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The presence of preoperative neurodegeneration biofluid markers in patients with postoperative delirium

Jacqueline M. Leung, M.D., M.P.H.[1], **Julio C. Rojas, MD, PhD**[2], **Christopher Tang**[1], **Brandon Chan**[2], **Argentina Lario-Lago, PhD**[2], **Adam L. Boxer, MD, PhD**[2], **Quyen Do, PhD**[3], **Joel H. Kramer, PsyD.**[2], **Zhiyuan Du, M.S.**[3], **Pang Du, Ph.D.**[3], **Laura P. Sands, Ph.D.**[4], **Perioperative Medicine Research group**[1]

[1]Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California, USA

[2]Memory and Aging Center, Department of Neurology, Weill institute for Neurosciences, University of California San Francisco, San Francisco, California, USA

[3]Virginia Tech, Department of Statistics, Blacksburg, Virginia, USA

[4]Virginia Tech, Center for Gerontology, Blacksburg, Virginia, USA

Abstract

Background: The pathophysiology of delirium is incompletely understood including what molecular pathways are involved in brain vulnerability to delirium. We determined whether preoperative plasma neurodegeneration markers were elevated in patients who subsequently developed postoperative delirium through a retrospective case-control study.

Methods: Inclusion criteria were patients ≥65 years of age, undergoing elective noncardiac surgery with a hospital stay of ≥ two days. Concentrations of preoperative plasma P-tau181, neurofilament light chain (NfL), amyloid β_{1-42} ($A\beta_{42}$), and glial fibrillary acidic protein (GFAP) concentrations were measured with digital immunoassay platform. The primary outcome was postoperative delirium measured by the Confusion Assessment Method. We did a propensity score matching on age and sex with nearest neighbor such that each patient in the delirium group was matched on age and sex with a patient in the no delirium group.

Results: Our initial cohort consists of 189 patients with no delirium and 102 patients who developed postoperative delirium. Of 291 patients aged 72.5 ± 5.8 years, 50.5% were women, and 102 (35%) developed postoperative delirium. The final cohort in the analysis consisted of a no delirium (n=102) and a delirium (n=102) groups matched on age and sex using the propensity

Corresponding Author: Jacqueline M Leung, MD, MPH, 521 Parnassus Avenue, Room 4228, San Francisco, CA 94143-0648, Phone 1-415-476-0711; Jacqueline.Leung@ucsf.edu.

Conflict of interest: Rojas – Site PI for clinical trials sponsored by Eli Lilly and Eisai. Boxer -- has served as a consultant to AGTC, Alector, Alzprotect, Amylyx, Arkuda, Arrowhead, Arvinas, Aviado, Boehringer Ingelheim, Denali, Eli Lilly, GSK, Humana, Life Edit, Merck, Modalis, Oligomerix, Oscotec, Roche, Transposon and Wave. He has received research support from Biogen and Eisai for serving as a site investigator for clinical trials, as well as from Regeneron. He has received research support from the National Institutes on Aging: NIH U19AG063911, R01AG073482, R56AG075744, R01AG038791, RF1AG077557, R01AG071756, U24AG057437; Rainwater Charitable Foundation, Bluefield Project to Cure FTD, GHR Foundation, Alzheimer's Association, Association for Frontotemporal Degeneration, Gates Ventures, Alzheimer's Drug Discovery Foundation, UCSF Parkinson's Spectrum Disorders Center and the University of California Cures AD Program

score method. Of the four biomarkers assayed, the median value for NfL was 32.05 pg/ml for the delirium group *vs.* 23.7 pg/ml in the no delirium group. The distribution of biomarker values significantly differed between the delirium and no delirium groups (p-value =0.02 by the Kolmogorov-Smirnov test) with the largest cumulative probability difference appearing at the biomarker value of 32.05 pg/ml.

Conclusions: These results suggest that patients who subsequently developed delirium are more likely to be experiencing clinically silent neurodegenerative changes before surgery, reflected by changes in plasma NfL biomarker concentrations, which may identify individuals with a preoperative vulnerability to subsequent cognitive decline.

Summary Statement:

Patients who subsequently developed delirium are more likely to be experiencing clinically silent neurodegenerative changes preoperatively, reflected by changes in plasma biomarker concentrations, which may identify individuals with a preoperative vulnerability to subsequent cognitive decline.

