Postoperative cognitive dysfunction in older surgical patients associated with increased healthcare utilization: a prospective study from an upper-middle-income country

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Abstract

Background: Perioperative neurocognitive disorder includes postoperative cognitive dysfunction (POCD) and postoperative delirium (POD). Concerning inconclusive consequences of POCD compared with POD, we explored the association between either POCD or POD and functional decline as well as healthcare utilization.

Methods: Patients aged at least 60 years who underwent a major operation were enrolled. POCD was defined as a decrease in the Montreal Cognitive Assessment (MoCA) score (≥ 2) 1 week after surgery. Postoperative delirium (POD) was defined according to the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The primary outcome was instrumental activities of daily living (IADLs) 3 months after discharge. Secondary outcomes were the length of stay (LOS), hospital cost, and factors that affected functional decline 3 months after surgery. The multivariate model, including potential confounding factors, namely age, gender, surgery type, and postoperative complications, was used to analyze possible factors that influenced a reduction in function, and the results were expressed by using adjusted relative risk (RR) and 95% CI.

Results: Two hundred eighty-nine patients with a mean age of 72 years were enrolled. The incidence of POCD at 1 week was 28.5%. At their 3-month follow-ups, the patients with POCD were not associated with IADL decline. Nevertheless, patients with POCD were more likely to need a prolonged LOS (11 days [1, 46] vs. 8 days [2, 42]; P = 0.01), and incur higher hospital costs (8973.43 USD [3481.69, 11 763.74] vs. 5913.62 USD [332.43, 19 567.33]; P < 0.001). Additionally, the patients experiencing POD demonstrated increased risks of reducing their IADLs (adjusted RR 2.33; 95% CI, 1.15–4.71; P = 0.02).

Conclusions: POCD at 1 week led to increased healthcare utilization in a middle-income country. POD during hospitalization was associated with a decline in function after surgery and increased health care utilization.

Keywords: Functional impairment, Hospital costs, Intensive care units, Mortality, Older patients, Postoperative cognitive dysfunction, Readmission, Surgical patients

Background

The number of older patients who undergo surgery has steadily increased due to the progressive aging of the population. Older people are vulnerable to perioperative...
complications. One of them is perioperative neurocognitive disorder [1], which includes postoperative cognitive dysfunction (POCD), a prolonged state of cognitive impairment that mainly affects higher-level cognitive skills and memory, and postoperative delirium (POD), an acute state of confusion and inattention. POCD was commonly found at approximately 17–43% [2–4], while the POD occurrence accounted for 20–55% [5, 6]. Unlike POD, POCD in terms of diagnosis and its consequences is not known widely [7]. POCD was first described in 1955 [8]. The pathophysiology of the condition has been proposed [9–12]. Neuroinflammation due to peripheral surgical trauma and volatile anesthetics is one of the most reported mechanisms. Furthermore, low intraoperative cerebral oxygenation and cerebral microemboli are other potential mechanistic etiologies. Cognitive deficits from POCD among older patients have been reported to vary, ranging from a few weeks to several years [11, 13, 14].

The diagnosis of POCD is contentious. It has been broadly defined as a drop in cognitive performance in a set of neuropsychological tests administered before and after surgery [15]. However, a variety of tests with different cutoff points have been applied. Considering the definitions of POCD utilized in the research arena, POCD may be underrecognized in some study cohorts and real-life practice because the set of cognitive batteries is not routinely examined either preoperatively or postoperatively. Furthermore, prior to the establishment of nomenclature for cognitive disorders in 2018 [16], subjective cognitive complaints and evidence of functional ability were not included in most POCD studies. In essence, although POCD was detected nearly 70 years ago, the consequences of the condition have yet to be discovered.

Normal cognitive function is necessary to maintain the usual activities of daily living of people. When POCD occurs, it might cause a decline in numerous cognitive domains, mainly the executive function and working memory, for several months. [17]. For this reason, POCD was discovered to be associated with a subsequent functional decline and increased morbidity and mortality after surgery, as shown by some studies [4, 18]. However, there is conflicting evidence for the association of POCD with postoperative function [19, 20]. As to mortality, the presence of POCD was associated with increased mortality in both noncardiac and cardiac surgery [21, 22]. Furthermore, a recent study revealed that the development of POCD was related to an increase in healthcare costs during the 1-year postoperative period [23]. Possible explanations could be differences in several factors: the time points for defining POCD, the diagnostic criteria applied, and the measurements used for functional outcomes. It should be noted that several studies could have reported cognitive disorders after surgery, such as the incidence of POCD, but did not do so. The reports commonly mixed the effects of POCD and POD as the analysis also included POCD with POD [24], and some studies might not have the details of delirium assessment when POCD was documented [22, 25].

In the present study, our objective was to investigate the effects of the association between POCD and functional decline after surgery. We hypothesized that POCD might produce unfavorable outcomes similar to those of POD but to a lesser extent. Therefore, the study explored the relationship between POCD and a reduction in function 3 months after the operation as well as other aspects (length of stay in an intensive care unit (ICU) and hospital, mortality rates, and cost of healthcare). Furthermore, POD and POCD could occur during the same period, so the association between POD and interested outcomes was also investigated. Additionally, factors that affected functional decline 3 months after surgery were also evaluated.

