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High C-reactive Protein Predicts Delirium Incidence, Duration, and Feature Severity after Major Non-cardiac Surgery

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Abstract

Objective—To examine associations between inflammatory marker C-reactive protein (CRP) measured preoperatively (PREOP) and on postoperative day 2 (POD2) with delirium incidence, duration, and feature severity.

Design—Prospective cohort study.

Setting—Two academic medical centers.

Participants—Adults aged ≥70 undergoing major non-cardiac surgery (N=560).

Measurements—Plasma CRP was measured using ELISA. Delirium was assessed from Confusion Assessment Method (CAM) interviews and chart review. Delirium duration was measured by number of hospital days with delirium. Delirium feature severity was defined as the sum of CAM-Severity (CAM-S) scores across all postoperative hospital days. We used generalized linear models to examine independent associations between CRP (PREOP and POD2, separately) and delirium incidence, duration, feature severity; prolonged hospital length of stay (LOS, >5 days); and discharge disposition.

Results—Postoperative delirium occurred in 24% of participants, 12% had ≥2 delirium days, and the mean(standard deviation) sum CAM-S was 9.3(11.4). After adjusting for age, sex, surgery type, anesthesia route, medical comorbidities, and postoperative infectious complications, participants with PREOP CRP ≥3mg/L had a 1.5 greater risk of delirium (95% confidence interval[CI] 1.1–2.1), 0.4 more delirium days (p<.001), more severe delirium (3.6 CAM-S points higher, p<.001), and a 1.4 greater risk of prolonged LOS (95 % CI 1.1–1.8) relative to patients with CRP <3mg/L. Using POD2 CRP, participants in the highest quartile (>235.73mg/L) were 1.5 times as likely to develop delirium (95% CI 1.0–2.4), had 0.2 more delirium days (p<.05), and had more severe delirium (4.5 CAM-S points higher, p<.001) than participants in the lowest quartile (<127.53mg/L).

Conclusions—High PREOP and POD2 CRP were independently associated with delirium incidence, duration, and feature severity. CRP may be useful to identify patients at-risk for delirium.

Keywords

Delirium; Postoperative; Delirium feature severity; C-reactive protein; Inflammation

INTRODUCTION

Delirium is characterized by acute change and fluctuations in attention, thinking, and consciousness. It occurs in 12–51% of surgical patients,¹ and delirium following major surgery has been associated with longer hospitalization,² higher rates of discharge to nursing homes,³ greater postoperative complications,⁴ and higher inhospital mortality.^{5,6} Despite our knowledge of its epidemiology, delirium remains a purely clinical diagnosis with no biomarkers to inform risk, diagnosis, or monitoring.

Delirium is frequently present in conditions where a systemic inflammatory response occurs, and there is growing evidence supporting a link between inflammation markers and delirium in varied settings. For instance, delirium has been associated with higher levels of pro-inflammatory cytokines in both surgical and medical patients.^{7,8} Additionally, delirium has been associated with proteins involved in the stress response, including one of the most commonly examined markers of systemic inflammation, the acute phase reactant C-reactive protein (CRP).^{9–16} However, these studies have been limited in that they used relatively small samples of patients who had either been admitted to medical wards, had experienced a cerebrovascular accident, or had undergone hip and vascular surgery. Furthermore, most studies examined CRP only at a single time point after patients became ill, and thus, lacked a true ‘pre-morbid’ baseline measure of CRP. In addition, most studies focused solely on the association of CRP with delirium incidence. No study has addressed whether additional delirium-related outcomes, such as delirium duration and feature severity, and important clinical outcomes previously associated with delirium (including hospital length of stay [LOS]) and post-acute facility discharge, are linked to CRP.

Our previous work demonstrated in a nested, matched case-control subset of the Successful Aging after Elective Surgery (SAGES) cohort that higher CRP preoperatively (PREOP) and on postoperative day 2 (POD2) levels could predict postoperative delirium in older patients.¹⁷ We now extend this research by examining the associations between CRP and postoperative delirium incidence, duration, feature severity; LOS; and discharge disposition across the entire SAGES study cohort.

