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Preoperative Plasma Tau-PT217 and Tau-PT181 Are Associated with Postoperative Delirium

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Abstract

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Justification of authorship

All authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; participated in drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be published. The following is the contribution of each author.

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Study supervision: Zhongcong Xie.

Objective: Identifying blood biomarker of postoperative delirium.

Summary Background Data: Phosphorylated Tau at threonine 217 (Tau-PT217) and 181 (Tau-PT181) are new Alzheimer's disease biomarkers. Postoperative delirium is associated with Alzheimer's disease. We assessed associations between Tau-PT217 or Tau-PT181 and postoperative delirium.

Methods: Of 491 patients (65 years old or older) who had a knee replacement, hip replacement, or laminectomy, 139 participants were eligible and included in the analysis. Presence and severity of postoperative delirium were assessed in the patients. Preoperative plasma concentrations of Tau-PT217 and Tau-PT181 were determined by a newly established Nanoneedle technology.

Results: Of 139 participants (73±6 years old, 55% female), 18 (13%) developed postoperative delirium. Participants who developed postoperative delirium had higher preoperative plasma concentrations of Tau-PT217 and Tau-PT181 than participants who did not. Preoperative plasma concentrations of Tau-PT217 or Tau-PT181 were independently associated with postoperative delirium after adjusting for age, education, and preoperative Mini-Mental State score (Odds ratio [OR] per unit change in the biomarker: 2.05, 95% CI:1.61–2.62, P<0.001 for Tau-PT217; and OR: 4.12; 95% CI:2.55–6.67, P<0.001 for Tau-PT181). The areas under the receiver operating curve (AUC) for predicting delirium were 0.969 (Tau-PT217) and 0.885 (Tau-PT181). The preoperative plasma concentrations of Tau-PT217 or Tau-PT181 were also associated with delirium severity (Beta Coefficient [β] per unit change in the biomarker: 0.14;95% CI: 0.09–0.19, P<0.001 for Tau-PT217; and β:0.41; 95% CI:0.12–0.70, P=0.006 for Tau-PT181).

Conclusions: Preoperative plasma concentrations of Tau-PT217 and Tau-PT181 were associated with postoperative delirium, with Tau-PT217 being a stronger indicator of postoperative delirium than Tau-PT181.

Keywords

Alzheimer's disease; postoperative delirium; Tau-PT217; Tau-PT181; Nanoneedle technology

INTRODUCTION

Postoperative delirium, one of the most common postoperative complications in older patients [1], is associated with nosocomial complications [2], extended hospital stays [3], a higher chance of institutional discharge [4, 5], and increased morbidity [5–8] and mortality [9, 10]. The annual health care costs in the United States attributable to postoperative delirium are $32.9 billion [11].

Population studies have demonstrated a strong bidirectional association between Alzheimer's disease (AD), AD Related Dementias (ADRD), and delirium [12]. Specifically, patients with underlying ADRD are 2.5 to 4.7 times more likely to develop delirium, and patients with delirium face a 12.5-fold increased incidence of newly diagnosed ADRD [4, 13–15]. The underlying pathogenic basis of this association, however, remains unclear.

Previous studies have shown that a higher preoperative cerebrospinal fluid (CSF) Tau/β-amyloid ratio was associated with higher incidence and greater severity of postoperative delirium [16]. These results suggest the potential association of AD neuropathogenesis

with postoperative delirium. However, in our prior work, we only measured Tau, not phosphorylated Tau, in CSF and not in plasma. Given the challenges of obtaining CSF in older surgical patients and that plasma biomarkers are efficient with low cost to perform delirium clinical research, we now examine newly emerging blood-based biomarkers of AD and their associations with delirium.

Tauopathy is one of the hallmarks of AD neuropathogenesis [17, 18]. Tau phosphorylation at threonine 217 (Tau-PT217) and 181 (Tau-PT181) are newly identified AD plasma biomarkers [19–27]. Specifically, a recent clinical investigation has shown that plasma Tau-PT181 can differentiate AD from other neurodegenerative disorders [23]. Plasma Tau-PT217 levels increase during the early preclinical state of AD patients when insoluble Tau aggregates are not yet detectable by Tau-positron emission tomography [26].

Plasma concentrations of interleukin 6 [28], c-reactive protein [29], neurofilament light [30], chitinase-3-like protein 1 [31], and metabolites [32] have been shown to associate with postoperative delirium. Moreover, a recent study showed that the changes between the preoperative plasma Tau concentration and the postoperative day 1 plasma Tau concentration were greater in patients who developed postoperative delirium and were associated with delirium severity. Plasma Tau concentrations also predicted the recovery from postoperative delirium [33]. However, the association between preoperative plasma concentrations of Tau-PT217 or Tau-PT181 and postoperative delirium has not been determined.