**Materials and methods**

**Study design and participants**

This prospective cohort study was conducted at a large university hospital and approved by the Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si 515/2017). We recruited Thai-speaking patients over 60 years of age admitted and scheduled for major elective surgery with general anesthesia. "Major surgery" was defined as a procedure involving organ ischemia, high intraoperative blood loss, high noradrenalin requirements, a long operating time, and perioperative blood transfusion. The postoperative factors considered in this study were the systemic inflammatory response and the need for intensive or intermediate care [26]. Patients were excluded if they were unable to undergo cognitive evaluations (for example, due to an inability to communicate in Thai); had severe visual or auditory dysfunction; had significant psychotic disorders affecting cooperation; had preoperative delirium; or were bedridden. We also excluded patients who could not be followed up during the postoperative period. The protocol for this study followed the guidelines of the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all study participants.

**Data collection**

Preoperatively, the baseline cognitive statuses of the patients were assessed using the Montreal Cognitive Assessment (MoCA)–Thai version [27] and the modified IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly) [28]. Furthermore, the functional statuses of the patients were determined using the
Barthel Index for activities of daily living (Barthel ADL Index) [29] and the Lawton–Brody Instrumental Activities of Daily Living (IADL) Scale [30]. Frailty status was evaluated using the FRAIL Scale (Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight) [31]. Depressive symptoms were evaluated with the PHQ-9 (the 9-item Patient Health Questionnaire) [32], while the quality of life was assessed with the EQ-5D-5L (the EuroQol 5-level, 5-dimensional questionnaire) [33]. Essential baseline information was collected from the enrolled patients: demographic data, comorbidities, body mass index, and the number of medications used. The baseline characteristics of the patients were obtained from medical records and interviews with the patients and their caregivers. Information relating to comorbid diseases and the types and sites of surgery was drawn from anesthetic records. In addition, a detailed analysis was made of intraoperative and postoperative data (type of surgery, anesthetic technique, operative time, and intraoperative and postoperative complications).

A psychologist visited enrolled participants with cardiovascular surgery on postoperative days 1 through 5 and those with noncardiac surgery on days 1 to 3. If the patients were medically stable (for example, no acute stroke or hypotension was present), their POD status was evaluated daily using the confusion assessment method for the intensive care unit (CAM-ICU) [34]. CAM-ICU was selected for use for several reasons: firstly, as the tool has formal instructions, healthcare personnel could evaluate postoperative patients similarly. Secondly, some patients were still intubated with respirators on the third postoperative day, so CAM-ICU was more appropriate for screening for POD than CAM. Lastly, healthcare personnel was formally trained in using the CAM-ICU in our setting.

Cognitive assessments
The cognitive test used in the current work was the MoCA–Thai version. It examines cognitive abilities in 8 domains (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation). Assessments were performed 1 or 2 days before surgery and at 1 week postoperatively (could be any day from D5 to D9). The total possible score was 30, with higher scores representing better performance [35]. The definition of POCD used in this investigation was based on the recommendation of an earlier study [16]. That work considered POCD as present when there was a postoperative decrease of 1 SD or more from the preoperative MoCA score. A previous validation study in the general Thai population reported that the SD of the MoCA was 2.14 [35]. Therefore, we defined POCD as a decrease of 2 or more points in the postoperative MoCA score.

Assessments to define the perioperative neurocognitive disorder
Figure S1 shows the timeline for assessing participants and defining POCD and POD. Preoperatively, MoCA and CAM-ICU were both administered. On postoperative days 1 through 5, CAM-ICU assessments were carried out daily by a psychologist. When CAM-ICU was positive, a geriatric fellow was notified to conduct a comprehensive clinical evaluation. If the participant exhibits clinical features of delirium according to the criteria of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [36], the diagnosis of POD is made. The MoCA test was administered one week postoperatively (could be any day from D5 to D9 depending upon the discharge planning) to determine their cognitive status. When a participant demonstrated a decline in the MoCA of at least two scores, a geriatric fellow was notified to conduct a clinical assessment. If the participant exhibits clinical features of delirium according to DSM-5 criteria, the diagnosis of POD is also made concomitant with POCD. For the participant with a decline in the MoCA score without POD, POCD was then defined. In case of a drop in MoCA occurred concurrently with POD assessed on a different day, the patient was also defined as having POCD with POD. After the patient was discharged, the medical record was thoroughly reviewed by the geriatrician team to identify any evidence of cognitive and behavioral changes. Whenever evidence in the medical record was sufficient to make a diagnosis of delirium, the POD was also defined.

