Can J Anesth/J Can Anesth (2014) 61:1084–1092
DOI 10.1007/s12630-014-0242-6

REPORTS OF ORIGINAL INVESTIGATIONS

The temporal relationship between early postoperative delirium and postoperative cognitive dysfunction in older patients: a prospective cohort study

Relation temporelle entre le délirium postopératoire précoce et les troubles cognitifs dysfonctionnels postopératoires chez les patients âgés: une étude prospective de cohorte

Emily Youngblom, MPH · Glen DePalma, MS · Laura Sands, PhD · Jacqueline Leung, MD

Received: 20 May 2014 / Accepted: 17 September 2014 / Published online: 7 October 2014

Abstract

Background *Postoperative delirium and cognitive dysfunction are frequent phenomena in older patients; however, few studies have examined the temporal relationship between these two conditions in the early postoperative period. Therefore, this study aimed to determine if postoperative delirium and postoperative cognitive dysfunction (POCD) coexist after major noncardiac surgery.*

Methods *This was a prospective cohort study of patients who were ≥ 65 yr of age undergoing noncardiac surgery. Patients were evaluated preoperatively and for two days postoperatively for delirium and POCD. Delirium was determined using the Confusion Assessment Method, and POCD was measured by three cognitive tests addressing changes in executive function, memory, attention, and concentration. For each postoperative day, patients' neurologic status was categorized into three mutually exclusive categories: delirium, POCD, or neither condition.*

Results *Four hundred sixty-one patients aged ≥ 65 yr of age were studied, and 421 patients with complete postoperative cognitive testing were reported. Eighty percent of patients experienced either delirium or POCD on the first day after surgery. Seventy percent of patients who had delirium on the first postoperative day also had delirium on the second postoperative day. Sixty-three percent of patients who had POCD on postoperative day one continued to have POCD on the next day. Sixteen percent of patients with delirium on day one were non-delirious on day two but met criteria for POCD on day two. Conversely, 15% of patients with POCD on day one became delirious on day two. Only 13% of patients did not experience delirium or POCD on either day after surgery.*

Conclusions *Eighty percent of surgical patients experienced some form of cognitive dysfunction the day after surgery, and few recovered by the second day after surgery.*

Résumé

Contexte *Le délirium postopératoire et les troubles des fonctions cognitives sont un phénomène fréquent chez les patients âgés. Cependant, peu d'études se sont intéressées à la relation temporelle entre ces deux affections au cours de la période postopératoire précoce. Cette étude a donc cherché à déterminer si le délirium postopératoire et les troubles cognitifs dysfonctionnels postopératoires (TCDP) coexistent après une chirurgie majeure non cardiaque.*

Author contributions *Emily Youngblom* and *Jacqueline M. Leung* were involved in data collection. *Emily Youngblom, Glen DePalma, Laura Sands,* and *Jacqueline M. Leung* were involved in data analysis and write up of the manuscript. *Laura Sands* and *Jacqueline M. Leung* were involved in the study design.

E. Youngblom, MPH · J. Leung, MD (✉)
Department of Anesthesia and Perioperative Care, University of California San Francisco, 521 Parnassus Ave, C-455, San Francisco, CA 94143-0648, USA
e-mail: leungj@anesthesia.ucsf.edu

G. DePalma, MS
Department of Statistics, Purdue University, West Lafayette, IN, USA

L. Sands, PhD
School of Nursing, Purdue University, West Lafayette, IN, USA

Méthodes *Il s'est agi d'une étude de cohorte prospective de patients âgés de 65 ans et plus, subissant une chirurgie non cardiaque, qui avaient été évalué en préopératoire et pendant deux jours en postopératoire, visant le délirium et les TCDP. L'existence d'un délirium a été déterminée au moyen de la méthode d'évaluation de l'état confusionnel (Confusion Assessment Method) et les TCDP ont été mesurés par trois tests cognitifs abordant les modifications de la fonction exécutive, la mémoire, l'attention et la concentration. Le statut neurologique des patients a été classé dans l'une des trois catégories (s'excluant mutuellement) au cours de chaque journée postopératoire: délirium, TCDP ou aucun de ces deux troubles.*

Résultats *Quatre cent soixante et un patients âgés de 65 ans et plus ont été étudiés et 421 patients ayant des tests cognitifs postopératoires complets ont été rapportés. Quatre-vingts pour cent des patients ont présenté un délirium ou des TCDP le premier jour suivant l'intervention chirurgicale. Soixante-dix pour cent des patients ayant eu un délirium au cours de la première journée postopératoire ont également présenté un délirium le deuxième jour. Soixante-trois pour cent des patients ayant eu des TCDP postopératoires le premier jour ont continué à avoir des TCDP le jour suivant. Soixante pour cent des patients ayant eu un délirium le premier jour n'étaient pas délirants le deuxième jour, mais répondaient aux critères de TCDP ce deuxième jour; inversement, 15 % des patients ayant des TCDP le premier jour sont devenus délirants le deuxième jour. Seuls 13 % des patients n'ont présenté ni délirium ni TCDP au cours des deux journées postopératoires.*

