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Authors

Zhang, Yu
Hu, Jun
Zuo, Weiguang
et al.

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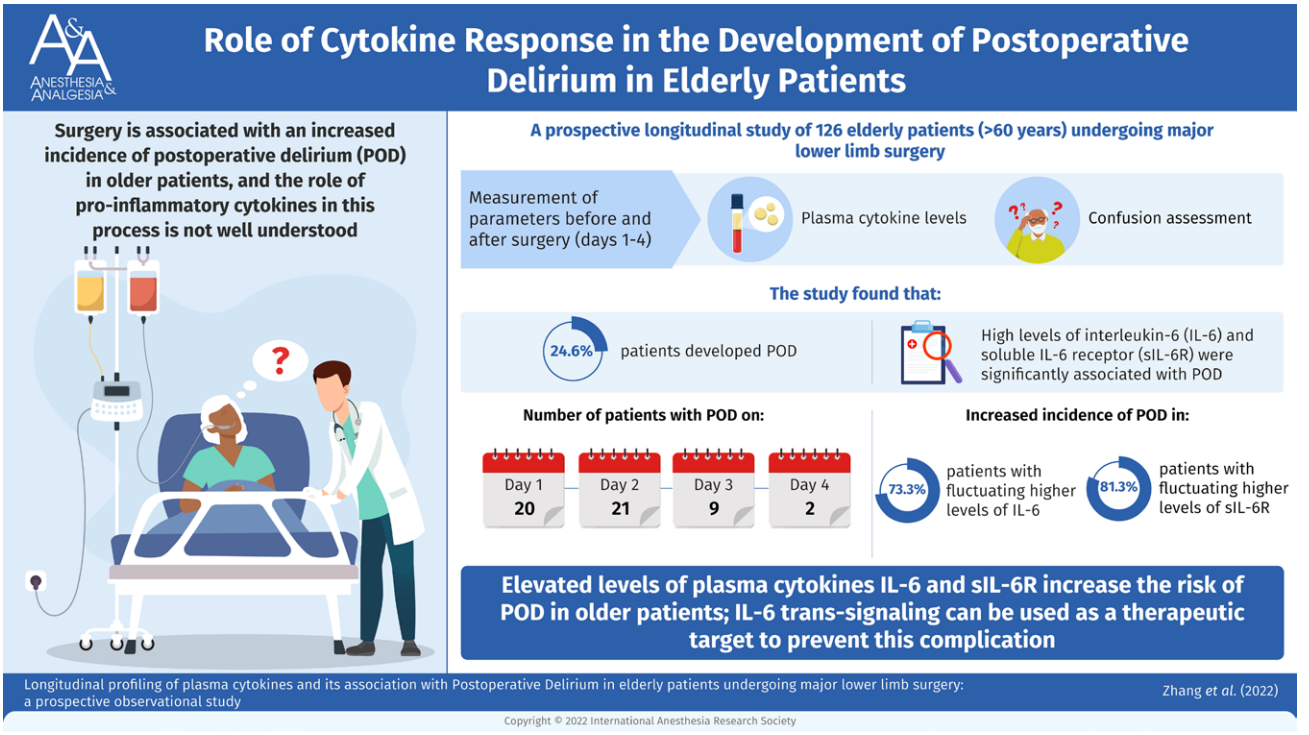
ORIGINAL CLINICAL RESEARCH REPORT

Longitudinal Profiling of Plasma Cytokines and Its Association With Postoperative Delirium in Elderly Patients Undergoing Major Lower Limb Surgery: A Prospective Observational Study

Yu Zhang, MD,*† Jun Hu, MD,*† Weiguang Zuo, MD,‡ Pei He, MD†, Qi Xue, PhD,*† Xiaomei Feng, MD, PhD,§ Ye Zhang, MD, PhD,*† and Mervyn Maze, MB, ChB‖



BACKGROUND: Surgery is accompanied by a systemic inflammatory response that may presage delirium in susceptible individuals. Little is known about the trajectory of plasma proinflammatory cytokines and their potential associations with postoperative delirium (POD). The current study longitudinally assessed both pro and anti-inflammatory plasma cytokine response and development of POD in older surgical patients to investigate associations with individual and/or clusters of cytokines that may indicate pathogenic mechanisms.

From the *Department of Anesthesiology, The Second Hospital of Anhui Medical University, Hefei, China; †Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, Anhui Medical University, Hefei, China; ‡Department of Clinical Laboratory, The Second Hospital of Anhui Medical University, Hefei, China; §Department of Anesthesiology, University of Utah, Salt Lake City, Utah; and ‖Department of Anesthesia and Perioperative Care and Centre for Cerebrovascular Research, University of California, San Francisco, San Francisco, California.

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Y. Zhang and J. Hu contributed equally to this work.

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Address correspondence to Ye Zhang, MD, PhD, Department of Anesthesiology, The Second Hospital of Anhui Medical University, and Key Laboratory of Anesthesiology and Perioperative Medicine of Anhui Higher Education Institutes, Anhui Medical University, 678 Furong Road, Hefei 230601, Anhui, China. Address e-mail: zhangye_hassan@sina.com.

