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The Role of Inflammation after Surgery for Elders (RISE) study: Study design, procedures, and cohort profile

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Abstract

Introduction: The Role of Inflammation after Surgery for Elders study correlates novel inflammatory markers measured in blood, cerebrospinal fluid (CSF) assays, and [^{11}C]-PBR28 positron-emission tomography imaging.

Methods: This study involved a prospective cohort design with patients who underwent elective hip and knee arthroplasty under spinal anesthesia. Sixty-five adults participated with their family members. Inflammatory biomarker assays were measured preoperatively on day 1 and postoperatively at one month.

Results: On average, participants were 75 years old, and 72% were female. 54% underwent total knee arthroplasty, and 46% underwent total hip arthroplasty. The mean Modified Mini-Mental State (3MS) Examination score was 89.3; four patients (6%) scored ≤77 points. Plasma assays were completed in 63 (97%) participants, cerebrospinal fluid assays in 61 (94%), and PET imaging in 44 (68%).

Discussion: This complex study presents an innovative effort to correlate peripheral and central inflammatory biomarkers before and after major surgery in older adults. Strengths include collecting concurrent blood, cerebrospinal fluid, and positron-emission tomography with detailed clinical characterization of delirium, cognition, and functional status.

The authors have declared that no conflict of interest exists.

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1. Background

Increasing evidence highlights the important role of systemic inflammation in many age-related conditions, such as frailty, dementia, and age-related cognitive decline [1]. Pre-existing systemic inflammation (from chronic illness, multimorbidity, metabolic syndrome, etc.) have been known to contribute to the pathogenesis of Alzheimer's disease (AD) and cognitive decline [2,3]. Systemic inflammation has also been linked to delirium and postoperative cognitive decline [4–6]. Although some degree of inflammation is essential for adaptive responses to major stressors such as surgery, exaggerated or prolonged responses can lead to disease, dysfunction, and adverse clinical outcomes [1,7]. We hypothesize that persons with pre-existing systemic inflammation are at risk for maladaptive, hyperinflammatory responses to surgery.

The increasing number of older persons undergoing major surgery has led to dramatic increases in the number of patients developing delirium and cognitive decline postoperatively. Delirium is an acute decline in attention and cognitive functioning that occurs in the face of major physiologic disruptions, such as surgery and acute medical illness. The incidence of delirium in surgical patients is 11–46% for cardiac surgery, 13–50% for noncardiac surgery, and 12–51% for orthopedic surgery [8]. Delirium has been associated with poor outcomes, including functional decline, prolonged hospitalization, institutionalization, increased healthcare costs, caregiver burden, mortality, and accelerated cognitive decline [9–11].

Our work in the Successful Aging after Elective Surgery (SAGES) study of 560 older patients undergoing major noncardiac surgery examined the role of inflammation in delirium pathophysiology. In a nested, matched case-control study (75 matched pairs) [12], delirious patients had higher levels of C-reactive protein (CRP) and interleukin-6 (IL-6) than matched nondelirious patients [13,14]. In the full SAGES cohort, patients in the highest quartile of preoperative CRP had higher delirium incidence, severity, and duration relative to patients in the lowest quartile [15]; similar associations were observed for CRP measured on postoperative day 2 (POD2) and delirium incidence, severity, and duration. Separate proteomics analyses identified CRP, alpha-1-antichymotrypsin, and zinc-alpha2-glycoprotein levels as differently expressed in patients with delirium relative to matched no-delirium controls [13,16]. Although these findings underscore the relationship between systemic inflammation and delirium, the potential role of neuroinflammation in delirium pathophysiology remains unclear.

The overarching goal of the Role of Inflammation after Surgery for Elders (RISE) study is to assess the correlation of blood plasma, cerebrospinal fluid (CSF), and imaging biomarkers of inflammation preoperatively and at one-month follow-up in a cohort of patients undergoing major orthopedic surgery under spinal anesthesia. [^{11}C]-PBR28, a conjugate of the radioisotope carbon ^{11}C and peripheral benzodiazepine receptor 28 (PBR28), will be used as a diagnostic imaging agent to detect translocator protein (TSPO)–expressing cells using positron emission tomography (PET). PBR28 is a ligand for the 18 kDa TSPO. TSPO is involved in a variety of functions, including immunologic responses, and thus, [^{11}C]-PBR28 PET has been applied to a number of diseases to demonstrate region-specific activated microglial cells as a marker of neuroinflammation [17,18]. In amyotrophic lateral sclerosis, for example, increased [^{11}C]-PBR28 binding has been observed in the motor cortices and corticospinal tract, consistent with typical histopathological findings in patients with amyotrophic lateral sclerosis [19].

