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REVIEW ARTICLE

Gynecology

Postoperative cognitive disorders and delirium in gynecologic surgery: Which surgery and anesthetic techniques to use to reduce the risk?

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Abstract

Despite their general good health, an increasing proportion of elderly individuals require surgery due to an increase in average lifespan. However, because of their increased vulnerability, these patients need to be handled carefully to make sure that surgery does not cause more harm than good. Age-related postoperative cognitive disorders (POCD) and postoperative delirium (POD), two serious consequences that are marked by adverse neuropsychologic alterations after surgery, are particularly dangerous for the elderly. In the context of gynecologic procedures, POCD and POD are examined in this narrative review. The main question is how to limit the rates of POCD and POD in older women undergoing gynecologic procedures by maximizing the risk–benefit balance. Three crucial endpoints are considered: (1) surgical procedures to lower the rates of POCD and POD, (2) anesthetic techniques to lessen the occurrence and (3) the identification of individuals at high risk for post-surgery cognitive impairments. Risks associated with laparoscopic gynecologic procedures include the Trendelenburg posture and CO_2 exposure during pneumoperitoneum, despite statistical similarities in POD and POCD frequency between laparoscopic and laparotomy techniques. Numerous risk factors are associated with surgical interventions, such as blood loss, length of operation, and position holding, all of which reduce the chance of complications when they are minimized. In order to emphasize the essential role that anesthesia and surgery play in patient care, anesthesiologists are vital in making sure that anesthesia is given as sparingly and quickly as feasible. In addition, people who are genetically predisposed to POCD may be more susceptible to the

Abbreviations: Ab1-40/42, β-amyloid 1-40/42; AD, Alzheimer's disease; AEP, auditory evoked potential; AI, artificial intelligence; AMPARs, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BBB, blood–brain barrier; BIS, Bispectral index; BMDMs, bone marrow-derived monocytes; CAM, confusion assessment method; CAM-ICU, confusion assessment method for the intensive care unit; CANTAB, Cambridge neuropsychological test automated battery; CNS, central nervous system; CRP, C-reactive protein; CSF, human cerebrospinal fluid; DAMPs, damage-associated molecular patterns; DRS, delirium rating scale; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalogram; Glu 2, glutamate 2; HMGB1, high mobility group box 1 protein; ICD-10, International classification of disease and related health problems; IgG, immunoglobulin; IKK, IκB kinase; IL-1β, interleukin-1 beta; IL-6, interleukin-6; LTP, long-term potentiation; MCI, mild cognitive impairment; ML, machine learning; ML, machine learning; MMPs, matrix metalloproteinases; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; NF-κB, nuclear factor kappa B; NMDA, N-methyl D-aspartate; NPTs, neurocognitive performance tests; NSE, neuron-specific enolase; PCEA, postoperative patient-controlled epidural analgesia; POCD, postoperative cognitive disorders; POD, postoperative delirium; ROS, reactive oxygen species; rSO2, regional oxygen saturation index; TIVA, total intravenous anesthesia; TLRs, Toll-like receptors; TNFα, tumor necrosis factor alpha; WMS, Wechsler memory scale.

disorder. The significance of a thorough strategy combining surgical and anesthetic concerns is highlighted in this article, in order to maximize results for senior patients having gynecologic surgery.

KEYWORDS
anesthesia, blood loss, duration of surgery, gynecologic surgery, pneumoperitoneum, postoperative cognitive disorders, postoperative delirium, surgical complications

1 | INTRODUCTION

Postoperative cognitive dysfunction (POCD) and postoperative dementia (POD) are subclinical conditions that commonly occur in elderly patients after surgery, negatively affecting memory, speech and attention. They represent two of the most prevalent postoperative complications.[1] Distinguishing early POCD from postoperative delirium, a closely related condition that usually manifests in the first 3 days after surgery and is frequently seen as a major prelude to the development of POCD, which is more likely to occur after 1 week and last for several months.[2] According to recent research, the incidence can vary from 10%–54% based on the patient's type, type of surgery, and a number of other factors that are detailed in this publication.[3] POCD is a widely recognized and thoroughly researched idea in the literature, particularly in the area of cardiac surgery. Because of its increased frequency following such surgeries—particularly since the early days of cardiac bypass procedures—it was initially identified in this sector. However, there are still a lot of unanswered questions, particularly in non-cardiac surgery.[4] POCD and POD have serious repercussions for patients as well as the country's healthcare system. Memory impairments, slower information processing, and delayed stimuli processing are experienced by patients with cognitive impairment and postoperative delirium. As a result, these patients require extended hospital stays, hospital and possibly home-based rehabilitation, and a decline in quality of life.[5] Healthcare expenditure for older individuals who undergo surgery and are diagnosed with postoperative neurocognitive disorders are higher for up to a year after treatment; these expenses are projected to be approximately 16 billion US dollars annually.[6] This demonstrates the financial burden associated with this possibly avoidable consequence.[7] The present study aimed to identify surgical and anesthesiological risk factors, elucidate the pathogenetic mechanisms involved, and stratify high-risk patients to develop strategies for prevention and management of the pathology.

2 | MATERIALS AND METHODS

In order to find the most recent information on POD and POCD, we carried out an extensive analysis of the Scopus and PubMed databases covering the period from 1990 to December 2023. A combination of terms such as “endoscopy”, “gynecology”, “prolonged and deep anesthesia”, “intraoperative complications”, “poor pain management”, “cognitive impairments”, “surgery”, “anesthesia”, “stress”, “time of surgery”, “delirium”, and “anesthetic technique” were used. Only peer-reviewed works with human participants were included. Cross-referencing allowed for the identification of other articles. Investigation reporting of macroscopic or functional cerebral lesion, epilepsy, and pre-existing mental illness, burdened neurologic history and acute cerebrovascular diseases, severe somatic pathology, severe concussion, stroke, burdened history of alcohol, drug, or poisoning and dementia were among the exclusion criteria used by the authors to exclude papers. All evaluated papers focused on patients aged between 50 and 80 years (Figure 1).

