BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2022.05.032
Advance Access Publication Date: xxx
Review Article

REVIEW ARTICLE

Perioperative risk factors associated with increased incidence of postoperative delirium: systematic review, meta-analysis, and Grading of Recommendations Assessment, Development, and Evaluation system report of clinical literature

Lior Mevorach[1,*], Ali Forookhi[1], Alessio Farcomeni[2], Stefano Romagnoli[3] and Federico Bilotta[1]

[1]Department of Anaesthesiology, Critical Care and Pain Medicine, Policlinico Umberto I Teaching Hospital, Sapienza University of Rome, Rome, Italy, [2]Department of Economics and Finance, Tor Vergata, University of Rome, Rome, Italy and [3]Department of Anaesthesia and Critical Care, Careggi University Hospital, Florence, Italy

*Corresponding author. E-mail: anesthesiologysapienza@gmail.com

Abstract

Background: Systematic reviews to date have neglected to exclusively include studies using a validated diagnostic scale for postoperative delirium and monitoring patients for more than 24 h. Evidence on current risk factors is evolving with significantly heterogeneous study designs, inconsistent reporting of results, and a lack of adjustment for bias.
Methods: This systematic review and meta-analysis aimed to identify risk factors for postoperative delirium in an adult patient population. Study designs suitable for this review included full-text articles, RCTs, observational studies, cohort studies, and case-control studies. Extracted variables from the 169 (7.4%) selected studies were included in qualitative synthesis, quantitative synthesis, and a postoperative delirium checklist. The 16 variables included in the checklist were selected based on consistency, direction of effect, number of studies, and clinical utility as a reference for future studies.
Results: A total of 576 variables were extracted, but only six were eligible for meta-analysis. Age (mean difference [MD]=4.94; 95% confidence interval [CI], 2.93–6.94; $P<0.001$), American Society of Anesthesiologists physical status >2 (odds ratio [OR]=2.27; 95% CI, 1.47–3.52; $P<0.001$), Charlson Comorbidity Index ≥2 (OR=1.9; 95% CI, 1.11–3.25; $P=0.0202$), and Mini-Mental State Examination (MD=−1.94; 95% CI, −3.6 to −0.27; $P=0.0224$) were statistically significant.
Conclusions: Risk factors can assist in clinical decision-making and identification of high-risk patients. Literature analysis identified inconsistent methodology, leading to challenges in interpretation. A standardised format and evidence-based approach should guide future studies.

Keywords: delirium; GRADE; intensive care unit; meta-analysis; perioperative; postoperative; review; risk factors

Editor's key points

- Previous research has identified risk factors for postoperative delirium without the use of validated scales or >24 h of patient monitoring. Risk of bias assessments were not based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.
- Novel risk factors for postoperative delirium, including ASA physical status, Charlson Comorbidity Index, and Mini-Mental State Examination, were found identified as significant in meta-analysis and GRADE assessment.
- Future researchers are advised to follow a standardised approach in defining validated scales, patient monitoring for >24 h, and data reporting.

Received: 10 March 2022; **Accepted:** 31 May 2022

In the past decade, studies examining the clinical relevance of postoperative delirium (POD) have steadily increased in number, from 119 in 2010 to 257 in 2015 to 550 in 2020.[1] In 2017, the POD task force of the European Society of Anaesthesiologists (ESA) published an initial version of the guidelines that included evidence extracted from studies published before March 2015.[2] The principal reported findings were: POD can complicate the clinical course up to 5 postoperative days and monitoring should be standard practice and be performed using a validated scale (Supplementary Table S1). As stated in this guideline, patients undergoing surgical procedures should be evaluated for POD risk factors; preoperative care should be optimised; and the relative risk should be communicated to the patients, their families, and members of the hospital care team. Because of limited evidence, the guideline gave Grade A scores only to three variables among the many associated with an increased risk of POD: alcohol-related disorders, preoperatively; duration of surgery, intraoperatively; and pain severity, postoperatively. In older patients, cognitive impairment, reduced functional status and/or frailty, malnutrition (low serum albumin), and sensory impairment were additionally identified as POD risk factors.

Studies on the risk factors for POD are continuously evolving because of the significantly subjective definitions of the condition, heterogeneous study designs, inconsistent reporting of methodology and results, and a lack of adjustment for the risk of bias.[3] Systematic reviews to date have neglected to exclusively include studies using a validated diagnostic scale for POD and monitoring of patients for more than 24 h.[4–6]

The purpose of this systematic review, conducted on behalf of the ESA POD task force, is to report clinical evidence on perioperative risk factors associated with increased POD incidence in the adult population. The risk factors were extracted from studies published between 2015 and 2020 using rigorous methodology and graded according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system. Variables with an adequate number of supporting articles were used to develop a POD checklist to guide future studies.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed as reporting standards. A professional medical librarian with expertise in systematic reviews and meta-analyses carried out a literature search to identify original clinical studies on POD, in December 2020. PubMed was searched for articles published between April 2015 and November 2020.

