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Delayed Recall and Working Memory MMSE Domains Predict Delirium following Cardiac Surgery

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Abstract

Background—Reduced preoperative cognition is a risk factor for postoperative delirium. The significance for *type* of preoperative cognitive deficit, however, has yet to be explored and could provide important insights into mechanisms and prediction of delirium. Our goal was to determine if certain cognitive domains from the general cognitive screener- the Mini Mental State Exam (MMSE) - predict delirium after cardiac surgery.

Method—Patients completed a preoperative MMSE prior to undergoing elective cardiac surgery. Following surgery, delirium was assessed throughout ICU stay using the Confusion Assessment Method for ICU delirium and the Richmond Agitation and Sedation Scale.

Results—Cardiac surgery patients who developed delirium (n=137) had lower total MMSE scores than patients who did not develop delirium (n=457). In particular, orientation to place, working memory, delayed recall, and language domain scores were lower. Of these, only the working memory and delayed recall domains predicted delirium in a regression model adjusting for history of chronic obstructive pulmonary disease, age, sex, and duration of cardiopulmonary bypass. For each word not recalled on the three-word delayed recall assessment, the odds of delirium increased by 50%. For each item missed on the working memory index, the odds of delirium increased by 36%. Of the patients who developed delirium, 47% had a primary impairment in memory, 21% in working memory, and 33% in both domains. The area under the receiver operating characteristics curve using only the working memory and delayed recall domains was 0.75, compared to 0.76 for total MMSE score.

Conclusion—Delirium risk is greater for individuals with reduced MMSE scores on the delayed recall and working memory domains. Research should address why patients with memory and executive vulnerabilities are more prone to postoperative delirium than those with other cognitive limitations.

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Keywords

confusion; screening; dementia; cognition; thoracic surgery; cardiovascular surgical procedures; Alzheimer's disease; cognitive dysfunction

Introduction

Postoperative delirium is a societal stressor from an economic and healthcare standpoint. Delirium occurs in at least 10–24% of the general patient population, with reports up to 50% of hospitalized older adults (over 65) [1]. Indirect costs of delirium due to loss of work and personal productivity have been estimated to total more than $164 billion in the U.S. alone [2]. Acute postoperative delirium has been shown to be an independent predictor of functional decline and mortality after cardiac and orthopedic surgeries [3]. Following cardiac surgery, delirium afflicts 20–30% of patients [4]. It is an acute condition that may present independently or in combination with dementia syndromes [5]. The accurate prediction of postoperative delirium could enable clinicians to initiate preventative therapies or counsel patients and families prior to surgery.

Cognitive impairment prior to surgery is a well-established delirium risk factor [6, 7, 8]. Specifically, reduced preoperative general cognition has been associated with a two to seventeen fold increase in risk [6, 9, 10, 11, 12, 13]. These findings, coupled with the prevalence of cognitive impairment in general medical and presurgical samples [14, 15], underscore the rationale of the U.S. Preventative Services Task Force's request for clinicians to remain alert for early signs of cognitive impairment in order to provide earlier intervention options [16]. The association between preoperative cognitive impairment and delirium provides an opportunity to predict postoperative delirium with preoperative neurocognitive testing.

Screening measures frequently referenced in the delirium literature to assess cognitive impairment include the Mini Mental State Exam [17], the Short Blessed Test [18], and short informant screening questionnaires (e.g., Informant Questionnaire on Cognitive Decline in the Elderly Short Form [19]). These measures provide a summary score of general cognition in domains of orientation, learning/memory, language, and construction. Outcome values are typically summarized to classify impairment or applied to predictive models (e.g., [8, 10, 20, 21, 22, 23, 24]).

Neuropsychological process approaches have revealed that the use of global cognitive scores (either applied as a threshold or as a continuous variable) constrain the application of assessing specific vulnerable cognitive domains and/or neuronal mechanisms to characterize patients [25, 26]. Examining the total score of a cognitive screener such as the MMSE may limit our appreciation for delirium vulnerability since the contributions of multiple cognitive domains are combined, diminishing information about specific cognitive domain deficits.