3 | RESULTS

The treatment of POCD and POD requires a multimodal strategy that incorporates anesthesia and surgical management, patient characteristics, and perioperative care. Through a comprehensive review of the literature, several key findings emerged, shedding light on effective strategies for reducing the acute morbidity of POD and the recurring long-term consequences of POCD in surgical patients. First and foremost, one of the most important factors in reducing the incidence of POCD and POD is to shorten the length of surgical procedures. Reduced stress and the release of inflammatory mediators are two benefits of shorter operating durations. They also lessen the need for sedative and analgesic drugs, which helps to mitigate the potential neurotoxic effects of prolonged anesthetic exposure. Additionally, the surgical method that is chosen is crucial to prevention. Even though laparoscopic surgery has benefits including less trauma and shorter hospital stays, neuronal perfusion may be impacted and cognitive deterioration may result from the Trendelenburg posture and CO_2 pneumoperitoneum. It is crucial to give careful thought to these variables in order to maximize surgical results and reduce the risk of POCD and POD. Another important surgical factor for cognitive impairment is perioperative blood loss. By properly controlling bleeding and reducing the need for blood transfusions, surgical patients' cognitive function may be protected by reducing the neuroinflammatory response linked to both POD and POCD. Risk is also greatly impacted by anesthesiologic variables. By adjusting the depth and kind of anesthesia to each patient's specific needs based on metrics like the Bispectral index (BIS), cognitive outcomes can be maximized and the prevalence of POCD and POD can be decreased. Furthermore, given the growing body of research indicating the potential advantages of regional anesthesia for particular patient categories, the decision between general and

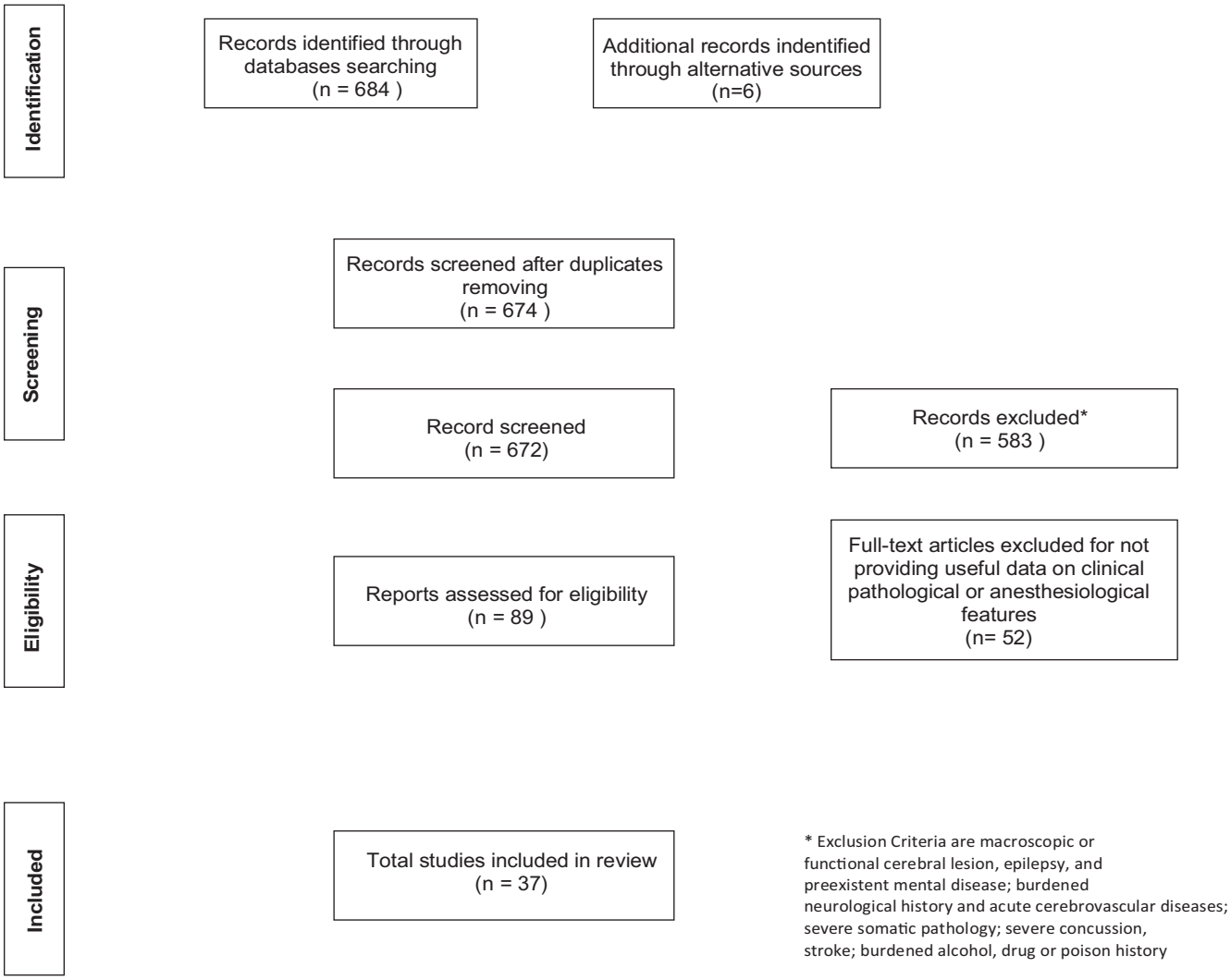

FIGURE 1 Flow diagram of the screened literature and papers included in this review.

regional anesthetic should be carefully considered. Age, genetic predisposition, and educational attainment are examples of subjective risk factors that highlight how complex the etiology of both POD and POCD is. By being aware of these variables and putting risk-adapted measures into practice, it may be possible to reduce the negative effects of POCD and POD on patient outcomes by early diagnosis and intervention. The following sections discuss and report the findings of further studies. The results are continued in Table 1.

3.1 | Inflammation: "the master of disaster"

Arefayne et al. conducted a systematic review involving 23 articles and 5077 patients (3694 non-cardiac and 1383 cardiac surgeries), analyzing the incidence, etiology, and comorbidities associated with POCD in elderly patients.[8] The condition shows a higher incidence in individuals above 75 years of age, particularly in patients undergoing cardiac or non-cardiac major surgery (≥2 h).[9] The risk factors need to be stratified into three major spheres: (a) those dependent on the type, duration, and characteristics of the surgery; (b) those related to the type, duration, depth of anesthesia and (c) patient-dependent risk factors.[10,11] Few articles in the literature analyze post-surgical pathologies following gynecological surgical procedures. The invasiveness of gynecological surgery has increased over time, making procedures longer, more destructive, and extensive.

Different are the etiological POD/POCD theory. The most accredited are the initiation of "inflammation" at the periphery, breakdown of the blood–brain barrier and oxidative stress.[12]

As per the hypothesis of peripheral beginning of inflammation, surgical trauma, even if aseptic, is what initiates inflammation in the surgical site. Injured cells passively release small biomolecules called damage-associated molecular patterns (DAMPs) at the injury site.[13] After surgical trauma, high mobility group box 1 protein (HMGB1), a specific DAMP, is released and binds to Toll-like receptors (TLRs) and the receptor for advanced glycosylation end products (RAGE) on the cell membrane of circulating bone marrow-derived monocytes (BMDMs).[14] Human studies demonstrate a correlation between plasma HMGB1 levels and inflammation severity in both non-cardiac surgery and non-surgical inflammatory conditions.[15] When HMGB1

TABLE 1 Risk factor results from the study indexed for level of evidence and impact factor..

