Biomarkers of cerebral injury for prediction of post-operative cognitive dysfunction in patients undergoing cardiac surgery

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Abstract

Objectives

To assess the ability of the biomarkers neuron-specific enolase (NSE), tau, neurofilament light chain (NFL), and glial fibrillary acidic protein (GFAP) to predict postoperative cognitive dysfunction (POCD) at discharge in patients who underwent cardiac surgery.

Design

Post hoc analyses (with tests being prespecified before data analyses) from a randomized clinical trial.

Setting

Single-center study from a primary heart center in Denmark.

Participants

Adult patients undergoing elective or subacute on-pump coronary artery bypass grafting and/or aortic valve replacement.

Interventions

Blood was collected before induction of anesthesia, after 24 hours, after 48 hours, and at discharge from the surgical ward. The International Study of Postoperative Cognitive Dysfunction test battery was applied to diagnose POCD at discharge and after three months. Linear mixed models of covariance were used to assess whether repeated measurements of biomarker levels were associated with POCD. Receiver operating characteristic (ROC) curves were applied to assess the predictive value of each biomarker measurement for POCD.

Measurements and Main Results

A total of 168 patients had biomarkers measured at baseline, and 47 (28%) fulfilled the POCD criteria at discharge. Patients with POCD at discharge had significantly higher levels of tau (p = 0.02) and GFAP (p = 0.01) from baseline to discharge. The biomarker measurements achieving the highest area under the ROC curve for prediction of POCD at discharge were NFL measured at discharge (AUC, 0.64; 95% confidence interval [CI], 0.54-0.73), GFAP measured 48 hours after induction (AUC, 0.64; 95% CI, 0.55-0.73), and GFAP measured at discharge (AUC, 0.64; 95% CI, 0.54-0.74), corresponding to a moderate predictive ability.

Conclusions

Postoperative serum levels of tau and GFAP were significantly elevated in cardiac surgery patients with POCD at discharge, however, the biomarkers achieved only modest predictive abilities for POCD at discharge. Postoperative levels of NSE were not associated with POCD at discharge.

Introduction

Post-operative cognitive dysfunction (POCD) is frequent after cardiac surgery, including both coronary artery bypass grafting (CABG) and aortic valve replacement (AVR), and may be detected in 15-50% of patients[1–5]. The occurrence of POCD is associated with implications of daily living functions reported by patients and relatives[6], as well as with decreased long-term survival[7]. The wide range of reported incidences reflect substantial heterogeneity in the POCD definition and lack of a gold-standard diagnostic modality, which hinder comparison of intervention studies targeting POCD[8]. Furthermore, neuropsychological testing for the detection of POCD is labor-intensive and time-consuming, which hinder routine evaluation in cardiac surgery patients. Accordingly, a biomarker with the potential to predict POCD would be of great clinical utility to identify patients at risk to implement preventive measures and could act as a surrogate marker for poor neurological outcome in clinical trials.

   Several novel biomarkers of neurologic injury are available. They include the neuroectodermic glycolytic enzyme neuron specific enolase (NSE), tau, a protein originating from the axonal cytoskeleton, neurofilament light chain (NFL), a protein integrated in the neuronal and axonal cytoskeleton, and glial fibrillary acidic protein (GFAP), originating from the astroglia cell cytoskeleton (PMID: 27632903). All biomarkers have been associated with acute brain injury and have been suggested as markers of brain injury after cardiac surgery[10–16]. However, the ability of the biomarkers to predict POCD after cardiac surgery remains unknown. Accordingly, the aim of the present study was to investigate the ability of NSE, tau, NFL, and GFAP to predict POCD at discharge in patients undergoing elective or subacute CABG and/or AVR.

Methods

Patients in the present study were all participants in the assessor-blinded, randomized, controlled 'Perfusion Pressure Cerebral Infarcts' (PPCI) trial, which was approved by the Regional Ethics Committee (project identifier, H-3-2013-110) and the Danish Data Protection Agency. All participants provided informed verbal and written consent prior to enrollment.

