

Preoperative cognitive status is a major contributing factor to postoperative delirium in cardiac surgery: A post-hoc analysis of a prospective study

MOMENI M.¹, TIRCOVEANU R.¹, KAHN D.¹, KHALIFA C.¹

¹Department of Anesthesiology, Cliniques universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain)/ Institut de Recherche Expérimentale et Clinique (IREC).

Corresponding author: Momeni M., Department of Anesthesiology, Cliniques universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain)/ Institut de Recherche Expérimentale et Clinique (IREC) Avenue Hippocrate 10, 1200 Brussels - Email: mona.momeni@uclouvain.be

Abstract

Background: We previously showed that in cardiac surgery preoperative cognitive status of the patient was the most predictive factor of postoperative delirium (POD), independently of other clinical, biological and neurophysiological variables included in different multivariable adjusted logistic regression models.

Objective: We aimed to find the best fitted model among our previously reported models.

Design and setting: Prospective study performed in a tertiary hospital

Methods: This is a post-hoc analysis of a study including 220 patients undergoing elective cardiac surgery with cardiopulmonary bypass. The day before surgery, patients were submitted to a battery of neurocognitive tests. Blood sample was collected before the start of anesthesia for neurofilament light (NfL) measurement. After induction of anesthesia a 32-channel electroencephalogram (EEG) was recorded. Alpha-band signal was recorded over frontal electrodes. The mean power of alpha-band activity was extracted from individual frequency spectra. Patients were screened for POD until discharge from the hospital.

Main outcome measures: Association between the studied exposures and the incidence of POD were assessed by fitting multivariable adjusted logistic regression models. Comparisons between models were assessed using the Likelihood Ratio Test and the Akaike Information Criterion.

Results: In a model where patient's baseline cognition was not evaluated, postinduction mean frontal alpha power and baseline serum NfL concentration both significantly predicted POD. However, in multivariable regression models where baseline cognition was available, it was consistently the only variable that predicted POD. Addition of postinduction mean alpha power and baseline serum NfL concentration to a model where baseline cognition was known, did not statistically improve the predictive value.

Conclusions: Whenever baseline cognition is included in a multivariable model predicting POD, it remains the only significant variable. This highlights the importance of the evaluation of baseline cognition whatever clinical, neurophysiologic or biological information would be used.

Trial registration: NCT03706989

Key words: Postoperative delirium, Cognitive function, Serum neurofilament light, alpha-band power.

Introduction

Improved global access to healthcare resources has resulted in a significant increase of surgical procedures performed each year¹. This is even more true as the general population is getting older². Perioperative neurocognitive disorders (PNDs) including postoperative delirium (POD) and delayed neurocognitive recovery up to 30 days after surgery, are among the most frequent postoperative complications and may affect up to

53% of patients³. POD by itself puts the patient at high risk of morbidity and mortality and increased use of health care resources⁴. It is therefore crucial to identify patients at risk of POD, and to optimize postoperative outcomes.

It is now widely recognized that preexisting cognitive impairment is an important leading factor of PNDs^{5,6}. However, performing a complete battery of neurocognitive tests is time-consuming and necessitates expertise and manpower. Moreover, there are no guidelines as to which preoperative

test to use in detecting cognitive impairment. And in many studies cognitively impaired patients are not included.

We previously showed that in cardiac surgery patients, preoperative cognitive status of the patient is the most predictive factor of POD^{7,8}. In the first study which focused on neurophysiological markers of delirium⁷, we showed that lower post-induction mean frontal alpha electroencephalogram (EEG) power was significantly associated with the probability of developing POD, independently of age and only whenever patient's baseline cognitive status was not considered⁷. In the second study which focused on biological markers of delirium⁸, and which included the same cohort of patients, we showed that baseline serum neurofilament light (NfL), a marker of axonal injury, was significantly higher in patients who experienced POD and was correlated with patient's cognitive status. However, when patient's baseline cognition was not considered in a model predicting POD, baseline serum NfL increased the hazard of developing POD independently of other variables⁸.

In this work, we sought to compare our previously reported models that independently predicted POD, with the aim to find the most suitable model incorporating significant variables which would be useful in clinical practice. We hypothesized that the cognitive status of the patient would be the most significant predictor of POD in cardiac surgery patients.

