



# Incidence and Factors Related to Prolonged Postoperative Cognitive Decline (POCD) in Elderly Patients Following Surgery and Anaesthesia: A Systematic Review

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**Aim:** The aim of this systematic review is to explore the current literature to provide evidence regarding the incidence and risk factors of prolonged POCD in elderly patients following cardiac and non-cardiac surgical interventions.

**Methods:** The PubMed and Google Scholar databases were searched using appropriate keywords and search engines for adequate evidence from studies meeting the inclusion criteria so as to reveal the end-point, which was the presence of prolonged POCD in elderly patients following surgery and anaesthesia. The incidence of POCD at different time intervals and the variables predicting the occurrence of POCD were analysed.

**Results:** The results of 23 articles covering 5077 patients (3694 non cardiac and 1383 cardiac surgeries) were carefully analysed. POCD occurs from the first postoperative day and lasts for potentially long periods. The incidence of POCD in this review ranged from 2.2% to 35.7%. More specifically, it ranged from 2.2% to 31.5% in non-cardiac surgeries and 11.8% to 35.7% in patients who had undergone cardiac surgeries. Some of the independent risk factors (predictors) for the development of POCD were advanced age, high concentration of neuroinflammatory mediators detectable in plasma, low SpO<sub>2</sub>, longer anaesthetic and surgical duration, and depth of anaesthesia.

**Conclusion:** This review can only provide limited evidence of prolonged POCD (more than a year) and further research that involves better study designs, larger samples, involving longer follow-up, and at different sites (multicentre) is highly advised. This in turn may help researchers and clinicians to discover the actual causes and risk factors and develop appropriate preventive and treatment protocols to tackle POCD in the ageing surgical population.

**Keywords:** incidence, postoperative, cognitive dysfunction/decline, elderly patients, surgery, anaesthesia

## Introduction

Perioperative cognitive impairment and cognitive decline (dysfunction) are commonly seen side effects among elderly surgical patients who have undergone either cardiac or non-cardiac surgical interventions. Both postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are common neurocognitive complications affecting the postoperative course and outcome of the care of older patients following surgical and anaesthetic treatments for different pathologies.<sup>1-4</sup>

Specifically, POCD occurs more often in patients aged  $\geq 75$  years who have undergone major cardiac and non-cardiac procedures involving massive tissue trauma and systemic neuroinflammatory surges.<sup>5-7</sup> The exact mechanisms, causes, risk factors, and incidence of POD and POCD are still not known, with reported incidence ranging from 13% to 50%.<sup>8</sup> This makes risk stratification of patients for POCD challenging, and as such, the diagnosis and treatment of POCD remains unresolved in the geriatric population after surgery and anaesthesia.<sup>2,8-10</sup>

