BJA Open

BJA Open, 2 (C): 100006 (2022)

doi: 10.1016/j.bjao.2022.100006
Advance Access Publication Date: 14 April 2022
Original Research Article

ORIGINAL RESEARCH ARTICLE

Impact of perioperative inflammation on days alive and at home after surgery

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Abstract

Background: Perioperative inflammation is associated with perioperative complications, including delirium, that are associated with a reduced number of postoperative days alive and at home at 90 days (DAH90). We tested whether inflammation was associated with DAH90 even when adjusting for perioperative factors, and whether inflammation independently was associated with DAH90 when adjusting for delirium.
Methods: We conducted a prospective cohort study of major, non-intracranial surgical patients who were older than 65 yr (n=134). We measured postoperative delirium incidence and severity, and changes in interleukin (IL)-8 and IL-10 in blood plasma. Our primary outcome, DAH90, was analysed using quantile regression.
Results: Before adjusting for delirium, a postoperative day 1 increased IL-8 was associated with fewer DAH90 at the 0.75 quantile (β=−0.082; 95% confidence interval [CI], −0.19 to −0.006) after adjusting for demographic (age and sex) and perioperative factors (cardiovascular surgery, National Surgical Quality Improvement Program risk of death, and operative time). IL-10 was similarly associated with DAH90 at the 0.5 (β=−0.026; 95% CI, −0.19 to −0.001) and 0.75 (β= −0.035; 95% CI, −0.07 to −0.006) quantiles. Neither cytokine was significantly associated with DAH90 once delirium and baseline Trail Making Test B were added to the models.
Conclusions: Perioperative inflammation predicts DAH90, but when delirium is added to the model inflammation loses significance as a predictor, whereas delirium is significant. Targeting perioperative inflammation may reduce delirium and moderate hospital readmission and mortality.
Clinical trial registration: NCT03124303.

Keywords: days alive and at home; delirium; hospital readmission; inflammation; mortality; surgery

Perioperative inflammation is associated with major surgical complications,[1–3] including delirium, and has been posited as a risk factor for impaired postoperative recovery. We recently showed that delirium is associated with a reduced number of days alive and at home 90 days after surgery (DAH90)[4] similar to other postoperative complications.[5–7] Days alive and at home (DAH) is a patient-centred outcome that has been proposed to capture the impact of both morbidity and mortality in the surgical setting.[5–7] It is easy to measure and reflects surgical severity and postoperative complications. DAH overcomes limitations that other endpoints may have; for example premature hospital discharge (reducing length of stay) may be associated with increased mortality; mortality alone does not capture the spectrum of postoperative complications; and some complications are not severe, whereas others may exert profound effects.[5,6]

Received: 20 December 2021; **Accepted:** 1 March 2022

Therefore, we propose DAH90 as a useful patient-centred outcome that – if altered – meaningfully impacts individuals.

Inflammation is a key precipitant for delirium; we recently have shown that perioperative increases in inflammatory markers, in particular cytokines interleukin (IL)-8 and 10, correlate with delirium severity[8–10] (and the associated EEG changes[9]) and perioperative neuronal[8,10] and cardiac injury.[11] Not all studies have found associations between cytokines and delirium,[12] but we have recently validated our finding with IL-8 in a second prospective cohort of data.[13] Prior associations between delirium and adverse long-term outcomes[14,15] have not excluded whether delirium is merely a marker of exaggerated perioperative inflammation, or itself is associated with poorer outcomes. Herein we sought to disambiguate the role of delirium from the associated perioperative inflammatory response in determining longer-term outcomes.