Therefore, the objective of the present prospective observational cohort study was to determine the association between Tau-PT217 or Tau-PT181 and the presence or severity of postoperative delirium in patients who had surgery under general or spinal anesthesia. We hypothesized that elevated preoperative plasma concentrations of Tau-PT217 and Tau-PT181 would be associated with an increased presence and severity of postoperative delirium in patients.

METHODS

Study Enrollment.

This prospective observational cohort study was performed at Massachusetts General Hospital, Boston, MA, between 2016 and 2020. The Mass General Brigham Institutional Review Board approved the study protocol. Patients were included if they were scheduled to have an elective knee replacement, hip replacement, or laminectomy under general or spinal anesthesia at the study hospital, were 65 years or older, and were proficient in English.

Subjects were excluded from participation if they had any of the following: (1) past medical history of neurological and psychiatric diseases including AD, other forms of dementia, stroke, or psychosis; (2) severe visual or hearing impairment; (3) were current smokers; or (4) taking antibiotics within one week of the day of surgery because disturbance of gut microbiota may affect brain function. Eligible patients were approached for participation by clinical research coordinators during preoperative clinic visits. Written informed consent was obtained at the time of enrollment, prior to initiation of the study procedures. There have been no significant changes in the surgery or anesthesia practice since the start of

the study. The manuscript was written according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria.

Anesthesia, Surgery, and Plasma Sample Collection.

All participants received standardized perioperative care, including standard postoperative pain management (e.g., patient-controlled analgesia [PCA] with hydromorphone). Depth of sedation was at the discretion of the treating provider but was not captured in the current study.

Sample Preparation.

Five ml of blood was collected from the participants before the anesthesia and surgery when the intravenous catheter was inserted. Blood samples were centrifuged at 500 g for 10 minutes, and plasma supernatant was collected. The plasma was collected in an EDTA tube and was immediately placed on ice. The plasma was then stored in a −80 °C degree freezer until the time of measurement when the samples were thawed. All of the measures in the current study were performed using the same methods with double-blind design.

Exposures - Measurement of Tau-PT217 and Tau-PT181 in Plasma by Nanoneedle.

The primary exposures of interest were the measurements of Tau-PT217 and Tau-PT181 from preoperative blood samples. The measurement of the phosphorylated Tau was performed blinded to postoperative delirium status to avoid bias. As Tau-PT217 and Tau-PT181 present at an ultra-low abundance level not detectable with traditional western blot or enzyme-linked immunosorbent assays (ELISA) in blood, we developed in-house phosphorylated Tau assays using the Nanoneedle technology to measure preoperative plasma concentrations of Tau-PT217 and Tau-PT181 (Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/SLA/D851). The Nanoneedle technology is described in more detail in the Supplemental Information, Supplemental Digital Content 1, http://links.lww.com/SLA/D851. The protein levels are reported in relative units specific to the Nanoneedle technology (i.e., relative concentration with arbitrary unit) since Tau-PT217 or Tau-PT181 recombinant protein standards are not available at present. Therefore, the term plasma concentration used throughout the manuscript refers to relative concentration but not absolute concentration of Tau-PT217 or Tau-PT181 in the plasma of participants. All samples from the participants were randomly assigned to different Nanoneedle batches during the measurement of Tau-PT217 or Tau-PT181. The assays of Tau-PT217 and Tau-PT181 were performed in triplicate with 5 ul in each well of the batch. The average intra-assay coefficient of variations (CV) of plasma Tau-PT217 and Tau-PT181 in the postoperative delirium group were 39.9% and 21.0%, respectively. But the difference among the values of plasma Tau-PT217 and Tau-PT181 obtained in the three measurements was not significant.

All measurement results were above the lower limit of detection of the Nanoneedle assay. Assay specificity was validated with dot blot measurement of the phospho-specific antibodies against an array of synthesized peptides phosphorylated at different residues along the full-length Tau protein (Supplemental Figure 2, Supplemental Digital Content 1, http://links.lww.com/SLA/D851). Accuracy of the Nanoneedle method was validated by

comparing measurements of Tau-PT217 and Tau-PT181 in cell culture samples using gold standard ELISA method (Supplemental Figure 3, Supplemental Digital Content 1, http://links.lww.com/SLA/D851).

Outcomes.

