A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality

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ABSTRACT

Background: Delirium is an acute and reversible geriatric syndrome that represents a decompensation of cerebral function. Delirium is associated with adverse postoperative outcomes, but controversy exists regarding whether delirium is an independent predictor of mortality. Thus, we assessed the association between incident postoperative delirium and mortality in adult noncardiac surgery patients.

Methods: A systematic search was conducted using Cochrane, MEDLINE/PubMed, Cumulative Index to Nursing and Allied Health Literature, and Embase. Screening and data extraction were conducted by two independent reviewers. Pooled-effect estimates calculated with a random-effects model were expressed as odds ratios with 95% CIs. Risk of bias was assessed using the Cochrane Risk of Bias Tool for Non-Randomized Studies.

Results: A total of 34 of 4,968 screened citations met inclusion criteria. Risk of bias ranged from moderate to critical. Pooled analysis of unadjusted event rates (5,545 patients) suggested that delirium was associated with a four-fold increase in the odds of death (odds ratio = 4.12 [95% CI, 3.29 to 5.17]; I^2 = 24.9%). A formal pooled analysis of adjusted outcomes was not possible due to heterogeneity of effect measures reported. However, in studies that controlled for prespecified confounders, none found a statistically significant association between incident postoperative delirium and mortality (two studies in hip fractures; n = 729) after an average follow-up of 21 months. Overall, as study risk of bias decreased, the association between delirium and mortality decreased.

Conclusions: Few high-quality studies are available to estimate the impact of incident postoperative delirium on mortality. Studies that controlled for prespecified confounders did not demonstrate significant independent associations of delirium with mortality. (Anesthesiology 2017; 127:78-88)

DELIRIUM is a fluctuating, neuropsychiatric geriatric syndrome that represents a decompensation of cerebral function and can result in acute and reversible cognitive decline.[1] Causes of delirium are multifactorial and can be related to acute physical stressors, such as surgery.[2] More than 51-million surgeries occur annually in North America,[3] and in some high-risk surgical populations up to 50% of patients may develop postoperative delirium.[2,4,5]

Despite the growing body of evidence that associates delirium with mortality,[6–9] the causal relationship of delirium with mortality is difficult to ascertain due to the high risk of confounding bias. Many of the strongest risk factors for postoperative delirium, such as advanced age, comorbidity, preexisting cognitive dysfunction, and high-risk surgery, are also independent risk factors for mortality.[7,10] Because delirium is a disease state and not an intervention, causal inference depends on the conduct and reporting of high-quality observational studies.

What We Already Know about This Topic

- Although the occurrence of delirium in the perioperative period is associated with increased mortality, it is not clear whether delirium *per se* is an independent predictor of mortality.
- A meta-analysis of the extant literature on perioperative delirium in patients undergoing noncardiac surgery was performed. Importantly, the risk of bias, particularly with respect to confounding variables that may independently contribute to mortality, in each of the reviewed studies was determined.

What This Article Tells Us That Is New

- Patients who develop delirium are at increased risk of death.
- However, in the studies with reduced bias and adequate control for confounding, an independent association between delirium and mortality was not apparent.

Studies to date have produced conflicting results regarding the association between postoperative delirium and mortality in the perioperative setting. A recent study conducted

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by Gottschalk *et al.*[11] in elderly patients with hip fracture demonstrated that incident postoperative delirium was not independently associated with mortality. In contrast, Dubljanin-Raspopović *et al.*[12,13] found that, in a similar population of patients with hip fracture, postoperative delirium was an independent predictor of mortality. The divergent findings may be at least partly explained by the differing approach to control for confounding. Although both studies included variables to account for age, sex, and American Society of Anesthesiology (ASA) score, Gottschalk *et al.*[11] additionally controlled for preexisting cognitive impairment, as well as several postoperative variables. Dubljanin-Raspopović *et al.*[12,13] did not account for baseline cognitive function, which is the strongest known predictor of delirium[14,15] and an independent predictor of postoperative mortality.[16,17] This comparison exemplifies the potential fragility of the delirium–mortality association depending on choice of confounders included in adjusted models.

Existing systematic reviews have examined the association of delirium with mortality in mixed patient populations; however, none of these studies focused specifically on surgical patients who develop incident postoperative delirium.[8,18] Furthermore, to our knowledge, no existing review uses a systematic approach to account for the multiple sources of confounding known to be pertinent to the delirium–mortality relationship in perioperative patients. Therefore, we conducted a systematic review to specifically examine the independent association of incident postoperative delirium with mortality in adult noncardiac surgery patients.