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METHODS: A prospective longitudinal study sought to enroll patients >60 years old who were scheduled for major lower limb surgery under general anesthesia. Blood was obtained preoperatively and postoperatively from day 1 through postoperative day 4 for measurement of plasma interleukin-1β (IL-1β), IL-2, IL-4, IL-6, soluble IL-6 receptor (sIL-6R), IL-10, and tumor necrosis factor-α (TNF-α). Participants were assessed for POD twice daily for 4 days using the confusion assessment method. Trajectory of postoperative changes in plasma cytokines was determined by a group-based trajectory modeling analysis that was informed by distinct cytokines identified by time-dependent Cox regression model.

RESULTS: One hundred eighty-eight patients were assessed for eligibility of whom 129 underwent major surgery and 126 had complete datasets for final analysis. POD was diagnosed in 31 of 126 patients (24.6%). Time-dependent Cox regression model identified that higher IL-6 and sIL-6R levels were associated with higher risk of developing POD. A two-cluster model (stable lower and fluctuating higher levels) was considered to be the most statistically appropriate model for IL-6 and sIL-6R trajectory. More participants with fluctuating higher IL-6 were delirious (73.3% vs 18.0%, $P = .001$) as were those with fluctuating higher sIL-6R (81.3% vs 16.4%, $P = .001$).

CONCLUSIONS: As higher IL-6 and sIL-6R levels were significantly associated with higher risk of POD and the combination is required for IL-6 trans-signaling, it is possible that activation of this pathway may be associated with POD. Furthermore, it will be important to determine whether high levels of the combination of IL-6 and sIL-6R can be an early biomarker for the subsequent development of POD. (Anesth Analg 2023;136:34–42)

KEY POINTS

- **Question:** Does the trajectory of the cytokine response to surgery in elderly patients informs the likelihood of developing postoperative delirium (POD)?
- **Findings:** Longitudinal analysis of the trajectories of plasma cytokines after surgery showed that patients with fluctuating higher levels trajectories of IL-6 and sIL-6R are more prone to POD.
- **Meaning:** This finding will promote further investigation to understand the role of IL-6 transsignaling in the development of POD and whether this pathway represents a druggable target to prevent and/or ameliorate this common postoperative complication in elderly patients.

GLOSSARY

3MS = modified minimental state examination; **aHR** = adjusted hazard ratio; **ASA** = American Society of Anesthesiologists; **BIC** = Bayesian information criteria; **BMI** = body mass index; **CAM** = confusion assessment method; **CI** = confidence interval; **CSF** = cerebrospinal fluid; **DOS** = duration of surgery; **GBTM** = group-based trajectory modeling; **IL-10** = interleukin 10; **IL-1β** = interleukin 1β; **IL-2** = interleukin 2; **IL-4** = interleukin 4; **IL-6** = interleukin 6; **IL-6R** = IL-6 receptor; **IQR** = interquartile range; **LOS** = length of stay; **mIL-6R** = membrane-bound interleukin 6 receptor; **PD** = postoperative day 1; **PET** = positron emission tomography; **POD** = postoperative delirium; **PRE** = preoperative; **SAGES** = Successful Aging After Elective Surgery; **sIL-6R** = soluble interleukin 6 receptor; **STAT3** = signal transducer and activator of transcription 3; **STROBE** = Strengthening the Reporting of Observational Studies in Epidemiology; **TNF-α** = tumor necrosis factor-α

An extensive body of evidence suggests that inflammation and immune dysregulation play important roles in the pathogenesis of neuropsychiatric disorders, including cognitive decline.[1] A link between inflammation and postoperative delirium (POD) has also been reported,[2] and patients undergoing therapy with immune modulators can develop delirium.[3] Cytokines contribute to a cascade of events in the initiation and resolution of inflammation. Hospital-acquired delirium has been associated with higher serum levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)-α, as well as, proresolving cytokines such as IL-10 and IL-4 in some[4,5] but not all studies.[6,7] A possible explanation for this inconsistency may relate to variation in the timing and the specific cytokine that is measured over the perioperative period. Monitoring a single cytokine at a single time point is unlikely to reflect the dynamic pattern of inflammation that is associated with POD; yet, most of the studies exploring the relationship have measured a restricted number of cytokines at limited time points.