Risk factors	Level of evidence	Impact factor	Publication year
Long lasting surgery (>450 min is a significant predictor of POCD)[56]	A	I	2020
Laparoscopic approach (Trendelenburg position, CO_2 pneumoperitoneum)[59,60]	B	IIa	2018, 2016
Blood loss[61]	B	IIa	2022
Local versus general anesthesia[75–77]	E	C	1990, 1982, 2011
Propofol[78,79]	A	I	2018, 2010
Neuronal hypoperfusion[65,66]	D	IIb	2016, 2017
Sevoflurane[80]	C	IIb	2019
Pain[82]	D	IIb	2013
Anesthetic depth (BIS index)[90]	A	I	2021
Age >60 years[96–98]	A	I	2016, 2021, 2020
Educational level[100]	A	I	2017

Note: Level of evidence: A, evidence from systematic reviews or meta-analyses of RCTs; B, evidence from at least one properly designed RCT; C, evidence from well-designed controlled trials without randomization; D, evidence from well-designed case–control or cohort studies; E, evidence in literature highly conflicting.

Impact factor: I, strong incidence based on evidence; IIa, moderate incidence based on evidence; IIb, weak incidence based on evidence; C, no incidence possible due to the lack of consensus.

Abbreviations: BIS, Bispectral index; POCD, postoperative cognitive disorders.

binds to both TLR-4 and RAGE, it activates nuclear factor kappa B (NF-κB), a transcription factor that controls the expression of proinflammatory cytokines. NF-κB is usually found in the cytosol attached to the inhibitor IκB when it is not active. Phosphorylation of IκB by IκB kinase (IKK) leads to the release of NF-κB, allowing it to enter the nucleus and upregulate proinflammatory cytokines.[14] Activated by NF-κB, proinflammatory cytokines like interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFα) trigger additional release of HMGB1, creating a positive feedback loop that amplifies the inflammatory response.[15] The second theory involves the breakdown of the blood–brain barrier. Proinflammatory cytokines in the periphery disrupt blood–brain barrier (BBB) permeability by upregulating COX-2 protein and matrix metalloproteinases (MMPs), enabling them to enter the central nervous system (CNS). Normally the tight cellular junctions of the BBB allow the passive movement of water, gases, and small lipid-soluble molecules through diffusion.[16] Proinflammatory cytokines IL-1 and TNFα can induce COX-2 upregulation in neurovascular endothelial cells, leading to local prostaglandin synthesis and disruption of BBB permeability.[17] TNFα, IL-1β, and IL-6 have been detected in hippocampal tissue in rats and in human cerebrospinal fluid (CSF) after surgical trauma, indicating a compromised BBB.[18] Increased cytokine levels in the CNS have been linked to memory impairment in mice and cognitive dysfunction in humans.[18,19] To support the thesis of dysregulated BBB permeability, Immunoglobulin G (IgG), which is not typically found in the brain under normal circumstances, has also been observed in hippocampal slices in rats after undergoing surgery.[20] Likewise, proteins specific to the CNS, such as S100β protein and neuron-specific enolase (NSE), are detected in the blood plasma of patients with POCD after both cardiac and non-cardiac surgeries.[21,22] The third theory is the microglial activation. In conditions of inflammation and BBB breakdown, the microglia transforms into two distinct activated forms, known as M1 and M2.[23] The M1 phenotype exhibits strong phagocytic properties and promotes inflammation, whereas the M2 phenotype participates in tissue repair and remodeling and exhibits anti-inflammatory properties.[24] As expected, proinflammatory mediators like TNFα or lipopolysaccharide encourage the differentiation of microglia into the M1 phenotype.[25] Peripheral surgery outside triggers the release of mast cells within the CNS, leading to the activation of microglia. Once activated, microglia continue to enhance the production of proinflammatory cytokines, exacerbating neuroinflammation and contributing to the development of POCD.[12] The final analyzed etiologic factor is oxidative stress. Apart from the inflammatory mechanisms outlined earlier, surgical trauma can lead to oxidative stress and decrease antioxidant levels in the body. This process results in the formation of superoxide radicals and other reactive oxygen species (ROS), which may directly harm neural tissues. Furthermore, peripheral oxidative stress can disrupt the BBB, indicating a connection between oxidative stress and the neuroinflammatory pathway.[26]

What all the pathways described so far have in common is undoubtedly the development of inflammation at the CNS level, resulting in clinical manifestations of POCD. Memory formation in the hippocampus relies on a process called long-term potentiation (LTP), initiated by high-frequency glutamatergic activation of hippocampal neurons.[27] At rest, presynaptic glutamatergic Schaffer cells communicate with postsynaptic CA1 collateral neurons. The CA1 neurons contain three types of glutamate receptors: the metabotropic Glu2 receptor, and the ionotropic AMPA and NMDA receptors. Under normal, low-frequency stimulation, glutamate acts on all receptors, but magnesium blocks N-methyl D-aspartate (NMDA) channels. However, during high-frequency stimulation, postsynaptic

depolarization activates NMDA receptors, leading to calcium influx and second messenger system activation. This process phosphorylates and increases the number and sensitivity of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAR) receptors, enhancing synaptic strength and facilitating memory formation.[28] Due to the abundance of cytokine receptors, the hippocampus is particularly sensitive to elevated levels of proinflammatory cytokines like IL-1 and TNFα during neuroinflammatory events.[29] Upon activation of these cytokine receptors at elevated levels, there is a reduction in the expression of metabotropic glutamate 2 (Glu-2) receptors, leading to increased AMPA/NMDA signaling, thereby disrupting the process of long-term potentiation (LTP).[30] When cytokine receptors are activated at high levels, there is a decrease in the expression of metabotropic Glu2 receptors, leading to heightened AMPA/NMDA signaling, which disrupts the process of LTP.[30] Additionally, HMGB1 can enhance glutamate signaling through NMDA, causing increased glutamate influx into hippocampal neurons, ultimately resulting in glutamate toxicity.[31] Moreover, TNFα can inhibit inhibitory neurotransmission by reducing GABA receptor expression, upsetting the balance between excitatory and inhibitory neurotransmission, and ultimately promoting glutamate toxicity.[32] To summarize, the aforementioned effects, through various pathways, all lead to hippocampal toxicity, causing neuronal necrosis, and deficits in memory and cognition.

