JAMA Network Open

Original Investigation | Neurology

Perioperative Factors Associated With Postoperative Delirium in Patients Undergoing Noncardiac Surgery

An Individual Patient Data Meta-Analysis

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Abstract

IMPORTANCE Postoperative delirium (POD) is a common and serious complication after surgery. Various predisposing factors are associated with POD, but their magnitude and importance using an individual patient data (IPD) meta-analysis have not been assessed.

OBJECTIVE To identify perioperative factors associated with POD and assess their relative prognostic value among adults undergoing noncardiac surgery.

DATA SOURCES MEDLINE, EMBASE, and CINAHL from inception to May 2020.

STUDY SELECTION Studies were included that (1) enrolled adult patients undergoing noncardiac surgery, (2) assessed perioperative risk factors for POD, and (3) measured the incidence of delirium (measured using a validated approach). Data were analyzed in 2020.

DATA EXTRACTION AND SYNTHESIS Individual patient data were pooled from 21 studies and 1-stage meta-analysis was performed using multilevel mixed-effects logistic regression after a multivariable imputation via chained equations model to impute missing data.

MAIN OUTCOMES AND MEASURES The end point of interest was POD diagnosed up to 10 days after a procedure. A wide range of perioperative risk factors was considered as potentially associated with POD.

RESULTS A total of 192 studies met the eligibility criteria, and IPD were acquired from 21 studies that enrolled 8382 patients. Almost 1 in 5 patients developed POD (18%), and an increased risk of POD was associated with American Society of Anesthesiologists (ASA) status 4 (odds ratio [OR], 2.43; 95% CI, 1.42-4.14), older age (OR for 65-85 years, 2.67; 95% CI, 2.16-3.29; OR for >85 years, 6.24; 95% CI, 4.65-8.37), low body mass index (OR for body mass index <18.5, 2.25; 95% CI, 1.64-3.09), history of delirium (OR, 3.9; 95% CI, 2.69-5.66), preoperative cognitive impairment (OR, 3.99; 95% CI, 2.94-5.43), and preoperative C-reactive protein levels (OR for 5-10 mg/dL, 2.35; 95% CI, 1.59-3.50; OR for >10 mg/dL, 3.56; 95% CI, 2.46-5.17). Completing a college degree or higher was associated with a decreased likelihood of developing POD (OR 0.45; 95% CI, 0.28-0.72).

(continued)

Key Points

Question What factors are associated with postoperative delirium (POD) after noncardiac surgery?

Findings In this systematic review and meta-analysis of individual patient data from 21 studies that enrolled 8382 patients, male sex, older age, being underweight, lower educational level, smoking, history of delirium, living under care or being institutionalized, greater number of comorbidities, polypharmacy, higher preoperative C-reactive protein serum level, American Society of Anesthesiologists status III or IV, and longer duration of surgery/anesthesia were independently associated with delirium.

Meaning Results of this study suggest that the factors discussed may be used to explain the expected risk of developing POD and help clinicians to consider perioperative preventive strategies to optimize patient outcomes.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis of individual patient data, several important factors associated with POD were found that may help identify patients at high risk and may have utility in clinical practice to inform patients and caregivers about the expected risk of developing delirium after surgery. Future studies should explore strategies to reduce delirium after surgery.

JAMA Network Open. 2023;6(10):e2337239. doi:10.1001/jamanetworkopen.2023.37239

Introduction

Delirium is a neuropsychiatric syndrome characterized by acute and fluctuating impairment in attention, memory, perception, and consciousness. Postoperative delirium (POD) affects up to 50% of hospitalized surgical patients and is associated with increased morbidity and mortality,[1,2] postoperative cognitive decline, poor functional recovery, prolonged hospitalization, higher rates of hospital readmission, and increased health care resource expenditures.[3-5] Prevention and treatment of POD may be achievable through pharmacological, psychological, and nonpharmacological interventions.[6]

It is essential to identify patients at risk for POD because adequate and well-timed interventions may reduce POD and its associated complications.[6,7] Several systematic reviews and meta-analyses have explored factors associated with POD, often with conflicting results.[8-17] Furthermore, meta-analysis of aggregate data to identify factors have important limitations, some of which can be addressed by individual patient data (IPD) meta-analysis.[18,19] The advantages of using IPD for meta-analyses of factors include standardizing statistical analyses across included studies, improved statistical modeling, reduced risk of overfitting, and the ability to investigate more complex associations and interactions.[20,21] We performed a systematic review of clinical studies and conducted an IPD meta-analysis to identify factors associated with POD after noncardiac surgery, that addresses limitations of prior reviews.

