PRESCREENING FOR DEMENTIA IN THE OLDER ADULT SURGICAL POPULATION: A SYSTEMATIC REVIEW

A Major Paper Presented

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A Major Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Nursing

in

The School of Nursing

Rhode Island College

2021

Abstract

In the older adult surgical population, individuals with dementia are at higher risk for postoperative delirium (POD) which has been associated with a decline in patients' postoperative function, longer hospital length of stay (LOS), and increased morbidity and mortality (Kassahun, 2018). Although the neuropathology of POD remains not fully understood, the pathology of dementia and Alzheimer's disease (AD) in particular, has been highly researched. Alterations in dementia-associated biomarkers are seen up to a decade before clinical signs and symptoms are evident resulting in difficulty predicting POD in the older adult population (Olsson et al., 2016). Amyloid-ß 1-42 (Aß42), a dementia-associated biomarker most commonly seen in AD, that aggregates in the brain forming amyloid-ß plaques (Hall & Guyton, 2011). Research on Aß42 suggested that reduced cerebrospinal fluid (CSF) Aß42 concentration reflects the accumulation of Aß42 in the brain and seen before clinical emergence of the disease (Fagan, 2006). The purpose of this systematic review was to determine whether the preoperative CSF concentration of Aß42 in non-dementia older adult surgical patients predicts the incidence of POD. A comprehensive literature review was completed using CINAHL and PubMed/MEDLINE investigating POD and possible relationships with dementia and dementia-associated biomarkers. The PRISMA framework was used to identify eligible studies. Descriptive data tables were completed that reported pertinent data and study outcomes. Individual studies were assessed using the Critical Appraisal Skills Programme (CASP) checklist. A cross-study analysis table was created to compare outcomes across the studies. The findings of this systematic review are inconclusive but suggest that CSF Aß42 may be a potential independent predictor of POD in the older adult surgical population.

Table of Contents

Prescreening for Dementia in the Older Adult Surgical Population: A Systematic Review

Background/Statement of the Problem

In the older adult surgical population, those with dementia are at higher risk for postoperative delirium (POD) which has been associated with a decline in postoperative function, longer hospital length of stay (LOS), and increased morbidity and mortality, yet the neuropathology of POD remains not fully understood (Kassahun, 2018). Alterations in dementia-associated biomarkers are seen up to a decade before clinical signs and symptoms are evident, resulting in difficulty predicting postoperative delirium in the older adult population (Olsson et al., 2016). Amyloid-ß 1-42 (Aß42) is a dementia-associated biomarker most commonly seen in Alzheimer's disease that aggregates in the brain forming amyloid-ß plaques resulting in the loss of neurons that control the limbic system and memory process (Hall & Guyton, 2011). Research on Aß42 suggested that reduced cerebrospinal fluid (CSF) Aß42 concentration reflects the accumulation of Aß42 in the brain and may be detected before emergence of clinical signs of the disease (Fagan, 2006). Since alterations in dementia-associated biomarkers are seen before the clinical emergence of dementia, a review of current literature is necessary to determine whether lower preoperative CSF Aß42 concentration can predict the incidence of postoperative delirium in older adults who display no signs or symptoms of dementia, also referred to as "non-dementia" patients throughout this systematic review. Research findings could potentially recommend the development and use of a prescreening intervention involving the analysis of CSF Aß42 so that providers may tailor their care to individuals with undiagnosed pre-existing dementia pathologies as their risk for developing postoperative

delirium may be equally high as the risk for the older adult surgical population with clinical signs of dementia. The purpose of this systematic review was to determine whether preoperative CSF concentration of Aß42 in non-dementia older adult surgical patients can predict the incidence of postoperative delirium.

Literature Review

A comprehensive review of the literature was performed utilizing CINAHL and MEDLINE/PubMed for randomized controlled trials and observational studies performed between 2010 and 2021. Keywords utilized in performing this search for primary sources included “older adult” AND “dementia” AND “delirium” AND “Alzheimer’s” AND “CSF”.

Postoperative Delirium

Postoperative delirium is defined as an acute psychological disorder characterized by disturbance and fluctuation of consciousness, attention, and cognition (Racine et al., 2017). Research has shown that the older adult population experiences a higher occurrence of postoperative delirium after anesthesia when compared to younger patients (Kassahun, 2018). Postoperative delirium has a demonstrated increase in healthcare costs required to provide high quality care specific to this patient population and continued research is needed to investigate this postoperative complication. In a study conducted by Leslie et al. (2008), investigators looked at the overall healthcare costs associated with postoperative delirium over one year. Their findings showed a 40% increase ($21,540) in annual healthcare costs for patients who develop delirium when compared to those who do not. This study suggests that research efforts towards eliminating this complication remain essential.

The phenomenon of postoperative delirium continues to be investigated as the pathophysiology is not entirely understood (Xie et al. 2014). Research in the field of postoperative delirium has progressed from observational studies of behavioral changes and cognitive dysfunction to a more scientific approach of investigating the neuroscience

component of postoperative delirium and the biological and chemical processes involving the aging brain. Fairly new research is focused on cerebrospinal fluid (CSF) and brain imaging biomarkers associated with dementia or Alzheimer's disease pathogenesis and their relationship with postoperative delirium. The purpose of these research efforts is to develop future strategies for prediction, prevention, and minimization of postoperative delirium incidence and severity (Department of Health and Human Services, 2016).