Outcome assessments
Three months after their surgeries, the patients visited the postoperative cognitive disorder clinic specifically for a comprehensive evaluation for our project. Their health statuses were determined by a multidisciplinary team (mainly a geriatrician and a psychologist, but other disciplines were involved when appropriate). The geriatrician performed a physical examination and a relevant history of cognition and function. Formal cognitive tests were carried out using the MoCA. Functional evaluations were performed for both basic activities of daily living (BADLs) and instrumental activities of daily living (IADLs). The quality of life related to health was also assessed using the EQ-5D-5L. Additional investigations were carried out according to clinical indications. Additionally, the length of hospital stay, the number of days in an ICU, the number of deceased patients during hospitalization, and hospital costs were also collected.
Functional assessments

Functional status was assessed using Thai versions of the Barthel ADL Index and the Lawton–Brody IADL Scale. The Barthel ADL Index measures BADLs related to 10 items: feeding, grooming, transferring (bed to chair and back), use of the toilet, mobility, dressing, use of stairs, bathing, bowel control, and bladder control [29]. The Lawton–Brody IADL Scale evaluates 8 IADLs: the ability to use a telephone, shopping, cooking, household chores, laundry, travel, medication management, and personal finance management [30]. The scoring method for the Barthel ADL Index considers whether the person being evaluated receives help while doing each task. The items are also weighted. The resulting BADL range is 0 to 100. The Lawton–Brody IADL Scale scores each item as 0 (the presence of disability) or 1 (no disability), giving an IADL range of 0 to 8. With both instruments, lower scores indicate higher levels of dependency. In this study, IADLS were chosen to assess functional decline because IADLS represent more complex physical and cognitive tasks than BADLs as they are more vulnerable to early pathological events in the brain [37]. A functional decline was defined as a drop of 2 or more points from the preoperative IADL score to that achieved 3 months after surgery.

Factors associated with functional decline

We evaluated preoperative and postoperative variables that could contribute to functional decline after surgery, namely, an age of 75 years or higher, Charlson comorbidity index, preoperative frailty score, moderate functional dependence at baseline, preexisting cognitive impairment, and baseline depression [38]. In addition, as postoperative complications could be related to reduced function after surgery, those medical complications were collected from medical records (using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10]). For the preoperative variables, moderate functional dependence was defined as Barthel ADL Index scores 0 to 70 [39]. The Thai version of the FRAIL scale consists of 5 items: fatigue (having less energy than in the past), resistance (inability to climb stairs), ambulation (inability to walk 1 block), number of illnesses (more than 5 concurrent illnesses), and loss of weight (> 5% in 1 year) [31]. Since 1 point is assigned to each component, FRAIL scale scores of 3, 4, or 5 are defined as frailty. Furthermore, the PHQ-9 was administered to establish the severity of depressive symptoms [32]. The modified IQCODE for dementia screening was also used to identify significant cognitive changes, with dementia being defined as scores of 3.42 or higher [40].

Statistical analysis

The sample size calculation was performed using nQuery Advisor 6.0.1 software to investigate the association between POCD and a decrease in IADLs occurring 3 months after surgery in patients undergoing major surgery. Other research found that patients with POCD had an IADL decline of 57.1%, while those without POCD had an IADL decline of 27.3% [41]. With 90% power and a 5% type I error (two-sided), a sample size of 56 subjects with the functional decline was required. In previous studies, the incidence of POCD in noncardiac surgery ranged from 14.1% to 41.1% [4, 41]. Therefore, the incidence of POCD was estimated at approximately 28% for the sample size calculation in this study. A total of 200 participants needed to be enrolled.

Descriptive statistics were used to examine clinical characteristics, perioperative variables, and outcomes of functional decline. Demographic data were reported as numbers and percentages for categorical independent variables (sex, education, American Society of Anesthesiologists [ASA] classification, comorbidity, Lawton–Brody IADL Scale, readmissions, and mortality). Continuous independent variables were represented by the mean ± SD or median (minimum, maximum) for normal and non-normal distributions (age, Charlson comorbidity index, modified IQCODE, MoCA, Barthel ADL Index, hospital LOS, and quality of life).

Regarding the possible factors associated with postoperative functional decline, we evaluated preoperative and postoperative variables that could contribute to functional decline after surgery, namely, an age of 75 years or higher, Charlson comorbidity index, preoperative frailty score, moderate functional dependence at baseline, preexisting cognitive impairment, and baseline depression. In addition, postoperative complications could be related to reduced function after surgery. For univariate analysis, the Chi-square test or Fisher’s exact test was used to examine all categorical risk factors. The Mann–Whitney U test or Independent t-test was used to investigate all continuous data. The strength of the association between POCD and POD with functional decline after surgery was assessed using relative risk (RR) and 95% CI. Subsequently, factors with \( P < 0.20 \) from univariate analysis or clinical meaningful were entered into a multiple logistic regression model of postoperative functional decline, using Poisson models with a log link function and robust standard errors expressed. The strength of the association was presented as adjusted relative risk and 95%CI. \( P \)-value < 0.05 was considered to indicate statistically significant differences. PASW Statistics for Windows, version 18.0, and Statistic Analysis System (SAS) Studio were employed for the statistical analyses.
Results
This study enrolled 289 patients who underwent major elective surgery with general anesthesia between December 2017 and February 2020. All were over 60 years of age (mean, 72.32 ± 6.70 years), and the majority (80.3%) had less than 6 years of education. Most participants (76.4%) were ASA class III or IV, 57.8% underwent cardiac surgery, and 50.9% had a Charlson comorbidity index greater than 5. Although most subjects did not have BADL impairment, 27.7% had some impairment in the IADL score (<8 for women and <5 for men). As to cognitive status, 14.5% had significant cognitive impairment, according to the modified IQCODE. Based on the comprehensive clinical assessments carried out in the study, it was possible to classify cognitive status after the operations as either POD or POCD with and without POD (Fig. S1). The prevalence of POCD at 1 week was 28.5%. The prevalence of POD was 14.5%, while the prevalence of POCD without POD was 14.9.