Methods

We registered our protocol in PROSPERO, published a detailed protocol,[22] and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (PRISMA-IPD) guidance for reporting the results of this review.[23] The original protocol considered both cardiac and noncardiac surgical procedures. We made the post hoc decision to separate these procedures because of major differences in factors and the risk of delirium after surgery.[24]

Information Sources

We performed systematic searches of MEDLINE, EMBASE, and CINAHL from inception to May 2020, and reviewed the gray literature using Google Scholar. We screened reference lists of included studies and relevant reviews to find additional studies that met our inclusion criteria. An experienced librarian refined the searches for individual databases. Our search strategy is available in our published protocol.[22]

Study Selection

Details of our eligibility criteria and study selection process are provided in our published protocol.[22] In brief, we included studies that (1) enrolled adults (>16 years) undergoing noncardiac surgery, (2) assessed perioperative factors associated with delirium, and (3) assessed delirium (up to 10 days after surgery) using the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition), *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), or *Diagnostic and Statistical*

Manual of Mental Disorders (Fifth Edition) (collectively, *DSM*) criteria by a trained individual or a validated delirium assessment tool. We excluded studies conducted in the intensive care unit setting, and studies that addressed delirium tremens, emergence delirium, delirium that occurred outside of the context of surgery, and studies where delirium was not systematically assessed for at least 2 days post surgery. We also excluded studies of patients who had intracranial surgery, since these types of surgery can affect the pathophysiology of POD.[24,25]

Pairs of reviewers independently screened titles, abstracts, and full-text articles of records retrieved through the searches using standardized, pilot-tested forms in Covidence, an online systematic review software,[26] and a crowdsourcing platform.[27] Any disagreements between reviewers were resolved through discussion and, if necessary, involvement of a third reviewer.

Collection of Individual Patient Data

We emailed the corresponding author of each study eligible for our review to gauge interest in sharing IPD. We provided the study protocol and discussed the requirements for data sharing with those interested in collaboration. The data custodian/representative of each respective institution was invited to sign a data sharing agreement, which specified the data (variables) requested, obligations, and ownership of data. The ethics of obtaining data collected from multiple sources across international boundaries and different legal systems were considered as part of the data sharing agreement.

Encrypted data received from study authors was stored in password-protected files on a secure McMaster University computer and only accessed by 2 of us (B.S. and L.M.). Data files were inspected for missing data and unusual outliers via range check for all included variables, and all identified issues were discussed and resolved (if possible) with the original study investigators. We excluded data from patients with preoperative delirium, and patients for which their POD status was not available.

Outcome Definition and Factors

Our primary outcome was POD diagnosed up to 10 days after a procedure or until discharge, whichever was earlier. Included studies used different validated tools to diagnose POD (**Table 1**).[28-47] We included the diagnostic tool as an independent factor in our final analysis model, to account for the variability in sensitivity and specificity of different tools.

We considered a wide range of perioperative factors such as age, sex, level of education, body mass index (BMI), smoking status, alcohol consumption, number of preoperative medications and polypharmacy, surgical procedure and its duration, cognitive function, number of comorbidities, Charlson Comorbidity Index, American Society of Anesthesiologists (ASA) physical status classification, being institutionalized, history of delirium, and preoperative serum C-reactive protein (CRP) level.

Risk of Bias Assessment

Pairs of reviewers independently evaluated the reporting quality of included studies using the Quality In Prognosis Studies (QUIPS) tool.[48] We assessed the study risk of bias using 5 domains: (1) study participation, (2) study attrition (≥20% missing data was considered high risk of bias), (3) exposure measurement, (4) outcome measurement, and (5) study confounding. We used a modified QUIPS tool to rate each domain as low or high risk of bias as opposed to the original low, medium, and high risk of bias and used the individual domains, rated as low or high risk of bias, to inform the overall risk of bias in each study. Studies with 4 or 5 low-risk domains were considered at overall low risk of bias, studies with 3 or more high-risk domains were considered at overall high risk of bias, and studies with 3 low risk domains were considered at overall medium risk of bias.

Data Synthesis and Analysis

The methods of IPD meta-analysis in prognostic research are relatively new compared with those of randomized clinical trials.[20,49] We addressed 2 methodologic issues regarding the analysis for our review: (1) method of meta-analysis (1-stage or 2-stage) and (2) management of missing data, where data were missing for some but not all patients in a single study (within-study missingness) or where data were missing for a factor for all patients in a given study (between-study missingness).

In a 2-stage model, data are pooled from each study separately and then aggregated estimates are combined across studies using conventional meta-analytic models.[50,51] Using a 1-stage method, only 1 model is fitted to all studies in a hierarchical approach by adding a term to indicate which patient belongs to which study–to account for clustering of patients within studies. Evidence from simulation and empirical studies has shown both approaches produce similar results.[50,51] We therefore followed our a priori plan to run the 1-stage approach as described in our protocol.