The initiation and resolution of the postoperative inflammatory response are affected by the degree of tissue damage,[8] perioperative pharmacological interventions,[9,10] and patient-based characteristics.[11] The dynamic inflammatory process can be described when using several different subclass patterns (clusters).[12] Recently, group-based trajectory modeling (GBTM) has been established as a statistical method that can be used to determine the number and characteristics of the trajectory clusters for individuals who will have a similar outcome progression.[13]

To overcome the limitations of previous investigations that sought to explore the relationship between inflammatory markers and POD, we measured 7 cytokines (IL-1β, IL-2, IL-4, IL-6, soluble IL-6 receptor [sIL-6R], IL-10, and TNF-α) at 5 timepoints (preoperative [PRE], postoperative day 1 [PD1] when inflammatory levels are likely to peak, postoperative day 2 [PD2], postoperative day 3 [PD3], and postoperative day 4 [PD4]) and assessed the occurrence of POD among older adults undergoing major lower limb surgery. We used GBTM analysis to establish clusters of trajectories, representing the progression of the postoperative inflammatory response. We hypothesized that these measurements and analyses would reveal clusters of plasma cytokines trajectories associated with development of POD after major lower limb surgery in susceptible adults.

METHODS

Study Design and Participants

A prospective, observational, longitudinal study was conducted at a university-affiliated, tertiary hospital (The second Hospital of Anhui Medical University, Hefei, China) following approval by the institutional review board (YX2020-056), and written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at chictr.org.cn (ChiCTR2000034209, principal investigator: Jun Hu, date of registration: June 28, 2020, https://www.chictr.org.cn/hvshowproject.aspx?id=153414). After obtaining written informed consent, patients aged ≥60 years, with an American Society of Anesthesiologists (ASA) physical status of I–III, who were scheduled for major lower limb surgery (including total hip replacement, knee replacement and femoral fracture surgery) requiring at least 4 days of postoperative inpatient care (see Figure 1 for STROBE diagram) were recruited from June 2020 to December 2021. Exclusion criteria included patients who were unable to give their own consent and those

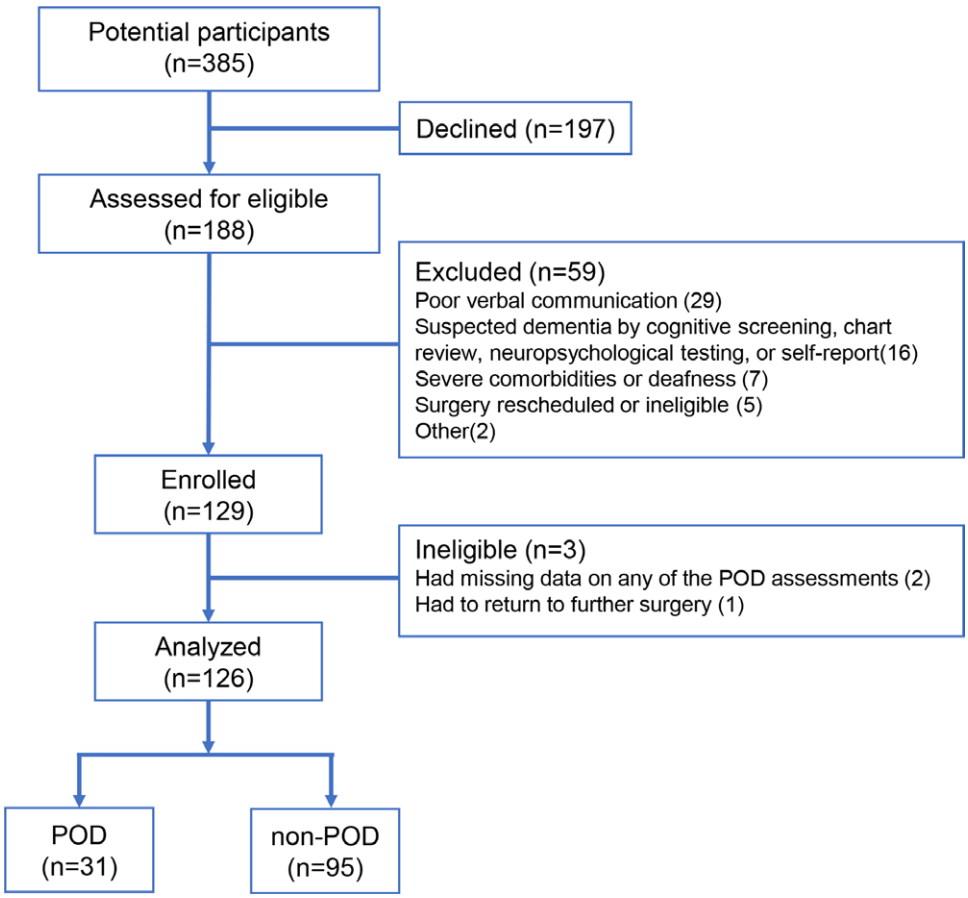

Figure 1. STROBE diagram of the study. POD indicates postoperative delirium; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

with severe pulmonary, cardiac, renal, hepatic, cerebrovascular comorbidities, chronic pain, and substance abuse disorders. Further exclusions were for patients with dementia or who were being treated with antipsychotic agents and in those in whom a screening test with modified minimental state examination revealed diminished cognitive capacity (using score cutoff of <75 for individuals with low education and a cutoff <80 for individuals with a high school education).[14]

Delirium Assessment

Assessment of delirium was performed twice daily (morning between 9:00 and 11:00 AM, and afternoon between 3:00 and 5:00 PM) for 4 postoperative days by trained POD assessors using the confusion assessment method (CAM),[15] which assesses four features of delirium, namely (1) acute onset of mental status changes or a fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Diagnosis of POD was established if a patient displayed both features 1 and 2, with either 3 or 4. In addition to the scheduled times, additional CAM assessment was undertaken when warranted by reports of confusion, agitation, hallucinations, delusions, and change in level of consciousness. Furthermore, chart review delirium diagnoses were accepted if adjudicated by at least two experts. Delirium assessors were blinded to the plasma cytokine results.