Conclusions *Quatre-vingts pour cent des patients chirurgicaux ont présenté une forme ou une autre de troubles des fonctions cognitives le jour suivant la chirurgie et peu avaient récupéré au deuxième jour postopératoire.*

A decline in cognitive status after surgery is common among older surgical patients. This may present in the form of delirium or more subtly in the form of postoperative cognitive dysfunction (POCD).[1] Postoperative delirium occurs in up to 10-60% of older patients and is associated with longer hospital stay, increased morbidity and mortality, and higher health care costs.[2] Delirium has been described as an acute confusional state featuring disturbances in attention and decreased awareness of the environment.[3] The definitive diagnosis of delirium in hospitalized patients is typically made by psychiatrists or neurologists according to the criteria described in *The Diagnostic and Statistical Manual of Mental Disorders – fifth edition (DSM-V)*.[4]

The development of delirium is thought to be a multifactorial process in which there is a complex interrelationship between baseline patient vulnerability and precipitating factors or insults.[5] In surgical patients, predisposing risk factors that increase the vulnerability for delirium include many factors, including age, preexistent cognitive impairment, and pain.[2,6] Insults that serve as precipitating factors include events related to surgery, such as type of surgery, blood loss, exposure to medications with central nervous system effects (e.g., opioids), and sleep disruption.[2,6-8]

In contrast, POCD is broadly defined as a decline from preoperative performance in cognitive domains such as memory, processing speed, or executive functioning after surgery. Postoperative cognitive dysfunction refers to subtle declines in cognitive functioning that can occur in the absence of delirium and are detectable through formal cognitive testing. Unlike delirium, POCD is not recognized in the *International Classification of Diseases* and is not listed as a diagnosis in the *DSM-V*. A typical patient with POCD is oriented but exhibits significant declines from his or her own baseline level of performance on one or more cognitive domains.[9,10] Assessing patients for POCD requires cognitive testing before (which serves as a baseline) and after surgery. A further distinction should be made between mild cognitive impairment (MCI) and POCD, because MCI is described as a memory impairment beyond that expected for subjects who are not demented (controlling for age and education).[11] Individuals with MCI have a greater decline in long-term cognitive functioning compared with those with no MCI,[12] whereas POCD that occurs soon after surgery has been described as short-lived.[1]

Postoperative cognitive dysfunction has been observed in 19-47% of noncardiac surgical patients[13] and frequently persists beyond the early postoperative period.[13] Postoperative cognitive dysfunction has also been associated with impairments in daily functioning,[14] premature departure from the labour market,[15] and dependency on government economic assistance after hospital discharge.[15] Both POCD and delirium should be distinguished from dementia, which describes a chronic and often insidious decline in cognitive function with significant functional impairment.

Few have considered whether POCD exists among patients whose cognitive symptoms do not meet standardized criteria for delirium. Among studies that measured POCD, most did not concurrently assess for delirium.[1,16,17] Furthermore, most studies did not measure POCD in the days soon after surgery, a time when many patients are scheduled for early discharge planning that includes receiving postoperative self-care instructions. Accordingly, this study aimed to determine the incidence of postoperative delirium and POCD in the first two days after noncardiac surgery and whether the presence of delirium or POCD on the first postoperative day persisted to the next day.

Methods

The study was conducted at one of the teaching hospitals at the University of California, San Francisco. This study is part of a larger prospective study evaluating the pathophysiology of postoperative delirium and POCD, including their interrelationship.[18,19] The study received approval from the Institutional Review Board (approved April 2001; renewed March 2014), and all patients provided written informed consent.

The inclusion criteria for the cohort were fluency in English, age 65 yr or older, scheduled for major noncardiac surgery requiring anesthesia, and expected to stay in the hospital for at least 48 hr postoperatively. The patients were recruited consecutively if their surgical procedures were conducted on Mondays to Wednesdays to allow for the two days of postoperative follow-up to be completed during a regular work week. Patients were typically recruited, and informed consent was obtained at the preoperative clinic within one week of the planned surgery.

Each patient was interviewed approximately one week before surgery and on the first two days after surgery. Patients' postoperative visits were conducted daily between 9 am - noon at bedside. At each time point, the presence of delirium was measured using the Confusion Assessment Method (CAM) via a structured interview.[18] The CAM was developed as a screening instrument based on operationalization of *DSM-III-R* criteria for use by non-psychiatric clinicians in high-risk settings. This method has a sensitivity of 94-100% and a specificity of 90-95% for delirium.[20,21] All research personnel administering the CAM were trained based on a detailed CAM manual developed by Inouye *et al.*[20] All cases of delirium were validated by a second investigator (L.P.S.) who reviewed a written summary of each patient's responses to the structured interview performed by the first investigator and discussed the assessment with that interviewer.