The strategy to handle missing data within and between studies was based on the extent and mechanism of missingness. We performed multiple-variable imputation using chained equations (MICE) and assumed data were missing at random–ie, conditional on the observed data, the probability of missingness does not depend on the missing values themselves, but it might depend on the observed variables. MICE is a flexible and practical approach with no distributional assumptions and can accommodate imputation for categorical and binary variables.[52,53] We applied multiple imputations to the set of variables selected in our final prognostic model when missingness was less than 40%.[54] For each variable with missing data, an indicator variable that takes 0 when

Table 1. Description of Included Studies

Source	Country	Study design	POD diagnostic tool	Type of surgery	POD, %	Sample size
Vasilian et al,[28] 2018	Romania	Prospective cohort	CAM	Femoral fracture caused by unintentional fall	66.3	98
Andreozzi et al,[29] 2020	Italy	Case-control	CAM	TKA patients	8.3	206
McAlpine et al,[30] 2008	Canada	Prospective cohort	CAM & MMSE	Gynecologic malignant tumor	17.5	103
Honda et al,[31] 2018	Japan	Case-control	*DSM* criteria, or diagnosis by attending physician or nurse	Patients with gastric cancer	4.8	1057
Dworkin et al,[32] 2016	USA	Prospective cohort	CAM	Any elective surgery	13.2	115
Sato et al,[33] 2016	Japan	Prospective cohort	*DSM-V*	Urologic surgery	4.7	215
Martinez et al,[34] 2012	Chile	Randomized trial	CAM	Any elective surgery	9.4	287
Kim et al,[35] 2016	South Korea	Prospective cohort	Nu-DESC & CAM	Major general surgery	20.0	1114
Mosk et al,[36] 2018	Netherlands	Retrospective cohort	DOSS & *DSM-IV*	Elective colorectal surgery	13.2	251
Thomson Mangnall et al,[37] 2011	Australia	Prospective cohort	CAM	Major elective colorectal .surgery	34.8	118
Van Grootven et al,[38] 2016	Belgium	Prospective cohort	CAM	Hip fracture undergoing surgery	43.3	164
Hight et al,[39] 2018	New Zealand	Prospective cohort	CAM-ICU	Any elective surgery	14.4	229
Sampson et al,[40] 2007	United Kingdom	Randomized trial	DSI	Elective total hip replacement	21.2	33
Dezube et al,[41] 2020	USA	Retrospective cohort	*DSM* criteria	Elective esophagectomy	16.9	378
Chuan et al,[42] 2020	Australia	before-after longitudinal]	3D-CAM	Isolated primary hip fracture	27.4	300
Watne et al,[43] 2014	Norway	Randomized trial	CAM	Hip fracture undergoing surgery	19.2	324
Visser et al,[44] 2015	Netherlands	Prospective cohort	DOSS	Vascular surgery	5.5	1294
Denhaerynck et al (unpublished)	Switzerland	Prospective cohort	DOSS	Any elective surgery	14.2	900
Brattinga et al,[45] 2022	Netherlands	Prospective cohort	DOSS	Any elective surgery	9.6	1019
Dhakharia et al,[46] 2017	India	Retrospective cohort	*DSM* criteria, or diagnosis by attending physician or nurse	Oncologic abdominal surgery	40.7	81
Zywiel et al,[47] 2015	Canada	Retrospective cohort	CAM	Hip fracture undergoing surgery	47.9	242

Abbreviations: CAM, Confusion Assessment Method; DOSS, Delirium Observational Screening Scale; DSI, Delirium Symptom Interview; *DSM*, *Diagnostic and Statistical Manual of Mental Disorders* (eligibility based on *DSM* versions II, IV, or V); MMSE, Mini Mental State Examination; Nu-DESC, Nursing Delirium Screening Scale; POD, postoperative delirium; TKA, total knee arthroplasty.

data were available and 1 when missing data were created. We explored associations between the indicator variable and the rest of variables, as well as the outcome variable, to inform the mechanism of missingness. Variables associated with missingness and the outcome variable were included in the imputation model. Binary logistic, multinomial logistic, and linear regression models were used to impute missing data for binary, categorical, and continuous variables. Missing data were imputed 10 times resulting in 10 complete data sets. Each data set was analyzed separately, and results were combined using Rubin rules. Imputations were performed in Stata version 16.1 (StataCorp) using the *mi impute chained* command set.

We included all a priori factors in univariate analysis if (1) they were available in at least 3 studies, and (2) had less than 70% missingness. Both cutoff points were based on consensus among our group and previous IPD meta-analyses of prognostic studies and simulation studies.[55-58] For variables with a missing rate between 40% to 70%, missing category was generated and used for regression modeling. We used a backward stepwise approach for multivariable regression to establish a reduced model that best explained the data. We used a multilevel mixed-effects logistic regression to perform 1-stage IPD meta-analysis using *melogit* in Stata. The *mi predict* and *roctab* commands were used to assess model performance using the area under the receiver operating characteristic curve value. The probability of experiencing POD across studies was calculated using the constant value from the multilevel model without factors (ie, marginal probability). This estimate then was used as the baseline risk to calculate absolute risk estimates for all factors using the following formula: *baseline risk − [(odds ratio × baseline risk)/(1-baseline+(odds ratio × baseline risk))]*.[59] The 95% CI for risk differences were calculated using the same formula and by applying lower and upper bounds of odds ratios (ORs) to the baseline risk. A $P < .05$ was considered statistically significant for all analyses.

Results

Description of Included Studies

Our searches yielded 14 973 records, of which 192 full-text studies were judged as eligible. We were unable to identify contact information for authors of 17 studies. We contacted study authors of the remaining 175 studies and received IPD data from authors of 21 studies (8528 patients) comprising 20 publications[28-47] and 1 unpublished study by K.D. et al. We excluded 146 patients for whom their POD status was not available, leaving 8382 patients for analyses (**Figure**).