Dementia and Delirium

Dementia is defined as a chronic global loss of cognitive brain function, memory, and attention. As the worldwide older adult population continues to grow, the number of individuals who are diagnosed with some form of cognitive dysfunction or dementia will also increase (Kassahun, 2018). In the older adult surgical population, pre-existing dementia or prior cognitive dysfunction serve as two of the greatest risk factors for postoperative delirium which is associated with negative outcomes such as decline in postoperative function, longer hospital lengths of stay (LOS), and increased morbidity and mortality (Mosk et al., 2017). Ultimately, overall healthcare costs increase as a result of providing quality care to individuals with delirium superimposed on dementia in order to prevent further deterioration.

In a study conducted by Fick et al. (2013), hospitalized dementia patients who developed delirium had longer hospital stays and poorer outcomes than dementia patients who did not develop delirium during hospitalization. The investigators conducted a 24-month prospective cohort study of 139 hospitalized patients greater than 65 years of age with pre-existing dementia. Their purpose was to look at delirium incidence and associated outcomes in adult dementia patients, i.e., the phenomenon of "delirium

superimposed on dementia" (DSD). The incidence of new delirium was found to be 32% in patients with preexisting dementia. Patients who developed delirium showed poor physical function at discharge and follow-up. These patients also showed a 25% short-term mortality rate which was defined as death within 30 days of their acute care hospitalization. In addition, there was an increased hospital length of stay (LOS) for DSD patients (9.1 days) compared to dementia patients who did not experience delirium (5.7 days) which was considered statistically significant (p <.0001). This study supports the findings previously mentioned by Leslie, et al. (2008) demonstrating the increased healthcare costs for delirium to provide quality care and treatment; however, given that study subjects were from one community hospital limits their findings to overall application to the entire older adult population with dementia. Further research including a more diverse group at various locations is warranted. This study identifies the importance of prescreening for dementia and assessing for delirium in the hospitalized older adult to decrease the incidence of postoperative delirium among the older adult surgical population.

Current preoperative evaluation does not routinely include dementia screening for the older adult surgical population (Kassahun, 2018). This could be due to the dearth of studies comparing postoperative outcomes for individuals with pre-existing dementia with an equal number of individuals without dementia that are also matched for sex and surgery type with similar patient characteristics and surgical variables (Kassahun, 2018). Because of this, the effects of dementia on the older adult surgical population in comparison to those who do not have dementia preoperatively and the resulting postoperative complications remains not fully understood.

With the aim of assessing morbidity and in-hospital mortality in the older adult surgical population, Kassahun (2018) conducted a retrospective randomized controlled trial of 240 patients that compared the outcomes between patients with pre-existing dementia compared with outcomes in non-dementia patients. The study group consisted of 120 patients with dementia matched for sex and surgery type and with the control group of 120 patients without dementia. Both groups underwent general or vascular surgery; none of the surgeries were related to trauma. A diagnosis of "dementia" was defined according to the tenth edition International Statistical Classification of Diseases and Related Health Problems and based on observations and recordings made in the patient's medical record during previous physician visits or hospital admissions. The morbidity and in-hospital mortality rates of both groups were assessed following surgery.

Findings demonstrated that there was an increase in an overall complication burden in the group with pre-existing dementia compared to the group without dementia. There was a 28.33% in-hospital mortality rate among the dementia group (34 deaths out of 20) versus a 20% in-hospital mortality rate for the non-dementia group (24 deaths out of 120). Specific complications or surgical outcomes that were found to be significantly different between the two groups included the surgical site infection, postoperative delirium, and pneumonia (p .018, < .001, and p < .001, respectively). Of the 120 patients with dementia, 39 patients (32.5%) experienced postoperative delirium. Of the 120 patients without dementia, 3 out of the 120 (2.5%) patients developed delirium which indicates an extremely rare occurrence or complication in this group of patients. The investigators linked postoperative delirium with an increase in intensive care unit stays and overall longer hospital stays for this population.

In a prior study conducted by Mosk et al. (2017), investigators found a statistically significant increase ($p < .001$) in postoperative delirium incidence in patients with pre-existing dementia, 97 patients out of 168 patients (57.74%), when compared to those without pre-existing dementia, 99 out of 398 patients (24.87%). This study was a retrospective cohort study which included 566 patients 70 years of age or greater who underwent arthroplasty or osteosynthesis following a hip fracture. Dementia patients were assessed based on prior documented medical records in an electronic medical record database or filing system. Patients were evaluated both preoperatively and postoperatively using the Delirium Observation Screening Scale (DOSS), a 25-item scale that recognizes early delirium that is based on the Diagnostic and Statistical-IV criteria through the observation of trained clinical staff. Areas assessed include consciousness, attention/concentration, thought process, memory/orientation, psychomotor activity, mood, and perception. The DOSS test performance characteristics demonstrated a high inter-rater reliability with an alpha of 0.93 and alpha of 0.96 as well as concurrent validity found to be statistically significant ($p \leq .001$) when compared against tools previously validated to assess delirium including the Confusion Assessment Method (CAM), Mini-Mental State Exam (MMSE), and Informant Questionnaire of Cognitive Decline in the Elderly (IQOCDE) (Schuurmans et. al, 2003).

