male: Female	Type of Surgery	Anesthetic Induction	Anesthetic Maintenance	Type of EEG Monitor	Definition/Detection Methods of Burst Suppression	Burst Suppression Detection Periods	Reported Parameters of Burst Suppression	Delirium Assessment Method	Delirium Follow-up, days	Delirium Screen per Day
Soehle 2015 ³³	Germany	Prospective, case-control	81	≥ 60, mean, 72.9 (SD, 6.2)	All	57:24	Cardiac surgery	Etomidate	Isflurane and sufentanil	BIS	Burst suppression is defined as the periods > 0.5 s, during which the EEG voltage does not exceed $\pm 5 \mu V$	During surgery	Burst suppression duration, burst suppression ratio	Confusion assessment method for the ICU	Until discharge	1
Fritz 2016 ⁸	USA	Retrospective cohort study	619	> 18, mean, 62 (SD, 14)	II–V	396:223	Cardiac: non-cardiac surgery, 542:77	Propofol	Volatile agents (sevoflurane, isoflurane, or desflurane, or a combination of these agents)	BIS (FP1 to F7)	BIS monitor calculates the burst suppression ratio, which describes the percentage of the preceding 63 s for which the EEG amplitude < $5 \mu V$; burst suppression ratio was captured once per minute using MetaVision software	During surgery	Incidence of burst suppression, odds ratio of postoperative delirium for increased in burst suppression duration	Confusion assessment method for the ICU	5	2
Muhlhofer 2017 ³⁴	USA	Prospective, case-control	41	> 40, mean, 62.3 (SD, 8.6)	II, III	20:21	Noncardiac surgery	Not described	Not described	SedLine brain monitor	The neurologists scored an epoch as having a burst suppression pattern if there was > 10 s of suppression of the EEG tracing present in each 30-s epoch	During surgery	Burst suppression ratio	Confusion assessment method	3	1
Hesse 2019 ³⁵	USA, New Zealand	Prospective, case-control	626	Median, 57 (inter-quartile range, 44–48)	I–IV	382:244	Noncardiac surgery	Not described	Propofol or volatile agents (sevoflurane or desflurane or isoflurane)	SedLine, BIS	Each EEG recording was inspected by two blinded independent observers for the occurrence of burst suppression; an EEG episode was defined as burst suppression if at least one bursting period could be detected between two suppression-like EEG episodes	During surgery, during induction, during maintenance	Incidence of burst suppression	Confusion assessment method for the ICU	15 min after arrival in the PACU and 60 min after the end of emergence	Twice in the PACU
Momeni 2019 ³⁶	Belgium	Prospective, case-control	1,513	18–99, median, 68 (inter-quartile range 58–77)	Not reported	1,070:443	Cardiac surgery, cardiac intervention	Propofol	Sevoflurane	NeuroSENSE depth of anesthesia monitor	Wavelet Analysis Value for Central Nervous System monitoring technology (delay-free, linear, and time-invariant quantifier of cortical activity) was used; EEG suppression is presented as the percentage of burst suppression ratio (low amplitude < $5 \mu V$)	During surgery	Burst suppression ratio	Chart review method	Until discharge	Not reported

(Continued)

Table 1. (Continued)

