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An Update on Postoperative Cognitive Dysfunction

Tiffany L. Tsai, BA[*], **Laura P. Sands, PhD**[#], and **Jacqueline M. Leung, MD, MPH**[¶]
Department of Anesthesia & Perioperative Care, University of California, San Francisco, 94143-0648 (Tsai & Leung), and School of Nursing, Purdue University, West Lafayette, IN 47907-2069 (Sands)

Introduction

Postoperative cognitive dysfunction or decline (POCD) is increasingly recognized as a common phenomenon after major surgery. [1-4] Because older age is a strong preoperative risk factor of POCD,[2 5] the incidence of POCD is expected to increase as the population of older surgical patients grows. Improving the measurement of POCD and identifying its etiology is clinically important, as recent studies have associated POCD with impairments in daily functioning,[6] premature departure from the labor market,[7] and dependency on government economic assistance after hospital discharge.[7]

In this chapter, we will review the definitions of POCD and discuss current methodological issues in this growing area of research. We will also present relevant hypotheses on its pathophysiology and discuss the long-term significance of POCD.

Broadly speaking, POCD refers to problems in thinking and memory after surgery. POCD is not recognized yet in the International Classification of Diseases and is not listed as a diagnosis in the Diagnostic and Statistical Manual. The term POCD is used mostly in literature to represent a decline in a variety of neuropsychological domains including memory, executive functioning, and speed of processing. POCD has been defined in a consensus statement as "a spectrum of postoperative central nervous system (CNS) dysfunction both acute and persistent … including brain death, stroke, subtle neurologic signs and neuropsychological impairment." [8]

POCD should be distinguished from delirium or dementia. Delirium describes an acute confusional state featuring disturbances in attention and decreased awareness of the environment.[9,10] Delirium symptoms fluctuate during the course of the day, and the patient often is disoriented. In addition, hallucinations and inappropriate communication or behavior may be observed in the presence of delirium. In contrast, a typical patient with POCD is oriented but exhibits significant declines from his or her own baseline level of performance on one or more neuropsychological domains.[11-14] After surgery, changes in cognitive status may present in the form of a frank delirium or POCD, or both. POCD differs from dementia, which describes a chronic, often insidious, decline in cognitive

Corresponding Author: Jacqueline M. Leung, MD, MPH.
[*]Research Associate
[#]Professor, School of Nursing
[¶]Professor of Anesthesia & Perioperative Care

function. Alzheimer's disease remains the most common form of dementia, but there is considerable overlap in neurodegenerative disease.

Selection of neurocognitive tests to measure POCD

Most studies of POCD have focused on describing changes in brain functioning, and more specifically, have studied either performance-based or self-report perceptions of changes in memory, executive function, attention, learning, language, visual spatial skills, mathematics, motor function and anxiety or depression.[15] Selection of neurocognitive tests to document these cognitive changes varies extensively between studies.[15] This variability in choice of tests may be due to the absence of a clear, theoretically derived and empirically tested model which describes the causes and outcomes of cognitive changes associated with the surgical experience. Therefore, while a consensus-recommended battery of tests was established over 10 years ago,[8] it was not accompanied by this necessary model,[16] nor did it have an explanation of how the tests within the battery met the consensus definition of POCD. Without the adoption of such a model, it is difficult to conclude whether tools intended to detect POCD are, in fact, assessing the presence of POCD.

Since the consensus guidelines were published in 1995, diagnostic criteria for POCD have been suggested. One stated criterion specified that there must be significant changes in neuropsychological tests involving several of the following domains: learning and memory, attention, executive functioning and language.[17] Additional areas for assessment suggested by Deiner and Silverstein include declines in perception and abstract thinking.[18] Although these guidelines provide guidance for the selection of tools to assess for POCD, they were not accompanied with specific justification for the choice of cognitive domains that should be assessed when testing a patient for POCD. [16]

Recent reviews of POCD after cardiac 15 and noncardiac [19] surgery reveal that the two most commonly assessed cognitive domains assessed were 1) learning and memory and 2) attention and concentration. Of the studies included in these reviews, 97% of studies including patients undergoing cardiac surgery included a memory and learning test and 70% of studies including patients undergoing noncardiac surgery included a memory and learning test. Similarly, 94% of studies including patients undergoing cardiac surgery included an attention and concentration test and 57% of studies including patients undergoing noncardiac surgery included an attention and concentration test. About one-third of studies included tests of verbal and language skills and tests of visual and spatial skills. Still, fewer studies included tests of numerical reasoning (6% for both types of subjects) or executive function (14% for cardiac surgery and 6% for noncardiac surgery subjects.) Few studies reported the percent of subjects who experienced significant decline in performance after surgery for each cognitive test. Consequently, it is difficult to determine whether patterns of deficits in specific domains emerge across studies. One review concluded that declines in memory and attention and psychomotor function were consistently found after coronary artery bypass graft (CABG), but cautioned that the domains of POCD detected are likely to be a function of the tests used to assess POCD. [20] Increased reporting of results for individual tests would help inform the development of a conceptual framework that explains which domains of cognitive functioning are expected to be affected by different surgical experiences.