Of the 566 older adult patients, 168 (29.68 %) had a preexisting diagnosis of dementia prior to surgery. Of the 566 patients, delirium (either preoperative, postoperative, or both) was observed in 196 patients (34.63% of all subjects). It was noted that patients of both groups experienced delirium preoperatively. Prior research identifying independent precipitating factors for delirium can explain possible reasons for

preoperative delirium in a hip fracture population: placement of urinary catheters (due to immobility caused by the hip fracture), more than three medications added (new pain medication or antibiotics for infection), and malnutrition (loss of appetite and decreased mobility) (Inouye & Charpentier, 1996). However, study findings did differentiate between the incidence of preoperative delirium from postoperative delirium in their results. In the group of 168 patients with a pre-existing diagnosis of dementia, 97 (57.73%) experienced delirium. Of these 97 dementia patients, 27 patients (27.82%) had delirium before surgery and 70 (72.16%) patients displayed postoperative delirium. When dementia patients with preoperative delirium were eliminated, 41.67% (70 out of the 168 dementia patients) were found to have postoperative delirium. These findings were compared against the non-dementia group of 398 patients. In the non-dementia group, 99 out of 398 patients developed delirium (24.87%), 19 patients experienced preoperative delirium and 80 patients developed postoperative delirium. Out of the 196 patients who had any form of delirium, the overall incidence of postoperative delirium was statistically significant ($p < .001$) between dementia and non-dementia patients: 70 out of all 168 dementia patients (41.67%) versus 80 out of all 398 non-dementia patients (20.1%). Furthermore, delirium correlated with an increased hospital stay ($p= .001$), 94 out of all 196 delirium patients (47.96%) had higher rates of complications ($p < .001$) and 59 out of all 196 delirium patients (30.10%) had a higher rate of mortality within six months ($p < .001$). Ultimately, this study showed that dementia appears to be one of the most important risk factors for delirium and that risk factors, such as dementia, should be assessed upon admission in order to help prevent delirium incidence.

Dementia Biomarkers and Delirium

Based on the findings from the prior three studies, patients with pre-existing diagnosed dementia are likely to have worse surgical outcomes, specifically an incidence of postoperative delirium when compared to non-dementia patients. However, as previously stated, not only does preoperative evaluation not routinely prescreen for dementia signs or symptoms but biomarker pathology presents before clinical diagnosis. Although there has been a higher probability of and risk for postoperative delirium in dementia patients, older adults without clinical signs or symptoms of dementia have developed delirium postoperatively resulting in the same negative consequences.

The field of research involving the neuropathophysiology of postoperative delirium remains in its beginning stages as The National Institute on Aging is currently funding clinical trials examining potential links between dementia biomarkers and postoperative delirium with hopes to discover a biomarker can be utilized as a prescreening intervention and predictor for postoperative delirium (Department of Health and Human Services, 2016). The following studies explored dementia biomarkers in non-dementia older adult patients and the incidence of delirium. Researchers have studied the pathophysiology of diagnostic biomarkers for dementias such as Alzheimer's disease (AD) and its relationship to postoperative delirium. The following studies' findings suggest that dementia biomarkers, which are present long before clinical signs and symptoms, could be potential predictors for postoperative delirium in non-dementia patients.

McGhee et al. (2014) utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to investigate multiple clinical trials that utilized

different biomarker modalities in Alzheimer's disease (AD) progression. The purpose for this review was to analyze multiple quantitative research studies in order to suggest the study of specific biomarkers in future AD clinical trials. Using the PRISMA framework, their database search identified 8,234 records. Their electronic search strategy was verified by hand-searching which revealed a sensitivity of 100% and specificity of 99.1%. After removing duplicate identified articles, 5,416 remained. They screened the 5,416 articles and found that 22 of them were review articles, and further narrowed the remaining articles by reading abstracts. Authors found that 308 could be assessed for eligibility. Full-text articles were excluded if there were no diagnostic criteria, analysis included people without Alzheimer's disease, and if the primary sources were a longitudinal or cross-sectional study. Data extracted also included participant study size and participant characteristics, biomarkers investigated, methods used, and follow-up findings. Data was assessed twice for quality by a single reviewer using a questionnaire from a prior biomarker systematic review

After the extraction and analyzing of 59 studies investigating 9 biomarkers using PRISMA, the median quality score for the 56 studies was low at 7.0 out of a possible 16.0. Authors found this was due to a low sample size (median of 31) and due to only 76% of the studies performed a correlational statistical analysis among the two variables: the specific biomarker and clinical measure of disease progression. The authors did examine how many studies utilized each biomarker modality and their association with disease progression. They reported a significant association with AD progression in the most commonly used modality which was the brain MRI. In the 17 out of 59 studies that used a brain MRI as a biomarker modality, 14 reported significant clinical findings with

disease progression. However, this modality was only utilized in 29% of the studies incorporated in their review. Authors did suggest that further research involving this modality was warranted. The authors felt that they did not have enough information to merit the recommendation of a specific biomarker modality for future clinical trials on Alzheimer's disease progression.