The following specific aims will compare findings at and across two time points: (1) examine the correlation of inflammatory biomarkers between plasma and CSF; (2) examine the correlation of inflammatory biomarkers from plasma with [^{11}C]-PBR28 PET signal; and (3) examine the correlation of inflammatory biomarkers from CSF with [^{11}C]-PBR28 PET signal. Finally, we hope to identify new plasma-based biomarkers for neuroinflammation using advanced proteomics approaches for biomarker discovery. Identification and quantification of biomarkers involved in delirium and the inflammatory response to surgery is fundamental to advance our pathophysiological understanding and develop appropriately targeted treatments. We hypothesize that delirium is a manifestation of a maladaptive response to systemic inflammation associated with surgery and may be associated with heightened cognitive and functional decline postoperatively.

2. Methods

2.1. Overview

Fig. 1 presents the inflammatory pathways and correlations planned for the study. At baseline, before surgery, we hypothesize that elevated levels of inflammatory biomarkers will be associated with increased delirium risk. At POD1, we hypothesize that delirium will be associated with exaggerated levels of inflammatory biomarkers in plasma. At one month, we hypothesize that delirium and/or cognitive decline will be associated with persistently increased levels

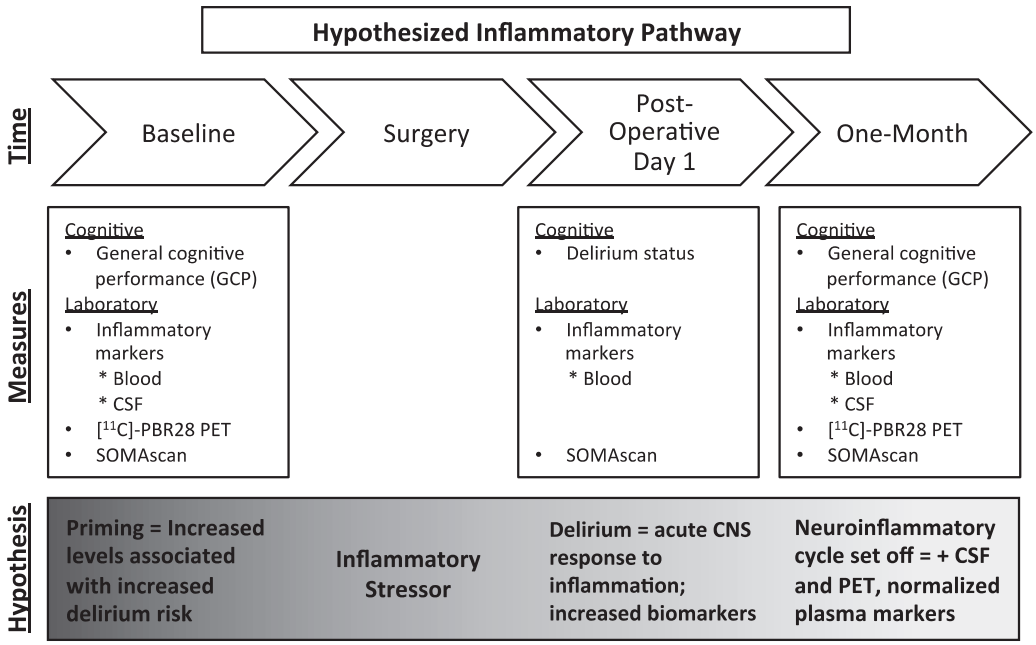

Fig. 1. Hypothesized inflammatory pathway in delirium. Abbreviations: CSF, cerebrospinal fluid; PET, positron emission tomography.

of CSF inflammatory markers and/or [^{11}C]-PBR28 PET signal; as per our prior work, we hypothesize that the plasma levels of inflammatory markers will normalize by one month [11].

The RISE study is a prospective cohort of 65 older adults undergoing elective knee or hip arthroplasty under spinal anesthesia. Sixty-three (97%) patients received phlebotomy at baseline, 60 (92%) received phlebotomy postoperatively, 61 (94%) underwent lumbar puncture at baseline and/or one-month follow-up, and 44 (68%) received PET imaging during at least one time point. Inflammatory markers from each source are measured and correlated across both time points. The present article describes the design, methods, and baseline characteristics of the study cohort.