Many studies have used composite measures of cognitive functioning to assess patients for the presence of POCD. Nearly a third of studies of POCD in patients undergoing noncardiac surgery incorporated composite measures of functioning in their protocol. [19] The most commonly used composite measure was the Mini Mental State Examination (MMSE); it was included in 21% of reviewed studies. An important debate is whether composite

measures and composite scores should be used to detect POCD. Composite measures and composite scores do not differentiate which areas of neuropsychological functioning are affected by the surgical experience. Understanding specific areas of neuropsychological functioning involved in POCD would not only advance conceptual models of POCD, but would also help in specifying which self-care activities are likely to be affected by POCD. In contrast, Rasmussen and colleagues [21] suggest that the use of composite tests or scores is not problematic because the purpose of the postoperative neuropsychological testing is to detect the presence of general, rather than specific, changes in cognitive functioning.

Administration of neuropsychological tests

There are many procedural issues that should be considered when administering a neuropsychological protocol for the purpose of detecting POCD. 21،22 Those issues might be categorized into the following: test selection, test administration, and test scoring for the purpose of detection of POCD. Test selection should be guided by choosing tests that have validity for detecting change in functioning in those domains of expected to be negatively affected by the surgical experience. In addition, there are several practical issues that should be considered when choosing tests for the assessment of POCD. For example, it is important to choose tests with difficulty levels that do not result in floor effects (many subjects scoring the lowest score possible) or ceiling effects (many subjects scoring the highest score possible). [22] Tests that do not have floor or ceiling effects are likely to have greater sensitivity to detecting a change in functioning associated with surgery. Choosing tests with parallel versions reduces potential practice effects from remembering test stimuli from earlier administrations. This is particularly problematic for word-list learning tasks because some subjects are able to recall words from a prior administration of the task. The parallel versions should be administered in a different order between subjects (e.g. ordered according to a Latin-square design) to avoid a potential form by occasion bias in results. 23 Tests should be validated for the language in which they will be administered. For example, the difficulty of word list generation tasks that require the subject to list as many words as possible that begin with a specific letter varies depending on the letter specified. 24 Difficulty levels will vary across languages for the same letter.

Administration of tests used to detect POCD should be standardized across occasions and subjects. Consensus recommendations include that testing be conducted by “the same suitably qualified and trained individual and that the tests minimize subjectivity and be performed in a standardized manner.”[8] This recommendation is meant to reduce variance in subjects' tests scores that cannot be ascribed to the subjects' ability alone. Because preoperative performance may be negatively affected by surgery-associated anxiety, [22] it has been suggested that the administration of mood and anxiety scales with the neuropsychological tests would allow for statistical adjustment of cognitive test scores by subjects' mood state. [21]

Although a variety of scoring methods for the detection of POCD have been used across studies, investigators generally agree that scoring methods should consider 1) baseline performance, 2) practice effects, and 3) change on more than one neuropsychological test. [8,16,22,25] Baseline assessments allow determination of whether an actual change in cognitive functioning occurred subsequent to the surgical event. Nearly half of studies of POCD have been conducted in adults undergoing cardiac surgery, a population at risk for cognitive changes due to underlying heart or vessel disease. [26] Practice effects refer to improvement in performance due to familiarity with test procedures and can occur in patients with [27] and without existing cognitive impairment. [28] A common way of measuring practice effects is to measure the average improvement in performance for a group of matched controls. An important question is how well the matched controls truly match the surgical population to

which they are compared. For example, studies that provide comparisons between subjects and controls reveal that controls differ from subjects with fewer males,[5,29] lower depression levels,[5] and lower rates of co-morbidity [30] and lower attrition rates in the control group.[29]

Timing of Assessment for POCD

Another methodology issue in the study of POCD is that no general consensus has been established thus far regarding the optimum timing of assessments after surgery. In previous studies, cognitive function was measured beginning 1 day to as long as 5 years after surgery. POCD can be broadly divided into acute, intermediate and late or long-term changes based on information from previous studies. Specifically, acute POCD has been used to describe cognitive decline detected within one week after surgery, intermediate POCD for changes within 3 months, and long-term POCD for changes 1-2 years following surgery. However, the exact significance of detecting POCD at these various time points is unclear. The time interval at which a diagnosis of POCD holds the greatest clinical significance has not been determined, nor have any studies invalidated the importance of conducting assessments at a specific time point.

