RESEARCH ARTICLE

Association of CSF Alzheimer's disease biomarkers with postoperative delirium in older adults

Tamara G. Fong MD, PhD[1,2,3] | Sarinnapha M. Vasunilashorn PhD[3,4,6] | Yun Gou MA[2] | Towia A. Libermann PhD[3,7,8] | Simon Dillon PhD[7,8] | Eva Schmitt PhD[2] | Steven E. Arnold MD[3,10] | Pia Kivisäkk MD, PhD[3,10] | Becky Carlyle PhD[10] | Esther S. Oh MD, PhD[11,12,13] | Kamen Vlassakov MD[3,14] | Lisa Kunze MD[3,15] | Tammy Hshieh MD, MPH[2,3,16] | Richard N. Jones ScD[9] | Edward R. Marcantonio MD, SM[3,4,5] | Sharon K. Inouye MD, MPH[2,3,5] | For the RISE Study Group

[1] Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[2] Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife, Boston, Massachusetts, USA

[3] Harvard Medical School, Boston, Massachusetts, USA

[4] Division of General Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[5] Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[6] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

[7] Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[8] Beth Israel Deaconess Medical Center Genomics, Proteomics, Bioinformatics and Systems Biology Center, Boston, Massachusetts, USA

[9] Departments of Psychiatry and Human Behavior and Neurology, Warren Alpert Medical School, Brown University, Providence, Rhode Island, USA

[10] MGH Institute for Neurodegenerative Disease, Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, USA

[11] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[12] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[13] Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[14] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

[15] Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

[16] Division of Aging, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence
Tamara G. Fong, MD, PhD, Aging Brain Center, Institute for Aging Research, Hebrew Senior-Life, 1200 Centre Street; Boston, MA 02131 USA.
Email: tfong@bidmc.harvard.edu

Tamara G. Fong, Sarinnapha M. Vasunilashorn, Edward R. Marcantonio and Sharon K. Inouye contributed equally to this study.

Abstract

Introduction: The interaction between delirium and dementia is complex. We examined if Alzheimer's disease (AD) biomarkers in patients without clinical dementia are associated with increased risk of postoperative delirium, and whether AD biomarkers demonstrate a graded association with delirium severity.

Methods: Participants ($n = 59$) were free of clinical dementia, age ≥ 70 years, and scheduled for elective total knee or hip arthroplasties. Cerebrospinal fluid (CSF) was collected at the time of induction for spinal anesthesia. CSF AD biomarkers were measured by enzyme-linked immunosorbent assay (ELISA) (ADX/Euroimmun); cut points for amyloid, tau, and neurodegeneration (ATN) biomarker status were A = amyloid beta $(A\beta)_{42}$ <175 pg/mL or $A\beta_{42/40}$ ratio <0.07; T = p-tau >80 pg/mL; and N = t-tau >700 pg/mL. Confusion Assessment Method (CAM) and CAM-Severity (CAM-S) were rated daily post-operatively for delirium and delirium severity, respectively.

Results: $A\beta_{42}$, tau, and p-tau mean pg/mL (SD) were 361.5 (326.1), 618.3 (237.1), and 97.1 (66.1), respectively, for those with delirium, and 550.4 (291.6), 518.3 (213.5), and 54.6 (34.5), respectively, for those without delirium. Thirteen participants (22%) were ATN positive. Delirium severity by peak CAM-S [mean difference (95% confidence interval)] was 1.48 points higher (0.29-2.67), $P = 0.02$ among the ATN positive. Delirium in the ATN-positive group trended toward but did not reach statistical significance (23% vs. 7%, p = 0.10). Peak CAM-S [mean (SD)] in the delirium group was 7 (2.8) compared to no delirium group 2.5 (1.3), but when groups were further classified by ATN status, an incremental effect on delirium severity was observed, such that patients who were both ATN and delirium negative had the lowest mean (SD) peak CAM-S scores of 2.5 (1.3) points, whereas those who were ATN and delirium positive had CAM-S scores of 8.7 (2.3) points; other groups (either ATN or delirium positive) had intermediate CAM-S scores.

Discussion: The presence of AD biomarkers adds important information in predicting delirium severity. Future studies are needed to confirm this relationship and to better understand the role of AD biomarkers, even in pre-clinical phase, in delirium.