Methods

The data were collected between 31 August 2015 and 18 February 2020 from an ongoing perioperative cohort study, Interventions for Postoperative Delirium: Biomarker-3 (IPOD-B3),

Table 1 Baseline characteristics of study participants by DAH90 quantile. Percentages have been rounded and may not total 100. *n=152. One patient is missing because TMTB was not collected before surgery. †n=144. Nine patients are missing because the MoCA was not collected before surgery. ‡n=149. Four patients are missing because the survey set was not collected before surgery. ¶n=152. NSQIP was not calculated for one patient. §Diabetes treated with an oral antidiabetic drug or insulin before surgery. ‖Congestive heart failure in the 30 days before surgery. #Current smoker within 1 yr before surgery. **Preoperative systolic blood pressure collected at a clinic visit. ††Hypertension treated with medication. ‡‡Area under the curve for intraoperative blood pressure calculated as <10% of preoperative mean arterial pressure. n=152. One patient is missing because the AUC was calculated as 0. AUC, area under the curve; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DAH90, days alive and at home at 90 days; ENT, ear, nose, and throat; GDS, Geriatric Depression Scale; IADL, Index of Activities of Daily Living; MoCA, Montreal Cognitive Assessment; NSQIP, National Surgical Quality Improvement Program risk of serious complications (SC) or death (D) from surgery; OSA, obstructive sleep apnoea; SD, standard deviation; TIA, transient ischaemic attack; TMTB, Trail Making Test B.

	0–50% DAH90 (n=70)	50–75% DAH90 (n=43)	75–100% DAH90 (n=40)	All DAH90 (n=153)
Patient characteristics				
Age, mean (SD), yr	72.1 (4.6)	70.6 (4.1)	73.3 (5.2)	72.0 (4.7)
Sex, no. (%)				
Female	25 (36)	23 (53)	13 (32)	61 (39.9)
Male	45 (64)	20 (47)	27 (68)	92 (60.1)
Education, no. (%)				
<12 yr	2 (3)	0 (0)	1 (2)	3 (2.0)
12 yr	21 (30)	7 (16)	11 (28)	39 (25.5)
>12 yr	45 (64)	36 (84)	28 (70)	109 (71.2)
Unknown	2 (3)	0 (0)	0 (0)	2 (1.3)
TMTB, mean (SD), s*	98.6 (58.0)	80.4 (38.0)	82.0 (40.5)	89.1 (49.1)
MoCA, mean (SD)†	23.1 (2.9)	24.4 (2.3)	24.6 (2.6)	23.8 (2.8)
GDS-15, mean (SD)‡	2.5 (2.7)	2.5 (2.9)	2.5 (2.0)	2.5 (2.6)
ASA score, mean (SD)	2.8 (0.7)	2.9 (0.7)	2.6 (0.5)	2.8 (0.7)
NSQIP-SC, mean (SD)¶	23.16 (11.58)	14.44 (8.79)	9.42 (3.57)	17.13 (10.96)
NSQIP-D, mean (SD)¶	3.68 (4.25)	2.52 (3.15)	0.95 (1.19)	2.64 (3.55)
Diabetes, no. (%)§				
No	48 (69)	38 (88)	29 (72)	115 (75.2)
Oral	13 (19)	4 (9)	9 (22)	26 (17.0)
Insulin	9 (13)	1 (2)	2 (5)	12 (7.8)
CHF (30 days prior), no. (%)‖	1 (1)	1 (2)	0 (0)	2 (1.3)
Smoker status, no. (%)#	14 (20)	6 (14)	5 (12)	25 (16.3)
COPD history, no. (%)	23 (33)	8 (19)	6 (15)	37 (24.2)
OSA, no. (%)	23 (33)	15 (35)	16 (40)	54 (35.3)
BMI, mean (SD)	29.14 (5.99)	27.47 (5.67)	29.49 (5.47)	28.76 (5.79)
Blood Pressure, mean (SD)**	128.8 (16.8)	124.0 (16.3)	134.6 (15.0)	129.0 (16.6)
Hypertension, no. (%)††	55 (79)	26 (60)	32 (80)	113 (73.9)
Katz IADL, mean (SD)‡	5.9 (0.3)	6.0 (0.2)	5.8 (0.8)	5.9 (0.5)
Stroke/TIA, no. (%)	6 (9)	3 (7)	4 (10)	13 (8.5)
Procedure characteristics				
Surgery type, no. (%)				
Vascular	30 (43)	11 (26)	13 (32)	54 (35.3)
Cardiac	7 (10)	9 (21)	0 (0)	16 (10.5)
Thoracic	1 (1)	3 (7)	1 (2)	5 (3.3)
ENT	1 (1)	0 (0)	0 (0)	1 (0.7)
General	8 (11)	3 (7)	2 (5)	13 (8.5)
Spinal or orthopaedic	14 (20)	15 (35)	23 (58)	52 (34.0)
Urological or gynaecologic	9 (13)	2 (5)	1 (2)	12 (7.8)
Blood loss, mean (SD), ml	3630.6 (5980.5)	531.9 (717.1)	299.5 (273.0)	1888.9 (4356.6)
Operation time, mean (SD), min	462.2 (186.6)	265.9 (96.1)	194.5 (64.6)	337.0 (182.8)
AUC BP <10%, mean (SD)‡‡	226 353.6 (262 954.4)	97 260.8 (89 086.8)	82 971.8 (64 493.3)	152 101.9 (197 640.2)