Table 1 presents the baseline characteristics of the patients with and without POCD. Patients with POCD tended to have older age, lower education, higher ASA class, baseline depression, and preoperative frailty compared with those without POCD. However, the differences were nonsignificant. Interestingly, a higher cognitive status was found in the POCD group than in the non-POCD group (mean MoCA scores, 20.86 vs. 18.48; P = 0.01). However, there were no significant differences in the other variables of the 2 groups.

| Variable                                | No POCD (n = 148) | POCD at 1 week (n = 59) | P-value |
|-----------------------------------------|------------------|------------------------|---------|
| Age                                     | 72.64 ± 6.48     | 70.88 ± 7.15           | 0.09    |
| Male                                    | 83 (56.1%)       | 36 (61.0%)             | 0.54    |
| Education levels                        |                  |                        |         |
| 6 years or less                         | 114 (77.0%)      | 49 (83.1%)             | 0.45    |
| More than 6 years                       | 34 (23.0%)       | 10 (16.9%)             |         |
| BMI                                     | 24.33 ± 4.18     | 24.22 ± 4.32           | 0.86    |
| ASA class                               |                  |                        |         |
| Class II                                | 41 (27.7%)       | 6 (10.2%)              | 0.01*   |
| Class III                               | 101 (68.2%)      | 48 (81.4%)             | 0.06    |
| Class IV                                | 6 (4.1%)         | 5 (8.5%)               | 0.30    |
| Charlson comorbidity index              | 5.78 ± 1.78      | 5.68 ± 1.92            | 0.73    |
| Charlson comorbidity index > 5          | 73 (49.3%)       | 27 (45.8%)             | 0.76    |
| Cardiovascular disease                  | 125 (84.5%)      | 56 (94.9%)             | 0.06    |
| Endocrine disease                       | 113 (76.4%)      | 46 (78.0%)             | 0.86    |
| Respiratory disease                     | 14 (9.5%)        | 5 (8.5%)               | 1.00    |
| Nervous system disease                  | 39 (26.4%)       | 11 (18.6%)             | 0.28    |
| CKD: 3a, 3b, 4, 5                       | 53 (35.8%)       | 28 (47.5%)             | 0.16    |
| Modified IQCODE ≥ 3.42                  | 23 (16.2%)       | 7 (12.1%)              | 0.52    |
| MoCA                                    | 18.48 ± 5.05     | 20.86 ± 5.40           | 0.01*   |
| PHQ-9 ≥ 7                               | 7 (4.7%)         | 7 (11.9%)              | 0.12    |
| Barthel ADL Index; score 0–70, moderately disabled | 6 (4.1%) | 2 (3.4%) | 1.00 |
| Barthel ADL Index; score 100             | 94.52 ± 9.98     | 94.32 ± 12.77          | 0.91    |
| Barthel ADL Index; score < 100           | 60 (41.1%)       | 24 (40.7%)             | 1.00    |
| IADL score                              | 6.67 ± 1.70      | 6.37 ± 2.11            | 0.33    |
| IADL score < 8 for women or score < 5 for men | 37 (25.0%) | 15 (25.4%) | 1.00 |
| Frailty                                 | 15 (10.1%)       | 12 (20.3%)             | 0.07    |
| Quality of life at admission            | 0.85 ± 0.17      | 0.88 ± 0.17            | 0.37    |

Data are presented by n (%) or mean ± SD

Abbreviations: ADL activities of daily living, ASA American Association of Anesthesiologists, BMI body mass index, CKD chronic kidney diseases, FRAIL Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, IADL Lawton–Brody instrumental activities of daily living, PHQ-9 9-item Patient Health Questionnaire, MoCA Montreal cognitive assessment, POCD postoperative cognitive dysfunction
including the Charlson comorbidity index and preoperative IADL impairment.

Table 2 compares the demographic data of the non-POD and POD groups. Most patients with POD were more likely to have ASA class III (90.5% vs. 66.8%; \( P = 0.002 \)); a higher mean Charlson comorbidity index (6.55 vs. 5.83; \( P = 0.03 \)); preoperative cognitive impairment (28.2% vs. 12.2%; \( P = 0.01 \)); a lower mean MoCA score (16.76 vs. 19.47; \( P = 0.01 \)); and previous delirium (4.8% vs. 0.0%; \( P = 0.02 \)) than those without POD. Although statistically nonsignificant, the POD group tended to have preoperative IADL impairment and baseline frailty rather than non-POD one.

Table 3 illustrates the outcomes of the participants whose cognitive status could be documented using the MoCA. POCD with POD groups (16 cases) were excluded from the analysis. At 3 months, a functional decline was found in 22.2% of the participants with 1-week POCD and 24.0% of those without POCD (\( P = 0.83 \)). Compared with individuals without cognitive changes, the participants with POCD were more likely to suffer from unfavorable outcomes, namely, longer ICU and hospital stays and higher hospital costs. More specifically, the POCD group had a longer median stay in the ICU (2 days [0, 14] vs. 1 day [0, 11]; \( P = 0.01 \)); a longer median hospital stay (11 days [1, 46] vs. 8 days [2, 42]; \( P = 0.01 \)); and a higher median hospital expenditure (8973.43 USD [3481.69, 11763.74] vs. 5913.62 USD [332.43, 19567.33]; \( P < 0.001 \)).