Early assessments of POCD likely capture a different phenomenon than what late assessments of POCD capture, and each are accompanied by a unique set of issues. Surgery-related factors may affect test performance in the immediate postoperative period, including acute pain,[31-33] the use of drugs,[23,34] nausea, limited mobility, and fatigue. Thus, it has been argued that patients should not be evaluated for POCD until at least one week postoperatively.[8,13,35] Recent evidence suggested this delay might be arbitrary, as negative outcomes are associated with POCD detected in the first week after surgery. In a 2008 study of patients undergoing noncardiac surgery, POCD detected at hospital discharge (mean duration of stay, <7 days) was associated with an increased risk of death within the first 3 months after surgery.[5] Restricting testing to only the later postoperative period is also problematic because many patients are already discharged within one week after surgery. In fact, recent data from the National Center for Health Statistics showed that the average lengths of stay for patients between the ages of 45 to 84 years are currently between 5.0 to 5.6 days.36 It has been reported that the average length of stay of patients over 50 years of age who underwent major noncardiac surgery with no postoperative complications was 4 days.37 In our study, 88% of those identified with POCD were discharged within a week of surgery.33 In addition, Rohan and colleagues reported that 47% of patients undergoing minor noncardiac surgery were found to have POCD before discharge. [38] These findings suggest that limiting screening for POCD to seven days *after* surgery could result in missed recognition of POCD in many surgical patients. In-hospital patient education usually includes detailed instructions for wound care, administration of new medications, symptom monitoring, and details of needed restrictions in daily activities. If post-surgical patients are experiencing POCD at the time of they are given self-care discharge instructions, their ability to understand and recall these instructions may be limited and may put them at risk for post-surgical complications.

The rate of patient attrition is noted to be lower in studies assessing for early than late POCD. Newman *et al.* [19] reported a 5.4% attrition rate for evaluations performed between 7 and 21 days after noncardiac surgery; 19% for evaluations between 22 days and 132 days; and 17% for evaluations beyond 6 months postoperatively. Patient attrition may be selective. In cohort studies, patients unavailable for follow up were more likely to be older patients who had worse baseline cognitive performance[39] or were sicker.[40] If patients experiencing cognitive decline are more likely to decline assessment, this selective attrition will bias study results toward the null, obscuring the detection of cognitive changes postoperatively.

POCD assessments that occur in the immediate postoperative period are important for elucidating the relationship between POCD and delirium. Because POCD and delirium both feature deficits in attention, whether they are related events on a continuum or distinct conditions remains unclear. In a retrospective analysis of the International Study for Postoperative Cognitive Dysfunction (ISPOCD) research data, patients with postoperative delirium had a higher incidence of POCD one week postoperatively.[39] The ISPOCD study was not initially designed to measure postoperative delirium as a primary outcome, so validated measures of delirium were not incorporated in the study protocol. It is not clear whether detection of delirium via chart reviews and the Mini Mental State Examination (MMSE) performance has similar sensitivity and specificity for detecting delirium as that of commonly used measures such as the Confusion Assessment Methods (CAM).10 Although the ISPOCD results seem to suggest that postoperative delirium and POCD appear to be discrete events, other research provides support to the continuum hypothesis, specifically, that POCD is a subclinical from of delirium. For example, Monk *et al.* found that patients who were delirious after major noncardiac surgery were also more likely to have POCD at hospital discharge. [5] Furthermore, areas of cognitive functioning that show decline in patients with POCD such as attention are common with criteria for detecting delirium. In a study of older orthopedic patients, Lowry *et al.* identified a group of patients with "sub syndrome delirium," defined as those not meeting the CAM criteria for delirium but showing a decline in global cognitive functioning as measured by the MMSE.[41] These patients exhibited greater declines in performance on attention tasks than did non-delirious patients within the first week after surgery. Because most cases of delirium occur in the early postoperative period, an improved understanding of the relationship between POCD and delirium will be derived from additional studies that perform neurocognitive testing and delirium assessment simultaneously within the first several days after surgery.