2.2. *Study sample – recruitment and eligibility*

Patients aged 70 years or older, English speaking, and scheduled for hip or knee arthroplasty with planned spinal anesthesia were eligible. Inclusion criteria required planned admission for at least 24 hours and surgery scheduled at least 15 days in advance, to allow for baseline assessment and [^{11}C]-PBR28 PET scan. Total hip and knee arthroplasties were chosen for this study, given their delirium risk and frequent use of spinal anesthesia [20]. Approval to approach patients for potential enrollment was obtained from participating surgeons. Potentially eligible participants were identified by preoperative clinic schedules and operating room–booking schedules. Potential participants were called for eligibility screening and capacity assessment and for obtaining informed consent.

The exclusion criteria included active psychotic disorder, total blindness (precluding neuropsychological testing), contraindication to spinal anesthesia, and contraindication to MRI or [^{11}C]-PBR28 PET and certain TSPO polymorphisms further described in the following. Contraindications for lumbar puncture for spinal anesthesia included coagulation abnormalities, active anticoagulant or antiplatelet medications (other than low-dose aspirin), present use of oral steroids, and previous major spine surgery with instrumentation (other than discectomy). Patients not eligible for MR/PET included (1) contraindications to MRI studies such as cardiac pacemaker, intracardiac defibrillators, metallic particles, prosthetic heart valves, and severe claustrophobia; (2) prior radiation exposure exceeding safety guidelines; (3) inability to discontinue anti-inflammatory drugs for one week before scanning; (4) present use of oral steroids; (5) body mass index $\geq$33 (due to MR-PET scanner size limitations); and (6) inability to schedule the [^{11}C]-PBR28 PET at least 72 hours before surgery. Patients were also excluded for the rs6971 polymorphism (Ala/Ala or Ala/Thr) of the TSPO gene. The TSPO gene is present in 20–30% of population and results in low-affinity binding for the PET radiotracer [^{11}C]-PBR28 [21], which make these scans uninterpretable. We decided to exclude any potential participant with the TSPO gene because their scans would not be usable to detect neuroinflammation.

Study sites included 3 enrollment sites, 1 procedure site, and the study-coordinating center all in Boston, Massachusetts. The 3 enrollment sites were the Beth Israel Deaconess Medical Center (BIDMC), Brigham and Women's Hospital (BWH), and Brigham and Women's Faulkner Hospital (BWFH). The BIDMC is an academic medical center with

673 beds, over 40,000 admissions, and 10,000 operations per year. The BWH is an academic medical center with 777 beds, over 46,000 admissions, and 28,500 operations per year. The BWFH is a community-teaching hospital with 162 beds and over 11,000 operations per year. The procedure site for lumbar puncture and [^{11}C]-PBR28 PET scans was the Massachusetts General Hospital (MGH), an academic medical center with 999 beds, 48,000 admissions, and 42,000 operations per year. The study-coordinating center was based in the Marcus Institute for Aging Research at Hebrew SeniorLife (HSL). The Institutional Review Board approved of the Partners Healthcare system (MGH, BWH, BWFH) all study procedures with ceded review from BIDMC and HSL.

2.3. Patient and proxy interview content and variables

Patients were enrolled between April 26, 2017, and February 13, 2019. Trained lay interviewers conducted prescreening evaluations involving telephone interview, medical record review, and safety screening for lumbar puncture and MR-PET imaging. The baseline interview is a face-to-face interview in the patient's home, which includes complete neuropsychological testing and delirium assessment. The interview also assesses demographics, educational level, comorbidities, medications, family history of dementia, tobacco and alcohol use, hearing and vision, Activities of Daily Living (ADLs) [22], Instrumental Activities of Daily Living (IADLs) [23], Medical Outcomes Study Short-Form 12 (MOS SF-12) score [24], and depression. Caregiver interviews conducted at baseline include the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [25], Family Confusion Assessment Method (FAM-CAM) [26], and questions about any recent changes in cognitive functioning. In the hospital, patients were assessed daily with 10-15 minute interviews which included brief cognitive screening, digit span test, Confusion Assessment Method (CAM) [27], CAM-Severity (CAM-S) rating [28], and an adapted Delirium Symptom Interview [29]. A follow-up interview with complete neuropsychological testing was conducted at one month after hospitalization. Table 1 lists the study measures and time points of assessment.