KEYWORDS
AD biomarkers, delirium

1 | BACKGROUND

Delirium is an acute decline in cognition and attention, and is a common complication of acute illness, trauma, and surgery in older adults, associated with multiple adverse outcomes including increased morbidity and mortality, falls, loss of cognitive and physical function, and independence.[1–3] In contrast, Alzheimer's disease (AD) and Alzheimer's-related dementias (AD/ADRD) refer to an insidious neurodegenerative condition characterized by chronic and progressive cognitive decline. Both delirium and dementia are common causes of cognitive impairment among older adults, and they share a complex inter-relationship, occurring independently, concomitantly, and/or interactively. Persons with AD/ADRD have a four- to five-times increased risk of delirium, and the prevalence of delirium among patients with AD/ADRD ranges from 22% to 89% of hospitalized, nursing home, and community-dwelling populations age 65 and older.[4] Delirium in persons with AD/ADRD can have cumulatively worse outcomes than either AD/ADRD or delirium alone, substantially increased risk for death, functional dependence, placement in a nursing facility, mortality, and accelerated cognitive decline.[4–6]

Although AD/ADRD was previously an entirely clinical diagnosis, a conceptual shift has occurred such that AD is now considered on a continuum, with identification of biological features (molecular pathology or biomarkers) of AD even among cognitively normal individuals, prior to the occurrence of any clinical symptoms. Three core cerebrospinal fluid (CSF) biomarkers for the diagnosis of AD have been documented previously, with reduced CSF levels of $A\beta_{42}$ and elevated CSF levels of total tau (t-tau) and phosphorylated tau (p-tau) found in AD and mild cognitive impairment (MCI) confirmed in many studies.[7] On the other hand, CSF AD biomarkers in the context of delirium have yielded inconsistent findings. Some studies have shown that patients with delirium have a reduced CSF $A\beta_{42}$/tau ratio,[8] or that patients without clinically evident dementia who developed delirium had lower CSF $A\beta_{42}$ levels, higher t-tau levels, and lower ratios of $A\beta_{42}$ to t-tau and p-tau relative to those did not have delirium.[9] In contrast, other studies did not find significant differences in pre-operative CSF $A\beta_{42}$, t-tau, and p-tau levels between participants who did and did not develop delirium.[10]

In this article, we applied the ATN biomarker framework to distinguish AD from non-AD causes of cognitive impairment with three types of biomarkers: beta amyloid ($A\beta$) deposition (A), pathologic tau

(phosphorylated tau, T), and neurodegeneration (total tau, N).[11] Our aims are to determine whether positive CSF AD biomarkers, as defined by ATN status, are associated with an increased risk of postoperative delirium and delirium severity. We also examine whether the presence of CSF AD biomarkers and delirium demonstrate a graded association with delirium severity; that is, whether delirium severity scores are lowest in AD biomarker-negative/delirium-negative individuals, intermediate among individuals positive in one or the other, and highest in individuals with both positive AD biomarkers and delirium.

2 | METHODS

2.1 | Study sample

The Role of Inflammation after Surgery for Elders (RISE) study is a prospective observational cohort of older adults undergoing elective knee or hip arthroplasty under spinal anesthesia. The study design and methods have been described in detail previously.[12] In brief, eligible participants were age 70 years and older, English speaking, with an anticipated length of stay in the hospital of at least 24 hours. Total knee and hip arthroplasties were chosen for this study due to their delirium risk and use of spinal anesthesia.[13] Exclusion criteria were evidence of active psychotic disorder, contraindication to spinal anesthesia, including coagulation abnormalities, active anticoagulant, or antiplatelet medications other than low-dose aspirin, current use of oral steroids, and prior major lumbar spine surgery with instrumentation. A total of 65 patients met all eligibility criteria and were enrolled between April 26, 2017 and February 13, 2019. Study sites included three enrollment sites, the Beth Israel Deaconess Medical Center (BIDMC), Brigham and Women's Hospital (BWH), and Brigham and Women's Faulkner Hospital (BWFH), and the study-coordinating center based at the Marcus Institute for Aging Research at Hebrew SeniorLife (HSL), all in Boston, Massachusetts. Written informed consent for study participation was obtained from all participants according to procedures approved by the institutional review board of Partners Healthcare System (BWH and BWFH), with ceded review from BIDMC and HSL.