Postoperative cognitive dysfunction was measured by the Digit Symbol Substitution Test,[22] the timed Verbal Fluency Test,[23] and the Word List Learning Task[24] in order to assess the cognitive domains of memory and learning (word list), verbal and language skills (verbal fluency), and attention, concentration, and perception (digit symbol test). These tests target domains that are sensitive to drug effects[25] and have been used and validated in a large number of older surgical patients.[16] The other important consideration is that, in contrast to previous studies evaluating patients at least one week after the planned surgery, our study focused on evaluating cognitive status in the immediate two days after surgery. Hence, we had to be sensitive to reduce the burden of cognitive testing for patients who have recently undergone surgery. To address the potential confounding effects of learning from repeated cognitive testing, we administered different forms of the cognitive tests using a Latin square design to prevent potential confounding of form by occasion.[26] The multiple test forms used were randomized using the Latin square treatment structure where the two blocking factors were measurement occasion (e.g., first and second postoperative days) and form number. Earlier research provides evidence of equivalence of the four forms of each cognitive test.[27]

For each test, we determined whether the patient experienced a significant decline from preoperative baseline using prediction intervals.[25] A decline from preoperative performance of four or more points for the word list or seven or more points for the verbal fluency and the digit symbol tests was considered significant decline, and the patient was classified as having POCD for that day. If decline in performance was observed for at least one postoperative day, we concluded that POCD occurred for that patient.[19] The above scores were determined in earlier studies of community living older adults who were similar in demographic and clinical characteristics to the subjects in this study but had not undergone an intervention that could cause cognitive change.[28-30] In addition to the above tests, cognitive status was also measured preoperatively using the Telephone Interview for Cognitive Status (TICS) instrument[31] which was adapted from the Mini Mental Status Examination. The TICS allowed us to evaluate the baseline cognitive status of patients, but patients were not excluded based on the TICS values.

To distinguish whether patients had developed postoperative delirium and/or POCD (or neither), we used a hierarchical method. If a patient met the criteria for delirium, that patient was classified as having delirium. If a patient did not meet criteria for delirium but met the criteria for POCD, that patient was classified as having POCD. Finally, the patient who did not meet criteria for delirium or POCD was classified as having neither condition.

Other demographic variables measured included age, sex, education level, and alcohol intake. Preoperative symptoms of depression were measured by the 15-item Geriatric Depression Scale.[32] Functional status was measured using the Activities of Daily Living (ADL)[33] and the Instrumental Activities of Daily Living (IADL).[34] If a patient could not perform independently without assistance in one or more of the activities related to either ADL or IADL, that patient would be considered dependent on support to perform the activities listed.

Table 1 Demographic data by postoperative day one cognitive status

		Number of patients	Neither $n = 93$	POCD $n = 166$	Delirium $n = 162$
Age (yr)			72.6 (5.8)	73.0 (5.8)	75.0 (6.4)
Sex	Female	225	20%	35%	46%
	Male	196	20%	35%	46%
Education Level	High school or incomplete	109	22%	27%	52%
	Some college or additional higher education	312	23%	42%	35%
ADL dependency (one or more)	Yes	164	10%	112%	77%
IADL dependency (one or more)	Yes	189	22%	35%	44%
Preoperative Scores	TICS		32.2 (3.8)	33.8 (3.1)	30.9 (4.6)
	GDS		3.4 (4.3)	2.5 (2.4)	3.6 (3.1)
Surgery Type	Knee	69	10%	40%	49.08%
	Hip	80	21%	40%	40%
	Spinal	100	16%	37%	46%
	Abdominal	108	27%	35%	38%
	Thoracic	22	42%	32%	26%
	Other	42	36%	28%	36%
ASA Class	I	5	0%	40%	60%
	II	187	25%	42%	33%
	III	216	22%	35%	44%
	IV	13	16.67%	33%	50%
Anesthesia Duration (Hours)			4.4 (1.6)	4.5 (2.1)	5.4 (3.5)
Type of Anesthesia	General	301	24%	35%	42%
	General + regional	76	19%	47%	33%
	Regional	44	21%	43%	36%
Type of Postop Analgesia	PCA only	260	20%	36%	44%
	Epidural only	46	20%	43%	37%
	PCA and epidural	30	21%	29%	50%
	Neither PCA nor epidural	85	34%	41%	24%

Values are reported as number, percent, or mean (SD)

ADL = activities of daily living; IADL = instrumental activities of daily living; TICS = Telephone Interview for Cognitive Status; GDS = geriatric depression score; ASA = American Society of Anesthesiologists; PCA = patient-controlled analgesia; postop = postoperative

The level of comorbidity was determined using the Charlson comorbidity index.[35] Other perioperative data obtained from chart review included the type of surgery and the American Society of Anesthesiologists' risk classification.[36] Additional perioperative variables measured included the type of surgery, type of anesthesia, anesthesia duration, and type of postoperative analgesia.

The Pearson Chi square test of association was used to test if there was a relationship between cognitive status on postoperative day one and that on postoperative day two, and the Cramer's V statistic was used to measure the strength of the relationship. The Pearson Chi square statistic was also used to assess the relationship between place of discharge and postoperative cognitive status, and Fisher's exact test was used to assess the relationship between the incidence of preexistent dementia and postoperative cognitive status. One-way analysis of variance (ANOVA) was used to analyze the relationship between preoperative cognitive status (as measured by the Telephone Interview for Cognitive status) and postoperative cognitive status. A two-way ANOVA was