Table 1
Study variables and time points

Assessments	Initial/baseline	Hospital (daily)	1 month
Demographic and Clinical Characteristics			
Demographics (age, gender, race/ethnicity, education, marital status, living situation, and occupation)	X		
Past medical history and comorbidities	X		
Any family history of dementia	X		
Social history (smoking and alcohol consumption)	X		
Surgery type, anesthesia duration, postoperative complications		X	
Cognition, delirium, and proxy measures			
Patient			
Full neuropsychological battery (including logical memory)	X		X
Brief cognitive assessment (including days of week/months of year backwards)		X	X
Confusion Assessment Method (CAM), CAM-Severity (CAM-S)	X	X	X
Modified Delirium Symptom Interview (DSI)		X	X
Proxy			
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	X		
Family Confusion Assessment Method (FAM-CAM)	X		
Activities of daily living (ADLs)	X		
Instrumental activities of daily living (IADLs)	X		
Functional and well-being variables			
Hearing, vision	X		
Physical function			
ADLs	X		X
IADLs	X		X
Subjective health and well-being			
Medical Outcomes Study Short-Form 12 (MOS SF-12)	X		X
Geriatric Depression Scale (GDS)	X		
Pain	X	X	
Sleep disturbance		X	

2.4. Interview and data management procedures

2.4.1. Interviewer training and standardization

All study interviewers underwent four weeks of training and standardization. At weekly staff meetings, coding questions, standardization, and missing data are discussed.

2.4.2. Data management

Research Electronic Data Capture (REDCap) was used to collect and track interview and medical record data, provide follow-up interview timelines, and produce completion reports that are reviewed weekly at the staff meeting. Paper forms are used to collect parts of the interviews that require written tasks (e.g. neuropsychological

testing) or when internet access is unavailable for REDCap. Interviewers recheck all interview data; finalized forms are checked by a second independent rater. Derived variables were defined in Variable Definition Sheets available to the study team, with explanations of missing records and any changes. Missing data were closely monitored to assess for coding errors and to verify absence of any systematic errors in data collection.

2.5. Laboratory procedures

Phlebotomy is performed on patients at three time points: baseline (PREOP; at home or during preadmission testing clinic visit at BIDMC, BWH or BWFH), postoperative day 1 (POD1), and approximately one month postoperatively (PO1MO). At each time point, 20 milliliters (mL) of blood is collected into one heparinized and one ethylenediaminetetraacetic acid (EDTA) tube (10 mL in each). During processing, plasma and cellular material are separated using low-speed centrifugation (1500 relative centrifugal force [rcf]) and stored at −80°C. All blood time points will be used for measurements of targeted inflammatory markers via enzyme-linked immunosorbent assay (ELISA) platforms (Ella System, ProteinSimple, San Jose, CA; Meso Scale Discovery [MSD], Gaithersburg, MD), and for biomarker discovery with the highly multiplexed SOMAscan proteomics platform (SomaLogic; Boulder, CO).

The baseline blood was used to determine eligibility for [^{11}C]-PBR28 PET scan based on TSPO 18 kDa genotyping. DNA was extracted from whole blood using a well-described technique [30] that yields large quantities of purified DNA of high molecular weight that can be amplified using polymerase chain reaction and restriction enzyme digestion. Allele-specific polymerase chain reaction assays were conducted to determine the presence of TSPO genotype (rs6971), a study exclusion criterion.

CSF was acquired in the immediate preoperative period during induction of spinal anesthesia (PREOP) and at one-month after surgery (PO1MO) via lumbar puncture. CSF was collected by aspiration or dropwise collection directly into the collection tubes. Samples were stored at −80°C in polypropylene tubes until analyzed. To minimize potential contamination of CSF sample with blood, the sample was centrifuged at 1000 rcf for 10 minutes to separate before storage in 0.5 mL aliquot tubes at −80°C. CSF at both time points will be used for measurements of inflammatory markers via ELISA platforms.

2.5.1. Immunoassays

Plasma and CSF concentrations of the inflammatory proteins CRP, IL-6, and Chitinase 3-Like 1 glycoprotein (CHI3L1, also known as YKL-40 [tyrosine {Y}, lysine {K}, leucine {L} with molecular weight of 40]) from heparinized plasma and CSF samples at PREOP, POD1, and PO1MO time points will be measured using Ella. Ella is a next generation, fully automatized ELISA that uses microfluidic channels and generates results from factory-calibrated standard curves included in each microfluidic Simple Plex. Ultimately, the Ella System provides a wider dynamic range, requires less sample, yields faster results (including triplicate values), and tighter coefficients of variation (CVs) than standard 96-well ELISA plates. CVs are generally $\leq$5%; for any CV $>$10%, the assay is repeated.

Other proinflammatory cytokines will be measured in plasma and CSF, including IL-7, IL-8, IL-15, IL-16, MCP-1, MDC, and MIP-1b, using the MSD electrochemiluminescence platform, providing highly sensitive and reliable results for these analytes [25]. To evaluate the contribution of AD pathology to delirium and postoperative cognitive decline and their interrelationship with inflammation, AD biomarkers amyloid-β_{42} and amyloid-β_{40} will be measured in both CSF and plasma, and total tau and phospho-tau (181) will be measured in CSF (ELISAs from ADX/Euroimmun, run on an automated EUROAnalyzer I; Euroimmun, Lubeck, Germany). We plan to stratify results by AD biomarker status (positive vs. negative) to assess differential effects in these groups in our data analyses. We are not adequately powered to examine statistical differences but will be able to examine trends in these exploratory analyses.

