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# **C-Reactive Protein for Risk Prediction of Postoperative Delirium and Postoperative Neurocognitive Disorder**

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### **Competing interests**

The authors declare no conflicts of interest.

### **Trial registration**

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**Abbreviated Title:** C-Reactive Protein and Cognitive Outcome

### **Authors' contributions**

Conceived and designed the experiments: CS, FMR. Performed the experiments: CS, WRB, FMR. Analyzed the data: CK, GV, SKP, GL. Wrote the manuscript: CK, SKP, GL. Reviewed and commented the manuscript: All authors.

### **Key Points**

**Question:** Is C-reactive protein predictive for postoperative delirium (POD) and postoperative neurocognitive disorder (NCD)?

**Findings:** Preoperative CRP levels were associated with POD but not postoperative NCD after three months, whereas higher preoperative CRP levels showed higher risk for POD.

**Meaning:** Assessment of CRP before surgery might allow risk stratification of POD, which should be considered in clinical routine and further interventional studies.

## Abstract

*Background.* Postoperative delirium (POD) and postoperative neurocognitive disorder (NCD) are frequently seen in the elderly. Development of biomarkers for preoperative risk prediction is of major relevance. As inflammation present before surgery might predispose to POD and postoperative NCD development, we aim to determine associations between preoperative C-reactive protein (CRP) and the incidence of POD and postoperative NCD.

*Methods.* In this observational study, we analyzed 314 patients enrolled in the SuDoCo trial, who had a preoperative CRP measurement the day before surgery. Primary outcomes were POD assessed according DSM-4 from day 1 until day 7 after surgery and postoperative NCD assessed 3 months after surgery. We conducted multivariable logistic regression analysis adjusted for age, sex, randomization, body mass index, MMSE, ASA status, infection/autoimmune disease/malignoma and types of surgery to determine associations between CRP with POD and postoperative NCD, respectively.

*Results.* Preoperative CRP was independently associated with POD [OR 1.158 (95%CI 1.040, 1.291);  $p=0.008$ ]. Patients with CRP values  $\geq 5$  mg/L had a 4.8-fold increased POD risk [OR 5.771 (95%CI 1.765, 12.899;  $p=0.002$ )] compared to patients with lower CRP values. However, no association was seen between preoperative CRP and postoperative NCD [OR 0.552 (95%CI 0.193, 1.581);  $p=0.269$ ].

*Conclusions.* Preoperative CRP levels were independently associated with POD but not postoperative NCD after three months. Moreover, higher preoperative CRP levels showed higher risk for POD. This strengthens the role of inflammation in the development of POD. Assessment of CRP before surgery might allow risk stratification of POD.

### **Keywords:**

C-reactive protein (CRP), biomarker, inflammation, pathophysiology, postoperative delirium (POD), postoperative cognitive dysfunction (POCD), postoperative neurocognitive disorder (NCD)

## Editorial Comment

Delirium and neurocognitive decline after surgery have few reliable biomarkers. This observational study found that even small elevations of preoperative CRP were independently and linearly associated with delirium within 1 week but not with neurocognitive disorder at 3 months. Postoperative CRP was not a risk factor these findings.

### Introduction

Postoperative delirium (POD) is a costly complication associated with increased morbidity, longer hospital admission, reduced quality of life and a 2.4-fold increase in 1-year mortality in older surgical patients<sup>1,2</sup>. As one of the most common postoperative complications in the elderly, POD is seen in 21% of patients after orthopedic surgery, in 39% after vascular and cardiac surgery and in up to 87% in the critically ill<sup>3-5</sup>. Postoperative neurocognitive disorder (NCD), also called postoperative cognitive dysfunction ('POCD')<sup>6</sup>, is often seen as an adverse outcome related to POD, although research on this association has produced conflicting results<sup>7,8</sup>. Whilst POD develops in the immediate postoperative period, postoperative NCD is a late-onset complication coming up within several weeks after surgery. Both POD and postoperative NCD are age-related conditions with an expected increase in prevalence in the aging societies<sup>9</sup>.