Methods

This post-hoc analysis is part of a PhD thesis which aimed to discriminate cardiac surgery patients at risk of POD. Complete study design has been reported previously^{7,8}. The primary outcome was to analyze the association between lower intraoperative frontal alpha band power of the EEG and POD⁷.

The study was approved in September 2018 by "Comité d'Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc" (B403201837550, Brussels, Belgium) and registered in ClinicalTrials.gov (NCT03706989). Written informed consent was obtained from all participants, according to the Declaration of Helsinki. Enrolment started on May 15, 2019 and was completed on December 15, 2021. Adult patients undergoing normothermic elective cardiac surgery with cardiopulmonary bypass (CPB) were included. Exclusion criteria were as follows: emergencies, re-interventions, endocarditis, ventricular assist devices, heart transplantation, minimally invasive and robotic surgeries, preoperative delirium, history of psychiatric disorders or alcoholism, non-French

speaking patients, preoperative renal replacement therapy, liver dysfunction (liver function tests three-fold higher than the upper normal values), and use of antiepileptic treatment.

Anesthesia and CPB protocols were standardized to limit any bias regarding the risk of POD. After surgery, patients were screened for POD until discharge from the hospital using the confusion assessment method for intensive care unit (CAM-ICU) and confusion assessment method (CAM) on the ICU and ward, respectively, and a chart review.

Preoperative neuropsychological testing

The day before surgery, enrolled patients were submitted to a battery of neurocognitive tests (Figure 1)⁹: the 16-item Free and Cued Selective Reminding Test (FCSRT); Modified Visual Reproduction Test from the Wechsler Memory Scale; Digit Span Test from the revised version of the Wechsler Adult Intelligence Scale (WAIS-R); Trail Making Test; and Digit Symbol test from the WAIS-R. Sample-specific z-scores ([individual result – mean of the cohort]/standard deviation of the cohort) were computed from each test result. For the FCSRT z-score, only the sum of the results of the three free recalls were considered. For the Trail Making Test, only the difference (time part B minus time part A) was considered. Ultimately, a global cognitive z score was calculated after averaging the individual z scores. The final global cognitive z score was used to determine the patient's preoperative cognitive status.

Neurofilament light quantification in serum

Blood sample was collected before the start of anesthesia for neurofilament light (NfL) measurement. Blood was sampled in 4.9-ml serum tubes. After centrifugation (1800 rounds/min at room temperature for 10 minutes), the serum was aliquoted in 1.8-ml polypropylene microtubes and stored at -80 °C in the biobank of Cliniques universitaires Saint-Luc (Brussels, Belgium). Single-molecule array technology (Simoa, Quanterix, USA) was used for NfL quantification¹⁰. Measurements were performed in singlicate by certified technicians. Interassay coefficients of variation were 11.9% for a quality control sample with a NfL concentration of 16.4 pg mL⁻¹ and 8.8% for a quality control sample with a concentration of 170.3 pg mL⁻¹. NfL data were log transformed to obtain normally distributed data (log₁₀).

EEG recording and preprocessing

The 5-minute surface EEG recordings were obtained using a 32-channel BioSemi ActiveTwo EEG recording system (BioSemi B.V.,