The search terms used were (delirium OR confusion OR confusion* OR disorientation OR bewilderment) AND (postoperative OR postoperative period OR postoperative period* OR post-surgical OR post-surgical OR anaesthesia recovery period OR anaesthesia recovery period* OR postanesthesia). Queries returned 2291 articles dealing with risk factors, prophylaxis, treatment, monitoring, and outcomes associated with POD; 1243 (54.3%) of the articles were considered potentially relevant for the update of the 2017 POD guideline and assigned to five working groups: basic science, risk factors, preventive measures, neuromonitoring, and treatment and outcomes.

Two expert reviewers selected 484 articles from the 1243 assigned. The 484 included articles had the following selection criteria: full-text articles, RCTs, observational studies, cohort studies, and case-control studies, and were considered suitable study designs for the present review. The exclusion criteria used were: case report, comment, letter to the editor, editorial, erratum, reply, study protocols, cross-sectional study, mixed surgical and other disciplines with no separate presentation of surgical population results, non-English language publication, paediatric patients (age <18 yr), diagnosis of POD using non-validated scales, postoperative monitoring for less than 24 h,[7] and articles on emergence agitation and postoperative cognitive dysfunction.

Two additional reviewers (LM, AF) performed a secondary screening of the assigned articles, which monitored postoperative patients for at least 24 h using any one of the validated scales listed in the 2017 ESA POD guideline (Supplementary Table S1). From the original studies that were found to be suitable, the following variables were extracted into a dedicated data extraction form consisting of: type of study, number of patients, type of POD scale used, statistically significant *P*-value and odds ratio (OR) of preoperative, intraoperative, and postoperative risk factors that were associated with increased POD incidence. Variables found to be significant in multivariate analyses were preferably noted where such analysis was performed. The study design is summarised in the PRISMA flowchart (Fig. 1).

The reviewers decided to classify the risk factors into three groups: preoperative, intraoperative, and postoperative in advance. Before data extraction began, a meta-analysis was planned to be performed based on the following criteria: (1) standardised methodology for measurement; (2) >5 studies conducted on the variables. To perform a meta-analysis, it is required to have at least five studies measuring statistically significant pooled OR and mean difference (MD) variables.

Quality assessment

The risk factors in each relevant article were assessed and the strength of evidence supporting these variables was determined using the GRADE system.[8]

The POD checklist listed the risk factors identified in the majority of studies. Furthermore, a cut-off value was specified based on a reported sensitivity analysis, when feasible, or alternatively a conventionally used cut-off value. Risk factors supported by more than five references listed in the POD checklist were rated for the quality of evidence using the GRADE system.[9]

According to GRADE, quality of evidence is assessed based on factors such as study design, risk of bias,[10] imprecision,[11] inconsistency,[12] indirectness,[13] publication bias,[14,19] and effect size. There are four levels of evidence (also referred to as certainty or quality of evidence): very low, low, moderate, and high. As a general starting point, RCTs are considered to be of high quality, whereas observational studies, which were primarily included in this systematic review, are deemed of low quality because of residual confounding inherent to the study design.

The studies supporting the selected variables were assessed by two reviewers working independently according to the Newcastle–Ottawa scale[9] for risk of bias using Risk-of-bias VISualization (robvis) tool.[8,18] The heterogeneous nature of the included studies led to the selection of a random-effect model for pooling of the data, which was mapped to illustrate the results of the analysis in forest plots. In studies performing multivariate analyses, variables were only included from the results of the multivariate comparison. If no multivariate analysis was performed, statistically significant variables were included from univariate analysis. The use of multivariate