A prospective cohort study conducted by Racine et al. (2017) investigated the relationship between the neurodegenerative biomarker identified as the AD signature and its relation to the incidence of delirium in older postoperative adults who underwent major elective non-cardiac surgery. The AD signature refers to the decrease in cortical thickness or atrophy of specific brain regions associated with cognitive decline and dementia progression. This study enrolled 145 non-dementia patients greater than 70 years-old who underwent a preoperative MRI and daily postoperative delirium incidence and severity assessment until discharge. FreeSurfer software at Massachusetts General Hospital and Harvard University was used to determine cortical thickness in AD signature regions of the brain. Delirium incidence was diagnosed using the Confusion Assessment Method (CAM). Delirium severity was diagnosed using the CAM-Severity (CAM-S). Multiple logistic regression was used to analyze AD signature and delirium incidence. Multiple linear regression was used to analyze associations between AD signature association and CAM-S peak (or highest daily score) and the sum of CAM-S scores for each hospitalization day.

Among the entire study group, 32 out of 145 participants (22.06%) developed delirium postoperatively. Multiple logistic regression analysis of all 145 patients showed that neither occurrence or incidence of delirium (measured by CAM) could be predicted

based on cortical thickness of the AD signature region (*OR* = 1.15, 95% C.I. [0.8, 1.6], C-statistic 0.61). However, in the 32 participants who developed delirium, linear regression analysis showed an association between cortical thickness and delirium severity measured by CAM-S peak (b = 1.2, 95% C.I [-2.2, -0.3]) and CAM-S score sum (b = -6.0, 95%C.I. [-9.8, -2.1]). On average, a 1/10 mm reduction in AD signature cortical thickness was associated with an increase of 1.2 points on the CAM-S peak score as well as an increase of 6 points on the CAM-S summed score (p = .014 and p = .004 respectively). These results demonstrated that delirium severity was associated with thinning in the AD signature regions in patients without a diagnosis of dementia. The researchers concluded that preoperative brain imaging that analyzes cortical thickness in regions of the brain, like the AD signature, where neurodegeneration precludes a clinical diagnosis of Alzheimer's Disease, may help to predict severity of postoperative delirium in non-dementia surgical patients.

A prospective cohort study conducted by Xie et al. (2014) investigated the relationship between CSF dementia biomarker concentrations and delirium. The presence of ß-amyloid proteins and Tau protein levels have been linked to Alzheimer's disease pathology. ß-amyloid plaques and Tau protein neurofibrillary tangles were hallmark features in the brain of an individual presenting with clinical signs and symptoms of the disease (Querfurth & LaFerla, 2010). Previous research investigated the amount of these two protein biomarkers in the brain compared to cerebrospinal fluid (CSF) and found that a lower ß-amyloid protein level in CSF, specifically Aß42, was associated with a higher ß-amyloid protein content in the brain and that a higher Tau level in CSF were associated with higher Tau protein content in the brain (Tolboom et al, 2009). Research suggests

reduced CSF Aß42 concentration reflects the accumulation of Aß42 in the brain (Strozyk et al., 2003; Blennow et al., 2015). In addition, research has shown lower CSF Aß42 in individuals with AD compared to individuals without the disease (Blennow et al., 2004) and that higher CSF Tau is associated with the progression of AD (Blom et. al, 2009). These findings, combined with this research group's prior published study which found an association between CSF Aß42/Tau ratios and postoperative cognitive changes in older adults without dementia, led to their question of whether CSF Aß42/Tau ratios were also associated with incidence or severity of postoperative delirium in the same population.

Xie et al. (2014) enrolled 153 patients greater than 63 years-old without a prior diagnosis of AD, other forms of dementia, stroke or psychosis and candidates for spinal anesthesia who were undergoing an elective total hip or knee replacement. Incidence of postoperative delirium was assessed using the CAM and the severity of postoperative delirium was assessed using the Memorial Delirium Assessment Scale (MDAS). The MDAS is a scale of 10 items rating 0 to 3 points for a maximum total of 30 points. A score greater than or equal to 13 indicated a presence of delirium with higher scores representing more severe delirium although this study solely used MDAS scores for severity and to supplement CAM rather than as the tool to diagnosis delirium. The validity study demonstrated a high correlation between scores using MDAS and the Delirium Rating Scale (DRS) ($r = 0.88$, $p < .0001$), the MMSE ($r = .91$, $p < .001$), and clinician's global ratings of delirium severity ($r = .89$, $p < .0001$) (Briebart et al., 1997). One milliliter of CSF was collected from each subject by an anesthesiologist with the spinal needle prior to the administration of the anesthetic through this needle. CSF

concentration of Aß40, Aß42, and Tau proteins were measured using enzyme-linked immunosorbent assay (ELISA) kits by one researcher twice so that the relative differences in values were consistent. Data was presented as median and interquartile range (25-75%) for Aß40/Tau or Aß42/Tau ratios. Statistical analysis with the Mann-Whitney test was used to determine the difference in ratios between subjects with and without delirium. Taking into account that the relationship between ratios and postoperative may not be linear (threshold effect), researchers divided the ratios into quartiles and implemented the Chi-square test to compare the postoperative delirium incidence between lowest ratio quartile and a combination of the second, third, and fourth quartiles. Finally, multiple linear regression was used to analyze the relationship between Aß40/Tau or Aß42/Tau ratios and MDAS scores.