Cytokine Assays

Concentrations of interleukin-1β (IL-1β), IL-2, IL-4, IL-6, sIL-6R, IL-10, and TNF-α were determined with commercially available R&D Biosystems Human Magnetic Luminex Performance Assay, high sensitivity cytokine kit (LHSCM0000-6-Plex and LBAM000-1-plex). The details of collection, processing, storage, and analysis of blood samples, and limits of detection for each cytokine are given in Supplementary Digital Content 1, Appendix S1, http://links.lww.com/AA/E75. The number of individuals assayed for each cytokine at each time point is given in Supplementary Digital Content 1, Table S1, http://links.lww.com/AA/E75. All assays were completed in duplicate. We examined the quality parameters, including fit probability of the standard curve, and coefficient of variations. All fit probabilities and coefficient of variations met predefined quality criteria.

Anesthesia and Surgical Events

Anesthesiologists received minimal direction regarding the choice of anesthetic as previous literature has not found a difference between different anesthetic techniques and delirium.[16] The protocol requested that the clinical anesthesia team avoid the use of anticholinergic agents and dexmedetomidine, which have been reported to impact development of POD.[17,18] We recorded major intraoperative variables, such as type of anesthesia, location of surgery, anesthetics and analgesics administered, and surgical duration. The majority of patients were extubated at the end of surgery and transferred to the postanesthesia care unit.

Sample Size Justification

The sample size calculations were based on the relationship between POD and plasma inflammatory markers that are involved in IL-6 trans-signaling. Because the cutoff range for plasma IL-6 levels and POD varied by two orders of magnitude (9 to 900 pg/mL), we focused on a study that reported on higher levels of sIL-6R in those with delirium (median 43.7 ng/mL) than in those without delirium (median 36.3 ng/mL).[19] We conservatively estimated that the incidence of delirium would be 20% in present study, and 20% dropout rate was anticipated. Power analysis using a 2-sample *t*-test with an effect size of 17% change in plasma sIL-6R (assuming a pooled standard deviation = 10) indicated that 120 patients were required for a two-sided alpha of 5% with 80% power.

Statistical Analysis

Patients were divided into POD and non-POD groups according to the results of the delirium assessment. Statistical calculations were performed using SPSS for Windows, version 20 (SPSS Inc). Categorical variables were analyzed using χ^2 or Fisher exact tests. Continuous variables were analyzed with Mann-Whitney U test or *t* test depending on the sample size and distribution and skewness of the data. The assumption of a normal distribution of data was tested with the Kolmogrov-Smirnov test. We used the Cox regression model with time-dependent variables to evaluate time-to-POD given the time-varying nature of plasma cytokines. Univariable analysis was conducted for each of the 7 cytokines to estimate unadjusted associations. Multivariable analysis was then conducted by including IL-2, IL-6, and sIL-6R and controlling for 5 well-established POD risk factors (ie, age, sex, body mass index [BMI], anesthesia, and surgical location). We then used a latent growth-curve approach to identify subgroups in which IL-6 and sIL-6R levels followed similar patterns over time using GBTM-based clusters of trajectory method in SAS. Model selection involved the iterative estimation of the number of trajectory groups and the shape of each trajectory group. Statistical criteria for determining the number of trajectory groups and polynomial degrees for each group included the Bayesian information criterion (BIC) in which smaller values of BIC indicate better model fit. Other criteria included nonoverlapping confidence intervals (CIs) and reasonable size (≥10% of the sample) in each identified trajectory group. After identifying the optimal trajectory group solution, we compared

the incidence of POD between the different trajectories using χ^2 square or Fisher exact tests.

RESULTS

Characteristics of Individuals With and Without POD

Out of 188 patients assessed for eligibility, 129 patients entered the study of which 3 patients were excluded for reasons described in the STROBE diagram (Figure 1) leaving 126 patients for analysis. Demographic and clinical characteristics of the individuals are shown in Table 1. The median age was 71 years (interquartile range [IQR], 67–79 years), and 56 of 126 (44.4%) were men. The most common ASA status was an ASA of 2 (93/126, 73.8%). The majority of patients were living independently (116/126, 92.1%). Thirty-one (24.6%) of the patients developed POD. Twenty-six patients were diagnosed POD according to the interview-based method, 12 patients according to the chart-based method, and 5 through a combined approach. The number of patients with POD on PDs 1–4 was 20, 21, 9, and 2, respectively. The delirium duration was 1 or 2 days in 27 patients and 3 days or more in 4 patients. Patients with POD were more likely to be older and had longer postoperative hospital stay. In addition, patients with fixation of subtrochanteric/femoral shaft fractures and knee arthroplasty were more likely to develop delirium than patients with hip arthroplasty.