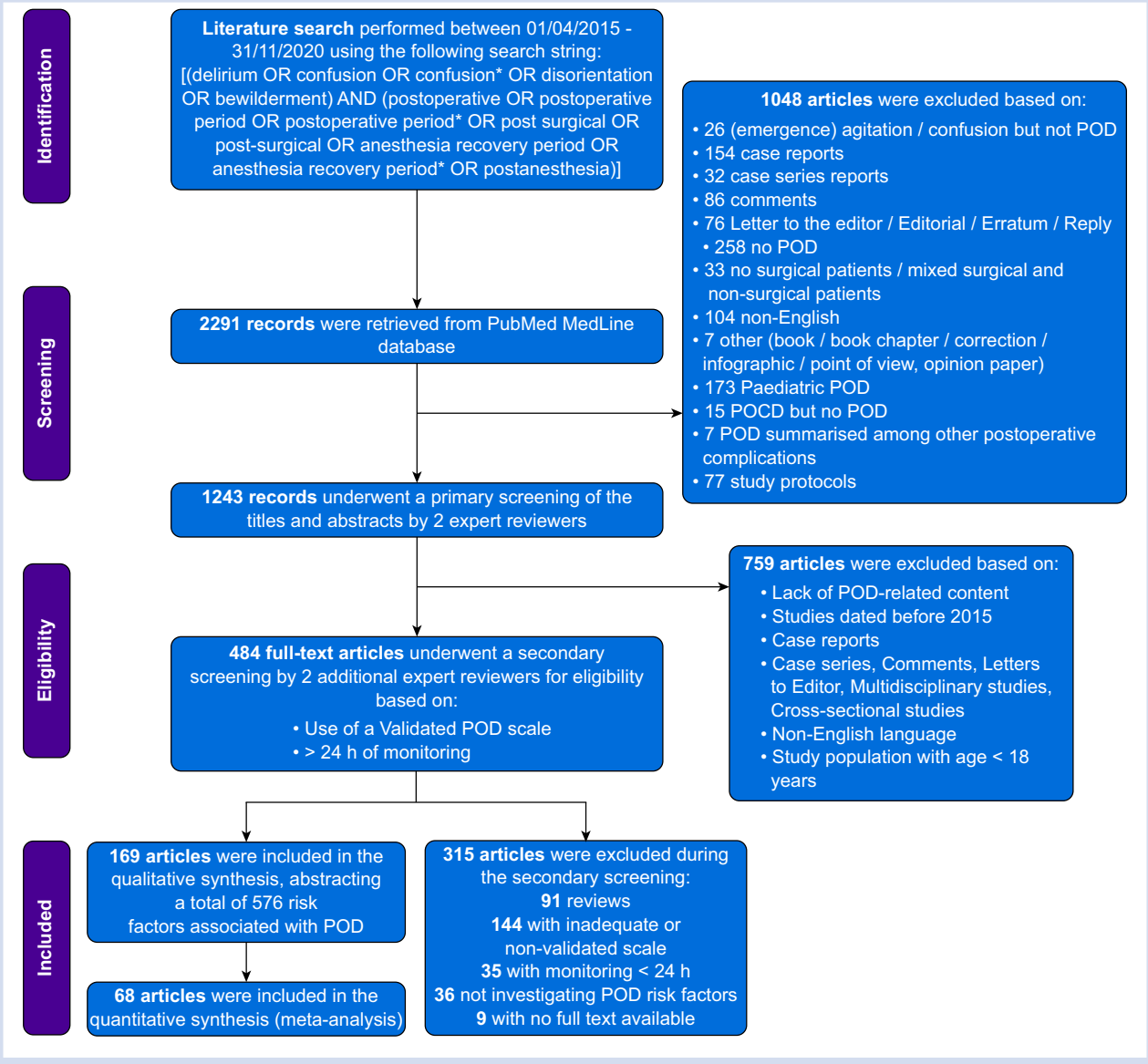

Fig 1. Exclusion process flowchart. POD, postoperative delirium; POCD, post-operative cognitive dysfunction.

analysis was taken into account during the risk of bias assessment.

Quantitative synthesis

Eligible risk factors were subjected to a risk of bias assessment according to the Newcastle–Ottawa scale. A summary plot and traffic light plots illustrated the bias attributable to selection, comparability, and outcome. Forest plots and funnel plots were used to demonstrate the overall direction of effect and publication bias, respectively.

Development of postoperative delirium checklist

Upon the completion of the data extraction process, risk factors were evaluated based on their clinical utility and the number of studies supporting the variables in order to create a POD checklist. Variables with more than five supporting papers were included in the checklist.

Statistical analysis

An OR was assigned to dichotomous variables and a MD to continuous variables for each meta-regression. In the pooled model, ORs were computed for ASA physical status >2, Charlson Comorbidity Index (CCI) $\geq$2, and male sex, using the Mantel–Haenszel method. From each of the studies included in the pooled analysis, the 95% confidence interval (95% CI) estimates of ORs were extracted in order to determine the direction of effect. MD was calculated for age, ASA physical status score, Mini-Mental State Examination (MMSE) score, BMI, and CCI, using the inverse variance method, when

Table 1 GRADE summary of findings for risk factors included in meta-analysis. American Society of Anesthsiologists; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; POD, postoperative delirium.