Pathophysiology of POCD

The exact pathophysiology of POCD remains undefined. Previous studies on POCD have focused on investigating the risk factors associated with early POCD. Table 1 describes the variables that have been shown to be associated with early/intermediate POCD. In terms of patient-related baseline factors, or sometimes called predisposing factors, increasing age and lower levels of education have been identified as the main ones in the early study by the International Study on Postoperative Dysfunction (ISPOCD) [2]. In a subsequent study by Johnson *et al.* [3] that included only a subset of the population reported in the initial study, the avoidance of alcohol intake was determined to be a predisposing factor for POCD. Patient's preoperative cognitive status also has been shown to be associated with POCD. [42]

Whether patients have a genetic predisposition for development of POCD genotype is not well understood because findings from studies to date are conflicting. Genetic studies from population-based investigations 43,[44] have demonstrated a relationship between certain genotypes and the risk of dementia and cognitive decline. Specifically, elevated risk of Alzheimer's disease has been demonstrated among individuals with the E4 allele of the apolipoprotein E (APOE) gene in many populations.[45,46] The E4 allele of APOE is associated with earlier onset of Alzheimer's disease. 47 However, the APOE E4 genotype is neither necessary nor sufficient for the occurrence of Alzheimer's disease. 47 The APOE polymorphism also affects response to trauma, age-related cognitive decline [48] and several other disorders. [49-51] APOE is a polymorphic protein associated with plasma lipoproteins. Three major isoforms can be recognized, designated as APOE2, APOE3 and APOE4, according to their relative position after isoelectric focusing. [52] APOE is unique among apolipoproteins in that it has a special relevance to nervous tissue. [53] APOE is involved in the mobilization and redistribution of cholesterol in repair, growth, and maintenance of myelin and neuronal membranes during development or after injury. [54-56] The three smaller

studies that demonstrated an association between APOE allele and cognitive decline were conducted in patients undergoing carotid endarterectomy and cardiac operations. [57-59] The largest study that failed to demonstrate an association between apolipoprotein E genotype and POCD measured at one week or 3 months after surgery was conducted in patients undergoing noncardiac surgery. [60] However, this study likely underestimated the incidence of POCD since they considered any patients who were not "fit enough for testing" as not having POCD. Recently, McDonagh *et al.* conducted a study in 394 older patients undergoing noncardiac surgery and similarly reported that apolipoprotein E4 was not associated with POCD measured at 6 weeks or at one year after surgery. [42] Similarly, other biomarkers such as B-type natriuretic peptide, C-reactive protein, D-dimer, matrix mettaloproteinase-9, neuron-specific enolase, and S-100b also had no association with POCD measured at 6 weeks or at one year after surgery. The results on apolipoprotein E4 are in contrast to our work in 190 older patients undergoing noncardiac surgery, in which, the presence of one copy of the E4 allele was associated with an increased risk of early postoperative delirium. [61] Even after adjusting for co-variates, patients with one copy of the e4 allele were still more likely to have an increased risk of early postoperative delirium compared to those without the E4 allele. In contrast to the studies by Abildstrom et al., [60] and by McDonagh et al., [42] we measured delirium in the first few days after surgery whereas the other investigators measured POCD at 6 weeks after surgery. One small study in critically ill patients corroborated our findings that apolipoprotein E4 was associated with a longer duration of delirium. [62] Methodological differences between delirium and cognitive assessments, difference in the timing of assessments, and potential differences in patient populations among different studies may result in differences in the findings. Nevertheless, the possible link between postoperative delirium and genetic predisposition is intriguing.

What is the possible mechanism between apolipoprotein and postoperative delirium? Previous studies suggest that the effects of APOE are mediated through alterations in lipid transport in regenerating neurons, proinflammatory cytokine release from activated microglia, amyloid precursor protein metabolism, increased blood brain carrier permeability, alterations in platelet function, and systemic inflammation. [63,64,65] One hypothesized mechanism is that APOE e4 allele diminishes the capacity for repair in cases of cerebral injury or capacity for homeostasis/maintenance. Whether this mechanism occurs to increase the likelihood of developing postoperative delirium remains to be proven.