First Author, Year	Country	Study Design	Number of Patients	Age, yr	ASA Physical Status Criteria	Male: Female	Type of Surgery	Anesthetic Induction	Anesthetic Maintenance	Type of EEG Monitor	Definition/Detection Methods of Burst Suppression	Burst Suppression Detection Periods	Reported Parameters of Burst Suppression	Delirium Assessment Method	Delirium Follow-up, days	Delirium Screen per Day
Pedemonte 2020 ²⁷	USA	Retrospective cohort study	141	>60, mean, 69.6 (SD, 7.6)	II–IV	109:50 (N = 159)	Cardiac surgery	Intravenous agent	Isoflurane	SedLine brain monitor (Fp1, Fp2, F7, F8)	Two independent anesthesiologists manually identified patients who exhibited burst suppression by analyzing EEG data in the spectral and time-series domain; burst suppression was defined as the presence of ≥ 3 consecutive suppression events within 60-s periods during CPB.	During CPB	Incidence of burst suppression	Confusion assessment method	3	2
Wildes 2019 ²	USA	Prospective, randomized controlled trial	1,213	≥ 60 , median, 69 (range, 60–95)	I–IV	669:563 (N = 1,232)	Cardiac: non-cardiac surgery, (N = 1,232)	Not described	Volatile agents	BIS	Burst suppression ratio was captured at 1-min intervals using MetaVision software; duration of suppression was quantified as the cumulative number of minutes with burst suppression ratio $> 1\%$	During surgery	Burst suppression duration	Confusion assessment method or confusion assessment method for the ICU	5	1
Evered 2021 ⁴	Australia, China, USA	Prospective cohort study	515	≥ 60 , mean, 71 (SD, 6.8)	III, IV	332:183	Cardiac: non-cardiac surgery, 1:514	Not described	Volatile agents (isoflurane/sevoflurane/desflurane)	BIS	Burst suppression ratio was defined as the percentage of time that the EEG was isoelectric during each BIS time series epoch; if the burst suppression ratio > 0 , burst suppression was defined as being present	During surgery	Incidence of burst suppression, burst suppression duration	3D-CAM or confusion assessment method for the ICU	5	2
Jung 2021 ²⁸	Germany	Prospective case-control	80	> 18 , mean, 66.3 (SD, 10.5)	I–III	47:33	Noncardiac (major abdominal) surgery	Propofol or thiopental	Sevoflurane and intravenous sufentanil	Narcotrend-Compact M	Burst suppression duration was defined as duration of Narcotrend Index in stages F0/F: Narcotrend stage F0 is characterized by the burst suppression pattern, showing alternating bursts of EEG activity and periods with a very flat EEG curve	From start of induction until the end of the last suture	Burst suppression duration	3D-CAM	7	2
Koch 2021 ²⁹	Germany	Prospective case-control	237	≥ 65 , mean, 72.8 (SD, 5.3)	I–IV	126:111	Noncardiac surgery	Propofol or thiopental	Propofol or volatile agents (sevoflurane or desflurane or isoflurane)	SedLine brain monitor	Burst suppression is characterized by alternating epochs of near-isoelectric activity and α -band activity	From induction of anesthesia until extubation	Incidence of burst suppression, burst suppression duration	DSM-5, NuDesc, confusion assessment method or confusion assessment method for the ICU	7	2

(Continued)

Table 1. (Continued)

First Author, Year	Country	Study Design	Number of Patients	ASA Physical Status Criteria	Age, yr	Male: Female	Type of Surgery	Anesthetic Induction	Anesthetic Maintenance	Type of EEG Monitor	Definition/Detection Methods of Burst Suppression	Burst Suppression Detection Periods	Reported Parameters of Burst Suppression	Delirium Assessment Method	Delirium Follow-up, days	Delirium Screen per Day
Lele 2022 ³⁰	USA	Retrospective case-control	112	Not reported	>18, median, 59.8 (inter-quartile range, 18.8)	61:51	Noncardiac (spine) surgery	Propofol	Propofol	2-Channel Cadwell system (C3, C4)	Burst suppression is defined as an EEG pattern characterized by paroxysmal bursts of theta and/or delta waves at times intermixed with sharp and faster waves, alternating with intervening periods of attenuation or suppression (<10 μ V) lasting > 50% of the record; an experienced EEG technician visually assessed 1-min EEG epochs for the presence and degree of burst suppression	During surgery	Incidence of burst suppression duration	Confusion assessment method	Until discharge	1
Lutz 2022 ³¹	Germany	Prospective case-control	116	I-IV	>18, mean, 61.4 (SD, 16.9)	88:28	Elective surgery	Not described	Propofol or volatile agents (sevoflurane or desflurane)	10-channel EEG (NIM-Eclipse neuromonitoring system, Fp1/2, F1/2, C3/4, P3/4, O1/2)	The authors checked for any intraoperative EEG burst suppression by visually inspecting the raw EEG	During surgery, during perinduction, during maintenance	Incidence of burst suppression	Confusion assessment method for the ICU	15, 60 min after emergence	Twice in the PACU
Linassi 2023 ³²	Italy	Prospective cohort study	107	I-II	$\geq$ 18, median, 61.4 (inter-quartile range, 49.0–73.8)	Female 107	Noncardiac (breast) surgery	Propofol	Propofol	Entropy	The occurrence of burst suppression was verified by the display of a positive burst suppression ratio as indicated by the entropy module; burst suppression was defined as a burst suppression ratio > 5% episode, which means $\geq$ 3 s of suppressed activity in 1 min of EEG activity	During surgery	Incidence of burst suppression	Confusion assessment method for the ICU	15, 45 min after return of responsiveness	Twice in the PACU
Koch 2023 ³³	Germany	Prospective cohort study	1,058	I-IV	>60, mean, 69.7 (SD, 6.3)	571:487	Noncardiac surgery	Thiopental, propofol, or etomidate	Propofol or sevoflurane or desflurane	BIS	The authors determined intraoperative signatures of burst suppression activity by calculating a burst suppression probability for each time point; this probability is calculated as the ratio of time points within a second surrounding the given point that have an amplitude < 60% quantile of the data amplitudes; if the probability surpassed 80%, the point was marked as a suppression point	During surgery	Burst suppression duration, burst suppression ratio	DSM-IV	7	2