Materials and Methods

We carried out this systematic review and meta-analysis of prospective observational studies following recommendations of the Meta-Analysis of Observational Studies in Epidemiology group.[19] The protocol for the systematic review was registered with the International Prospective Register of Systematic Reviews (CRD42015029805, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015029805) and was conducted in accordance with Cochrane Collaboration guidelines.[20] This manuscript is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[21]

Search Strategy

Cochrane, MEDLINE, Cumulative Index to Nursing and Allied Health Literature, and Embase databases were systematically searched using a strategy designed in consultation with an information specialist. The search strategy was then reviewed and finalized using the peer review of electronic search strategy checklist.[22] Key words for delirium (*i.e.,* delirium, delirious, acute confusion, cognitive dysfunction, and cognitive impairment) were combined with surgery-specific key words (*i.e.,* postoperative complications, postoperative care, postsurgery, noncardiac surgery, surgical patients, and hip fractures) and mortality key words (*i.e.,* hospital mortality and death; see Supplemental Digital Content 1, http://links.lww.com/ALN/B434, which outlines our full search strategy). Abstracts and other gray literature were excluded, because methodologic descriptions would be insufficient to assess the risk of bias and validity of study findings. The bibliographies of the included studies were hand searched to identify any additional articles that met our inclusion criteria. There were no language restrictions. Our search was restricted to articles after January 1981, because a formal nomenclature to differentiate delirium from dementia was first established with the Diagnostic and Statistical Manual of Mental Disorders (3rd edition) in 1980.[23]

Inclusion and Exclusion Criteria

Eligible studies were included if they met the following criteria: (1) adults (>18 yr of age) undergoing noncardiac surgery; (2) incident postoperative delirium (new-onset delirium that occurs during the postoperative course) was prospectively identified using a validated instrument or diagnosed prospectively based on Diagnostic and Statistical Manual of Mental Disorders criteria; and (3) reported quantitative data (*i.e.,* event rates, risk ratios [RRs], odds ratios [ORs], or hazard ratios [HRs]) to measure the association between delirium and mortality. Studies were excluded if: (1) there were cardiac surgery patients, because the risk factors for delirium (*e.g.* cardiopulmonary bypass) and nature of clinical care (*e.g.,* routine intensive care unit admission after surgery) differ significantly between cardiac and noncardiac surgical populations); (2) surgery-specific subgroups and their outcome data could not be extracted independent of other types of patients (*e.g.,* noncardiac surgery patients combined with nonsurgical or cardiac surgical patients); (3) the majority of patients had preexisting (*i.e.,* not incident postoperative) delirium; or (4) the subgroup with incident delirium and the patient outcome data could not be extracted independent of preexisting delirium cases (*i.e.,* present before surgery).

Selection of Included Studies

Titles and abstracts of identified studies were independently screened in duplicate (G.M.H., K.W., J.D.). Study screening and selection, as well as data collection, were performed using DistillerSR (Evidence Partners, Canada). Relevant abstracts were selected and the full-text articles reviewed. Any disagreements were resolved by consensus decision in discussion with the senior team members (D.I.M., M.M.L.). Study design, demographic data, exposure, and outcome data were extracted. A calibrating exercise was performed to ensure that interrater agreement was high for both the study selection and data extraction. After the data extraction, authors were contacted to verify missing data and offer clarifications as needed.

Assessment of Risk of Bias

Risk of bias was assessed in duplicate by the primary author and senior author using the method outlined in the Cochrane Risk of Bias Tool for Non-Randomized Studies.[24] The risk of bias was assessed as low, moderate, high, or critical for each of confounding bias, selection bias, measurement bias (outcome or exposure), missing data bias, and selection bias. Any disagreement was resolved by consensus.

Statistical Analysis

For the unadjusted analysis, we included any study that reported the effect of incident delirium on mortality and extracted the number of events relative to the total number of participants in the delirium and control groups (*i.e.,* crude event rates).

For the primary adjusted analysis, we extracted quantitative data (*i.e.,* ORs, RRs, and HRs) that were adjusted for prespecified key confounders reflecting the association between incident delirium and mortality. In keeping with Witlox *et al.*,[8] our primary analysis included only studies that adjusted for age, sex, comorbidity, and baseline cognitive status. Because ASA score describes illness severity and predicts both delirium and mortality, studies controlling for ASA score were considered to account for comorbid illness. To identify additional perioperative confounders, we searched the literature for reviews or key articles that described risk factors for both postoperative mortality and postoperative delirium.[10,14,25,26] We then identified key variables that predicted both delirium and mortality. Based on this search, the type and urgency of surgery were also identified as key perioperative confounding variables for delirium and mortality. Therefore, these variables were included in our list of required adjusted variables for a study to be included in our the primary analysis (table 1). Based on best-practice recommendations, control for confounding was determined to be inadequate if the key variables were not included in the final adjusted model, despite clinical and epidemiologic grounds for their inclusion.[27–30] We also planned a secondary adjusted analysis, in which we included measures of association (*i.e.,* ORs, RRs, and HRs) that were adjusted for any confounders.