Trained clinical research coordinators interviewed participants on postoperative day 1 and/or 2. Confusion Assessment Measurement (CAM) is a diagnostic algorithm used to determine the presence or absence of delirium, which has high reliability [34, 35]. One hundred of the 139 participants had the CAM on both days, and 3 of the 18 participants with postoperative delirium and 36 of the 121 participants without postoperative delirium had the CAM on one day. Delirium was assessed using the CAM once per day between 8:00 am and 12:00 noon. The primary outcome was the presence of postoperative delirium defined based on CAM performance on either postoperative day 1 or postoperative day 2.

The secondary outcome was the severity of postoperative delirium, represented by the Memorial Delirium Assessment Scale (MDAS) [35, 36], which quantifies symptoms related to delirium based on 10 features. Each feature is scored from 0 (best) to 3 (worst symptom) with a maximal score of 30. MDAS scores were evaluated for all patients, regardless of whether they met CAM criteria for delirium on that day. In the present study, the diagnosis of delirium presence was based on the results from CAM. The MDAS score was used to assess the severity of delirium independent of the results obtained from CAM. Postoperative MMSE was performed as part of CAM [34, 37] and also for MDAS calculation on postoperative day 1 and/or day 2 [37].

Statistical Power Calculation.

We calculated, based on estimates from our previous study [16], and performed in the design phase of the study, that a sample size of 130 participants would be sufficient to determine a Pearson correlation > 0.20 between plasma Tau concentrations and MDAS delirium severity scores, assuming a two-sided hypothesis test with 80% power and 5% type I error.

Statistical Analysis.

Descriptive statistics were conducted using methods appropriate for the variables under study. Means and standard deviations were used for continuously scaled variables that were normally distributed. Medians and 25^{th} and 75^{th} percentiles were used for skewed or ordinal data. Frequency counts and percentages or proportions were used for categorical variables. Differences in baseline characteristics between those who did and did not develop delirium were assessed with a t-test, Mann Whitney U-test (for non-normal continuous data), chi-square or Fisher's exact test (in the case of small cell counts), as appropriate. Because each plasma sample was measured in triplicate, generalized estimating equations were used to model variability across measurements. For this model, the subject was the clustering variable. The delirium outcome was specified as a binomial variable with a logit link. An independent covariance structure was assumed. Estimation was conducted using a robust (i.e., sandwich) estimation approach. Results are presented as odds ratio (OR) per one unit change in the biomarker and their associated 95% confidence intervals (CI). Youden's Index was utilized in order to evaluate the biomarker cutoff that best predicted the presence of

delirium. Results are presented as the area under the receiver operating characteristic curve (AUC) for that Tau-PT217 and Tau-PT181 cutoff, sensitivity, and specificity. The AUC was calculated by computing the numeric value of the area under the ROC curve using the trapezoidal rule to assess the probability that the model would score a randomly drawn positive sample higher than a randomly drawn negative sample. The association between the biomarkers and delirium severity was estimated using a similar approach to delirium presence but with a Gaussian distribution and identity link. Results are presented as the beta coefficient (β) per unit change in Tau-PT217 or Tau-PT181 value and its associated 95% CI. Models were created to adjust the associations between the biomarkers and outcomes for age, education, and preoperative MMSE for both the primary and secondary outcomes. Variables for adjustment were based on previous studies as deemed clinically relevant. The assumptions for each model were considered by examining the residuals and calibration curves to ensure the models adequately fit the data. All analyses were conducted using R4.0.5 statistical software (Vienna, Austria). Where appropriate, all analyses use two-tailed hypothesis testing, with statistical significance interpreted at $p < 0.05$.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

RESULTS

A total of 491 patients were screened, of which 220 participants were enrolled between November 2016 and February 2020. Eighty-one participants were excluded due to becoming ineligible after enrollment (N = 3), no longer expressing interest in participating (N = 22), having no plasma samples collected (N = 51, surgery being canceled or rescheduled to conflicting date, plasma collection complications), or having no assessment of postoperative delirium on any of two days owing to participants being discharged the same day of surgery or not feeling well enough to complete testing (N = 5). Thus, 139 participants were included in the final data analysis (Figure 1). There were no significant complications among participants during the immediate postoperative period.

The baseline demographic and clinical characteristics of the 139 participants are presented in Table 1. There were no significant differences in age, gender, ethnicity, surgery type, anesthesia type, or preoperative Mini-Mental State Examination (MMSE) score between the participants with postoperative delirium (N = 18) and those without postoperative delirium (N = 121). The participants who developed postoperative delirium had less education years and lower postoperative MMSE score than the participants who did not develop postoperative delirium.