Most included studies were cohort studies (n = 15). Study populations were acquired from 15 countries, including Europe (9 studies [43%]), Asia (4 studies [19%]), North America (4 studies [19%), Australia and New Zealand (3 studies [14%]), and 1 study (5%) from South America. The Confusion Assessment Method (CAM) and CAM-ICU (intensive care unit) were the most frequently used diagnostic tools for POD assessment (12 studies [57%]), followed by the Delirium Observation Screening Scale (DOSS) (4 studies [19%]), and *DSM* criteria (4 studies [19%]) (Table 1).

Most patients underwent elective procedures (85%), including abdominal surgery (35%), orthopedic surgery (26%), and vascular surgery (17%). The median duration of surgery across studies was 203 minutes (interquartile range [IQR], 122-292 minutes). Approximately half (58%) of patients were male and the median age was 71 years (IQR, 63-78 years); only 8% of patients were 85 years of age or older. The characteristics of included patients are described in **Table 2**. eFigure in Supplement 1 provides the risk of bias assessments among the included studies.

Univariate Multilevel Mixed Model

The probability of experiencing POD across studies was 17.7%, calculated from an intercept-only model with an intraclass correlation coefficient of 0.21 (95% CI, 0.13-0.34). The results of univariate analyses without imputation (complete case analysis) and after performing MICE imputation were similar to estimates for factors. Older age, being underweight (BMI [calculated as weight in kilograms divided by height in meters squared] <18.5), male sex, less educated, being institutionalized,

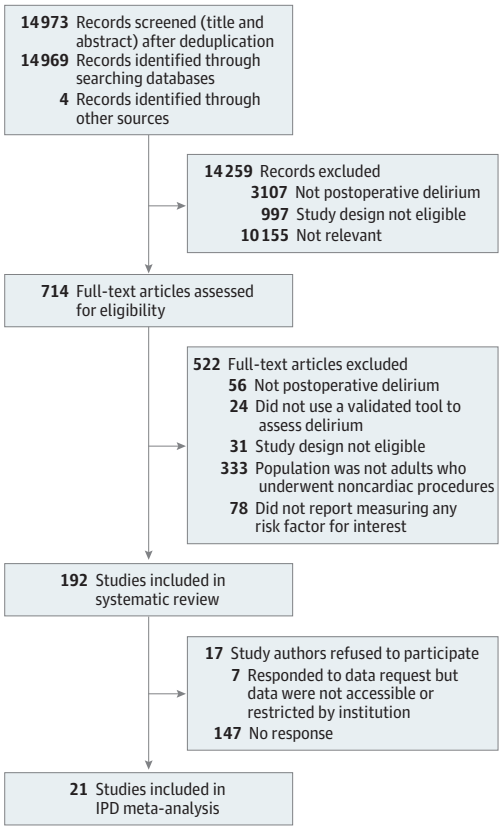
preoperative cognitive impairment, being prescribed 5 or more medications, having a history of delirium, elevated preoperative serum CRP level, type of surgical procedure, higher ASA status, longer duration of surgery/anesthesia, and having more comorbidities as well as a higher Charlson Comorbidity Index were associated with greater risk of developing POD. The results of univariate multilevel mixed-effects logistic regression are provided in **Table 3**.

Multivariable Multilevel Mixed-Effects Model With MICE

In our final adjusted model, factors that had a statistically significant association with POD were male sex (OR, 1.28; 95% CI, 1.08-1.50), older age (OR for age 65-85 years, 2.67; 95% CI, 2.16-3.29, OR for age older than 85 years: 6.24; 95% CI, 4.65-8.37), being underweight (BMI <18.5) (OR, 2.25; 95% CI, 1.64-3.09), less education (OR for having a diploma [at least 12 years of education], 0.71; 95% CI, 0.51-0.99, OR for having a college degree or more [>12 years of education], 0.45; 95% CI, 0.28-0.72), being a smoker (OR, 1.37; 95% CI, 1.09-1.72), having a history of delirium (OR, 3.90; 95% CI, 2.69-5.66), being institutionalized (OR, 1.54; 95% CI, 1.07-2.23), comorbidities (OR for 1 comorbid condition, 1.34; 95% CI, 1.02-1.76, OR for 2 comorbid conditions, 1.37; 95% CI, 1.02-1.83, OR for 3 comorbid conditions: 1.61; 95% CI, 1.16-2.23, OR for 4 or more comorbid conditions, 1.86; 95% CI, 1.28-2.71), receiving 5 or more medications (OR, 1.83; 95% CI, 1.47-2.29), having a higher Charlson Comorbidity Index (OR for 1-unit increase, 1.09; 95% CI, 1.01-1.18), higher preoperative serum CRP level (OR for 1-5 mg/dL, 1.74; 95% CI, 1.29-2.34, OR for 5-10 mg/dL: 2.35; 95% CI, 1.59-3.50, OR for >10 mg/dL, 3.56; 95% CI, 2.46-5.17), ASA status of 3 (OR, 1.76; 95% CI, 1.05-2.95), ASA status of 4 (OR, 2.43; 95% CI, 1.42-4.14), and longer duration of surgery/anesthesia (OR for each 1 hour increase, 1.11; 95% CI, 1.05-1.17).