In view of the societal burden associated with postoperative cognitive decline, extensive effort has been given to the identification of biomarkers allowing risk prediction<sup>10</sup>.

Inflammatory markers are particularly of interest as one of the mechanisms discussed as contributing to the development of POD is uncontrolled neuro-inflammation in response to the surgical trauma<sup>11</sup>. Elevated levels of procalcitonin and pro-inflammatory cytokines including IL-1 $\beta$ , -2, -6, -8 and Tumor necrosis factor (TNF)- $\alpha$  have been found in delirious patients both after surgery and in the critically ill<sup>12-15</sup>. Likewise, development of postoperative NCD has been attributed to increased IL-1 $\beta$ , -6 and TNF- $\alpha$  concentration suggesting a common pathogenesis of both conditions<sup>16,17</sup>. Yet, to the moment, no convincing evidence exists indicating benefits for any biomarker measurement as few studies assessed a broad spectrum of inflammatory markers before surgery, with investigations limited to commonly available routine parameters such as white blood cell count and C-

reactive protein (CRP). However, reasonable evidence supports the use of CRP for risk stratification of surgical patients. Both Dillon<sup>18</sup> and Xiang<sup>19</sup> found elevated CRP levels before surgery to be predictive for POD. This was confirmed in a more recent meta-analysis by Liu et al.<sup>20</sup> who identified an association of preoperative CRP with POD in non-cardiac patients compared to cardiac surgery patients. As for postoperative NCD, results on the association of preoperative CRP and postoperative NCD remain controversial. Although Wu et al.<sup>21</sup> found elevated CRP levels at baseline in patients with postoperative NCD compared to those without, others demonstrated that postoperative rather than preoperative CRP is associated with postoperative NCD development<sup>22-24</sup>.

To the moment, the influence of preoperatively measured inflammatory markers on both POD and postoperative NCD has not been investigated within one study sample. In this investigation, we hypothesized that preoperative CRP levels are associated with the incidence of both POD and postoperative NCD three months after elective surgery.

## Material and Methods

### Study Design

In this secondary subgroup analysis of the SuDoCo trial<sup>25</sup>, we analyzed 314 patients aged  $\geq 65$  years scheduled for elective surgery, who had preoperative CRP values available on the day before surgery. The SuDoCo trial was conducted at the Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum and Campus Charité Mitte. Between March 2009 and May 2010, 1155 patients were enrolled and randomly assigned to receive bispectral index (BIS) blinded or BIS guided anesthesia. Primary outcome measures were postoperative delirium (POD) and postoperative NCD. The detailed study design and recruitment procedure have been described previously<sup>25</sup>. This clinical trial meets the requirements set out by the ICH-GCP and Declaration of Helsinki. Written informed consent was obtained from all patients. The trial was registered prior to patient enrolment at [isrctn.com](http://isrctn.com) (36437985, Principal investigator: Prof. Claudia Spies, Date of registration: 02 March 2009). This study was ethically approved by the Institutional Review Board (Ethikkommission der Charité – Universitätsmedizin Berlin, EA1/242/08).

### Study population and data collection

Patients were eligible if at least 60 years of age, scheduled for elective surgery with estimated surgical time  $\geq 60$ min and a Mini-Mental State Examination (MMSE) of  $\geq 24$  at baseline. A

total of 1155 patients were enrolled in the SuDoCo trial. In addition, an age- and MMSE-matched control group of 93 non-surgical participants was recruited for postoperative NCD calculation. For the purpose of this secondary analysis, patients' charts were searched for measured CRP values. Patients with preoperative CRP levels more than 1 day prior to surgery were excluded leaving a total of 314 cases in the final sample. Data collection at baseline included demographic characteristics, presurgical Charlson comorbidity index (CCI) based on comorbidities assessed by self-reported medical history upon enrolment and cognitive performance according to MMSE. All intraoperative and postoperative data, i.e. duration and type of surgery, length of ICU stay (LOS ICU) and length of hospital stay (LOS) were collected prospectively.