Certainty assessment								No. of patients		Quality of evidence*	Comments and recommendations
Risk factor	No. of studies included in bias assessment	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delirium	No delirium		
Older age	63	Observational studies	Serious	Not serious	Not serious	Not serious	No Publication bias was detected. Possible confounding in multivariate analysis in some studies owing to Testimation (Overfitting) bias	6059	11 4758	⊕◯◯◯ Very Low	Critical risk factor Age is the most critical variable regarding the risk of POD. It is the factor that is almost always reported in demographics and data is readily available.
Higher ASA physical status	27	Observational Studies	Serious	Not serious	Not serious	Not serious	Minor evidence of Publication bias found. Possible confounding in multivariate analysis in some studies owing to Testimation (Overfitting) bias	2697	81 334	⊕◯◯◯ Very Low	Critical risk factor Higher ASA score is a critical risk factor supported by extensive literature.
Lower Mini-Mental State Examination (MMSE) score	15	Observational Studies	Serious	Not serious	Not serious	Not serious	No Publication bias was detected. Possible confounding in multivariate analysis in some studies owing to Testimation (Overfitting) bias	616	1912	⊕◯◯◯ Very Low	Critical risk factor Lower MMSE score has been shown to be predictive of POD.
Higher Charlson Comorbidity Index (CCI)	12	Observational Studies	Serious	Not serious	Not serious	Not serious	No Publication bias was detected for CCI as mean difference, however there were too few studies to conclude evidence of publication bias for CCI >2. Possible confounding in multivariate analysis in some studies owing to Testimation (Overfitting) bias	1789	8914	⊕◯◯◯ Very Low	Critical risk factor Higher CCI has been consistently shown to be linked with POD.
Sex (male or female)	17	Observational Studies	Serious	Not serious	Not serious	Not serious	Minor evidence of Publication bias found. Possible confounding in multivariate analysis in some studies	3355	8052	⊕◯◯◯ Very Low	Not statistically significant Both male and female sex have been shown to be associated with

Continued

Table 1 Continued

Certainty assessment								No. of patients		Quality of evidence*	Comments and recommendations
Risk factor	No. of studies included in bias assessment	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delirium	No delirium		
							owing to Testimation (Overfitting) bias				POD in different studies.
Low body mass index	11	Observational studies	Serious	Not serious	Not serious	Not serious	No Publication bias was detected. Possible confounding in multivariate analysis in some studies owing to Testimation (Overfitting) bias	2127	37 706	⊕◯◯◯ Very Low	Not statistically significant There have been studies reporting both a high (obesity) and low BMI (underweight) being associated with POD. The majority of studies point towards a low BMI.

studies recorded these variables as means or medians rather than providing cut-offs for OR calculations. The inter-quartile range for the sample sizes was assumed to be approximately 1.35 standard deviations because the distribution of outcomes was similar to that of the normal distribution. Heterogeneity between the studies was assessed using the I^2 statistics. If an I^2 >25% was observed with either categorical or continuous predictor, the DerSimonian and Laird random-effects model was chosen; otherwise, fixed-effects models were used. The results were summarised using forest plots. Analyses were performed on R version 3.5.1 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was determined at a *P*-value of 0.05. A reproducible technical report of the statistical analysis methodology is available in the Supplementary material.

Results

Of 484 articles analysed, 169 used a validated scale to monitor patients for longer than 24 h and were considered suitable to extract perioperative risk factors. All included articles were observational studies. A total of 576 risk factors were extracted: 302 preoperative risk factors, 108 intraoperative risk factors, and 163 postoperative risk factors. The 302 preoperative risk factors were categorised into eight major groups: comorbidities, demographics, laboratory analysis, medications, habits, setting of preoperative care, transfusions, and surgical variables. The 108 intraoperative were categorised into 12 major groups: surgical variables, blood variables, duration of surgery, anaesthesia administered, drugs administered, haemodynamics, haemo-gas analysis, cerebral pathology, laboratory analysis, imaging, positioning in surgery, and monitoring. The 163 postoperative were categorised into 16 major groups: pathologies, stay duration, intubation, laboratory analysis, drugs administered, overall complications, transfusions, surgery variables, catheters, setting of postoperative care, use of restraints, diet, haemodynamics, and readmission to the ward and physical examination. All variables were listed along with their respective studies in a comprehensive table (Supplementary Table S2).

The 576 extracted variables were distributed between three subgroups for results synthesis: (1) Qualitative synthesis group – to make recommendations; (2) Quantitative synthesis group – to perform the meta-analysis; (3) POD checklist group. When the inclusion criteria were met, a variable could be analysed in more than one sub-analysis.

Qualitative synthesis group

The objective of the qualitative synthesis was to provide a clinically relevant group of variables which could be readily measured or recorded. Although they could not be included in the meta-analysis because of a lack of uniform clinical reporting, some of the results are noteworthy and further investigation is warranted in order to ascertain the clinical significance of these variables. The following 50 variables were found to be potentially representative of a POD risk profile (Supplementary Table S4).