The results of the study did not show a statistic significance between the average Aß40/Tau or Aß42/Tau ratio between those who developed delirium compared to those who did not (Aß40/Tau ratio 12.2 and Aß42/Tau 1.3 in the delirium group; Aß40/Tau ratio 12.6 and Aß42/Tau 1.4 in the non-delirium group). However, investigators found a significant difference in these ratios when the subjects were divided into quartiles. The lowest quartile ratio when compared to the other 3 quartile ratios were found to have an increased incidence of postoperative delirium: 31.58% (12 out of 38 subjects) in the 1st quartile compared to 16.52% (19 out of 115 subjects) in the combined 2nd, 3rd, and 4th quartiles for both Aß40/Tau and Aß42/Tau, respectively (p .= 482). They also found that there was an increase in delirium severity based on MDAS scores. The median of the highest MDAS scores were found to be in the first quartile or those with the lowest Aß40/Tau and Aß42/Tau ratios. The lowest quartile Aß40/Tau ratio had a median MDAS

score of 4 compared with a median score of 3 in the combined 2nd, 3rd, and 4th quartiles (p = 0.034) and the lowest quartile Aß40/Tau ratio had a median MDAS score of 4 compared with a median score of 3 in the combined 2nd, 3rd, and 4th quartiles (p = 0.062). Linear regression showed a significant negative correlation between the highest MDAS scores and Aß40/Tau and Aß42/Tau (Aß40/Tau -0.12 +/- 0.05, p = 0.014 and Aß42/Tau -0.65 +/- 0.26, p = 0.013). Furthermore, multiple linear regression remained significantly negatively correlated after adjusting for age and gender (Aß40/Tau -0.12 +/- 0.05, p = 0.018 and Aß42/Tau -0.62 +/- 0.27, p = .022). In conclusion, the researchers found that subjects with the lowest quartile CSF Aß40/Tau or Aß42/Tau ratios were more likely to develop postoperative delirium and increased severity of delirium suggesting these protein biomarkers could play a role in postoperative delirium pathogenesis.

As demonstrated in the above studies, presence of dementia biomarkers in non-dementia patients have been associated with either increased incidence or severity of postoperative delirium, suggesting that there may be an association between the neuropathology of dementia and postoperative delirium. A relationship between dementia biomarkers and delirium could help predict the incidence of postoperative delirium in the older adult surgical population even when clinical signs and symptoms of the disease are not clinically apparent. If dementia biomarkers are found to predict postoperative delirium incidence, pre-screening for these biomarkers as a preoperative or perioperative intervention to help prevent postoperative delirium could be supported and changes in perioperative and postoperative care would be individualized for those with an “aging” brain as opposed to the general care for an older adult. However, previous studies have not compared biomarker levels between non-dementia patients and dementia patients and

the resulting postoperative delirium outcomes. Thus, biomarkers have only been suggestive of predicting postoperative delirium in non-dementia patients. In order to determine biomarkers as a predictor for postoperative delirium, a comparison must be investigated between patients without clinical signs and symptoms of dementia against those with dementia. The purpose of this systematic review was to determine whether the CSF concentration of Aß42 in non-dementia older adult surgical patients could predict the incidence of postoperative delirium.

Framework

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used as the framework for this systematic review. The PRISMA guideline incorporates a checklist and flow diagram, also referred to as the PRISMA Statement (Moher et al., 2009). The PRISMA flow diagram (Appendix A) describes the four phases used to perform a systematic review: identification, screening, eligibility, and inclusion. The diagram incorporates the numbers of articles included and excluded throughout these phases and essentially summarizes the search strategy utilized for finding relevant randomized controlled trials to be reported in a systematic review (Polit & Beck, 2017). The PRISMA checklist (Appendix B) identifies the 27 items included in what has been deemed to be essential in proper reporting of a systematic review. Liberarti et al. (2009) suggest that PRISMA is an appropriate guideline for systematic reviews to assess, analyze, and report potential benefits or risks of implementing specific healthcare intervention.

Methods

Purpose

The purpose of this study was to determine whether dementia biomarkers, specifically Aß42, would be able to predict postoperative delirium in the older adult surgical population by analyzing biomarker concentration in both patients with pre-existing dementia and non-dementia patients and comparing results between both groups. A systematic review was conducted to find current and relevant research to answer the proposed question: "Will analysis of dementia-associated biomarker Aß42 concentration in CSF in a non-dementia patient be able to predict the incidence of postoperative delirium in the older adult surgical population?"

Search Strategy

A search for primary sources was conducted using multiple databases including CINAHL, MEDLINE/PubMed, OVID Medline and EMBASE. Keywords included "delirium", "Alzheimer's disease", "dementia", and "biomarkers". The Boolean operator "AND" between search terms was used to find most relevant articles.

Inclusion/Exclusion Criteria

Inclusion criteria included studies conducted between 2011 and present, originally published in the English language, and study participants consisting of human subjects only. Inclusion criteria included both United States and international studies. The population included in each study were limited to older adults greater than or equal to the age of 65 undergoing an elective surgical operation involving spinal anesthesia so that CSF would be easily obtained prior to administration of anesthetic. Included studies compared dementia and non-dementia patients. The individuals considered to have a pre-

existing dementia diagnosis required that it was documented in their medical records preoperatively and had been clinically diagnosed by a physician or psychiatrist. Preoperative screening interventions for dementia must have included CSF protein analyzation of dementia-associated biomarkers, specifically Aß42. CSF biomarker Aß42 must have been analyzed as an individual concentration or as ratio with another dementia-associated biomarker (e.g., T-tau or P-tau) since ratios have been previously and commonly reported in order to increase the predictive value for a dementia-related association on a dependent variable or outcome. The outcome investigated must have been either postoperative delirium incidence or severity.

