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Postoperative Delirium: A Review of Risk Factors and Tools of Prediction

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Abstract Over one-third of the surgeries in the United States are performed on patients aged 65 and older, and delirium is one of the most common postoperative complications in this population. Postoperative delirium is a heterogeneous disorder, and as such it is not surprising that the reported predisposing and precipitating factors are widely variable. Knowledge of the risk factors that predict postoperative delirium will aid in early identification of patients at highest risk in order to allow targeted use of resources including geriatric consults, specialized units, and nonpharmacologic interventions.

Keywords Postoperative delirium · Elderly · Risk factors · Predictors

Introduction

Postoperative delirium (POD) is a pervasive complication in elderly surgical patients that is associated with increased morbidity and mortality. Depending on the patient population, type of operation, and diagnostic criteria used, the incidence of POD ranges widely from 10 to 70 %, with higher incidences tending to occur in the oldest patients and following hip fracture repair, cardiac, vascular, or emergency surgery [1–4]. POD has been associated with increased length of hospitalization, duration of time in an intensive care unit, risk of comorbid conditions including cognitive impairment and functional decline, and 6–12 month mortality rate [5–8, 9•].

Delirium is diagnosed using objective tools. There are several validated tools in use for the diagnosis and grading of delirium, including the Confusion Assessment Method (CAM), CAM-ICU, Delirium Detection Score (DDS), and the Nursing Delirium Screening Scale (Nu-DESC). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines delirium as a disturbance in attention, awareness, and cognition that develops over a short period of time and must fluctuate in severity. The DSM-5 notes that there is generally evidence that the disturbance is a direct physiological consequence of a medical condition, substance intoxication or withdrawal, exposure to a toxin, or due to multiple etiologies, but cannot be better explained by another neurocognitive disorder or a severely reduced level of arousal [10]. Delirium can have several forms, including hypoactive, hyperactive, or mixed. The hypoactive form is generally underdiagnosed since the patients tend to be in a passive state.

Identifying patients at highest risk of developing delirium is a necessary first step in order to facilitate prevention, early diagnosis, and treatment. Here we will review the recent literature on the predictors of postoperative delirium as they relate to the preoperative, operative, and postoperative periods. We will discuss efforts toward the development and validation of risk stratification models to predict those at highest risk for POD, and we will consider the use of perioperative biomarkers as predictors of POD.

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Preoperative Predictors of Delirium

The risk factors for delirium are often divided into precipitating versus predisposing factors. The precipitating factors can be thought of as the "insults" that occur throughout the perioperative course, and the predisposing factors are the patient's baseline vulnerabilities. Delirium is considered a geriatric syndrome; thus, there is no single factor that directly contributes to the condition, but rather, it is the result of a constellation of the baseline vulnerabilities and precipitating factors described below [11]. Originally described in elderly hospitalized patients, a predictive model for delirium was developed based on the number of precipitating and predisposing factors present [11].

An understanding of the predisposing risk factors for POD can facilitate preventive efforts beginning in the preoperative period. The most commonly cited factors include advanced age, baseline cognitive and functional impairment, and the presence of multiple medical comorbidities. Additionally, there does appear to be a gender bias in the risk of developing POD with multiple studies reporting that men are at increased risk. Patients with preoperative neuropsychiatric conditions including dementia, depression, prior history of POD, use of psychotropic medications, or a history alcohol abuse are more likely to have a perioperative course complicated by POD. Various comorbidities have been linked to the development of POD including heart failure, renal dysfunction, diabetes mellitus, and atrial fibrillation. Additional risk factors are described below. Traditionally, the study of deleterious postoperative neurocognitive outcomes has been separated into cardiac versus non-cardiac surgical populations due to concerns regarding the effect of cardiopulmonary bypass on cognitive function.