2.5.2. Proteomics: SOMAscan

We will use an innovative technology for biomarker discovery, the aptamer-based, highly multiplexed, sensitive proteomics platform, SOMAscan, which uses high affinity protein capture reagents called SOMAmers (slow off-rate modified aptamers) [31–37]. SOMAmers are modified DNA aptamers, oligonucleotides that bind with high specificity to preselected proteins. SOMAscan simultaneously quantifies 1305 clinically relevant human proteins in plasma by transforming each individual protein concentration into a corresponding SOMAmer concentration, which is then quantified using DNA microarray [31–37]. Compared with other mass spectrometry (MS)–based proteomics technologies, SOMAscan offers a median lower limit of detection of 40 femtometer ($<$1 picograms/mL), greater dynamic range of $>$8 logs, and higher reproducibility ($\sim$5% median CV). Plasma proteins span a dynamic range of up to 12 logs, and many relevant biomarkers are likely low abundant (e.g., cytokines) and not be readily detected by MS-based strategies [38]. SOMAscan has been successful for biomarker discovery in multiple diseases [35,37,39], including AD. SOMAscan has been well-validated against other proteomic platforms, including liquid chromatography-mass spectrometry/mass spectrometry and gold-standard ELISA measures [39,40].

We will perform SOMAscan analysis on 50 μL of heparin plasma and 20 μL CSF at preoperative baseline and postoperative 1-month time points using the SOMAscan manual assay (version 1.3k) with the standard protocol from SomaLogic [31–37,41]. SOMAscan analysis will be performed at the BIDMC Genomics, Proteomics, Bioinformatics and

