HHS Public Access

Author manuscript

Am J Geriatr Psychiatry. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Am J Geriatr Psychiatry. 2021 December ; 29(12): 1212–1221. doi:10.1016/j.jagp.2021.02.001.

Association of Depressive Symptoms With Postoperative Delirium and CSF Biomarkers for Alzheimer's Disease Among Hip Fracture Patients

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Abstract

Objectives: While there is growing evidence of an association between depressive symptoms and postoperative delirium, the underlying pathophysiological mechanisms remain unknown. The goal of this study was to explore the association between depression and postoperative delirium in hip fracture patients, and to examine Alzheimer's disease (AD) pathology as a potential underlying mechanism linking depressive symptoms and delirium.

Methods: Patients 65 years old or older (N = 199) who were undergoing hip fracture repair and enrolled in the study "A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients" completed the 15-item Geriatric Depression Scale (GDS-15) preoperatively. Cerebrospinal fluid (CSF) was obtained during spinal anesthesia and assayed for amyloid-beta (Aβ) 40, 42, total tau (t-tau), and phosphorylated tau (p-tau)$_{181}$.

Results: For every one point increase in GDS-15, there was a 13% increase in odds of postoperative delirium, adjusted for baseline cognition (MMSE), age, sex, race, education and

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AUTHOR CONTRIBUTIONS

Conception and Design: CC, FS, KN, PR, NW, JL, EO; Data acquisition: FS, KN, PR, NW, EO; Statistical design and analysis: GK, JL; Drafting of manuscript CC; Interpretation of data and critical Revisions: CC, FS, KN, PR, NW, JL, HZ, SI, EM, KB, CL, EO. All authors approved of the final version of submission. Funding acquisition are as outlined under "Acknowledgements".

CSF AD biomarkers (OR = 1.13, 95%CI = 1.02–1.25). Both CSF A 42/t-tau (β = −1.52, 95%CI = −2.1 to −0.05) and A 42/p-tau$_{181}$ (β = −0.29, 95%CI = −0.48 to −0.09) were inversely associated with higher GDS-15 scores, where lower ratios indicate greater AD pathology. In an analysis to identify the strongest predictors of delirium out of 18 variables, GDS-15 had the highest classification accuracy for postoperative delirium and was a stronger predictor of delirium than both cognition and AD biomarkers.

Conclusions: In older adults undergoing hip fracture repair, depressive symptoms were associated with underlying AD pathology and postoperative delirium. Mild baseline depressive symptoms were the strongest predictor of postoperative delirium, and may represent a dementia prodrome

Keywords

Alzheimer's disease; delirium; csf; amyloid; tau; depression; mild behavioral impairment; hip fracture; postoperative

INTRODUCTION

Delirium is a syndrome defined by acute changes in attention and cognition[1] that commonly occurs in hospitalized older adults after acute illness or surgery. Delirium is associated with increased morbidity and mortality, longer hospital stays, as well as physical and cognitive decline.[2] The estimated annual health care costs associated with delirium and its downstream effects are over $164 billion dollars in the United States.[3] Although delirium occurs in various clinical settings, the risk is especially high among older adults undergoing hip fracture surgery, with incidences ranging from 13% to 56%.[4] In hip fracture studies with active screening, delirium is one of the most common postoperative complications, more common than urinary tract infection or pneumonia in some studies.[5]

Risk factors for postoperative delirium include cognitive impairment, older age, medical comorbidities, and neuropsychiatric conditions including depression.[4,6] Associations between preoperative depression and postoperative delirium have been reported extensively in cardiac surgery populations.[7] Similar associations have been reported in patients undergoing hip surgery.[8–10] The latter studies, however, have been limited to *clinically significant depression*. Findings have been mixed in studies examining the association between mild depressive symptoms and postoperative delirium with reports that show positive[11,12] or no association.[13]

While there is growing evidence of an association between depression and postoperative delirium, the pathophysiological mechanisms underlying this association and whether this association is driven by a common etiology remains unknown. In Alzheimer's disease (AD), a risk factor for postoperative delirium, depression and other neuropsychiatric symptoms have been the focus of growing interest as early manifestations or prodromal symptoms of an underlying neurodegenerative disease process.[14] Biomarkers of AD have been examined in relation to depression[15,16] and to delirium,[17–20] with mixed results. The goal of our study was to 1) explore the association between depression and postoperative delirium in a hip

fracture population, and 2) to examine AD pathology as a potential mechanism accounting for associations between depressive symptoms and delirium.