The design paper and primary results have been published[17,18]. The study included adult patients having elective or subacute CABG and/or AVR. Patients were randomized to either a MAP target of 40-50 mmHg (low target group) or a MAP target of 70-80 mmHg (high target group) during cardiopulmonary bypass (CPB). The CPB pump flow was fixed at 2.4 liters per minute per square meter body surface area plus 10-20%, and the allocated MAP levels were achieved by boluses of phenylephrine up to a maximum of 2.0mg, which was followed by continuous infusion of norepinephrine up to 0.4 μg per kg per min. During CPB, the following targets were applied: arterial oxygen saturation above 96% (and PaO2 above 13 kPa), normocapnia (PaCO2 between 4.5 and 6.0 kPa), normothermia (temperature above 36.5°C, and transfusion of packed red blood cells if hematocrit was below 24%; or higher in case of lactic acidosis or low mixed venous saturations. Other treatment was at the discretion of the treating physician[17]. In brief, no significant differences were found between the two MAP allocation groups regarding presence of postoperative MRI verified cerebral infarcts, POCD, impaired cerebral metabolism, long-term cognitive dysfunction or survival [18–20].

Biomarker measurements

All blood samples were collected per protocol. Prior to initiation of CPB, blood was collected from a radial artery catheter. After 24 hours from anaesthesia induction, after 48 hours from anaesthesia induction, and prior to discharge from the surgical department, a venous blood

sample was collected. In all cases, a total of 9 mL blood was drawn and divided in ethylenediamine-tetraacetate (EDTA), citrate-coated and heparin-coated tubes. Samples were centrifuged at 3000 rpm for 10 minutes, and plasma was extracted in polypropylene test tubes and stored at − 80 °C until assaying.

NSE concentration was measured using standard clinical chemistry assays on a Cobas platform (Roche Diagnostics, Penzberg, Germany). T-tau, GFAP and NFL concentrations were measured with commercially available Single molecule array (Simoa) kits (Quanterix, Billerica, MA). For all biomarker assays, calibrators were run in duplicates, and obvious outlier calibrator replicates were masked before curve fitting. Samples were diluted four-fold and run in singlicate. Two quality control (QC) levels were run in duplicates in the beginning and the end of each run.

For tau, a QC sample with a concentration of 4.9 pg/mL achieved a repeatability of 4.2% with an intermediate precision of 4.4%, while a QC sample with a concentration of 21.3 pg/mL achieved a repeatability of 5.5% with an intermediate precision of 8.5%. The validated measurement interval for tau was 1.22 – 317 pg/mL with a lower limit of quantification (LLoQ) of 1.22 pg/mL. For NFL, a QC sample with a concentration of 6.3 pg/mL achieved a repeatability of 8.3% with an intermediate precision of 9%, while a QC sample with a concentration of 48.5 pg/mL achieved a repeatability of 8.1% with an intermediate precision of 8.2%. The dynamic range for NFL was 1.9 – 1800 pg/mL with an LLoQ of 1.9 pg/mL. For GFAP, a QC sample with a concentration of 82.4 pg/mL achieved a repeatability of 4.5% with an intermediate precision of 5.9%, while a QC sample with a concentration of 223 pg/mL achieved a repeatability of 8.2% with an intermediate precision of 8.2%. The dynamic range for GFAP was 5.48 – 4000 pg/mL with an LLoQ of 0.69 pg/mL.

Assessment of POCD

The applied definition of POCD has been reported previously[20]. Cognitive function was evaluated the day before scheduled surgery, again either after 1 week, at hospital discharge, whichever came first, and after 2 to 4 months after surgery. The International Study of Postoperative Cognitive Dysfunction (ISPOCD) test battery, including Visual Verbal Learning test, the Concept Shifting test, the Stroop Colour Word Interference test and the Letter Digit Coding test with evaluation of seven neuropsychological variables, was used for all evaluations[21]. At baseline, the Mini-Mental State Examination (MMSE) was administered and patients with a score of 24 points or less underwent no further cognitive evaluation during the trial[20]. ISPOCD test results were corrected for learning effects and variability in test performance between sessions.

The change from baseline to the postoperative test in the individual patient was calculated and we subtracted the average change in healthy controls (using data collected by Krenk et al.[22]) to correct for learning effects, where after this corrected change was divided by the standard deviation (SD) of the control group's change in performance to yield a Z-score in each variable[20,21]. The composite Z-score was calculated as the sum of individual Z-scores divided by the SD of the control group's sum of Z-scores. POCD was defined as the presence of either 2 out of 7 individual Z-scores above 1.96 or a composite Z-score above 1.96[20], and POCD at discharge was our dichotomized primary endpoint.

The ISPOCD test battery includes adherence to the test procedure as an assessment. As such, only data considered 'complete and reliable' are included in the ISPOCD score. As test performance can be affected by limitations of cognitive and/or physical nature, we conducted an exploratory analysis including data not categorized as 'complete and reliable' after three months, as cerebral injury could be the cause.