Longitudinal Profiling of Plasma Cytokines Profiles and POD

Concentrations of 7 plasma cytokines sampled over multiple days (PRE, PD1, PD2, PD3, and PD4) were quantified in groups that did/did not develop POD. The longitudinal data on 7 cytokines, based on 614 observations (Supplementary Digital Content 1, Table S1, http://links.lww.com/AA/E75), are presented in Figure 2. By univariate analysis, patients who developed delirium had a greater exposure to IL-2, IL-6, and sIL-6R. The adjusted models revealed that higher IL-6 (adjusted hazard ratio [aHR], 1.013; 95% CI, 1.008–1.017; Table 2) and sIL-6R (aHR, 1.095; 95% CI, 1.062–1.130; Table 2) were significantly associated with higher risk of POD. The association between IL-2 and delirium occurrence was not statistically significant (aHR, 1.028; 95% CI, 0.959–1.102; Table 2).

GBTM Analysis of IL-6 and sIL-6R Trajectories

To assess how cytokine trajectory varied over time in relation to POD, IL-6 and sIL-6R concentrations were analyzed by GBTM. The optimal solution identified 2 trajectories of IL-6 throughout the study period (Supplementary Digital Content 1, Table S2, http://links.lww.com/AA/E75); adding quadratic polynomials did not result in a better model fit. The 2 trajectories of IL-6 were: (1) stable lower IL-6 levels (88% or n = 111; median [IQR] = 16.7 [8.3–29.0] pg/mL) and (2) fluctuating higher levels of IL-6 (12% or n = 15; median [IQR] = 78.0 [31.4–131.6] pg/mL) (Figure 3A). Participants with fluctuating higher IL-6 were more likely to be delirious (73.3% vs 18.0%; Fisher exact tests; P = .001). Also, there were 2 best-fit trajectories for sIL-6R, namely (1) stable lower sIL-6R levels (87.0% or n = 110; mean [IQR] = 15.2 [9.8–43.4] ng/mL); and (2) fluctuating higher levels of sIL-6R (13.0% or n = 16; mean [IQR] = 34.0 [25.5–45.0] ng/mL) (Figure 3B). Participants with fluctuating higher sIL-6R were more likely to be delirious (81.3% vs 16.4%; Fisher exact tests; P = .001).

Table 1. Characteristics of Individuals With and Without POD

	All (N = 126)	POD (n = 31)	Non-POD (n = 95)	*P*
Age, y	71 (67–79)	81 (68–85)	69 (67–75)	.0004
Male	56 (44.4)	18 (58.1)	38 (40.0)	.0971
Weight, kg	64 (54–69)	63 (54–68)	65 (55–69)	.6465
Height, cm	161 (156–168)	162 (155–168)	161 (156–168)	.9180
BMI	23.8 (22.2–25.5)	23.7 (22.1–24.8)	24.0 (22.2–25.9)	.3734
ASA physical status (I/II/III)	5/93/28 (4.0%/73.8%/22.2%)	1/19/11 (3.2%/61.3%/35.5%)	4/74/17 (4.2%/77.9%/17.9%)	.1234
Living independently	116 (92.1)	27 (87.1)	89 (93.7)	.2597
Low educational level	60 (47.6)	16 (51.6)	44 (46.3)	.6808
3MS score	81(88–92)	81 (88–91)	81(87–93)	.4173
Smoking	31 (24.6)	10 (32.3)	21 (22.1)	.3364
Hypertension	43 (34.1)	13 (41.9)	30 (31.6)	.3830
Diabetes mellitus	22 (17.5)	7 (22.6)	15 (15.8)	.4184
Surgical location				
Femur/patella	51 (40.5)	20 (64.5)	31 (32.6)	.0069
Hip/acetabulum	58 (46.0)	9 (29.0)	49 (51.6)	
Tibia/fibula/foot	17 (13.5)	2 (6.5)	15 (15.8)	
DOS, min	118 (93–141)	106 (78–136)	119 (96–142)	.1864
LOS, d	6 (5–7)	7 (5–9)	6 (5–7)	.0162

Values are expressed as median (interquartile range) or n (% of respective group).

Abbreviations: 3MS, Modified Mini-Mental State Examination; ASA, American Society of Anesthesiologists; BMI, body mass index; DOS, duration of surgery; LOS, length of stay after surgery; POD, postoperative delirium.