ASA, American Society of Anesthesiologists; BIS, Bispectral Index; 3D-CAM, 3-min diagnostic interview for confusion assessment method delirium; CPB, cardiopulmonary bypass; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; EEG, electroencephalogram; ICU, intensive care unit; NuDesc, Nursing Delirium Screening Scale; PACU, postanesthesia care unit.

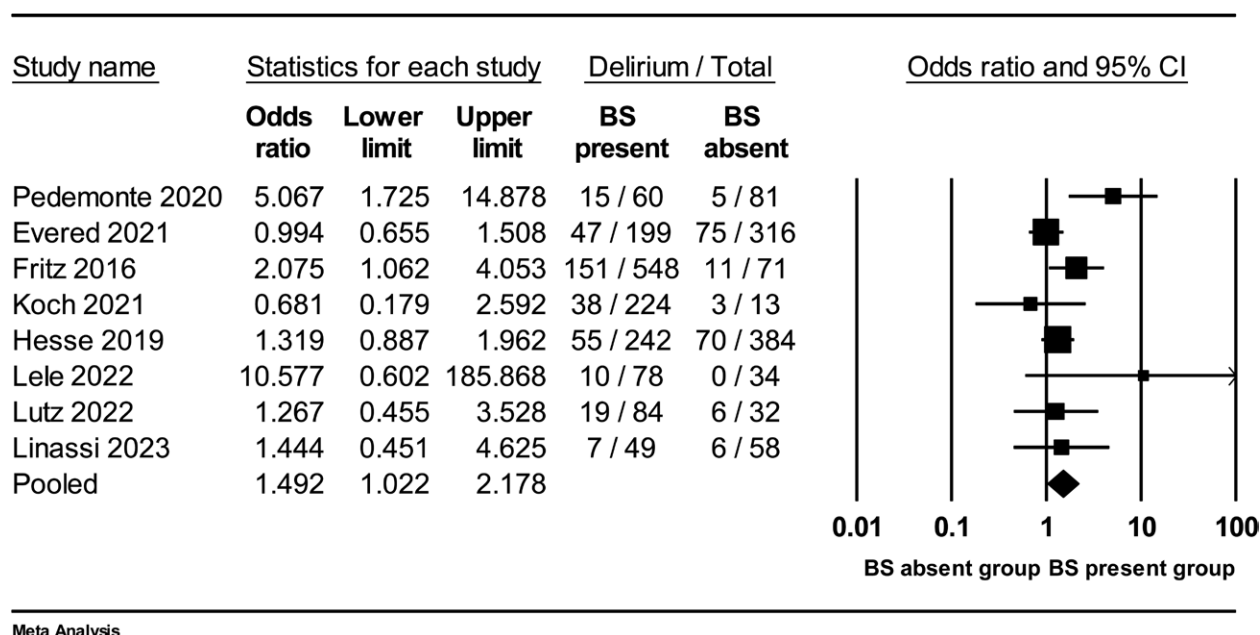


Fig. 2. Forest plot for analysis comparing the incidence of postoperative delirium between the intraoperative burst suppression present group and burst suppression absent group. BS, burst suppression; CI, confidence interval.

= 0.027; seven studies; $n = 3,272$; fig. 3).^{2,4,29,30,23,28,33} When applying the Hartung–Knapp–Sidik–Jonkman method, the statistical significance was not changed (standardized mean difference, 0.462; 95% CI, 0.223 to 0.702). We conducted sensitivity analyses in which one study was removed per time. This did not change the statistical significance (Supplemental Figure S3, <https://links.lww.com/ALN/D718>). Due to the availability of only one study reporting the odds ratio for burst suppression duration and postoperative delirium,⁶ it could not be included in our pooled analysis.