METHODS

Study Sample

The SAGES Study is a prospective observational study focused on elucidating novel risk factors, including biomarkers, of delirium and its associated long-term cognitive and functional decline.^{18,19} Between 2010–2013, SAGES enrolled 560 dementia-free adults

aged 70 who were scheduled for elective major non-cardiac surgery. Major inclusion and exclusion criteria have been previously published.¹⁸ Patients with dementia were excluded from SAGES using a previously reported detailed, sequential screening process.¹⁸ Informed consent for study participation was obtained from all subjects according to procedures approved by the institutional review boards of Beth Israel Deaconess Medical Center and Brigham and Women's Hospital, the two surgical sites, and Hebrew SeniorLife, the study coordinating center, all located in Boston, MA.

Specimen Collection

All patients underwent serial blood collection, including PREOP and on POD2. When possible, the sampling was incorporated into clinical blood draws taken in the pre-admitting testing center prior to operation (PREOP) and on the surgical wards (POD2). During phlebotomy, mechanical disruption was minimized to prevent hemolysis or platelet activation. Blood was stored on ice in heparinized tubes until processing. During processing, low speed centrifugation was used to separate plasma from cellular material, and plasma was stored at -80°C until laboratory analysis. Nearly all samples satisfied rigorous quality control standards (99%), including 4 hours between blood draw and processing. Phlebotomy was performed on average 2 weeks prior to the index surgery (mean 13 ± 15 days).¹⁹

CRP Enzyme-Linked Immunosorbent Assay

CRP at PREOP and POD2 were measured in the entire SAGES sample using a high-sensitivity enzyme linked immunosorbent assay (ELISA) kit from R&D, with all standards and samples run in duplicate. Each 96-well plate contained the standard curve and cases and controls across both timepoints. Coefficient of variations (CVs) of duplicate measures were generally 5%. If any CV was $>10\%$, that plasma sample was repeated. An internal calibrator sample for both PREOP and POD2 time points was present on every 96-well ELISA plate. The cross plate variation was consistently below the range of 5–10% based on the internal calibrator value. ELISA plates were read using a BioTek MX plate reader at Optical Density (OD)=450. A 4-parameter logistic curve was used with final calculations determined in an Excel template containing built-in macros for optimizing the best-fit model (<http://www.rheumatologie-neuss.net/index-Dateien/RheumatologieNeuss13.htm>).

Delirium

Presence of postoperative delirium was determined from daily interviews from POD1 until hospital discharge, supplemented by a validated chart review method.²⁰ Trained study staff conducted structured cognitive assessments of attention, orientation, and memory. Delirium, assessed using the Confusion Assessment Method (CAM) diagnostic algorithm, was defined as having an acute onset of change or fluctuating mental status, inattention, and either disorganized thinking or altered level of consciousness.^{21,22} Presence of delirium by chart review was adjudicated by at least two delirium experts, and discordance was resolved by consensus.²³ Patients were considered delirious if delirium was present on either the CAM (score based on the daily interview) or the chart review method on any postoperative day; otherwise, patients were considered non-delirious.^{19,20}

Delirium Duration and Feature Severity

We also examined the association of CRP with delirium duration and feature severity. Delirium duration was determined by summing the total number of postoperative days the patient was considered delirious by either the CAM or chart review methods from the day after surgery until hospital discharge. Delirium feature severity was quantified using the CAM-Severity long form (CAM-S LF) score.²⁴ The CAM-S LF represents the sum of severity ratings of 10 CAM features (range 0–19, 19 most severe); each scored as 0 (absent), 1 (present, mild), and 2 (present, marked) – except for fluctuating course, which is scored 0 (absent) and 1 (present). Our primary outcome for delirium feature severity was defined as the sum of all CAM-S scores (sum CAM-S), which considers both intensity and duration and thus reflects the total ‘burden’ of delirium features across the entire hospitalization. We previously described sum CAM-S and found it to be the delirium feature severity measure most strongly associated with clinical outcomes²⁴. In supplementary analyses, we examined peak CAM-S score, defined as the highest CAM-S score on any postoperative day, an alternate delirium feature severity measure previously associated with clinical outcomes.²⁵

Length of Stay (LOS) and Discharge Disposition

To examine the predictive validity of CRP for clinical outcomes related to delirium, we examined its relationship with hospital LOS and post-acute facility discharge. Prolonged LOS (defined as >5 days; average LOS=5.2 days) and post-acute facility discharge (defined as discharge to a nursing home, rehabilitation or sub-acute facility) were determined from medical record review. No patients resided in a nursing home prior to surgery.