Where possible, we performed a meta-analysis for the primary outcome of mortality. Pooled-effect outcomes were calculated using inverse variance methods with random-effects models and expressed as ORs and 95% CIs. Heterogeneity was assessed using the I^2 statistic. Statistical analyses were performed in STATA 10.0 (StataCorp LLC, Texas). Figures were created in RevMan 5.3 (The Cochrane Collaboration, Denmark). *P* values of less than 0.05 were considered statistically significant.

Table 1. Key Confounders in the Delirium–Mortality Relationship

Key Confounders
Age
Sex
Comorbidity (*e.g.,* ASA)
Previous cognitive impairment
Surgery type
Surgery urgency

ASA = American Society of Anesthesiology.

Results

Our search identified 4,968 citations, of which 445 citations were selected for a full-text review. After full-text review, a total of 34 studies met our eligibility criteria (see Supplemental Digital Content 2, http://links.lww.com/ALN/B435, which lists all of the studies that met our primary, secondary, and tertiary analyses); 2 studies met criteria for our primary analysis, and 6 studies met criteria for secondary analysis (table 2). The three most common reasons for excluding a citation after full-text review were as follows: (1) conference abstract only citation; (2) the definition of delirium was not validated or it was reported as an outcome variable (not an exposure); or (3) no mortality data were reported. Thirty four of the included studies were published in English, one in Korean,[31] and one in Spanish.[32] A Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart outlining the search results is shown in figure 1.[33]

Of the 34 studies (n = 7,738 patients) identified through our search, 21.5% of patients developed incident postoperative delirium, and 10.8% of patients died after surgery. Of those patients found to be delirious, 21.8% died compared with an 8.7% mortality rate for nondelirious patients. The mortality outcome ascertainment time frame varied between studies, including in-hospital mortality (8 studies; n = 1,274), 30 days to 6 months (13 studies; n = 2,413), and more than 6 months (13 studies; n = 4,051). For studies that reported multiple mortality outcome ascertainment time frame variables, we used the longest time frame reported for our analysis.

Risk of Bias

Overall and categorical risk of bias for each included study in the primary and secondary analyses are summarized in table 3. There was 80% agreement between raters across all of the studies and risk of bias domains. At no time did any disagreement on ratings for a given domain for a given study differ by more than 1 level (*e.g.,* if one rater said moderate, the other rater would have said low or serious, not critical). Lack of control for confounding and bias related to the selection of the reported result were the two categories that resulted in the high and critical risks of bias found. As a result, there were 2 studies at a moderate risk of bias, 6 with high risk of bias, and 26 studies that were of a critical risk of bias.

Impact of Incident Postoperative Delirium on Outcomes

Of the studies that met our inclusion criteria, there were 2 studies (n = 729) that adjusted for our prespecified key confounders (fig. 2).[11,34,35] Both studies were conducted in patients who were undergoing emergency hip fracture surgery. A pooled analysis of these two studies was not possible, because one citation reported an adjusted HR[11] and one

Table 2. Studies Included in the Primary and Secondary Analysis

First Author (yr)	Study Design	Surgery Type	Surgery Urgency	Study Size, n	Age (Mean), yr	Sex, % Women	ASA, ≤2	Delirium Diagnosis	Baseline Cognitive Impairment (Proportion)	Mortality (Length of Follow-Up)*	Crude OR (Unless Otherwise Specified) (95% CI)	Adjusted OR (Unless Otherwise Specified) (95% CI)	Primary/ Secondary Analysis	Event Rates (for Mortality)
Gottschalk (2015)[11]	Prospective cohort	Orthopedics (hip fracture)	Emergency	459	81.3	73	0.16	CAM	Dementia (0.26)	49 mo (mean F/U)	(HR) 1.65 (95% CI: 1.32 to 2.06)	HR = 1.2 (0.93–1.54)	Primary	Delirious: 127/151 Nondelirious: 213/308
Radinovic (2014)[35]; Radinovic (2015)[34]	Prospective cohort	Orthopedics (hip fracture)	Emergency	270	78.1	74	0.19	CAM	GDS >6 (0.31), SPMSQ (mean = 5.7)	30 d	3.47[b] (95% CI: 1.29 to 10.83)	0.46 (0.13–1.65)	Primary	Delirious: 21/143 Nondelirious: 6/127
Veiga (2013)[37]	Prospective cohort	General surgery (hepatectomy)	Elective	70	59‡	50	0.33	ICDSC	N/A	6 mo	13.78 (95% CI: 3.4 to 55.6)	9.33 (1.35–64.61)	Secondary	Delirious: 9/17 Nondelirious: 4/53
Abelha (2013)[36]§; Veiga (2012)[38]	Prospective cohort	Major noncardiac (mixed)	Elective	562	66‡	37	0.34	ICDSC	N/A	6 mo	4.26† (95% CI: 2.37 to 7.53)	2.562 (1.36–4.82)	Secondary	Delirious: 28/89 Nondelirious: 46/473
Dubljanin-Raspopović (2012)[13]; Dubljanin-Raspopović (2015)[12]	Prospective cohort	Orthopedics (hip fracture)	Emergency	344	78.2	80	0.58	CAM	Cognitive impairment (SPMSQ) <3 (0.11)	12 mo‖	4.67 (95% CI: 2.97 to 7.34)	2.31 (1.36–3.90)	Secondary	Delirious: 28/43 Nondelirious: 59/301
Bickel (2008)[39]	Prospective cohort	Orthopedics (hip surgery)	Mixed (elective = 0.72, fracture = 0.28)	200	73.8	69.5	N/A	CAM	MMSE (average = 27.1)	38 mo	4.8 (95% CI: 2.1 to 10.8)	1.7 (0.6–5.0)	Secondary	Delirious: 15/41 Nondelirious: 17/159
Furlaneto (2007)[42]	Prospective cohort	Orthopedics (hip fracture)	Emergency	85	80.26	83.5	N/A	CAM	Dementia (0.43)	48 mo	(HR) 1.83 (no CIs reported)	HR = 1.28 (0.66–2.47)	Secondary	Delirious: 15/25# Nondelirious: 24/60#
Nightingale (2001)[40]; Holmes (2000)[41]	Prospective cohort	Orthopedics (hip fracture)	Emergency	316**	80.3††	78††	N/A	Geriatric mental state (AGECAT); delirium rating scale	N/A	2 yr	3.32† (1.99–5.56)	HR = 2.404‡‡ (1.66–3.48)	Secondary	Delirious: 62/108§§ Nondelirious: 60/208§§