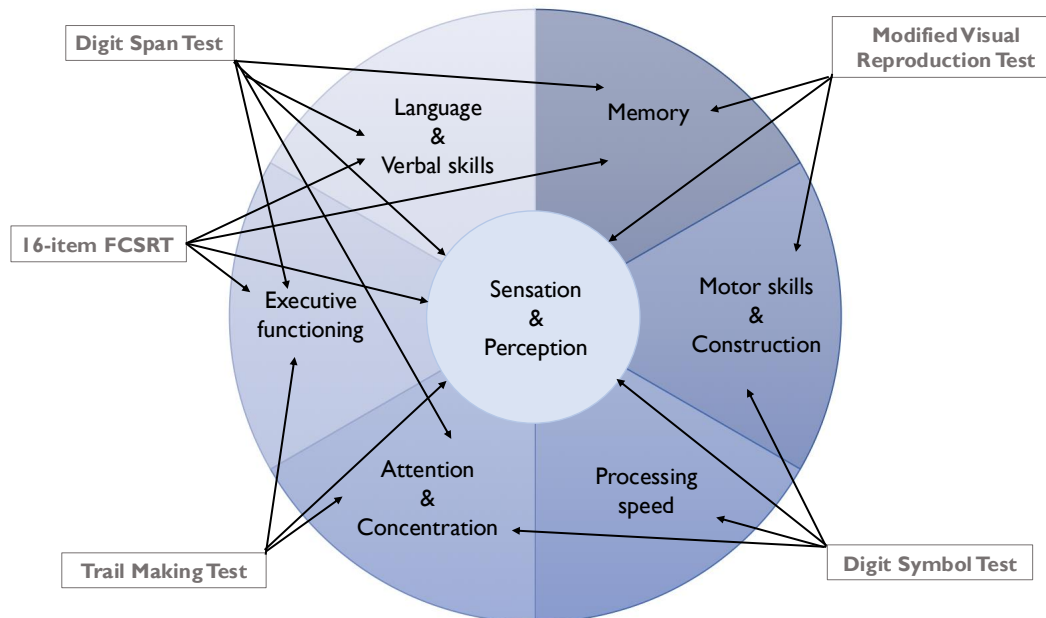


Fig. 1 — Cognitive test battery assessing key cognitive abilities, executive function as well as related neuropsychological testing.

Abbreviation: 16-item FCSRT, 16-item free and cued selective reminding test.
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Amsterdam, The Netherlands) (Figure 2). All the recordings were performed by a single person (CK), approximately 30 minutes after the induction of anesthesia and before surgical skin incision. Exclusion of any post-induction episodes of EEG burst-suppression were systematically assessed before collecting the data. The electrodes were applied on the scalp following the International 10-20 System. Electrode offset was assessed before recording and optimized to below 50 μV using a low impedance high conductive gel (SignaGel®, Parker Laboratories Inc., USA). The signal was digitized (sampling rate 2048-Hz) using a DC coupled amplifier. Additional electrodes were placed above and lateral to the right eye, and on the right arm to measure and assess artefacts related to eye movements and peripheral muscular activity, respectively. All EEG pre-processing steps were performed by a single trained person (CK), using Letswave 6 (<https://www.letswave.org/>), an open-source comprehensive EEG analysis toolbox for MATLAB® [A. Mouraux, Institute of Neuroscience (IoNS), UCLouvain, Brussels, Belgium].

After linear detrending, the data were re-referenced to the average of all scalp electrodes. Channels that exhibited large amplitude artefacts on a significant portion of the recording were visually identified and interpolated using the average of the three closest surrounding channels. After a Fast Fourier Transform (FFT) band-pass filter (0.5 to 47 Hz) was applied, the continuous EEG recordings were segmented into 5-s successive epochs. Epochs presenting signal with an amplitude greater than

$\pm 200 \mu\text{V}$ were excluded. An FFT with a Hanning window taper was applied on the individual pre-processed EEG epochs, leading to a spectral resolution of 0.1 Hz. Each spectrum was finally averaged before performing data extraction. To achieve the primary objective of this study, specific attention was paid to the alpha-band signal recorded over frontal electrodes. Alpha (α) frequency band was defined as the canonical range from 8 to 12 Hz. The frequency spectra from the following electrodes were averaged: Fp1, Fp2, AF3, AF4, F3, F4, F7, F8 and Fz. The mean α power (μV^2) of α -band activity was extracted from each individual frequency spectrum.

Considering that power data extracted from the EEG were not normally distributed, we converted the results in a decibel (dB) scale, using the formula:

$$\text{power (dB)} = 10 \cdot \log \text{power } (\mu\text{V}^2)$$

Statistical analysis

A Kolmogorov-Smirnov test was used to check the normality of data distribution. Continuous variables are presented as means $\pm$ SD or medians (25th percentile to 75th percentile). Categorical variables are presented as numbers (percentages). Comparisons of continuous variables between patients with or without POD were performed using an independent Student-t test or a Mann-Whitney U test, depending on the normality assumption. A Pearson chi-square test or a Fisher's exact test was used to compare categorical variables between the two groups.