### Table 2: Comparison of baseline characteristics of non-POD and POD groups

| Variable                        | No POD (n = 247) | POD (n = 42) | P-value |
|---------------------------------|----------------|-------------|---------|
| Age                             | 72.12 ± 6.77   | 73.50 ± 6.91| 0.23    |
| Male                            | 136 (55.1%)    | 28 (66.7%)  | 0.18    |
| Education levels                |                |             |         |
| 6 years or less                 | 198 (80.2%)    | 34 (81.0%)  | 1.00    |
| More than 6 years               | 49 (19.8%)     | 8 (19.0%)   |         |
| BMI                             | 24.29 ± 4.11   | 23.81 ± 4.52| 0.47    |
| ASA class                       |                |             |         |
| Class II                        | 65 (26.3%)     | 3 (7.1%)    | 0.01*   |
| Class III                       | 165 (66.8%)    | 38 (90.5%)  | 0.002*  |
| Class IV                        | 17 (6.9)       | 1 (2.4%)    | 0.49    |
| Charlson comorbidity index      | 5.83 ± 1.94    | 6.55 ± 2.27 | 0.03*   |
| Charlson comorbidity index > 5  | 120 (48.6%)    | 27 (64.3%)  | 0.07    |
| Cardiovascular disease          | 215 (87.0%)    | 39 (92.9%)  | 0.44    |
| Endocrine disease               | 180 (72.9%)    | 36 (85.7%)  | 0.09    |
| Respiratory disease             | 25 (10.1%)     | 8 (19.0%)   | 0.11    |
| Nervous system disease          | 56 (22.7%)     | 15 (35.7%)  | 0.08    |
| CKD: 3a, 3b, 4, 5               | 91 (36.8%)     | 24 (57.1%)  | 0.01*   |
| Modified IQCODE ≥ 3.42          | 29 (12.2%)     | 11 (28.2%)  | 0.01*   |
| MoCA                            | 19.47 ± 4.85   | 16.76 ± 6.76| 0.01*   |
| Previous Delirium               | 0 (0.0%)       | 2 (4.8%)    | 0.02*   |
| PHQ-9 ≥ 7                       | 13 (5.3%)      | 3 (7.1%)    | 0.71    |
| Barthel ADL Index; score 0–70, moderately disabled | 10 (4.1%) | 1 (2.4%) | 1.00 |
| Barthel ADL Index; score 100    | 94.85 ± 9.95   | 94.04 ± 13.80| 0.65 |
| Barthel ADL Index; score < 100  | 93 (38.3%)     | 17 (40.5%)  | 0.86    |
| IADL score                      | 6.67 ± 1.79    | 5.90 ± 2.38 | 0.05    |
| IADL score < 8 for women or score < 5 for men | 63 (25.5%) | 16 (38.1%) | 0.09 |
| Frailty                         | 31 (12.6%)     | 7 (16.7%)   | 0.46    |
| Quality of life at admission    | 0.85 ± 0.17    | 0.87 ± 0.17 | 0.72    |

* Indicates statistical significance (<0.05). Data are presented by n (%) or mean ± SD

Abbreviations: ADL activities of daily living, ASA American Association of Anesthesiologists, BMI body mass index, CKD chronic kidney diseases, FRAIL Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, IADL Lawton–Brody instrumental activities of daily living, PHQ-9 9-item Patient Health Questionnaire, MoCA Montreal cognitive assessment, POD postoperative delirium

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analysis, the overall interpretations were the same (Appendix 2: Table S2).

Another set of analyses was performed for patients with POD (Table 4). They were compared with people who did not develop POD, and the POCD with POD group was excluded from the analysis. At the 3-month follow-up, IADL decline was discovered in 22.7% of the participants without POD compared with 47.4% of the participants with POD ($P=0.03$). The participants with POD were more likely to suffer from unfavorable outcomes, namely, a longer stay in the ICU, an increased hospital LOS, higher hospital expenditure, and a higher mortality rate. More specifically, the group with POD had a longer stay in the ICU (5 [0, 53] vs. 1 [0, 57]; $P<0.001$);

### Table 3
Postoperative outcomes of patients with POCD (includes only those participants who could be administered the MoCA 1 week after surgery to establish their POCD status)