Baseline Sample Characteristics

Baseline information on education and cognitive performance was collected. Total years of education was measured by patient self-report. Preoperative cognitive functioning was measured using the General Cognitive Performance (GCP), a composite variable of commonly used neuropsychological measures.²⁶ Medical record review was used to gather information on the Charlson comorbidity index.²⁷

Potential Confounders

We adjusted for potential confounders including age, sex, surgical procedure, anesthesia route, Charlson index (which includes preoperative connective tissue disease), and postoperative infectious complications. Surgical procedures were categorized into three types: orthopedic, vascular, and colorectal.^{18, 19} We reviewed medical records to obtain information on preoperative comorbidities (e.g., connective tissue disease), anesthesia route (general or spinal), and postoperative complications. Postoperative infectious complications (urinary tract infection, pneumonia, wound infection) were further verified and adjudicated by three physicians. We did not control for postoperative medications because of the risk of over-controlling for variables potentially along the causal pathway to delirium.^{36,37}

Statistical Analysis

We used generalized linear models (GLM) with a log-link and normal error distribution to determine the association between CRP (PREOP and POD2) and delirium incidence,

prolonged LOS, and post-acute facility discharge. For delirium duration and feature severity, we used GLM with an identity-link and normal error distribution. For all outcomes, separate analytic models examined postoperative delirium risk, duration, feature severity; prolonged LOS; or post-acute facility discharge by considering CRP quartiles at PREOP and POD2 based on the SAGES sample distribution. For CRP at PREOP, we also examined a CRP cutpoint previously validated to indicate high-risk for cardiovascular disease (≥ 3 mg/L).²⁸ A high-risk cutpoint analysis could not be completed for CRP at POD2 because postoperative CRP levels were much higher than those in community based samples. All reported analytic models adjusted for age, sex, surgery type, anesthesia route, preoperative Charlson comorbidity index, and postoperative infectious complications.

Consideration of Subsyndromal Delirium (SSD)

We further considered the association between CRP (PREOP and POD2) and a three-level outcome: delirium, SSD, and no delirium (Supplementary Materials include detailed methods).

Added Value of CRP in Predicting Delirium Risk

We investigated the added value of CRP at PREOP and POD2 to an existing delirium risk prediction tool, the Inouye delirium risk score²⁹ (Supplementary Materials include detailed methods).

All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Table 1 reports the clinical characteristics of our study sample, which included no missing data. On average, our sample was 76.7 years old (standard deviation [SD] 5.2), highly educated (15.0[SD 2.9] years total), and had a higher than average US preoperative general cognitive performance (GCP) score (57.6[SD 7.3]). More than half of the study sample was female (58%). Most patients underwent orthopedic surgery (81%), 87% had general anesthesia, 12% had a Charlson comorbidity index of ≥ 3 , 8% had preoperative connective tissue disease, and 11% had a postoperative infectious complication. Twenty-four percent of the study sample developed postoperative delirium, 12% had ≥ 2 delirium days, and the average sum CAM-S was 9.3[SD 11.4].

Figure 1 plots the distribution of CRP at PREOP and POD2. There was a strong effect of surgery on CRP, with POD2 CRP levels nearly 100 times higher than PREOP levels. Figures 2a and 2b illustrate the median levels and inter-quartile range for PREOP and POD2 CRP levels (respectively) by postoperative delirium status (no delirium, SSD, delirium). Figure 2a suggests a threshold effect, with elevated PREOP CRP only in the delirium group. Figure 2b shows increasing POD2 CRP levels across the delirium categories, suggesting a dose-response relationship.