Statistical analysis

All tests were pre-specified prior to data analysis. Throughout, normally distributed continuous variables were presented as mean ± standard deviation (SD) and non-normally distributed continuous variables were presented as median (interquartile range, IQR). Normality was assessed visually after application of QQ plots. Categorical variables were presented as counts (frequencies). We presented baseline characteristics for patients with viable biomarker measurements at baseline, stratified by presence of POCD at discharge.

We presented the levels of biomarkers at the four sampling time points, stratified by POCD at discharge. To assess, whether repeated measurements of biomarker levels over time were associated with the presence of POCD, we applied linear mixed models (LMM) of covariance pre-specifying an unstructured covariance. We presented the p-values for the between-group differences for all biomarkers. Further, all LMM were tested for interaction between time and presence of POCD as a marker of different development of biomarker levels over time in the two groups.

For exploring the associations between biomarker levels and composite Z-score, we applied linear regression models with composite Z-score as the dependent variable and each biomarker level as the independent predictor. Logarithmic transformation was applied as appropriate to approximate normal distribution, and beta estimates with 95% CI for the regression coefficient were presented. For further analyses of predictive values, we only included biomarker measurements with a significant association to the composite Z-score. As a secondary analysis, we repeated the linear regression models with composite Z-score after three months as dependent variable.

To assess the overall ability of each biomarker to predict POCD at discharge, we applied univariable receiver operating characteristics (ROC) curves. Further, we applied multivariable ROC curves with adjustment for suspected confounders, including age, sex, and type of surgery. For biomarker levels with an area under the ROC curve greater than 0.60, we conducted exploratory analyses to present cut-off values for the highest combined sensitivity and specificity (optimized Youden index). A significance level of 0.05 was applied throughout, and SAS software, version 9.4 (SAS institute, Cary, North Carolina, USA) was used for all statistical analysis.

Results

In the PPCI trial, a total of 197 patients were randomized, with 98 patients being allocated to the high MAP group and 99 patients being allocated to the low MAP allocation group[18]. A total of 169 (86%) patients underwent the ISPOCD test battery at discharge, and of those patients, 168 (99%) had biomarkers measured at baseline. A total of 47 (28%) of patients with measured biomarkers fulfilled the criteria for POCD at discharge, and 13 (7.7%) fulfilled the POCD criteria after three months. In the exploratory analysis including ISPOCD data not categorized as 'complete and reliable', 17 (10%) patients fulfilled the POCD criteria after three months. Patients with POCD at discharge were significantly older (70 ± 8.6 years versus 65 ± 9.9 years, p = 0.004), had a significantly higher median EURO score 2.3 (1.5 - 3.7) versus 1.5 (0.98 - 2.4), p = 0.002), and underwent aortic valve replacement more frequently (24 (51%) versus 41 (34%), p = 0.04). Patients with POCD at discharge were more likely to be actively working at time of surgery (38 (81%) versus 72 (60%), p = 0.009), had a CCS score below 2 more frequently (21 (45%) versus 75 (62%), p = 0.04), and received a lower median number of coronary grafts (1 (0 - 3) versus 2 (0 – 3), p = 0.004) (Table 1).

Levels of biomarkers versus POCD at discharge

We found a significant association between higher biomarker levels after surgery and POCD for tau (p = 0.02) and GFAP (p = 0.01). However, we found no significant differences between the levels of NSE or NFL in patients with versus without POCD at discharge (Figure 1).

Associations between biomarkers and composite Z-score at discharge and after three months

Neuron-specific enolase levels were associated with composite Z-score at discharge only when measured at baseline. Tau levels were associated with composite Z-score at all time points with the exception at 24 hours (p=0.09). NFL levels were associated with composite Z-score only when measured at discharge, while GFAP levels were associated with composite Z score at all time points (Table 3).

We found a significant association between NFL measured at baseline and composite Z-score after three months (estimate 0.36±0.13, p=0.005), while NFL measured after 24 hours (estimate 0.22±13, p=0.09), after 48 hours (estimate 0.25±13, p=0.06) and at discharge (estimate 0.04±0.13, p=0.79) were not associated with composite Z-score after three months. We found no other significant associations between biomarker values and composite Z-score after three months.