Characterizing MMSE domains assists with dementia assessment. For example, MMSE orientation to time and delayed recall domains predict rate of decline in patients with prodromal dementia (i.e., mild cognitive impairment) [27] and older adult nursing home

residents [28], while MMSE visuoconstruction and orientation to place domains appear most sensitive to predicting falls in elderly patients [29]. Jefferson and colleagues associated Alzheimer's disease with greater impairment in orientation to time and delayed recall domains, small vessel vascular disease with working memory and visuoconstruction domain deficits, and Parkinson's disease with errors in sentence writing accuracy [30]. These MMSE subscore profiles fit expectations regarding dementia pathology patterns and specific cognitive deficits. Similar associations between specific domains and delirium may exist.

The primary purpose of the current study was to test the hypothesis that MMSE domains (e.g., orientation, delayed recall, working memory, language, and visuoconstruction) predict postoperative delirium after adjusting for known clinical and demographic factors. We also explored the ability of MMSE domains to predict delirium types, hypoactive delirium versus hyperactive delirium [31].

Methods

Study Design and Intervention

The current study was conducted using a cohort of cardiac surgery patients well characterized for cognitive status, perioperative patient characteristics, and postoperative delirium [32]. The study followed guidelines from the Declaration of Helsinki, was approved by the Vanderbilt University Medical Center Institutional Review Board, and all participants provided written informed consent. Adult patients undergoing elective cardiac surgery at Vanderbilt University Medical Center were recruited. Patients with statin intolerance, acute coronary syndrome, need for emergency surgery, liver dysfunction, current use of potent CYP3A4 inhibitors including azole antifungals, protease inhibitors, and macrolide antibiotics, current renal replacement therapy, history of kidney transplant, or pregnancy were excluded.

Cognitive Assessment Procedures

At study enrollment, each participant completed the MMSE [17]. The MMSE is a thirty point scale (range 0–30; 30=max) that assesses seven different cognitive elements or domains: 1) orientation to time (range 0–5), 2) orientation to place (range 0–5), 3) three word registration (range 0–3), 4) delayed recall of the three words (range 0–3), 5) working memory (spelling the word "WORLD" backwards or counting backwards by seven (range 0–5), 6) language involving comprehension of a three step command, naming, repetition, and sentence writing (range 0–8), and 7) visuoconstruction involving the copy of intersecting pentagons (range 0–1).

Following surgery, research personnel assessed delirium twice daily while patients were in the intensive care unit (ICU) using the Confusion Assessment Method for ICU delirium (CAM-ICU) [33] and the Richmond Agitation and Sedation Scale (RASS) [34]. The CAM-ICU assesses cardinal features of delirium by determining fluctuations in mental status, inattention, disorganized thinking, and altered level of consciousness [33]. It has been well validated to identify delirium across adult medical and surgical critical care patient populations. The RASS is a structured assessment of sedation and agitation and provides

rating from negative five (unarousable) to positive four (combative). The RASS was used to classify patients into hypoactive and hyperactive delirium [34]. A CAM positive patient with a RASS <0 was classified 'Hypoactive', while a CAM positive patient with a RASS > 0 was classified 'Hyperactive'. Participants with both hyper and hypo active delirium periods were classified as 'Both'.

Standardized patient management

Anesthesia, surgery, and ICU management were conducted according to institutional protocols. Patients received general anesthesia, consisting of midazolam, propofol, and fentanyl induction and isoflurane and fentanyl maintenance. During wound closure a propofol infusion was started. Patients were transported to the ICU intubated and sedated. When subjects were normothermic, hemodynamically stable, and chest tube drainage was <100 ml/h, propofol was discontinued, and subjects were assessed for extubation. Postoperative medication use and fluid management was at the discretion of the intensive care physicians. Atypical antipsychotics, specifically quetiapine or olanzapine, and haloperidol were used to treat delirium. Patients were transferred out of the ICU to the hospital ward when hemodynamically stable off vasoactive infusions, not requiring invasive or non-invasive ventilator support, and not requiring the infusion of greater than 5 units/hour of insulin to maintain euglycemia.