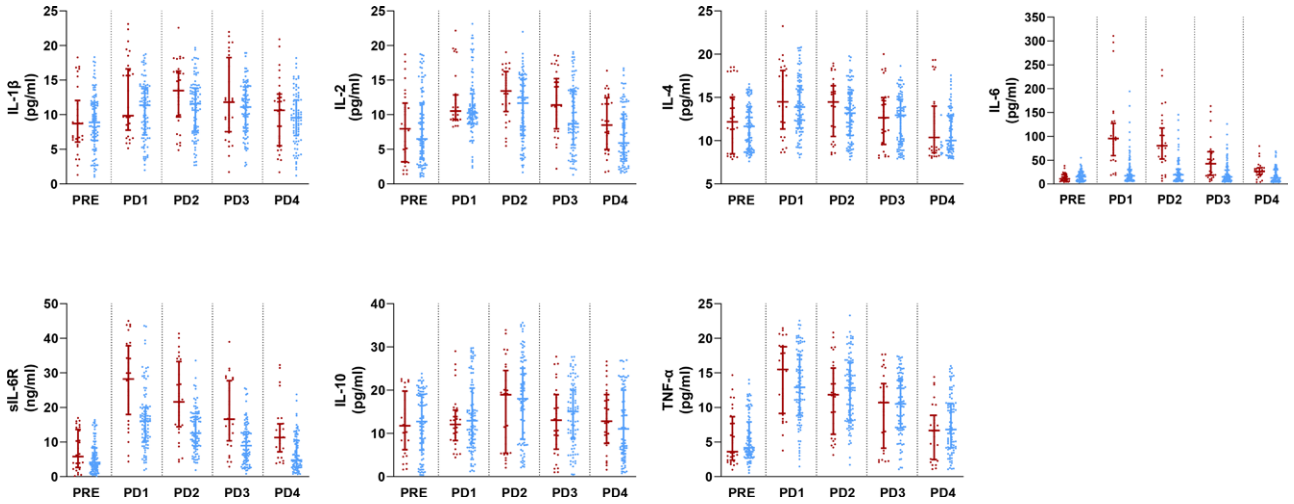

Figure 2. Plasma cytokine profiles of individuals with and without POD over time. The scatter plot of 7 cytokines, at each of 5 perioperative time points, is grouped according to whether the patient did (red dots) or did not (blue dots) develop postoperative delirium. Values are expressed as median (interquartile range). IL-10 indicates interleukin 10; IL-1β, interleukin 1β; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; PD1, postoperative day 1; PD2, postoperative day 2; PD3, postoperative day 3; PD4, postoperative day 4; POD, postoperative delirium; PRE, preoperative; sIL-6R, soluble interleukin 6 receptor; TNF-α, tumor necrosis factor-α.

Table 2. Time-Dependent Cox Regression Showing Delirium and Plasma Cytokines

	Univariate analysis		Multivariate analysis[a]	
Cytokines variable	**Unadjusted hazard ratio (95% CI)**	***P* value**	**Adjusted hazard ratio (95% CI)**	***P* value**
IL-6	1.021 (1.017–1.024)	.000	1.013 (1.008–1.017)	.000
sIL-6R	1.117 (1.090–1.143)	.000	1.095 (1.062–1.130)	.000
IL-2	1.107 (1.046–1.171)	.000	1.028 (0.959–1.102)	.439
IL-1β	1.040(0.981–1.102)	.190		
IL-4	1.033 (0.953–1.118)	.430		
IL-10	1.001 (0.970–1.034)	.939		
TNF-α	1.019 (0.966–1.076)	.489		

Abbreviations: BMI, body mass index; IL-10, interleukin 10; IL-1β, interleukin 1β; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; sIL-6R, soluble interleukin 6 receptor; TNF-α, tumor necrosis factor-α.

[a]Model adjusted for age, sex, BMI, anesthesia, and surgical location.

DISCUSSION

In this prospective, longitudinal study, the relationship between 7 cytokines, collected at 5 time points, and POD among older patients undergoing major elective lower limb surgery was examined. The major findings of our study are as follows. There was considerable interindividual variation in plasma cytokine responses to surgery. Postoperative levels of IL-6 and sIL-6R were higher in patients with, compared to those without, POD. Older patients and those with fixation of subtrochanteric/femoral shaft fractures and knee arthroplasty were more likely to develop delirium. We developed 2 cluster trajectory models for each of IL-6 and sIL-6R based on the GBTM analysis. We observed a high prevalence of POD in participants, who were categorized with fluctuating higher level clusters. These results show that more patients with fluctuating higher level trajectories of IL-6 and sIL-6R experienced POD.

Among 14 published studies evaluating the role of perioperative IL-6 in the development of POD, 7 explicitly sought to evaluate the risk of preoperative IL-6 and POD, 3 explored the association of postoperative IL-6 and POD, and only 4 included both preoperative and postoperative IL-6 levels.[20,21] As these studies compared cytokine levels at a single time point, a pattern of IL-6 change could not be identified. In these studies, delirium was not consistently associated with increased IL-6 either preoperatively or postoperatively. Therefore, it was not precisely known whether and how IL-6 contributes to the development of neurocognitive symptoms. Through multiple IL-6 measurements and by also measuring sIL-6R, an ingredient required for IL-6 trans-signaling we are able to address whether changes in the IL-6 trans-signaling cluster associates with delirium in a surgical population at high risk for perioperative neurocognitive disorders.