Each of the plasma samples was randomly assigned to different batches of the Nanoneedle measurement for Tau-PT217 and Tau-PT181. The measurement was performed in triplicate by using Nanoneedle technology (Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/SLA/D851). Before the measurement, specificity of antibody used in the assay was tested using peptide array (Supplemental Figure 2, Supplemental Digital Content 1, http://links.lww.com/SLA/D851) and accuracy of the Nanoneedle technology was validated against the gold standard ELISA method (Supplemental Figure 3, Supplemental

Digital Content 1, http://links.lww.com/SLA/D851). In the present study, there was no significant difference among the values of plasma Tau-PT217 (F = 0.530, P = 0.589, one-way analysis of variance [ANOVA]) and Tau-PT181 (F = 0.022, P = 0.978, one-way ANOVA) obtained in the three different measurements.

The participants who developed postoperative delirium had higher preoperative plasma concentrations of Tau-PT217 (11.77 + 4.97 arbitrary unit [a.u.] versus 1.97 + 1.08 a.u., P < 0.001) and Tau-PT181 (2.25 + 0.61 a.u. versus 1.06 + 0.63 a.u., P < 0.001) than participants who did not develop the postoperative delirium (Table 1 and Figure 2).

Preoperative plasma concentrations of Tau-PT217 and Tau-PT181 were associated with postoperative delirium.

Results of the unadjusted analyses and multivariable models are presented in Table 2. After adjustment for age, education, and preoperative MMSE, the preoperative plasma concentrations of Tau-PT217 (OR 2.05, 95% CI: 1.61 – 2.62, P < 0.001) and Tau-PT181 (OR 4.12, 95% CI: 2.55 – 6.67, P < 0.001) were associated with postoperative delirium in separate models. Preoperative plasma concentrations of Tau-PT217 and Tau-PT181 had high sensitivity (0.956 and 0.882) and variable specificity (0.864 and 0.400) for predicting postoperative delirium (Figure 3). The AUC for Tau-PT217 and Tau-PT181 were 0.969 and 0.885, respectively (Figure 3).

Preoperative plasma concentrations of Tau-PT217 and Tau-PT181 were associated with the severity of postoperative delirium.

In the crude models, increased preoperative plasma concentrations of Tau-PT217 or Tau-PT181 were associated with an increase in postoperative delirium severity. This association persisted after adjustment for age, education, and preoperative MMSE (β coefficient: 0.14, 95% CI: 0.09 – 0.19, P < 0.001 for Tau-PT217 and 0.41, 95% CI: 0.12 – 0.70, P = 0.006 for Tau-PT181; Table 2).

DISCUSSION

This prospective observational cohort study revealed that patients with higher preoperative plasma concentrations of Tau-PT217 or Tau-PT181 were more likely to experience delirium and also had higher postoperative delirium severity. These data suggest that Tau phosphorylation, part of the AD neuropathogenesis, contributes, at least partially, to the development of postoperative delirium and that Tau-based plasma proteins can serve as risk biomarkers of postoperative delirium in patients.

Increasing evidence suggests that plasma Tau-PT217 and Tau-PT181 are newly identified AD plasma biomarkers [19–27, 38]. Previous research shows that plasma Tau-PT181 concentrations can distinguish amyloid β-positive MCI and AD patients (highest levels), Aβ-positive cognitively unimpaired older adults and MCI patients (intermediate levels), and Aβ-negative young adults and cognitively unimpaired older adults (lowest levels) [23]. Moreover, plasma Tau-PT181 concentration distinguishes AD dementia from frontotemporal dementia, vascular dementia, progressive supranuclear palsy, corticobasal syndrome, Parkinson's disease, or multiple systems atrophy [23]. Additional research suggests that

changes in plasma levels of Tau-PT217 were associated with the changes in CSF levels of Tau-PT217 [24] and the development of AD [25, 27].

In the present study, we found both Tau-PT217 and Tau-PT181 were associated with the presence and severity (Table 2) of postoperative delirium. The findings indicate that patients with underlying AD neuropathogenesis are more likely to develop delirium, consistent with findings from the previous studies [4, 13–15, 33]. Moreover, it is important to perform better preoperative brain health assessments in patients. Future studies should investigate the role of Tau hyperphosphorylation in postoperative delirium in both clinical and pre-clinical settings.