Statistical analysis

Data were checked for integrity, distributional form, and missingness. Wilcoxon rank sum tests were used to compare delirium and no-delirium groups on numeric and ordinal measures. Chi-square tests were used to compare delirium and no-delirium groups on binary and categorical measures. Kruskal-Wallis tests were used to compare types of delirium groups (Hypoactive; Hyperactive; Both) on MMSE domains. We used stepwise logistic regression modeling to identify non-cognitive factors and MMSE domains most predictive of delirium. The stepwise approach allowed inclusion of multiple predictors known to be correlated with delirium while avoiding poor parameter estimation due to multicollinearity. The covariates included in the initial stepwise logistic regression model of non-cognitive factors included predictors that were significant at the 0.05 level in bivariate testing. Spearman correlation of cognitive domains was conducted to check for collinearity among domains. The final regression model was then constructed with the MMSE domains and the non-cognitive predictors retained in the stepwise model. Hypothesis testing was two-sided using a level of significance of .05. SAS version 9.4 (Cary, N.C.) software was used for all analyses.

Results

Participants

Five hundred ninety-four patients completed the preoperative MMSE and comprised the study cohort. The MMSE was given on average (SD) 4.5 (7.3) days prior to surgery. There were 413 males (69.5%) and 181 females (30.5%) with a mean (SD) of 65.6 (12.2) years. See Table 1.

Delirium was present in 137 (23.1%) patients, and the duration of delirium lasted between 0.5 and 7.0 days (median, 1.5 days [10^{th} to 90^{th} percentile, 0.5 to 3.5 days]). More patients had hypoactive delirium (n=108; 18.2% of the total cohort) than hyperactive delirium (10; 1.7%) or mixed delirium (19; 3.2%). The mean (SD) length of hospital stays for the delirium and no-delirium groups were 10.6 (6.1) and 7.4 (2.7) days, respectively ($p < 0.001$).

Individuals who developed delirium were older, more frequently female, and had fewer years of education. Preoperatively, individuals who developed delirium had lower estimated glomerular filtration rate, lower hematocrit, and greater prevalence of prior cardiac surgery, congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular atherosclerosis, and atrial fibrillation. Intraoperatively, delirium was more common among individuals who had valve surgery and those who had surgery with cardiopulmonary bypass (CPB).

MMSE Performance

The median MMSE score (10^{th} to 90^{th} percentile) in the cohort was 29 (26 to 30), with a perfect score of 30 earned by 222 patients. Of those scoring less than 30, the delayed recall domain was the most common to contain an error (39.0%), followed by the two orientation domains (25.5%), the working memory domain (24.8%), the language domain (10.9%), and the visuoconstruction domain (4.6%). A single individual failed to repeat the three words during MMSE word registration and, thus, this variable was removed from further analysis or reporting in the tables.

The delirium group scored, on average, one point lower on the MMSE total score relative to the no-delirium group. The delirium group scored significantly lower in each domain than the no-delirium group with the exception of the orientation to time and visuoconstruction. See Table 2.

The overall MMSE scores were not different among patients with hypoactive, hyperactive, or mixed delirium subtypes. Analyses of MMSE domains among groups of patients with each delirium subtype, however, revealed that the mixed delirium group scored lower on each domain than the hypoactive or hyperactive subtype groups with only a statistically significant difference observed for the orientation to time domain (Table 2).

MMSE and Delirium

The demographic, baseline laboratory, and surgical group differences (from Table 1) were entered into a stepwise logistic regression with delirium as the outcome variable. History of COPD, along with age, sex, and coronary bypass time were retained in the stepwise model. The results of the logistic regression model for non-cognitive factors are presented in Table 3.

MMSE domains were assessed for potential collinearity before including them in the final logistic regression model. The highest association was between the working memory domain and the orientation to place domain (Spearman rho of 0.26; a magnitude well below the threshold of 0.70 which indicates collinearity). Therefore, all MMSE domains except registration were included in regression modeling.

The delayed recall and working memory MMSE domains were significant predictors of delirium in the final model (see Table 4). After adjusting for age, sex, COPD, and duration of CBP, the odds of delirium increased by 50% for each word not recalled on the delayed recall domain assessment. For each item missed on the working memory domain the odds of delirium increased by 36%.

Of the 86 patients who experienced delirium and made at least one error in either delayed recall or working memory, 40 patients (46.5%) made an error only in delayed recall, 18 (20.9%) made an error only in working memory (i.e., no errors on delayed recall), and 28 (32.6%) showed deficits on both the delayed recall and working memory domains.