Preoperative: low haemoglobin levels, low haematocrit, low red blood cell count (RBC), increased mean corpuscular volume (MCV), low serum albumin, low albumin/globulin ratio, increased creatinine, low serum sodium, increased serum sodium, low serum calcium, low serum potassium, increased white blood cell (WBC) count, increased neutrophil count,

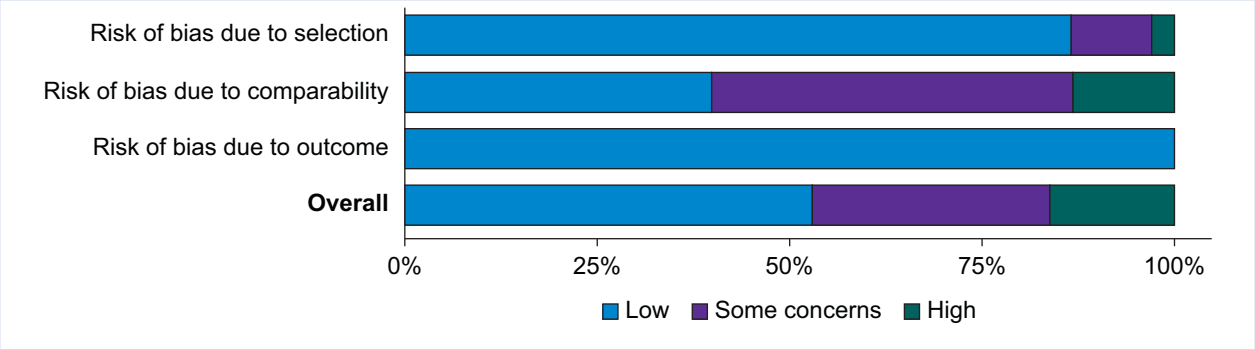

Fig 2. Summary plot of the 68 studies subject to Newcastle–Ottawa scale assessment.

increased total/peripheral lymphocyte count, increased C-reactive protein (CRP).

Intraoperative: administration of packed RBC, fresh frozen plasma (FFP), cryoprecipitate transfusion, platelet administration, hydroxyethyl starch, crystalloid, albumin. Also increased blood loss, dexmedetomidine, increased opioids dose and propofol, hypotension, increased duration of anaesthesia, and general anaesthesia.

Postoperative: longer duration of mechanical ventilation, increased creatinine, decreased haemoglobin, increased length of hospital stay, and increased length of stay in the ICU.

Quantitative synthesis group

A total of six risk factors were found to be eligible for quantitative synthesis. A GRADE Summary of Findings table was made to summarise the body of evidence for each risk factor (Table 1).

The Newcastle–Ottawa scale was used to assess 68 articles supporting the variables deemed to be suitable for quantitative synthesis regarding their risk of bias. The overall results of assessment are summarised in a summary plot (Fig. 2). In addition, risk of bias visualisation traffic light plots were used to indicate the three major criteria assessed in the scale for each study: D1 (risk of bias) attributable to selection; D2 (risk of bias) attributable to comparability; D3 (risk of bias) attributable to outcome (Supplementary Table S3). In general, studies tended to have low to moderate risk of bias attributable to selection and comparability, but almost no risk of bias attributable to outcome when validated scales were used for diagnosing POD.

In the meta-analysis, a random-effects model was used for ASA physical status >2, CCI ≥2, male sex. Meanwhile, a fixed-effects model was used for Age, ASA physical status, MMSE, BMI, and CCI score. The cut-offs that were used for the separation of data into dichotomous outcomes were chosen based on the scores most patients with POD had from the included studies. Most patients with POD had ASA physical status >2 and CCI ≥2.

The results of were presented as forest plots for each risk factors (see Supplementary Figures): Age as MD; Male sex as OR; ASA physical status score >2 as OR; ASA physical status as MD; CCI as MD; CCI ≥2 as OR; MMSE as MD; BMI as MD (see Supplementary material).

Older age (pooled MD=4.94 yr; 95% CI, 2.93–6.94; I^2=0.00; P<0.001), ASA physical status >2 (pooled OR=2.27; 95% CI, 1.47–3.52; I^2=81.73; P<0.001), CCI ≥2 (pooled OR=1.9; 95% CI, 1.11–3.28; I^2=63.99; P=0.0202), Lower MMSE as MD (pooled MD=−1.94; 95% CI, −3.6 to −0.27; I^2=0.00; P=0.0224) were found to be statistically significant risk factors.

Male sex (pooled OR=1.77; 95% CI, 0.85–3.67; P=0.125), ASA physical status as MD (pooled MD=0.05; 95% CI, −0.24 to 0.34; I^2=0.00; P=0.735), CCI as MD (pooled MD=1.13; 95% CI, −0.19 to 2.48; I^2=0.00; P=0.097), and BMI as MD (−1.51; 95% CI, −4.91 to 1.89; I^2=0.00; P=0.384) were not found to be statistically significant. The results of the analysis along with the statistical methods used are shown in Table 2.