Cardiac Surgery

Delirium after cardiac surgery has been described since the 1950s [12]. Demographic variables associated with delirium after cardiac surgery include older age and male gender. Many different types of medical comorbidities have been associated with delirium including history of stroke, diabetes mellitus, atrial fibrillation, hypertension, renal dysfunction, anemia, gastritis, hypoalbuminemia, and heart failure [13–19]. In addition, vascular risk factors have been associated with the development of POD following cardiac surgery, including atherosclerosis [20], peripheral artery disease, cerebrovascular disease [21], carotid artery stenosis, and smoking [22]. Some classes of medications have been found to be deliriogenic when administered in the preoperative period. One study found that preoperative beta-blocker administration was associated with a lower incidence of POD whereas diuretic therapy was associated with an increased incidence [23]. Despite a common suggestion that the preoperative use of benzodiazepines may be associated with POD, there are no existing studies to support this theory.

Table 1 Preoperative predictors of postoperative delirium in non-cardiac surgery

Type of surgery	Preoperative risk factors	References
Abdominal, colorectal, liver	Age, male, ASA status 3–4, impaired mobility, low preoperative regional oxygen saturation, poor preoperative functional/nutritional status, hypoalbuminemia, alcohol abuse, preoperative renal replacement therapy, APACHE II score	[43–45, 48, 68, 99, 100]
Vascular	Age, preoperative cognitive impairment, depression, history of CVA or TIA, previous amputation, frailty, renal insufficiency, elevated CRP, high ASA status, number of pack years smoked, number of psychoactive medications, preoperative administration of beta-blockers	[32, 39, 101–103]
Gynecological	Age, number of prescription medications	[89]
Orthopedic	Age, male, OSA, low satisfaction of social support, history of psychiatric illness, decreased functional status, decreased verbal memory, attentional deficits, preoperative cognitive impairment, BMI <20, fracture occurring indoors, number of medical comorbidities, abnormal rapid screening cognitive test results	[34, 35•, 41, 46, 104–106]
Spine	Age, CNS disorder, diabetes mellitus, history of prior surgeries, anemia, hypertension, renal failure, coagulopathies, fluid/electrolyte disorders, hearing impairment, high-dose methylprednisolone, alcohol/drug abuse, depression, psychotic disorders, weight loss	[33, 66, 107]
Head & neck	Age, hypertension, cognitive impairment, MCV >95 femtoliters, not abstaining from alcohol for at least one continuous week in the preceding year, having ever been advised to cut back on alcohol	[42, 98]
Urological	Prior history of delirium, impairment in IADLs, poorer clock drawing test scores	[47]

ASA American Society of Anesthesiologists, *APACHE* Acute Physiologic and Health Evaluation, *CVA* cerebrovascular accident, *TIA* transient ischemic attack, *CRP* C-reactive protein, *OSA* obstructive sleep apnea, *BMI* body mass index, *CNS* central nervous system, *MCV* mean corpuscular volume, *IADL* instrumental activities of daily living

Patients who develop delirium tend to have preoperative markers of poor baseline cognitive function including low Mini-Mental State Examination (MMSE) scores, poor executive function (on preoperative neuropsychiatric battery), poor performance on a semantic fluency test, and subjective memory complaints [21, 24–27]. History of depression, use of psychoactive medications, alcohol use, and high preoperative pain scores [28] are associated with delirium after cardiac surgery. One study found that cardiac surgery patients with high levels of dispositional optimism, as a behavioral trait, had a significantly lower incidence of POD than patients who were less optimistic [29]. Other preoperative predictors of POD include abnormalities in the deep white matter and the thalamus [24] and low preoperative regional cerebral oxygen saturation [30].

Noncardiac Surgery

The literature on delirium after noncardiac surgery includes a wide range of surgeries, patient populations, and research methodologies. We have synthesized these studies to include general themes across studies; however, we emphasize that findings may not apply to all populations. Table 1 lists preoperative predictors of POD following noncardiac surgery organized by type of operation. Demographic factors commonly associated with POD in noncardiac surgery include advanced age and male gender.