INTRODUCTION

Postoperative delirium is a common yet serious cognitive condition that affects 10–60% of patients after major surgery.[1] Delirium is an acute confusional state defined by alterations in attention, consciousness and disorganized thinking. [1,2] Delirium has also been shown to be associated with decreased long-term physical and cognitive functioning. [3,4] Patients and families frequently are concerned that exposure to major surgery and anesthesia will result in postoperative delirium, which has been hypothesized as a prodrome for subsequent long-term cognitive decline. Understanding the pathophysiology of postoperative delirium and its association with long-term cognitive changes is important for designing the appropriate research studies that address the mechanism for the association. We hypothesized that patients who subsequently developed postoperative delirium have a pre-existent brain vulnerability secondary to prodromal neurodegenerative changes that can be tracked with biofluid markers of neurodegeneration. Although a preoperative cognitive screen may identify risk for the older individuals, neuropathology exists even prior to the onset of cognitive changes in about 30% of cases. [5] Prior studies have focused on neuroinflammation and biomarkers that may be elevated after surgery. However, few studies have evaluated whether preoperative biomarkers of brain vulnerability contribute to postoperative cognitive events. Of the studies that assessed the association between preoperative biomarkers and postoperative delirium, conflicting results have been found due to small sample sizes, heterogeneous biomarkers being examined, and methods of statistical analysis.[6–10] Accordingly, we conducted a study to examine the prevalence of established markers of neurodegeneration in older surgical patients undergoing elective major surgery and to determine if the presence of preoperative biomarkers of neurodegeneration is associated with postoperative delirium.

METHODS

The study was approved by the Institutional Review Board for human research and informed consent was obtained preoperatively from each study patient. The study was conducted at the University of California, San Francisco Medical Centre between January 2002 to December 2010. Data for this study were collected from two separate studies. One study assessed the effects of nitrous oxide on postoperative delirium which showed that there was no effect of nitrous oxide, the intervention, on postoperative delirium. [11] The other study was an observational study of risks associated with postoperative delirium. [12] Inclusion criteria for both studies were identical which included consecutive men or women who were ≥ 65 years of age, undergoing major noncardiac surgery requiring general anesthesia, who were expected to remain in the hospital postoperatively for ≥ 48 hours, and also had plasma banked preoperatively for the biomarkers assay. Additional inclusion criteria for this study included preoperative banking of blood and separation of plasma which was stored at the appropriate temperature. Exclusion criteria for both studies were patients who could not complete the delirium testing such as those who were expected to remain intubated postoperatively, particularly if they would be sedated for postoperative ventilation. Patients were not excluded based on their preoperative cognitive performance and our study cohort was largely cognitively unimpaired. The demographic data of the two studies which included age, sex and preoperative cognitive status was similar between the two studies, hence the data were combined.

For both studies, preoperatively on the day of surgery, blood was collected by phlebotomy in EDTA tubes, and centrifuged at 2,500 g for 10 min at room temperature. Plasma was then aliquoted in 1.5mL cryogenic tubes and stored at −80°C until analyses. For those blood samples where the plasma was isolated and stored, plasma was analyzed according to vendor protocols, for neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), amyloid β_{1-42} ($A\beta_{42}$), and phosphorylated tau 181 (P-tau181), using commercially available kits for single molecule arrays in an HD-X analyzer (Quanterix, Billerica, MA). Lowest level of quantification and average coefficient of variations were respectively 0.4 pg/ml, 4.5% for NfL; 0.38 pg/ml, 2.7% for $A\beta_{42,}$: 2.8 pg/ml, 7.4% for GFAP; and 0.08 pg/ml, 5.4% for P-tau181. Analyzed samples underwent only one thaw cycle prior to use. Samples were run in duplicate, with kits from the same lot by an investigator blinded to group allocation.

P-tau181, NfL, $A\beta_{42}$, and GFAP were chosen in this study because they are robust markers associated with neurodegeneration detectable in blood. Their clinical utility as markers of neurodegeneration has been validated in multiple large cohorts. High P-tau181 discriminates individuals with underlying Alzheimer's Disease (AD) pathology. Blood P-tau181 correlates with both amyloid plaque and neurofibrillary tangle burden, as detected by florbetapir or flortaucipir brain PET imaging, and with tau brain deposition as determined by Braak neuropathological staging. Blood P-tau181 is elevated in the setting of AD pathology, including asymptomatic individuals. [13] NfL is a sensitive, but non-specific marker of axonal injury. Blood NfL is elevated in individuals with AD and frontotemporal dementia (FTD). [14] High blood NfL is increased in prodromal stages of AD [15] and has also been detected in asymptomatic individuals at short-term risk of progression to symptomatic FTD. [16,17] Blood NfL concentrations are responsive to inflammatory disease activity and therapeutic

interventions. [18] Aβ_{42} is found in amyloid plaques, and it is believed that Aβ_{42} triggers pathological changes in tau, and that at later stages tau becomes unyoked from Aβ_{42}. [19] GFAP is a marker of astroglial activation that mirrors inflammation at different stages of neurodegeneration. [20] GFAP has shown to be a marker of white matter integrity and executive function in cognitively intact older adults. [21]

For both studies, baseline cognitive status was measured preoperatively using the Telephone Interview of Cognitive Status instrument (TICS) [22] which was adapted from the Mini Mental State Examination. For the occurrence of delirium, we used the Confusion Assessment Method Rating Scale (CAM) [23] which was developed as a screening instrument based on operationalization of DSM-III-R criteria for use by nonpsychiatric clinicians in high-risk settings. Presence of postoperative delirium was based on CAM criteria which includes the following three types of symptoms: 1) acute onset of change in mental status compared to the pre-operative CAM assessment, 2) inattention, and 3) either disorganized thinking or altered level of consciousness. The CAM assessments were conducted by research associates whose training was guided by the CAM Training Manual and Coding Guide, and whose assessments were validated by either Dr. Leung or Dr. Sands. The CAM was administered before surgery and daily after surgery for up to three days. No patients met CAM criteria for delirium prior to surgery. The primary outcome was incident delirium on any of the first three postoperative inpatient days. For the clinical trial, both patients and the research associates were blinded as to whether the patient was in the intervention or control group. The intervention was shown not to affect incident delirium.