*Data include the longest mortality frame reported. †Data were calculated using STATA 10.0 (OR with Cornfield approximation using cci command). ‡Data show the median. §Data are from Abelha *et al.* 2013.[36] ‖Data are from Dubljanin-Raspopović *et al.* 2012.[13] #Data were calculated using the predicted percentages reported in the text (Furlaneto *et al.* 2007).[42] **Data only included well and delirious patients. ††Data were calculated from table 1 in Holmes (2000).[41] ‡‡Data are from Holmes (2000).[41] §§Data are from Nightingale (2001),[40] the same population as Holmes (2000).[41]

AGECAT = Automated Geriatric Examination for Computer Assisted Taxonomy; CAM = confusion assessment method; F/U = follow-up; GDS = geriatric depression scale; HR = hazard ratio; ICDSC = Intensive Care Delirium Screening Checklist; MMSE = Mini–Mental State Examination; N/A = not applicable; OR = odds ratio; SPMSQ = Short Portable Mental Status Questionnaire.

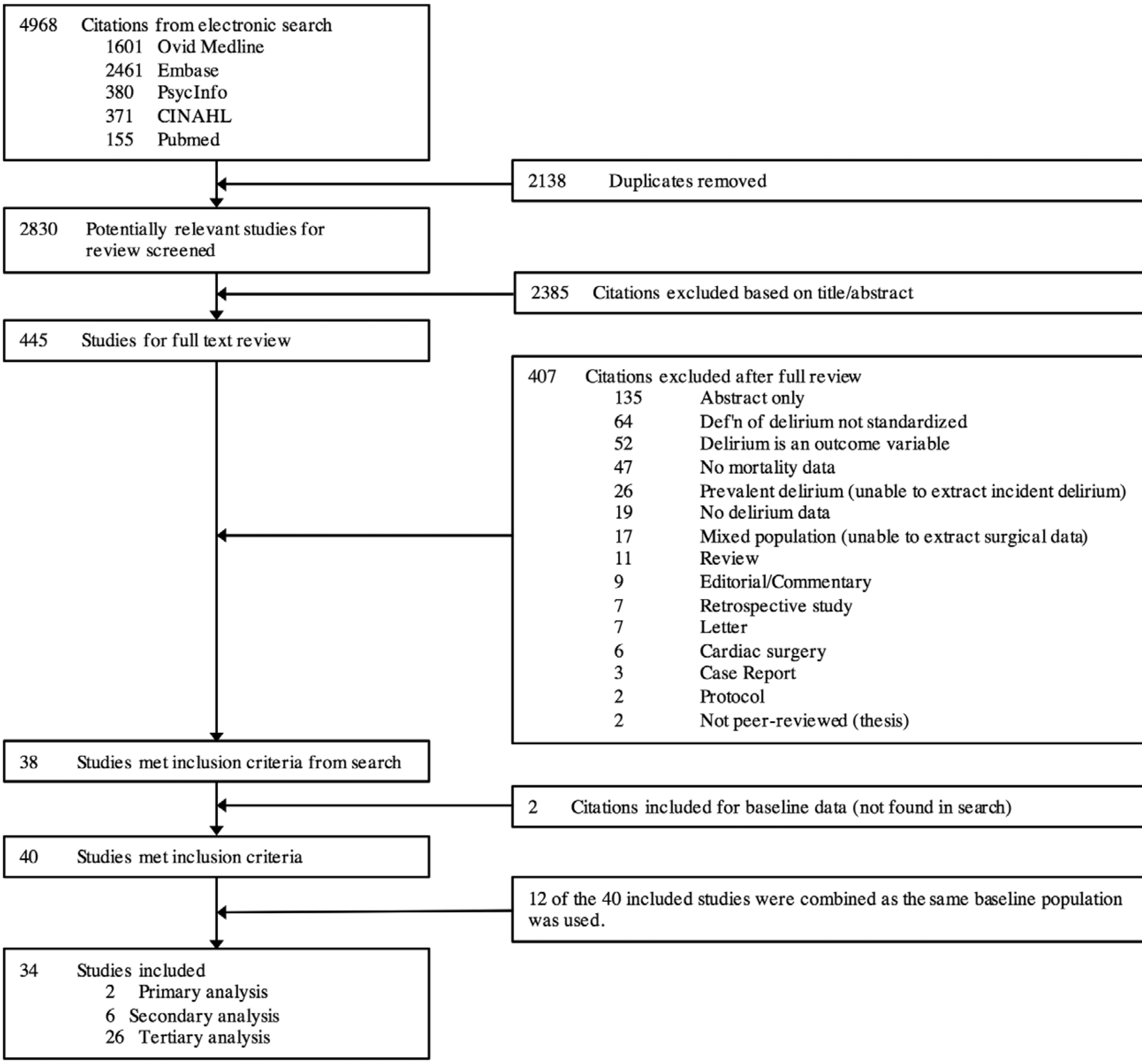

Fig. 1. Identification, review, and selection of articles included in the systematic review. CINAHL = Cumulative Index to Nursing and Allied Health Literature.

reported an adjusted OR.[34] Neither of these studies found a statistically significant association between incident postoperative delirium and mortality after an average follow-up of 21 months (range, 30 days to 49 months). Their adjusted effect estimates were HR at 1.2 (95% CI, 0.93 to 1.54)[11] and OR at 0.46 (95% CI, 0.13 to 1.65),[34,35] respectively.

There were six additional studies[12,13,36–42] (n = 1,577) that calculated adjusted effect estimates to assess the effect of postoperative delirium on mortality, but these authors did not include all of our predefined key confounders in their adjusted effect estimate (table 3). The six adjusted studies were conducted in orthopedic hip fracture patients,[12,13,40–42] hip surgery,[39] general surgery,[37] and a mixed surgical population.[36,38] Given the heterogeneity of the adjusted effect measure types reported, it was not possible to conduct a pooled analysis. Four studies found that delirium was an independent predictor of mortality,[12,13,36,38,40,41] whereas two studies[39,42] did not (fig. 3). These studies presented an average follow-up of 26 months (range, 6 to 48 months).