METHODS

Participants

We analyzed data from a cohort of 199 consecutive hip fracture patients enrolled in the randomized clinical trial "A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients" (STRIDE) study who completed the 15-item Geriatric Depression Scale (GDS-15)[21] preoperatively. Details of STRIDE have been published elsewhere.[22,23] Briefly, individuals ≥65 years old with a preoperative Mini-Mental State Exam (MMSE)[24] score ≥15 who were undergoing emergency hip fracture repair with spinal anesthesia were included. Exclusion criteria included preoperative delirium, stage IV congestive heart failure, or severe chronic obstructive pulmonary disease. Informed consent was obtained from patients or legal representatives for patients unable to give informed consent. The trial was approved by a Johns Hopkins Institutional Review Board.

Study Procedures

Baseline demographic data were collected from patients, informants, and medical records by trained research staff prior to surgery. MMSE and GDS-15 were administered by research staff prior to surgery. GDS-15 is a 15-question screening tool designed to assess depressive symptoms in older adults; a score >5 is often used as a cut-off for major depressive disorder.[25] A consensus panel of two psychiatrists and one geriatrician blinded to the intervention scored the Clinical Dementia Rating Sum of Boxes (CDR-SB), which is a modification of the previously published CDR (Morris et al., 1993; Oh et al., 2018). The CDR scoring was based on assessment of all available clinical cognitive data, the Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)[28] and other history collected from the patient and informant prior to surgery. A global score of 0 represents normal cognition, while scores of 1, 2, and 3 represent mild, moderate or severe dementia respectively. Medical comorbidities were quantified using the Charlson Comorbidity Index (CCI).[29] Other baseline assessments included American Society of Anesthesiologists (ASA) physical status classification, fracture type, activities of daily living (ADL) scale, and instrumental activities of daily living (IADL) scale.

Procedures for CSF collection have been described in detail.[27] Briefly, CSF was collected at the onset of routine spinal anesthesia. CSF samples were analyzed for amyloid-beta (A) 40, A 42, total tau (t-tau), and phosphorylated tau (p-tau)$_{181}$ at the Clinical Neurochemistry Laboratory of the Sahlgrenska University Hospital, Mölndal, Sweden. A 40 and A 42 were assayed using MSD electrochemiluminescence assay (Meso Scale Discovery, Rockville, MD, USA), and t-tau and p-tau$_{181}$ were assayed using INNOTEST enzyme-linked immunosorbent assays (Fujirebio, Ghent, Belgium) according to the manufacturer's specifications.

Postoperative delirium was diagnosed by a consensus diagnosis panel of experts from postoperative day 1 to 5 or hospital discharge. The diagnosis of delirium was made

by a multidisciplinary consensus panel based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria using several data sources, including the confusion assessment method,[30] the Delirium Rating Scale-Revised-98 (DRS-R98),[31] digit span, a review of medical records, and family/nursing staff interviews. Study team members involved in assessing delirium were blinded to GDS-15 scores.

Statistical Analysis

Baseline demographics were compared using Chi-square or Fisher exact tests for dichotomous variables and student t tests for continuous variables. Logistic regression models were estimated to examine associations between baseline GDS-15 score and incident postoperative delirium.