Assessment of Descriptive Characteristics

Preoperative characteristics are shown in prior research to increase risk for postoperative delirium in older adults undergoing elective surgery. [11,24,25] The characteristics included age, sex, history of cerebrovascular disease, the American Society of Anesthesiologists (ASA) risk score, and surgical risk as shown in table 1. Surgical risk was estimated using the guidelines from the American College of Cardiology and American Heart Association update for the perioperative cardiovascular evaluation for noncardiac surgery. [26] Each of the characteristics was collected either at the preoperative interviews or abstracted from medical records.

Statistical analysis

The distributions of the preoperative characteristics biomarkers by delirium status were examined using descriptive statistics, including means, standard deviations, and percent with the preoperative characteristic. To assess whether characteristics differed between those with and without delirium, we computed t-tests for continuous valued variables and chi-square tests for categorical variables.

Our initial cohort consisted of 189 patients who did not develop postoperative delirium (non-delirium group) and 102 patients who developed postoperative delirium (delirium group). However, prior studies [27,28] have shown age and sex differences in expressions of biomarkers associated with cognitive functioning. Therefore, we conducted a propensity score matching on age and sex with nearest neighbor [29] such that each patient in the

delirium group was matched with a patient in the non-delirium group. To examine the age and sex balance in the resulting matching sample, we adopted two commonly used graphical tools [30]: the density or histogram plot and the Love plot. The first tool plots, for a continuous covariate, the probability densities of the covariate or for a categorical covariate the side-by-side proportion histograms of the covariate, before and after the matching adjustment. To make the Love plot, a standardized mean difference (SMD) [30] is first calculated for each matching variable, continuous or categorical, before and after the matching adjustment. A SMD with the absolute value greater than 0.1 is considered as an indicator of imbalance. The Love plot then presents the SMDs per matching covariate laid out in a horizontal fashion with the two vertical lines of SMD = 1 and SMD = −1 superimposed. Covariates with SMDs falling out of these two lines are considered unbalanced. Once covariate balance was achieved through the matching adjustment, we then performed all the statistical analyses on these matched non-delirium and delirium groups, each with 102 patients (Figure 1).

For each biomarker, we first constructed a group-wise relative frequency plot, visually comparing the relative frequencies of the biomarker measurements for the delirium and non-delirium groups. As shown in the relative frequency plots (Figure 2, panels A-D), none of the four biomarkers could be considered as normally distributed. Therefore, nonparametric statistical methods that do not assume that the data belonged to a specific distribution family are appropriate here. Table 2 shows the median and interquartile range of each biomarker, in addition Table 2 also provides the results from the Kolmogorov-Smirnov (KS) test, a nonparametric statistical test which we used to numerically compare the biomarker measurements between the non-delirium and delirium groups. The KS test examines the entire distribution of each biomarker. This test first calculates the empirical cumulative distribution function (eCDF) for the biomarker measurements of each group. Each eCDF, considered as an estimate of the true but unknown cumulative distribution function, is a nondecreasing step function on the range of biomarker measurements such that the height of the step at a biomarker value x represents the cumulative probability of the biomarker taking a value no greater than x. After obtaining the eCDFs for the two groups, the KS test takes the absolute difference of the two eCDFs, which is also a function on the range of biomarker measurements. The test then claims a significant difference between the distributions of the biomarker measurements for the two groups when the supreme or maximum of this absolute difference function is greater than the critical value determined by the test procedure. To gain more insight on the biomarker difference between the two groups, we also made graphical representations of the KS test for each biomarker. Besides showing the test result (rejection or failure to reject), the graph also shows at which subrange(s) of biomarker values the delirium and non-delirium groups differ the most.

RESULTS

Due to budgetary constraints, we processed biomarkers for only 306 of the most recently recruited 809 patients who met the inclusion criteria for the current study. However missing data in key co-variates resulted in 291 patients who were included in the present analysis (Figure 1). Of 291 patients, 102 (35%) developed postoperative delirium (Table 1). The propensity score matching resulted in two groups, a delirium and a no delirium group, that were matched on age and sex. Each group included 102 patients (Figure 1). For the

age covariate, the density plot (Figure 2 Panel A) showed more similar densities after the matching. The Love plot (Figure 2 Panel B) clearly showed age was slightly unbalanced before matching but became balanced after matching. For gender, it was clearly unbalanced in the original sample with a higher proportion of females in the delirium group. This imbalance was corrected in the matched sample where the proportions of males and females were similar in both patient groups.