3.2 | The POCD and POD diagnostics

POCD and POD present numerous challenges in diagnosis, leading to an inevitable underestimation of the incidence of the complication. The POCD lacks a clear definition and it is not included in the DSM-5 manual. However, POD is defined by the International Classification of Diseases and Related Health Problems (ICD-10), which is the gold standard for diagnosis.[33] Moreover, to diagnose the POCD, it would be necessary to assess with an objective method (neurocognitive tests) before and after surgery,[34] all listed in Table 2. Diagnostic criteria for POD diagnosis are a disruption in attention, cognition, and/or awareness that arises rapidly and exhibits a fluctuating course. The changes in brain function should be distinct from the patient's usual baseline. Specialists have recognized three forms of delirium: hyperactive, hypoactive, and mixed types.[35] The diagnosis is primarily clinical but can be aided by biomarkers,[36] imaging investigations[37] and diagnostic tools (as neurocognitive tests).[38] A recent review from Schaefer et al. combines data from the literature with the aim of finding a marker that can, with a solid confidence interval, assist in the diagnosis and establish the severity grade of POCD and POD. Since the central nervous system is the source of the pathology, as has been indicated in the paper thus far, it makes sense to look for the implicated marker in CSF.[36] Hall et al. described three major POCD and POD markers' groups in CSF. Markers such as tau protein and β-amyloid 1-40/42 (Ab1-40/42) have been studied, but there is no clear evidence of their prognostic role. Additionally, disease markers of delirium include neurotransmitters, metabolites, and their precursors, although the widely promoted neurotransmitter acetylcholine was not clearly associated with delirium in CSF samples. Another focus was on inflammation markers such as interleukins 1, 6, 8 and 10, and C-reactive protein (CRP). Disease markers of delirium primarily included markers of neuronal cell damage like protein S-100 and NSE. However, these results were inconsistent. The CSF lactate levels suggested disruption of the brain's normal aerobic metabolism. While the CSF biomarkers may seem like the preferred choice for POCD and POD related biomarkers, their use is limited by two significant factors. First, the timing of CSF sampling is crucial, yet unlike peripheral blood sampling, the CSF sampling is not readily available. Regarding the peripheral blood, the only reliable marker appears to be beta-amyloid. Several studies have focused on beta-amyloid concentration in plasma or the ratio between Ab1-40/42, but they did not achieve statistical significance when correlated with POD.[39] Regarding the POCD and POD diagnosis through imagining, Ilse et. analyzed the changing after surgery through magnetic resonance imaging (MRI) in patients after surgery. As a first step, the author attempts to establish a correlation between the incidence of POD and preoperative global, cortical, and subcortical brain volume. Two studies are considered, but they provide conflicting data, possibly due to fewer included patients and lower study quality. One of the studies was likely underpowered since it involved a small sample size of non-small cell lung cancer 23 patients.[40] The other study on 79 patients conducted a postoperative imaging and relied on qualitative MRI analyses instead of quantitative ones.[41] Two additional studies have examined brain volume loss in specific regions and the incidence of POCD. Unfortunately, these studies are statistically insignificant due to a very small pool of included patients (31 and 28 patients) These studies revealed potential markers in certain specific brain regions within the medial temporal lobe, but there is limited evidence regarding these associations.[42,43] A recent systematic review from Huang et al. suggested that the brain mass decrease which mainly occurs manly in thalamic and hippocampal regions, as well as reductions in cerebral blood flow, may be associated with POCD, while presurgery/pre-existing and postoperative white matter pathology may be associated with POD. However, the evidence from these studies is relatively weak.[44] The third used parameter to POD/CD diagnostic is represented from the neuropsychological tests. The first try in this field was led from Moller et. al who evaluated pre- and postoperative cognitive function of the patients through the Wechsler memory scale (WMS).[45] Following this, a series of manuscripts were published introducing new, increasingly advanced and current neurocognitive performance tests (NPTs), promising to simplify diagnosis. In 1998, Moller et al. conducted a comprehensive prospective study using a rigorously screened battery of NPTs, including visual-verbal learning tests, concept-shifting tests, Stroop color-word interference tests, pen-and-paper memory scanning tests, letter-digit coding, and four-box tests, to assess cognitive status. *Z*-scores were utilized as the criterion for POCD.[46] Subsequently, various sets of NPT batteries, derived from the aforementioned tests, became commonly employed for clinical assessment. NPT-based *Z*-scores are increasingly recognized by clinical

TABLE 2 Most used neurocognitive performance tests (NPTs) classifications and their principal features explaining the most common and utilized NPTs, including their respective pros and cons, as well as the various cognitive spheres examined.

Name of the test/test battery	Cognitive spheres evaluated	Sensitivity Specificity	Evaluation system	Global evaluation
MINI-MENTAL STATE EXAMINATION[38]	Temporal and spatial orientation, linguistic skills, immediate memory, delayed recollection, focus, numerical computation, visual–spatial aptitude, and executive functioning	**Low**	Point evaluation system with a total of 30 and cutoff score 23/24	**Pros**: Cover the majority of cognitive domains **Cons**: Low sensitivity Suitable as screening tool
MONTREAL COGNITIVE ASSESSMENT SCALE (MoCA)[103]	Cognitive abilities encompass visuospatial skills, executive functioning, naming, memory, attention, language comprehension, abstraction, and orientation	**Sensitivity** 80.48% **Specificity** 81.18%	Point evaluation system with a total of 30 and cutoff score 24/25	**Pros**: High sensitivity and specificity **Cons**: Low sensitivity Screening tool for MCI
VISUAL/AUDITORY VERBAL LERNING TEST[104]	Working memory	**High** sensitivity **and** specificity	15 words are 5x displayed. After 20 min they must be recalled	Especially adept at detecting initial cognitive decline, it can reliably differentiate MCI and normal cognitive function
CONCEPT SHIFTING TEST[105]	Conceptual transfer and executive function	**No data**	Circle task, sequential pattern, cognitive assessment, alphanumeric sequences	**Pros**: Evaluates the ability to shift between different concepts or rules, which is a key aspect of executive function **Cons**: Susceptibility to demographic factors like gender, age, and education level
PAPER AND PENCIL MEMORY SCREENING TEST[106]	Working memory, visual scanning speed, and information processing speed	**Sensitivity** 86% **Specificity** 92%	Uses sheets with random letters	**Pros**: Brief procedure (~5 min) **Cons**: Literacy dependency and influences of age and education
STROOP COLOR INTERFERENCE TEST[107]	Attention, information processing speed, execution, and anti-interference ability	**No data**	3 cards, 4 steps: Color written in black or incongruously color have to be read and recalled	**Pros**: Cognitive evaluation in patients with multiple sclerosis or schizophrenia **Cons**: Not suitable for visually impaired, color blind, illiterate patients.
GROOVED PEGBOARD TEST (GPT)[108]	Working memory, visual–spatial skills, executive functioning, attention, psychomotor speed, motor control, cognitive flexibility.	**Sensitivity** 85% **Specificity** 95%	Metal plate with 25 holes containing differently positioned slots and pegs with ridges. Pegs can only be inserted when ridges align with slot orientations.	**Pros**: Studies suggest good test–retest reliability, making it a dependable tool for measuring changes in performance over time **Cons**: It may not capture the full range of cognitive abilities or motor functions relevant to certain populations or conditions