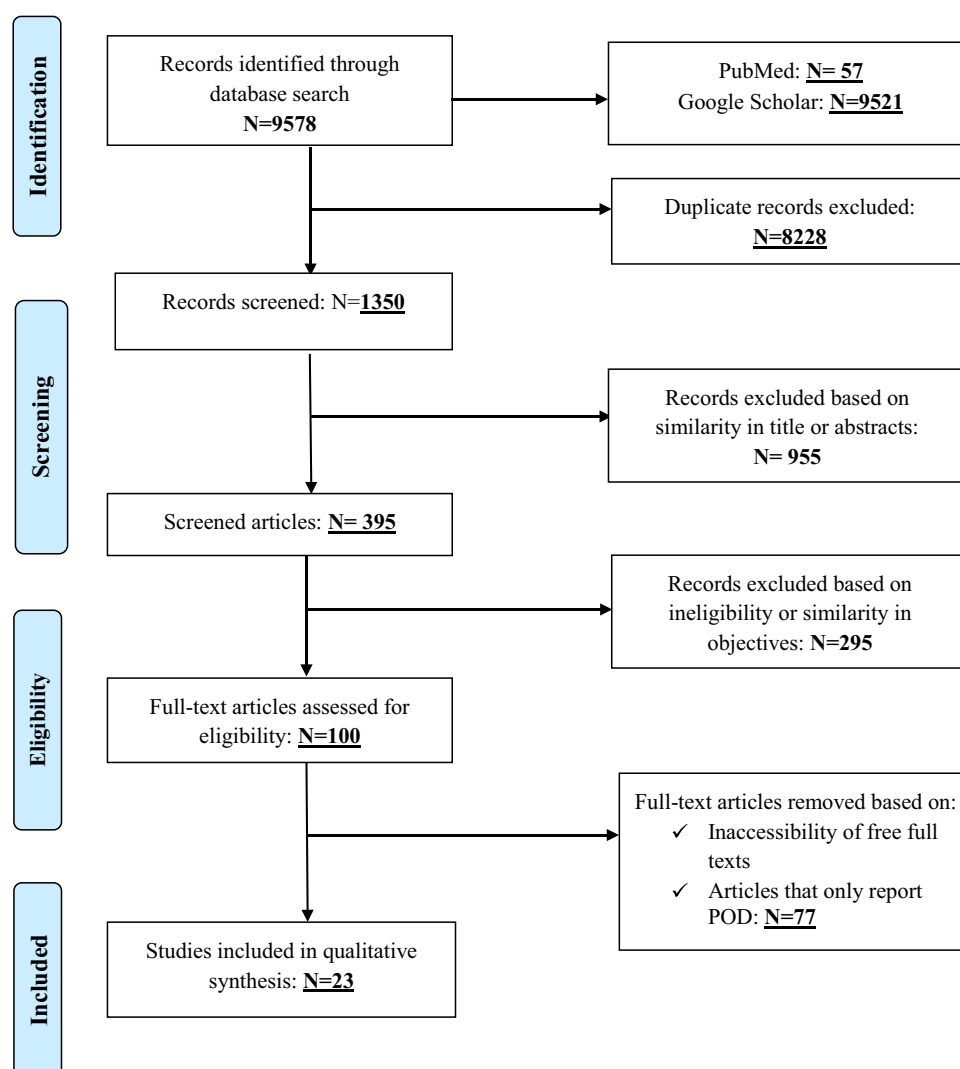
As has been demonstrated in several studies, the risk factors involved in the development of POCD are: a) patient related factors, ie, advanced age, frailty, multimorbidity, presence of preoperative neurocognitive impairment, mobility and malnutrition issues, and polypharmacy; b) surgery-related factors, ie, prolonged and extensive surgeries with substantial tissue trauma and inflammation, such as cardiac surgeries; and c) anaesthesia-related factors, ie, the use of various general anaesthetics, such as inhalational anaesthetics, sedatives, and benzodiazepines, and depth of anaesthesia.<sup>11–13</sup> POD and POCD may seem to be similar, though they are different entities. According to the *Diagnostic and Statistical Manual of Mental Disorders* fifth Edition (DSM-V), delirium is defined as an acutely developing deficit in attention (reduced ability to direct, focus, sustain, and shift attention), coupled with a change in cognition (memory deficit, disorientation, or perceptual disturbance).<sup>1</sup>

On the contrary, defining and diagnosing POCD is challenging in that it mainly refers to a longer-lasting decline in cognitive function mostly following surgery and anaesthesia. Diagnosis of POD is based on the presence of suggestive symptoms. To have a clear definition of POCD, one must evaluate preoperative (baseline) neurocognitive function to know how many of these functional parameters are missing post-surgery and anaesthesia. Due to their close similarity, many clinicians face difficulties in differentiating POD from early POCD. Given the fact that POD is a strong predictive variable for POCD, it is always seen with in the first 3 days post-surgery and anaesthesia, whereas early POCD occurs in the last days of the first week, with the potential to stay longer.<sup>14</sup> Although POCD in some patients can stay for weeks to months, it can persist for longer periods (up to over a year), causing permanent dementia in some patients.<sup>15–18</sup> There is limited availability of data on the occurrence of POCD for prolonged periods and even persistent cognitive impairment. The purpose of this review is to explore if there is evidence showing prolonged POCD in elderly patients following anaesthesia and surgery, as these patients are potentially prone to developing permanent cognitive decline and dementia.

## Methods

We conducted this review from October 2022 to January 2023. The Medical Subject Headings (MeSH) platform was used to generate appropriate keywords for our search to give us an adequate number of studies for our review. Therefore, a literature search was performed on Google Scholar and PubMed using the keywords ‘incidence’ AND ‘postoperative’ AND ‘cognitive dysfunction’ OR ‘cognitive decline’ AND ‘elderly patients’. Filters were used to get free and full-text articles using different study designs in the last 10 years on elderly patients aged  $\geq 60$  years. We obtained a total of 9578 articles (57 from PubMed and 9521 from Google Scholar). After removing duplicates ( $n=8228$ ), 1350 articles remained. Of these, 955 were excluded after going through their titles and abstracts. Of the 395 articles screened, 295 were removed for such reasons as ineligibility or similarity in objectives. Of the remaining 100 studies, 77 were excluded for such reasons as inaccessibility of free full texts and for reporting POD alone. Finally, 23 studies were included to conduct the final qualitative review, and the references cited in each eligible study were examined to identify their appropriate use. This systematic review was done in line with the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Figure 1).