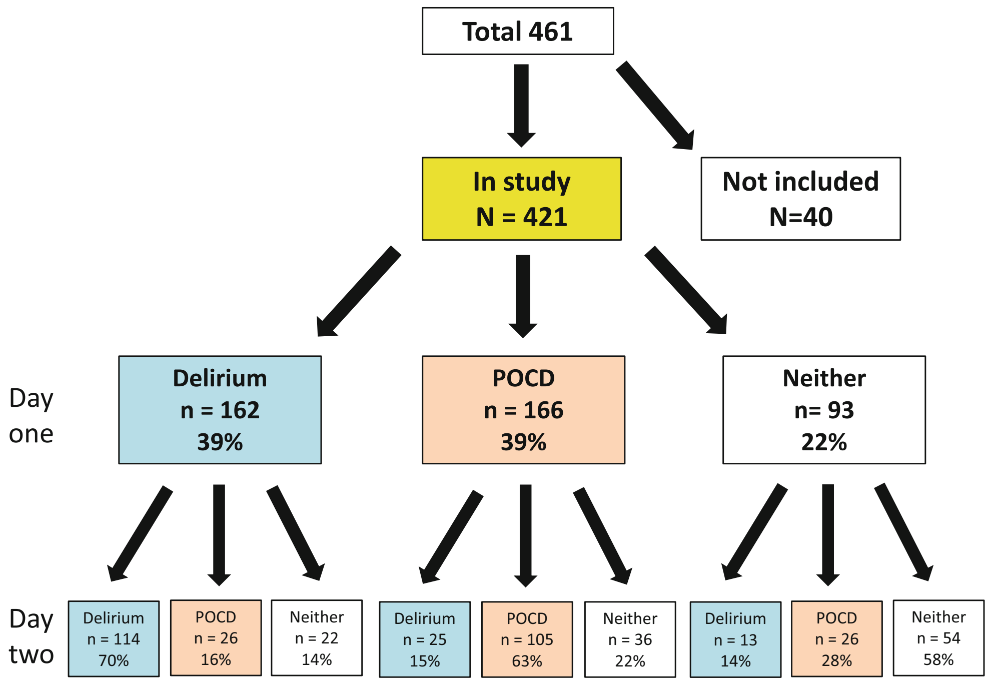

Fig. 1 The study flow chart is shown in Fig. 1. Overall, 461 patients were recruited, but 421 patients were included in this study. The reasons for excluding 40 patients included eight who were discharged early, 22 who refused testing, one was too sedated, and nine were physically incapable of performing the cognitive tests. The patients' cognitive status for postoperative days one and two is shown here, stratified by the presence of delirium, no delirium but presented signs of POCD, or neither. POCD = postoperative cognitive dysfunction

used to analyze the relationship between hospital length of stay and the explanatory variables, including cognitive status and surgery type. For this analysis, hospital length of stay was analyzed on the log scale but transferred back to the original scale for interpretation. All statistical analysis was performed with SAS® version 9.2 (Cary, NC, USA) and R 2.15.1.

Results

Four hundred sixty-one patients provided consent to participate in the study during June 2001 to December 2010. Forty patients were excluded from the analysis because they did not meet criteria for delirium and did not complete the cognitive tests on either postoperative day one or two, which left 421 patients for analysis. Specifically, eight of the forty patients were discharged early, 22 refused, one was too sedated, and nine were physically incapable of performing the cognitive tests.

This current study reports on patients with complete delirium and cognitive assessments on the first two postoperative days. The mean (SD) age of the study patients was 73.7 (6) yr; 53.3% were female. The majority of patients underwent either abdominal or spinal surgery, and 62% of patients received patient-controlled analgesia using hydromorphone for postoperative pain control (Table 1).

No patient had preoperative delirium. Two hundred (48%) of the 421 patients experienced postoperative delirium; delirium occurred in 162 (39%) patients on postoperative day one and 152 (36%) patients on the subsequent day. The relationship between cognitive status on postoperative day one and postoperative day two is shown in Fig. 1. The Cramer's V statistic of 46.7 indicates a strong association between the cognitive status on day one and that on day two. The presence of delirium on the first postoperative day was strongly associated with the presence of delirium on the subsequent day ($\chi^2 = 183.9$; $P < 0.0001$). For example, 114/162 patients (70%) who had delirium on the first postoperative day also had delirium on the next day.

In patients without concurrent delirium, POCD occurred in 166 (39%) patients on postoperative day one and 157 (37%) patients on postoperative day two. The presence of POCD on the first postoperative day was likely to persist to the second postoperative day; 105/166 (63%) patients who had POCD on postoperative day one continued to have POCD on the next day. More than half of the patients (54/93; 58%) with neither postoperative delirium nor POCD on postoperative day one continued to be free of either delirium or POCD on postoperative day two. Descriptive details of the changes in each cognitive test are shown in Table 2.