2.2 | Data collection

Participants underwent prescreening by telephone interview and medical record review. Trained research associates conducted baseline face-to-face interviews in the patient's home 2 weeks before surgery, including complete neuropsychological testing, from which a General Cognitive Performance (GCP) score was created.[14] The GCP is a weighted composite summary measure calibrated to a nationally representative sample of adults age ≥70 years[15] to yield a mean score = 50 and SD = 10.[16] Baseline interviews also included delirium assessment, and hearing and vision screening, and collection of standardized information on demographics, educational level, co-morbidities, medications, family history of dementia, tobacco and alcohol use, activities of daily living (ADLs),[17] instrumental activities of daily living (IADLs),[18]

RESEARCH IN CONTEXT

1. **Systematic review**: Persons with Alzheimer's disease (AD) and AD-related dementias (ADRD) have an increased risk for delirium, and delirium in persons with AD/ADRD experience cumulatively worse outcomes than AD/ADRD or delirium alone. Prior studies examining AD biomarkers in delirium have been inconsistent.

2. **Interpretation**: Among patients without clinical dementia who were amyloid, tau, and neurodegeneration (ATN) biomarker-positive, delirium rate trended toward but did not reach statistical significance. Delirium severity was higher in ATN positive compared to those who were ATN negative. Delirium severity scores were lowest in ATN-negative/delirium-negative individuals, intermediate among individuals positive in one or the other, and highest in individuals ATN positive/delirium positive. This suggests that pre-clinical dementia biomarkers are associated with delirium severity.

3. **Future directions**: Studies with larger and more diverse cohorts will help confirm the findings reported here. With a larger sample, effects of amyloid versus non-amyloid pathology, and the relationship of delirium, ATN biomarker status, and clinical outcomes can be examined.

Medical Outcomes Study Short-Form 12 (MOS SF-12) score,[19] and Geriatric Depression Scale.[20]

Caregiver interviews conducted at baseline include the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[21] the Family Confusion Assessment Method (FAM-CAM),[22] and questions about any recent changes in cognitive functioning. Following surgery, from the first postoperative day through discharge, participants underwent a 10- to 15-minute daily delirium assessment. The Confusion Assessment Method (CAM),[23] a well-validated and standardized method for identification of delirium, with a sensitivity of 94% [95% confidence interval [CI] 91-97], specificity of 89% (95% CI 85-94), and inter-rater reliability of 0.70 to 1.00 was used to identify delirium daily during the entire hospital stay.[24] Patients were classified with delirium if they had a positive CAM on any day throughout the hospital stay. The CAM Severity score (CAM-S), ranging from 0 to 19 (19 = most severe), was calculated using the long-form CAM assessment.[25] Because a minimum of three features is required for CAM delirium, peak CAM-S scores of 0 to 2 represent the group without CAM-defined delirium. Some patients without delirium received scores >2 based on non-specific delirium features (eg, disorientation, memory impairment, psychomotor agitation), which can be present in conditions unrelated to delirium.[26] For this study, we examined delirium severity using the peak CAM-S score (CAM-S peak), which is the highest value of CAM-S occurring during the daily hospital assessments.[26] Brief cognitive testing of attention, orientation, and memory, and an adapted Delirium Symptom Interview[27] were all used to score the CAM and CAM-S.

2.3 | Data management

Trained research associates were required to undergo 4 weeks of training and standardization on all study and interview procedures. Coding questions, standardization, and missing data were discussed at weekly staff meetings. Study data including interview and medical record data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Hebrew SeniorLife.[28,29] REDCap was also used to provide follow-up interview timelines and to produce completion reports that are reviewed weekly at the staff meeting. Missing data were closely monitored to assess for coding errors and to verify absence of any systematic errors in data collection.

2.4 | Laboratory procedures

CSF was acquired in the immediate pre-operative period during induction of spinal anesthesia (PREOP) by aspiration or gravity collection directly into low-retention polypropylene collection tubes. Samples were kept on ice until pre-processing, and were frozen within 4 hours of collection (in most cases <2 hours). To minimize cellular contamination of CSF samples, the sample was centrifuged at 1000 relative centrifugal force for 10 minutes at 4°C before being removed to a new tube for storage in 0.5 mL aliquots at −80°C.