Exclusion criteria included studies that were not originally published in the English language, were outside the 10-year time frame of 2011 to present, patients under the age of 65, non-surgical patients, surgical patients that are non-orthopedic, did not involve both a dementia group and non-dementia group, no documentation of prior cognitive status or lack of documentation for a clinical dementia diagnosis by a medical professional for all subjects, prescreening interventions that did not involve dementia biomarker collection, and whose findings did not examine the outcome of postoperative delirium.

Data Collection

The PRISMA four-phase flow diagram (Appendix A) and PRISMA checklist (Appendix B) was used to select studies chosen to implement in this systematic review. After initial screening, full-text reading of articles was conducted for review inclusion.

Pertinent information was collected from each of the studies identified for this systematic review and was organized into individual data tables (Appendix D, Tables D1

- D4) to compare studies. Individual study data extracted included study purpose, design, sample size of dementia and non-dementia patients, and methods on how dementia and delirium were assessed, outcomes measured, results for CSF Aß42 (or other biomarkers) and postoperative delirium for both dementia and non-dementia patients as well as both groups, and study limitations. Next, individual CASP questionnaires (Appendix E, Tables E1-E4) were completed to assess validity, reliability, and applicability of each study by answering 12 relevant questions evaluating the integrity of each study. Study specific findings included the total number of participants in each study, gender, and average age characteristics, as well as the number of participants in the dementia and non-dementia group. Outcomes examined included the number of participants who developed postoperative delirium in the dementia and non-dementia groups and outcomes for Aß42 concentration and postoperative delirium in the dementia and non-dementia group. In addition to Aß42 concentration values, the outcomes for Aß42 as a combined ratio with other dementia-associated biomarkers were examined since some of the studies looked at multiple dementia-associated biomarkers and postoperative delirium outcome. Lastly, the overall study outcome for Aß42 as predictor for postoperative delirium was extracted in order to ultimately answer the question posed in this systematic review. All study specific findings were organized in a cross-study analysis data table (Appendix F) to compare the results among each individual study.

Critical Appraisal

The quality of evidence was rated using the Critical Appraisal Skills Programme (CASP). CASP is a 3-step approach to rating evidence and offers multiple checklists to assess for quality depending on the type of research or study performed (Critical

Appraisal Skills Programme [CASP], 2018). The CASP Cohort Study (Appendix C) was utilized to critically appraise articles that have met inclusion criteria for this review.

Data Synthesis & Cross Study Analysis

After data was extracted from studies meeting inclusion criteria and individual critical appraisals were completed, a cross study analysis was implemented with all studies which compared the total number of participants in the dementia and non-dementia groups, the number of participants who developed postoperative delirium in each group, group outcomes for Aß42 concentration and as a biomarker ratio, and overall study outcome for Aß42 as predictor for postoperative delirium.

Results

Four research studies met inclusion criteria and were selected for incorporation into this systematic review. The initial search utilizing “delirium” among selected databases resulted in 15,452 studies. The addition of the second keyword “Alzheimer’s” resulted in 1,035 studies. Adding a third search term, “dementia”, resulted in 993 studies. The last keyword added to the search was “biomarker” and resulted in a final total of 10 articles. Prior to article screening, 3 articles were excluded as duplicates leaving a total of 7 articles to be screened. After screening the articles 3 were excluded for not meeting inclusion criteria for this systematic review. Finally, the remaining 4 studies were selected for this systematic review to determine whether or not the analysis of dementia-associated biomarker Aß42 concentration in CSF in non-dementia patients will be able to predict the incidence of postoperative delirium in the older adult surgical population.

Individual Studies

The prospective cohort study by Chan et al. (2021) (Appendix D, Table D-1) was conducted to determine whether depression and postoperative delirium were linked to AD pathology and to determine whether AD pathology could predict a linkage between depression and postoperative delirium. A cohort of 199 consecutive hip fracture patients previously enrolled in a randomized controlled trial, “A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients” (STRIDE) were enrolled in this study if they met inclusion criteria. Inclusion criteria for study subjects was an age of greater than or equal to 65 years-old, a preoperative MMSE score greater than or equal to 15, and plan for a hip fracture repair under spinal anesthesia. Exclusion criteria included preoperative delirium. Dementia status was assessed utilizing the MMSE as well as an

evaluation by a consensus panel of two psychiatrists and one geriatrician using the Clinical Dementia Rating Sum of Boxes (CDR-SB). This evaluation was based on assessing all available clinical cognitive data and the Short IQCODE. Global score of 0-3 (none, mild, moderate, severe dementia). Postoperative delirium was assessed using the Diagnostic and Statistical Manual of Mental Disorders (4th edition) using several sources including CAM, DRS-98, digit span, medical records, and family/nursing staff interviews. CSF Aß40 and Aß42 using MSD electrochemiluminescence assay while T-tau and P-tau were assayed using INNOTEST ELISA assays. Among the 199 patients enrolled, 56 were male, 143 were female, with the average age of a subject being 86 years old. The dementia group contained 80 study subjects and the non-dementia group contained 119 subjects. Although not pertinent to this systematic review, the primary purpose for this study was to determine a link between depression and postoperative delirium in dementia and non-dementia patients. Depression was determined using the GDS-15, a 15-question screening tool designed to assess depressive symptoms in older adults. Although the goal of this study was to explore the association between depression and postoperative delirium and to examine AD pathology as a potential mechanism for depressive symptoms and delirium, other variables (listed in Table D-1) including dementia-associated biomarkers were analyzed which deemed this study appropriate for this systematic review.