In the adjusted models, plasma Tau-PT217 (AUC 0.969) had an increased ability to discriminate delirious patients from non-delirious patients in comparison to Tau-PT181 (AUC 0.885; Figure 3). These results were consistent with the previous findings that plasma Tau-PT217 has significantly higher accuracy than plasma Tau-PT181 in differentiating the neuropathologically defined AD from non-AD, clinical AD dementia versus other neurodegenerative diseases or among the PSEN1 mutation carriers versus PSEN1 mutation noncarriers [25, 27].

Previous studies have demonstrated that the increase in plasma concentrations of Tau-PT217 occurs earlier than changes in positron emission tomography signal of Tau in cortex [26]. Thus, the findings from present study specifically suggest that there is an association between pre-clinical AD neuropathogenesis (e.g., elevation in plasma Tau-PT217) and the development of postoperative delirium. Future research should evaluate whether the development of postoperative delirium could be a clinical manifestation of preclinical AD. This will take on increasing importance as effective treatments for AD become available, particularly if they need to be started in the pre-clinical phase to be most effective.

Plasma Tau-PT217 and Tau-PT181 are associated with the development of AD and long-term cognitive impairment [19–27]. But whether plasma Tau-PT217 and Tau-PT181 can also serve as predictors of postoperative delirium remains unknown. Therefore, the present study focused on assessing whether preoperative plasma Tau-PT217 and Tau-PT181 are associated with postoperative delirium. In future studies, we will use the established system to determine whether both preoperative and postoperative plasma Tau-PT217 and Tau-PT181 are associated with the development of other types of perioperative neurocognitive disorders, including delayed neurocognitive recovery and postoperative neurocognitive disorder.

The average of MDAS score of the participants in the present study was 6.6 (Table 1). Breitbart et al. stated that MDAS Scores ≥ 13 indicate the presence of delirium [36]. However, the participants in the study by Breitbart et al. included psychiatry consult patients [36]. On the other hand, Marcantonio et al. showed that the best MDAS cutoff for postoperative delirium was 5 in the participants with surgery for hip fracture repair [35]. Therefore, an average MDAS score of 6.6 in present study is plausible though on the very mild side.

A strength of the present study includes the application of the novel Nanoneedle technology to detect phosphorylated Tau in blood samples (Figure 2 and Supplemental Figure 1, 2 and 3, Supplemental Digital Content 1, http://links.lww.com/SLA/D851). The Nanoneedle

sensors have critical dimensions smaller than 100 nm, i.e., 50–500 times smaller than the bead-based detecting platforms. Each nanoneedle is a single molecule biosensor, functionalized with capture antibodies, allowing precise quantitation of analytes by digitally counting the number of nanoneedles with a positive signal. Compared to existing methods, nanoneedles require less sample volume (2–5 μl), have better sensitivity and lower per assay cost due to their scalable fabrication process.

Limitations of the present study included that we used arbitrary units instead of the actual concentrations of Tau-PT217 and Tau-PT181. This is because we did not have the recombinant protein of Tau-PT217 or Tau-PT181 at present to build the concentration curve. However, the use of arbitrary units, which enable measuring the relative plasma concentrations of Tau-PT217 and Tau-PT181, still well demonstrated the association between plasma concentrations of these proteins with the presence and severity of postoperative delirium. Second, our sample size was small, relatively lacking in diversity, and we recruited from only one large hospital. Future studies should confirm our findings in larger, more diverse samples. Third, we did not determine the association between plasma biomarkers and preoperative and/or postoperative cognitive impairment in the present study because we only focused on the identification the plasma Tau-PT217 and Tau-PT181 as a predictor of postoperative delirium. In the future, we will use the established Nanoneedle technology to identify plasma biomarkers of preoperative and postoperative cognitive disorders. In addition, we did not perform preoperative CAM assessments since these participants had elective cases and the rate of preoperative delirium would be very low based on the findings from previous studies by Mei et al. (0 of 606 participants) [39] and Shi et al. (3 of 192 participants) [40]. However, given that we did not assess for preoperative delirium, we use the term “postoperative delirium” or “presence of postoperative delirium” for the primary outcome of the current study rather than “incidence of delirium”. Finally, the average CVs in the triplicate measurements of plasma Tau-PT217 and Tau-PT181 (39.9% and 21.0%, respectively) were larger than the average CVs in our validation experiment with cell culture samples (19.6% and 16.6%, respectively). This is likely due to the complex plasma matrices and small sample volumes (5 ul) used in our plasma Tau-PT217 and Tau-PT181 measurements. However, there was no significant difference among the values of plasma Tau-PT217 and Tau-181 obtained in different measurements. Future efforts include developing calibrators to quantify both proteins in absolute concentrations (e.g., pg/ml), as well as further optimizing the assay conditions to achieve lower CVs.