2.5 | Biochemical procedures

AD biomarkers $A\beta_{42}$ and $A\beta_{40}$, and t-tau and p-tau (181) were measured in CSF. Enzyme-linked immunosorbent assays (ELISAs) (ADX/Euroimmun) of $A\beta_{42}$, $A\beta_{40}$, t-tau, and p-tau were run on an automated EUROAnalyzer I (Euroimmun, Lubeck, Germany) according to the manufacturer's protocol in the Alzheimer's Clinical & Translational Research Unit (ACTRU) at the Massachusetts General Hospital Institute for Neurodegenerative Diseases (MIND). The analytic and clinical performance of all four AD biomarkers has been validated (and verified in ACTRU) with average coefficients of variation (CVs) below 5% for all four assays. CSF samples were thawed and clarified with brief centrifugation, and inserted into the EuroImmun Analyzer I, which performs all assay steps. Three quality control samples (supplied in the kit) and three reference pooled CSF samples (ACTRU biobank) were included on each plate, to monitor and control for plate to plate variability. All samples were run in duplicate. In this study mean duplicate CVs were 3.2% for $A\beta_{42}$, 5.1% for p-tau (181) and 3.8% for t-tau.

2.6 | Statistical analysis

Biomarker cut points were taken from a high contrast clinically defined cohort using the Euroimmun AD platform in AD ($n = 54$) and non-AD controls ($n = 31$). Both studies included analysis of the same reference pool samples, allowing for direct comparison of distributions.

Cut points for the CSF AD biomarkers were selected to maximize specificity (96-100%), as our intent in the RISE study was to use ATN biomarker status as an important stratification variable and not for clinical diagnosis. The AD biomarker status was categorized as abnormal (A+) if CSF Ab_{42} <175 pg/mL or $Ab_{42}/_{40}$ ratio <0.07; tau was categorized abnormal (T+) if CSF p-tau was >80 pg/mL; and biomarker of neuronal degeneration or neuronal injury was categorized as abnormal (N+) if CSF t-tau was >700 pg/mL. Baseline demographics were compared among different ATN groups using chi-square test for dichotomous variables and analysis of variance (ANOVA) test for continuous variables. An unadjusted generalized linear model with log link function was used to estimate the association between ATN biomarker status and delirium incidence and severity. We used STATA Version 15 for all statistical analyses; for these analyses, a two-sided P value of < 0.05 was used to indicate statistical significance.

3 | RESULTS

3.1 | Demographics

Characteristics of the full cohort are described in **Table 1**. Participants ($n = 59$) included older adults who were on average (SD) 75.1 (4.9) years old at the time of study enrollment; 41 (69%) were women and 4 (7%) were non-White. The sample was generally healthy, with only 7(12%) with a Charlson Comorbidity Index score of ≥2. On average, participants had 15.5 (3.6) years of education and a baseline cognitive performance of 59.4 (9.5) points on the general cognitive performance (GCP) [national mean 50, standard deviation 10 points].[14] Baseline Modified Mini-Mental State (3MS) Examination score of ≤77, indicating cognitive impairment, was observed in four patients (6%). Although none of the characteristics were significantly different, there was more functional impairment (ie, impairment with ADL and IADL), higher geriatric depression scores, and medical comorbidities in the negative ATN group by standardized mean differences. Although we expected the ATN-negative group to have fewer impairments, perhaps this is related to a volunteer bias, where the patient defers having surgery until the orthopedic issue affects functional status, or takes a more cautious approach due to medical and psychiatric comorbidities.

3.2 | CSF biomarker distribution

Table 2 shows the distribution of the cohort by ATN status. Although our initial intent was to use the ATN to identify patients with preclinical AD, due to the small number of participants in the individual ATN groups, we elected to define patients either as biomarker-negative ($A^-T^-N^-$), while those with one or more biomarker present (A^+, T^+, or N^+) would be designated as ATN biomarker-positive, on the assumption that any abnormal ATN biomarker is sufficient to identify brain vulnerability. By including the amyloid negative ($A^-T^-N^+$ and $A^-T^+N^+$) in taking this broad approach we hope to capture preclinical AD/ADRD. Of the 59 participants enrolled in the study, 46 (78%)