| Variable                              | No POCD $(n=148)$ | POCD $(n=43)$ | $P$ value |
|---------------------------------------|-------------------|---------------|-----------|
| Barthel ADL Index at 3 months         | 94.60±11.62       | 92.22±13.27   | 0.29      |
| Declined basic ADL n (%); Barthel reduced ≥ 5 points | 30 (23.8%) | 9 (25.0%) | 0.88 |
| Declined IADL, n (%); score reduced ≥ 2 points | 30 (24.0%) | 8 (22.2%) | 0.83 |
| IADL score at 3 months               | 6.43±1.9         | 6.25±1.9     | 0.60      |
| Worsened quality of life at 3 months; n (%) | 37 (28.9%) | 9 (25.0%) | 0.68 |
| Health utility, score                | 0.89±0.14        | 0.89±0.20    | 0.80      |
| Frailty at 3 months, (3–5), n (%)    | 11 (8.7%)        | 6 (16.7%)    | 0.22      |
| Readmission at 3 months, n (%)       | 16 (10.8%)       | 6 (14.0%)    | 0.59      |
| Mortality at 3 months, n (%)         | 3 (2.0%)         | 1 (2.3%)     | 1.00      |
| Hospital LOS, days; median (min, max) | 8 (2, 42) | 11 (1,46) | 0.01* |
| Total cost, USD; median (min, max)   | 5913.62 (332.43, 19 567.33) | 8973.43 (3481.69, 11 763.74) | <0.001* |
| ICU LOS, days; median (min, max)     | 1 (0, 11)        | 2 (0, 14)    | 0.01*     |
| Ventilator, days; median (min, max)  | 1 (0, 8)         | 1 (0, 3)     | 0.03*     |

*Indicates statistical significance (< 0.05)

POCD includes participants who had MoCA administered 1 week after surgery to establish their POCD status but did not include patients with POD

### Abbreviations
ADL activities of daily living, FRAIL: Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, IADL: Lawton–Brody instrumental activities of daily living, ICU: intensive care unit, LOS: length of stay, POCD: postoperative cognitive dysfunction, ventilator: length of time on a ventilator

### Table 4
Postoperative outcomes of patients with POD

| Variable                              | No POD $(n=247)$ | POD $(n=26)$ | $P$ value |
|---------------------------------------|------------------|-------------|-----------|
| Barthel ADL Index at 3 months         | 93.69±12.68      | 87.63±19.95 | 0.06      |
| Declined basic ADL n (%); Barthel reduced ≥ 5 points | 49 (25.1%) | 6 (31.6%) | 0.58 |
| Declined IADL score 2, n (%); score reduced ≥ 2 points | 44 (22.7%) | 9 (47.4%) | 0.03* |
| IADL score at 3 months               | 6.33±1.89        | 5.10±2.42   | 0.04*     |
| Worsened quality of life at 3 months; n (%) | 57 (28.9%) | 7 (36.8%) | 0.60 |
| Health utility, score                | 0.90±0.15        | 0.86±0.19   | 0.33      |
| Frailty at 3 months, (3–5), n (%)    | 22 (11.3%)       | 3 (15.8%)   | 0.47      |
| Readmission at 3 months, n (%)       | 32 (13.2%)       | 6 (25.0%)   | 0.13      |
| Mortality at 3 months, n (%)         | 6 (2.4%)         | 7 (26.9%)   | <0.001*   |
| Hospital LOS, days; median (min, max) | 8 (1, 57) | 17 (5, 70) | <0.001* |
| Total cost, USD; median (min, max)   | 5981.68 (332.04, 53 455.42) | 11 501.52 (2857.64, 86 953.34) | <0.001* |
| ICU LOS, days; median (min, max)     | 1 (0, 57)        | 5 (0, 53)   | <0.001*   |
| Ventilator, days; median (min, max), | 1 (0, 11)        | 1 (0, 57)   | <0.001*   |

*Indicates statistical significance (< 0.05)

POD includes participants who had DSM-5 administered to establish their POD status but did not include patients with POCD

### Abbreviations
ADL: activities of daily living, FRAIL: Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight, IADL: Lawton–Brody instrumental activities of daily living, ICU: intensive care unit, LOS: length of stay, POD: postoperative delirium; ventilator: length of time on a ventilator
an increased hospital LOS (17 days [5, 70] vs. 8 days [1, 57]; \( P < 0.001 \)); a higher hospital expenditure ($11 501.52 USD [2,857.64, 86,953.34] vs. $5981.68 USD [332.04, 53 455.42]; \( P < 0.001 \)); and a higher 3-month mortality rate (26.9% vs. 2.4%; \( P < 0.001 \)). Table S3 shows the results without excluding the POCD with POD group. The overall interpretations were similar, except for no difference in IADL decline at month 3 between the POD group and the non-POD one.

Table 5 presents the factors associated with functional decline at the 3-month follow-up. The multivariate model included relevant covariates, namely age, gender, surgery type, POCD, and postoperative complications (POD, pneumonia, acute kidney injury (AKI), arrhythmia, and