The primary outcome of this review is exploring the incidence of prolonged postoperative cognitive decline in older ( $\geq 60$  years) patients following both cardiac and non-cardiac surgeries. We have included evidence where authors made a follow-up of patients at different time points up to 1 year. The secondary outcomes focused on risk factors associated with the development of prolonged POCD in this age group. We included data that were published between 2012 and 2022. These included multiple study designs and data-analysis methods reporting the incidence of POCD and the risk factors related to it. Literature reporting any cognitive abnormality other than POCD was excluded, but we used studies that reported POCD that occurred immediately after surgery and POCD that persisted up to 1 year. We appraised the quality of the articles used to determine if they were methodologically sound and met the inclusion criteria. We did this using the mixed-method appraisal tool.<sup>20</sup> The relevant data from each selected study were carefully extracted and are summarised in tables (Tables 1 and 2).



**Figure 1** PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guideline showing the allocation of evidence for final review.

**Notes:** PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10):e1-34. Creative Commons.<sup>19</sup>

## Results

### Basic Description of Reviewed Literature

Our electronic database search (Figure 1) yielded 9578 citations (57 from PubMed and 9521 from Google Scholar). A total of 395 articles were screened, and of these we assessed 100 articles to get 23 studies to conduct our final review. Of these 23 articles, there were two cross-sectional studies, 13 randomised controlled trials, two clinical trials, and six cohorts (observational studies) (Tables 1 and 2).

### Incidence of POCD

The incidence of POCD in aged patients who had undergone cardiac and non-cardiac surgeries at different time points of the postoperative period was 2.2%–35.7%. The maximum incidence of POCD seen in those patients who had undergone non-cardiac surgery (n=3694) was 31.5% and the minimum 2.2%, which were measured at the first postoperative week and at 3 months respectively. Among the study participants had undergone cardiac surgery (n=1383), the maximum incidence of POCD was 35.7% and minimum 11.8%. These two articles measured POCD at the first postoperative week. Regarding the follow-up time, five studies followed patients up to 12 months and four reported POCD at 3 months. There

**Table 1** Incidence of POCD and predicting factors in elderly patients after non-cardiac surgeries (n=16 articles)

Author, country	Study design	Sample size	Data analysis	Type of surgery	Age, years	Overall incidence (%)	Predicting variables
Tang <sup>20</sup> China	RCT	200	One way ANOVA, $\chi^2$ , Fisher's exact test	GI (rectal resection)	60–99	31.5 at week 1	Use of sevoflurane (no statistical significance)
Valentin <sup>21</sup> Brazil	RCT	140	Generalised estimation equation	Non-cardiac and non-neurologic	60–87	26 at week 1	High serum S100 $\beta$ and lack of dexamethasone premedication
Cosmo <sup>22</sup> Italy	RCT	571	Pearson $\chi^2$ test and Spearman rho test	Major abdominal	>60	10.5 at week 1	Not specified
Saleh <sup>23</sup> China	RCT	141	$\chi^2$ test and logistic regression	GI	>60	26 at week 1	Advanced age, longer anaesthesia and surgical duration, and lack of preoperative cognitive training
Silbert <sup>24</sup> Australia	Prospective observational clinical trial	351	t, Mann–Whitney U tests	Non-cardiac	>60	2.6 at 12 months	Presence of preoperative cognitive impairment
Mehanna Gabrielli <sup>25</sup> USA	Prospective cohort	167	Parametric and non-parametric methods	Spine, thoracic, urological, and general	>65	2.2 at 3 months	No predicting variable found
Zhu <sup>26</sup> China	Double-blinded randomised clinical consort	134	$\chi^2$ test, repeated-measure ANOVA	Orthopaedic surgery	>65	9 at 3 months	High serum levels of IL1 $\beta$ , IL6 and TNF $\alpha$ (P<0.05)
Zhu <sup>27</sup> China	RCT	132	One-way ANOVA and $\chi^2$ test	Gastric cancer resection	65–92	15 at week 1	No predictor variable found
Xi <sup>28</sup> China	RCT	68	Fisher's exact test, $\chi^2$ test	GI tumour resection	>62	31.3 at day 3	—
Wang <sup>23</sup> China	Prospective cohort	126	Multiple logistic regression	Hip-fracture fixation	>65	29 at week 1	High expression of FKBP51 in leucocytes and glucocorticoid resistance
Sun <sup>29</sup> China	RCT	300	Repeated-measure and one way ANOVA	Hip-joint replacement	75–90	9.3 at week 1	No predictor variable found
Fan <sup>30</sup> China	Retrospective analysis	572	Logistic regression	Laparoscopic GI	>60	12 at day 3	History of cerebral infarction, low SpO <sub>2</sub> , and longer duration of surgery
Quan <sup>31</sup> China	RCT	120	Spearman's, Mann–Whitney U, and $\chi^2$ tests	Abdominal	>60	12.5 at 3 months	Light anaesthesia
Orhun <sup>32</sup> Turkey	RCT	116	Student's t and Fisher's exact tests	General and urological	>60	25 at week 1	No predictor variable found
Zhang <sup>13</sup> China	RCT	392	Logistic regression	Major cancer	65–90	19 at week 1	No predictor variable found
Li <sup>12</sup> China	RCT	164	Unpaired t and Kruskal–Wallis tests	Knee arthroplasty	>65	13 at 12 months	No predictor variable found