For each biomarker, we assessed whether there were significant differences between the delirium and no delirium groups. Table 2 shows that the KS test for P-tau 181 is not significant (p=0.29), indicating that the distributions of P-tau181 values for the no delirium and delirium groups are not significantly different. Figure 3, panel A shows that the two groups differ the most when the P-tau181 value is 1.74, but the difference (shown in red) is far below the critical value (shown in blue). The KS test for the biomarker NfL (Table 2) shows significant differences between the no delirium and delirium groups (p-value = 0.02). The median value for NfL was 32.05 pg/ml for the delirious group vs 23.7 pg/ml in the non-delirious group. The distribution of biomarker values significantly differed between the delirium and no delirium groups (p-value =0.02 by the KS test) with the most difference appearing at the biomarker value of 32.55 pg/ml. The no delirium group had more values below this threshold compared to the delirium group. The plot also showed that the two groups differed mostly in the region of lower NfL biomarker values. The KS test for the biomarker GFAP is not significant, revealing that the distributions of GFAP values for the delirium and no delirium groups are not significantly different. Figure 3, panel C shows that the two groups differ the most when the GFAP value is 94.85 pg/ml, where the difference is far below the critical value (shown in blue). The KS test for the biomarker $A\beta_{42}$ is not significant meaning that the distributions of $A\beta_{42}$ values for the two groups are not significantly different. Figure 3, panel D shows that the two groups differ the most when the $A\beta_{42}$ value is 7.9 pg/ml, where the difference is far below the critical value (shown in blue).

Because most perioperative pathways in the prevention of postoperative delirium includes the performance of a preoperative cognitive screen, we performed a secondary data analysis to determine if preoperative cognitive status is associated with different levels of preoperative biomarker levels. The results reveal very low correlations between preoperative cognitive status measured by TICS and each biomarker. Respectively the Pearson's correlation coefficients for each biomarker were −0.08 (Pt 181), −0.17 (NfL), −0.08 (GFAP) and 0.02 ($A\beta_{42}$).

DISCUSSION

In this prospective cohort study of older patients undergoing major noncardiac surgery, we found that one of the four analytes yielded significant results. The distribution of NfL values significantly differed between the delirious and non-delirious groups. Specifically, the non-delirious group had more values below a threshold value compared to the delirious group. These results suggest that patients who subsequently developed delirium may be more likely to be experiencing clinically silent neurodegenerative changes before surgery.

There is a robust literature discussing the relationship between biomarkers detected in the cerebrospinal fluid (CSF) and plasma and Alzheimer's disease and related dementias (ADRD) [31–33], however, this was not the focus of the present study. Rather, the primary outcome of our study is postoperative delirium. Another major distinction between prior studies and our present proposal is that we focus on preoperative *baseline* biomarkers and *not changes in biomarker levels* with surgery given the goal of our study is risk identification, and not the effects of surgery. Most studies that evaluated changes in biomarkers after surgery had limited samplings of biomarkers, typically on only one postoperative day, heterogeneous statistical analyses, and it is unclear if these biomarker changes were temporary and whether changes in biomarkers after surgery are associated with long-term consequences. Furthermore, prior studies of change in biomarkers did not investigate the complexity of causes for change in biomarkers, which could be due to reasons other than perioperative procedures. For example, even in the absence of surgery, older adults hospitalized for acute illness are at risk for long-term cognitive changes. [34]

A recently published systematic review on biomarkers of delirium concluded that there was insufficient evidence to support the use of any biomarker as a sole risk or disease marker of delirium. [35] Studies that investigated preoperative biomarkers showed conflicting results (Table 3). For example, for NfL, Halaas *et al.* found an association between preoperative levels and postoperative delirium, and Fong found an association between NfL and the sum of scores from all days in the hospital on the CAM severity scale, but not for incident postoperative delirium or days of delirium. [6,7] However, Casey *et al.*, found no such association. [9] These differences in results may be secondary to different patient cohorts or heterogeneous ways to analyze the results statistically. As for T-Tau, two studies in non-cardiac surgical patients found no association between preoperative levels and postoperative delirium, [6,36] but one small study in cardiac surgical patients found an association. [10] As to GFAP, Ballweg *et al.,* [36] found no association between preoperative GFAP levels and postoperative delirium, a result similar to what we reported here. A recent study reported new AD biomarkers such as phosphorylated Tau at threonine 217 (Tau-PT217) and 181 (Tau-PT181) to be associated with increased risk of POD [37]. Finally, for Aβ_{42}, conflicting results are found. Although a study of hip fracture patients showed that CSF Aβ_{42} levels were not significantly different between groups, [8] other studies in patients undergoing elective arthroplasty showed that low CSF Aβ_{42} levels were associated with postoperative delirium, [38] or those in the lowest quartile of preoperative CSF Ab40/Tau and Ab42/Tau ratio had higher incidence of postoperative delirium. [39] One additional study showed that delirious patients had lower ratios of Aβ_{42} to T-tau relative to those without delirium. [40] The prior investigations involved samples collected from CSF and the association of plasma Aβ_{42} with postoperative delirium is less well investigated.