Twenty seven[11–13,32,34–61] of the 34 studies (n = 5,545) presented unadjusted event rates available for pooled analysis (fig. 4). Seven studies were not included in the pooled analysis because two studies[62–64] had no event rates and five studies[31,65–68] had zero values in their two-by-two tables, making it impossible to obtain an OR.[69] The 27 studies used for pooled analysis had a mean follow-up of 12.3 months (range, 1 to 60 months), and 355 of 1,199 patients with delirium (29.6%) had an increased risk of death compared with 440 of 4,352 control subjects (10.1%). The pooled OR suggested that incident postoperative delirium was associated with an unadjusted four-fold increase in the odds of mortality (OR = 4.12 [95% CI, 3.29 to 5.17]; I^2 = 24.9%).

Table 3. Risk of Bias Assessment Showing the Methodologic Quality of the Studies Included in the Primary and Secondary Analyses and Confounding Variables Included in the Delirium–Mortality Effect Estimate (Primary and Secondary Analyses Only)

	Risk of Bias Assessment							Confounding Variables Included in the Delirium–Mortality Effect Estimate						
Analysis (First Author)	Bias due to Confounding	Bias due to Selection of Participants into the Study	Bias due to Measurement of Outcomes or Exposure	Bias due to Missing Data	Bias due to Measure-ment of Outcomes	Bias due to Selection of the Reported Result	Overall Risk of Bias	Age	Sex	Comorbidity (*e.g.,* ASA)	Previous Cognitive Impairment	Surgery Type	Surgery Urgency	Adjusted OR/HR (95% CI)
Primary analysis														
Gottschalk (2015)[11]	🟡	🟢	🟢	🟢	🟢	🟡	🟡	●	●	●	●	●	●	HR = 1.2 (0.93–1.54)
Radinovic (2015/2014)[34,35]	🟡	🟡	🟢	🟡	🟢	🟡	🟡	●	●	●	●	●	●	OR = 0.46 (0.13–1.65)
Secondary analysis														
Dubljanin-Raspopovic (2015/2012)[12,13]*	🔴	🟡	🟢	🟡	🟡	🟡	🔴	●				●	●	OR = 2.31 (1.36–3.90)
Abelha (2013)[36]; Viega (2012)[38]	🔴	🟡	🟢	🟢	🟢	🟡	🔴	●	●	●		●		OR = 2.562 (1.36–4.82)
Viega (2013)[37]	🔴	🟢	🟢	🟡	🟢	🟡	🔴	●				●		OR = 9.33 (1.35–64.61)
Bickel (2008)[39]	🔴	🟢	🟢	🟢	🟢	🟡	🔴	●	●	●	●	●		OR = 1.7 (0.6–5.0)
Furlaneto (2007)[42]†	🔴	🟢	🟢	🟡	🟢	🟡	🔴			●	●	●	●	HR = 1.28 (0.66–2.47)
Nightingale (2001)[40]; Holmes (2000)[41]‡	🔴	🟡	🟢	🟡	🟢	🟡	🔴	●	●	●		●	●	HR = 2.404 (1.66–3.48)