which was approved by the University of Wisconsin–Madison Institutional Review Board (2015-0374) and registered with ClinicalTrials.gov (NCT03124303, NCT01980511). Adult patients aged 65 yr or older who were scheduled to undergo major elective non-intracranial surgery were recruited for the study. All patients were anticipated to stay in hospital for at least 2 days and to undergo general anaesthesia. The study excluded patients with a documented history of dementia and those residing in a nursing home.

For up to 4 days postoperatively in the hospital, patients were assessed for delirium twice daily using the Confusion Assessment Method (CAM)/3D-CAM, or the CAM-ICU if the patient's trachea was intubated. Participants also had blood drawn preoperatively and in the morning (06.00–10.00) of each postoperative hospital day for 4 days (if still admitted). Intraoperative data were also collected, including the American College of Surgeons' National Quality Improvement Program for surgical risk of death (NSQIP-D) score. Cognition was measured using Trail Making Test B (TMTB) preoperatively.

Plasma samples, collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes, were de-identified, processed, and stored at −80°C before being sent for biomarker analysis to Eve Technologies (Calgary, Canada). Cytokine multiplex enzyme-linked immunosorbent assay (ELISA) was completed for a battery of 10 cytokines. We focused on IL-8 and IL-10 as we have previously shown that these inflammatory biomarkers are strongly associated with delirium in our cohort.[8,10] Values measured as below the detectable range were entered as 0.001 pg ml^{-1}. Overall, 134 participants in our cohort had preoperative and postoperative day 1 (POD1) plasma samples analysed for IL-8 and IL-10 to determine the perioperative change in the inflammatory response. We concentrated on the POD1 inflammatory response to avoid any selection bias associated with earlier hospital discharge as per our prior methodology.[8,10]

Statistical analysis

Based on prior literature, and because of the highly skewed and bimodal distribution of the outcome (Supplementary Figure S1), we used quantile regression.[4,7] Power analysis was not conducted as this was an extended analysis of a prior investigation.[4] Outliers for IL-8 and IL-10 were rejected by a univariate approach that detected anomalous measurements from the assays. Histograms for preoperative and POD1 samples were constructed to qualitatively identify measurements that did not fit within the distribution of the rest of the data (Supplementary Figure S2). Sensitivity analyses based on using all available data (inclusion of outliers) were also conducted. Quantile regression results using the change in log10-transformed IL-8 or IL-10 concentrations are available in Supplementary Tables S5–S10.

Our primary outcome was a quantile regression model to identify possible predictors of DAH90 at the 50th and 75th percentiles. The model estimates the effects of independent variables on DAH90 when predicting the median DAH90 (0.5 quantile) or 75th percentile (greater DAH90). The 0.5 and 0.75 quantiles were selected based on the distribution of the data (Supplementary Figure S1). All quantile regression models were then bootstrapped with 10 000 iterations to provide a better estimate of the confidence intervals (CIs) for our findings.