Table 3 shows the factors independently associated with POD from the multivariable multilevel mixed-effects model. The model performance assessed using the area under the receiver operating

Figure. Flow Diagram for Study Selection



IPD indicates individual patient data.

characteristic curve was 0.81 (95% CI, 0.79-0.82), indicating a good prognostic model; however, we did not perform any statistical validation or evaluated the calibration curve. We did not find any significant interaction between the independent factors. eTable in Supplement 1 provides the results of sensitivity analysis excluding Dhakharia et al,[46] (at high risk of bias), which showed no important differences in results.

Table 2. Characteristics of 8382 Included Patients

Preoperative factor	Patients, No. (%)		Total patients, No.
	No delirium	With delirium	
Postoperative delirium diagnosis method			
DSM & *ICD-10*	48 (59.3)	33 (40.7)	81
CAM	1493 (74.2)	518 (25.8)	2011
DSI	26 (78.8)	7 (21.2)	33
CAM & Nu-DESC	902 (81.0)	211 (19.0)	1113
CAM & MMSE	85 (82.5)	18 (17.5)	103
DOSS & *DSM-IV*	218 (86.8)	33 (13.1)	251
DOSS	2852 (90.8)	288 (9.2)	3140
DSM criteria	1525 (92.4)	125 (7.6)	1650
Surgical procedure type			
Orthopedic	1672 (75.7)	536 (24.3)	2208
Liver	92 (80.7)	22 (19.3)	114
Thoracic	317 (82.1)	69 (17.9)	386
Abdominal	2573 (87.7)	362 (12.3)	2935
Gynecologic	263 (89.2)	32 (10.9)	295
Vascular	1318 (91.7)	120 (8.3)	1438
Laparoscopic	389 (92.0)	34 (8.0)	423
Other	525 (90.1)	58 (10.0)	583
Procedure type			7791
Elective	5857 (88.7)	750 (11.4)	6607
Emergency	635 (76.7)	193 (23.3)	828
Urgent	206 (57.9)	150 (42.1)	356
Sex			7264
Female	2557 (83.0)	525 (17.0)	3082
Male	3620 (86.6)	562 (13.4)	4182
Age, median (IQR), y	70 (62-77)	78 (71-85)	8232
≤65 y	2481 (94.0)	158 (6.0)	2639
65-85 y	4137 (84.0)	787 (16.0)	4924
>85 y	407 (60.8)	262 (39.2)	669
BMI, median (IQR)	25.0 (22.3-28.0)	24.4 (21.2-27.8)	7378
<25	3155 (85.3)	544 (14.7)	3699
25-30	2173 (87.6)	307 (12.4)	2480
>30-35	768 (87.8)	107 (12.2)	875
>35	282 (87.0)	42 (13.0)	324
Smoking status			4064
Nonsmoker	1828 (83.9)	351 (16.1)	2179
Ex-smoker	694 (89.9)	78 (10.1)	772
Smoker	945 (84.9)	168 (15.1)	1113
Operation time, median (IQR), minutes	209 (133-293)	148 (71-264)	3578
ASA physical status			5567
1	329 (92.9)	25 (7.1)	354
2	2352 (89.9)	263 (10.1)	2615
3	1912 (79.8)	483 (20.2)	2395
4	124 (61.1)	79 (38.9)	203

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAM, Confusion Assessment Method; DOSS, Delirium Observation Screening Scale; DSI, Delirium Symptom Interview; *DSM*, *Diagnostic and Statistical Manual of Mental Disorders* (eligibility based on *DSM* versions II, IV, or V); *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision;* MMSE, Mini Mental State Examination; Nu-DESC, Nursing Delirium Screening Scale.

Table 3. Estimated Associations for Factors of Postoperative Delirium From Univariate and Multivariable Multilevel Mixed-Effects Logistic Regression With and Without MICE Imputation