In conclusion, we demonstrated that patients who developed postoperative delirium had higher preoperative plasma concentrations of Tau-PT217 or Tau-PT181 than those who did not develop postoperative delirium. Preoperative plasma concentration of Tau-PT217 or Tau-PT181 predicted the presence and severity of postoperative delirium, with Tau-PT217 being the most strongly associated with these outcomes. These results will promote more research to confirm these associations and to further understand the mechanisms underlying the interaction of delirium and ADRD, ultimately leading to better interventions for both delirium and ADRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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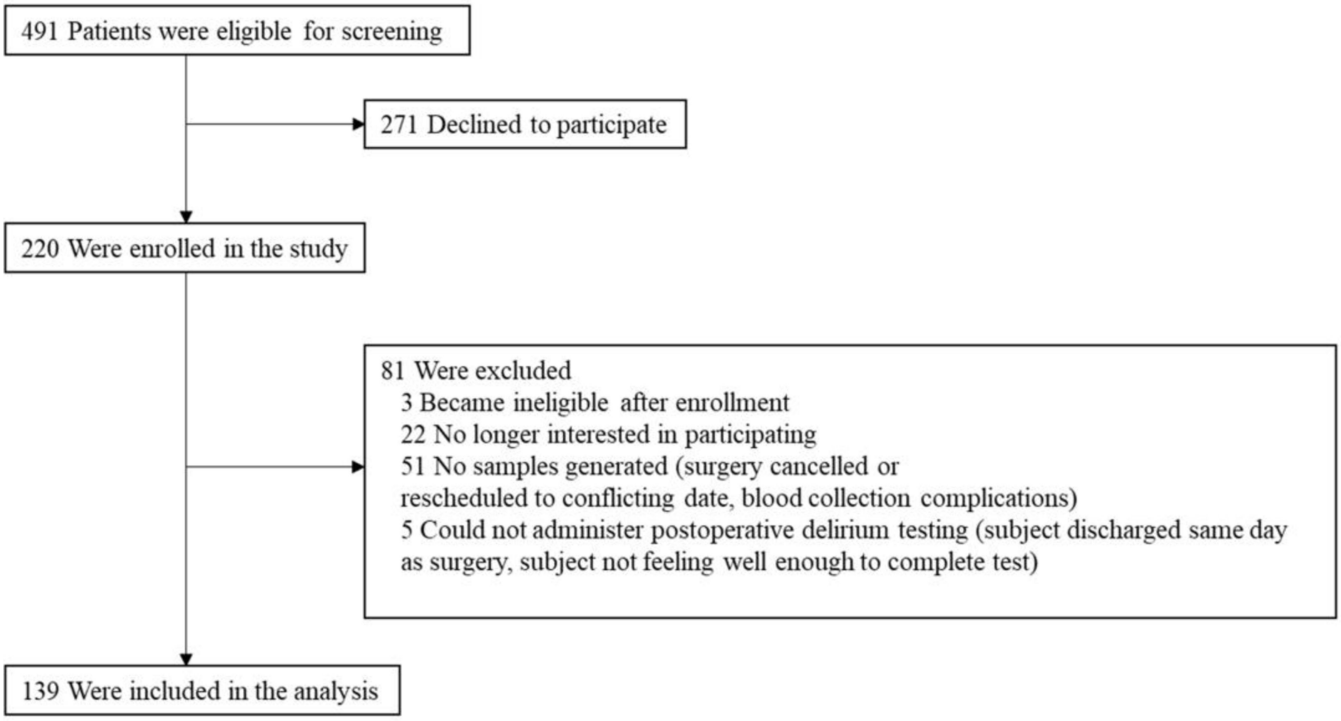

Figure 1. Flow diagram.

The flow diagram shows that 491 participants were screened for the studies, and 220 were initially enrolled. Eighty-one participants were excluded, resulting in 139 participants for the final data analysis.