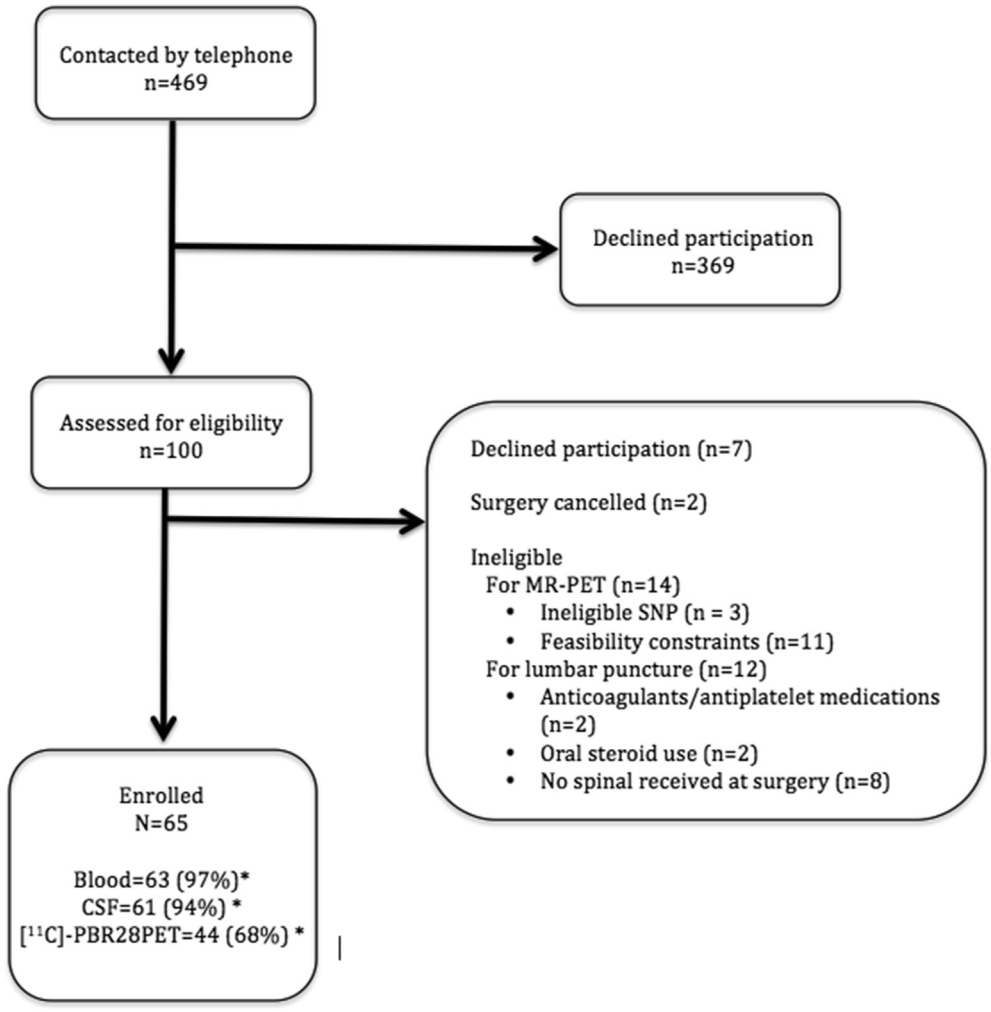

Fig. 2. Enrollment flow into the RISE study (Consort Diagram). Abbreviations: RISE, Role of Inflammation after Surgery in Elders; [^{11}C]-PBR28 PET, positron emission tomography; SNP, single nuclear polymorphism; CSF, cerebrospinal fluid. *At baseline and/or one-month.

Systems Biology Center, a SomaLogic certified site. Owing to the tight CV of ~5%, samples are run as singlets, which is standard for SOMAscan. Calibration is accomplished using 5 replicates of pooled plasma or CSF samples per run of 26 test samples. The final readout is directly proportional to the amount of target protein in the initial sample. Protein data from the SOMAscan analysis will be normalized using a singular value decomposition–based method [42,43].

2.6. Magnetic resonance and positron emission tomography imaging

Patients underwent integrated magnetic resonance-positron emission tomography (MR-PET) brain imaging at the Martinos Center for Biomedical Imaging at MGH (Boston, MA) on a 3 Tesla MAGNETOM Tim Trio scanner (Siemens Healthineers, Erlangen, Germany) with the Siemens Biograph mMR PET insert and using an 8-channel head coil. Patients completed MR-PET preoperatively and at one month postoperatively.

The radioligand [^{11}C]-PBR28 was synthesized on site [44] and injected as a slow intravenous bolus (up to 15 millicurie) through the catheter. PET images were acquired in a list mode format for 60 minutes scanning time beginning 30 minutes afterinjection to complete PET image acquisition in the 30–90 minutes after injection timeframe and, simultaneously, 60 minutes of MR imaging. The Biograph mMR Dixon sequence was used for attenuation correction during scanning, and an internal method was used after scanning for additional attenuation correction, as described previously [45]. PET data were reconstructed in 5-minute frames and a 30-minute frame over the 60-90 minute time point. We followed approaches detailed in previous publications [46,47].

For analysis of [^{11}C]-PBR28 PET data, we will follow established approaches [19,45,48]. Briefly, after acquisition and image reconstruction with corrections for normalization, dead time, isotope decay, photon attenuation, and expected random and scatter coincidences, attenuation correction maps will be created using MR-based methods. We will first create late-uptake [^{11}C]-PBR28 PET images