The association between GDS-15 and postoperative delirium was assessed using a series of 4 logistic regression models. Model 1 contained a regression equation for GDS-15 with incident postoperative delirium as the dependent variable. Model 2 added demographics (age, sex, race, and education), model 3 added baseline clinical measures (CCI and MMSE), and model 4 added CSF biomarkers of AD (A 42/p-tau$_{181}$ ratio) to the equation (n = 151). A 42/p-tau$_{181}$ ratio was selected over other CSF biomarkers due to its higher specificity for AD [32] and association with baseline depression in our own analysis (Table 1). Low A 42/p-tau$_{181}$ ratios are found in individuals with clinical AD diagnosis.[32] We also examined whether baseline CSF AD biomarkers were associated with depressive symptoms. Linear regression models were estimated to examine the association between baseline depressive symptoms and baseline CSF A 40, A 42, t-tau, p-tau$_{181}$, A 42/t-tau, and A 42/p-tau$_{181}$ in a subset of patients with available CSF data (n = 151). Models were adjusted for age, sex, race, education, and Charlson comorbidity score (Table 2).

On an exploratory basis, using machine learning program, KappaTree,[33] an R adaptation of ROC4, a public domain program (http://www.stanford.edu/~yesavage/ROC.html), we conducted receiver operating characteristic (ROC) analyses and computed weighted *kappas* to identify predictors of delirium out of a list of 18 variables (below). The KappaTree program implements a form of recursive partitioning in that it cycles through each possible cutoff of each candidate predictor variable and iteratively branches on the best cutoff for the best variable at each node as a function of weighted kappa. In our application, sensitivity and specificity were equally weighted, the program was constrained such that once a variable had been branched on, it would not branch on that same variable again. Variables considered: age, sex, race, education, MMSE, GDS-15 (continuous and dichotomized at ≤5 versus >5), CCI, vascular index, American Society of Anesthesiologists (ASA) physical status classification, activities of daily living (ADL) scale, instrumental activities of daily living (IADL) scale, fracture type, APOE status, CDR global score, CDR-SB, A 42/t-tau, and A 42/p-tau$_{181}$ ratio.

Statistical analyses were performed with STATA 16 software[34] and R package KappaTree.[35] Significance was set at two-sided $p < 0.05$.

RESULTS

To assess for associations of depression with baseline variables, we compared those with more severe symptoms defined by GDS-15 >5 to those with GDS-15 ≤5 (Table 1). The two groups did not differ significantly on demographics. There were also no differences in baseline CSF A 40, A 42, t-tau, p-tau$_{181}$, or A 42/t-tau with the exception of lower A 42/ptau$_{181}$ ratios in the depressed group (Table 1). Seventy three (37%) of the overall cohort developed postoperative delirium. A greater proportion of those with GDS-15 >5 developed delirium compared to those with GDS-15 ≤5 (53.3 % versus 34.7%, Chi-square test: X^2 = 4.22, df = 1, p = 0.04).

The distribution of GDS-15 scores across the cohort is in Figure 1. Both CSF A 42/t-tau and A 42/p-tau$_{181}$ ratios were inversely associated with higher GDS-15 scores (Table 2).

Table 3 displays odds of incident postoperative delirium in relation to baseline characteristics. Higher GDS-15 and lower MMSE scores were associated with greater odds of postoperative delirium, even after adjusting for demographics, medical comorbidity, and AD biomarkers. Age, sex, race, education, CCI, CSF Aβ1–42/p-tau$_{181}$ were not associated with odds of developing postoperative delirium. In a separate model with Aβ1–42/t-tau in lieu of Aβ1–42/p-tau$_{181}$, Aβ1–42/t-tau was also not associated with odds of developing post-operative delirium (data not shown).

In KappaTree analyses (Fig. 2), out of 18 factors, GDS-15 had the highest classification accuracy for delirium (Kappa = 0.28). Fifty-two patients (71%) among those who developed delirium had pre-operative GDS >2. In the GDS-15 >2 group who developed delirium, 41 (78%) had MMSE ≤25. Six (29%) individuals who developed delirium and had GDS-15 ≤2 also had MMSE ≤20. In those with GDS-15 ≤2 and MMSE >20 who developed delirium, 9 (60%) had Aβ1–42/t-tau ratio ≤1.2. Thus, of those who developed delirium 41 (56%) had mild or more severe depressive symptoms *plus* cognitive impairment, 11 (15%) had at least mild depression, 9 (12%) had abnormal CSF but neither depression nor cognitive impairment, and another 6 (8%) had cognitive impairment alone.