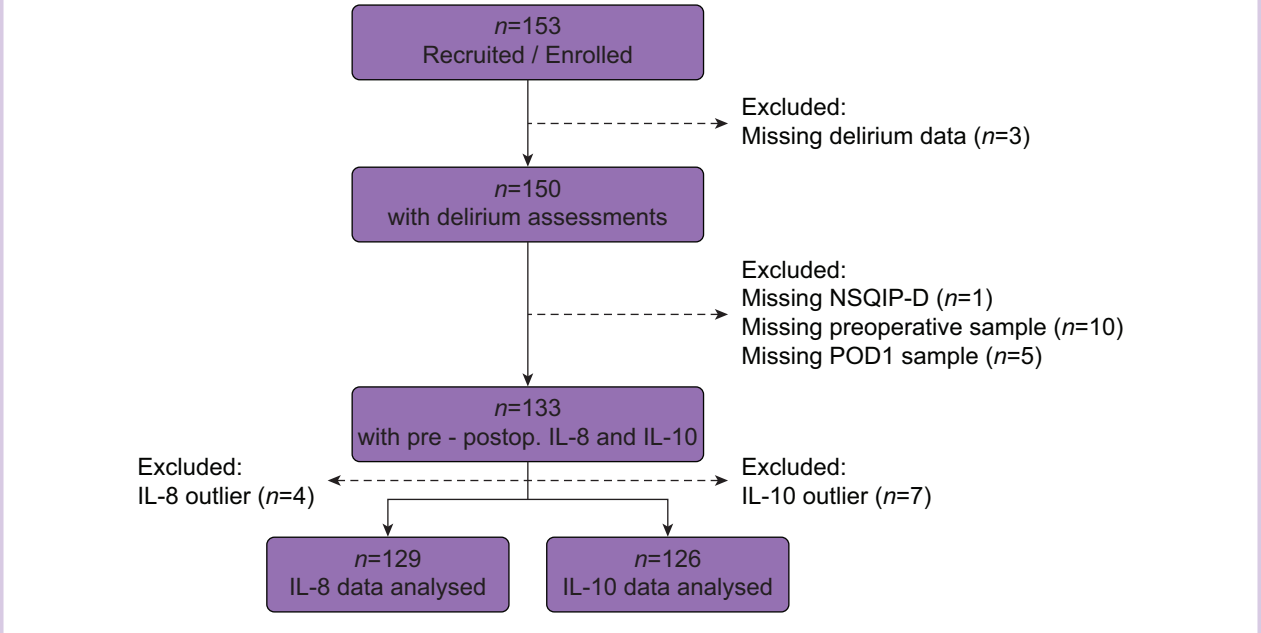

Fig 1. Strengthening the Reporting of Observational Studies in Epidemiology diagram for IPOD-B3. IL, interleukin; IPOD-B3, Interventions for Postoperative Delirium: Biomarker-3; NSQIP-D, National Quality Improvement Program for surgical risk of death; POD1, postoperative day 1.

In our primary outcome model, we ran quantile regression models to test whether IL-8 or IL-10 concentrations were associated with DAH90 based on their strong associations with delirium in our dataset.[8 10] These models included the preoperative to POD1 change in IL-8 or IL-10 concentration as a predictor of DAH90. Secondary models included delirium (and its cognitive predictor preoperative TMTB) to test whether inflammation was still associated with DAH90, if delirium was included. Significance was defined as $P \leq 0.05$ or a CI that does not include 0. All statistical analyses were conducted using RStudio version 3.4.1 (RStudio, Inc., Boston, MA, USA).

Results

The characteristics of the cohort (n=153) (Fig. 1) separated by quantile are reported in Table 1. Overall, participants were aged 72 yr (standard deviation [SD], 4.7) on average, and the majority underwent cardiovascular (70/153, 46%) or spinal/orthopaedic (52/153, 34%) surgery. Inflammation measured by POD1 change in IL-8 and IL-10 concentrations appeared to vary with quantiles of DAH90 (Fig 2). We then tested these cytokines in bootstrapped quantile regression models with covariates, age, sex, dichotomous cardiovascular surgery type,