The utility of a model including only the two significant MMSE domains (delayed recall, working memory) was compared to the utility of a model including all MMSE domains by calculating and comparing the area under the receiver operating characteristics (ROC) curves for each model. Each of these logistic regression models included age, sex, history of COPD, and duration of CPB. The area under the ROC curve for the two significant domains was 0.75, while the area under the ROC curve was 0.76 in the model where the total MMSE score was included; this demonstrates the majority of the predictive ability of the MMSE for postoperative delirium resides in the delayed recall and working memory domains.

Discussion

Cardiac surgery patients who developed postoperative delirium had lower preoperative total MMSE scores than patients who did not develop delirium. When predicting delirium, we identified three important characteristics of the preoperative MMSE. First, the delayed recall and working memory domain functions were significantly impaired in patients that subsequently developed delirium, independent of the effects of other cognitive domains and the effects of non-cognitive risk factors of delirium. In fact, the odds of postoperative delirium increased 50% for each missed item of the delayed recall domain and 36% for each missed item of the working memory domain. Second, for those with delirium, almost half (47%) had a primary memory domain deficit. These findings suggest not all cognitive domains are equal in predicting delirium. Third, the sensitivity for predicting delirium for these two subtests was close to that of the MMSE total score alone. Examining specific cognitive domains can therefore provide as much information, if not more, than a simple global cognitive score.

To our knowledge, our investigation is the first to examine whether MMSE domains provide independent predictive value regarding delirium risk. When cognitive type of impairment has been examined in previous studies, time intensive neuropsychological tools have been used (e.g., [35, 36]). Although these investigations used more rigorous neuropsychological tests, we found similar results regarding vulnerability of learning and executive systems.

Memory and executive functions are intimately related but can also be dissociated from one another anatomically and functionally. Delayed memory functions such as those reflected by the MMSE word recall have been associated with three neuroanatomic regions within the brain (and the pathways that interconnect them). These are the medial temporal lobe

(hippocampus, entorhinal cortex [37, 38, 39], the thalamus (dorsomedial, anterior nuclei [40, 41]) and the basal forebrain which innervates the hippocampus with essential cholinergic neurons [42,43,44]. Executive functions, particularly those involving processing speed and mental flexibility (i.e., working memory such as counting backwards or spelling a word backwards), are most commonly associated with the frontal cortex [45, 46] and subcortical nuclei (e.g., caudate, thalamus, and associated frontal-subcortical and frontal-parietal white matter connections [47]). Insults or inefficiencies in these neuroanatomical areas and cognitive domains increase risk for postoperative cognitive complications. Indeed, memory and executive domains are also considered critical areas for the presentation of postoperative cognitive dysfunction [48, 49]. Older individuals as well as those with certain dementias such as Alzheimer's disease experience integrity decline within these neuroanatomical regions [e.g., [50]].

While we do not know the precise prevalence and extent of dementia in our sample, 11% of those with delirium had MMSEs at or below 24 prior to surgery (a score shown to have high sensitivity for dementia in community samples [51]). Alzheimer's disease pathologies as well and other neuropathologies are also likely in our sample, given recent retrospectively acquired evidence there are circulating levels of Amyloid-beta40 in cardiovascular patients [52], cardiovascular risk factors associate with frontal and temporal thinning [53, 54] and cardiovascular risk factors are also risk factors for Alzheimer's disease [55, 56]. Furthermore, subcortical small vessel vascular disease such as cerebral infarcts and white matter abnormalities associate with reduced working memory, processing speed, and memory-learning consolidation [57, 58] and are frequent among older adults planning cardiothoracic surgery [59].

Overall, our findings underscore the relevance of the U.S. Preventive Services Task Force [16] statement that cognitive screening offers the opportunity for prehabilitation and insight into potential avenues for intervention. Within the pre-surgical environment anesthesia modifications or formal postoperative rehabilitation may be appropriate based on type of cognitive impairment observed presurgically. Given the global increase in older adults, failure to screen at least for delayed recall and working memory impairment may hinder early intervention for the underlying causes of delirium or dementia.

There are study limitations. We did not identify specific domains predictive of hypo versus hyperactive delirium. This may be the result of a small sample of delirium subtypes available for statistical analysis. More pressing, we cannot yet use these data to construct a delirium prediction model without validation in additional cohorts. To build this prediction model, we encourage a systematic approach involving: 1) prospective identification of risk factors to include in the model (herein our cognitive domain findings can be applied), 2) incorporation of multicenter cohorts with uniform MMSE and risk factor measurement approaches across sites, and 3) delirium assessment using validated and consistent instruments to ensure reproducibility. Until such models are developed, clinicians are encouraged to remain sensitive to patients' presurgical cognition and particularly memory and executive functions. These individuals may warrant closer clinical monitoring for postoperative changes.