### Assessment of CRP

Preoperative CRP values assessed as clinical routine samples were obtained by chart review. For CRP measurement, the laboratory of the Charité – Universitätsmedizin Berlin used an immunoturbidimetric assay. To allow for comparability and to avoid bias by factors possibly influencing CRP levels in the preoperative period such as preoperative stress, only samples assessed at maximum 1 day before surgery were considered. We limited CRP measurements to 1 day prior to surgery in order to account for potential heterogeneity caused by time differences. Considering CRP measurements assessed up to 7 days prior to surgery would have yielded a larger sample size, though at the expense of comparability. Given that most patients were seen the day before surgery in the premedication office, the use of a prespecified time point for CRP assessment contributed to the standardization of preoperative risk assessment. For postoperative analyses of CRP levels, we retrieved all available measurements within the charts and determined the maximum levels until postoperative day 7.

### Delirium Assessment

POD was defined according to the 4th revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-4) criteria<sup>26</sup>. Patients were screened for POD twice daily from the first until the seventh postoperative day. POD screening was performed by trained research team members who were instructed and supervised by psychiatrists.

## Cognitive Assessment

A set of six neuropsychological tests comprising four computer based tests of the CANTAB test battery and two paper pencil tests was administered both preoperatively and three months after surgery. The test battery included assessment of attention (Motor Screening Test, Choice Reaction Time test), memory (Pattern Recognition Memory, Spatial Recognition Memory and visual Verbal Learning Test) and executive function (Stroop-Color-Word-Test). Parallel test versions were available for different test time points. For postoperative NCD calculation, patients were referenced to the expected change within the control group to calculate the reliable change index (RCI) as proposed by Rasmussen et al. <sup>27</sup>. Postoperative NCD was diagnosed, if either two or more RCI scores below -1.96 and/or a combined RCI score of all tests below -1.96 was detected. Though this was termed ‘postoperative cognitive dysfunction’ (POCD) within the initial SuDoCo trial <sup>25</sup>, we followed the updated nomenclature for cognitive change after surgery according to the international consensus working group which recommends ‘Postoperative NCD’ instead of POCD for a persisting cognitive deficit exceeding 30 days after surgery <sup>6</sup>.

## Statistical analysis

Data are expressed as median with (25%; 75% percentiles) or frequencies (%), respectively. Differences between groups were tested using Mann-Whitney-U tests for continuous data and Chi-Square test for qualitative data. Multivariable logistic regression analysis was performed with POD and postoperative NCD as outcome, respectively, and preoperative CRP levels as continuous independent variable. Models were adjusted for age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) status ( $\leq 2$  versus  $\geq 3$ ), Mini-mental State Examination (MMSE), infection or autoimmune disease or malignoma (yes versus no), randomization (BIS blinded versus open), type of surgery (intrathoraco-abdominal versus other procedures). In a post-hoc analysis, we reran the primary analysis using our laboratory reference value of  $\geq 5$  mg/L as a cut-off rather than absolute CRP values for categorizing risk groups. Hosmer-Lemeshow-test was performed for each logistic regression model in order to test whether the observed event rates match the expected event rates. In addition, the overall prediction accuracy (calibration) of the adjusted logistic regression models was calculated. To assess the crude discrimination ability of preoperative CRP (ability to accurately separate those with and without POD), we plotted the unadjusted Receiver Operating Characteristic curve (ROC) and report the area under the curve (AUC) with 95% confidence intervals (CI).

Moreover, we conducted a sensitivity analysis and reran our primary analysis using the same logistics regression model including preoperative CRP measurements assessed up to 7 days prior to surgery. As a further sensitivity analysis and to assess potential selection bias, we compared our patient sample with all patients of the SuDoCo study that did not have a CRP assessment one day prior to surgery (Supplement Table 2). In a secondary analysis, we studied the influence of postoperative inflammation on POD and postoperative NCD, thereby rerunning the primary models by using the postoperative maximum CRP instead of preoperative CRP.

Odds ratios (OR) with 95%-confidence intervals and the corresponding p-values were calculated for each factor. A two-tailed p-value  $< 0.05$  was considered statistically significant. All p-values constitute exploratory data analysis and do not allow for confirmatory generalization of results. Calculations were performed with IBM© SPSS© Statistics, Version 25, © Copyright 1989, 2010 SPSS Inc. Calculations.