| Variable                      | Univariate analysis | P-value | Multivariate analysis | P-value |
|-------------------------------|---------------------|---------|-----------------------|---------|
|                               | Crude RR (95% CI)   |         | Adjusted RR\(^a\) (95% CI) |         |
| **Cognition**                 |                     |         |                       |         |
| No cognitive change (n = 163) | 1                   |         | 1                     |         |
| POCD (n = 37)                 | 0.96 (0.51–1.81)    | 0.91    | 1.01 (0.49–2.09)      | 0.96    |
| POD (n = 26)                  | 2.44 (1.63–3.66)    | < 0.05* | 2.33 (1.15–4.71)      | 0.02*   |
| POCD with POD (n = 14)        | 1.49 (1.01–2.21)    | 0.14    | 1.33 (0.50–3.55)      | 0.56    |
| Preoperative frailty          |                     |         |                       |         |
| (n = 31)                      | 0.99 (0.55–1.79)    | 1.00    | –                     | –       |
| Preoperative Barthel ADL Index; score ≤ 70 (n = 9) | 1.14 (0.44–2.95)    | 0.72    | –                     | –       |
| Preoperative Modified IQCODE  |                     |         |                       |         |
| ≥ 3.42 (n = 37)               | 0.94 (0.53–1.67)    | 0.85    | –                     | –       |
| Female (n = 100)              | 1.05 (0.70–1.56)    | 0.89    | 1.22 (0.73–2.04)      | 0.45    |
| Age ≥ 75 years (n = 85)       | 1.14 (0.76–1.71)    | 0.55    | 1.04 (0.62–1.76)      | 0.88    |
| Charlson comorbidity index    |                     |         |                       |         |
| ≥ 5 (n = 183)                 | 1.24 (0.75–2.06)    | 0.41    | –                     | –       |
| Baseline PHQ-9                | 1.15 (0.50–2.62)    | 0.75    | –                     | –       |
| Cardiac surgery (n = 136)     | 1.14 (0.76–1.71)    | 0.57    | 0.73 (0.44–1.29)      | 0.26    |
| Postoperative complications (n = 240) | 1.14 (0.76–1.71)    | 0.57    | 0.73 (0.44–1.29)      | 0.26    |
| Pneumonia (n = 12)            | 1.78 (0.97–3.25)    | 0.19    | 0.53 (0.14–1.94)      | 0.34    |
| Acute kidney injury (n = 24)  | 2.25 (1.49–3.37)    | < 0.05* | 1.93 (0.77–4.84)      | 0.16    |
| Arrhythmia (n = 48)           | 1.60 (1.06–2.41)    | 0.01*   | 0.93 (0.49–1.76)      | 0.82    |
| Urinary tract infection (n = 6) | 1.74 (0.76–3.98)    | 0.36    | –                     | –       |
| Convulsion (n = 3)            | 1.14 (0.22–5.74)    | 1.00    | –                     | –       |
| Reoperation (n = 14)          | 2.08 (1.26–3.43)    | 0.03*   | 1.19 (0.35–4.04)      | 0.78    |

\(^a\) Indicates statistical significance (< 0.05)

POCD includes participants who had MoCA administered 1 week after surgery to establish their POCD status but did not include patients with POD

POD includes participants who had DSM-5 administered to establish their POD status but did not include patients with POCD

POCD with POD includes participants who had MoCA administered 1 week after surgery and DSM-5 administered to establish their POCD status and POD status, respectively

The model adjusted for gender, age, type of surgery, pneumonia, acute kidney injury, arrhythmia, and reoperation

Abbreviations: Barthel ADL Barthel activities of daily living, POCD postoperative cognitive dysfunction, POD postoperative delirium
to demonstrate a difference in short-term mortality. There-
sample size of the present study may have been too small
need a larger sample size with a longer-term follow-up.

...months after surgery showed that the
increase the risk of death during the first three postopera-
tive cognitive disorders, POCD in this study did not
association between POCD and postoperative functional
decline. In the present study, patients experiencing POCD
at 1 week were not associated with a decrease in IADLs
3 months after surgery, whereas the POD group showed
an increased risk of functional decline. Previous evidence
from cardiac and noncardiac surgery showed that the
appearance of POCD between the first and third months
after surgery could cause a decrease in IADLs [20, 25, 41].
Furthermore, patients with POCD 1 week after noncardiac
surgery had an increased risk of leaving the labor market
due to a decrease in function compared with non-POCD
patients [22]. In contrast, another study did not report any
differences in the 3-month functional outcomes for POCD
patients after undergoing cardiac surgery [19]. That study
proposed that the preexisting cognitive status of a patient
was the main factor that affected postoperative functional
changes. Interestingly, participants in the present study
who developed POCD were more likely to have a better
cognitive status than the non-POCD patients. This finding
might contribute to the lesser adverse effects of POCD on
functional outcomes. However, another possibility could
be since the definition of POCD utilized in this study using
the drop in brief assessment might not be sensitive enough
to classify patients with this condition.

Regarding other negative consequences of postopera-
tive cognitive disorders, POCD in this study did not
increase the risk of death during the first three postopera-
tive months. In contrast, POD did have a significant risk of
increased mortality. A previous study reported that
POCD patients at discharge were more likely to die before
their 3-month follow-up [4]. The population of that work
was similar to that of this study but had an even younger
age. Other investigations found that POCD was associated
with both short- and long-term mortality [21, 22, 44]. The
sample size of the present study may have been too small
to demonstrate a difference in short-term mortality. There-
fore, the association between POCD and mortality might
need a larger sample size with a longer-term follow-up.

Furthermore, we explored the relationship between
POCD and healthcare utilization. Interestingly, POCD
patients were more likely to use the healthcare system
than those who did not have the condition. The increased
utilization was evidenced by the more prolonged ICU
and hospital stays and the higher costs. Furthermore, a
higher proportion of patients with POCD were readmit-
ted to the hospital than those without POCD, although
the difference was nonsignificant. The result of this study
is consistent with a previous investigation of increased
healthcare costs during the 1-year postoperative period
[21]. Our findings highlight the consequences of POCD:
although clinically subtle, POCD has noticeable effects
on healthcare system expenditure. Considering the
increasing magnitude of this disease as the population
gradually ages, an appropriate strategy would be to have
multidisciplinary teams handle the condition.