TABLE 1 Baseline patient characteristics

	Total N = 59	ATN positive N = 13	ATN negative N = 46	SMD
Age at surgery, years (SD)	75.1 (4.9)	75.3 (4.6)	75.0 (5.0)	0.134
Female sex, no. (%)	41 (69)	9 (69)	32 (70)	−0.007
Non-White, no. (%)	4 (7)	1 (8)	3 (7)	0.044
Education, years (SD)	15.5 (3.6)	16.4 (2.4)	15.3 (3.8)	0.277
Currently married/living with partner, no. (%)	33 (56)	7 (54)	26 (57)	−0.052
Lives in a nursing home, no. (%)	1 (2)	0 (0)	1 (2)	−0.209
Lives alone, no. (%)	39 (66)	7 (54)	32 (70)	−0.319
GCP score at baseline, score (SD)	59.4 (9.5)	60.3 (8.8)	59.2 (9.8)	0.220
Any ADL impairment, no. (%)	4 (7)	0 (0)	4 (9)	−0.432
GDS Score, score (SD)	1.9 (2.1)	1.0 (1.5)	2.1 (2.1)	−0.432
Any IADL impairment, no. (%)	4 (7)	0 (0)	4 (9)	−0.432
CCI ≥2, no. (%)	7 (12)	1 (8)	6 (13)	−0.598
Surgery type, no. (%)				−0.142
Total knee	33 (56)	8 (62)	25 (54)	
Total hip	26 (44)	5 (38)	21 (46)	
$A\beta_{42}$ pg/mL (mean)	531.2 (297.9)	332.8 (286.5)	587.2 (279.1)	−1.108
$A\beta_{42/40}$ ratio	0.11 (0.03)	0.07 (0.03)	0.12 (0.03)	−1.438
Tau, pg/ml (mean)	528.4 (216.0)	802.8 (264.5)	450.9 (116.4)	2.275
p-tau, pg/mL (mean)	59.0 (40.2)	111.9 (55.4)	44.0 (14.8)	1.953

ADLs = activities of daily living, CCI = Charlson Comorbidity Index, higher score predicts higher mortality; GCP = general cognitive performance, mean score = 50, higher score is better; GDS = Geriatric Depression Scale, 0-15 points, higher is worse depression; IADL = instrumental activity of daily living; M = mean, no. = number; SD = standard deviation; SMD = standardized mean difference.

TABLE 2 Distribution by ATN biomarker status

ATN Classification	N = 59, N (%)
Biomarker negative	
$A^-T^-N^-$	46 (78%)
Amyloid pathology	
$A^+T^-N^-$	3 (4%)
$A^+T^+N^-$	2 (3%)
$A^+T^-N^+$	1 (2%)
$A^+T^+N^+$	4 (7%)
Suspected Non-amyloid pathology	
$A^-T^+N^-$	0
$A^-T^-N^+$	2 (3%)
$A^-T^+N^+$	1 (2%)

ATN = amyloid, tau, and neurodegeneration.
The biomarker level of $A\beta$ pathology was categorized as abnormal (A^+) if CSF $A\beta_{42}$ <175 pg/mL or $A\beta_{42/40}$ ratio <0.07; biomarker of tau pathology was categorized abnormal (T^+) if CSF p-tau was >80 pg/mL; and biomarker of neuronal degeneration or neuronal injury was categorized as abnormal (N^+) if CSF t-tau was >700 pg/mL.

were ATN biomarker-negative. Among the 13 (22%) who were ATN biomarker-positive, 10 (17%) had amyloid biomarkers (A^+ with T^+ and/or N^+), whereas 3 (5%) were amyloid negative (A^- with T^+ and/or

N^+). None of the participants had any known pre-existing dementia after review of baseline neuropsychological testing, IQCODE scores, and clinical adjudication.

3.3 | The relationship with delirium incidence and severity

Six of 59 (10%) had CAM-positive delirium following surgery. This delirium incidence is in line with other cohorts of elective orthopedic procedures[30,31] and probably relates to use of spinal anesthesia and/or improvements in post-operative delirium prevention. Individuals who were ATN biomarker-positive (any pattern), compared with those who were ATN biomarker-negative, experienced a higher rate of delirium, but this difference did not achieve statistical significance (23% vs 7%, P = 0.10). Delirium severity was significantly higher among ATN-positive individuals, with a mean difference (95% CI) in peak CAM-S points of 1.48 (0.29-2.67), P = 0.02 (Table 3).