Association between the exposures and the incidence of POD were assessed by fitting



Fig. 2 — Intraoperative setup of the 32-channel BioSemi ActiveTwo electroencephalogram recording system.

multivariable adjusted logistic regression models. Covariates were selected based on clinical relevance, results of univariate analyses and specific study hypotheses.

Model 1 is a model including age (in deciles), patient's baseline cognition and post-induction mean frontal EEG α power. Model 2 is a model including age (in deciles), patient's baseline cognition and baseline serum NfL. Model 3 is a model including age (in deciles), post-induction mean frontal EEG α power and baseline serum NfL. Model 4 incorporates all aforementioned variables being age (in deciles), post-induction mean frontal EEG α power, baseline

serum NfL as well as patient's baseline cognition.

Because models were hierarchical, comparisons between models were assessed using both the Likelihood Ratio Test (LRT) and the Akaike Information Criterion (AIC) that presents the best fitted model when the lowest. A P-value < 0.05 was considered statistically significant. All statistics were performed using IBM SPSS Statistics version 27.

Results

Baseline characteristics of the population is detailed in Table I. Among the 220 included

Table I. — Baseline characteristics of patients with and without delirium.

	Non-delirious patients (n = 155)	Delirious patients (n = 65)	P-value
Age, years	67 (59, 74)	74 (64, 79)	$<0.001^a$
Sex, male	128 (82.6)	52 (80.0)	0.65 ^c
EuroSCORE II, %	1.5 (0.9, 2.5)	2.4 (1.3, 4.0)	$<0.001^a$
Global cognitive z-score	0.21 ± 0.84	-0.52 ± 1.14	$<0.001^b$
Hypertension	115 (74.2)	52 (80.0)	0.36 ^c
Dyslipidemia	110 (71.0)	55 (84.6)	0.03 ^c
Smoking	75 (48.4)	38 (58.5)	0.17 ^c
Diabetes mellitus	41 (26.5)	21 (32.3)	0.38 ^c
LVEF, %	61 (57, 69)	60 (53, 66)	0.20 ^a
GFR, mL min ⁻¹	79 (63, 90)	70 (55, 86)	0.02 ^a
Hb, g dL ⁻¹	14.3 ± 1.4	13.7 ± 1.2	0.002 ^b
Baseline NfL, pg mL ⁻¹	13.52 (9.80, 20.36)	18.64 (13.52, 28.16)	$<0.001^a$

Continuous variables are expressed as means $\pm$ SD or as medians and percentiles (P25-P75). Categorical variables are expressed as numbers and percentages.
P-values refer to group comparison by a: Mann-Whitney U test; b: Student-t test; c: Chi-square test.
Abbreviations: EuroSCORE: European System for Cardiac Operative Risk Evaluation; Hb: Hemoglobin; GFR: Glomerular Filtration Rate; LVEF: Left Ventricular Ejection Fraction; NfL: Neurofilament Light.

subjects, 65 (29.5%) patients suffered from POD. Patients who experienced POD were significantly older (years; 74 [64, 79] vs 67 [59, 74]; $P < 0.001$), with higher EuroSCORE (European System for Cardiac Operative Risk Evaluation) II scores (%; 2.4 [1.3, 4.0] vs 1.5 [0.9, 2.5]; $P < 0.001$). They also had a lower preoperative global cognitive z-score (-0.52 ± 1.14 vs 0.21 ± 0.84 ; $P < 0.001$).

Intra- and postoperative data are represented in Table II. Although the CPB time (minutes) was significantly longer in delirious patients (112 ± 40 vs 99 ± 33 ; $P = 0.02$), there was no significant difference regarding the type of surgery between patients with or without POD. Baseline serum NfL concentrations were significantly higher in delirious patients. Patients suffering from POD had a more prolonged stay (days) both in the ICU (4 ± 3 vs 2 ± 1 ; $P = 0.004$) and in the hospital ($8 [7, 10.5]$ vs $8 [7, 9]$; $P = 0.006$).