Burst Suppression Ratio: Delirium versus No Delirium Groups

The burst suppression ratio was significantly higher in the delirium group (standardized mean difference, 0.150; 95% CI, 0.055 to 0.245; $I^2 = 0\%$; 95% CI, 0 to 85%; $\tau^2 = 0.00$; four studies; $n = 2,684$; fig. 4).^{23,24,26,33} Since no heterogeneity was observed, the Hartung–Knapp–Sidik–Jonkman method and sensitivity analysis were not performed.

Quality of the Evidence

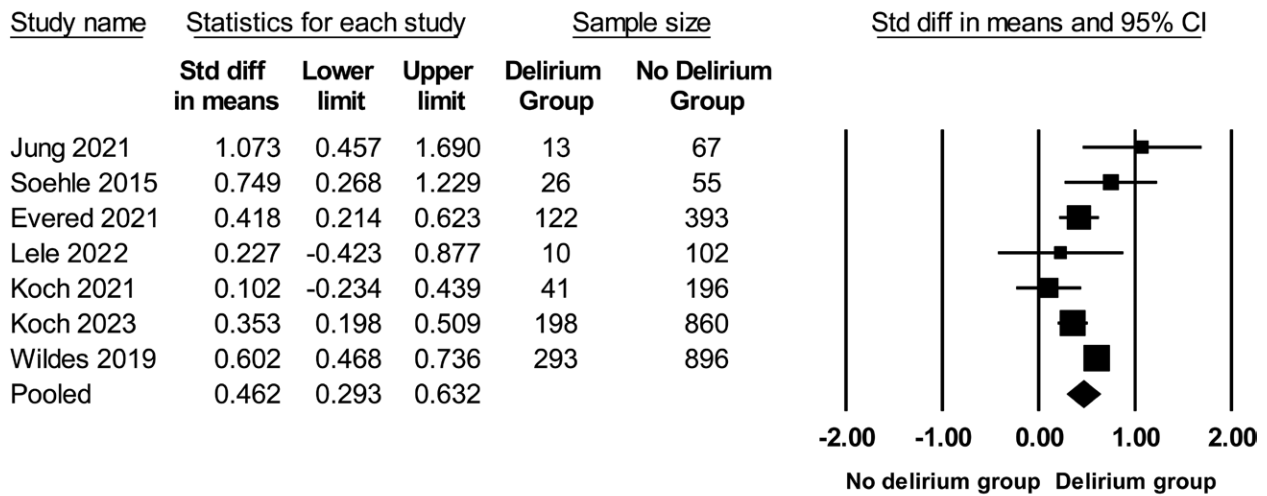
The GRADE quality of evidence for each outcome was low or very low (table 2; Supplemental Table S2, <https://links.lww.com/ALN/D718>). Because too few studies have reported our predefined secondary outcomes, including the severity of postoperative delirium (no study), duration of postoperative delirium (no study), incidence of postoperative cognitive dysfunction (no study), length of hospital

stay (one study),³⁰ processed EEG index values (two studies),^{24,29} burst suppression duty cycle (no study), and burst suppression probability (no study), meta-analyses for these outcomes were not performed.