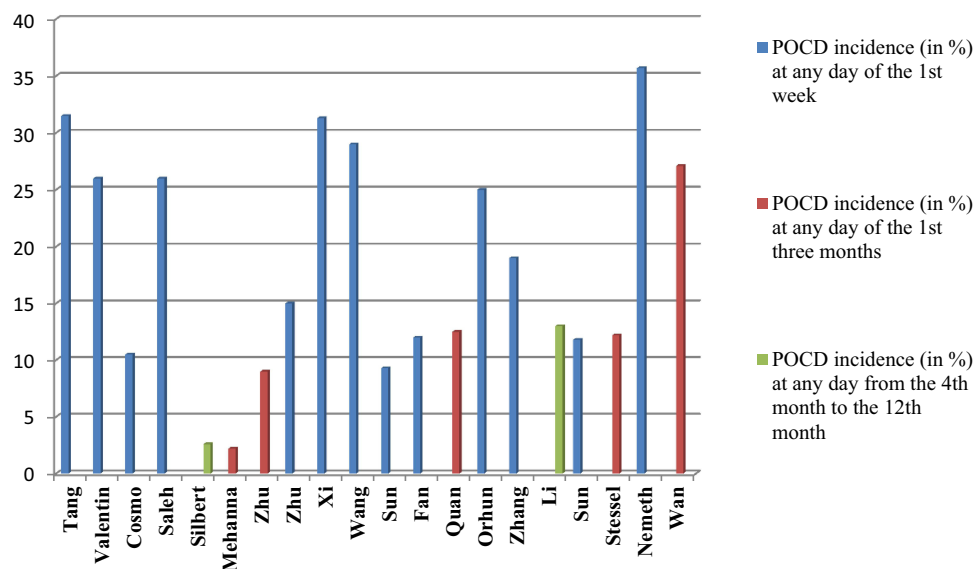
**Abbreviations:** GI, gastro-intestinal; RCT, randomised controlled trial; SpO<sub>2</sub>, saturation of peripheral oxygen.