*Data used backward regression (without controlling for sex or ASA) and only included significant variables in the model. †Univariate analysis was performed with confounders and then included significant variables into the model. ‡It is not clear how concurrent diagnoses of delirium/dementia were handled.

Risk of bias rating scale: low = 🟢, moderate = 🟡, serious = 🔴, critical = ●.

ASA = American Society of Anesthesiologists; HR = hazard ratio; OR = odds ratio.

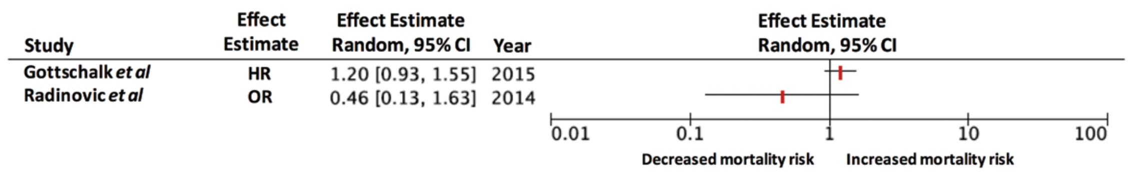

Fig. 2. Primary analysis: forest plot of adequately adjusted event rates (all key confounders included in the statistical model). Note that the point estimates and lower CI values shown in this figure are identical to values found in the articles. Given the variation in statistical techniques used to obtain adjusted odds ratios (ORs), the upper CI value in this figure may not be identical to reported values found in the individual studies (see Supplemental Digital Content 2, http://links.lww.com/ALN/B435, which lists all of the studies that met our primary, secondary, and tertiary analyses). HR = hazard ratio.

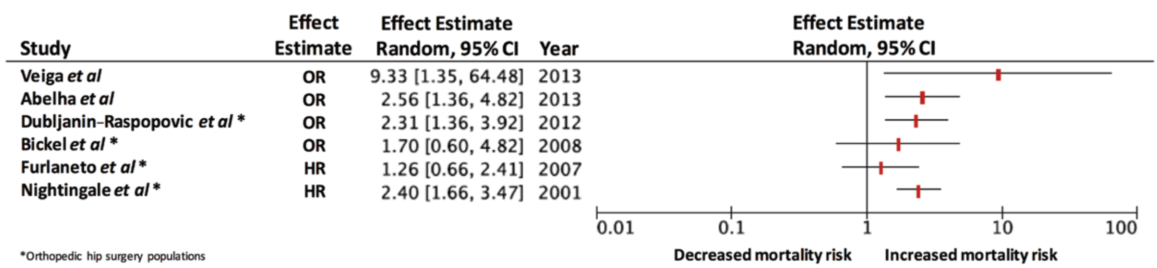

Fig. 3. Secondary analysis: forest plot of inadequately adjusted event rates (not all of the key confounders included in the statistical model). Note that the point estimates and lower CI values shown in this figure are identical to values found in the articles. Given the variation in statistical techniques used to obtain adjusted odds ratios (ORs), the upper CI value in this figure may not be identical to reported values found in the individual studies (see Supplemental Digital Content 2, http://links.lww.com/ALN/B435, which lists all of the studies that met our primary, secondary, and tertiary analyses). HR = hazard ratio.