Different multivariable logistic regression models were compared to predict POD. In our

previous studies we showed that age⁷, global cognitive z-score^{7,8}, postinduction mean frontal α power⁷, and baseline serum NfL concentrations⁸ were associated with the incidence of POD. We subsequently compared 4 models including these variables to define the best fitted model predicting POD in cardiac surgery patients. The results of these models are illustrated in Table III. In models where baseline cognition was evaluated (model 1, 2 and 4), global cognitive z-score was consistently the only variable that predicted POD. However, model 4 yielded the lowest Akaike Information Criterion, suggesting that the model was the best fitting model for prediction of POD compared with other models (model 1 and model 2) that included global cognitive z-score, even if there was no statistically significant difference when model 4 was compared to model 1 ($P = 0.096$) and when model 4 was compared to model 2 ($P = 0.072$). In a model (Model 3) where patient's baseline cognition was not evaluated, postinduction mean

Table II. — Intra- and postoperative characteristics of patients with and without delirium.

	Non-delirious patients (n = 155)	Delirious patients (n = 65)	P-value
Type of surgery			
Isolated CABG	74 (47.7)	26 (40)	0.18 ^c
Single non-CABG	35 (22.6)	10 (15.4)	
2 interventions	30 (19.4)	20 (30.8)	
≥3 interventions	16 (10.3)	9 (13.8)	
Surgical time, minutes	226 ± 57	238 ± 60	0.17 ^b
CPB time, minutes	99 ± 33	112 ± 40	0.02 ^b
Aortic cross-clamp time, minutes	78 ± 29	87 ± 32	0.06 ^b
Mean postinduction alpha power, dB	-11.59 ± 3.37	-14.03 ± 4.6	<0.001 ^b
Reintervention for bleeding	8 (5.2)	4 (6.2)	0.77 ^c
ICU length of stay, days	2 ± 1	4 ± 3	0.004 ^b
Hospital length of stay, days	8 (7, 9)	8 (7, 11)	0.006 ^a
Continuous variables are expressed as means ± SD or as medians and percentiles (P25-P75). Categorical variables are expressed as numbers and percentages.			
P-values refer to group comparison by a: Mann-Whitney U test; b: Student-t test; c: Chi-square test.			
Abbreviations: CABG: Coronary Artery Bypass Grafting; CPB: Cardiopulmonary bypass; ICU: Intensive Care Unit.			

Table III. — Comparison of different multivariable logistic regression models for prediction of postoperative delirium.

Variables	Model 1	Model 2	Model 3	Model 4
Age, deciles	1.09	1.00	1.14	0.94
OR (95% CI)	(0.75 - 1.58)	(0.67 - 1.48)	(0.78 - 1.68)	(0.62 - 1.42)
Global cognitive Z-score	0.57	0.54	-	0.59
OR (95% CI)	(0.38 - 0.85)	(0.36 - 0.79)		(0.39 - 0.89)
Postinduction mean alpha power, dB	0.91	-	0.89	0.92
OR (95% CI)	(0.83 - 1.00)		(0.82 - 0.97)	(0.84 - 1.01)
Baseline serum NfL (log 10), pg mL ⁻¹	-	3.83	4.33	3.42
OR (95% CI)		(0.90 - 16.20)	(1.03 - 18.29)	(0.80 - 14.67)
AIC	245.25	245.72	249.12	244.48
LRT x 2 (model 4 vs 1, model 4 vs 2, Model 4 vs 3)	2.77	3.24	6.64	
Degree of freedom	1	1	1	
P-value	0.096	0.072	0.010	
Bold characteristics indicate $P < 0.05$.				
Abbreviations: OR: Odds Ratio; CI: Confidence Interval; NfL: Neurofilament light; AIC: Akaike Information Criterion; LRT: Likelihood Ratio Test.				

frontal α power and baseline NfL concentration both significantly predicted POD. However, when model 3 was compared to model 4, the latter revealed to be statistically significantly better ($P = 0.01$). In other words, whenever baseline cognition is included in a model, there is no added value of other clinical, neurophysiologic or biological variables that were tested in this study.