Table 2 shows the relative risk of postoperative delirium by CRP PREOP and POD2 quartiles examined in separate models. Unadjusted and adjusted models yielded similar results, indicating a significant association between CRP (for both PREOP and POD2) and

postoperative delirium (only results for adjusted models shown). After adjusting for age, sex, surgery type, anesthesia route, preoperative Charlson comorbidity index, and postoperative infectious complications, patients with PREOP CRP values in quartile (Q)4 had a significantly increased risk of developing postoperative delirium relative to patients in Q1, with a significant trend of increasing risk across the CRP quartiles. Finally, patients with PREOP ≥ 3 mg/L were 1.5 times as likely to develop delirium relative to patients with CRP levels <3 mg/L.

Considering POD2 CRP, patients with values in Q4 had an increased risk of postoperative delirium compared to patients in Q1, with a significant trend of increasing risk across CRP quartiles. Exclusion of 131 patients taking drugs that might influence CRP levels, including steroids, non-steroidal anti-inflammatory drugs, and immune modulators, did not change these findings.

Higher CRP quartile was generally associated with a greater risk of developing SSD, but this association did not achieve statistical significance (Supplementary Table S1).

Table 2 also reports the associations between CRP and delirium duration and feature severity. All models yielded consistently strong associations for patients with CRP values in the highest quartile (Q4) for PREOP and POD2 CRP having more delirium days and greater delirium feature severity relative to those in Q1. For instance, relative to patients in Q1 for PREOP CRP, on average patients in Q4 for PREOP CRP experienced almost one half more delirium days and had sum CAM-S scores 3.6 points higher. There was also a significant trend across the CRP quartiles for both delirium days and feature severity. There was also a significant trend across the CRP quartiles for both delirium days and feature severity. Similar to the findings for sum CAM-S, higher CRP at both time points was associated with higher peak CAM-S scores (Supplementary Table S2).

Table 3 shows the relative risk of LOS and post-acute facility discharge by CRP (PREOP and POD2). Patients with PREOP CRP in Q4 were 1.7 times as likely to have a prolonged LOS (>5 days) relative to patients in Q1. Moreover, this increased risk was observed for patients with high-risk PREOP CRP ≥ 3 mg/L, who were 1.4 times as likely to have a LOS >5 days relative to patients with CRP levels <3 mg/L. Higher CRP on POD2 was associated with an increased risk of having a prolonged LOS (p-trend=0.03) and an increased risk of post-acute facility discharge (p-trend=0.04).

Added Prediction Analyses

Supplementary Table S3 reports the prevalence of the Inouye delirium risk score factors by delirium status, and the Supplemental Text reports results for the prediction analyses.

DISCUSSION

In this study of older adults without dementia undergoing elective major noncardiac surgery, we observed significant associations of PREOP and POD2 CRP with delirium incidence, duration, and feature severity. Patients with high levels of PREOP (and POD2) CRP had greater delirium incidence, longer delirium duration, and more severe delirium relative to

patients with lower levels of PREOP (and POD2) CRP. Moreover, a significant dose-response relationship was observed for PREOP and POD2 CRP with all three delirium outcomes, such that higher CRP was associated with worse outcomes. Our results suggest that PREOP CRP may be an important risk marker for delirium incidence and that CRP measured PREOP and on POD2 may aid in predicting and monitoring the severity of postoperative delirium.

A current model of delirium pathophysiology proposes that individuals predisposed to a heightened inflammatory response when exposed to an acute stressor (e.g., surgery or infection) are at increased risk for delirium.³¹ It is postulated that under certain conditions, systemic inflammatory mediators cross the blood-brain barrier, activate brain microglia, and initiate neuroinflammation.²⁹ This model has gained substantial attention in recent years,³² and our findings linking CRP with delirium incidence and feature severity lend support for the role of systemic inflammation in delirium pathophysiology. Moreover, emerging evidence from animal models,³² and from human studies,³³ suggests that heightened systemic inflammation may indeed affect the brain. For instance, several studies have demonstrated that animals sacrificed after being exposed to systemic inflammatory insults, such as lipopolysaccharide and gram negative bacteria, showed evidence of neuroinflammation on brain autopsy. In humans, increasing evidence of an association between neuroinflammation and dementia has been reported.^{34,35}