Table 2 Descriptive summary of cognitive tests

Cognitive tests	Preoperative	Postoperative day one	Postoperative day two
Digit symbol test	38.2 (11.0)[A]	30.2 (11.3)[B]	31.5 (12.0)[B]
Word list	17.4 (4.1)[A]	14.8 (4.2)[B]	15.8 (4.3)[C]
Verbal fluency	23.1 (10.3)[A]	19.0 (9.1)[B]	20.4 (10.4)[B]
	Estimate	95% CI	*P* value
Digit Symbol Test			
Preoperative - postoperative day one	8.03	(5.6 to 10.4)	$P < 0.001$
Preoperative - postoperative day two	6.7	(4.4 to 9.0)	$P < 0.001$
Postoperative days one - two	−1.3	(−3.9 to 0.5)	$P = 0.571$
Word list			
Preoperative - postoperative day one	2.6	(1.8 to 3.4)	$P < 0.001$
Preoperative - postoperative day two	1.5	(0.7 to 2.3)	$P < 0.001$
Postoperative days one - two	−1.0	(−1.8 to −0.2)	$P = 0.016$
Verbal fluency			
Preoperative - postoperative day one	4.0	(2.2 to 5.9)	$P < 0.001$
Preoperative - postoperative day two	2.7	(0.8 to 4.5)	$P = 0.002$
Postoperative days one - two	−1.4	(−3.4 to 0.6)	$P = 0.223$

CI = confidence interval

The Table shows the mean (SD) for all three cognitive tests administered during the pre- and postoperative periods. Different letters (A, B, C) represent significant differences between days within each test

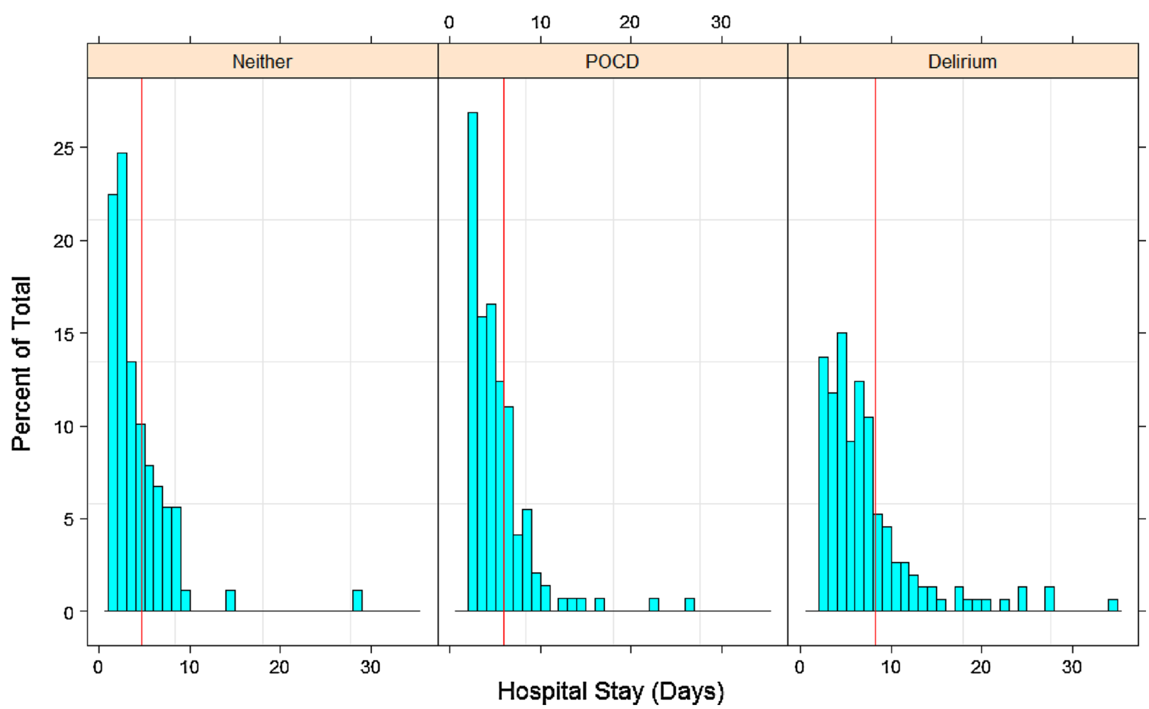

Fig. 2 For hospital length of stay, *post hoc* analysis after Tukey adjustment (alpha = 0.05) showed that the hospital length of stay was significantly longer in patients with delirium than in those with POCD or with neither condition. Nevertheless, the hospital length of stay in patients with POCD was not significantly different from those with neither condition. The red line indicates the mean for each group. Specifically, the mean (SD) length of stay in patients with delirium was 8.2 (7.5) days, 5.9 (4.8) days in those with POCD, and 4.7 (3.6) days in those with neither condition. POCD = postoperative cognitive dysfunction

Only 22 (14%) patients who had delirium on the first day were free of delirium or POCD on the second day. Similarly, only 36 (22%) patients who had POCD on the first day were free of POCD or delirium on the second day. Altogether, only 54 (13%) patients were free from either delirium or POCD on the first two days after surgery (Fig. 1).

The preoperative cognitive status, as measured by the TICS, was significantly different between the subgroups [delirium: 30.9 (4.6); POCD: 33.8 (3.1); neither: 32.2 (3.8); $F = 21.27$; $P < 0.001$]. Specifically, patients with postoperative delirium had lower TICS scores compared with those with only POCD or neither condition. Nevertheless, the incidence of pre-existent dementia, as documented on medical records, was not significantly different between the subgroups [neither: 16 (4%); POCD: 4 (1%); and delirium: 16 (4%); $P = 0.123$]. Patients with postoperative delirium were more likely to be discharged to a destination other than home after surgery (42% of those with delirium *vs* 18% with POCD and 17% with neither condition; $\chi^2 = 29.4$; $P < 0.001$).