A recent review from the Alzheimer's Association concluded that blood based markers have promise to revolutionize the diagnostic and prognostic work-up of AD, and to improve the design of interventional trials. [41] Several of the biomarkers investigated in the present study such as plasma p-tau, Aβ_{42}, NfL, and GFAP have been proposed to be important markers that should have longitudinal measurements in prospective cohort studies. [41] For many years, CSF NfL has been used as a neuroaxonal injury marker. Its level is elevated in cognitively asymptomatic patients at risk of neurodegenerative dementia.

[16,42,43] NfL is a biomarker that has been found to be associated with myriad neurological conditions including both peripheral nerve disorders and central nervous system disorders from traumatic brain injury to multiple sclerosis and Parkinson disease. The association of higher levels of NfL preoperatively with postoperative delirium suggests that patients may have evidence of neurodegeneration. In contrast, *postoperative* NfL elevation shown by Fong *et al.* may have a different etiology, such as neuronal injury of some kind. Our study differs from the study from Fong *et al.,* as we aimed to determine *preoperative* vulnerability of patients rather than detecting the effect of surgery, which may be rather non-specific due to the general inflammatory response after major surgery. It should be noted that NfL has a strong age relationship. [41] In our analysis, we used propensity score nearest neighbor matching for age and sex, so the significant association between preoperative NfL and postoperative delirium persists even after considering age and sex. GFAP on the other hand is a non-specific marker of astroglial activation. [44] Its blood concentration is strongly reflective of Aβ accumulation in the brain prior to neuronal damage or in response to neuronal damage in dementia. P-tau181, a marker of AD that is elevated in prodromal states, [13] did not have strong associations with delirium. Whether this signals a lack of association between AD and postoperative delirium, or low relevance of tau biology in delirium deserves further investigation. A limitation of this study is that it did not assess P-tau217 or 231 that have much stronger associations with brain amyloidosis than P-tau181 in preclinical AD. Furthermore, our study cohort also did not consist of patients with significant cognitive impairment or dementia which might have precluded them from undergoing major elective surgery.

Our present results suggest that incipient neurodegeneration may have been present in patients with seemingly intact cognition before surgery as measured by the TICS and medical records for a diagnosis of dementia. If evidence of neurodegeneration exists before surgery as our present results suggest, then postoperative delirium may only be a surrogate marker of what is to come, that is the predisposition of developing long-term cognitive decline including conversion to AD. Our present results support that delirium may be an intermediary outcome, not independent of pre-existent vulnerability, as evidenced by markers of neurodegeneration.

Taken together, our results and those from other investigators show that there is a role of using proteomics in the investigation of the pathophysiology of perioperative cognitive changes. Our study results are novel in that we focus on baseline patient vulnerability rather than the effects of surgery. However, our results should be considered as preliminary, even though we have a relatively large sample size, and we only examined four biomarkers. Future investigations should consider other molecular biomarkers that may be upstream to the neurodegeneration markers which are considered to be terminal neuropathology, not easily amendable to modification.

There are several potential limitations of our study. First, we included only four biomarkers in this study, and newer AD biomarkers have been recently reported. [45] Second, there is a concern that long-term storage may affect the reliability of blood biomarkers for AD and neurodegeneration. However, a recent study reported that AB_{40}, AB_{42}, TTau and NfL can be measured from serum or plasma stored up to 20 years at 80°C with only small variability in

concentration. [46] Third, this is a single center study, and the results will need to be validated by future studies including other cohorts. Lastly, we have not conducted long-term follow up to evaluate whether patients with preoperative evidence of neurodegeneration will have a greater decline in cognition, an area which we will pursue in future studies.

In summary, we have preliminary evidence to suggest that biofluid markers of neurodegeneration measured before surgery may have prognostic significance in predicting postoperative delirium. Plasma biomarkers may have value in monitoring the preclinical phases in neurodegenerative disease. These results need further confirmation along with long-term follow up.