(Continues)

TABLE 2 (Continued)

Name of the test/test battery	Cognitive spheres evaluated	Sensitivity Specificity	Evaluation system	Global evaluation
TRAIL MAKING TEST (TMT)[109]	Visual scanning, attention, executive skills	**Sensitivity** 100% **Specificity** 90%	Two parts: A: Numbers from 1 to 25, Part Numbers and letters alternated. Measures visual scanning speed (Part A) and executive function (Part B)	**Pros**: Widely used, one of the most widely used neuropsychological tests, making it familiar to many clinicians and researchers **Cons**: Scoring can be complex, particularly when interpreting results in relation to normative data
BOSTON NAMING TEST (BNT)[110]	Language functioning, semantic memory, executive function, visual recognition	**Sensitivity** 85% **Specificity** 94%	A set of line drawings or pictures representing common objects is shown. The examiner presents each drawing to the participant and asks them to name the object depicted in the drawing	**Pros**: The test is standardized, making it a reliable tool for assessing naming abilities across different individuals and populations. **Cons**: While the BNT assesses naming abilities, it may not capture other aspects of language and cognitive function, potentially limiting its diagnostic value in certain cases
NATIONAL INSTITUTES OF HEALTH (NIH) EXAMINER[111]	Working memory, inhibition, scene switching, fluency, planning, insight, social cognition, and behavior	**No data**	Participants undergo assessment in each subset, which may involve tasks, questions, or scenarios designed to evaluate specific executive function domains.	**Pros**: The NPT is designed to be efficient and suitable for a wide range of age groups and cognitive levels **Cons**: Time-consuming, potentially leading to fatigue or reduced motivation in participants.
CAM-ICU[112]	Attention, level of consciousness, fluctuation in mental status, presence of alterations in mental status, disorganized thinking	**Sensitivity** 84% **Specificity** 95%	Quick and non-verbal assessment tool used to diagnose delirium in ICU patients	**Pros**: It does not rely on verbal communication, making it suitable for patients who cannot speak due to intubation or other conditions **Cons**: Proper training is necessary for accurate administration and interpretation, which may require resources and time
THE CAMBRIDGE NEUROPSYCHOLOGICAL TEST AUTOMATED BATTERY (CANTAB)[113]	Memory, attention, executive function, processing speed, visual perception, sustained attention, spatial memory	**No data**	The CANTAB is a computerized cognitive assessment tool. Participants engage with tasks using touchscreen or mouse	**Pros**: Provides computerized precise and automated data collection **Cons**: Initial setup and licensing fees may be expensive for institutions

Abbreviations: ICU, intensive care unit; MCI, mild cognitive impairment.

researchers as a diagnostic measure for POCD. With advancements in science and technology, cognitive evaluation methods have progressed from traditional pen-and-paper tools to computer-based tests, and now to the use of lightweight and convenient tablet devices equipped with digital assessment tools. Theoretically, the inclusion of more NPTs in a battery enhances the comprehensiveness and sensitivity of cognitive function evaluation.[38] We want to clarify that none of the aforementioned neuropsychological tests has achieved the status of diagnostic gold standard for POCD.[47] An ideal NPT should fulfill certain criteria, including high sensitivity, specificity, test–retest reliability, and intertester reliability. Moreover, the evaluation procedure should be straightforward, uncomplicated, and brief. Other prerequisites for an ideal NPT encompass patient cooperation, availability of alternative versions or minimal learning effects, existence of normative data, sensitivity to subtle changes in cognitive function, availability of versions in various languages, and resilience to interference from non-cognitive factors.[38]

3.3 | Surgical triggers for POCD and POD development in gynecologic surgery

As reiterated several times in the manuscript, the onset of the complication is well-established and well-studied in the case of cardiac surgery,[4] as well as major abdominal or orthopedic surgery.[34,43] For gynecology, the same cannot yet be stated. Pioneers in the field, Dale et al., published a study on attention loss following major gynecologic surgery as early as 2005.[48] The author examined 20 female patients, whose mean age was 48.6 years, who had major gynecologic surgery, including an abdominal hysterectomy performed under general anesthesia. A sustained attention to response task (SART) test was completed by the patient prior to surgery, as well as 24, 48, and 72 h later. The results revealed severe deficiencies ($P < 0.05$) 72 h after surgery.[48] The study revealed a number of shortcomings, starting with the small sample size. Other shortcomings were the paucity of information on anesthetic drugs, surgical procedures, blood loss, and the medical histories of the patients.

Conversely, a much more recent case control study including 50 patients (40–60 years old) was carried out by Chen et al. A small mental test was used to assess the patients both before surgery and on the first 5 days after the procedure, with 50 patients undergoing surgery and the same number in the control group. The observation group's alerting ($P = 0.003$ vs. control group, $P = 0.015$ vs. baseline), orienting ($P < 0.001$ vs. both baseline level and control group), and executive control networks ($P = 0.007$ vs. control group, $P = 0.002$ vs. baseline) all showed significant impairment on the first postoperative day. By the fifth postoperative day, the alerting network efficiency had returned to preoperative levels ($P = 0.464$ vs. baseline), and the orienting network efficiency had partially recovered ($P = 0.031$ vs. first postoperative day) but not to preoperative levels ($P = 0.01$ vs. baseline). The executive control network did not recover by the fifth postoperative day ($P = 0.001$ vs. baseline, $P = 0.680$ vs. first postoperative day).[49] This study has numerous deficiencies in statistical and scientific quality, since it fails to provide a precise description of the type of surgery performed (Laparotomic? Laparoscopic? Length? Blood loss?) Regarding the laparoscopy instance, what was the pCO_2 reached? Additionally, what was the BIS attained during anesthesia? Was propofol the only sedative used? Was there concurrent spinal anesthesia? Lastly, what information was available regarding the anesthesia and patient characteristics (ASA classification, educational attainment, comorbidities?).