DISCUSSION

In this study of older adults who presented with hip fracture requiring surgery, higher GDS-15 scores were associated with greater odds of postoperative delirium, even after adjusting for baseline cognitive function, age, sex, race, education and CSF AD biomarkers. Additionally, findings from KappaTree analysis suggest that the presence of even mild depressive symptoms (with an optimal cutoff of GDS-15 >2) is a strong predictor of postoperative delirium, beyond both cognition (measured by MMSE) and AD biomarkers (CSF A 42/t-tau). Taken together, these findings suggest that depressive symptoms, even at a low severity, may be a useful predictor of postoperative delirium in hip fracture patients.

Our findings build on previous studies examining the relationship between depression and postoperative delirium in the hip fracture population that have found significant associations between depression[8,9] or clinically significant depressive symptoms[10] and postoperative delirium. Postoperative delirium has also been identified as a risk factor for depression

following hip fracture.[36] The latter studies focused only on clinical depression as opposed to mild depressive symptoms, which have been of increasing interest in the field of AD and are far more prevalent in outpatient populations.

Mild Behavioral Impairment (MBI) is a construct that describes a syndrome of late-life neuropsychiatric symptoms of any severity, including depression, not attributable to another current psychiatric disorder, occurring *with or without* concurrent Mild Cognitive Impairment (MCI).[14] Late-life *mild* depressive symptoms, a form of MBI, are risk factors for progression to MCI or all-cause dementia.[37–40] Hence, depressive symptoms in late-life may represent early noncognitive manifestations of dementia with a shared neurodegenerative etiology. This is supported by our finding that even very mild depressive symptoms predicted post-operative delirium, while increasing severity of depressive symptoms was inversely associated with both CSF A 42/t-tau and A 42/p-tau$_{181}$ ratios, patterns suggestive of brain AD pathology.[41] Thus, we propose that *mild depressive symptoms can be a dementia prodrome that place older adults at risk for delirium after a hip fracture*.

In examining the relationship between AD CSF biomarkers and delirium, our findings were mixed. These biomarkers were not associated with postoperative delirium after adjusting for covariates but were a stronger predictor of delirium than most other patient characteristics in the KappaTree analysis. In a study of hip fracture patients that excluded individuals with dementia, no association between baseline CSF Aβ42, tau or p-tau levels and postoperative delirium was observed.[19] In another study of hip fracture patients with and without dementia, CSF Aβ42, t-tau, Aβ40/t-tau and Aβ42/p-tau (but not p-tau) were associated with postoperative delirium after adjusting for age, sex, and premorbid cognition.[18] In individuals with dementia, however, CSF biomarker levels did not differ between those with and without delirium. In studies of elective hip and knee surgery patients, postoperative delirium has been associated with low CSF Aβ42,[17] Aβ40/t-tau and Aβ42/p-tau ratios.[17,20] Some of these differences may be accounted for by the significantly older age of hip fracture versus elective orthopedic patients, as well as by variability of brain pathology across study populations. Even though AD brain pathology is highly prevalent in older adults 65 and older,[42] with increasing age other neuropathological processes become common.[44] Based on our findings we propose an additional reason for the mixed associations between CSF biomarkers, cognition, and delirium: the presence or absence of noncognitive manifestations of AD and other neurodegenerative disease (MBI), in this case depressive symptoms. Fifty-two of 73 (71%) of patients who developed delirium had mild or more severe depression. Added together the presence of MBI (depression), cognitive impairment (MMSE ≤20), or abnormal CSF AD biomarkers accounted for 67/73 (92%) cases of delirium.