Discussion

The results of this post-hoc analysis in cardiac surgery patients confirm that the best way to identify patients at high risk of delirium is to evaluate their cognitive status^{5,6,11}. However, performing a complete battery of neurocognitive tests as performed in this study is time-consuming and requires expertise. Additionally, some patients may feel tired and/or discouraged when put at a complete cognitive evaluation lasting 50 to 60 minutes. Other succinct tests need therefore to be chosen in daily clinical practice, although no clear guidelines are available regarding this choice. Currently, easy to perform tests are available that can predict patients at risk of POD. Mini-Cog test is one of these options¹². This tool is easy to perform and includes 3 steps: (1) three words registration, (2) clock drawing and (3) three words recall. The Mini-Cog test has been used in identifying patients at risk of PND's. In a prospective observational study of 153 thoracic surgical patients ≥ 65 years old, Li et al.¹³ found that a preoperative Mini-Cog score indicative of cognitive impairment was associated with a significant higher risk of POD (Odds Ratio[95% Confidence Interval], 2.37 [1.1 - 5.18]; $P = 0.028$). In another prospective observational study including 80 surgical patients ≥ 65 years old, Tiwary et al.¹⁴ investigated whether there was an agreement between the Mini-Cog test administered in the preoperative clinic (approximately 1 week before surgery) and immediately before surgery. They also evaluated whether a positive screening for cognitive dysfunction using the Mini-Cog test on the day of surgery was associated with POD in the post-anesthesia care unit. The authors found a high agreement (κ [95% Confidence Interval], 0.78[0.69 - 0.87]; $P < 0.001$) between the two timings of Mini-Cog assessment. Patients with a Mini-Cog score compatible with cognitive impairment (scores ≤ 2) had an estimated 12.8 times higher odds of POD compared to patients with scores > 2 (Odds Ratio[95% Confidence Interval], 12.8 [2.6 - 63.8]; $P = 0.002$). This suggests that Mini-Cog is useful to screen surgical patients at risk of POD, even if their cognitive status is evaluated on the

day of surgery, implicating some degree of anxiety.

Another simple cognitive screening tool is the Montreal Cognitive Assessment (MoCA)¹⁵. MoCA test is translated and validated in several languages. MoCA evaluates in approximately 10 minutes several cognitive domains (short-term memory, visuospatial skills, executive functions, attention, working memory, language and spatiotemporal orientation). A recent systematic review and meta-analysis has shown that a MoCA cut-off score of < 26 had 87% sensitivity and 72% specificity in identifying cognitive impairment in surgical populations¹⁶. In a prospective study of 173 elective vascular surgery patients, Styra et al.¹⁷ found that patients with a preoperative MoCA score < 15 (indicative of moderate to severe cognitive impairment), were significantly at higher risk of developing POD (Odds Ratio[95% Confidence Interval], 6.13 [1.56 - 24.02]; $P = 0.02$).

In addition to screening tests of global cognitive function, targeted tests on some specific cognitive domains might also be useful to omit the time needed for a complete neurocognitive evaluation. Indeed, it has been suggested that poor performances on tests evaluating executive functions, such as the Trail Making Test, might be a predictor of POD¹⁸⁻²⁰. We recently showed that among a complete battery of neurocognitive tests, the Modified Visual Reproduction Test was independently of the other cognitive tests (Figure 1), the only test that identified patients at risk of POD⁹. One of the main advantages of this test compared to the other tests is that it does not depend on literacy or language proficiency.

Preoperative cognitive tests, even if succinct, have therefore the capacity to help clinicians in identifying cognitively vulnerable subjects. This is important as informing the patients and their family about the risk of PNDs is a first step in a better-tailored anesthetic care²¹. In elderly population, preoperative cognitive evaluation can best be combined with frailty screening²². In this way strategies to optimize medication use, comorbidity treatment and eventually nutrition can be started, although robust results are still lacking²³. Some studies have suggested that preoperative cognitive training can increase cognitive reserve and improve postoperative cognitive recovery²⁴, although large sample-sized studies are needed to show whether cognitive training may effectively prevent POD in cardiac surgery patients²⁵.

Our study has several limitations. It is a post-hoc analysis of a prospective study in cardiac surgery patients. These results need to be confirmed in other surgical settings. We had not calculated a priori sample size calculation for the current analyses.

Sample size of this study was based on the primary outcome, which was to analyze the association between lower intraoperative frontal alpha band power of the EEG and POD⁷. We only included elective cardiac surgery patients. Our results can therefore not be generalized to all cardiac surgery patients.

In summary, our results confirm that whenever baseline cognition is included in a multivariable logistic regression model, it remains the only significant variable predicting POD.

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