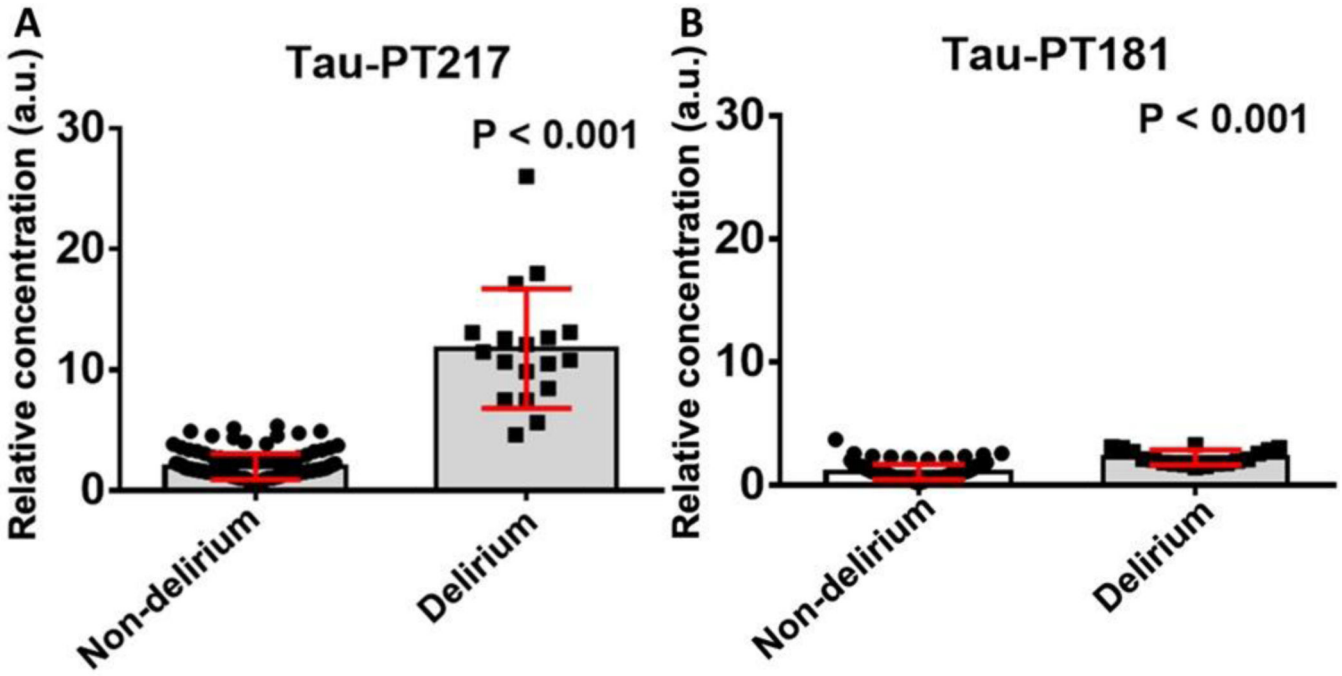

Figure 2: Different preoperative plasma concentrations of Tau-PT217 and Tau-PT181 between the participants with postoperative delirium and those without postoperative delirium.

Participants who developed postoperative delirium (N = 18) had higher preoperative plasma concentrations of Tau-PT217 (**A**) and Tau-PT181 (**B**) than the participants who did not develop postoperative delirium (N = 121). The student's t-test was used to analyze the data presented in Figures 2A and 2B. The P values refer to the differences in the preoperative plasma concentrations of Tau-PT217 or Tau-PT181 between the participants with postoperative delirium and the participants without postoperative delirium. Error bar indicates standard deviation. Tau-PT217, Tau phosphorylation at threonine 217; Tau-PT181, Tau phosphorylation at threonine 181; a.u., arbitrary unit.