Value of biomarkers for prediction of POCD at discharge

With the exception of tau measured at baseline and GFAP measured at baseline, all biomarkers with a significant association to composite Z-score were significant predictors of POCD at discharge, with areas under the ROC curves ranging from 0.63 to 0.64 (Table 3). Adjusting the ROC analyses for sex, age, and type of surgery increased the area under the ROC curves to a range of

0.67 to 0.70 (Table 3). Optimization of the Youden index in univariable analyses yielded the following cut-off values, sensitivities and specificities for the different biomarkers: Tau after 48 hours, cut-off 2.8 pg/mL, sensitivity 0.78 and specificity 0.53; Tau at discharge, cut-off 1.7 pg/mL, sensitivity 0.84 and specificity 0.45; NFL at discharge, cut-off 25 pg/mL, sensitivity 0.79 and specificity 0.48; GFAP after 24 hours, cut-off 120 pg/mL, sensitivity 0.77 and specificity 0.48; GFAP after 48 hours, cut-off 110 pg/mL, sensitivity 0.77 and specificity 0.51; GFAP at discharge, cut-off 102 pg/mL, sensitivity 0.77 and specificity 0.51.

In the exploratory analysis, including ISPOCD data not categorized as 'complete and reliable', the biomarkers achieved the following AUC's for prediction of POCD after three months: Tau at baseline 0.54 (0.39 – 0.70), tau after 48 hours 0.60 (0.44 – 0.76), tau at discharge 0.61 (0.46 – 0.77), NFL at discharge 0.58 (0.43 – 0.73), GFAP at baseline 0.57 (0.40 – 0.73), GFAP after 24 hours 0.59 (0.44 – 0.74), GFAP after 48 hours 0.55 (0.38 – 0.71), GFAP at discharge 0.53 (0.35 – 0.71).

Discussion

The present analyses suggest that tau and GFAP levels after cardiac surgery are significantly higher in patients with POCD at discharge compared to patients without POCD at discharge. In accordance, levels of tau and GFAP were significantly associated with composite Z-score at discharge at all timepoints, with the exception of tau measured after 24 hours (p=0.09). Both biomarkers measured after surgery showed a modest predictive ability for POCD at discharge with area under ROC curves of 0.63-0.64. While the predictive ability was too low for the biomarkers to act as stand-alone tests for POCD, future studies could explore if a combination of the biomarkers and clinical markers can detect patients at high risk for POCD. The ability to screen for POCD early after cardiac surgery could facilitate early diagnosis, and potentially be used to target

interventions at an early stage. In addition, postoperative tau and GFAP levels could be used as surrogate markers in clinical pilot trials investigating neuroprotective interventions in cardiac surgery.

The measured biomarkers have all emerged in recent years. The biomarker NSE is a glycolytic enzyme present in cells of neuroectodermic origin[23]. Accordingly, NSE is present in both neurons and erythrocytes, and NSE is sensitive to hemolysis. The lack of difference in NSE levels between patients with POCD versus patients without POCD could be a result of hemolysis caused by the CPB circuit in both groups. Supporting this is the fact that NSE levels have been associated with poor outcome in numerous other settings of acute neuronal damage[10,11,24].

Tau is an axonal cytoskeleton protein, and elevated levels have been shown to be highly predictive of poor neurological outcome after cardiac arrest[25]. Further, elevated levels of tau have been associated with neurocognitive decline after CPB in a smaller study, which showed higher tau levels 6 hours after surgery compared to 4 days after surgery[11]. This is in accordance with our results, with peak tau levels being reached 24 hours after surgery.

Neurofilaments are integrated in both the neuronal and axonal cytoskeleton, and levels of NFL have shown to be higher in cardiac surgery patients undergoing CPB than in cardiac surgery patients not undergoing CPB[15,26]. Whether this difference in NFL levels is caused by a true difference in the magnitude of neuronal damage or by unmeasured confounding is unknown. In our study, NFL was the only biomarker to reach peak values at discharge, *i.e.*, relatively late after surgery, and only NFL measured at discharge was associated with composite Z score and was predictive of POCD. The late peak of NFL is in line with a previous study finding peak NFL levels 7 days after surgery. This study suggested that since NFL is the main intermediary filament in neurons, it is unlikely that release of NFL reflects anything but neuronal damage[15].

As an astroglia cell cytoskeleton protein, GFAP measured in serum has been associated with outcome after cardiac arrest, stroke, and traumatic brain injury, and GFAP has been suggested as a marker of acute brain injury in children undergoing cardiac surgery[12–14,27]. To our knowledge, the present study is the first to investigate the associations between levels of GFAP versus POCD in adult patients undergoing CABG and/or valve surgery. GFAP levels peaked after 24 hours, and the strongest association between GFAP and composite Z-score at discharge was seen at this timepoint. Accordingly, GFAP could be an early marker of POCD.