Table 2 Results of meta-analysis. American Society of Anesthesiologists CCI, Charlson Comorbidity Index; CI, confidence interval; MD, mean difference; MMSE, Mini-Mental State Examination; OR, odds ratio.

Risk factor	Statistical method	Pooled OR	Pooled MD	95% CI Lower limit	95% CI Upper limit	I^2 (Heterogeneity)
Age	Inverse variance	–	4.94	2.93	6.94	0
ASA physical status >2	Mantel–Haenszel	2.27	–	1.47	3.52	81.73
CCI ≥2	Mantel–Haenszel	1.9	–	1.11	3.28	63.99
MMSE (as MD)	Inverse variance	–	−1.94	−3.6	−0.27	0
Male sex	Mantel–Haenszel	1.77	–	0.85	3.67	80.03
ASA physical status (as MD)	Inverse variance	–	0.05	−0.24	0.34	0
CCI (as MD)	Inverse variance	–	1.13	−0.19	2.48	0
Body mass index (as MD)	Inverse variance	–	−1.51	−4.91	1.89	0

Table 3 Postoperative delirium checklist. CCI, Charlson Comorbidity Index; MMSE, Mini-Mental State Examination; RASS, Richmond Agitation Sedation Scale.

Predictor
Preoperative
Age (yr)
<75
>75
High ASA physical status (>2)
No
Yes
High CCI score (≥2)
No
Yes
Low MMSE score (<25)
No
Yes
Lower haemoglobin (g dl^{-1})
≥11.1
<11.1
Intraoperative
Blood transfusion
No
Yes
Cardiac surgery
No
Yes
Orthopaedic surgery
No
Yes
Hypotension (mm Hg)
No
Yes
Longer duration of surgery
No
Yes
Longer duration of anaesthesia
No
Yes
Postoperative
Longer duration of mechanical ventilation
No
Yes
Increased length of hospital/ICU stay
No
Yes
High creatinine
No
Yes
Pulmonary infection (including Pneumonia)
No
Yes
Cerebral/psychiatric pathology (e.g. abnormal RASS score, sleep disorders, stroke, emergence agitation, brain oedema, convulsions, low MMSE score)
No
Yes

Funnel plots showed no sign of publication bias for age, CCI, MMSE, and BMI. Minor evidence of publication bias was noted for male sex and ASA physical status score >2. There were too few studies using a CCI ≥2 to assess for publication bias.

POD checklist group

Sixteen risk factors were selected to create a POD checklist on the basis of the number of studies supporting them and those with statistically significant *P* values and significant ORs on both univariate and multivariate analyses (Table 3). Of these 16 variables, 12 were not included in the quantitative synthesis as they were not measured in the same manner (i.e. homogeneous). However, the variables in question showed a consistent trend in the literature, associated with an increased risk of POD. Two preoperative variables that had a sensitivity analysis were given a cut-off score: age more than or equal to 75 (Appendix 1, –165) and haemoglobin (<11.1 g dl^{-1}) (Appendix 1, –107). Other variables in the checklist that did not have studies performing a sensitivity analysis to determine a cut-off score were: (1) Preoperative – ASA physical status, CCI, MMSE; (2) Intraoperative – blood transfusion, intraoperative hypotension (mean arterial pressure <60 mm Hg), cardiac surgery, orthopaedic surgery, longer duration of surgery and anaesthesia; (3) Postoperative – longer duration of mechanical ventilation, increased length of hospital or ICU stay, high creatinine, pulmonary infection (including pneumonia), and cerebral or mental pathology.

Discussion

In this systematic review, 484 full-text articles were reviewed in order to extract statistically significant risk factors for POD, among which the utmost clinical significance was attributed to: older age, ASA physical status >2, CCI ≥2, and lower MMSE.

Within the framework of ESA guidelines revision, the current review is intended to report clinical evidence related to perioperative (preoperative, intraoperative, postoperative) risk factors, with the six variables that were found eligible for meta-analysis summarised using GRADE.

The ESA POD guideline published in 2017 encountered some challenges in reporting risk factors. One of them is the lack of standardised monitoring. Although it is challenging to assess different populations using the same assessment tools, the guideline established a list of validated diagnostic scales that should be incorporated by hospital care teams as standard practice (Supplementary Table S1). Quality assessment of the selected studies reviewed in the guideline was also inconsistent and was graded inaccurately. In addition, the guideline was peer-reviewed by the ESA's scientific committee, which was mentioned under the conflicts of interest.

In spite of the beneficial recommendation supporting the use of validated scales as an assessment tool, the guideline failed to offer any further clinically relevant indications for identifying high-risk patients.