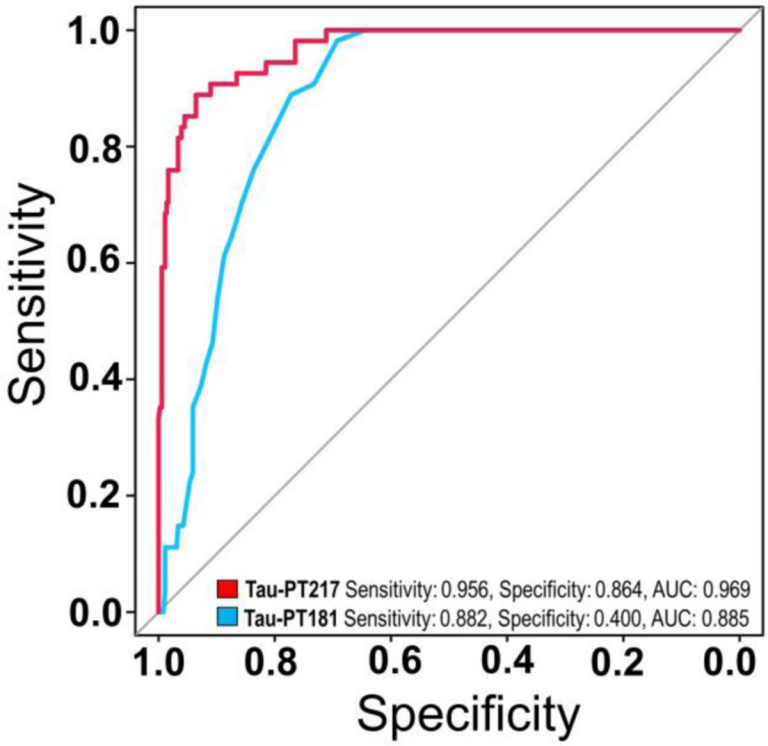

Figure 3. The sensitivity, specificity, and AUC (Area Under The Curve) ROC (Receiver Operating Characteristics) curve of preoperative plasma concentration of Tau-PT217 and Tau-PT181 in predicting postoperative delirium.

Tau-PT217 reported a higher discriminatory ability than Tau-PT181. This can be observed in the AUC, or area under the ROC curve.

Table 1.

Demographic characteristics and plasma concentrations of phosphorylated tau in the participants

	Total N = 139	**Delirium, N = 18**	**No Delirium, N = 121**	**P-values**
Age, mean + SD	73 + 6	73 + 5	73 + 6	0.828
Female, n (%)	76 (55)	9 (50)	67 (55)	0.561
Non-white or Hispanic, n (%)	8 (6)	2 (11)	6 (5)	0.277
Educational attainment, years, mean + SD	16.36 + 2.39	15.5 + 1.51	16.29 + 2.91	0.024
Surgery type, n (%)				0.907
Knee replacement	96 (69)	13 (72)	83 (69)	
Hip replacement	33 (24)	3 17)	30 (25)	
Spinal stenosis	10 (7)	2 (11)	8 (7)	
Anesthesia type, n (%)				0.800
General	62 (45)	7 (39)	55 (45)	
Spinal	77 (55)	11 (61)	66 (55)	
MMSE, mean + SD				
Pre-anesthesia/surgery score	29.11 + 1.03	28.94 + 1.11	29.13 + 1.02	0.223
Post-anesthesia/surgery score	28.76 + 1.42	27.56 + 2.00	28.94 + 1.23	0.001
Peak score of MDAS, mean + SD	2.96 + 2.20	6.61 + 2.03	2.41 + 1.64	< 0.001
Tau-PT217 (arbitrary unit)	3.23 ± 4.32	11.77 + 4.97	1.97 + 1.08	< 0.001
Tau-PT181 (arbitrary unit)	1.20 ± 0.89	2.25 + 0.61	1.06 + 0.63	< 0.001

MDAS (Memorial Delirium Assessment Scale); MMSE, mini-mental status examination; S.D., standard deviation; Tau-PT217, Tau phosphorylation at threonine 217; Tau-PT181, Tau phosphorylation at threonine 181.

Table 2.

Tau-PT217 and Tau-PT181 were significant predictors of postoperative delirium presence and severity [*]

	Presence of Postoperative Delirium [**]			
	Unadjusted		***Adjusted for Age, Education, and Preoperative MMSE***	
	Odds Ratio (95% CI)	**P-Value**	**Odds Ratio (95% CI)**	**P-Value**
Tau-PT217	1.93 (1.59, 2.35)	<0.001	2.05 (1.61, 2.62)	<0.001
Tau-PT181	3.65 (2.25, 5.92)	<0.001	4.12 (2.55, 6.67)	<0.001
The Severity of Postoperative Delirium [***]				
	Unadjusted		***Adjusted for Age, Education, and Preoperative MMSE***	
	β Coefficient (95% CI)	**P-Value**	**β Coefficient (95% CI)**	**P-Value**
Tau-PT217	0.14 (0.09, 0.19)	<0.001	0.14 (0.09, 0.19)	<0.001
Tau-PT181	0.39 (0.10, 0.68)	0.009	0.41 (0.12, 0.70)	0.006

Tau-PT217, Tau phosphorylation at threonine 217; Tau-PT181, Tau phosphorylation at threonine 181; CI, confidence interval.

[*] Models were created to adjust the associations between the biomarkers and outcomes for age, education, and preoperative MMSE based on previous studies as deemed clinically relevant.

[**] Results are presented as odds ratio (OR) per one unit change in Tau-PT217 or Tau-PT181 value and its associated 95% confidence intervals (CI) with the null hypothesis of 1.

[***] Results are presented as the beta coefficient (β) per one unit change in Tau-PT217 or Tau-PT181 value and its associated 95% CI with the null hypothesis of 0.