Regardless of the tool used for measurement, (i.e., number of comorbidities, American Society of Anesthesiologists status, Acute Physiologic and Health Evaluation II, frailty score) sicker patients are at an increased risk for developing delirium postoperatively. Specific medical comorbidities associated with the development of POD include diabetes mellitus, renal insufficiency, congestive heart failure, obstructive sleep apnea, and hearing impairment. Vascular risk factors including tobacco exposure, history of cerebrovascular accident or transient ischemic attack, or previous amputation have been shown to increase the risk of delirium. Laboratory derangements associated with POD include anemia, coagulopathies, fluid/electrolyte disorders, or elevated C-reactive protein. One study suggested that a longer period of preoperative fluid fasting (>6 h) increases the risk of POD when compared to shorter periods of fluid fasting (2–6 h) [31]. Interestingly, a retrospective review found that while statin administration reduced the odds of POD, preoperative administration of beta-blockers increased the odds POD [32]. This conclusion is contradictory to the finding that preoperative beta-blocker therapy was protective in a cardiac surgery population, as mentioned above [23]. Another group identified high-dose methylprednisolone as a preoperative risk factor [33].

In addition to medical comorbidities, preoperative cognitive impairment, psychiatric illness, and poor functional and nutritional status predispose surgical patients to postoperative delirium. Deficits in executive function, attention [34], verbal memory [35•], or prior history of delirium are associated with the development of POD [36–38]. In addition to depression, the number of psychoactive medications [39], stress level, and quality of life are risk factors for developing POD [40]. Patients reporting low satisfaction with social support had an increased likelihood of developing POD [41]. Further, patients with low albumin levels, poor nutritional status, BMI <20, or history of alcohol abuse have an increased likelihood of developing delirium postoperatively [42–46]. Poor preoperative functional status [44, 45], impairment in instrumental activities of daily living [47], and impaired mobility have all been correlated with POD [48]. Few studies have explored the genetic factors that predispose patients to postoperative delirium. While some have found that the presence of the apolipoprotein E-e4 allele (ApoE4) increases the risk of POD [49, 50], other studies found no association between ApoE4 and delirium [51].

Intraoperative Predictors of Postoperative Delirium

While an understanding of the preoperative or predisposing predictors for POD can alert care team members to patients with an inherent risk, identifying the precipitating intraoperative and postoperative factors can change the approach to patient care. Irrespective of the type of surgery, the most consistently identified intraoperative predictors of POD include blood loss or transfusion as well as surgical duration, urgency, complexity, and invasiveness. Other factors that have been explored include certain classes or doses of medications, type of anesthetic, depth of anesthesia, and abnormal vital signs including blood pressure, temperature, and oxygen saturation.

Cardiac Surgery

Specific to cardiac surgery, intraoperative predictors of POD include increased duration of the surgery, aortic cross clamp time [23, 52], extracorporeal circulation time [26, 53], and the use of an intra-aortic balloon pump [13, 54]. Additionally, the risk of POD increases with increasing urgency [14, 15] and complexity of the cardiac operation [13]. For example, valve replacement procedures seem to be higher risk than coronary artery bypass grafting (CABG) [27, 55, 56]. Other intraoperative variables reported to increase the risk of POD include lower intraoperative body temperature [57], lower mean perfusion pressures during cardiopulmonary bypass [58], and the use of retrograde rather than antegrade arterial perfusion [59]. High variations of intraoperative oxygen partial pressures, high fluctuations of hematocrit levels, and blood product transfusion are associated with the development of POD [14]. In addition to transfusion [13, 60], hemofiltration [15] and increased volume load during cardiac surgery have also been reported to increase the risk for POD [17]. A new case–control study of cardiac surgery patients found no difference in the odds of patients developing POD if they were transfused red blood cells (RBC) with a storage age of >14 days when compared to patients transfused RBCs with a storage age of <14 days [61]. Whitlock and coauthors recently explored whether there was a difference in POD after cardiac or thoracic surgery between patients randomized to BIS-guided or end-tidal anesthetic concentration (ETAC)-guided anesthesia [62••]. The group reported a non-significant trend toward less delirium in the BIS-guided group. Others have found that larger cumulative amounts of fentanyl administered intraoperatively are associated with POD following cardiac surgery [52, 63].