We examined the distribution of peak CAM-S scores stratified by ATN biomarker-positive (ATN+) or biomarker-negative (ATN-) status and delirium presence (Del+) or absence (Del-) (Figure 1). There was a gradient in scores observed, such that those who were both ATN biomarker and delirium negative had the lowest mean (SD) peak CAM-S scores at 2.5 (1.3), whereas those who were both ATN and delirium positive had the highest peak mean (SD) CAM-S scores of

TABLE 3 Delirium severity by ATN biomarker status

Outcome	Total N = 59	Positive N = 13	Negative N = 46	Mean difference(95% CI)	P
Peak CAM-S, long form, mean (SD)	3.0 (2.0)	4.2 (2.9)	2.7 (1.6)	1.48 (0.29-2.67)	.02

ATN = amyloid, tau, and neurodegeneration; CAM-S = Confusion Assessment Method – Severity; SD = standard deviation.
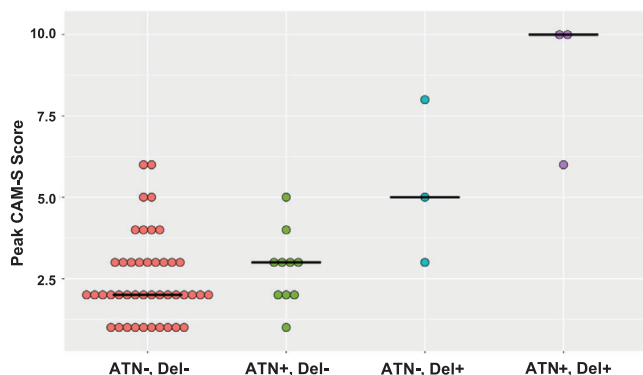

FIGURE 1 Plot of Peak CAM-S Scores by ATN biomarker-positive (ATN+) or biomarker-negative (ATN−) and delirium presence (Del+) or absence (Del−). Peak CAM-S, ranging from 0 to 19, with higher scores equaling greater delirium severity, is the highest single CAM-S rating across all hospital days for each patient. Note that a minimum of three features is required for CAM delirium; therefore peak CAM-S scores of 0 to 2 represent no (CAM-defined) delirium; some patients without delirium received scores ≥2 based on non-specific delirium features (eg, disorientation, memory impairment, psychomotor agitation), which can be present in conditions unrelated to delirium. Black line indicates median score. Red = ATN−, Del− (n = 43); Green = ATN−, Del+ (n = 10); Blue = ATN+, Del− (n = 3); Purple = ATN+, Del+ (n = 3). ATN = amyloid, tau, and neurodegeneration; CAM-S = Confusion Assessment Method–Severity

8.7 (2.3). Those who were positive for either delirium or ATN but not both had intermediate mean (SD) scores; specifically, ATN+ Del- had a peak CAM-S score of 2.8 (1.1), and ATN- Del+ had a peak CAM-S score of 5.3 (2.5). ANOVA demonstrated a P-value < 0.001, with significant differences by post hoc t-tests, correcting for multiple comparisons, between all four groups.

4 | DISCUSSION

In this study of relatively healthy older adults without cognitive impairment undergoing elective orthopedic surgery, the prevalence of both amyloid and non-amyloid biomarkers as evidenced by positive CSF ATN biomarker status was 22%. There was a trend toward higher rates of delirium in the ATN+ group, but this did not achieve statistical significance in this small sample. We found delirium severity to be associated with positive ATN biomarker status. Because the peak CAM-S score that we used for delirium severity may reflect sub-syndromal delirium, or non-specific symptoms, it is possible to find an association with delirium severity, but not delirium incidence, as seen here, but also

in our other work (ie,[32]). In the case of the ATN-positive population, where the mean (SD) CAM-S score was 2.8 (1.1), we would not expect a significant number of true delirium cases, but either subsyndromal delirium or nonspecific symptoms, including memory impairment, could be present and associated with the ATN-positive biomarker status. Patients who were positive for ATN biomarkers and developed delirium experienced a more severe delirium than patients who had delirium but were ATN biomarker-negative. The observed gradient effect suggests that when delirium occurs in individuals with any ATN biomarker, this increases delirium severity beyond the level of either delirium or ATN biomarkers alone.