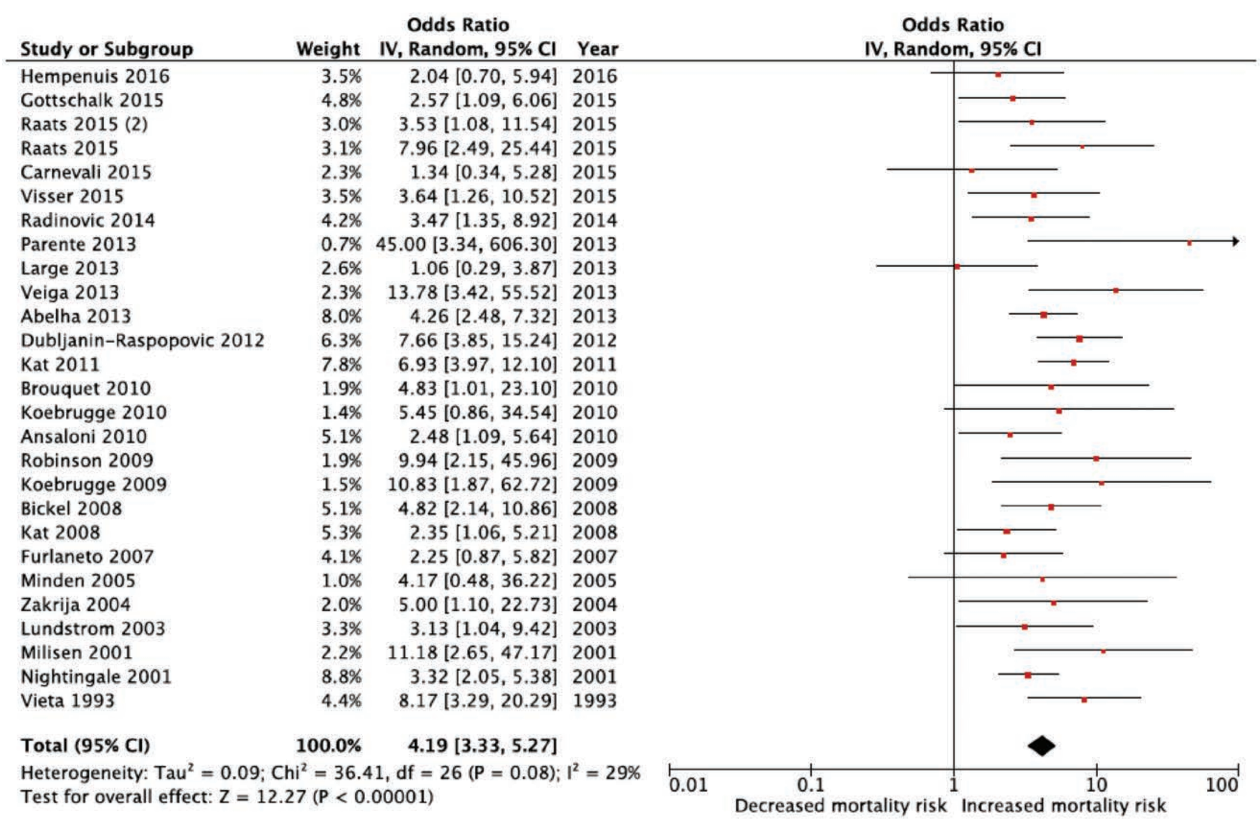

Fig. 4. Tertiary analysis: forest plot of unadjusted event rates available for pooled analysis. Note THAT The point estimates and lower CI values shown in this figure are identical to values found in the articles. Given the variation in statistical techniques used to obtain adjusted odds ratios, the upper CI value in this figure may not be identical to reported values found in the individual studies (see Supplemental Digital Content 2, http://links.lww.com/ALN/B435, which lists all of the studies that met our primary, secondary, and tertiary analyses). df = degrees of freedom.

Discussion

On an unadjusted basis, death is far more common in patients who become delirious after surgery. However, based on our findings there is currently insufficient evidence to support a causal relationship between delirium and postoperative mortality. Because inspection of forest plots when studies were grouped by risk of confounding bias demonstrated a decrease in the effect size estimates for delirium as control for confounding improved, this suggests that, within the perioperative population, either the true effect of postoperative delirium on mortality risk may be substantially smaller than previously reported, or delirium may simply be an indicator of underlying factors that predispose a patient to an increased risk of death rather than a true independent risk factor. We found only two studies that adjusted for our predefined key confounding variables, and in both studies no significant association was found between incident postoperative delirium and mortality.

The major strength of this study is that we sought to investigate the independent nature of delirium as an exposure on mortality in a fashion specific to the perioperative setting. This systematic review and meta-analysis is, to our knowledge, the first study of its kind to systematically synthesize data on the impact of incident delirium on mortality in perioperative patients. Furthermore, our protocol was registered *a priori* and designed in keeping with best-practice methods, which should limit the risk of bias in our results. The present study also has limitations. First, no included study was at low risk of bias. Second, although this study was restricted to noncardiac surgical patients, the surgical populations remained heterogeneous. Third, the mortality outcome windows were variable. The variable duration of mortality follow-up from the surgical period may have altered the causative impact that a perioperative delirious episode would have on mortality; however, given a recent study by Smith *et al.*[70] that reinforced that early mortality risk stratification is consistent over the first postoperative year, we believed that it was appropriate not to stratify by outcome ascertainment window despite the variations in follow-up duration between studies. Fourth, we were unable to use data on the duration of the delirium given the heterogeneity and paucity of our data (inconsistently reported by 9 of 34 studies). Finally, the cause of death was not examined in our review; however, such data could help to explain a possible causal relationship between delirium and mortality and should be considered in future prospective studies.