While the biomarkers included in this analysis have been shown to be highly predictive of poor outcome after cardiac arrest[10,25,27], we found a modest predictive ability for POCD after cardiac surgery. One potential explanation for this could be different pathophysiological mechanisms underlying neuronal damage after cardiac arrest versus cardiac surgery. Neuronal damage after resuscitated cardiac arrest is attributed to the 'post cardiac arrest syndrome', caused by global ischemia during the cardiac arrest and ensuing reperfusion injury after return of spontaneous circulation. As such, the post cardiac arrest syndrome is thought to primarily cause global cerebral injury. In contrast, cerebral injury following cardiac surgery is thought to be caused, to a large degree, by embolization and focal breakdown of the blood-brain-barrier, causing regional cerebral injury[28,29]. The clinical implications of regional cerebral injury are a result of both the strategic location of the injury and the magnitude of the injury. Blood levels of the analyzed biomarkers are thought to correlate with the magnitude of cerebral injury but not with the strategic location of the injury. This could explain why the biomarkers are highly predictive of outcome in conditions of global cerebral injury (ex. after cardiac arrest) but of more limited predictive value in conditions where regional cerebral injury plays a larger part (ex. after cardiac surgery).

Attempts to quantify the prevalence of neurocognitive changes after cardiac surgery have led to variable results, and the prevalence of POCD shortly before discharge after cardiac surgery is reported between 15 and 50% [1–6]. Similar large variations are reported after later follow-up. One of the main explanations for this wide range in POCD prevalence across studies is that most studies lack a control group, *i.e.*, a group of patients with a similar age and ideally a similar burden of cardiovascular and/or neurologic disease. Therefore, cognitive deficits have been defined as an arbitrary change within the study population from before to after surgery. This arbitrary change has been defined differently in different studies, and Mahanna *et al*. found that the incidence of cognitive decline ranged from 1% to 34% after 6 weeks, depending on which definition was applied[30]. In the present study, POCD was defined by application of the ISPOCD test battery, and POCD was defined as two individual test Z-scores above 1.96 or a composite test Z-score above 1.96 [21]. As such, a patient in the present study had to perform similar to the lowest performing 2.5% of the control group, either in two individual tests or in the composite test score to meet the POCD definition. The applied POCD definition is therefore highly specific, albeit less sensitive, compared to definitions used in older studies, which could explain the low prevalence of POCD after three months. In accordance with the heterogeneity in POCD definitions, a recent paper submitted recommendations for aligning the nomenclature for cognitive change associated with anaesthesia and surgery[9]. Future studies investigating cognitive disorders after cardiac surgery could attempt to adhere to these recommendations in order to make results more generalizable.

The presented results should be interpreted in light of the following limitations. While the analyses were prespecified, we chose *a priori* to include all measured biomarkers at all measured timepoints. Accordingly, we include a relatively large number of comparisons, and the results should be considered exploratory, and should be validated in future large and prospective cohorts.

The biomarkers were measured 24, 48, and 72 hours after surgery. Both tau and GFAP levels peaked after 24 hours, and it is possible that earlier measurements would increase the predictive value. In contrast, NFL levels peaked at discharged, and it is possible that later measurement would be superior. Due to the limited number of patients with POCD after three months, our analyses were underpowered towards this endpoint.

Conclusion

Postoperative serum levels of tau and GFAP were significantly elevated in cardiac surgery patients with POCD at discharge, however, the biomarkers achieved only modest predictive abilities for POCD at discharge. Levels of NFL measured at discharge were modestly predictive for POCD at

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Table 1. Baseline demographics stratified by presence of post operative cognitive dysfunction (POCD) at discharge