Subgroup Analyses and Exploratory Analyses

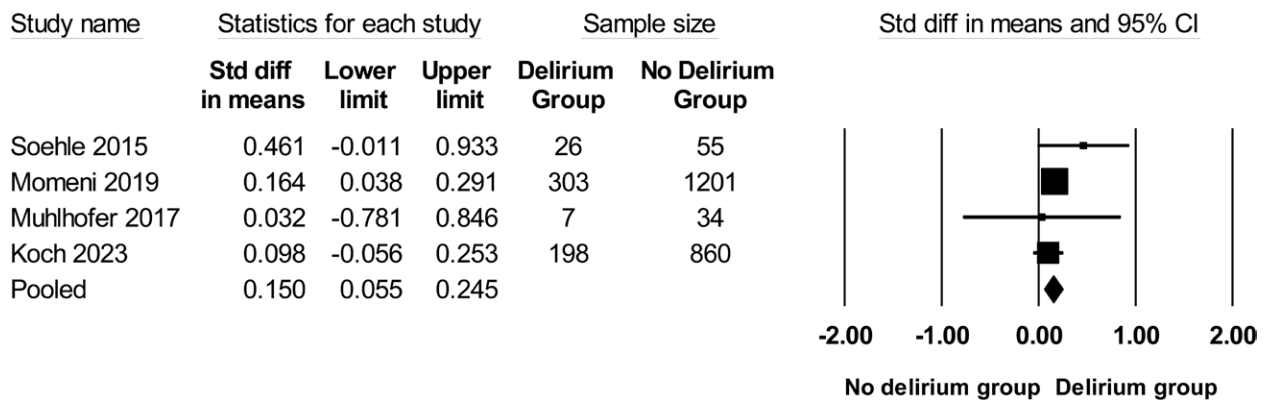
We conducted a prespecified subgroup analysis; however, a few studies were included in each subgroup. For the primary outcome, the subgroup analysis of the studies involving cardiac surgery was not performed because only one study satisfied the criteria.²⁷ The subgroup analysis of six studies involving noncardiac surgery,^{4,25,29–32} including the study by Evered *et al.*, which involved 514 noncardiac and 1 cardiac surgery patient,⁴ did not reach statistical significance but markedly reduced the degree of statistical heterogeneity (odds ratio, 1.172; 95% CI, 0.901 to 1.524; $I^2 = 0\%$; 95% CI, 0 to 75%; $\tau^2 = 0.0$; six studies; $n = 1,713$; Supplemental Figure S4, <https://links.lww.com/ALN/D718>). The subgroup analysis of studies including only patients aged greater than 60 yr did not reach statistical significance (odds ratio, 1.492; 95% CI, 0.504 to 4.417; $I^2 = 76\%$; 95% CI, 21 to 93%; $\tau^2 = 0.683$; three studies; $n = 893$; Supplemental Figure S5, <https://links.lww.com/ALN/D718>).^{4,27,29} The subgroup analysis according to the anesthetic agents and type of EEG monitors could not be performed owing to the limited number of studies.

We performed additional subgroup analyses to explore the factors related to heterogeneity based on the timing of delirium assessment. The subgroup analysis of studies



Meta Analysis

Fig. 3. Forest plot for analysis comparing the duration of burst suppression between postoperative delirium present group and postoperative delirium absent group. CI, confidence interval.



Meta Analysis

Fig. 4. Forest plot for analysis comparing the burst suppression ratio between postoperative delirium present group and postoperative delirium absent group. CI, confidence interval.

involving postanesthesia care unit delirium reduced the degree of statistical heterogeneity markedly but did not show statistically significant results (odds ratio, 1.324; 95% CI, 0.930 to 1.884; $I^2 = 0\%$; 95% CI, 0 to 90%; $\tau^2 = 0.0$; three studies; $n = 849$; Supplemental Figure S6, <https://links.lww.com/ALN/D718>).^{25,31,32} Conversely, the subgroup analysis of studies involving postoperative delirium excluding postanesthesia care unit delirium showed a substantial degree of statistical heterogeneity

(odds ratio, 1.799; 95% CI, 0.862 to 3.753; $I^2 = 68\%$; 95% CI, 17 to 88%; $\tau^2 = 0.405$; five studies; $n = 1,624$; Supplemental Figure S7, <https://links.lww.com/ALN/D718>).^{4,6,27,29,30} We also performed a subgroup analysis based on the detection methods of burst suppression occurrence. The pooled odds ratio indicated a slightly stronger relationship between burst suppression and delirium in the subgroup analysis of studies involving visual inspection of the spectrogram (odds ratio, 1.720;

Table 2. Effect Size, Statistical Heterogeneity, and Quality of Evidence in Each Outcome

Outcomes	Studies	Participants	Effect Sizes (95% CI)	Statistical Heterogeneity*	GRADE
The incidence of postoperative delirium	8	2,473	Odds ratio, 1.492 (1.022–2.178)	44%	Very low
Duration of electroencephalogram burst suppression	7	3,272	Standardized mean difference, 0.462 (0.293–0.632)	63%	Very low
Burst suppression ratio	4	2,684	Standardized mean difference, 0.150 (0.055–0.245)	0%	Low

*Presented as a I^2 statistic.

GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

95% CI, 0.868 to 3.408; $I^2 = 53\%$; 95% CI, 0 to 83%; $\tau^2 = 0.290$; five studies; $n = 1,232$; Supplemental Figure S8, <https://links.lww.com/ALN/D718>)^{25–27,30,31} compared with studies involving burst suppression ratio calculated from EEG monitors (odds ratio, 1.345; 95% CI, 0.808 to 2.237; $I^2 = 41\%$; 95% CI, 0 to 82%; $\tau^2 = 0.086$; three studies; $n = 1,241$; Supplemental Figure S9, <https://links.lww.com/ALN/D718>).^{4,6,32} We also performed a subgroup analysis on the duration of burst suppression, exploring different quantification methods for suppression duration. The pooled effect size for the duration of burst suppression was statistically significant in both the subgroup of studies involving assessments based on visual inspection of the spectrogram (standardized mean difference, 0.339; 95% CI, 0.120 to 0.558; $I^2 = 38\%$; 95% CI, 0 to 79%; $\tau^2 = 0.019$; four studies; $n = 1,488$; Supplemental Figure S10, <https://links.lww.com/ALN/D718>)^{23,29,30,33} and the subgroup of studies involving assessments based on machine-generated indices calculated from commercial EEG monitor (standardized mean difference, 0.577; 95% CI, 0.360 to 0.795; $I^2 = 59\%$; 95% CI, 0 to 88%; $\tau^2 = 0.020$; three studies; $n = 1,784$; Supplemental Figure S11, <https://links.lww.com/ALN/D718>).^{2,4,28}

Since only one study reported the odds ratio of burst suppression during CPB for age,²⁷ we could not perform a meta-analysis on this outcome. Alternatively, we performed a meta-analysis on studies with available age data separately for the delirium and nondelirium groups. The delirium group was significantly older than the nondelirium group (mean difference, 5.419; 95% CI, 3.119 to 7.720; $I^2 = 73.01\%$; $\tau^2 = 7.69$; nine studies; $n = 2,904$; Supplemental Figure S12, <https://links.lww.com/ALN/D718>).^{23–26,28–32}

Publication Bias

Funnel plots were symmetric for all comparisons (Supplemental Figures S13 through S15, <https://links.lww.com/ALN/D718>); however, interpreting this as evidence against publication bias is limited because fewer than 10 studies were included in each comparison.^{18,34}

Discussion

In this systematic review and meta-analysis, the primary analysis revealed a significant correlation between intraoperative burst suppression and the development of postoperative delirium. We also found that longer durations and higher ratios of burst suppression were associated with postoperative delirium. However, our results should be interpreted cautiously because the number of relevant studies was limited, and significant heterogeneity was observed across the studies.

Previous literature has indicated a potential link between intraoperative burst suppression and postoperative delirium;¹ however, studies have varied in their assessment of burst suppression–related parameters, such as incidence,^{6,27} duration,²³ and ratio.^{23,26} These variations have made clinical application challenging. Therefore, we systematically synthesized existing evidence to investigate the association between each burst suppression–related variable and postoperative delirium. Our primary analysis yielded contradictory results when using the DerSimonian and Laird random effects and Hartung–Knapp–Sidik–Jonkman models regarding the association between the presence of burst suppression and postoperative delirium. The Hartung–Knapp–Sidik–Jonkman model adjusts the CI to reflect uncertainty in estimating between-study heterogeneity,³⁵ resulting in no statistical significance for our primary outcome. These results show model dependency and sensitivity of our primary findings to model choice, highlighting the need for further investigations to establish a conclusive relationship. However, both the duration and ratio of burst suppression showed significant correlations with postoperative delirium. Hence, quantifying burst suppression using the duration or ratio could potentially provide better predictive value for postoperative delirium compared to simply assessing the occurrence of burst suppression.