Results of the two-way ANOVA showed only cognitive status to have an association between hospital length of stay and the explanatory variables, surgery type and cognitive status (cognitive status $F = 18.6$, $P < 0.001$; surgery type $F = 1.16$, $P = 0.28$; surgery type * cognitive status $F = 2.69$; $P = 0.069$) (Fig. 2).

Discussion

In this prospective cohort study of a group of older patients who have undergone major noncardiac surgery, we found that 80% of the patients experienced either postoperative delirium or POCD on the first day after surgery. For patients who did not develop delirium on the first postoperative day, close to 40% had POCD. Furthermore, the majority of patients who had delirium or POCD on the first postoperative day did not recover by the second day after surgery. Approximately 16% of the patients who were delirious on the first postoperative day recovered but met criteria for POCD. Similarly, the same proportion of patients who were not delirious on the first day after surgery became delirious the next day. Our results are novel in that few studies simultaneously measured both delirium and POCD, particularly in the early postoperative period. Furthermore, our study results may be particularly important because of the focus on early cognitive testing which may be more likely to uncover the effects of drugs or anesthetics on cognition.

Assessment of cognitive functioning using a combination of a validated delirium scale and cognitive tests known to be sensitive to drug effects revealed that a substantial number of older patients undergoing noncardiac surgery had either delirium or POCD on the first two days after surgery. Our results suggest there is validity to patient and/or caretaker complaints of memory and thinking problems in the period soon after surgery.[37] The types of cognitive dysfunction exhibited by patients in this study may affect patients' ability to understand and carry out self-care instructions which, in turn, could reduce postoperative functioning, delay discharge, or even risk re-admission. This observation poses a clinical dilemma because detailed cognitive status is not currently evaluated in the clinical setting. Greater clinical attention to the evaluation of cognitive status soon after surgery may help with appropriate discharge planning, including the need for home care or discharge to a destination other than home.[13]

Our study provides novel information about the incidence of early postoperative delirium and POCD using validated measures. Nearly all studies that included assessments of POCD measured cognitive status one week after surgery, which prevented observation of the peak onset period of cognitive dysfunction and underestimated its incidence. Few studies assessed POCD and delirium in the early postoperative period. One study that measured both delirium and cognitive status for the first three days after surgery likely underestimated the incidence of cognitive dysfunction after surgery due to the measurement tools. The investigators determined delirium by reviewing medical records, which has previously been shown to provide inaccurately low rates of delirium.[13] Also, they defined POCD as a two-point decline on the Mini Mental State Exam, a tool that is validated as a screen for chronic cognitive impairment, such as dementia, but not validated for acute cognitive change that can occur in the postoperative setting. Thus, it is not surprising that the incidence of delirium (17%) and POCD (23%) in the first two days after surgery were half that reported in this study. Although methods of measurement and incidence rates differed between the two studies, both studies provide evidence that early postoperative cognitive changes are common occurrences in older surgical patients.

The overall rate of delirium of 48% reported in our study is comparable with previous studies of older surgical patients undergoing major surgery.[2,38-40] Among high-risk groups (such as hip fracture), rates of postoperative delirium amongst studies have been reported from 16-62%.[41] Nevertheless, studies performed in more homogeneous patient populations, such as those undergoing orthopedic major joint arthroplasty, have reported lower rates of delirium.[39,42]

The incidence of POCD in our study (52%) was higher than that reported by previous investigators;[1,17,43,44] however, previous investigators measured POCD at one week after surgery. For example, the International Study of

Postoperative Cognitive Function (ISPOCD1) evaluated 1,218 elderly patients who had undergone major noncardiac surgery and found that 26% of them had POCD one week after surgery.[1] In a second report by the ISPOCD group in middle-aged patients (aged 40-60 yr), they reported an incidence of 19.2% of POCD in patients after noncardiac surgery.[16] Nevertheless, the incidence of POCD reported by Monk *et al*. was similar to that reported in our present study. In this study of 1,064 patients aged 18 yr of age or older undergoing noncardiac surgery, these investigators found that POCD was present in 117 (37%) young, 112 (30%) middle-aged, and 138 (41%) elderly patients[45] at hospital discharge. Therefore, older age appears to be related to a higher incidence of POCD. Other factors that may account for the difference in results include different cognitive tests being used, different criteria used to define POCD, and timing of cognitive assessments.

Although a variety of scoring methods for the detection of POCD have been used across studies, investigators generally agree that scoring methods should consider baseline performance, practice effects, and change on more than one neuropsychological test.[46-49] Prior studies using controls often included control groups that differed from the subjects, e.g., control groups with fewer males,[45,50] lower depression levels,[45] lower rates of comorbidity,[47] and lower attrition rates.[50] Therefore, the use of controls to correct for learning effects for repeated cognitive tests remains controversial.