Strengths of this study include examination of CSF AD biomarker profile in a relatively large, well-characterized cohort of hip fracture patients. In addition, GDS-15 was completed before surgery, and would not have been influenced by symptoms of delirium as individuals with preoperative delirium were excluded from the study. Our study should, however, be interpreted within the context of its limitations. This was a relatively small secondary analysis of a single-site clinical trial, which may limit findings to individuals motivated to participate in a clinical trial. Patients on oral anticoagulants and congestive heart

failure were excluded, which may have excluded individuals with cognitive deficits related to vascular causes. Our findings, therefore, may not be generalizable to older patients with hip fracture and significant cardiovascular disease. Further study is required in this subpopulation. The GDS-15 has been validated for assessment of depression in mild-to-moderate dementia, with good correlation[45] to the Cornell Scale of Depression in Dementia,[46] and diagnosis of depression using DSM-IV criteria.[47] While it has not been validated in severe dementia, our cohort consisted only of 6 participants with severe dementia (CDR = 2). Future studies should also assess for neuropsychiatric symptoms outside of depression.

In summary, we found that in older individuals undergoing surgery for traumatic hip fracture, baseline depressive symptoms (a form of MBI) were the strongest predictor of postoperative delirium, and that symptoms of depression were associated with underlying AD pathology. Assessment for depressive symptoms may be a useful addition to the standard clinical assessment in identifying individuals at risk of postoperative delirium.

Acknowledgments

UNCITED REFERENCES

[26,43]

HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. KB reports serving as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. CL is a consultant for Astellas, Roche, Karuna, SVB Leerink, Maplight, Axsome, and has a research grant from Functional Neuromodulation Ltd, outside the submitted work.

Research reported in this publication was supported by 5KL2RR025006 [Johns Hopkins Institute for Clinical and Translational Research (ICTR) which is funded in part by Grant Number UL1 TR 001079 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH)] (EO, NW), K23AG043504 (NIA/NIH) (EO), R01AG057725 (NIA/NIH) (EO), R01 AG033615 (NIA/NIH) (FS, KN, NW), P50 AG005146 (CL), R24AG054259 (NIA/NIH) (SKI), P01AG031720 (NIA/NIH) (SKI), K24AG035075 (ERM), and the Roberts Gift Fund (EO). Hjärnfonden, Sweden, #FO2017–0243 (KB), Swedish Research Council #2017–00915 (KB), Swedish and European Research Councils (HZ), UK Dementia Research Institute (HZ), Swedish State Support for Clinical Research (HZ), and Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement #ALFGBG-715986 (KB). HZ is a Wallenberg Scholar. The funding sources had no role in the design, conduct, or reporting of this study.

This study was supported by 5KL2RR025006 [Johns Hopkins Institute for Clinical and Translational Research (ICTR) which is funded in part by Grant Number UL1 TR 001079 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH)] (EO), K23AG043504 (NIA/NIH) (EO, NW), R01AG057725 (EO), R01 AG033615 (NIA/NIH) (FS, KN, NW), P50 AG005146 (CL), R24AG054259 (NIA/NIH) (SKI), K24AG035075 (ERM), P01AG031720 (NIA/NIH) (SKI), and the Roberts Gift Fund (EO). Hjärnfonden, Sweden, #FO2017–0243 (KB), Swedish Research Council #2017–00915 (KB), Swedish and European Research Councils (HZ), UK Dementia Research Institute (HZ), Swedish State Support for Clinical Research (HZ), and Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement #ALFGBG-715986 (KB). HZ is a Wallenberg Scholar. The funding sources had no role in the design, conduct, or reporting of this study.