Noncardiac Surgery

Intraoperative blood loss and/or blood product transfusion also predicts the development of POD following noncardiac surgery [64–69]. As is similarly reported in the cardiac surgery literature, increased surgical duration, urgency [70, 71], and complexity are risk factors for the development of POD following noncardiac surgery. In aortic aneurysm surgery, delirium occurs more commonly after open repair than after endovascular repair [71, 72]. At least two studies have indicated that intraoperative hypotension is a risk factor for POD. The first defined hypotension as a systolic blood pressure <90 mmHg requiring vasopressors or fluid resuscitation [47], and the second defined hypotension as a mean arterial pressure ≤60 mmHg or the prolonged use of a vasoactive substance [43].

Investigators have sought to determine whether there is an association between postoperative delirium and choice of anesthetic agent, technique, or depth. Interestingly, the choice of regional versus general anesthesia does not appear to affect the likelihood of delirium after surgery [73–75]. Recent investigations have focused on whether the depth of anesthesia plays a role. A single randomized controlled trial (RCT) compared the development of POD following hip fracture repair under spinal anesthesia combined with "light" versus "deep" propofol sedation [76••]. Despite a relatively small sample size ($n = 57$ participants/group), there was a significantly lower prevalence of POD in the light sedation group [76••]. Two other recent RCTs found that BIS-guided general anesthesia, when compared to routine care, significantly reduced the incidence of POD after noncardiac surgery [77•, 78•]. Though these two trials randomized patients to receive BIS-guided anesthesia versus routine care, neither study explored the role of assignment to specific anesthetic depths. Another area of interest is whether particular medications are more likely to cause postoperative delirium. A recent RCT comparing maintenance of anesthesia with sevoflurane or propofol found no difference in the incidence of delirium between the two groups [79]. Radtke and coauthors found the intraoperative use of fentanyl, as opposed to remifentanil, to be an independent predictive factor for POD [31].

Postoperative Predictors

Perhaps the least studied to date are the postoperative variables predisposing patients to delirium. The strongest predictors include postoperative admission to an intensive care unit (ICU), longer length of stay in the ICU, and increased duration of mechanical ventilation and intubation. Postoperative complications associated with the development of POD include postoperative infections, stroke, vascular events, and systemic inflammatory response syndrome (SIRS). Other contributors include the presence of invasive lines, use of physical restraints, sleep disruption, blood product transfusion, electrolyte derangements, postoperative pain, and the use of psychotropic medications.

Recent attention has been focused on the contributions of postoperative pain and analgesic medications in the development of POD. Just as the presence of a high level of preoperative pain is a predisposing factor, increased postoperative pain intensity is a precipitating factor for POD development [80–83]. Though increased pain is a risk factor, the method of pain control and choice of analgesic also have implications in POD. Continuous lumbar plexus or femoral nerve block significantly reduced the incidence of delirium when compared to PCA alone following either total hip [84] or total knee [85] arthroplasty. Similarly, fascia iliaca compartment block decreased the occurrence of delirium following hip surgery in patients considered intermediate risk for POD [86]. Patients using patient-controlled analgesia (PCA) are more likely to develop POD than those using oral opioids [80, 87], and morphine PCA carries an increased risk when compared to fentanyl PCA [88]. Others found that patients who received doses of opioids in addition to the standard PCA regimen were at an increased risk for POD [89]. When comparing analgesics for pain control, postoperative meperidine [90–92] and tramadol have been found to be associated with delirium postoperatively [48].