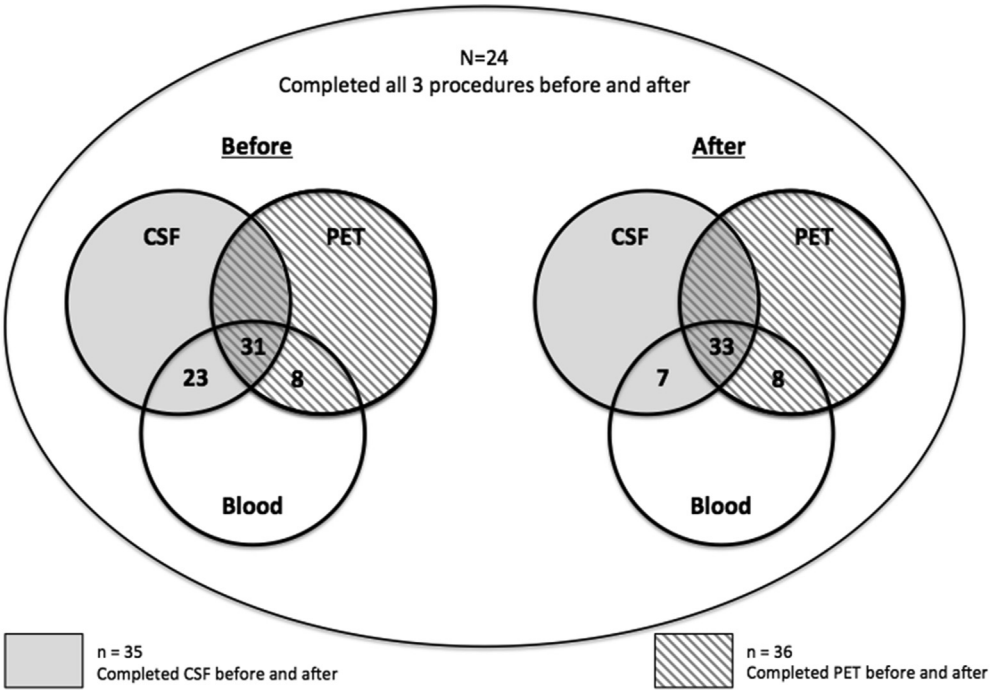

Fig. 3. Patient contributions of plasma, cerebrospinal fluid, and [^{11}C]-PBR28 PET imaging. A total of 65 patients were enrolled in the RISE study. Overall, 24 patients completed all 3 biomarker procedures at both time points (preoperatively and one month postoperatively). Owing to logistic constraints, some patients could not complete all study components. The distributions of biomarkers completed are detailed in this figure. Collection of plasma was completed in 63 (97%) patients. CSF assay was completed in 61 (94%) patients, with 56 at baseline and 40 at one month. [^{11}C]-PBR28 PET imaging was competed in 44 (68%) patients, with 39 at baseline and 41 at follow-up. Abbreviation: [^{11}C]-PBR28 PET, positron emission tomography.

for 60-90 min after injection and quantify the PET data as standardized uptake values (SUVs). Individual SUV 60–90 min images will then be registered to each individual's reconstructed T1-weighted MRI scan and to Montreal Neurological Institute space, spatially smoothed (6 mm full width at half maximum) and intensity-normalized. To account for the large interindividual variability in the global PET signal, SUV will be normalized by whole-brain PET uptake and will be expressed as SUVr (SUV ratios). We will analyze the PET using (1) whole brain voxel-wise analyses and (2) regions of interest (ROI) analyses. T1 images will be processed and analyzed using FreeSurfer (version 6.0) as we have done previously [49–51].

2.7. *Sample size considerations*

The projected sample size was estimated based on detecting correlations among plasma, CSF, and [^{11}C]-PBR28 PET imaging biomarkers, with a target correlation of $r = 0.60$ or greater. The effect size was determined based on the previous work on inflammatory markers in plasma and CSF [52]. Our early-stage study was initially designed to enroll 18 individuals, which would provide approximately 80% power to detect nominally "moderate" correlations to 0.6 between biomarkers. The study ultimately enrolled 25 participants, which will provide 91% power to detect effects of this size and 80% power to detect correlations of 0.52 or greater.

3. Results

Of 469 patients approached, 100 were fully screened. Of these, 14 patients were ineligible for MR-PET, 12 patients were ineligible for lumbar puncture, 7 patients refused participation, and surgery was canceled in 2 patients. The study flow diagram is shown in Fig. 2. A total of 65 patients were enrolled into the RISE study. Overall, 24 patients completed all 3 biomarker procedures at both time points (PREOP and PO1MO). Owing to logistic constraints, mainly new medical ineligibility for the procedure or patient unavailability, some patients could not complete all study components. Sixty-three (97%) patients contributed plasma, 61 (94%) contributed CSF, and 44 (68%) completed [^{11}C]-PBR28 PET imaging. Fifty-six patients contributed CSF at baseline and 40 contributed CSF at approximately one month postoperatively (mean follow-up of 39 days with standard deviation of 10 days). Thirty-nine patients underwent PET imaging at baseline and 41 underwent PET imaging one month postoperatively. Thirty-one patients contributed all 3 biomarkers only at PREOP; 33 patients contributed all 3 biomarkers only at PO1MO. Distributions of biomarkers completed are detailed in Fig. 3.

Baseline characteristics of the cohort are shown in Table 2. On average, participants were 75 years old, 72% were female, 5% were non-white (non-Hispanic) race, 5% were of Hispanic ethnicity, 52% were married, and 65% were living alone. Mean education was 15.6 (SD 3.5)

Table 2
Baseline characteristics of study participants

Characteristics	Full sample (n = 65)
Age at surgery, mean years (SD)	75.1 (4.7)
Female sex, n (%)	47 (72)
Race, n (%)	
White	62 (95)
Black or African American	2 (3)
More than one race	1 (2)
Hispanic ethnicity, n (%)	3 (5)
Education, mean years (SD)	15.6 (3.5)
Education, years completed, n (%)	
0–12 years	12 (18)
13–16 years	27 (42)
17 + years	26 (40)
Married (vs. unmarried), n (%)	34 (52)
Lives alone (vs. with other), n (%)	42 (65)
Modified Mini-Mental State (3MS) Examination, mean (SD)	89.3 (6.5)
Scored $\leq$ 77 (indicating cognitive impairment), n (%)	4 (6)
Charlson Comorbidity Score, n (%)*	
0	45 (70)
1	10 (15)
$\geq$ 2	10 (15)
Baseline function, n (%)	
Any ADL impairment	4 (6)
Any IADL impairment	5 (8)
Surgery type, n (%)	
Total knee arthroplasty	35 (54)
Total hip arthroplasty	30 (46)

Abbreviations: SD, standard deviation; IADL, Instrumental Activity of Daily Living.