Seventy-five ASA I pregnant women who had an elective cesarean section were examined by Altun et al. To test the effects, the women were split into three groups and given various forms of anesthetic. Three groups of 25 people each were given different treatments: sevoflurane for group 1, desflurane for group 2, and spinal anesthesia for group 3. The Trieger dot test, clock drawing test, and mini-mental state evaluation were performed 1 day before surgery and again one, three, and 24 h later. In conclusion, sevoflurane or desflurane, as well as spinal anesthesia, did not impact cognitive functions in patients undergoing cesarean operations.[50] In conclusion, because of their length, wide surgical field, and significant blood loss, the most extensive and prolonged interventions in the gynecologic field—primarily gynecologic oncology surgery—pose the highest risk of developing postoperative confusion and delirium (POCD and POD).[51]

A recent analysis by Fan et al. involved 572 individuals who had laparoscopic surgery. To look at possible factors that might affect the results, they used logistic regression. Logistic regression analysis results showed that among elderly patients undergoing laparoscopic surgery, low SpO_2 levels during anesthesia induction (odds ratio [OR] 2.03, 95% confidence interval [CI]: 1.19–4.47), a history of cerebral infarction (OR 3.12, 95% CI: 1.02–5.13), and a prolonged duration of surgery (OR 1.82, 95% CI 1.01–3.16) were risk factors for POCD. On the other hand, in older patients undergoing laparoscopic surgery, preoperative dexmedetomidine administration (OR 0.70, 95% CI: 0.08–0.94), postoperative patient-controlled epidural analgesia (PCEA) (OR 0.43, 95% CI: 0.01–0.91), general anesthesia combined with continuous epidural block (OR 0.59, 95% CI: 0.04–0.87), and pre-emptive analgesia (OR 0.75, 95% CI: 0.13–0.90) were found to be protective factors against POCD.[52]

3.4 | Duration of surgery and risks of POCD and POD development

Surgical techniques intended to lessen POCD must have a few qualities: they need to be brief. Reducing the length of surgery is essential to lowering the incidence of POCD. Shortening the duration of surgery not only minimizes stress and inflammatory mediator production, but it also successfully reduces the requirement for sedative and analgesic drugs.[53]

A retrospective investigation was conducted by Uccella et al. on 258 patients who underwent a hysterectomy in uteri weighing less than 1500 g for benign disease. Of these patients, 55 underwent open surgery (21.3%) and 203 underwent laparoscopy

(78.7%). Comparing the mean operating time for laparoscopy, which was 120 min (50–360 min), with that of open surgery, which was 85 min (35–240 min). The cases were observed to be substantially lengthier when the hysterectomy was done via laparoscopy.[54] Extended surgical procedures necessitate extended exposure to general anesthesia. Research on animals has demonstrated that extended exposure to general anesthesia may result in neurotoxicity and the development of POCD.[3,55] According to Otomo et al., a surgery lasting more than 450 min is also a significant predictor of POCD.[56] A systematic review conducted by Segal-Gidan et al. found that a shorter duration of surgery was linked to a reduced risk of POCD.[57]

3.5 | Wise choice of the surgical access in relation to the type of operation

In gynecology, laparoscopic surgery has become more and more common. The scientific community can clearly see the benefits: less discomfort, less stress to the surgical site, and a shorter hospital stay. For these reasons, it is the preferred method for many gynecologic procedures. Nonetheless, there are certain hard points associated with laparoscopy, including the Trendelenburg position, CO_2 pneumoperitoneum, and iatrogenic intra-abdominal pressure rise.

Máca et al. examined how some markers changed following open surgery in contrast to laparoscopic procedures. S100 is one of the indicators most strongly associated with neuronal injury and, hence, the beginning of POCD.[58,59] Their findings showed that on days 1 and 2 ($P=0.02$), the laparoscopic surgery subgroup had significantly greater levels of S100A8 protein than the laparotomy group, and on day 2 ($P=0.03$), they had higher levels of S100A12 protein.[59]

Liu et al. carried out another study that lends credence to this argument. They assessed 225 adult female patients who underwent gynecologic laparoscopy (group II, $n=110$) and laparotomy (group I, $n=115$), with scores based on the American Society of Anesthesiologists' physical status categories I and II. The laparoscopic group's pneumoperitoneum was achieved by insufflation of CO_2 up to a pressure of 15 mmHg. They tampered with the patient's serum concentrations of neuron-specific enolase (NSE) and S100β both before and after the procedure, when the patient was still unconscious. Following that, patients had Mini-Mental State Examinations (MMSEs) at predetermined intervals: 1 day prior to surgery and 6, 12, 24, and 72 h following the procedure. The medium S100β serum concentration increased in the laparoscopic group and did not go back to basal level even 1 day after surgery. In group I (laparotomy), the mean S100β serum concentration also increased, although it decreased to the basal level in the 6 h postoperatively.[60]

3.6 | Blood loss and risk of POCD and POD

Perioperative blood loss is another surgical cause for the development of POCD and POD.[61] The impact of perioperative blood loss on cognitive function deficits following colon cancer surgery was reported by Bošković et al. There was a statistically significant difference in cognitive status as measured by the MMT score between the number of postoperative blood transfusions on the first day ($P=0.016$) and the total number of blood transfusions received ($P=0.026$). Compared to patients without cognitive impairment, patients with cognitive impairment received significantly more blood transfusions on the first post-surgery day (0.38 ± 0.49) and more blood transfusions overall (1.92 ± 1.23). The latter group had a lower total number of blood transfusions (1.16 ± 1.04) and considerably fewer blood transfusions on the first post-surgery day (0.11 ± 0.32).[61] Early POCD is associated with a larger percentage of hematic cortisol, which is triggered by a hemorrhage.[62] Hippocampus area volume decreases when high cortisol levels are sustained over an extended period of time, suggesting that stress may have an impact on hippocampus neurons.[63,64] Prolonged and severe neuroinflammation can result in functional manifestations including damage or neuronal death in POD.[12]

3.7 | Intraoperative neuronal perfusion and risk of POCD and POD

The brain is essential to cognition, and its hypoperfusion can affect an individual's capacity for thought. Following the introduction, it would appear reasonable to conclude that neural performance plays a major part in the prevalence of POD and POCD. Sadly, there are divergent views in the literature. The first stream of thought postulates that altered cognitive performance after surgery is associated with decreased blood flow to the brain,[65,66] while the second stream demonstrated that patients with different $rScO_2$ levels did not exhibit different rates of POCD.[67]

3.8 | Anesthesiologic triggers for POCD and POD development in gynecologic surgery

Located on the other side of the surgical drape is another important component that helps prevent the development of cognitive complications following surgery. From the perspective of anesthesiology, the issues that need to be addressed are the effects of the length of anesthesia, the differences in effect between total intravenous general anesthesia and inhalation anesthesia, certain medications that are frequently used in anesthesia, and the possibility of these medications causing POD and POCD. Because many binding sites for volatile anesthetics have been found on both α- and β-tubulin, these drugs are thought to be potential triggers for POCD development, possibly via modifying tau phosphorylation and tubulin.[68,69] To date, there is no proof in the literature that there is a direct correlation between the incidence of POCD in humans and the use of a particular anesthetic. However, the same cannot be said for a study on animals, which shows that isoflurane leads to hippocampal neuron necrosis, especially in older animals

and bring to beta-amyloid 1–42 accumulation and consequent apoptosis.[70,71] Zhang et al. compared fentanyl to sufentanil and POD and POCD onset. Sufentanil demonstrated superior hemodynamic stability and provided effective analgesic and sedative effects compared to fentanyl, with no increased occurrence of adverse events. Notably, patients receiving sufentanil experienced quicker recovery, exhibited reduced maximum SctO decline, and had a lower incidence of POCD compared to those receiving fentanyl. These results indicate that sufentanil may be preferable for elderly patients undergoing open surgery.[72]