Variable[a]	Unadjusted without imputation		Unadjusted with MICE		Adjusted with MICE		Risk difference, % (95% CI)
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
Procedure or surgery (n = 8382)							
Orthopedic	1 [Reference]		1 [Reference]		1 [Reference]		
Abdominal	0.61 (0.39 to 0.96)	.03	0.61 (0.39 to 0.96)	.03	1.08 (0.68 to 1.71)	.75	1.15 (−4.94 to 9.19)
Vascular	0.58 (0.36 to 0.92)	.02	0.58 (0.36 to 0.92)	.02	0.71 (0.44 to 1.15)	.16	−4.45 (−9.06 to 2.13)
Laparoscopic	0.36 (0.19 to 0.68)	.002	0.36 (0.19 to 0.68)	.002	0.64 (0.33 to 1.26)	.20	−5.60 (−11.07 to 3.62)
Thoracic	1.50 (0.44 to 5.06)	.51	1.50 (0.44 to 5.06)	.51	3.21 (0.98 to 10.56)	.06	23.14 (−0.29 to 51.73)
Obstetrics and gynecology	0.34 (0.18 to 0.67)	.002	0.34 (0.18 to 0.67)	.002	0.66 (0.30 to 1.46)	.31	−5.27 (−11.64 to 6.2)
Liver	0.72 (0.37 to 1.37)	.31	0.72 (0.37 to 1.37)	.31	1.37 (0.68 to 2.78)	.38	5.06 (−4.94 to 19.72)
Other elective	0.46 (0.28 to 0.77)	.003	0.46 (0.28 to 0.77)	.003	0.65 (0.39 to 1.08)	<.99	−5.44 (−9.96 to 1.15)
Procedure type (n = 5567)							
Elective	1 [Reference]		1 [Reference]		NA	NA	NA
Urgent	1.61 (0.84 to 3.05)	.15	2.13 (1.06 to 4.26)	.04	NA	NA	NA
Emergency	2.76 (1.83 to 4.15)	<.001	1.88 (1.34 to 2.65)	<.001	NA	NA	NA
ASA status (n = 7791)							
1	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
2	1.86 (1.20 to 2.88)	.01	1.69 (1.04 to 2.73)	.03	1.09 (0.66 to 1.81)	.72	1.29 (−5.27 to 10.32)
3	4.42 (2.84 to 6.86)	<.001	3.77 (2.35 to 6.05)	<.001	1.76 (1.05 to 2.95)	.03	9.76 (0.72 to 21.12)
4	7.33 (4.24 to 12.66)	<.001	6.61 (3.75 to 11.64)	<.001	2.43 (1.42 to 4.14)	.001	16.62 (5.69 to 29.4)
Operation time, h (n = 3578)	1.09 (1.03 to 1.15)	.004	1.08 (1.02 to 1.14)	.01	1.11 (1.05 to 1.17)	.001	1.57 (0.72 to 2.4)
Sex (n = 7264)							
Female	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Male	1.24 (1.45 to 1.07)	.01	1.23 (1.43 to 1.05)	.01	1.28 (1.08 to 1.5)	.004	3.89 (1.15 to 6.69)
Age, y (n = 8232)							
≤65	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
66-85 y	3.36 (2.76 to 4.10)	<.001	3.31 (2.72 to 4.02)	<.001	2.67 (2.16 to 3.29)	<.001	18.78 (14.02 to 23.74)
>85 y	8.79 (6.70 to 11.52)	<.001	8.61 (6.57 to 11.28)	<.001	6.24 (4.65 to 8.37)	<.001	39.60 (32.30 to 46.59)
BMI (n = 7378)							
Normal (18.5-25)	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Underweight (<18.5)	2.30 (1.73 to 3.06)	<.001	2.28 (1.73 to 3.01)	<.001	2.25 (1.64 to 3.09)	<.001	14.91 (8.37 to 22.22)
Preobesity (25-30)	0.92 (0.78 to 1.09)	.33	0.91 (0.77 to 1.08)	.29	0.91 (0.75 to 1.09)	.30	−1.33 (−3.81 to 1.29)
Obesity class I (>30-35)	0.92 (0.72 to 1.17)	.50	0.9 (0.71 to 1.14)	.36	0.85 (0.65 to 1.11)	.24	−2.24 (−5.44 to 1.57)
Obesity class II (>35)	0.88 (0.61 to 1.26)	.49	0.84 (0.6 to 1.19)	.33	0.77 (0.53 to 1.12)	.17	−3.49 (−7.47 to 1.71)
Educational level (n = 1773)							
Less than diploma (<12 y)	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Diploma (12 y)	0.62 (0.46 to 0.83)	.001	0.62 (0.46 to 0.83)	.002	0.71 (0.51 to 0.99)	.04	−4.45 (−7.82 to −0.15)
College degree or more (>12 y)	0.37 (0.24 to 0.58)	<.001	0.39 (0.26 to 0.60)	<.001	0.45 (0.28 to 0.72)	.001	−8.88 (−12.02 to −4.29)
Smoking (n = 4064)							
Nonsmoker	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Ex-smoker	0.96 (0.72 to 1.30)	.81	1.01 (0.75 to 1.36)	.93	0.88 (0.63 to 1.21)	.43	−1.79 (−5.77 to 2.95)
Smoker	1.20 (0.97 to 1.48)	.09	1.21 (0.98 to 1.50)	.07	1.37 (1.09 to 1.72)	.01	5.06 (1.29 to 9.3)
Alcohol consumption (n = 3793)							
None	1 [Reference]		1 [Reference]		NA	NA	NA
Any use	0.98 (0.80 to 1.20)	.85	0.97 (0.80 to 1.19)	.80	NA	NA	NA
Institutionalized (n = 3359)							
No	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Yes	2.86 (2.03 to 4.02)	<.001	2.83 (2.01 to 3.98)	<.001	1.54 (1.07 to 2.23)	.02	7.18 (1.01 to 14.71)
History of delirium (n = 3356)							
No	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Yes	5.95 (4.28 to 8.27)	<.001	6.34 (4.56 to 8.82)	<.001	3.9 (2.69 to 5.66)	<.001	27.92 (18.95 to 37.2)