It remains to be determined whether patients who did not meet the criteria for delirium but have POCD should be considered as a group with subsyndromal delirium. The definition of subsyndromal delirium remains ill defined, as investigators have used a variety of definitions, including requiring one or more core CAM symptoms, not meeting the criteria for delirium, or not progressing to delirium.[51] Because the definition of POCD is equally heterogeneous among published studies and differs substantially from that for subsyndromal delirium, it remains unclear whether POCD and subsyndromal delirium are similar entities on the same spectrum of cognitive dysfunction. Further research is necessary to determine the relationship between subsyndromal delirium and POCD.

There are a few potential limitations of our study. First, because we performed delirium screening and cognitive testing on only the first two postoperative days, later cases of delirium and cognitive changes might be missed. Second, we measured delirium only once daily, and given the fluctuating nature of delirium, we might have missed cases of delirium that occurred in the afternoons or evenings. Third, we did not include a tool to measure the severity of delirium, which should be considered in future studies of delirium and POCD.

The National Institute for Health and Care Excellence has published guidelines that discuss the importance of the assessment for delirium in older surgical patients and described the cost-effectiveness of interventions to prevent delirium. Nevertheless, no such practice guidelines exist for the assessment of POCD in the early postoperative setting. Given that 52% of older surgical patients were found to have POCD in the first two postoperative days, it is imperative to follow up with future investigations of POCD in the early postoperative setting. Future studies are needed to determine how such cognitive changes affect patients' post-discharge functioning and ability to perform self care and to assess the cost-effectiveness of treatments to prevent POCD.

Funding This project was supported in part by the National Institute of Aging, National Institutes of Health, Bethesda, MD, Grant # NIH 1RO1AG031795-05 (Leung).

Declaration of interests None of the authors has a conflict of interest to declare.

References

1. *Moller J*, *Cluitmans P*, *Rasmussen LS*, *et al*. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998; 351: 857-61.
2. *Dasgupta M*, *Dumbrell AC*. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. J Am Geriatr Soc 2006; 54: 1578-89.
3. *Lipowski ZJ*. Delirium (acute confusional states). JAMA 1987; 258: 1789-92.
4. *American Psychiatric Association*. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013. Available from URL: dsm.psychiatryonline.org (accessed September 2014).
5. *Inouye SK*, *Charpentier PA*. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996; 275: 852-7.
6. *Marcantonio ER*, *Goldman L*, *Mangione CM*, *et al*. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994; 271: 134-9.
7. *Leung JM*, *Sands LP*, *Paul S*, *Joseph T*, *Kinjo S*, *Tsai T*. Does postoperative delirium limit the use of patient-controlled analgesia in older surgical patients? Anesthesiology 2009; 111: 625-31.
8. *Flink BJ*, *Rivelli SK*, *Cox EA*, *et al*. Obstructive sleep apnea and incidence of postoperative delirium after elective knee replacement in the nondemented elderly. Anesthesiology 2012; 116: 788-96.
9. *Blumenthal JA*, *Mahanna EP*, *Madden DJ*, *White WD*, *Croughwell ND*, *Newman MF*. Methodological issues in the assessment of neuropsychologic function after cardiac surgery. Ann Thorac Surg 1995; 59: 1345-50.
10. *Mackensen GB*, *Gelb AW*. Postoperative cognitive deficits: more questions than answers. Eur J Anaesthesiol 2004; 21: 85-8.
11. *Petersen RC*, *Smith GE*, *Waring SC*, *Ivnik RJ*, *Tangalos EG*, *Kokmen E*. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56: 303-8.