The association of elevated IL-6 levels and POD corroborates a recent meta-analysis of observational studies in noncardiac surgical settings,[20] as well as a study involving cardiac surgical patients.[22] Wirtz et al[23] measured IL-6 levels at frequent intervals in 30 patients. They reported a trend of IL-6 levels rising rapidly in the

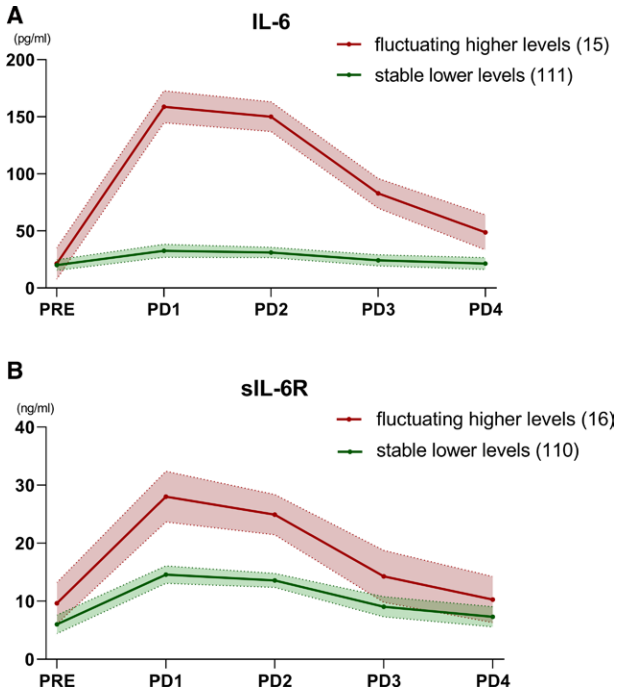

Figure 3. Perioperative trajectories of IL-6 and sIL-6R. Trajectories of circulating levels of IL-6 (A) and sIL-6R (B), from preoperatively to PD 1 to 4, were analyzed by group-based trajectory modeling. The solid lines depict the mean values, and the dashed areas depict the 95% CIs. CI indicates confidence interval; IL-6, interleukin 6; PD1, postoperative day 1; PD2, postoperative day 2; PD3, postoperative day 3; PD4, postoperative day 4; sIL-6R, soluble interleukin 6 receptor; PRE, preoperative.

first 6 hours, then more gradually in the next 6 hours to a peak at 12 hours, and then plateauing above baseline levels for the next 4 days. This trend was similar to that observed in the current investigation, in which the elevated IL-6 returned to baseline by the fourth day after surgery. In a subcohort derived from a large case-control study, Capri et al[24] found that high levels of IL-6 preoperatively were significantly associated with the onset of POD in older adults admitted for either elective or emergency surgery. In a nested, matched case-control subset of the successful aging after elective surgery (SAGES) cohort study,[25] Vasunilashorn et al[26,27] reported that higher IL-6 levels on PD 2 may be predictive of POD in elderly patients undergoing major noncardiac surgery.[5] However, the association of higher IL-6 levels and POD has been refuted in other studies.[6,7] Forsberg et al[28] examined the short- and long-term impact of abdominal surgery on neuroinflammation assessed by activation of microglia by positron emission tomography (PET). There was no association shown between changes in microglial activation and systemic levels of either plasma IL-10 or TNF-α ($P > .05$), whereas trend level significance was reached for IL-6. There were significant correlations between acute changes in IL-6 and long-term changes in cognitive tests (visual verbal learning test, cumulated, $P < .041$ as well as letter-digit coding test, $P < .015$).[28]

IL-6 exerts its biological functions via 2 major pathways, namely, the classic-signaling and trans-signaling pathways. In the classic signaling pathway, IL-6 binds to the membrane-bound IL-6 receptor (mIL-6R) triggering the dimerization of gp130 resulting in intracellular signaling only in those cells that express mIL-6R (hepatocytes, monocytes/macrophages, neutrophils, and some lymphocytes). In the trans-signaling pathway, IL-6 interacts with sIL-6R to form the IL-6/sIL-6R heteroduplex, which can bind to gp130 on any cell and initiate intracellular signaling without a requirement for mIL-6R.[29] sIL-6R is either produced as a soluble form from an alternatively spliced mRNA or it is proteolytically cleaved form from cell types that express mIL-6R. The trans-signaling process, rather than the classical pathway, probably mediates most of the proinflammatory responses to IL-6.[30] A review of the literature revealed only one previous investigation that reported on the association between sIL-6R and POD.[19] In that study involving 151 hip-fracture patients, preoperative cognitive impairment was present in 60 subjects; in this cognitively impaired subgroup, the onset of POD was associated with higher levels of sIL-6R in the cerebrospinal fluid (CSF) but did not achieve statistical significance. In a subcohort of 150 patients from the SAGES study, the proteomic signature of surgery in older adults and its association with postoperative outcomes was sought. Interestingly, along with the incremental change in IL-6 that was associated with postoperative complications, the signal transducer and activator of transcription 3 (STAT3), a downstream effector of IL-6 trans-signaling as well as a regulator of the transcription of IL-6, was also statistically associated with postoperative complications.[31]