Outcomes of this study by Chan et al. (2021) were mixed for AD biomarkers. The study reported that 47 of the 80 dementia patients (58.75%) and 26 of the 119 non-dementia patients (21.85%) had postoperative delirium. Multiple logistic regression model of the incidence of postoperative delirium in relation to multiple baseline

characteristics showed that out of the 18 characteristics analyzed, higher GDS-15 scores and lower MMSE scores were associated with greater odds of postoperative delirium (p = .02 and p = .006 respectively). For the purpose of this systematic review, the outcome for Aß42 concentration and postoperative delirium was analyzed. Based on their findings, there was no difference between the dementia and non-dementia group. Their outcomes demonstrated that individual AD biomarker concentrations were not associated with the odds of developing postoperative delirium after adjusting for covariates (p = .89). However, KappaTree analysis was used to identify factors with the highest classification accuracy for postoperative delirium. Aß42/T-tau ratios showed to be a stronger predictor of postoperative delirium than most of the 18 patient characteristics for the entire population being the third strongest predictor of postoperative delirium with the GDS-15 being the first and highest predictor followed by the MMSE as the second highest or strongest predictor. As previously stated, 73 out of 199 patients (36.68%) developed postoperative delirium. Because their KappaTree analysis computed characteristics based on weighted kappa, Aß42/T-tau ratio was analyzed as a predictor for delirium in those with GDS-15 < or equal to 2 and MMSE >20 or those with no dementia nor depressive symptoms preoperatively, i.e., 15 out of 73 (20.55%) delirium patients. Out of the 15 patients who developed delirium that had no depressive symptoms or preoperative dementia, 9 out of 15 (60%) had an abnormal Aß42/T-tau ratio of ≤ 1.2, which demonstrates AD biomarkers as a higher predictor of postoperative delirium among other patient variables in patients without a preclinical diagnosis of dementia.

When evaluating the integrity of this study utilizing the CASP questionnaire (Appendix E, Table E1) the primary reason this study was incorporated into this

systematic review was because the researchers examined multiple variables including dementia-associated CSF biomarker concentrations and ratios and the outcome of postoperative delirium. Although their primary purpose was to determine a relationship between depressive symptoms and postoperative delirium in dementia and non-dementia patients, their findings for Aß42/T-tau ratio allowed them to make the conclusion that this biomarker ratio was among one of the stronger predictors for postoperative delirium, supporting the inclusion of this study into the systematic review. However, this study was noted to have several limitations. First, this was a small secondary analysis of a single-site clinical randomized trial which may limit findings to individuals motivated to participate in a clinical trial and second, patients on anticoagulants or those with congestive heart failure were excluded thus decreasing the generalizability to a broader adult surgical population.

In an observational single-site study by Cunningham et al. (2019) (Appendix D, Table D-2) 279 patients were enrolled to determine whether APOE €4 (a glycoprotein subtype involved in AD development), CSF Aß42, T-tau, and P-tau would independently predict the risk of postoperative delirium. Inclusion criteria for patients included age ≥ 65 years-old and believed to be without a diagnosis of dementia admitted for primary elective hip or knee arthroplasty. All patients completed an MMSE preoperatively to determine dementia status. Among the 279 study subjects, there were 42 in the dementia group and 237 in the non-dementia group. In the dementia group, 23 were male, 19 were female, and the average age was 74 years old. In the non-dementia group, 100 were male, 137 were female, and the average age was also 74 years old. CSF levels were obtained upon spinal anesthesia prior to surgery. CSF levels of T-tau, P-tau, and Aß42 biomarkers

were quantified and analyzed using ELISA. Patients were assessed postoperatively for delirium once daily for the first 3 days using CAM and utilized at additional times if a nursing staff reported signs or symptoms of delirium. Univariate logistic regression was utilized for baseline characteristics between delirium and no delirium groups. Variables that had p-values significant at the 10% level were entered into binary logistic regression as independent predictors with postoperative delirium as the dependent variable. Although initial criteria for this study excluded a preoperative diagnosis of dementia, researchers found that there was a wide range of MMSE scores and the possibility of enrolling those with preoperative dementia. Thus, analyses were rerun to separate non-dementia patients (preoperative MMSE > or equal to 24) from the total cohort (dementia and non-dementia patients) and analyzed delirium in both groups.

Outcomes of this study by Cunningham et al. (2019) found CSF Aß42 concentration to be the strongest independent predictor of postoperative delirium after elective arthroplasty in older adults without a prior diagnosis of dementia. In the entire cohort of 279 patients, a total of 40 patients developed delirium, i.e., 8 dementia patients (19.04% of entire dementia group) and 32 non-dementia patients (13.5% of entire non-dementia group). This research group reported the baseline characteristics associated with postoperative delirium for the entire study cohort (dementia and non-dementia) and in the MMSE ≥ 24 subgroup (non-dementia) that showed a statistical significance between the delirium and non-delirium groups included age (p = .005 and p = .009, respectively), knee versus hip surgery (p = .014 and p = .015, respectively), MMSE (p = .012 and p = .012, respectively), and CSF Aß42 concentration (p = <.001 and p = <.001, respectively). Binary logistic regression with independent predictors of postoperative delirium found

CSF Aß42 concentration to be significant at the 5% level with the lowest p-value of 0.001 in both the total cohort and in the non-dementia subgroup when compared to other independent predictors of delirium including age, ASA status, CCI, IQR, IQ, CSF T-tau, CST P-tau, type of surgery, and IV opioids.