We focused only on mortality as an outcome because mortality is reliably measured, is of importance to multiple stakeholders in the perioperative setting, and confounding variables in the delirium–mortality relationship are relatively well defined. Other outcomes are also relevant to patients, clinicians, and the healthcare system; however, a methodologically sound analysis of other outcomes (*e.g.,* complications, length of stay, discharge disposition, or quality of recovery) was not possible due to limitations in measurement of these outcomes and unclear sources of confounding.

Delirium is common after surgery, particularly in older patient populations.[7] At baseline, patients who develop delirium tend to differ substantially from patients who do not become delirious, and these differences (*e.g.,* advanced age, comorbidity burden, baseline cognitive status, surgical indication and urgency, and sex) are also consistently associated with an increased risk of death. Therefore, the delirium–mortality relationship is likely to be highly confounded. Because of this confounded relationship, any attempt at identifying an independent association between delirium and mortality requires careful control of these factors. In the two studies that we identified with adequate confounder control,[11,34,35] no significant independent association of delirium on postoperative mortality was identified. In contrast, Witlox *et al.*[8] examined the risk of delirium on postdischarge mortality among all of the hospitalized patients. In their primary analysis that included effect estimates from seven studies (three of which included surgical patients) that controlled for the confounders age, sex, comorbidity or illness severity, and baseline dementia, they found a significant increase in mortality risk (pooled HR = 1.95 [95% CI, 1.51 to 2.52]) associated with delirium. However, their result must be interpreted in consideration of additional sources of bias, such as combining substantially heterogeneous populations, combining both prevalent and incident delirium, and a lack of control for confounders specific to the perioperative setting. In fact, none of the surgical studies included in the primary analysis by Witlox *et al.*[8] met our *a priori* criteria for adequate confounder control, mainly due to a lack of control for surgery-specific confounders. A secondary analysis from Witlox *et al.*[8] that combined unadjusted effect estimates from 17 strictly surgical studies found a pooled OR of 2.94 (95% CI, 2.30 to 3.75) associating delirium with mortality, a finding that is in keeping with the unadjusted pooled OR found in our study. Therefore, we suggest that the divergence of our findings from those of Witlox *et al.*[8] are accounted for by an approach to confounder control that was specifically defined for perioperative patients in our study and/or potential differences between the pathophysiology of postoperative delirium in medical *versus* surgical patients. In fact, there is some evidence suggesting that delirium in patients with hip fractures is more likely to result in complete recovery than other forms of delirium.[71]

Although our findings do not support an independent association between postoperative delirium and mortality, this finding is not conclusive. First, only two of 34 studies that we identified had adequate control for confounding based on a minimum set of required variables. Our six predefined confounding variables likely represent a set of factors that are necessary but not fully sufficient to control for confounding in the delirium–mortality relationship. In addition, our inclusion criteria did not specify required methods for confounder definitions, handling of quantitative variables, or statistical methods that would be preferred in low risk-of-bias observational studies. Next, studies in our primary analysis included only patients undergoing hip surgery; therefore, we are unable to generalize our findings to other noncardiac surgery populations and, in particular, to patients undergoing elective surgery. Finally, the two studies included in our analysis featured two different outcome ascertainment periods (30 days *vs.* 49 months), and although neither found a significant difference in mortality, they each reported a different directional association (short-term follow-up study-adjusted OR = 0.46; long-term follow-up study-adjusted HR = 1.2). Therefore, if the relationship between incident delirium and postoperative mortality is to be understood in a fashion that allows for causal inference and evidence-based clinical care, appropriately powered multicentered studies of relevant patient populations with a reliable delirium definition, complete capture of long-term mortality, granular control for confounding using best-practice methods in observational research, and a time-to-event analysis will be needed.

Until such studies are available, clinicians should consider the following when interpreting our results. Although our article suggests that delirium may not independently change the risk of mortality, there are many other reasons that clinicians might seek to prevent delirium in the perioperative setting. Delirium can be a frightening and unpleasant experience for patients and their families. In addition, we have not assessed the impact of delirium on other important outcomes. Finally, many interventions used to decrease delirium risk (*e.g.*, orientation, mobilization, and opioid sparing analgesia,) would likely positively impact other geriatric-specific risks.

The available literature does not support an independent association between delirium and mortality after noncardiac surgery. However, unadjusted results indicate that patients who develop delirium are at an increased risk of death. As the risk of bias decreased, the association between delirium and mortality decreased; and in the lowest risk-of-bias studies, no association was present. Therefore, given the increasing population of older patients presenting for surgery, low risk-of-bias studies are urgently needed to solidify our understanding of the delirium–postoperative mortality relationship.

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Competing Interests

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