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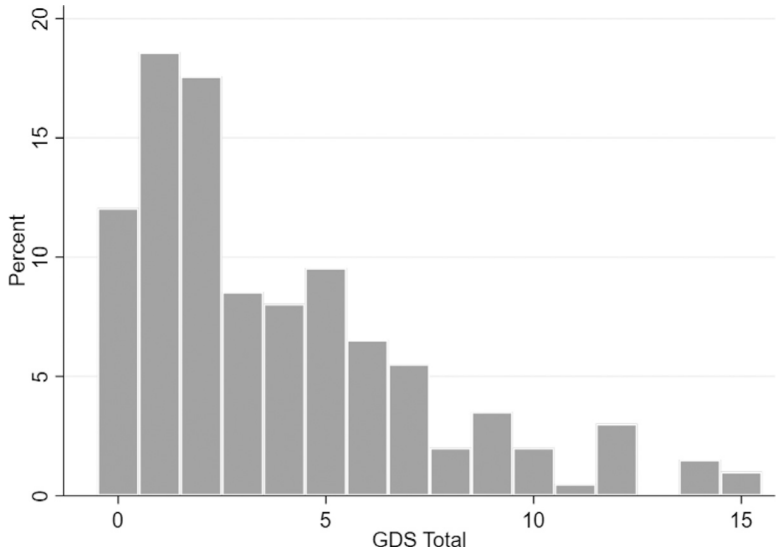

FIGURE 1.

Frequency of Geriatric Depression Scale-15 (GDS-15) scores. GDS-15 >5 is clinically significant depression.[25]

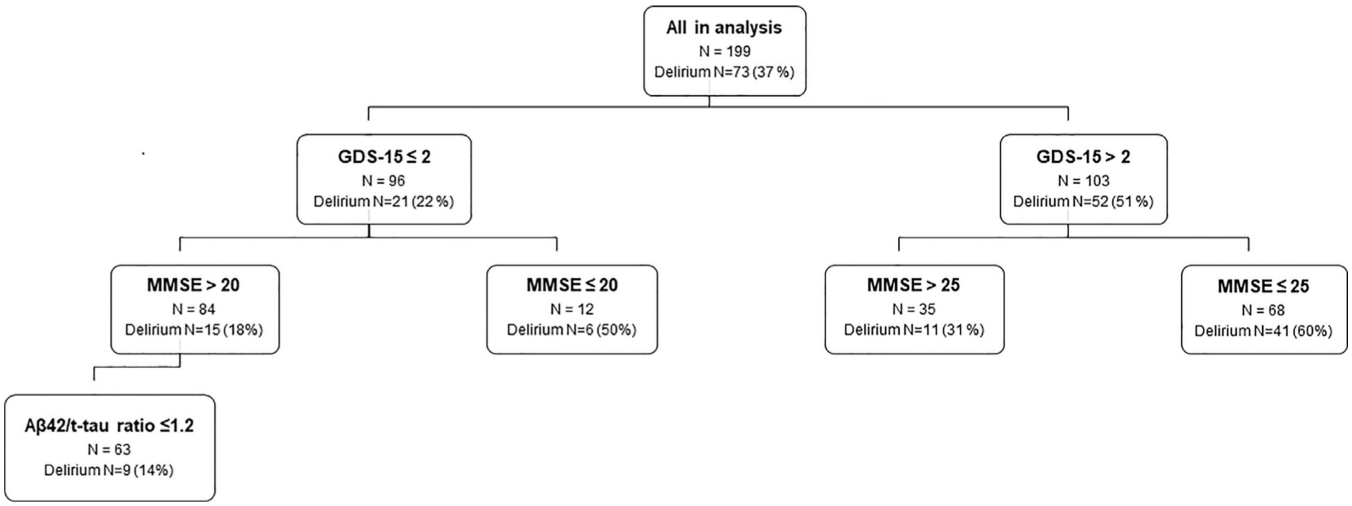

FIGURE 2.

KappaTree analysis. Using receiver operating characteristic analyses and computation of weighted kappa, KappaTree analysis was used to identify factors with the highest classification accuracy for delirium. Abbreviations: Aβ42/t-tau= CSF β-amyloid 1–42 to total tau ratio; GDS-15, Geriatrics Depression Scale-15 (short form)[21] (15 items, max. score = 15 points; higher score = worse depression; cut-off score of >5 for depression); MMSE, Mini-Mental State Examination[24] (10 items, max. score = 30 points.