Our previous work,¹⁷ a proteomics approach designed for discovery of proteins associated with delirium incidence, used a matched case-control study design of patients with and without delirium, which imposed significant constraints on the types of analyses we could perform. For instance, the case-control study did not consider patients with SSD and required delirium cases to have delirium on POD2 to correspond with the time of blood draw. While the inclusion of only carefully selected delirium cases and delirium-free controls allows for maximal contrast to discover biomarkers, it is not representative of the full clinical cohort. The current study substantially extends this previous work by: 1) examining the association between PREOP CRP and delirium incidence in a more clinically representative surgical sample, 2) including patients with SSD, and 3) examining four additional outcomes: delirium duration, delirium feature severity, LOS, and post-acute facility discharge. Additional strengths of our study include the consistent findings across all four outcomes and evidence of a dose-response effect, which underscores the robustness of our results and strengthens our conclusion of an association between CRP (PREOP and POD2) and delirium.

This study adds new, clinically relevant information to the literature on CRP and delirium. CRP might be a useful marker for risk stratification of patients before major surgery given its observed association with delirium incidence, duration, feature severity, and prolonged LOS. In particular, the addition of CRP at PREOP and POD2 to the Inouye delirium risk score²⁹ significantly improved the predictive model, lending further support for the use of CRP to identify patients who may benefit from proactive interventions. Of note, it was not our primary Aim to examine the association of CRP with LOS and discharge disposition; rather, these were added as secondary outcomes to support the association of CRP with

delirium. Nonetheless, our findings of the association of CRP with these outcomes are interesting, and warrant further exploration in future studies.

Some limitations about our study warrant mention. First, our analyses were limited to examination of a single marker of inflammation, CRP. Although CRP is the most clinically used summary marker of inflammation, it will be important to examine the associations of other more specific markers of inflammation (e.g., cytokines) on delirium incidence and feature severity, in addition to examining their joint effects. A priority area for future research will be to explore the synergistic effects of multiple inflammatory markers on delirium incidence and feature severity. Second, the availability of blood on POD2 may not align with delirium occurring several days following surgery. Third, a detailed examination of postoperative medication use and its influence on inflammation and delirium is beyond the scope of the current manuscript. In future work, we plan to conduct detailed pharmacoepidemiologic analyses to address this important question. Fourth, our findings may not be generalizable to the overall population of older adults undergoing major scheduled surgery since we enrolled adults without dementia from two academic medical centers in one geographic region and had a low minority representation. Future studies with more diverse samples are required. Contrary to expectations, we did not find an association between CRP and SSD, but our power was limited by the small size of this group within the sample.

In conclusion, we found that high PREOP and POD2 CRP was associated with delirium incidence, duration, and feature severity. If these findings are validated in future studies, CRP may be useful clinically to stratify patients at risk of delirium prior to surgery and to track its severity. Our findings also provide robust support for the role of inflammation in delirium pathophysiology, and may motivate development of new pathophysiologically-based intervention strategies to prevent and/or treat this common, morbid, and costly geriatric syndrome that threatens the independence of older patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Distributions of C-reactive protein at PREOP and POD2

Abbreviations: PREOP=preoperative, POD2=postoperative day 2

*Insert: Expanded plot of PREOP CRP with X-axis plotted for values up to 60 mg/L

Figure 2. Median levels of C-reactive protein by delirium status at (A) PREOP and (B) POD2
Abbreviations: CRP=C-reactive protein, PREOP=preoperative, POD2=postoperative day 2

*For graphical readability, PREOP CRP values >20 mg/L were not plotted.

Height of the box represents the interquartile range (the distance between the 25th and 75th percentiles).

The diamond symbol in the box interior represents the group mean.

The horizontal line in the box interior represents the group median.

The vertical lines (“whiskers”) extending from the box indicate the group minimum and maximum values.