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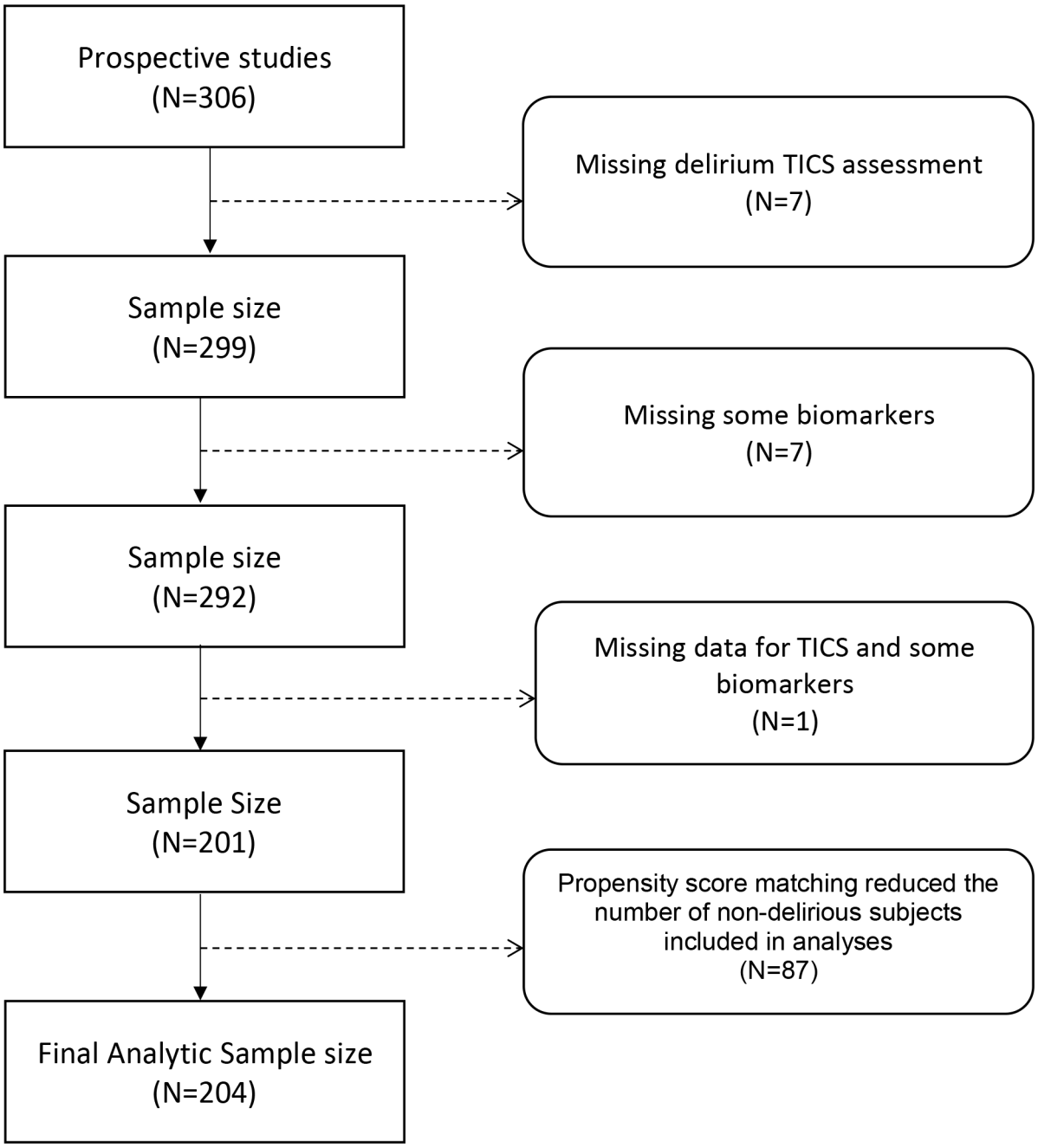