The mechanism behind burst suppression remains uncertain, with two main hypotheses proposed: the cortical hypersensitivity hypothesis and the metabolic hypothesis.^{1,7} Based on these, we can postulate potential explanations for the association between burst suppression and postoperative delirium. First, exposure to high doses of anesthetics,

which lead to EEG suppression by depleting extracellular calcium, has been considered a contributing factor to postoperative delirium.^{1,7} A substudy⁴ of the Anaesthetic Depth and Complications after Major Surgery (BALANCED) study³⁶ revealed a reduced risk of postoperative delirium by targeting lighter anesthesia, supporting this hypothesis. They observed significantly lower minimum alveolar concentration (MAC) of volatile anesthetics and shorter duration of burst suppression in the lighter anesthesia targeting group.⁴ Additionally, some studies indicated a significant association between lower MAC values and less burst suppression.^{6,28} Fritz *et al.* observed that higher concentrations of volatile anesthetic were associated with greater suppression ratios, with an odds ratio of nonzero suppression ratio being 1.5 per 0.5 MAC unit.⁶ Jung *et al.* also observed significantly lower MAC values and shorter burst suppression durations in the delirium group compared to the no delirium group.²⁸ However, the ENGAGES randomized clinical trial reported that EEG-guided anesthesia did not reduce the incidence of delirium, despite reducing EEG suppression time and MAC of the anesthetic agent.² However, although there was no significant difference in the incidence of postoperative delirium at the group level (EEG guidance *vs.* usual care group), data from the ENGAGES trial suggest increased duration of burst suppression in patients with postoperative delirium compared to those without postoperative delirium.² Conflicting results from several other randomized controlled trials evaluating the impact of EEG guidance make it challenging to explain the association solely by anesthesia overdose.^{37–39}

Recent reports have increasingly explored the mediating role of burst suppression in delirium occurrence, considering various clinical risk factors.^{22,27,40} The findings from these mediation analyses^{22,27,40} provide valuable insights into another potential mechanism: susceptible patients with brain vulnerability may be more likely to exhibit EEG suppression, and general anesthesia and surgery can serve as a neural stress test, resulting in higher postoperative delirium incidence.^{1,7} This concept was demonstrated in the study by Pedemonte *et al.*, where burst suppression during CPB mediated the effect of lower physical function on delirium occurrence.²⁷ Moreover, EEG suppression mediated a small portion of the effect of preoperative abnormal cognition on postoperative delirium.²² The EEG suppression time also mediated a significant portion of the association between frailty and delirium severity in geriatric noncardiac surgery patients,⁴⁰ providing support for this mechanism. Additionally, Fritz *et al.* found that patients experiencing burst suppression at lower volatile anesthetic concentrations (“heightened sensitivity” to volatile anesthetics) had higher rates of postoperative delirium, supporting the hypothesis of brain vulnerability.²¹ However, only one of these studies was included in our analysis due to the availability of relevant information.²⁷ Given the predominantly observational nature

of included studies in our analysis, we cannot determine whether burst suppression serves as a marker or mediator of postoperative delirium. Future studies on EEG and delirium should acknowledge this uncertainty, and further investigations into the potential mediating roles of burst suppression are required to understand the complex relationships between intraoperative burst suppression and postoperative delirium.

Most studies have reported burst suppression during intraoperative periods, including peri-induction and maintenance periods.^{4,6,29} However, burst suppression during these periods can have different implications.⁴¹ During peri-induction periods, burst suppression often occurs because of high effect-site concentrations of intravenous induction agents, which may not necessarily indicate excessive anesthetic dosage or brain vulnerability.¹ In contrast, during maintenance periods, burst suppression could be attributed to an anesthetic overdose or patient vulnerability.⁴¹ Two studies included in this meta-analysis separately reported the incidence of burst suppression during peri-induction and maintenance periods.^{25,31} Their findings indicated a significant association between burst suppression during maintenance periods and postoperative delirium.^{25,31} This suggests that assessing burst suppression separately according to anesthetic phases may provide more informative insights into the clinical implications of burst suppression.⁴¹

This study has limitations. First, a significant degree of clinical heterogeneity was observed among the included studies. Due to the limited availability of studies, we included those meeting our eligibility criteria to enhance external validity. Consequently, our analysis encompassed studies with various surgical types, timings of delirium assessments, anesthetic agents, and definitions of burst suppression. To improve quality of evidence in this area, the following issues should be considered when designing future clinical studies. While completely standardizing the protocols for anesthesia, EEG monitoring, and delirium assessment may be impractical, using a single anesthetic agent, validated EEG devices, analysis software, preprocessing and analysis methods, and validated delirium assessments is desirable. Stratified randomization based on key variables such as patient age and type of surgery can ensure balanced groups, and multicenter collaborations will enhance the generalizability of findings. Comprehensive data collection and detailed reporting will improve future meta-analyses and adjustments for confounding factors. Second, our subgroup analysis includes a limited number of studies, potentially contributing to insignificant results. Furthermore, some subgroup analyses showed small τ^2 with high I^2 (Supplemental Figures S9 through S11, <https://links.lww.com/ALN/D718>). This can be explained by small sample sizes,^{23,28,32} secondary analyses,^{4,6,29,33} or converting graphical data into numerical format during data extraction,² potentially leading to