No a priori sample size calculation was performed in this retrospective observational substudy. Nevertheless, a power analysis based on the given sample size was performed. General assumptions are that the proportion of POD is 0.2 for the average CRP level, and that the multiple correlation of CRP with other covariates adjusted for in a multivariate logistic regression model is 0.2. With a sample size of  $n=314$ , in a 2-sided logistic regression test ( $\alpha = 0.05$ ) odds ratios of 1.62 or higher could be detected with a power of at least 80% for CRP as continuous variable (nQuery Advisor 7.0).

## Results

### Study population and characteristics

Of 314 patients assessed up to seven days after surgery, 72 (22.9%) developed POD and 12 out of 153 patients with complete cognitive assessment developed postoperative NCD after three months (7.8%). Figure 1 depicts a flow diagram of patient numbers. Patients with POD were significantly older, had lower cognitive baseline performance and elevated pre-surgical CRP levels compared to those without POD (Table 1). Patients with postoperative NCD after three months, however, were also older and demonstrated lower preoperative cognitive status but similar CRP levels before surgery compared to patients without postoperative NCD (Table 1). The distribution of preoperative CRP assessment of all 314 patients is shown in Figure 2. To evaluate differences between patients with postoperative NCD assessment and

those lost to follow-up, both cohorts were compared. Characteristics of both cohorts are shown in Supplement Table 1. Patients who were lost to follow-up after three months were more likely to undergo intrathoraco-abdominal surgeries and to experience longer duration of surgery. Preoperative CRP was higher while MMSE scorings were lower in the lost to follow-up cohort.

### Preoperative C-reactive protein is associated with POD

Multivariable logistic regression analysis revealed significant associations between preoperative CRP levels and POD [OR 1.158 (95%CI 1.040, 1.291);  $p=0.008$ ; adjusted Nagelkerke  $R^2=0.251$ ; Hosmer-Lemeshow-Test:  $p=0.581$ , overall accuracy of predicted versus observed POD status: 80.4%, Table 2]. Post-hoc multivariable logistic regression analysis demonstrated that patients with preoperative CRP levels of  $\geq 5$  mg/L were at 4.8-fold higher risk [OR 4.771 (95%CI 1.765, 12.899);  $p=0.002$ ; adjusted Nagelkerke  $R^2=0.258$ , Hosmer-Lemeshow-Test:  $p=0.846$ , overall accuracy of predicted versus observed POD status: 81.7%] to develop POD compared to normal range values. Among patients with CRP  $\geq 5$  mg/L, POD occurred in 14 out of 23 patients (60.9%) compared to 58 out of 291 patients (19.9%) with lower levels.

The ROC curve (Supplementary Figure 1) showed low to moderate discrimination ability as measured by the AUC: 0.654 95%CI (0.582, 0.727).

Additionally, we reran our primary analysis again considering preoperative CRP measurements assessed up to 7 days before surgery. No association was seen between CRP levels and POD [OR 1.052 (95%CI 0.995, 1.112);  $p=0.074$ ; adjusted Nagelkerke  $R^2=0.164$ ] or postoperative NCD development [OR 1.035 (95%CI 0.939, 1.139);  $p=0.491$ ], adjusted Nagelkerke  $R^2=0.150$ ]. Comparison between patients with and without CRP assessment  $\leq 1$  day before surgery is shown in Supplement Table 2.

### Preoperative CRP is not associated with postoperative NCD

Using the same covariables as in the primary POD model, no association was seen between preoperative CRP and postoperative NCD [OR 0.552 (95%CI 0.193, 1.581);  $p=0.269$ ; adjusted Nagelkerke  $R^2=0.332$ ; Hosmer-Lemeshow-Test:  $p=0.395$ , overall accuracy of

predicted versus observed postoperative NCD status: 94.7% Table 2]. Likewise, no increased postoperative NCD risk was seen in patients with CRP levels  $\geq 5$  mg/L.