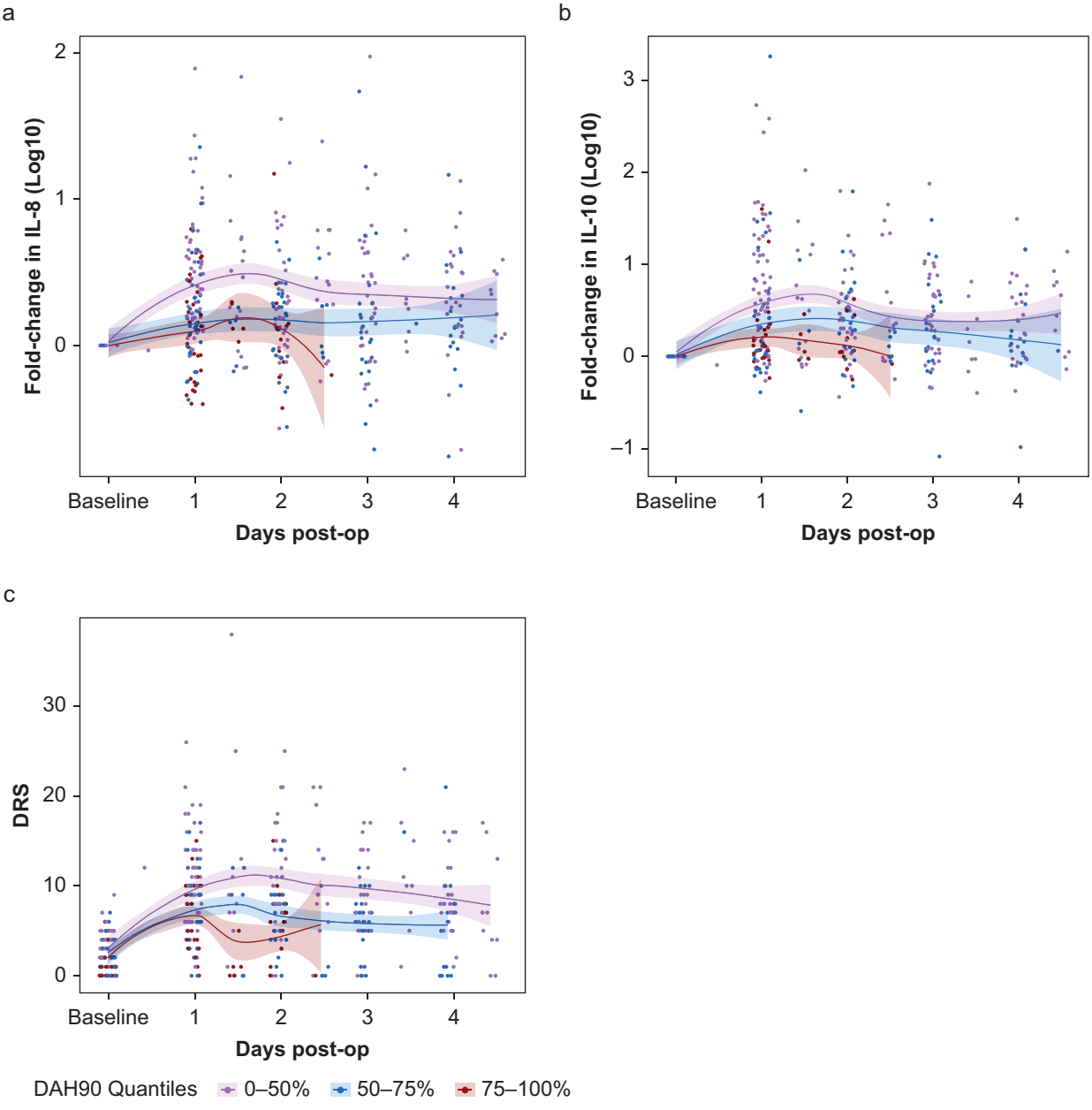

Fig 2. Postoperative time course of interleukin (IL)-8, IL-10, and delirium severity. (a) Fold-change in log10 IL-8 concentration, normalised to baseline, over postoperative days 1–4. (b) Fold-change in log10 IL-10 concentration, normalised to baseline, over postoperative days 1–4. (c) Fold-change in delirium severity from baseline to postoperative days 1–4. DAH90, days alive and at home at 90 days; DRS, Delirium Rating Scale-Revised-98.