higher sampling errors.¹⁴ Third, heterogeneity in age and pre-existing cognitive impairment could have unpredictably influenced burst suppression and delirium, potentially limiting the significance of our analysis. Although age has been suggested as a risk factor for burst suppression,⁴² we were unable to assess its role as a cofactor in the relationship between burst suppression and delirium due to limited data availability. Fourth, as this review predominantly involves observational studies, we cannot address whether burst suppression serves as a marker or mediator of postoperative delirium. Fifth, our data, mainly from observational studies, preclude inferring a causal relationship between burst suppression and postoperative delirium. To determine whether preventing burst suppression can reduce postoperative delirium, more interventional studies targeting the minimization of burst suppression are required. Last, some forest plots were cut off due to the scale limit for odds ratios in Comprehensive Meta-Analysis software, preventing further adjustments.

In conclusion, our systematic review and meta-analysis revealed higher odds of postoperative delirium in patients with intraoperative burst suppression. However, substantial heterogeneity among the included studies and sensitivity analysis results indicates caution in interpretation. Further studies with larger sample sizes and rigorous methodologies are required for conclusive evidence. Future research should focus on quantitatively assessing burst suppression and examining its temporal profile across different anesthetic phases to improve the quality of evidence in this area.

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Competing Interests

The authors declare no competing interests.

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Supplemental Digital Content

Supplemental file, <https://links.lww.com/ALN/D718>
Supplementary Material 1. Search strategy used in literature search and results

Supplemental Table S1. Quality assessment of included studies using the Cochrane Risk of Bias 2 and Newcastle–Ottawa quality assessment scale

Supplemental Table S2. GRADE level of evidence

Supplemental Figure S1. Sensitivity analysis of the incidence of postoperative delirium between the burst suppression present group and burst suppression absent group by removing one study at a time.

Supplemental Figure S2. Forest plot for analysis comparing the incidence of postoperative delirium between the group with burst suppression present during anesthetic maintenance and the group with burst suppression absent during anesthetic maintenance.

Supplemental Figure S3. Sensitivity analysis of the duration of burst suppression between postoperative delirium present group and postoperative delirium absent group by removing one study at a time.

Supplemental Figure S4. Subgroup analysis for primary outcome in studies involving noncardiac surgery.

Supplemental Figure S5. Subgroup analysis for primary outcome in studies involving patients aged greater than 60 yr.

Supplemental Figure S6. Subgroup analysis for primary outcome in studies that measured the incidence of postoperative delirium in the postanesthesia care unit.

Supplemental Figure S7. Subgroup analysis for primary outcome excluding the studies that measured the incidence of postoperative delirium in the postanesthesia care unit.

Supplemental Figure S8. Subgroup analysis for primary outcome in studies in which intraoperative occurrence of burst suppression was detected by inspecting the raw electroencephalogram spectrogram.

Supplemental Figure S9. Subgroup analysis for primary outcome in studies in which intraoperative occurrence of burst suppression was detected using the burst suppression ratio calculated by an electroencephalogram monitor.

Supplemental Figure S10. Subgroup analysis for duration of burst suppression in studies where the quantification of burst suppression duration was determined by visual inspection of the raw electroencephalogram spectrogram.

Supplemental Figure S11. Subgroup analysis for duration of burst suppression in studies where the quantification of burst suppression duration was based on the indices calculated by commercial electroencephalogram monitors.

Supplemental Figure S12. Exploratory subgroup analysis for age in studies where age data were available separately for the delirium group and nondelirium group.

Supplemental Figure S13. Begg's funnel plot for the analysis comparing the incidence of postoperative delirium between the intraoperative burst suppression present group and burst suppression absent group.

Supplemental Figure S14. Begg's funnel plot for the analysis comparing the duration of burst suppression between postoperative delirium present group and postoperative delirium absent group.

Supplemental Figure S15. Begg's funnel plot for the analysis comparing the burst suppression ratio between postoperative delirium present group and postoperative delirium absent group.

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