Table 1

Sample characteristics (N=560)

Characteristic	Total Sample N=560	Delirium N=134	No Delirium N=426
<i>Baseline measures:</i>			
Age (M $\pm$ SD)	76.7 $\pm$ 5.2	77.5 $\pm$ 5.0	76.4 $\pm$ 5.2
Female, N (%)	326 (58)	81 (60)	245 (58)
Non-white or Hispanic, N (%)	42 (8)		
Educational attainment, years, (M $\pm$ SD)	15.0 $\pm$ 2.9	14.7 $\pm$ 3.0	15.1 $\pm$ 9.9
Surgery Type, N (%)			
Orthopedic	454 (81)	105 (79)	349 (82)
Vascular	35 (6)	11 (8)	24 (6)
Gastrointestinal	71 (13)	18 (13)	53 (12)
Preoperative GCP (externally scaled, M $\pm$ SD)	57.6 $\pm$ 7.3	54.7 $\pm$ 6.5	58.5 $\pm$ 7.3
Charlson Comorbidity Index, N (%)			
0	257 (46)	54 (40)	203 (48)
1	139 (25)	23 (17)	116 (27)
2	97 (17)	38 (29)	59 (14)
3+	67 (12)	19 (14)	48 (11)
Vascular comorbidity, N (%)	214 (38)	60 (45)	154 (36)
Preoperative connective tissue disease, N (%)	44 (8)	10 (7)	34 (8)
Anesthesia route, N (%)			
General	485 (87)	122 (91)	363 (85)
Spinal	75 (13)	12 (9)	63 (15)
Postoperative infectious complications, N (%)	62 (11)	20 (15)	42 (10)
<i>Outcome measures:</i>			
Postoperative delirium, N (%)			
No delirium	370 (66)	0 (0)	426 (100)
Delirium	134 (24)	134 (100)	0 (0)
Total days with delirium, N (%)			
0	426 (76)	19 (14)	426 (100)
1	68 (12)	64 (48)	0 (0)
2	38 (7)	29 (22)	0 (0)
3+	28 (5)	22 (16)	0 (0)
Delirium severity ^a			
Peak CAM-S score (long form, M $\pm$ SD)	3.9 $\pm$ 3.2	8.1 $\pm$ 3.6	2.7 $\pm$ 1.6
Sum of all CAM-S scores (long form, M $\pm$ SD)	9.3 $\pm$ 11.4	21.6 $\pm$ 17.0	5.4 $\pm$ 4.4

Abbreviations: M=mean, SD=standard deviation; CAM-S=Confusion Assessment Method-Severity (score range 0–19, 19 most severe);

GCP=general cognitive performance (a composite measure of neuropsychological measures reflecting cognitive domains vulnerable to delirium,²⁶ where population mean=50 and SD=10, externally scaled to the Health and Retirement Survey ADAMS

^aDelirium feature severity measured in all patients (including patients without delirium)

Table 2

Associations of C-reactive protein with postoperative delirium, delirium duration, and delirium feature severity (sum of all CAM-S scores)

CRP measure (mg/L)	<u>Delirium Incidence</u>	<u>Delirium Duration (per day)^a</u>	<u>Sum CAM-S (per point)^a</u>
	RR (95% CI)	Days (95% CI)	Score (95% CI)
<u>CRP PREOP</u>			
Quartiles			
Q1 (0.95)	Reference	Reference	Reference
Q2 (0.95–2.56)	1.4 (0.8–2.3)	0.3 (0.2–0.5) ^b	1.5 (0.9–2.1) ^c
Q3 (2.56–6.39)	1.7 (1.0b–2.7)	0.3 (0.2–0.5) ^b	2.5 (1.8–3.2) ^c
Q4 (6.39)	1.8 (1.2–2.9)	0.4 (0.2–0.5) ^b	3.6 (2.9–4.3) ^b
p-trend ^d	<.01	<.01	<.01
High-risk cutpoint ^e			
3 vs. <3	1.5 (1.1–2.1)	0.2 (0.1–0.4) ^b	2.6 (2.1–3.2) ^b
<u>CRP POD2^f</u>			
Quartiles			
Q1 (127.53)	Reference	Reference	Reference
Q2 (127.53–177.05)	1.1 (0.6–1.7)	0.1 (–0.1–0.2)	1.2 (0.6–1.8) ^c
Q3 (177.05–235.73)	1.5 (1.0 ^g –2.3)	0.2 (0.0 ^h –0.4) ^c	3.5 (2.9–4.2) ^b
Q4 (235.73)	1.5 (1.0 ⁱ –2.4)	0.2 (0.0 ^j –0.4) ^c	4.5 (3.8–5.2) ^b
p-trend ^d	0.02	0.02	<.01