The novelties presented in this systematic review in comparison with the 2017 (previous) guideline were the following: (1) review of articles only using validated scales presented in the previous guidelines; (2) risk of bias assessment using GRADE in a methodologically consistent manner, presenting the selection bias, comparability bias, and outcome bias, in addition to testimation bias arising from multivariate analyses; (3) meta-analysis of the major variables cited in every source; (4) complete updated list of statistically significant risk factors in a pre-, intra- and postoperative setting.

The authors of the review, however, were not able to register this review's protocol with PROSPERO because of ongoing heavy workloads during the COVID-19 pandemic.

During the data extraction in this systematic review, the rigorous inclusion criteria deployed required at least one validated scale to assess patients, although some studies used both validated and non-validated scales in their assessments. In such cases where both scales (i.e. Diagnostic and Statistical

Manual of Mental Disorders, 4th Edition [DSM-IV] AND Confusion Assessment Method for the ICU [CAM-ICU]) were concurrently used, the methodology was deemed to be valid, and the studies were included in the review. Conversely, studies that used either one or the other (e.g. DSM-IV OR CAM-ICU) were considered invalid and were ruled out (Appendix 1, List of studies that qualified for the systematic review: 17, 34, 41, 45, 58, 62, 63, 80).

There were several limitations that arose during the systematic review. In the data extraction, an inconsistency was observed in measurements or assessments of certain variables, or rather the means of measurements were omitted altogether. Variables, such as blood transfusion or Instrumental Activities of Daily Living (IADL) (Appendix 1: 4, 32, 43, 47, 88, 151, 163) were both measured and assessed differently in different studies. In such cases, the definition of variables differed significantly, making pooled statistical calculations unfeasible, because homogeneity and a common definition of each variable are crucial.

A major methodological challenge was the largely unaddressed problem of testimation bias in literature generation. Owing to this bias, the ORs provided in the study may differ significantly from the true OR for determining whether or not a variable is associated with POD.[15] Multivariable logistic regression models can be significantly skewed if they are constructed with variables that have a large statistically significant effect, with no consideration of variables with a smaller effect that are, by definition, statistically insignificant. Hence the effect of the statistically significant variables would be overestimated, resulting in ORs with CIs that would exclude zero, whereas their true CIs do not. A further statistical limitation posed by observational studies is the interpretation of the effect size implied by ORs and lack of adjustments for potentially important confounders. The true incidence of POD in patients is unknown; therefore, the true effect size of the variables may be far from the magnitude of the OR.[16]

Reporting of well-established and defined variables may even indicate a limitation, as two variables may oppose each other. For example there is incongruity in data regarding sex susceptibility, as some studies suggest the male sex is more predisposed to POD, and other studies suggest the female sex is predominantly affected. Similarly with BMI, there were studies that associated low BMI with POD and others that associated obesity (BMI $\geq$30) with POD. The pooled statistics for both showed no statistically significant association with POD.

Much like other neurological complications, POD has a complex pathogenesis, aetiology, and a wide array of risk factors. There is no clear evidence as to whether the variables listed above directly influence POD risk or whether patients with POD are indirectly predisposed to those variables.

The qualitative synthesis group of risk factors are a starting point for research towards the optimisation of daily clinical care of patients at risk of POD, with the ultimate goal of reducing the patient's surgical stress response, optimising their physiologic function, and speeding their recovery. These recommendations can be evaluated for procedure-specific enhanced recovery after surgery protocol (ERAS).[17,20,21] Postoperatively, patients could potentially be evaluated by assessing the following aspects: (1) preoperative labs – haemoglobin, haematocrit, RBC, MCV, serum albumin, albumin/globulin ratio, creatinine, serum sodium, serum calcium, serum potassium, WBC, neutrophil count, total peripheral lymphocyte count, and CRP; (2) avoid unnecessary intraoperative blood product administration – packed RBC, FFP, cryoprecipitate transfusion, platelet, hydroxyethyl starch, crystalloid, albumin; (3) minimise unnecessary intraoperative blood loss; (4) intraoperative anaesthesia – avoid high dose of dexmedetomidine, opioids, and propofol; avoid unnecessary general anaesthesia, and increased duration of anaesthesia; (5) avoid intraoperative hypotension; (6) minimise duration of postoperative mechanical ventilation; (7) postoperative labs – creatinine, haemoglobin; and (8) adopt ERAS to minimise duration of stay – hospital and ICU stay.

Quantitative assessment of results revealed potential areas of focus for future research. The major risk factors involving POD were identified and are presented in Supplementary Table S2. Studies should aim to find clinical laboratory cut-off values with sensitivity and specificity analyses for assessing the variables that affect POD in order to facilitate their pooled statistical analysis. The authors suggest reporting POD as a scale (i.e. 1 to 5) to determine the extent of POD for weighted statistical analysis for greater comparability between POD and its risk factors. Several independent studies have found that increased age, sex, ASA physical status score >2, CCI $\geq$2, and MMSE all pose statistically significant risks for developing POD.