In summary, we found evidence that individuals with reduced MMSE delayed recall and working memory scores are at greater risk for postoperative delirium after cardiac surgery. Future researchers should address why memory and executively challenged patients are more prone to postoperative delirium after cardiac surgery, and assess efficacy of interventions that improve memory and executive function for the reduction of delirium in these patients.

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Table 1

Study cohort and results of bivariate comparisons between participants with and without delirium. Mean (standard deviation; SD) or percentage, as appropriate

Characteristic	All (n = 594) n (%) or mean (SD)	Delirium (n=137) n (%) or mean (SD)	No Delirium (n=457) n (%) or mean (SD)	p-value
Age, years	65.6 (12.2)	70.5 (9.7)	64.2 (12.5)	<0.001
Sex				<0.001
Female	181 (30.5%)	62 (45.3%)	119 (26.0%)	
Male	413 (69.5%)	75 (54.7%)	338 (74.0%)	
Race				0.17
Asian	4 (0.7%)	1 (0.7%)	3 (0.7%)	
Black	24 (4.0%)	9 (6.6%)	15 (3.3%)	
Hispanic	16 (2.7%)	6 (4.4%)	10 (2.2%)	
White	550 (92.6%)	121 (88.3%)	429 (93.9%)	
Years of education	13.2 (2.8)	12.8 (2.9)	13.3 (2.8)	0.043
Medical history				
Body mass index, kg/m^2	29.0 (6.1)	28.4 (5.7)	29.1 (6.2)	0.36
Weight, kg	86.4 (19.8)	81.1(17.3)	87.9 (20.3)	<0.001
Current smoking	83 (14.0%)	21 (15.3%)	62 (13.57%)	0.60
Ejection fraction	52.6 (10.9)	51.8 (1.5)	52.9 (10.9)	0.42
Congestive heart failure	235 (39.6%)	66 (48.2%)	169 (37.0%)	0.02
Atrial fibrillation	138 (23.2%)	45 (32.9%)	93 (20.4%)	0.003
Prior cardiac surgery	103 (17.3%)	34 (24.8%)	69 (15.1%)	0.008
Coronary artery disease	403 (67.9%)	95 (69.3%)	308 (67.4%)	0.67
Seizure disorder	7 (1.2%)	1 (0.7%)	6 (1%)	0.58
Hypothyroidism	92 (15.5%)	28 (20.4%)	64 (14%)	0.07
Diabetes	192 (32.3%)	44 (32.12%)	148 (32.4%)	0.95
COPD	63 (10.6%)	25 (18.3%)	38 (8.3%)	<0.001
Obstructive sleep apnea	86 (14.5%)	18 (13.1%)	68 (14.9%)	0.61
Peripheral vascular disease	167 (28.1%)	41 (29.9%)	126 (27.6%)	0.59
Cerebral vascular accident	39 (6.6%)	14 (10.2%)	25 (5.5%)	0.05
Transient ischemic event	17 (2.9%)	2 (1.5%)	15 (3.3%)	0.38
Charlson comorbidity index	2.4 (1.9)	2.9 (2.0)	2.2 (1.8)	<0.001
Medication use				
Atorvastatin treatment	297 (50%)	65 (47.5%)	232 (50.8%)	0.50
Baseline statin	402 (67.7%)	85 (62.0%)	317 (69.4)	0.11
Benzodiazepine	84 (14.1%)	22 (16.1%)	62 (13.6)	0.46
Anti-depressant	98 (16.5%)	29 (21.2%)	69 (15.1%)	0.09
Baseline laboratory data				
eGFR *, ml/min/1.73 m^2	70.2 (22.3)	64.0 (22.0)	72.0 (22.0)	<0.001
Hematocrit, %	39.7 (5.1)	38.7 (5.3)	40.0 (5.0)	0.01
Creatinine, mg/dL	1.1 (0.4)	1.2 (0.5)	1.1 (0.4)	0.40