3.9 | General versus regional anesthesia and risk of POCD and POD

A recent comprehensive review comparing the onset of POCD with general versus regional anesthesia was headed by Davis et al.[73] Twelve of the 16 investigations concluded that, 7 days following surgery, there was no discernible difference in cognitive performance between general and regional anesthetic. Hole et al. examined the effects of epidural anesthesia against general anesthesia in patients undergoing hip replacement surgery among the remaining four. Seven of the 31 patients under general anesthesia and none of the patients under regional anesthesia had postoperative mental abnormalities.[74]

Patients undergoing orthopedic surgeries were randomly assigned to receive either spinal anesthetic or general anesthesia in research of Jones et al. A follow-up of 3 months was conducted, and 129 patients finished cognitive function testing. The choice reaction time test showed a substantial improvement ($P < 0.05$) in favor of general anesthesia.[75]

The effects of local and general anesthesia on patients undergoing cataract surgery were compared by Karhunen et al. In one subset of memory testing, the Luria test, there was a statistically significant advantage favoring general anesthetic over local anesthesia, despite the fact that most cognitive tests revealed no difference between the two groups. However, Karhunen et al. did observe an overall decline in memory function in both anesthesia groups.[76] The effects of epidural and general anesthesia on patients having hip and knee surgery were compared by Mandal et al. At 7 days following the procedure, they discovered a significant difference, favoring regional anesthesia only in the mini-mental status examination.[77]

3.10 | Inhalational versus total intravenous general anesthesia and risk of POCD and POD

Negrini et al. completed a comprehensive review in which they assess the incidence of POCD and POD with two different types of general anesthesia: whole intravenous general anesthesia versus inhalational general anesthesia. According to the results of this systematic review and meta-analysis, which are consistent with a previous Cochrane systematic review from 2018 that examined the same issue findings, POCD-DCR may be less common in the first 30 days following surgery when total intravenous anesthesia (TIVA) is utilized as opposed to inhalational anesthesia.[78] Propofol and TIVA may be beneficial in reducing POCD because of their capacity to lower inflammation. Research has indicated that propofol has anti-inflammatory characteristics when compared to inhalational drugs.[79] Additionally, in vivo study results have shown that animals given propofol had lower levels of circulating cytokines and other inflammation mediators.[15] It is true that further research is needed to properly understand the possible function anesthetics may have in the inflammatory cascade. Sevoflurane and other inhalational agents have some evidence to support their usage, especially in ischemia–reperfusion cell models. Nonetheless, in the context of cardiopulmonary bypass surgery, results supporting inhalational anesthetics in ischemia–reperfusion models have been produced.[80]

3.11 | Propofol and risk of POCD development

An investigation on the effects of inhalation and propofol anesthesia on postoperative cognitive dysfunction in elderly noncardiac surgery patients was carried out by Pang et al. on 1854 patients in this meta-analysis. Comparing propofol anesthesia to inhalation anesthesia, they discovered that the incidence of POCD was considerably reduced between postoperative days 2–6 (risk ratio [RR]: 0.37, 95% CI: 0.15–0.88, $P = 0.025$). Additionally, the mini-mental state examination (MMSE) scores after propofol anesthesia were notably higher than those after inhalation anesthesia (standard mean difference [SMD]: 0.59, 95% CI: 0.07–1.11, $P = 00.026$). Furthermore, levels of IL-6 and TNF-α were significantly lower after propofol anesthesia compared to inhalation anesthesia (SMD: −2.027, 95% CI: −3.748 to −0.307, $P = 0.021$; SMD: −0.68, 95% CI: −0.93 to −0.43, $P < 0.001$). Resumed propofol anesthesia demonstrates superiority over inhalation anesthesia in reducing the incidence of early POCD.[81]

3.12 | Pain sparing post-surgery to avoid POCD and POD development

In their investigation, Chi et al. used aged mice that had laparotomies performed while being administered various analgesics. The study suggests that providing older rats with enough postoperative analgesia can delay the onset of spatial memory impairment after isoflurane anesthesia and laparotomy. Moreover, memantine administration pharmacologically alleviated spatial memory impairment in rats without receiving analgesic treatment, and the observed postoperative memory losses associated with an increase in hippocampal NRs. These findings highlight the need of postoperative pain treatment in preventing older patients' POCD.[82]

3.13 | Bispectral index guided anesthesia: simply a MUST?

A number of randomized controlled experiments have been carried out to assess how anesthetic depth affects POD and POCD. Though there is still disagreement over it. The kind and degree of anesthetic, the kind, length, and invasiveness of the surgical procedure, the age of the patient, and their inherent qualities are some of the variables affecting the results. Among these factors, studies highlight that the depth of anesthesia is often the most influential.

Monitoring of the electroencephalogram (EEG), which includes the BIS, E-entropy, auditory evoked potential (AEP), and the narcosis index, is a simple technique that is frequently used in surgery to determine the level of anesthesia.[83] In addition to providing extensive information about the level of anesthesia, the BIS is used to determine the lowest dose of narcotic medicine needed to induce and sustain anesthesia.[84] A BIS of 35 or less was categorized as deep anesthesia, whereas a BIS of 50 or higher was termed light anesthesia.[85]

According to Needham et al., the value is not supposed to be evaluated at itself, but a correlation in the time is indispensable, because POCD is directly correlated to the time spent with a BIS of <40.[86] Youngli et al. conducted a recent systematic review involving over 3100 patients to investigate the role of anesthesia depth in triggering POD and POCD, as well as inflammation (48). A meta-analysis utilizing a random-effects model revealed a significantly reduced incidence of POCD in patients receiving light anesthesia on the first day after surgery (RR = 0.14, 95% CI: 0.04–0.45; I2 = 0.00, $P > 0.10$), as well as after 90 days (RR = 0.72, 95% CI: 0.54–0.96; I2 = 0.00, $P > 0.10$).