TABLE 1.

Baseline Characteristics by Depression Status

Characteristics	Total(N = 199)	GDS-15 ≤5(n = 169)	GDS-15 >5(n = 30)	$X^2_{(df)}/t_{(df)}$	p Value
Age, years, mean (SD)	81.9 (7.7)	81.7 (7.6)	82.8 (8.3)	$t_{197} = -0.70$	0.49
Female, No. (%)	145 (72.9)	123 (72.8)	22 (73.3)	$X^2_1 = 0.004$	0.95
Race, White, No. (%)	193 (97.0)	164 (97.0)	29 (96.7)	$X^2_1 = 0.01$	0.91
Education level, No. (%)				Fisher Exact	0.27
Less than high school	76 (38.2)	63 (37.3)	13 (43.3)		
High school	76 (38.2)	62 (36.7)	14 (46.7)		
Some college	28 (14.1)	26 (15.4)	2 (6.7)		
College or higher	19 (9.5)	18 (10.7)	1 (3.3)		
Charlson Comorbidity Index, mean (SD)	1.49 (1.73)	1.49 (1.77)	1.63 (1.73)	$t_{197} = -0.41$	0.68
MMSE, mean (SD)	24.3 (3.68)	24.5 (3.50)	23.1 (4.52)	$t_{197} = 1.98$	0.05
CDR-SB, mean (SD)	1.47 (2.53)	1.36 (2.47)	2.19 (2.79)	$t_{195} = -1.64$	0.10
CDR-Global, N. (%)				Fisher Exact	.20
0	81 (41.1)	72 (42.9)	9 (31.0)		
0.5	94 (47.7)	80 (47.6)	14 (48.3)		
1	16 (8.1)	12(7.1)	4 (13.8)		
2	6 (3.1)	4 (2.4)	2 (6.9)		
CSF biomarkers, mean (SD)					
A 40 (pg/ml)	5044.47 (1794.82)	5084.02 (1836.82)	4834.98 (1567.81)	$t_{168} = 0.66$	0.51
A 42 (pg/ml)	297.71 (162.19)	304.05 (169.20)	264.13 (115.04)	$t_{168} = 1.17$	0.24
t-tau (pg/ml)	495.30 (281.34)	492.41 (292.70)	510.60 (215.17)	$t_{168} = -0.31$	0.76
p-tau (pg/ml)	56.92 (25.36)	55.74 (25.80)	63.11 (22.33)	$t_{167} = -1.39$	0.17
A 42/A 40 [a]	0.58 (0.20)	0.59 (0.20)	0.56 (0.19)	$t_{168} = 0.84$	0.40
A 42/t-tau	0.71 (0.38)	0.73 (0.38)	0.60 (0.34)	$t_{168} = 1.70$	0.09
A 42/p-tau_{181}	5.73 (2.81)	5.96 (2.88)	4.50 (2.03)	$t_{167} = 2.51$	0.01

Abbreviations: Aβ40, amyloid-beta 1–40; Aβ42, amyloid-beta 1–42; CDR-SB, Clinical Dementia Rating Sum of Boxes score (modified);[27,48] CSF, cerebrospinal fluid; GDS-15, Geriatrics Depression Scale-15 (short form)[21] (15 items, max. score = 15 points; higher score = worse depression; cutoff score of >5 for depression); MMSE, Mini-Mental State Examination[24] (10 items, max. score = 30 points); No., Number; p-tau_{181}, phosphorylated tau_{181}; t-tau, total tau.

Baseline demographics were compared using Chi-square or Fisher exact tests for dichotomous variables and student t for continuous variables.

[a] Aβ 42/Aβ 40 ratio was calculated as Aβ 42/Aβ 40 × 10 as previously has been done.[27,48]

TABLE 2.