		POCD at discharge n = 47	No POCD at discharge n = 121	p
Demographics				
Age, years	mean ± SD	70 ± 8.6	65 ± 9.9	0.004
Male sex	n (%)	41 (87)	110 (91)	ns
Actively working	n (%)	38 (81)	72 (60)	0.009
Medical History				
Recent myocardial infarction	n (%)	8 (17)	37 (31)	ns
Hypertension	n (%)	39 (83)	106 (88)	ns
Diabetes mellitus	n (%)	27 (22)	13 (28)	ns
Current smoker	n (%)	23 (19)	10 (21)	ns
Current alcohol abuse	n (%)	2 (4.3)	10 (8.3)	ns
Symptoms				
CCS[a] score above 1	n (%)	21 (45)	75 (62)	0.04
NYHA[b] class				
I	n (%)	12 (26)	34 (28)	
II	n (%)	22 (47)	46 (38)	ns
III	n (%)	11 (24)	35 (29)	
IV	n (%)	2 (4.3)	6 (5.0)	
Objective Findings				
BMI, kg per m2	mean ± SD	27 ± 3.4	27 ± 3.9	ns
Heart rate, beats per minute	mean ± SD	71 ± 11	67 ± 13	ns
Left ventricular ejection fraction	median (IQR)	55 (45 - 60)	55 (45 - 60)	ns
P-creatinine, mg per dL	mean ± SD	90 ± 18	89 ± 24	ns
EuroSCORE II	median (IQR)	2.3 (1.5 - 3.7)	1.5 (0.98 - 2.4)	0.002
Surgical Procedure				
CABG[c]	n (%)	28 (60)	88 (73)	ns
No. of grafts	median (IQR)	1 (0 - 3)	2 (0 - 3)	0.04
AVR[d]	n (%)	24 (51)	41 (34)	0.04
MVR[e]	n (%)	3 (6.4)	6 (5.0)	ns
MAP during bypass	mean ± SD	57 ± 11	54 ± 12	ns
Duration, surgery, minutes	mean ± SD	192 ± 49	181 ± 45	ns
Duration, CPB[f], minutes	mean ± SD	98 ± 34	96 ± 62	ns
Duration, Cross clamp, minutes	mean ± SD	68 ± 30	61 ± 26	ns

a) Canadian Cardiovascular Society
b) New York Heart Association
c) Coronary artery bypass grafting
d) Aortic valve replacement
e) Mitral valve replacement
f) Cardiopulmonary bypass

Table 2. Associations (linear regression) between single biomarker measurements (logarithmically transformed; logarithm of 2, to approximate normal distribution) and composite Z score at discharge.

Biomarker	Time of measurement	Beta estimate ± standard deviation	p
Neuron specific enolase	Baseline	-0.16 ± 0.06	0.02
Neuron specific enolase	24h from induction	-0.06 ± 0.06	ns
Neuron specific enolase	48h from induction	-0.04 ± 0.06	ns
Neuron specific enolase	At discharge	-0.007 ± 0.06	ns
Tau	Baseline	0.37 ± 0.11	0.0007
Tau	24h from induction	0.14 ± 0.08	0.09
Tau	48h from induction	0.39 ± 0.10	0.0001
Tau	At discharge	0.51 ± 0.10	<0.0001
Neurofilament light	Baseline	0.12 ± 0.08	ns
Neurofilament light	24h from induction	0.11 ± 0.08	ns
Neurofilament light	48h from induction	0.16 ± 0.08	ns
Neurofilament light	At discharge	0.28 ± 0.08	0.0003
Glial fibrillary acidic protein	Baseline	0.30 ± 0.09	0.0006
Glial fibrillary acidic protein	24h from induction	0.32 ± 0.08	<0.0001
Glial fibrillary acidic protein	48h from induction	0.21 ± 0.06	0.001
Glial fibrillary acidic protein	At discharge	0.24 ± 0.08	0.002

Table 3. Area under th
e Receiver Operating Characteristics Curves for the prediction of post operative cognitive dysfunction at discharge. Data presented for biomarkers with a significant association to composite Z score (see table 2.)

Biomarker	Time of measurement	Area under the ROC[a] curve	Multivariable Area under the ROC curve[b]
Tau	Baseline	0.60 (0.50 - 0.69)	0.69 (0.61 - 0.78)
Tau	48h from induction	0.63 (0.54 - 0.72)	0.70 (0.61 - 0.79)
Tau	At discharge	0.63 (0.53 - 0.72)	0.68 (0.59 - 0.78)
Neurofilament light	At discharge	0.64 (0.54 - 0.73)	0.68 (0.58 - 0.77)
Glial fibrillary acidic protein	Baseline	0.59 (0.49 - 0.69)	0.68 (0.59 - 0.77)
Glial fibrillary acidic protein	24h from induction	0.63 (0.54 - 0.73)	0.67 (0.58 - 0.76)
Glial fibrillary acidic protein	48h from induction	0.64 (0.55 - 0.73)	0.69 (0.60 - 0.78)
Glial fibrillary acidic protein	At discharge	0.64 (0.54 - 0.74)	0.68 (0.58 - 0.77)

a) Receiver operating characteristics
b) Adjusted for sex, age, and type of surgery

Figure 1. Median (interquartile range) levels of biomarkers stratified by presence of POCD at discharge.