Figure 1.
Flow Chart for Inclusion of Patients in the Analytic Sample

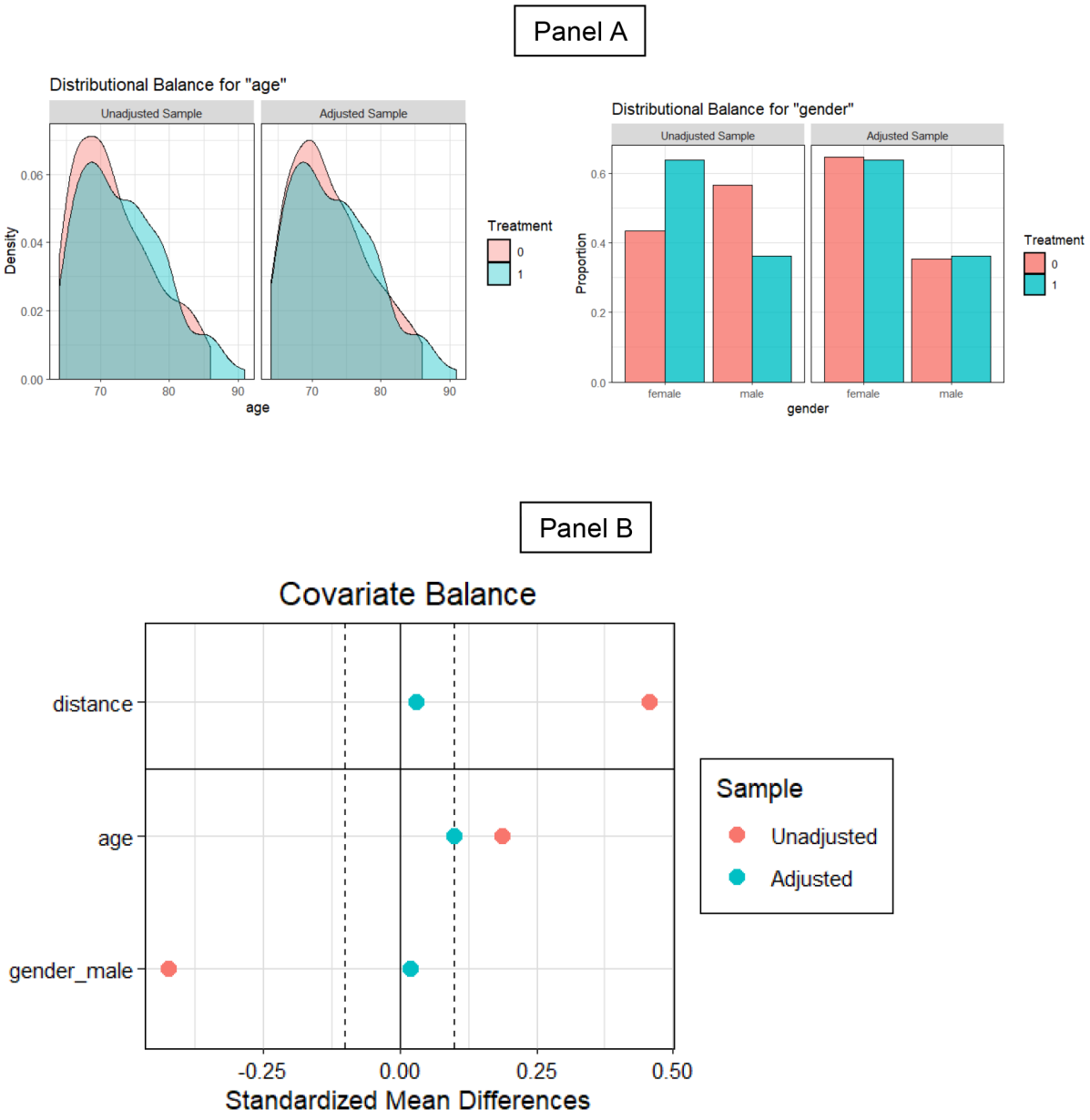

Figure 2.

Panel A contains the probability density plots of age and the proportion histograms of gender for the delirium and no delirium groups before and after the matching adjustment. Treatment in the legends depicts 1 = delirium group, and 0 = no delirium group. Panel B contains the plot of the standardized mean differences (SMDs) for the estimated propensity scores (distance) and the matching variables. The two dashed vertical lines correspond to SMD = 1 and −1. SMDs falling outside of the two lines indicate an imbalance for the variable.