We have previously hypothesized that delirium is triggered in the setting of an underlying brain vulnerability, such as dementia or even preclinical AD.[33] It is not yet known whether preclinical dementia is a more pronounced risk factor for delirium than those previously described, or if there are other novel "vulnerability" factors that might predispose toward the development of delirium. In our prior work, when we examined the cortical thickness in "AD signature" brain region by MRI, we also saw no association with delirium incidence, but the AD signature was associated with greater delirium severity among those who developed delirium.[32] As with the present study, these results suggest that perhaps underlying neurodegeneration due to preclinical AD may serve as a vulnerability factor that increases severity once delirium occurs. In prior work in RISE, we examined [^{11}C]PBR28 positron emission tomography (PET) as a measure of neuroinflammation, but we unexpectedly found that PBR28 binding in the brain was globally downregulated at 1 month following major orthopedic surgery, suggesting a paradoxical downregulation of the isotope binding in the brain. No significant relationship was identified between post-operative delirium and [^{11}C]PBR28 binding, possibly related to the small number (n = 6) of delirium cases in the sample.[34]

Prior studies have found a significant association between reduced CSF Aβ_{42} and increased t-tau with delirium status in adjusted analyses among patients without dementia, supporting the notion that preclinical AD brain pathology may play a role in delirium pathophysiology.[9] A recent study of older hip fracture patients found a higher than expected prevalence of positive ATN biomarkers (89% of patients who had no cognitive impairment), suggesting that a large proportion of individuals with hip fracture may have preclinical or prodromal AD; furthermore, the investigators hypothesized that postoperative delirium may also be due to brain vulnerability reflected by underlying AD pathology as well.[35]

The strengths of our study include detailed clinical characterization of the cohort, along with rigorous assessment of delirium status. We used the ATN framework that follows the recommended descriptive classification scheme for AD biomarkers. Finally, although

biomarker-based prevalence estimates of preclinical AD have not yet been established, a recent meta-analysis of longitudinal cohort studies identified a prevalence of 22%[36] similar to what we observed in our cohort. However, a few limitations should be noted. The data suggest that having positive ATN biomarker status increases the risk for delirium following surgery, although this did not achieve statistical significance. The design of the RISE study intended to use ATN biomarker status as an important stratification variable, but given the expense and complexity of the study, we were likely inadequately powered to examine statistical differences,[12] and larger patient cohorts are needed to confirm the findings reported here. With a larger sample, we would also be able to examine the effects of amyloid (A^+TN) versus nonamyloid biomarker status ($A^-T^+N^+$, $A^-T^-N^+$, or $A^-T^+N^-$), as well as to examine the relationship of delirium and ATN biomarker status with clinical outcomes, such as long-term cognitive decline and other post-surgical outcomes. Our ATN schema was defined based on CSF biomarkers only, since it was not feasible to include a neuroimaging marker within the design of the study. Confirmation of our approach with imaging measures will be an important area for future research. Finally, although the cut offs for abnormal biomarkers were rigorously established on population-based samples in our reference lab for this study, we cannot exclude the possibility that the prevalence of abnormal biomarkers may vary over different populations and individuals possessing biomarker values close to the cut points.

5 | CONCLUSION

In summary, we found that individuals without dementia but with biomarkers based on an ATN paradigm experienced non-significantly higher rates of delirium after total joint replacement surgery, with significantly greater delirium severity. If confirmed with additional studies, these findings would provide supporting evidence that preclinical dementia may contribute to delirium pathophysiology.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest

REFERENCES

1. Gleason L, Schmitt EM, Kosar CM, et al. Effect of delirium and other major complications on outcomes after elective surgery in older adults. *JAMA Surg.* 2015;150:1134-1140.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383:911-922.
3. Marcantonio ER. Delirium in hospitalized older adults. *N Engl J Med.* 2017;377:1456-1466.
4. Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *J Am Geriatr Soc.* 2002;50:1723-1732.
5. Fong TG, Jones RN, Marcantonio ER, et al. Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease. *Ann Intern Med.* 2012;156:848-856, W296.
6. Hshieh TT, Inouye SK, Oh ES. Delirium in the Elderly. *Clin Geriatr Med.* 2020;36:183-199.
7. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol.* 2016;15:673-684.
8. Xie Z, Swain CA, Ward SA, et al. Preoperative cerebrospinal fluid beta-Amyloid/Tau ratio and postoperative delirium. *Ann Clin Transl Neurol.* 2014;1:319-328.
9. Idland AV, Wyller TB, Stoen R, et al. Preclinical amyloid-beta and axonal degeneration pathology in delirium. *J Alzheimers Dis.* 2017;55:371-379.
10. Witlox J, Kalisvaart KJ, de Jonghe JF, et al. Cerebrospinal fluid β-amyloid and tau are not associated with risk of delirium: a prospective cohort study in older adults with hip fracture. *J Am Geriatr Soc.* 2011;59:1260-1267.
11. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14:535-562.
12. Hshieh TT, Vasunilashorn SM, D'Aquila ML, et al. The Role of Inflammation after Surgery for Elders (RISE) study: study design, procedures, and cohort profile. *Alzheimers Dement (Amst).* 2019;11:752-762.
13. Bruce AJ, Ritchie CW, Blizard R, Lai R, Raven P. The incidence of delirium associated with orthopedic surgery: a meta-analytic review. *International Psychogeriatrics.* 2007;19:197-214.
14. Jones RN, Rudolph JL, Inouye SK, et al. Development of a unidimensional composite measure of neuropsychological functioning in older cardiac surgery patients with good measurement precision. *J Clin Exp Neuropsychol.* 2010;32:1041-1049.
15. Langa KM, Plassman BL, Wallace RB, et al. The Aging, Demographics, and Memory Study: study design and methods. *Neuroepidemiology.* 2005;25:181-191.
16. Gross AL, Jones RN, Fong TG, Tommet D, Inouye SK. Calibration and validation of an innovative approach for estimating general cognitive performance. *Neuroepidemiology.* 2014;42:144-153.
17. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of adl: a standardized measure of biological and psychosocial function. *JAMA.* 1963;185:914-919.
18. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969;9:179-186.
19. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996;34:220-233.
20. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res.* 1982;17:37-49.
21. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. *Psychol Med.* 1989;19:1015-1022.
22. Steis MR, Evans L, Hirschman KB, et al. Screening for delirium using family caregivers: convergent validity of the Family Confusion

Assessment Method and interviewer-rated Confusion Assessment Method. *J Am Geriatr Soc*. 2012;60:2121-2126.

23. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113:941-948.

24. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. *J Am Geriatr Soc*. 2008;56:823-830.

25. Inouye SK, Kosar CM, Tommet D, et al. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. *Ann Intern Med*. 2014;160:526-533.

26. Vasunilashorn SM, Fong TG, Albuquerque A, et al. Delirium severity post-surgery and its relationship with long-term cognitive decline in a cohort of patients without dementia. *J Alzheimers Dis*. 2018;61:347-358.

27. Albert MS, Levkoff SE, Reilly C, et al. The delirium symptom interview: an interview for the detection of delirium symptoms in hospitalized patients. *J Geriatr Psychiatry Neurol*. 1992;5:14-21.

28. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *Journal of Biomedical Informatics*. 2019;95:103208.

29. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009;42:377-381.

30. Oh ES, Leoutsakos JM, Rosenberg PB, et al. Effects of ramelteon on the prevention of postoperative delirium in older patients undergoing orthopedic surgery: the RECOVER randomized controlled trial. *Am J Geriatr Psychiatry*. 2021;29(1):90-100.

31. Song K-J, Ko J-H, Kwon T-Y, Choi B-W. Etiology and related factors of postoperative delirium in orthopedic surgery. *Clin Orthop Surg*. 2019;11:297-301.

32. Racine AM, Fong TG, Travison TG, et al. Alzheimer's-related cortical atrophy is associated with postoperative delirium severity in persons without dementia. *Neurobiol Aging*. 2017;59:55-63.

33. Fong TG, Vasunilashorn SM, Libermann T, Marcantonio ER, Inouye SK. Delirium and Alzheimer disease: A proposed model for shared pathophysiology. *Int J Geriatr Psychiatry*. 2019;34(6):781-789.

34. Katsumi Y, Racine AM, Torrado-Carvajal A, et al. The Role of Inflammation after Surgery for Elders (RISE) study: examination of [(11)C]PBR28 binding and exploration of its link to post-operative delirium. *Neuroimage Clin*. 2020;27:102346.

35. Oh ES, Blennow K, Bigelow GE, et al. Abnormal CSF amyloid-beta42 and tau levels in hip fracture patients without dementia. *PloS one*. 2018;13:e0204695.

36. Parnetti L, Chipi E, Salvadori N, D'Andrea K, Eusebi P. Prevalence and risk of progression of preclinical Alzheimer's disease stages: a systematic review and meta-analysis. *Alzheimers Res Ther*. 2019; 11:7.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.