Maximum postoperative CRP is not associated with POD and postoperative NCD

192 out of 314 patients had postoperative CRP values available until postoperative day 7. Maximum postoperative CRP was not significantly associated with POD [OR 1.010 (0.962, 1.061);  $p=0.687$ ; adjusted Nagelkerke  $R^2 = 0.194$ ; Supplement Table 3] or postoperative NCD [OR 0.926 (0.813, 1.055);  $p=0.247$ ; adjusted Nagelkerke  $R^2 = 0.397$ ; Supplement Table 3] in multivariable logistic regression analysis.

## Discussion

Our investigation of older adults undergoing major elective surgery revealed an association between preoperative CRP and POD incidence. Each 1.0 mg/L increase in CRP was associated with a 15.8% increase of POD risk. Moreover, patients with preoperative CRP levels  $\geq 5$  mg/L were at 4.8-fold higher risk for POD compared to patients with lower CRP levels. These findings were independent of preexisting inflammatory conditions such as acute or chronic infection, autoimmune disease and malignoma. Using CRP as an isolated marker for POD prediction demonstrated low to moderate discrimination capability with an AUC of 0.654 [95%CI 0.582, 0.727] though significantly above the chance level when looking at the confidence interval of the AUC.

With adjustment for possible confounders, POD was still significantly associated with elevated CRP levels with a prediction accuracy (calibration) within our data above 80%. No association was found in our data between CRP and postoperative NCD incidence three months after surgery.

These findings add to the limited number of studies investigating the predictive value of preoperative CRP for POD and cognitive decline. Our results are consistent with those reported by the SAGES study group<sup>18,28</sup> and those of Xiang et al.<sup>19</sup>, who also observed higher CRP levels before surgery in elderly patients developing POD after non-cardiac surgery. These recent studies along with our findings represent emerging evidence for the use of CRP as a biomarker to risk stratify patients before surgery. As patients with preoperatively elevated inflammatory markers are at high risk of experiencing cognitive decline after surgery, strategies to increase early identification of this particular vulnerable group are

warranted. Even though risk stratification using CRP is hampered by the lack of an optimal threshold most predictive for POD to develop, we found evidence that higher CRP values increase POD risk and patients with values of 5 mg/L and above are at highest risk, as demonstrated in those patients by an increased POD incidence of 60.9% compared to 19.9% in patients with CRP below 5 mg/L. This supports preoperative CRP as a potential biomarker for risk stratification both in clinical routine and research investigations. Interestingly, no associations between postoperative maximum CRP and POD or postoperative NCD development was found.

Using a validated cutpoint of CRP  $\geq 5$  mg/L as a threshold to categorize patients into a high-risk group provides an opportunity to identify patients who might benefit from preventive strategies.

Definition of subgroups at risk might increase the effect of therapies aiming to reduce inflammation. Targeting anti-inflammatory pathways, e.g. by use of clonidine or regional anesthesia with local anesthetics, both of which have anti-inflammatory properties, could provide protection against further deterioration of imbalances due to neuro-inflammation <sup>29,30</sup>.

Failure to demonstrate a benefit of anti-inflammatory prevention strategies and therapies might be due to the inclusion of patients regardless of their presurgical inflammatory status <sup>31,32</sup>. This 'one-size-fits-all'-approach might limit clinical trials to develop therapies for a condition which notably affects patients with systemic inflammation before surgery.

Our findings emphasize the role of inflammation in POD pathogenesis. One of the mechanisms discussed as contributing to the development of POD is uncontrolled neuro-inflammation in response to the surgical trauma <sup>11</sup>. Cytokines released due to a peripheral injury induce an inflammatory response in the central nervous system via a neuroimmune axis leading to blood-brain barrier disruption and microglial activation <sup>33</sup>. Postoperatively elevated levels of chemokines, soluble TNF receptor-1, IL-6 and -8 have been associated with POD development <sup>34-37</sup>, while increased IL-1 $\beta$  was related to postoperative memory impairment in animal studies <sup>38</sup>. However, the extent to which a pre-inflammatory state contributes to cognitive decline remains poorly investigated. In our study, we observed significantly higher levels of inflammatory markers preoperatively in patients developing POD.