(continued)

Table 3. Estimated Associations for Factors of Postoperative Delirium From Univariate and Multivariable Multilevel Mixed-Effects Logistic Regression With and Without MICE Imputation (continued)

Variable[a]	Unadjusted without imputation		Unadjusted with MICE		Adjusted with MICE		Risk difference, % (95% CI)
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	
Preoperative cognitive impairment (n = 4312)							
No	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
Yes	5.55 (4.20 to 7.34)	<.001	5.74 (4.34 to 7.60)	<.001	3.99 (2.94 to 5.43)	<.001	28.48 (21.04 to 36.17)
Preoperative CRP serum level (n = 4150)							
<1 mg/dL	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
1-5 mg/dL	2.09 (1.58 to 2.76)	<.001	2.04 (1.54 to 2.69)	<.001	1.74 (1.29 to 2.34)	<.001	9.53 (4.02 to 15.78)
>5-10 mg/dL	2.77 (1.91 to 4.02)	<.001	2.67 (1.85 to 3.85)	<.001	2.35 (1.59 to 3.5)	<.001	15.87 (7.78 to 25.25)
>10 mg/dL	5.05 (3.58 to 7.12)	<.001	4.69 (3.35 to 6.56)	<.001	3.56 (2.46 to 5.17)	<.001	25.66 (16.9 to 34.95)
No. of preoperative comorbidities (n = 8102)							
None	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
1	1.89 (1.32 to 2.46)	<.001	1.88 (1.46 to 2.42)	<.001	1.34 (1.02 to 1.76)	.03	4.67 (0.29 to 9.76)
2	2.33 (1.57 to 3.09)	<.001	2.30 (1.77 to 2.98)	<.001	1.37 (1.02 to 1.83)	.04	5.06 (0.29 to 10.54)
3	3.38 (2.13 to 4.63)	<.001	3.35 (2.54 to 4.43)	<.001	1.61 (1.16 to 2.23)	.01	8.02 (2.27 to 14.71)
≥4	4.89 (2.99 to 6.79)	<.001	4.81 (3.59 to 6.46)	<.001	1.86 (1.28 to 2.71)	.001	10.87 (3.89 to 19.12)
Polypharmacy (preoperative) (n = 3158)							
<5 Medications	1 [Reference]		1 [Reference]		1 [Reference]	NA	NA
≥5 Medications	2.69 (2.21 to 3.28)	<.001	2.68 (2.20 to 3.26)	<.001	1.83 (1.47 to 2.29)	<.001	10.54 (6.32 to 15.3)
Charlson Comorbidity Index (not adjusted for age) (n = 8232)	1.27 (1.20 to 1.34)	<.001	1.27 (1.19 to 1.34)	<.001	1.09 (1.01 to 1.18)	.03	1.29 (0.15 to 2.54)

Abbreviations: ASA: American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; MICE, multiple-variable imputation using chained equations; NA, not applicable.

SI conversion factor: To convert CRP to nanomoles per liter, multiply by 9.524.

[a] Sample size for the unadjusted model without imputation. The final model is adjusted for delirium diagnostic tool. We used a backward stepwise approach for multivariable regression to find a reduced model that best explained the data. Model performance: area under the receiver operating characteristic curve = 0.81 (95% CI, 0.79-0.82).

Discussion

To our knowledge, this is the first IPD meta-analysis of factors associated with POD after noncardiac surgery. In pooled analysis of 8382 patients from 21 studies, we found that patients older than 65 years were at high risk of developing POD with the risk in patients older than 85 years being 6.2 times higher than those younger than 65 years old. Preoperative cognitive impairment and history of delirium were associated with nearly 4 times greater risk of experiencing delirium after surgery. Every hour increase in duration of surgery was associated with up to 11% greater risk of POD. In addition, having a low BMI (<18.5), with more comorbidities, a higher ASA status, and higher CRP serum level considerably increased the associated risk of POD. Other independent risk factors for POD included receiving more medications, smoking, being institutionalized, and being a male, while having higher level of education was associated with up to 55% lower risk of POD.

While there are several reviews on risk factors of POD, almost all focus on specific surgical procedure.[9-16] There are 3 systematic reviews that investigated factors associated with POD after elective surgical procedures.[8,17,60] All reviews combined cardiac and noncardiac surgical procedures and reported a nearly similar POD incidence rate to our finding. Watt et al[60] reported history of delirium, frailty, cognitive impairment, psychotropic medication use, smoking, older age, and ASA status as important factors. Abate et al[17] and Liu et al[8] only assessed the association of a limited risk factors with POD and reported type of anesthesia, hypotension, alcohol consumption, CRP, and interleukin 6 as important factors. We did not have enough information to assess the prognostic value of interleukin 6 and our findings showed alcohol consumption was not associated with an increased risk of POD.