Table 2 Bootstrap quantile regression model for perioperative factors, including interleukin (IL)-8 concentration, associated with DAH90. CI, confidence interval; DAH90, days alive and at home at 90 days; NSQIP-D, National Quality Improvement Program for surgical risk of death; POD1, postoperative day 1.

Outcome: days alive and at home at 90 days				
0.5 Quantile	**Beta coeff.**	**SE**	***t*-Value**	**CI (2.5%, 97.5%)**
Age	−0.017	0.082	−0.203	(−0.22, 0.10)
Sex	0.337	0.891	0.378	(−1.95, 1.76)
Cardiovascular surgery	0.246	1.341	0.183	(−2.15, 3.46)
NSQIP-D	−0.088	0.312	−0.283	(−0.87, 0.41)
Operative time	−0.017	0.009	−1.909	(−0.04, −0.009)[a]
POD1 change in IL-8	−0.137	0.088	−1.553	(−0.31, 0.02)
0.75 Quantile	**Beta coeff.**	**SE**	***t*-Value**	**CI (2.5%, 97.5%)**
Age	0.010	0.052	0.195	(−0.12, 0.09)
Sex	−0.119	0.541	−0.219	(−1.29, 1.07)
Cardiovascular surgery	0.447	0.787	0.568	(−1.22, 1.72)
NSQIP-D	−0.003	0.173	−0.016	(−0.37, 0.22)
Operative time	−0.012	0.003	−3.785	(−0.02, −0.007)[a]
POD1 change in IL-8	−0.082	0.055	−1.485	(−0.19, −0.006)[a]

[a] CI does not include 0.

NSQIP-D, and operative time. A POD1 increased IL-8 concentration was only associated with fewer DAH90 at the 0.75 quantile (β=−0.082; 95% CI, −0.19 to −0.006; Table 2). Sensitivity analysis including all available data suggested that IL-8 concentration predicted DAH90 at both the 0.5 and 0.75 quantiles (Supplementary Table S1). When preoperative cognition (TMTB) and postoperative delirium were added to the model, IL-8 concentration was no longer associated with DAH90 (Supplementary Table S2). Delirium remained a more significant predictor of fewer DAH90 at the 0.75 quantile (β=−2.345; 95% CI, −3.80 to −1.06) than the 0.5 quantile (β=−2.038; 95% CI, −7.72 to −0.23; Supplementary Table S2).

A POD1 increase in IL-10 concentration was a significant predictor of fewer DAH90 for a 95% CI for participants at the 0.5 (β=−0.026; 95% CI, −0.19 to −0.001) and 0.75 quantiles (β=−0.035; 95% CI, −0.07 to −0.006; Table 3 with similar results without outlier rejection, see Supplementary Table S3). This effect did not persist when postoperative delirium and preoperative cognition measured by TMTB were added to the models at either the 0.5 (β=−0.035; 95% CI, −0.17 to 0.008) or 0.75 quantiles (β=−0.020; 95% CI, −0.07 to 0.005; Supplementary Table S4). Longer operative time was a significant predictor of fewer DAH90 for all quantiles in our IL-8 and IL-10 models.

Discussion

We have shown that markers of perioperative inflammation are independent predictors of DAH90 when adjusting for perioperative factors but their impact is diminished when

Table 3 Bootstrap quantile regression model for perioperative factors, including interleukin (IL)-10 concentration, associated with DAH90. CI, confidence interval; DAH90, days alive and at home at 90 days; NSQIP-D, National Quality Improvement Program for surgical risk of death; POD1, postoperative day 1; SE, standard error.