Unlike other studies [38, 41], the present work did not
find any associations between a decrease in IADLs and
several preoperative and postoperative factors (age of
75 years or older, multiple comorbidities, preoperative
frailty, preexisting cognitive impairment, depression,
dependence at baseline, and postoperative complications).
This result could be because the current research focused
on elective surgery and had fairly robust participants in
terms of their functional status before surgery. Although
a substantial proportion of patients exhibited some degree
of cognitive impairment, the condition was not associ-
ated with decreased function at the 3-month follow-up.
This observation suggests that mild cognitive impairment
might not lead to a significant decline in function after
an operation. In this study, preoperative frailty status did
not contribute to the decline in IADLs. This finding dif-
fered from those of several other studies, which reported
a significant relationship between baseline frailty and poor
functional outcomes [49, 50]. The presence of preoperative
frailty might predict unfavorable results among older-old
and oldest-old patients [49]. As most of the participants in
our work were in the young-old age group, their frailty sta-
tus might not have made a significant contribution to post-
operative functional decline.

The study highlighted the consequences of POCD and
POD on clinical outcomes and healthcare utilization.
The research has several strengths and limitations. One
strength was that participants were prospectively screened
for POCD and POD, with physicians confirming positive
findings through clinical evaluations. This approach mini-
mized misclassifications of the conditions. Even though
POD was assessed for a shorter period after noncardiac
surgery and could potentially lead to under-recognition
of POD, geriatricians comprehensively reviewed through
medical records would minimize the issue. As to the neu-
ropsychological testing, we utilized a brief cognitive test,
MoCA, which covers multiple cognitive domains and is easy to use in daily practice. Still, this could be both a limitation and a strength. The limitation might be that MoCA is less comprehensive than multiple neuropsychological batteries. However, a brief test like MoCA can identify patients with adverse postoperative outcomes. It is also more practical than multiple batteries for wide adoption in clinical practice, particularly in resource-limited settings where neuropsychologists are scarce.

MoCA has recently been applied in several studies of POCD [13, 51]. Unfortunately, a considerable proportion of patients in those studies did not have MoCA performed postoperatively, leading to selection bias. By contrast, our analyses also included patients without MOCA reassessments and identified no significant differences from those with MoCA reassessments even though 28% of total participants were missing from the MoCA tests for the primary outcome assessments for several reasons, including death, medically unstable conditions, and refusing participation. Additionally, of 289, 21% had no functional outcome at month three due to death and loss to follow-up. Another consideration is that the sample size in our study could have lacked sufficient power to detect some outcomes of the POCD group (for example, functional outcome and mortality). Lastly, healthcare costs were underestimated by the current investigation because direct nonmedical expenditures were not assessed.

Conclusions
We showed that patients with POCD and those with POD were more likely to utilize healthcare services. Furthermore, POD increases the risk of developing functional decline after surgery. Therefore, the use of preventive measures, early detection, and appropriate interventions for POCD and POD among older surgical patients might be a critical factor in improving the standard of care of patients and reducing the burden on families and society.

Abbreviations
ASA: American Association of Anesthesiologists; Barthel ADL: Barthel activities of daily living; BMI: Body mass index; CKD: Chronic kidney diseases; FRAL: Fatigue, resistance, ambulation, illness, and loss of weight; IADL: Lawton–Brody instrumental activities of daily living; MoCA: Montreal cognitive assessment; POCD: Postoperative cognitive dysfunction; POD: Postoperative delirium.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12877-022-02873-3.

Acknowledgements
This study was supported by the Integrated Perioperative Geriatric Excellent Research Center. All authors declare no personal or professional conflicts of interest related to any aspect of this report. The authors thank Mr. Monai Saejuji and Ms. Manita Kerdomonkol for their valuable assistance in collecting and analyzing the data. They also thank Mrs. Rirada Preedachit kun for her statistical assistance. Finally, the authors gratefully acknowledge the professional editing of this paper by Mr. David Park.

Authors’ contributions
PS and AS: study design, data analysis and interpretation, and manuscript preparation and review. VS: study design, data interpretation, and manuscript review. CP: data collection and data interpretation. NS: data management. CJ: data collection and evaluation. All authors approved the final version of the manuscript.

Funding
This study was supported by the Faculty of Medicine, Siriraj Hospital Mahidol University (grant number IO) R016037003). The funders had no role in the study design, data collection, analyses, publishing decisions, or manuscript preparation.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was a database research project and did not involve any interventions or contact with patients. Individual patients were not identifiable. The analyses were approved by the Human Research Protection Unit, Faculty of Medicine Siriraj Hospital, Mahidol University (reference number Si 515/2017). The database is available to registered researchers. The protocol for this study followed all of the guidelines outlined in the Declaration of Helsinki and all of its later amendments. Written informed consent was obtained from all study participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests related to any aspect of this study.

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Received: 11 October 2021 Accepted: 24 February 2022
Published online: 16 March 2022

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