An additional finding of importance in our investigation was that the time point of CRP determination is crucial to accurate risk prediction. Taking into account all preoperative CRP measurements until day 7 before surgery no longer revealed an association between CRP and POD. Therefore, standardization for the assessment of risk markers is required to achieve comparability and avoid confounding of results by other preoperative factors.

Although postoperative NCD is often seen as a long-term complication of POD and evidence suggests that both conditions share a similar pathobiology<sup>8</sup>, we found no association between preoperative CRP and occurrence of postoperative NCD. One reason why this was not seen in our study sample might be that our power was limited by a considerable loss to follow up in the postoperative NCD cohort. Besides, postoperative NCD might not be attributable to increased CRP suggesting that causes other than preoperative inflammation contribute to postoperative NCD. In previous investigations, associations of both pre- and postoperative inflammatory markers with postoperative NCD development have been less conclusive than with POD, possibly indicating a different pathobiology than inflammation alone<sup>20</sup>.

Our findings demand further prospective studies to confirm the predictive value of CRP and possibly additional markers.

This study has several limitations. Preoperative CRP was not measured in the whole study sample, which means that values were only available in selected cases thereby creating a possible bias which we could not correct for. This was also seen when comparing patients with and without CRP measurement on day 1 prior to surgery: Patients without measurement experienced longer duration of surgery and were undergoing major surgery more often, however, developed POD less often. Yet, a POD rate of 22.9% as detected in our subgroup is consistent with those reported by others<sup>39</sup>. Findings regarding the relationship between CRP and postoperative NCD are limited by the fact that only 153 out of the 314 patients completed neurocognitive assessment after three months.

In conclusion, preoperatively elevated CRP levels were associated with an increased risk to develop POD while this was not seen for postoperative NCD. The use of CRP if assessed on day one before surgery might allow risk prediction of POD. In view of the burden associated with postoperative cognitive decline and the current lack of convincing evidence for pharmacologic intervention, identification and preventive measures are all the more important for patients at risk for postoperative cognitive decline.

#### **Availability of data and material**

Due to legal restrictions imposed by the data protection commissioner of the Charité – Universitätsmedizin Berlin, public sharing of study data with other researchers or entities is not allowed. Requests may be sent to [dai-researchdata@charite.de](mailto:dai-researchdata@charite.de).

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## Tables

**Table 1. Sample characteristics.**

Sample Characteristics							
	Total Sample (N=314)	7 days sample			3 months sample		
		POD (n=72)	no POD (n=242)	P value	Postoperative NCD (n=12)	no postoperative NCD (n=141)	P value
Age in years	70 (66; 75)	73 (68; 77)	69 (65; 74)	<0.001*	75 (70; 77)	69 (65; 74)	0.021*
Male sex	134 (42.7%)	36 (50.0%)	98 (40.5%)	0.152†	4 (33.3%)	65 (46.1%)	0.394†
BMI (kg/m <sup>2</sup> )	27 (24; 30)	27 (23; 29)	27 (24; 30)	0.129*	27 (26; 36)	27 (25; 30)	0.362*
ASA status				0.004†			0.013†
≤ 2	173 (55.1%)	29 (40.3%)	144 (59.5%)		3 (25.0%)	87 (61.7%)	
≥ 3	141 (44.9%)	43 (59.7%)	98 (40.5%)		9 (75.0%)	54 (38.3%)	
Baseline MMSE	30 (28; 30)	29 (28; 30)					