Outcome: days alive and at home at 90 days				
0.5 Quantile	**Beta coef.**	**SE**	***t*-Value**	**CI (2.5%, 97.5%)**
Age	−0.039	0.084	−0.470	(−0.26, 0.08)
Sex	0.338	0.875	0.386	(−1.39, 1.92)
Cardiovascular surgery	1.662	1.226	1.356	(−1.03, 4.39)
NSQIP-D	−0.298	0.268	−1.114	(−0.75, 0.30)
Operative time	−0.026	0.008	−3.459	(−0.04, −0.01)[a]
POD1 change in IL-10	−0.026	0.049	−0.529	(−0.19, −0.001)[a]
0.75 Quantile	**Beta coef.**	**SE**	***t*-Value**	**CI (2.5%, 97.5%)**
Age	−0.018	0.035	−0.518	(−0.13, 0.05)
Sex	−0.094	0.491	−0.192	(−1.10, 0.98)
Cardiovascular surgery	1.245	0.620	2.008	(−0.05, 2.73)
NSQIP-D	0.051	0.159	0.321	(−0.45, 0.21)
Operative time	−0.016	0.004	−4.233	(−0.02, −0.009)[a]
POD1 change in IL-10	−0.035	0.022	−1.596	(−0.07, −0.006)[a]

[a] CI does not include 0.

delirium is added to the model. Our prior work has established that delirium is associated with a reduced number of DAH postoperatively at 90 days.[4] Overall, our data indicate that delirium is associated with adverse long-term outcomes, even when adjusting for its potential precipitating causes. Of course, we cannot fully disambiguate whether delirium is a summative and concrete manifestation of precipitating factors or is itself driving postoperative outcomes. However, these data suggest that reduction of delirium may offer one way to improve DAH90. Our work and that of other groups suggest that modulating the inflammatory response may be one way to reduce delirium, and these data suggest they may also improve DAH90. Trials of perioperative immune modulation may be indicated.

Our data have several notable limitations. As this is an observational study, we are unable to establish causality. We did adjust for several potential confounders, including perioperative factors, suggesting that relatively exaggerated immune responses may be associated with poor patient outcomes. We consider delirium one of these key outcomes and hence further explored relationships with delirium. However, we cannot exclude the influence of unmeasured confounding on our results. We specifically studied a heterogeneous surgical cohort to derive the necessary variance to identify the effect of interest, but future cohorts should investigate this relationship in specific types of surgery.

We also must note that the beta estimates for the effect of inflammation are small. Although these represent incremental effects with each pg ml^{-1} increase in the cytokine, and thus may be greater than 100-fold higher in an individual participant, they still represent a small influence. That said, they were often statistically significant even adjusting for metrics of operative severity (e.g. operative time) and are potentially modifiable. We regard perioperative inflammation as a potentially important pathway to improve perioperative outcomes.

Our data directly link delirium to reduced DAH90, independent of other factors that are putatively causal for delirium. Risk-stratified implementation of delirium reduction schemes, targeted to high-risk individuals, may offer the greatest benefit to increase DAH90 for our patients. Some of these approaches may target the immune response – for example dexmedetomidine reduces perioperative inflammation[16] – and may reduce delirium,[17,18] and consequently DAH90. Similarly, although NSAIDs may have significant side-effects limiting their use, animal data suggest that they may curtail the effect of inflammation on electrophysiology[19] and cognition,[20] suggesting they may reduce delirium (and possibly increase DAH90). Similarly, melatonin has been suggested to be anti-inflammatory and may reduce delirium.[21] Although these therapies suggest several possible ways in which immune modulation may be used to improve perioperative outcomes, RCTs to establish causality are required. Similarly, any putative benefit will need to be weighed against potential risks, mandating that these questions are thoroughly and cautiously studied.

Authors' contributions

Research design: RDS, BK, CC, RL, RAP.
Data collection: DK, MP, CC, RL, RDS.
Data analysis: DK, with input from CC, BK.
Writing of the manuscript: DK, JT, RDS, with input from all authors.
All authors contributed to manuscript editing or writing and data interpretation.

Declarations of interest

The authors declare that they have no conflicts of interest.

Funding

This work was supported by US National Institutes of Health (R01 AG063849-01).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2022.100006.