A checklist of risk factors (Table 3) that was used to assess the risk of delirium in patients undergoing surgical procedures was developed according to the study's results. Solely 16 risk factors among the 165 studies were selected for the checklist. This list of variables is intended to serve as a point of reference for future research to focus on. The identified risk factors represent the most repeatedly observed variables which were found to be statistically significant in multivariate analyses, measured with a standardised methodology, referenced clearly, and variables that could not be included in the meta-analyses but nonetheless were clinically significant in assessing the risk of POD.

In conclusion, this systematic review reports preoperative, intraoperative, and postoperative risk factors allowing effective recognition of patients at high-risk for postoperative delirium. Early recognition of these patients will allow better clinical care in order to minimise their risk of postoperative delirium. Analysis of literature revealed that inconsistent methodological approaches existed. This, along with various other factors, including incongruent data reporting standards, make available literature challenging, confusing, and contradictory in certain aspects. The authors of this study believe that being methodologically consistent is a priority and should become a standard in future studies. The design of future studies and clinical practice should be based on the current knowledge and experience.

Authors' contributions

Full access to all of the data in the study: BF
Integrity of the data: BF
Accuracy of the data analysis: BF
Acquisition, analysis, or interpretation of data: LM, AF, FB, SR, AF
Drafting of the manuscript: LM, AF, FB, SR, AF
Critical revision of the manuscript for important intellectual content: LM, AF, FB, SR, AF
All authors significantly contributed to the conception, design and analysis of the study. All authors gave final approval to the published version.

Acknowledgements

We thank Henrik Kehlet from the Department of Clinical Medicine in the University of Copenhagen for his valuable input.

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.05.032.

References

1. https://pubmed.ncbi.nlm.nih.gov/?term=postoperative+deliriumandsort=date (accessed June 23, 2022).
2. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology Evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol* 2017; **34**: 192–214
3. Falegnami A, Patriarca R, Costantino F, Di Gravio G, Bilotta F. Surveying work-as-done in post operative delirium risk factors collection and diagnosis monitoring. *Appl Ergon* 2021; **92**, 103347
4. Zhu C, Wang B, Yin J, et al. Risk factors for postoperative delirium after spinal surgery: a systematic review and meta-analysis. *Aging Clin Exp Res* 2020; **32**: 1417–34
5. Watt J, Tricco AC, Talbot-Hamon C, et al. Identifying older adults at risk of delirium following elective surgery: a systematic review and meta-analysis. *J Gen Intern Med* 2018; **33**: 500–9
6. Hermanides J, Qeva E, Preckel B, Bilotta F. Perioperative hyperglycaemia and neurocognitive outcome after surgery: a systematic review. *Minerva Anestesiol* 2018; **84**: 1178–88
7. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th Edn. Washington, DC: American Psychiatric Association; 2013. p. 596–601
8. Wells GA, Shea B, O'Connell D, et al. *The newcastle–ottawa scale (NOS) for assessing the quality of non-randomized studies in meta-analysis*. Ottawa: Ottawa Hospital Research; 2000
9. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64**: 383–94
10. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64**: 401–6
11. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011; **64**: 407–15
12. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. *J Clin Epidemiol* 2011; **64**: 1283–93
13. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence—inconsistency. *J Clin Epidemiol* 2011; **64**: 1294–302
14. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. *J Clin Epidemiol* 2011; **64**: 1303–10
15. Steyerberg EW, Calster BV. Redefining significance and reproducibility for medical research: a plea for higher P-value thresholds for diagnostic and prognostic models. *Eur J Clin Invest* 2020; **50**, e13229
16. Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ* 1998; **316**: 989–91
17. Ljungqvist O, de Boer HD, Balfour A, et al. Opportunities and challenges for the next phase of enhanced recovery after surgery: a review. *JAMA Surg* 2021; **156**: 775–84 [published correction appears in JAMA Surg 2021; 156: 800]
18. McGuinnes L, Higgins J. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Syn Methods* 2020; **12**: 55–61
19. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* 2011; **64**: 1277–82
20. Kehlet H. Enhanced postoperative recovery: good from afar, but far from good? *Anaesthesia* 2020; **75**: e54–61
21. Awada HN, Luna IE, Kehlet H, Wede HR, Hoevsgaard SJ, Aasvang EK. Postoperative cognitive dysfunction is rare after fast-track hip- and knee arthroplasty – but potentially related to opioid use. *J Clin Anesth* 2019; **57**: 80–6

Handling Editor: Jonathan Hardman