The use of sedative agents postoperatively may have implications in the risk for POD, either by virtue of properties of the medications themselves or by their effect on sleep time and quality. Postoperative sleep deprivation

Table 2 Tools to predict postoperative delirium

Type of tool/scale	Brief description	References
Prediction scale	32 variables determined by literature review	Harasawa and Mizuno [108]
Clinical prediction rule	Variables: Age, alcohol abuse, poor cognitive status, poor functional status, abnormal serum, potassium, or glucose, noncardiac thoracic surgery, aortic aneurysm surgery	Marcantonio et al. [109]
Informant Questionnaire on Cognitive Decline in the Elderly (short IQCODE)	Self-administered 16-item questionnaire asking informant about subject's cognitive performance over previous 10 years	Priner et al. [110]
Delirium Screening in Cardiac Surgery (DESCARD)	Variables: hypertension, elective/urgent nature of surgery, fasting glucose, diabetes treatment, age, weight, total protein concentration	Krzych et al. [111]
Delirium Elderly At-Risk (DEAR)	Variables: cognitive impairment, substance use, age, dependence in ADL, sensory impairment	Freter et al. [112]
Preoperative prediction rule	MMSE, Geriatric Depression Scale, prior stroke/TIA, abnormal albumin	Rudolph et al. [19]
Prediction model	Model based on 9 pre- and intraoperative somatic and psychiatric risk factors	Bohner et al. [67]
Delirium risk checklist	Variables: Euroscore, age, cognitive impairment, number of comorbidities, history of delirium, alcohol use, type of surgery	Koster et al. [113]
Prediction model	Clock-drawing scores and male gender	Fisher and Flowerdew [114]
Delirium predicting scale	Variables: use of multiple medications, scores on cognitive tests, albumin level, hematocrit level, age	Goldenberg et al. [115]
Medical risk factor model	Variables: Visual impairment, severe illness, cognitive impairment, dehydration	Kalisvaart et al. [70]

ADL activities of daily living, *MMSE* mini mental sate examination, *TIA* transient ischemic attack

itself is deliriogenic [93]. The use of benzodiazepines in the postoperative period has been reported to contribute to the genesis of delirium [87, 90, 94]. The use of dexmedetomidine for sedation in the ICU following cardiac surgery is associated with a significantly lower risk of delirium when compared to agents including benzodiazepines and propofol [95, 96].

Metabolic or electrolyte abnormalities increasing the risk for POD include markedly abnormal postoperative levels of sodium, potassium, glucose, or albumin. Low hemoglobin or hematocrit levels, bleeding, and transfusion of blood products in the postoperative period are precipitating factors for POD just as they are in the intraoperative period. Postsurgical delirium has also been associated with an increased stress response, and postoperative norepinephrine levels were recently found to be much higher in patients who developed POD [97]. Other postoperative predictors include low postoperative oxygen saturations [98] and high body temperatures [17]. Postoperative complications associated with development of delirium include infections, low output syndrome, cardiogenic shock, SIRS, and cerebrovascular events.

Tools to Predict Postoperative Delirium

There are well-validated clinical tools that are widely used to diagnose delirium such as the Confusion Assessment Method (CAM) or the CAM-ICU. Over the past two decades, scientists have worked to develop and validate screening tools or checklists that can be used to stratify patients at-risk for postoperative delirium. These screening tools are generally comprised of various combinations of the risk factors described above.(Table 2) Most of the tools are designed to be used in the preoperative arena, and thus only take predisposing variables into account. These tools are designed to assist with early identification of the patients at highest risk in order to facilitate preoperative optimization by managing comorbidities or employing targeted prevention strategies. Recently, some instruments have begun to incorporate intraoperative variables as well and are designed to help clinicians identify at-risk patients in the early postoperative period.

Conclusions

Postoperative delirium is a heterogeneous disorder, and as such it is not surprising that the reported predisposing and precipitating factors are widely variable. Though only some factors are amenable to amelioration, identification of high risk individuals will still allow targeted use of resources including geriatric consults, specialized units, and nonpharmacologic interventions. Nevertheless, identifying patients at highest risk will take a concerted, multidisciplinary effort by primary care providers, geriatricians, surgeons, and anesthesiologists. Because of the complications associated with POD, including increased functional decline, cognitive impairment, cost of care, and risk of mortality, it is of utmost importance to identify patients at highest risk preoperatively, and to minimize the precipitating factors throughout the perioperative period.

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Compliance with Ethics Guidelines

Conflict of Interest Katie J. Schenning and Stacie G. Deiner declare that they have no conflict of interest.

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