Summary of Linear Regression Models Examining the Association Between Baseline Continuous GDS-15 With CSF Biomarkers

CSF Biomarkers	Estimate 95% CI)	t-Value	df	p Value
A 40	-2.69×10^{-4} [b]			
	$(-5.57 \times 10^{-4}, 3.69 \times 10^{-5})$	−1.74	163	0.08[a]
A 42	2.89×10^{-3} [b]			
	$(-6.30 \times 10^{-3}, 5.17 \times 10^{-4})$	−1.68	163	0.10[a]
t-tau	2.02×10^{-4} [b]			
	$(-1.76 \times 10^{-3}, 2.16 \times 10^{-3})$	0.20	163	0.84[a]
p-tau$_{181}$	0.01[b]			
	(−0.12-0.03)	0.93	162	0.36[a]
A 42/t-tau	−1.52			
	(−2.10, −0.05)	−2.04	163	0.04
A 42/p-tau$_{181}$	−0.29			
	(−0.48, −0.09)	−2.91	162	0.004

[a] p Value calculated by linear regression, adjusted for age, sex, race, education and Charlson comorbidity index. Change in CSF biomarker (pg/mL) per 1 point increase in GDS-15. Abbreviations: Aβ40, amyloid-beta 1–40; Aβ42, amyloid-beta 1–42; CI, Confidence Interval; CSF, cerebrospinal fluid; GDS-15, Geriatrics Depression Scale-15 (short form);[21] p-tau$_{181}$, phosphorylated tau$_{181}$; t-tau, total tau.

TABLE 3.

Multivariable Logistic Regression Model of Incident Postoperative Delirium in Relation to Baseline Characteristics

	Model 1			Model 2			Model 3			Model 4		
	OR 95% CI	**z**	**p Value**	**OR 95% CI**	**z**	**p Value**	**OR 95% CI**	**z**	**p Value**	**OR**	**z**	**p Value**
GDS-15	1.17 (1.07–1.28)	3.50	<0.001	1.16 (1.06−1.28)	3.32	0.001	1.15 (1.05−1.26)	2.95	0.003	1.13 (1.02−1.25)	2.43	0.02
Age	-	-	-	1.06 (1.01−1.10)	2.52	0.01	1.04 (0.10−1.09)	1.75	0.08	1.05 (0.99−1.10)	1.91	0.06
Female	-	-	-	0.83 (0.42−1.64)	−0.54	0.59	1.06 (0.51−2.18)	0.15	0.88	1.08 (0.47−2.47)	0.19	0.85
Race	-	-	-	4.17 (0.37−47.42)	1.15	0.25	5.78 (0.49−1.66)	1.39	0.16	6.49 (0.49−86.69)	1.41	0.16
Education level	-	-	-	0.95 (0.46−1.96)	−0.13	0.90	0.78 (0.36−1.66)	−0.65	0.51	0.76 (0.34−1.17)	−0.66	0.51
CCI	-	-	-	-	-	-	1.12 (0.93−1.34)	1.21	0.23	1.11 (0.90−1.36)	0.97	0.33
MMSE	-	-	-	-	-	-	0.88 (0.79−0.97)	−2.65	0.008	0.86 (0.77−0.96)	−2.73	0.006
A 42/p-tau$_{181}$	-	-	-	-	-	-	-	-	-	1.01 (0.89−1.15)	0.14	0.89

Model 1 contains univariable regression for GDS-15 and delirium. Model 2 adds demographic variables. Model 3 adds MMSE and CCI variables. Model 4 adds the CSF A 42/p-tau$_{181}$ variable. Z and p values calculated by linear regression, adjusted for covariates as indicated for each model.

Abbreviations: Aβ42/p-tau$_{181}$ = CSF amyloid-beta 1–42 to phosphorylated tau$_{181}$ ratio; CCI, Charlson Comorbidity Index;[29] CI, Confidence Interval; Geriatrics Depression Scale-15 (short form)[21] (15 items, max. score = 15 points; higher score = worse depression; cut-off score of >5 for depression); MMSE, Mini-Mental State Examination[24] (10 items, max. score = 30 points).