**Table 2** Incidence of POCD and predicting factors in elderly patients after cardiac surgery (n=7 articles)

Author, country	Study design	Sample size	Data analysis	Type of surgery	Age, years	Overall incidence (%)	Outcome variables
Sun <sup>33</sup> China	RCT	340	Multivariate logistic regression	Radiofrequency ablation for AF	75–89	11.8 at week 1	Intra-operative haemodynamic instability
Stessel <sup>34</sup> Belgium	Observational prospective cohort	180	Repeated-measure ANOVA	Endo-CABG	>64	12.2 at 3 months	Not specified
Nemeth <sup>35</sup> Hungary	Controlled prospective observational	42	Spearman correlation	Cardiac surgery	>60	35.7 at week 1	No predictor variable found
Wan <sup>36</sup> China	Cross-sectional	362	Logistic regression	CABG	>60	27.1 at week 3	Red cell distribution width of >14.7%
Brown <sup>37</sup> USA	Prospective observational	142	Linear regression	Primary or reoperative aortic bypass/aortic valve surgery	62–78	Not specified	POD predicts POCD at 1 month, not at 1 year
Sauër <sup>2</sup> Netherlands	Multicentre follow-up	184	Mann Whitney U, linear regression	Isolated CABG and valve surgery	>65	Not specified	POD predicts POCD at 1-month follow-up
Nomura <sup>38</sup> USA	Observational follow-up	133	Linear regression	CABG and valve surgery	>61	Not specified	Frailty predicts POCD at 1 month, not at 1 year

**Abbreviations:** RCT, randomised controlled trial; Endo-CABG, endoscopic coronary artery bypass grafting; POD, postoperative delirium; POCD, postoperative cognitive dysfunction.

was only one article that reported incidence of POCD at the third postoperative week (27.1%), and in the remaining 13, POCD was reported in the first postoperative week with a maximum incidence of 35.7% (cardiac surgery patients) and minimum incidence of 9.3%, which was present in patients who underwent hip-joint replacement (Figure 2).

**Figure 2** Incidence of POCD (postoperative cognitive decline) at three time points in the postoperative period in older patients undergone both cardiac and noncardiac surgeries.

## Predicting Variables of POCD in Elderly Patients

The authors mentioned diversified variables to independently predict POCD in elderly surgical patients. Among these variables, advanced age, elevated serum levels of different categories of inflammatory mediators, longer anaesthetic and surgical duration, and light depth of anaesthesia are the most commonly reported. There is a positive relationship between the presence of POD and POCD. Furthermore, concomitant frailty, low oxygen saturation, presence of preoperative cognitive impairment, and intraoperative haemodynamic instability are also reported as predictors of POCD. There are also authors ( $n=7$ ) who neither found nor specified any variable to predict POCD (Table 1 and Table 2).

## Discussion

In this systematic review, we aimed to show the incidence of prolonged POCD and the possible predictor variables in elderly patients who went through the course of surgery and anaesthesia for both cardiac and non-cardiac surgical pathologies in the postoperative period. Our literature search demonstrated a wide range of incidence of POCD, from as low as 2.2% (in non-cardiac surgery) to as high as 35.7% (in cardiac surgery). The possible explanation for this variation is that the authors used different measuring tools to define POCD, as the specificity, sensitivity, and validity of these tests is highly variable. The shortest time that patients were followed (observed) until they develop POCD was the first days of the first week and the longest time was 12 months (five articles). This again can be one reason for the variation in POCD incidence. One review in 2012 reported that POCD subsides a few days or weeks post-surgery.<sup>21</sup>

Though limited in number, there are studies reporting the incidence of prolonged POCD of up to 5–7 years post-surgery and anaesthetic exposure. POCD significantly affects the way old people live, compromising their quality of life and independence, which in turn increases health care–related costs, rate of hospitalizations, and overall socioeconomic burden. The risk of 1-year mortality also increases in elderly patients with POCD.<sup>22,23</sup>

We observed that advanced age and an increase in neuroinflammation are the predicting factors of persistent POCD. This finding is similar to a systematic review done by Susana and et al, in which advanced age and exposure to extensive surgical procedures and prolonged anaesthesia duration were found to be risk factors for the development of prolonged POCD.<sup>24</sup> It is known that the risk of having surgical pathologies and neurocognitive dysfunction increases with age. Due to such reasons, it is highly likely that this group of patients are at higher risk of developing POCD.<sup>25</sup> A systematic review of 22 articles reported that the incidence of POCD was 9%–54%, where advanced age was the main contributing factor.<sup>26</sup>

In this systematic review, the maximum incidence of POCD was 35.7%, which was measured in the first week post-cardiac surgery. A systematic review conducted by Patel et al reported a somewhat higher incidence of POCD (40%–60%), which was measured in the first 2 weeks post-cardiac surgical interventions. The authors of this review also reported the incidence of POCD at 3 months was 30%–40% and at 1 year was 10%–20%.<sup>27</sup> This supports the notion that the burden of POCD after cardiac surgery on elderly patients is significantly higher than most clinicians think.