All generalized linear log-link models adjusted for age, sex, type of surgery, anesthesia route, Charlson comorbidity index, and postoperative infectious complications (N=553 for CRP PREOP and N=556 for CRP POD2)

Delirium duration and sum of CAM-S was measured in all patients, including those without delirium. Therefore, values <1 are possible.

Abbreviations: CAM-S=Confusion Assessment Methods-Severity, CI=confidence interval, CRP=C-reactive protein, Q=quartile, PREOP=preoperative, POD2=postoperative day 2, RR=relative risk

^aFor the quartile CRP variable: The values represent the increase in delirium days (or CAM-S points) for patients in a given quartile relative to patients in quartile 1. For the high-risk cutpoint CRP variable: The values represent the increase in delirium days (or CAM-S points) for patients with CRP ≥ 3 mg/L relative to patients with CRP <3 mg/L.

^bp<.001

^cp<.001

^dp-trend determined from p-value from the association between the quartile-based CRP variable and delirium status

^eBased on a previously validated high-risk cutpoint for cardiovascular disease²⁸

^fNo high-risk cutpoint analysis was completed for CRP at POD2 because the scores are much higher than those in prior (community based) samples.

^gActual value 0.99 (not statistically significant)

^hActual value 0.03

ⁱActual value 1.01 (statistically significant)

j Actual value 0.004

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Table 3

Associations of C-reactive protein with length of stay and post-acute facility discharge

CRP measure	LOS > 5 days vs 5 days	Post-acute facility discharge
	RR (95% CI)	RR (95% CI)
<u>CRP PREOP</u>		
Quartiles		
Q1 (0.95)	Reference	Reference
Q2 (0.95–2.56)	1.5 (1.0 ^a –2.5)	1.0 (0.7–1.4)
Q3 (2.56–6.39)	1.8 (1.2–2.7)	0.9 (0.7–1.3)
Q4 (6.39)	1.7 (1.1–2.7)	0.9 (0.6–1.2)
p-trend ^c	0.02	0.30
High-risk cutpoint ^d		
3 vs. <3	1.4 (1.1–1.8)	1.1 (0.9–1.4)
<u>CRP POD2^e</u>		
Quartiles		
Q1 (127.53)	Reference	Reference
Q2 (127.53–177.05)	1.0 (0.7–1.6)	1.1 (0.8–1.5)
Q3 (177.05–235.73)	1.5 (1.0 ^a –2.2)	1.3 (0.9–1.7)
Q4 (235.73)	1.4 (0.9–2.1)	1.3 (1.0 ^b –1.8)
p-trend ^c	0.03	0.04

All generalized linear regression models adjusted for age, sex, type of surgery, anesthesia route, Charlson comorbidity index, and postoperative infectious complications (N=553 for CRP PREOP and N= 556 for CRP POD2). For the LOS outcome, postoperative infectious complications was not included in the model due to collinearity.

Abbreviations: CI=confidence interval, CRP=C-reactive protein, LOS=length of stay, Q=quartile, PREOP=preoperative, POD2=postoperative day 2, RR=relative risk

^aActual value 0.97 (not statistically significant)

^bActual value 0.99 (not statistically significant)

^cp-trend determined from p-value from the association between the quartile-based CRP variable and LOS or discharge disposition

^dBased on a previously validated high-risk cutpoint for cardiovascular disease²⁸

^eNo high-risk cutpoint analysis was completed for CRP at POD2 because the scores are much higher than those in prior (community based) samples