			30 (28; 30)	0.012*	29 (26; 30)	30 (29; 30)	0.023*
Preoperative CRP (mg/L)	0.3 (0.1; 1.0)	0.8 (0.2; 2.9)	0.3 (0.1; 0.8)	<0.001*	0.2 (0.1; 0.5)	0.3 (0.1; 0.6)	0.581*
Acute/chronic infection	19 (6.1%)	5 (6.9%)	14 (5.8%)	0.717†	0 (0)	5 (3.5%)	0.507†
Autoimmune disease	19 (6.1%)	3 (4.2%)	16 (6.6%)	0.445†	1 (8.3%)	12 (8.5%)	0.983†
Malignoma	85 (27.1%)	30 (41.7%)	55 (22.7%)	0.001†	3 (25.0%)	23 (16.3%)	0.442†
Randomization				0.060†			0.877†
BIS blinded	144 (45.9%)	40 (55.6%)	104 (43.0%)		5 (41.7%)	62 (44.0%)	
BIS guided	170 (54.1%)	32 (44.4%)	138 (57.0%)		7 (58.3%)	79 (56.0%)	
Intrathoraco-abdominal surgery	75 (23.9%)	27 (37.5%)	48 (19.8%)	0.002†	3 (25.0%)	19 (13.5%)	0.275†
Specialty				0.011†			0.460†
General Surgery	75 (23.9%)	26 (36.1%)	49 (20.2%)		1 (8.3%)	23 (16.3%)	
Trauma/Orthopedic Surgery	191 (60.8%)	34 (47.2%)	157 (64.9%)		9 (75.0%)	100 (70.9%)	
Urology	36 (11.5%)	7 (9.7%)	29 (12.0%)		1 (8.3%)	14 (9.9%)	
Gynaecology	4 (1.3%)	3 (4.2%)	1 (0.4%)		1 (8.3%)	1 (0.7%)	
Neurosurgery	4 (1.3%)	1 (1.4%)	3 (1.2%)		0 (0%)	1 (0.7%)	
Vascular	2 (0.6%)	0 (0%)	2 (0.8%)		0 (0%)	1 (0.7%)	
Other	2 (0.6%)	1 (1.4%)	1 (0.4%)		0 (0%)	1 (0.7%)	
Duration of surgery (min)	120 (85; 190)	168 (120; 273)	105 (75; 166)	<0.001*	103 (76; 251)	115 (80; 163)	0.881*
Max. postoperative CRP (mg/L)**	7.6 (4.5; 13.6)	9.8 (4.6; 16.6)	7.5 (4.4; 12.7)	0.221*	6.4 (5.4; 11.4)	7.2 (3.8; 12.7)	0.958*
POD	72 (22.9%)	72 (100%)	0 (0)	-	5 (41.7%)	25 (17.7%)	0.045†
Postoperative NCD	12 (3.8%)	5 (6.9%)	7 (2.9%)	0.045†	12 (100%)	0 (0)	-
ICU LOS	2 (1; 6.0)	3 (1; 7)	2 (1; 6)	0.348*	3 (1; -)	2 (1; 7)	0.436*
LOS	11 (9; 15)	15 (11; 22)	11 (8; 14)	<0.001*	11 (9; 14)	10 (8; 13)	0.416*

Data are shown as median with percentiles (25%; 75%) or as frequencies n (%). P values are calculated using the Chi Square test† or Mann-Whitney-U test\*, respectively.

ASA: American Society of Anesthesiologists; BMI: Body mass index, CRP: C-reactive protein; ICU: Intensive Care Unit; LOS: Length of Stay; MMSE: Mini-mental State Examination; NCD: Neurocognitive disorder; POD: Postoperative delirium. \*\*Postoperative CRP values in only 192 patients available.

**Table 2. Multivariable Regression Analysis for POD and postoperative NCD.**

Predictors	POD - Odds Ratio		Postoperative NCD - Odds Ratio	
	(95%CI)	P value	(95%CI)	P value
<b>Preoperative CRP (mg/L)</b>	<b>1.158 (1.040, 1.291)</b>	<b>0.008</b>	<b>0.552 (0.193, 1.581)</b>	<b>0.269</b>
Age in years	1.096 (1.046, 1.148)	<0.001	1.144 (1.011, 1.295)	0.033
Sex (Male <sup>#</sup> )	1.655 (0.357, 1.202)	0.172	2.809 (0.639, 12.352)	0.172
BMI (kg/m <sup>2</sup> )	0.948 (0.889, 1.012)	0.108	1.142 (0.980, 1.331)	0.089
ASA status ( $\leq 2^{\#}$ )	1.744 (0.943, 3.226)	0.076	2.034 (0.407, 10.171)	0.387
Baseline MMSE	0.842 (0.699, 1.015)	0.072	0.576 (0.355, 0.933)	0.025
Infection/autoimmune disease/malignoma (no <sup>#</sup> )	1.139 (0.568, 2.283)	0.714	2.667 (0.342, 20.826)	0.349
Randomization (BIS blinded <sup>#</sup> )	1.729 (0.950, 3.147)	0.073	0.898 (0.220, 3.654)	0.880
Intrathoraco-abdominal surgery	2.379 (1.122, 5.044)	0.024	3.318 (0.426, 25.842)	0.252

NCD: Neurocognitive disorder; POD: Postoperative delirium.