Quan et al. conducted a study involving 120 elderly patients (aged >60 years) undergoing abdominal surgery under intravenous anesthesia monitored by BIS. Patients underwent pre- and post-surgery evaluations (at 7 days and 3 months) using a battery of nine neuropsychological tests. Results revealed a higher incidence of POCD at 7 days in the light anesthesia group compared to the deep anesthesia group (19.2% vs. 39.6%, $P = 0.032$ vs. $P = 0.558$). Laboratory analysis further supported these findings, demonstrating lower levels of CRP and IL-1ß in the deep anesthesia group compared to the light anesthesia group ($P < 0.05$). In conclusion, deep anesthesia guided by BIS, in combination with intravenous anesthesia, appears to offer superior outcomes in terms of postoperative POCD and inhibition of peripheral inflammation compared to light anesthesia.[87] Ling et al. conduced a systematic review with the goal to establish a relationship among anesthesia's depth and POCD and POD, mortality and length of the hospital stay. As reiterated many times, these two complications have been extensively studied in the cardiology field. Kunst et al., in their study monitoring elderly patients undergoing coronary artery bypass grafting, discovered that BIS monitoring significantly decreased postoperative delirium. However, they detected no difference in cognitive function at 6 weeks compared to the control group without BIS monitoring.[88]

Quan et al. showed that deep anesthesia, as opposed to light anesthesia, decreased the incidence of short-term POCD in patients undergoing abdominal surgery under complete intravenous anesthesia.[87] On the other hand, Wildes et al. compared an EEG-guided group getting standard anesthetic care with a control group during the ENGAGES trial, which involved elderly patients undergoing major surgery. The incidence of POD did not differ between the two groups, according to their findings.[89]

Although a number of meta-analyses have been carried out, none of them have yet taken into account the results of the most recent BALANCED study or its at-risk substudy. The BALANCED Anesthesia Study, which involved 6644 patients, demonstrated that intentionally aiming for light anesthesia (BIS reading of 50) with a volatile-agent-based general anesthetic does not yield appreciably better results than intentionally aiming for deep anesthesia (BIS reading of 35).[90]

Ling et al. summarized their study reporting that the depth of anesthesia stands as one of the potentially adjustable risk factors to mitigate the impact of anesthesia on patients' cognitive function. A high BIS value correlated with reduced POD and POCD at 3 months among elderly patients. However, this association did not result in a significant difference in length of stay and mortality.[91]

These studies suggest that the length and degree of anesthesia may have a cumulative effect; however, they are not conclusive. Furthermore, during preoperative screening, the use of BIS in the high-risk group for POCD may function as a useful tool for tracking anesthetic modifications intended to lower the risk of POCD in addition to perhaps serving as an indicator for predicting the development of POCD.[3]

3.14 | Subjective risk factor for POCD and POD development

The secret to successfully treating or preventing POCD and POD high-risk patients before closely monitoring them using a risk-adapted logic may lie in identifying their characteristics. Additionally, understanding the characteristics of the individuals is crucial to deciphering the causes behind POCD and formulating preventative or therapeutic measures.

While gender has not been proved to be a risk factor in and of itself, older men with an APOE4 allele were found to be considerably more likely to experience post-traumatic stress disorder (POCD) within a week (odds ratio [OR], 1.89, 95% CI: 1.36–2.6278, $P < 0.01$) when using the random-effects model. Furthermore, in the medium-term, 1–3 months following surgery, a significant correlation was seen between APOE4 and POCD (OR: 1.67, 95% CI: 1.003–2.839, $P = 0.049$).

However, APOE4 did not exhibit a significant association with POCD 1 year after surgery (OR: 0.98, 95% CI: 0.57–1.70, $P = 0.9449$)

or with POD (OR: 1.28, 95% CI: 0.85–1.91, $P = 0.23$).[92] Alcohol abuse is also a recognized risk factor.[46,93–95]

3.15 | Aging and risk of POCD and POD

Age-wise, the first consensus judgment on POCD and POD has now been achieved, covering both short- and long-term perspectives.[96–98] There are different ideas linking aging with POCD. Persistent, low-level neuroinflammation is a key trait that is linked to the cognitive impairment associated with aging, according to Luo et al. It is interesting to note that new research indicates that the neuroinflammatory mechanisms causing POCD change with age. This suggests that the development of postoperative cognitive impairment may be influenced by age-related changes, specifically neuroinflammation.[99]

3.16 | Cognitive reserve and risk of POCD

The most commonly assessed cognitive reserve measure was educational attainment, and longer educational attainment was associated with a lower risk of post-OCD disease (RR per year increment 0.90; 95% CI: [0.87; 0.94]). Furthermore, every extra year of education was associated with a 10% reduction in the incidence of POCD over a six-month follow-up period. These results highlight the fact that more years of education are protective against POCD, while lower levels of education are generally recognized as a risk factor.[100]

3.17 | Future projects on risk of POCD and POD with the assistance of artificial intelligence

Artificial intelligence (AI)-assisted initiatives in the future have enormous promise in a variety of healthcare and cognitive assessment fields. The effect of AI-based general anesthetics on cognitive outcomes has been clarified by Lunardini et al., especially in relation to POCD in surgical patients. Research has clarified the complex relationship—particularly in older patients—between surgical anesthetic and POCD, emphasizing the necessity of thorough monitoring techniques.[101]

Furthermore, identifying those who are at risk of developing Alzheimer's disease (AD) from moderate cognitive impairment (MCI) is a major difficulty in the field of AD. The potential of machine learning (ML) algorithms in conjunction with neuropsychological measurements has been investigated by Veneziani et al. in order to provide a potent method for the automatic classification of MCI patients and the prediction of AD conversion. The results of meta-analyses show that machine learning (ML) can be effectively applied to neuropsychological measures even in the face of heterogeneity, especially when it comes to optimizing classification accuracy for screening.[102]

The translation of AI-driven insights into clinical practice has the potential to revolutionize cognitive assessment methodologies, offering more accurate diagnoses and personalized interventions for patients.

4 | CONCLUSIONS

In conclusion, a thorough and multidisciplinary strategy that takes into account surgical, anesthesiological, and patient-related aspects is necessary for the prevention and management of POD and POCD. The risk factors to avoid are similar, given that POD and POCD are assimilable as two very similar illnesses, with POD being an acute condition and POCD representing a sequela that lasts over time. For surgery patients, healthcare providers can improve overall quality of care and maximize cognitive results. In order to improve our comprehension of the mechanisms underlying both complications and provide focused strategies to lessen their effects on patient morbidity and death, further research and cooperation are necessary.

AUTHOR CONTRIBUTIONS

Conceptualization: Andrea Tinelli and Giovanni Pecorella. Methodology: Giovanni Pecorella and F.dR. Formal analysis: Giovanni Pecorella. Investigation: Martina Licchelli and Gaetano Panese. Data curation: Martina Licchelli and Gaetano Panese. Writing—original draft preparation: Giovanni Pecorella. and Filippo De Rosa. Writing—review and editing: Andrea Tinelli and Josè Tony Carugno. Supervision, Andrea Tinelli, Filippo De Rosa and Josè Tony Carugno. Project administration: Giovanni Pecorella and Gaetano Panese. All authors have read and agreed to the published version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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