References

1. Owens CD, Ridker PM, Belkin M, et al. Elevated C-reactive protein levels are associated with postoperative events in patients undergoing lower extremity vein bypass surgery. *J Vasc Surg* 2007; **45**: 2–9
2. Dieleman JM, Nierich AP, Rosseel PM, et al. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA* 2012; **308**: 1761–7
3. Jacob KA, Leaf DE, Dieleman JM, et al. Intraoperative high-dose dexamethasone and severe AKI after cardiac surgery. *J Am Soc Nephrol* 2015; **26**: 2947–51
4. Kunkel D, Parker M, Casey C, et al. Impact of postoperative delirium on days alive and at home after surgery: a prospective cohort study. *Br J Anaesth* 2021; **127**: e205–7
5. Bell M, Eriksson LI, Svensson T, et al. Days at home after surgery: an integrated and efficient outcome measure for clinical trials and quality assurance. *EClinicalMedicine* 2019; **11**: 18–26
6. Myles PS. More than just morbidity and mortality — quality of recovery and long-term functional recovery after surgery. *Anaesthesia* 2020; **75**(Suppl 1): e143–50
7. Jerath A, Austin PC, Wijeysundera DN. Days alive and out of hospital: validation of a patient-centered outcome for perioperative medicine. *Anesthesiology* 2019; **131**: 84–93
8. Casey CP, Lindroth H, Mohanty R, et al. Postoperative delirium is associated with increased plasma neurofilament light. *Brain* 2019; **143**: 47–54
9. Tanabe S, Mohanty R, Lindroth H, et al. Cohort study into the neural correlates of postoperative delirium: the role of connectivity and slow-wave activity. *Br J Anaesth* 2020; **125**: 55–66
10. Ballweg T, White M, Parker M, et al. Association between plasma tau and postoperative delirium incidence and severity: a prospective observational study. *Br J Anaesth* 2021; **126**: 458–66
11. Sanders RD, Craigova L, Schessler B, et al. Postoperative troponin increases after noncardiac surgery are associated with raised neurofilament light: a prospective observational cohort study. *Br J Anaesth* 2021; **126**: 791–8
12. Khan SH, Lindroth H, Jawed Y, et al. Serum biomarkers in postoperative delirium after esophagectomy. *Ann Thorac Surg* 2022; **113**: 1000–7
13. Wu JG, Taylor J, Parker M, et al. Role of interleukin-18 in postoperative delirium: an exploratory analysis. *Br J Anaesth* 2022; **128**: e229–31

14. Sanders RD, Pandharipande PP, Davidson AJ, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. *BMJ* 2011; **343**: d4331
15. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA* 2017; **318**: 1161–74
16. Wang K, Wu M, Xu J, et al. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. *Br J Anaesth* 2019; **123**: 777–94
17. Sanders RD, Wehrman J, Irons J, Dieleman J, Scott D, Shehabi Y. Meta-analysis of randomised controlled trials of perioperative dexmedetomidine to reduce delirium and mortality after cardiac surgery. *Br J Anaesth* 2021; **127**: e168–70
18. Duan X, Coburn M, Rossaint R, Sanders RD, Waesberghe JV, Kowark A. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. *Br J Anaesth* 2018; **121**: 384–97
19. Sultan ZW, Jaeckel ER, Krause BM, et al. Electrophysiological signatures of acute systemic lipopolysaccharide-induced inflammation: potential implications for delirium science. *Br J Anaesth* 2021; **126**: 996–1008
20. Griffin EW, Skelly DT, Murray CL, Cunningham C. Cyclooxygenase-1-dependent prostaglandins mediate susceptibility to systemic inflammation-induced acute cognitive dysfunction. *J Neurosci* 2013; **33**: 15248–58
21. Campbell AM, Axon DR, Martin JR, Slack MK, Mollon L, Lee JK. Melatonin for the prevention of postoperative delirium in older adults: a systematic review and meta-analysis. *BMC Geriatr* 2019; **19**: 272

Handling editor: Phil Hopkins