We only included studies and data in which POD was assessed systematically using a validated tool. We also adjusted our model for different diagnostic tools used across the included studies. The performance of our final model was high (area under the receiver operating characteristic curve = 0.81), which attests to the robustness of the adjusted model. We did not formally assess the model validity or evaluate the calibration curve in the current report; however, we report details of the prediction model development process and the associated results in a separate publication.[61] We used advanced statistical modeling to handle missing participant data when appropriate.

Implication for Practice and Future Research

Given the high rates of POD among different noncardiac surgical procedures, extenuating strategies are required by different stakeholders for effective prevention and management of POD. Adequate preoperative evaluation and preparation of patients, caregivers, and physicians to appropriately manage treatment for patients at high risk, and create awareness toward modifiable risk factors, can be important steps toward mitigating the risk of POD. Developing bedside tools to help identify patients at risk and target modifiable risk factors in patient at higher risk of POD can improve patient care, reduce delirium-associated hospital costs, and help with defining appropriate populations to perform multicenter trials of interventions.

Limitations

The main limitation was low response rate to our requests for sharing IPD, and many investigators declined to participate in our study. The start of the project coincided with the COVID-19 pandemic, and requests were sent while many critical care physicians were dealing with the first peak of the pandemic and many nonclinician researchers were in lockdown with no access to their study data. The second limitation is the high rate of between-study missingness and that we were unable to study several important clinical variables (such as opioid use, pain, type of anesthesia and drugs used to induce anesthesia, and use of psychoactive drugs and benzodiazepines) because of inconsistencies or absence among the included studies. We used a flexible and practical approach with no distributional assumption to handle imputations under the missing at random assumption and only applied it to variables with less than 40% missingness.

The third limitation relates to the inherent limitation of multiple logistic regression modeling. We needed to dichotomize or categorize some characteristics because they did not meet the distributional requisites. Despite using postestimations and predictive margins, it is possible that the choice of thresholds may have affected the results in a way that cannot be predicted. Finally, while we managed to include a number of risk factors in our model, because of the nature of observational studies residual confounding cannot be ruled out.

Conclusions

We found that sex, age, BMI, education, smoking, history of delirium, being institutionalized, having comorbidities, polypharmacy, serum CRP level, ASA status, and duration of surgery/anesthesia were independently associated with POD. These factors can be used in clinical practice to inform patients and caregivers about the expected risk of developing delirium after surgery and to explain which features should prompt clinicians to consider perioperative preventive strategies to optimize patient care.

ARTICLE INFORMATION

Accepted for Publication: August 21, 2023.

Published: October 11, 2023. doi:10.1001/jamanetworkopen.2023.37239

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Obtained funding: Sadeghirad, Dodsworth, Schmutz Gelsomino.

Administrative, technical, or material support: Dodsworth, Goettel, Buchan, Crandon, Pol, Brattinga, Terashima, Van Leeuwen, Neerland, Martinez, Hatakeyama, Milisen, van der Laan, Thomson Mangnall, Denhaerynck, Sampson, Zywiel, Nguyen, Moss, Krewulak.

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Conflict of Interest Disclosures: Dr Sadeghirad reported receiving partial funding by PIPRA-AG. during the conduct of the study. Dr Dodsworth reported receiving grants from EIT Health during the conduct of the study; and BTD is a founder, shareholder and employee of PIPRA AG (Zurich, Switzerland). Dr Schmutz Gelsomino reported receiving grants from EIT Health during the conduct of the study and being a founder, shareholder, and employee of PIPRA AG (Zürich, Switzerland). Dr Goettel reported receiving personal fees from PIPRA AG during the conduct of the study. Dr Spence reported receiving grants from AOP Global Health, personal fees from Trimedic Pharmaceuticals, and personal fees from PhaseBio outside the submitted work. Dr Chuan reported receiving grants from ANZCA Research grant, personal fees from GE Healthcare Speaker fees, and grants from MRFF Research grant outside the submitted work; in addition, Dr Chuan reported receiving royalties from Oxford University Press for *Regional Anaesthesia: A Pocket Guide*. Dr Goodlin reported that data acquisition was conducted while he was an employee of the Veterans Affairs Medical Center and with funds for a research associate provided by the Veterans Affairs. Dr Zywiel reported receiving personal fees from DePuy Synthes outside the submitted work. Dr Busse reported receiving support, in part, by a Canadian Institutes of Health Research Canada Research Chair in the prevention and management of chronic pain. Dr Mbuagbaw reported receiving grants from PIPRA during the conduct of the study. No other disclosures were reported.

Funding/Support: This work is partially funded by PIPRA-AG.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We would like to thank Darren Hight, MD, and Jessica McAlpine, MD, for providing their original study data. We also thank Katie O'Hearn, MSc, and James (Dayre) McNally, MD, PhD, for their support through insightScope platform and Rachel Couban, MA, MISt, for development of search strategies.

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SUPPLEMENT 1.

eTable. The Estimated Associations for Prognostic Factors of Post-Operative Delirium From Multivariable Multilevel Mixed-Effects Logistic Regression With MICE Imputation From Sensitivity Analysis Excluding High Risk of Bias Study

eFigure. Risk of Bias Assessments Among the Included Studies Using QUIPS Tool

eReferences

SUPPLEMENT 2.

Data Sharing Statement