12. *Morris JC*, *Storandt M*, *Miller JP*, *et al*. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001; 58: 397-405.
13. *Tsai TL*, *Sands LP*, *Leung JM*. An update on postoperative cognitive dysfunction. Adv Anesth 2010; 28: 269-84.
14. *Phillips-Bute B*, *Mathew JP*, *Blumenthal JA*, *et al*. Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 2006; 68: 369-75.
15. *Steinmetz J*, *Christensen KB*, *Lund T*, *Lohse N*, *Rasmussen LS, ISPOCD Group*. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110: 548-55.
16. *Johnson T*, *Monk T*, *Rasmussen LS*, *et al*. Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 2002; 96: 1351-7.
17. *Rasmussen LS*, *Johnson T*, *Kuipers HM*, *et al*. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003; 47: 260-6.
18. *Leung JM*, *Sands LP*, *Lim E*, *Tsai TL*, *Kinjo S*. Does preoperative risk for delirium moderate the effects of postoperative pain and opiate use on postoperative delirium? Am J Geriatr Psychiatry 2013; 10: 946-56.
19. *Wang Y*, *Sands LP*, *Vaurio L*, *Mullen EA*, *Leung JM*. The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am J Geriatr Psychiatry 2007; 15: 50-9.
20. *Inouye SK*, *van Dyke CH*, *Alessi CS*, *Balkin S*, *Siegal AP*, *Horwitz RI*. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113: 941-8.
21. *Wei LA*, *Fearing MA*, *Sternberg EJ*, *Inouye SK*. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc 2008; 56: 823-30.
22. *Wechsler D*. Wechsler Adult Intelligence Scale-Revised Edition. New York: The Pyschological Corporation; 1981.
23. *Borkowskit JG*, *Benton AL*, *Spreen O*. Word fluency and brain damage. Neuropsychologia 1967; 5: 135-40.
24. *Delis DC*, *Kramer JH*, *Kaplan E*, *Ober BA*. California Verbal Learning Test: Adult Version. San Antonio, TX: The Psychological Corporation; 1987.
25. *Sands LP*, *Katz IR*, *Doyle S*. Detecting subclinical change in cognitive functioning in older adults. Part II: initial validation of the method. Am J Geriatr Psychiatry 1993; 1: 275-87.
26. *Wallis WD, George JC*. Introduction to Combinatorics. CRC Press; 2010.
27. *Hinton-Bayre A*, *Geffen G*. Comparability, reliability, and practice effects on alternate forms of the Digit Symbol Substitution and Symbol Digit Modalities tests. Psychol Assess 2005; 17: 237-41.
28. *Sands LP*, *Katz IR*, *Doyle S*. Detecting subclinical change in cognitive functioning in older adults. Part I: explication of the method. Am J Geriatr Psychiatry 1993; 1: 185-96.
29. *Wright MC*, *Phillips-Bute B*, *Mark JB*, *et al*. Time of day effects on the incidence of anesthetic adverse events. Qual Saf Health Care 2006; 15: 258-63.
30. *Sands LP*, *Phinney A*, *Katz IR*. Monitoring Alzheimer's patients for acute changes in cognitive functioning. Am J Geriatr Psychiatry 2000; 8: 47-56.
31. *Brandt J*, *Spencer M*, *Folstein M*. The telephone interview for cognitive status. Neuropsychiatry Neuropsychol Behav Neurol 1988; 1: 111-7.
32. *Brink TL*, *Yesavage JA*, *Lum O*, *Heersema PH*, *Adey M*, *Rose TL*. Screening tests for geriatric depression. Clinical Gerontologist 1982; 1: 37-43.
33. *Katz W*, *Ford A*, *Moskokwitz R*, *Jackson B*, *Jaffe M*. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963; 185: 914-9.
34. *Lawton MP*, *Brody EM*. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9: 179-86.
35. *Charlson ME*, *Pompei P*, *Ales KL*, *MacKenzie CR*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40: 373-83.
36. *Longnecker DE*, *Murphy FL*. Dripps/Eckenhoff/Vandam Introduction to Anesthesia. 9th ed. Philadelphia: WB Saunders; 1997.
37. *Dijkstra JB*, *Houx PJ*, *Jolles J*. Cognition after major surgery in the elderly: test performance and complaints. Br J Anaesth 1999; 82: 867-74.
38. *Bohner H*, *Hummel TC*, *Habel U*, *et al*. Predicting delirium after vascular surgery: a model based on pre- and intraoperative data. Ann Surg 2003; 238: 149-56.
39. *Kalisvaart KJ*, *Vreeswijk R*, *De Jonghe JF*, *Van Der Ploeg T*, *Van Gool WA*, *Eikelenboom P*. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. J Am Geriatr Soc 2006; 54: 817-22.
40. *Robinson TN*, *Raeburn CD*, *Tran ZV*, *Angles EM*, *Brenner LA*, *Moss M*. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg 2009; 249: 173-8.
41. *Bitsch M*, *Foss N*, *Kristensen B*, *Kehlet H*. Pathogenesis of and management strategies for postoperative delirium after hip fracture: a review. Acta Orthop Scand 2004; 75: 378-89.
42. *Jankowski CJ*, *Trenerry MR*, *Cook DJ*, *et al*. Cognitive and functional predictors and sequelae of postoperative delirium in elderly patients undergoing elective joint arthroplasty. Anesth Analg 2011; 112: 1186-93.
43. *Williams-Russo P*, *Sharrock NE*, *Mattis S*, *et al*. Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology 1999; 91: 926-35.
44. *Williams-Russo P*, *Sharrock NE*, *Mattis S*, *Szatrowski TP*, *Charlson ME*. Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. JAMA 1995; 274: 44-50.
45. *Monk TG*, *Weldon BC*, *Garvan CW*, *et al*. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108: 18-30.
46. *Funder KS, Steinmetz J, Rasmussen LS*. Cognitive dysfunction after cardiovascular surgery. Minerva Anestesiol 2009; 75: 329-32.
47. *Lewis M*, *Maruff P*, *Silbert B*. Statistical and conceptual issues in defining post-operative cognitive dysfunction. Neurosci Biobehav Rev 2004; 28: 433-40.
48. *Murkin JM*, *Newman SP*, *Stump DA*, *Blumenthal JA*. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995; 59: 1289-95.
49. *Sauer AM*, *Kalkman C*, *van Dijk D*. Postoperative cognitive decline. J Anesth 2009; 23: 256-9.
50. *Keizer AM*, *Hijman R*, *Kalkman CJ*, *Kahn RS*, *Van Dijk D*. The incidence of cognitive decline after (not) undergoing coronary artery bypass grafting: the impact of a controlled definition. Acta Anaesthesiol Scand 2005; 49: 1232-5.
51. *Cole MG*, *Ciampi A*, *Belzile E*, *Dubuc-Sarrasin M*. Subsyndromal delirium in older people: a systematic review of frequency, risk factors, course and outcomes. Int J Geriatr Psychiatry 2013; 28: 771-80.