The relationship between frailty and delirium has been observed,[32] as well as an association between frailty and elevated sIL-6R.[33] Also, a common polymorphism in the IL-6 receptor gene (IL6R Asp358Ala; rs2228145 A > C), which leads to increased serum sIL-6R, has been implicated in several inflammatory diseases, including neuroinflammation with cognitive decline.[34] Thus, there is emerging evidence for the potential roles of the combination of IL-6 and sIL-6R for the development of POD and possibly other postoperative complications. Were these relationships to extend to causality, then IL-6 and sIL-6R may be druggable targets. In that context, olamkicept, a novel inhibitor of the IL-6/sIL-6R heteroduplex and, therefore, selective inhibitor of trans-signaling, has shown promising activity in a phase II trial of inflammatory bowel disease,[35] as well as in a murine sepsis model.[36] Interestingly, selective blockade of IL-6 trans-signaling did not disturb bone formation after osteotomy, whereas global IL-6 blockade delayed fracture healing.[37]

Besides IL-6 and sIL-6R, we also tested for possible associations of IL-1β, IL-2, IL-4, IL-12, and TNF-α with POD. Consistent with our findings, previous studies have found no relationship between TNF-α and delirium.[4,38] In a delirium study involving a cohort of oncologic surgery patients, plasma IL-1β, IL-6, and IL-10 were measured preoperatively and postoperatively; postoperative increase in plasma levels of IL-10 was associated with POD in multivariate logistic regression analysis, while IL-1β and IL-6 were not significantly associated with POD.[39] Capri et al[24] reported that low IL-2 levels were significantly associated with POD, while IL-1β and IL-10 were not significantly associated with POD in patients undergoing emergency or elective surgery.

Limitations

First, the study sample consisted of patients who were admitted to a single hospital, which may limit the generalizability of the findings. Second, the cytokines were measured in the circulation and may not necessarily reflect values of these parameters in the brain. Although these findings underscore the relationship between systemic inflammation and POD, the potential role of neuroinflammation in delirium pathophysiology remains unclear. Third, our results do not reflect the uncertainty that elevated levels of IL-6 and sIL-6R could be before, during, or after the onset of delirium; consequently, we have not established a causal relationship between the elevated cluster of trans-signaling ingredients and the occurrence of POD. An ongoing series of preclinical studies is more likely to establish the putative causal relationship between clusters of IL-6 trans-signaling biomarkers and POD.

CONCLUSIONS

We found that in older patients undergoing major lower limb surgery, IL-6 and sIL-6R measured at several time points were associated with delirium. GBTM analysis of the IL-6 and sIL-6R trajectory demonstrated that nearly 80% of the subjects who experienced delirium had fluctuating higher IL-6 and sIL-6R trajectories after surgery. Our data lend further support to a pathophysiologic model of delirium in which exaggerated IL-6 trans-signaling may be the mechanism whereby neuroinflammation is associated with POD. This finding has the potential to lead to new studies both to better understand the role of IL-6 trans-signaling in delirium and to design and target interventional strategies that modulate the inflammatory response to ameliorate this common and costly postoperative complication that has high morbidity and mortality.[40]

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DISCLOSURES

Name: Yu Zhang, MD.
Contribution: This author helped conceive and design the study, perform the experiments, analyze the data, and write and revise the manuscript.
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Name: Jun Hu, MD.
Contribution: This author helped conceive and design the study, perform the experiments, analyze the data, and write and revise the manuscript.
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Name: Weiguang Zuo, MD.
Contribution: This author helped perform the experiments and collect the blood sample.
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Name: Pei He, MD.
Contribution: This author helped perform the experiments and collect the blood sample.
Conflicts of Interest: None.
Name: Qi Xue, PhD.
Contribution: This author helped analyze the data.
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Name: Xiaomei Feng, MD, PhD.
Contribution: This author helped interpret the data and revise the manuscript.
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Name: Ye Zhang, MD, PhD.
Contribution: This author helped conceive and design the study, revise the manuscript, and supervise the overall study.
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Name: Mervyn Maze, MB, ChB.
Contribution: This author helped interpret the data and critically revise the manuscript for intellectual content.
Conflicts of Interest: M. Maze is a co-inventor on a patent for the use of dexmedetomidine for sedation. M. Maze has not and will not receive royalty payments for sales of dexmedetomidine and, since 2005, has not received any support from companies selling dexmedetomidine. M. Maze consulted for Masimo in 2010.

This manuscript was handled by: Robert Whittington, MD.

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