In addition to predisposing risk factors, numerous potential precipitating risk factors for POCD have been investigated (table 2). The early ISPOCD study reported that the duration of anesthesia, a second operation, postoperative infections, and pulmonary complications[2] increase the risk of POCD. In cardiac surgery, the use of cardiopulmonary bypass has been implicated as one of the precipitating factors. [66,67] During cardiopulmonary bypass, cannulation of the aortic root may result in cerebral microemboli, which could lead to POCD. [68] In addition, a profound systemic inflammatory response occurs with cardiopulmonary bypass, which may contribute to POCD. [69] However, despite the earlier reports that POCD is prevalent after cardiac surgery, [66,67] studies in patients who underwent cardiac surgery without the use of cardiopulmonary bypass did not demonstrate a lower incidence of POCD, despite a smaller embolic load in the middle cerebral artery measured by Doppler in patients undergoing off-pump surgery. [70,71] Thus, it remains inconclusive how surgery type actually affects POCD. Similarly, whether the type of anesthesia affects POCD remains inconclusive. In experimental settings involving animals, general anesthetics produced neurotoxicity and subsequent cognitive impairment in young and aged animals, but whether these changes are reproducible in clinical studies has not been determined. [72] Most previous studies compared the cognitive outcomes between general *vs.* regional anesthesia. Earlier studies suggested an association between general anesthesia and a higher incidence of cognitive dysfunction relative to epidural anesthesia. [73,74] However, recent

studies concluded that there was no relationship between anesthetic techniques and the magnitude or pattern of postoperative cognitive dysfunction. [1,2,4,75]

If anesthesia type did not seem to affect POCD, what about the conduct of anesthesia? The influence of intraoperative hypotension on POCD has also been evaluated. In a prospective, randomized study of older adults (age > 50 years) undergoing total hip replacement, Williams-Russo *et al.* [76] demonstrated that patients who underwent epidural anesthesia and were rendered markedly hypotensive had similar incidence of postoperative cognitive dysfunction as those who were maintained in the normotensive state. Taken together, to date, no single anesthetic type or technique has been identified to be superior in minimizing POCD for older surgical patients.

Given that the type of surgery and anesthetic type and management do not appear to influence rates of POCD, our group has focused on events in the postoperative period that may influence POCD, given that patients experience substantial pain postoperatively and are administered many medications with central nervous system effects. In 225 patients ≥ 65 years of age undergoing noncardiac surgery, we measured POCD in the first two postoperative days. [33] In patients without postoperative delirium, 13% of patients experienced POCD on day 1, 7% on day 2, and 15% had POCD on either day 1 or day 2 after the surgery. Multivariate regression analyses revealed that only postoperative analgesia was associated with the development of POCD. Compared to those receiving postoperative analgesia through a patient-controlled analgesia device that administered opioids intravenously, those who received postoperative analgesia orally were at significantly lower risk for the development of POCD. Our results demonstrate that older patients undergoing noncardiac surgery who are not delirious can experience significant declines in cognitive functioning postoperatively. Those at least risk of experiencing POCD were those who received postoperative analgesia orally. Opioid analgesics administered orally may result in a lower blood level of the drug due to first-pass effect when compared to intravenously administered narcotics which may directly cross the blood brain barrier. Alternatively, the use of oral narcotics for postoperative analgesia may be a marker for a less painful state. However, this result remains significant even when adjusting for the level of pain.

In addition to studies targeting the identification of risk factors of POCD, recent investigations have focused on identifying the pathophysiology for POCD. Surgery can result in a complex systemic response, which includes neuroinflammation. [77] Systemic and neural inflammation, which occur as a result of surgery, may directly affect patient outcome. For example, blood loss and tissue injury in orthopedic procedures might affect the immune system to produce an inflammatory response. [78] Data from preclinical studies support the concept that inflammation is a possible pathogenic mechanism for POCD, and cytokines such as interluekin-1β have been implicated. [79-81] However, the clinical relevance of these experimental findings remains to be determined. Future studies using translational and multidisciplinary approaches are indicated to determine the role of inflammation as a possible causative factor in the pathophysiology of POCD.

Finally, cognitive reserve and a patient's propensity in developing adverse postoperative neurological outcomes need to be considered when discussing the pathophysiology of POCD. A hypothetical construct coined “cognitive reserve” has been used to describe models of cognitive aging and situations where the brain sustains injury.[82] Surrogates of cognitive reserve have included education level, occupational attainment, and performance on tests of knowledge (such as vocabulary). Evidence that greater educational attainment is associated with a reduced relative risk of developing Alzheimer's disease has been demonstrated in many previous studies.[83-85] The association between lower occupational attainment and incident dementia has been found in a number of studies as well.86 Although

cognitive reserve is typically invoked as an important concept in dementia research, there is also evidence that cognitive reserve may play a protective role against POCD. As a result, future research targeting the role of cognitive reserve in POCD and postoperative delirium is an intriguing idea and should be pursued.