*The Charlson Comorbidity Score was calculated based on diagnoses abstracted from medical record review, scored from 0 to 35, with higher scores indicating more comorbidity.

years, with 67% completing at least some college. Patients were evenly distributed between total knee (54%) and total hip arthroplasty (46%). Only 8% of patients reported any impairment in IADLs at baseline and 15% had multiple comorbidities with the Charlson score $\geq$2. A baseline Modified Mini-Mental State (3MS) Examination score of $\leq$77, indicating cognitive impairment, was observed in 4 patients (6%).

4. Discussion

This article provides a comprehensive description of the RISE study methods and cohort, a complex and innovative examination of inflammatory markers associated with major surgery. The design allows a 3-way comparison of biomarkers obtained from plasma, CSF, and [^{11}C]-PBR28 PET imaging, over sequential time points before, immediate postoperative (plasma only), and one month after surgery. Although systemic inflammation has been postulated to lead to neuroinflammation and associated cognitive dysfunction, direct evidence has been lacking to date. This study will facilitate examination of the relationship of markers of systemic inflammation (from plasma) with 2 sources of potential markers of neuroinflammation (CSF and [^{11}C]-PBR28 PET). Importantly, these comparisons will also allow us to determine whether any plasma-based markers can approximate levels of neuroinflammation. Moreover, the change in levels of markers over time from preoperative to one-month postoperative periods will allow us to advance our pathophysiologic understanding of the temporal association of inflammation with delirium and cognitive changes over time.

Unique strengths of this study include the concurrent collection of plasma, CSF, and [^{11}C]-PBR28 PET imaging preoperatively and one month postoperatively, along with detailed clinical characterization of all patients with respect to delirium, cognitive and functional status, applying state-of-the-art approaches. The study is further strengthened by the novel, highly multiplexed SOMAscan approach for biomarker discovery in both plasma and CSF. This approach holds the potential to discover novel proteins of importance in the pathophysiology of delirium and postoperative cognitive decline.

Several caveats are worthy of comment. First, given the complexity and expense of the study, the sample size is modest (N = 65); however, the power should be adequate to accomplish our main study aims. Second, owing to real-world logistic constraints, only 24 patients completed all 3 biomarker procedures at baseline and one month, with many other completion patterns. In our future analyses, we hope to use approaches that will allow us to maximize the sample size for each of the proposed analyses. Finally, the sample is relatively well-educated, highly functional, and recruited from 3 hospitals in a single city. Thus, generalizability may be limited and the findings will ultimately need to be replicated in larger, more diverse samples across varied settings.

We provide this detailed description of the RISE study to enable clinicians and researchers to interpret our future study results. This novel study holds great potential to advance our pathophysiologic understanding of inflammation and inflammatory biomarkers in the surgical setting. Identification of plasma-based biomarkers of neuroinflammation will represent a major advance. Quantification of biomarkers and their patterns over time represents a fundamental step in understanding potentially maladaptive responses to surgery in older adults. Ultimately, we hope that findings from this study will facilitate development of pathophysiologically targeted treatment strategies to prevent perioperative complications such as delirium and postoperative cognitive decline.

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participated in the Role of Inflammation after Surgery in Elders (RISE) study.
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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources (PubMed). Although peripheral inflammatory biomarkers for delirium have been increasingly studied, biomarkers for inflammation in the central nervous system have not been well examined.
2. Interpretation: Based on present evidence, our study was designed to examine the intercorrelation of peripheral and central biomarkers of inflammation related to surgery and delirium in a cohort of older adults. We planned to correlate inflammatory biomarkers by plasma assay, cerebrospinal fluid assay, and [^{11}C]-PBR28 radiotracer positron-emission tomography neuroimaging performed before and after surgery. Here, we describe the study design, procedures, and the enrolled cohort.
3. Future directions: After all the assays have been completed, novel inflammatory biomarkers will be correlated across the 3 sources and examined for changes over time in relationship with surgery and delirium. This complex study will allow us to test our hypothesized inflammatory pathways and advance our understanding of the pathophysiology of delirium in older adults.

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