Multivariable logistic regression for the outcome POD and postoperative NCD, respectively, with adjustment for age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) status ( $\leq 2$  versus  $\geq 3$ ), Minimal State Examination (MMSE), infection or autoimmune disease or malignoma (yes versus no), randomization (BIS blinded versus open), body mass index (BMI), American Society of Anesthesiologists (ASA) status, type of surgery (intrathoraco-abdominal versus other procedures). . The final models included 312 patients for the POD model (two missing values in MMSE), and 152 patients (one missing value in MMSE) for the postoperative NCD model. <sup>#</sup>Reference value.

## Figure Legends

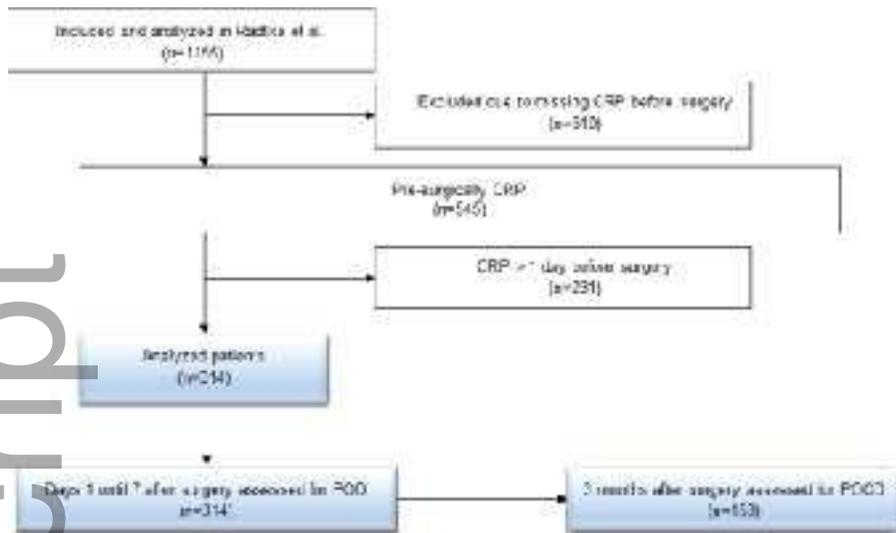
**Figure 1.** Consort diagram.

**Figure 2.** Histogram of all 314 preoperative CRP measurements on day before surgery.

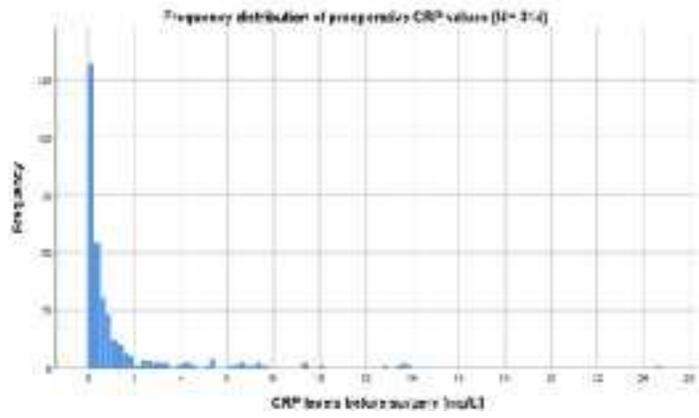
Laboratory reference value is  $<5$  mg/L. CRP median 0.32 mg/L, 25% percentile 0.14 mg/L and 75% percentile 0.95 mg/L.

**Supplement Figure 1.** ROC Curve for crude CRP values discriminating POD status.

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