Long-term significance of POCD

The question of whether major surgery and anesthesia ultimately lead to long-term cognitive decline is controversial. In a population study, Dijkstra *et al.*87 reported that the number of operations and the total duration of anesthesia were related to the number of subject health-related complaints but did not predict cognitive performance or memory complaints. Several other studies that included assessments more than 6 months after surgery similarly reported no decline in cognitive status from that measured before surgery.[88-92] However, two recent studies that included patients who had undergone noncardiac surgery reported that acute POCD was associated with increased mortality after surgery (for one study, at one year; and for the second study, at 3 months).[5,7] Also, in cardiac surgical patients, Newman *et al.*93 provided data showing that cognitive function at discharge was a significant predictor of long-term cognitive function. In contrast, a recent study by Avidan et al., provide results to the contrary. [94] In this study, the investigators enrolled participants from an Alzheimer's disease research center who had substantial pre-event data. The subjects were stratified into three groups based on whether they underwent surgery, were admitted to a hospital for a major illness not requiring surgery, or did not undergo surgery and had no major illness (control group). Subjects were assessed annually, and some were assessed for as many as 21 years. The battery of neuropsychological tests administered at each occasion was comprehensive of those domains of cognitive function known to be affected in the presence of drugs and other precipitating events. The sophisticated statistical methods used in this study allowed assessments of subjects' trajectory of cognitive performance before and after the event of interest. The study findings suggested that neither non-demented nor mildly demented individuals had accelerated long-term decline in cognitive function attributable to surgery or major illness compared with matched controls. Clearly, whether early POCD is related to accelerated long-term decline in cognitive function was not completely addressed by this study since cognitive assessments were not synchronized with hospitalization. Therefore, a definitive study to address the prognostic significance of cognitive dysfunction associated with surgery and/or hospitalization needs to include sufficient sample size and both short-term and long-term longitudinal assessments to more fully understand how major illness and surgery impacts quality of life and cognitive functioning, and to determine ultimately if there are reversible precipitating factors that are modifiable. Continuing research on POCD may also shed light about the pathophysiology of other neurodegenerative disease including Alzheimer's disease.

Summary

Numerous studies over the past decade have reported an acute change in cognitive status in adult patients after major surgery. Most evidence suggests that these early cognitive changes are transitory and do not persist in the long term. However, the prognostic significance of POCD remains a hotly debated topic, especially in light of recent data showing that patients with early POCD were at higher risk of mortality after discharge.

Furthermore, whether patients with early POCD actually have preexisting mild cognitive impairment and experience a steeper downward cognitive trajectory independent of the effect of anesthesia and surgery is another question that warrants further investigation. We anticipate that future studies will elucidate better the pathophysiology of POCD through the use of large sample sizes and longitudinally collected patient data in both the early and late

postoperative period. We also advocate for a theoretically derived and empirically tested model which describes the causes and outcomes of POCD. Such a model must be established in order to truly standardize the neurocognitive test battery and timing of administration in the study of POCD.

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Table 1

Patient-related risk factors for early/intermediate POCD

Patient-related risk factors	Supporting evidence
Age	ISPOCD, Stockton, Ancelin, Monk [2,5,91,95]
Education	ISPOCD, Monk [2,5]
Burden of illness	Monk [5]
Preoperative depression	Leung (delirium only) [96]
Preoperative cognitive impairment	Johnson [3]
Preoperative habits and drug use	Monk [5]
Apolipoprotein E4	Heyer, Telis, Leung, Tardiff[57-59,61]

Proposed patient-related risk factors of POCD and studies with supporting evidence.

ISPOCD = International Study on Post-Operative Cognitive Dysfunction

Table 2

Precipitating factors for early/intermediate POCD

Precipitating factors	Supporting evidence	Refuting evidence
Second operation	ISPOCD [2]	Monk [5]
Postoperative infection	ISPOCD [2]	Monk [5]
Respiratory complications	ISPOCD [2]	Monk [5]
General anesthetic	?	ISPOCD, Williams-Russo[4,76]
Anesthetic type	?	Leung [97]
Anesthetic maintenance (hypotension)	?	Williams-Russo[1]
Pain management	Leung [98,99]	?

Proposed precipitating factors for early or intermediate POCD and studies with supporting or refuting evidence.

ISPOCD = International Study on Post-Operative Cognitive Dysfunction