The maximum incidence of POCD in patients who underwent non-cardiac surgeries was 31.5%, which was found at the first week following surgery. This result is higher than that of a systematic review done by Kitsis et al, where most of the reviewed articles reported the incidence of POCD to be 10%–15% with a median incidence of 19.3%.<sup>28</sup> This difference shows that there is a wide variation among studies regarding the occurrence of postoperative cognitive decline in elderly surgical patients. Even though the causes of the development of POCD seem to be similar, there is a higher incidence of POCD in cardiac surgeries than in non-cardiac surgeries, and the mechanism involved to explain this discrepancy is that there is non-physiological perfusion during cardiopulmonary bypass and presence of cerebral microemboli.<sup>23,29</sup>

In this systematic review POD, which was measured by various test batteries, was found to be one of the independent risk factors to predict POCD. This finding is similar to the results of a study done by Brown et al, where the incidence of POD was 53.5%, and of these patients, a significant number had developed POCD at 1 month ( $P=0.02$ ) and 1 year ( $P=0.033$ ) following cardiac surgeries, respectively. The mechanism for the positive association of POD with POCD, as suggested by the authors of this article, is threefold: 1) insults in surgical neuroinflammation and altered cerebral blood

flow predispose aged surgical patients to POD and concomitant (long-lasting) POCD; 2) disturbance of the sleep–wake cycle commonly seen in patients with delirium might lead to changes in cognitive function; and 3) delirium causes changes in white-matter integrity and injury to the subcortical area of the brain, and these changes in turn negatively affect the speed of information-processing capacity in the aged surgical population, hence POCD.<sup>29</sup>

Factors like frailty and presence of preoperative cognitive impairment are also independent risk factors of POCD in both cardiac and non-cardiac elderly surgical patients.<sup>2,29–31</sup> This finding is in line with a systematic review and meta-analysis of 18 studies by Gong et al, 2022, where frailty was associated with an increase in 30-day and 6-month mortality rate. They also reported that the presence of frailty was a predictor of postoperative neurological, renal, vascular, and respiratory system complications in patients who went through both cardiac and non-cardiac surgical procedures.<sup>32</sup>

Even though the mechanism remains unclear, the surge in neuroinflammatory mediators following both cardiac and non-cardiac surgical interventions has been reported to be a strong predictor of POCD. We have seen that most of the literature in this review article supported this argument (n=8).<sup>25,33–39</sup> This is supported by a review done in Germany, where the authors found a strong association of general anaesthesia and neuroinflammation with prolonged POCD. The authors of this systematic review have specifically stated that anaesthetics generally increase neuroinflammation by altering the DNA expression and the function of histone-modifying enzymes of cells and that these changes in turn increase the blood concentration of some pro-inflammatory mediators like TNF $\alpha$ , IL6, and IL1B. Consequently, these factors challenge the normal integrity of the blood–brain barrier of the ageing brain in surgical patients, compromising their cognitive function.<sup>40</sup>

We have seen that no authors followed patients and measured the incidence of POCD for a prolonged time (more than a year). They did not specifically mention any justification for that, but put it as a limitation of their studies and recommended researchers to undergo further research involving longer follow-up.<sup>25,31,34,38,41–43</sup> The authors of all of the reviewed articles of our systematic review reported that surgical stress and neuroinflammation are the main predictors of the development of POCD. A 4-year follow-up study done in 2021 suggested that prophylactic (preoperative) administration of corticosteroids reduces the occurrence of longer POCD in elderly patients. They explained that administering 0.1 mg/kg of preoperative dexamethasone decreases the inflammatory response to surgical trauma following cardiac surgeries. This is evidenced by a decrease in the incidence of POCD in patients who took dexamethasone compared to the placebo group.<sup>44</sup>

## Strengths and Limitations

The strength of this review is that we have used a justifiable number of recent studies with diverse methodologies, which is helpful to avoid possible confounders. As a limitation, we extracted articles only from PubMed and Google Scholar, which might have limited our access to literature with more important information on prolonged POCD.

## Conclusion

We have seen very limited evidence showing incidence of prolonged POCD (more than a year), and further research is highly advised that involves better study designs, larger samples, longer follow-up, and different sites (multicentre). This in turn may help researchers and clinicians uncover the actual (root) causes and risk factors of long-lasting postsurgical cognitive decline and associated dementia and to develop appropriate preventive and treatment protocols to tackle POCD in the aged surgical population.

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## Disclosure

The authors declare that there are no conflicts of interest.



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