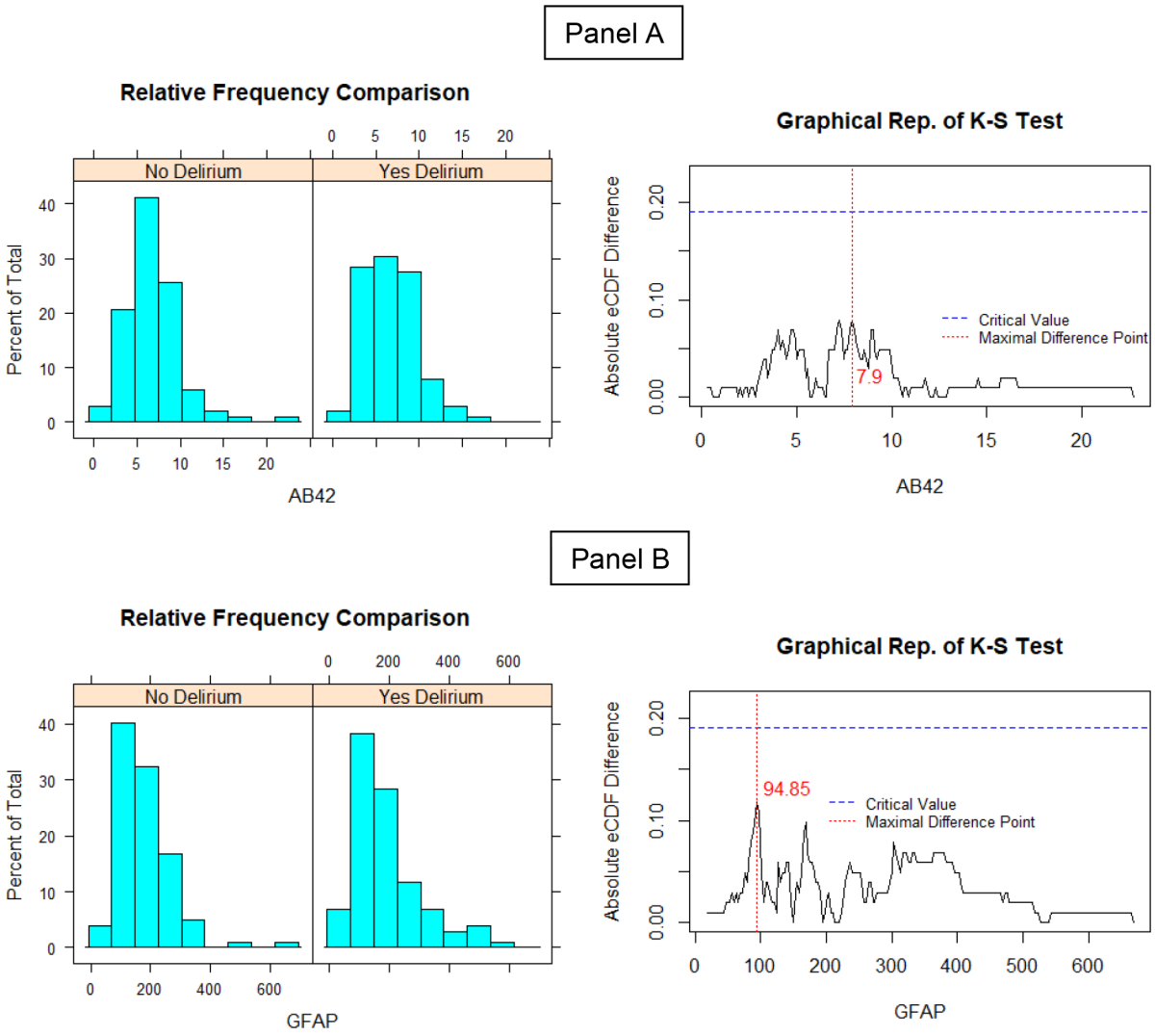

Figure 3.

The solid line is the difference between the two groups' eCDF. The red vertical line is consistent with the point where the largest difference is also the location of the K-S test. The blue horizontal line stands for the critical value of the KS test.

Table 1.

Sample Characteristics for the entire cohort and stratified by delirium status

	All patients	Postoperative delirium (no)	Postoperative delirium (yes)	p-value
N (%) for age and sex matched	204	102(50)	102(50)	
Age (yr), mean ± SD	72.91(5.82)	72.61(5.6)	73.22(6.06)	0.46
Sex Male, n (%)	73(35.78)	36(35.29)	37(36.27)	1
Female, n (%)	131(64.22)	66(64.71)	65(63.73)	
History of Cerebrovascular disease No	191(93.63)	96(94.12)	95(93.14)	1
Yes	13(6.37)	6(5.88)	7(6.86)	
ASA Classification, n(%) <=2	105(51.47)	57(55.88)	48(47.06)	0.26
>2	99(48.53)	45(44.12)	54(52.94)	
Surgery risk 1&2	169(82.84)	90(88.24)	79(77.45)	0.06
3	35(17.16)	12(11.76)	23(22.55)	

T-tests were used to assess differences between the delirium and no delirium groups for the variable age.

Chi-square tests were used to assess differences between the delirium and no delirium groups for the variables sex, history of cerebrovascular disease, ASA classification, and surgical risk.

ASA classification = American Society of Anesthesiologist physical classification

Table 2.

Biomarker descriptive statistics for the entire cohort and stratified by delirium status

Biomarker	All patients	Postoperative delirium (no)	Postoperative delirium (yes)	p-value*
P-tau 181 (pg/mL) Median (IQR)	2.3(1.64)	2.23(1.51)	2.45(1.69)	0.29
NfL (pg/mL) Median (IQR)	27.1 (27.15)	23.7 (19.5)	32.05 (33.9)	0.02
GFAP (pg/mL) Median (IQR)	156 (120.25)	154.5 (114.5)	157.5 (131)	0.48
Aβ_{42} (pg/mL) Median (IQR)	6.55 (3.85)	6.52 (3.4)	6.63 (4.34)	0.82

*P-value is based on the Kolmogorov- Smirnov test

IQR = inter-quartile range

Table 3

Summary of preoperative biomarkers and postoperative delirium from prior studies

Year	Author	Biomarker	Population	Sample size	Type	Results
2011	Whitlox [8]	beta amyloid, tau and Ptau	Hip fracture	76	CSF	No association
2014	Xie [39]	Ab_{40}, Ab_{42}, and Tau	Total arthroplasty	153	CSF	Lowest quartile of preoperative CSF Ab_{40}/Tau and Ab_{42}/Tau ratio had higher incidence (and greater symptom severity of postoperative delirium
2017	Idland [40]	$A\beta_{42}$, T-tau, and P-tau	Hip fracture	129	CSF	Delirious patients had lower ratios of Ab_{42} to T-tau and P-tau relative to those without delirium
2019	Cunningham [38]	$A\beta_{42}$	Arthroplasty	282	CSF	Low CSF Ab_{42} independent predictor of postoperative delirium
2018	Halaas [7]	NfL	Hip fracture	130 CSF 192 plasma	CSF & plasma	Positive association for plasma
2020	Fong [6]	NfL	Non-cardiac	108	plasma	Positive association
2020	Casey [9]	NfL	Non-cardiac	114	plasma	No association
2021	Ballweg [36]	T-tau	Non-cardiac	114	plasma	No association
2020	Fong [6]	T-tau	Non-cardiac	108	plasma	No association
2022	McKay [10]	T-tau	Cardiac	24	plasma	Positive association
2022	Liang [45]	P-tau 217/181	Non-cardiac	491	plasma	Positive association
2022	McKay [10]	P-tau 217/181	Cardiac	24	plasma	No association
2021	Ballweg [36]	GFAP	Non-cardiac	114	plasma	No association