Characteristic	All (n = 594) n (%) or mean (SD)	Delirium (n=137) n (%) or mean (SD)	No Delirium (n=457) n (%) or mean (SD)	p-value
Procedure characteristics				
CABG	290 (48.8%)	60 (43.8%)	230 (50.3%)	0.18
Valve surgery	386 (65.0%)	102 (74.5%)	284 (62.1%)	0.008
Ascending aorta surgery	53 (8.9%)	9 (6.6%)	44 (9.6%)	0.27
Cardiopulmonary bypass use	423 (71.2%)	112 (81.8%)	311 (68.1%)	0.002
Duration of cardiopulmonary bypass, min	108.6 (88.7)	130.5 (97.7)	102.0 (84.9)	0.003
Aorta cross clamp use	285 (48.2%)	73 (53.3%)	212 (46.7%)	0.18

* estimated glomerular filtration rate (eGFR; estimated using the CKD-Epi formula; see national kidney foundation https://www.kidney.org/professionals/KDOQI/gfr_calculator); COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft

Table 2

Mini mental state exam (MMSE) domain scores for all patients, those who did and did not develop delirium, and those who developed hypoactive, hyperactive, or mixed delirium. Scores are presented as mean (standard deviation; SD).

Domain	All (n = 594) mean (SD)	Delirium (n=137) m mean (SD)	No Delirium (n=457) m mean (SD)	p-value[(1)]	Hypoactive Only (n=108) mean (SD)	Hyperactive Only (n=10) M mean (SD)	Both (n=19) mean (SD)	p-value[(2)]
All domains (range 0–30)	28.6 (1.9)	27.6 (2.5)	28.8 (1.6)	<0.001	27.8 (2.4)	27.8 (2.0)	26.4 (3.1)	0.13
Orientation-Place (range 0–5)	4.7 (0.5)	4.6 (0.6)	4.8 (0.5)	<0.001	4.6 (0.6)	4.8 (0.4)	4.4 (0.8)	0.41
Orientation-Time (range 0–5)	4.9 (0.3)	4.9 (0.4)	5.0 (0.2)	.32	5.0 (0.2)	5.0 (0.0)	4.5 (0.9)	0.003
Working memory (range 0–5)	4.5 (1.1)	4.1 (1.5)	4.6 (0.8)	<0.001	4.2 (1.6)	3.9 (1.7)	3.9 (1.3)	0.28
Word Recall (range 0–3)	2.5 (0.7)	2.3 (0.9)	2.6 (0.7)	<0.001	2.3 (0.8)	2.3 (0.7)	1.9 (1.0)	0.18
Language (range 0–8)	7.9 (0.3)	7.8 (0.4)	7.9 (0.3)	<0.001	7.8 (0.4)	7.8 (0.4)	7.8 (0.4)	0.98
Visuoconstruction (range 0–1)	1.0 (0.2)	0.9 (0.3)	1.0 (0.2)	0.12	0.9 (0.2)	1.0 (0.0)	0.8 (0.4)	0.12

*(1)*Comparison of Delirium to No-delirium with Wilcoxon-Rank Sum test;

*(2)*Comparison of hypoactive, hyperactive, and both delirium subtypes with Kruskal-Wallis test;

Note: Registration (three word repetition) is not reported as all patients scored accurately (3 out of 3).

Table 3

Odds ratios for postoperative delirium for non-cognitive predictors retained in stepwise model

Variable	Odds Ratio Point Estimate	95% Confidence Limits		p-value
Age	1.05	1.03	1.07	<0.001
Sex	2.33	1.54	3.53	<0.001
History of COPD	2.13	1.20	3.78	0.01
Duration of cardiopulmonary bypass	1.00	1.00	1.01	0.01

COPD, chronic obstructive pulmonary disease

Table 4

Odds ratios for postoperative delirium associated for each 1-unit increase in Mini Mental State Exam domain subscores adjusted for other domains and non-cognitive delirium risk factors

Variable	Odds Ratio Point Estimate*	95 % Confidence Limits		p-value
Place Orientation	0.79	0.52	1.19	0.26
Time Orientation	1.20	0.57	2.53	0.63
Working Memory	0.74	0.61	0.89	0.002
Delayed Recall	0.67	0.50	0.89	0.01
Language	0.64	0.35	1.15	0.13
Visuoconstruction	1.30	0.47	3.64	0.61

*adjusted for age, sex, history of chronic obstructive pulmonary disease (COPD), and duration of cardiopulmonary bypass.