Furthermore, analysis of raw data for the average CSF Aß42 concentration for the purpose of this systematic review demonstrated a relationship between CSF Aß42 concentration in dementia and non-dementia patients and postoperative delirium outcomes. The average Aß42 concentration in the entire cohort was 601.7 ng/L with those who developed delirium found to be lower with an average of 496 ng/L and with those who did not develop delirium with an average of 619.2 ng/L. In evaluating each group individually, there was no significant difference between the average Aß42 concentration and postoperative delirium. However, in the non-dementia group (≥ 24 on MMSE) there were significant findings for those who developed delirium compared to those who did not. There was an overall lower average Aß42 concentration in non-dementia patients who developed delirium. Non-dementia patients who developed delirium had an average Aß42 concentration of 496.0 ng/L while the non-dementia patients who developed delirium had an Aß42 average concentration of 637.2 ng/L ($p <$ .001). In evaluating the outcome of Aß42 as a ratio with other dementia-associated biomarkers, there was no difference between those who developed delirium compared to those who did not develop delirium in the dementia group. The outcomes for Aß42 as a biomarker ratio was assumed to be lower given the previous finding that Aß42 concentration alone predicted incidence of postoperative delirium, thus Aß42 as a ratio with another dementia-associated biomarker was found to be highly correlated because of

the significance Aß42 concentration alone had on postoperative delirium in the non-dementia group. The study's statistical data was shown to be significant and supports Aß42 concentration being an independent predictor for postoperative delirium in the non-dementia older adult surgical population.

When evaluating the integrity of this study utilizing the CASP questionnaire (Appendix E, Table E2), there were additional variables reported by this research group that could have affected delirium outcomes such as age, comorbidities, and baseline functional abilities. One limitation of this study, as reported by this research group, was the possible inclusion of patients with preexisting clinical dementia. However, sensitivity analyses using an MMSE cut off of ≥ 24 mitigated this concern by promoting the integrity of this study and attempt to report accurate findings. Another limitation in this study included the absence of official screening of delirium preoperatively; however, this researcher group assumed that patients "must be well" to undergo elective surgery and any apparent delirium would have warranted a cancellation of going through with a surgical procedure. Based on their preoperative detection for delirium and using the MMSE for dementia diagnosis, the study was deemed applicable and appropriate for incorporation into this systematic review.

The prospective controlled study by Henjum et al. (2018) (Appendix D, Table D-3) was performed to determine a relationship between postoperative delirium and CSF concentration of the soluble fragment of TREM2 (sTREM2), a protein linked to prodromal and asymptomatic Alzheimer's disease, in hip fracture patients with and without dementia. Although the primary investigation involved the role of CSF sTREM2, additional dementia-associated biomarkers including Aß42, T-tau, and P-tau were

examined and for influence on postoperative delirium outcomes in dementia and non-dementia patients. Dementia was diagnosed based on ICD-10 dementia criteria and consensus by geriatrician and psychologist upon reviewing clinical data and medical records. There were 117 participants included in the study. In the dementia group, there was a total of 60 participants, 16 males, 41 females, with an average age of 84 years old. In the non-dementia group, there was a total of 57 patients, 16 males, 41 females, with an average age of 86 years old. CSF was collected at the onset of spinal anesthesia before administering anesthetic agents for the surgical procedure. CSF levels of sTREM2, T-tau, P-tau, and Aß42 were quantified and analyzed using ELISA. Delirium was assessed using CAM by a study physician or study nurse preoperatively and then daily until the fifth postoperative day or on additional days through to discharge in cases where symptoms of delirium were observed.

Outcomes of this study by Henjum et al. (2018) found that in subjects without pre-existing dementia and particularly those who developed delirium postoperatively, a higher level of sTREM2 was found in the CSF. CSF Aß42 concentration was analyzed in relation to sTREM2 due to the primary purpose of this study was the investigation between CSF sTREM2 and delirium. CSF Aß42 concentration correlated positively with sTREM2 in the entire cohort and in patients with dementia and correlated most positively with dementia patients with delirium. Although this study did not utilize tests for statistical significance for CSF Aß42 concentration as an independent predictor of postoperative delirium, extraction, and analysis of raw data for the purpose of this systematic review showed an apparent association between postoperative delirium outcomes with the overall average CSF Aß42 concentration in non-dementia patients.

In the non-dementia group of 57 patients, 13 patients (22.81%) developed delirium. The average Aß42 CSF concentration for non-dementia patients who did not develop delirium was 479 pg/mL while the average Aß42 CSF for the non-dementia patients who experienced delirium was 283 pg/mL. Although there was no statistical significance test performed, there was nearly half the concentration of Aß42 CSF in non-dementia patients who developed delirium compared with those who did not. In the dementia group consisting of 60 patients, 50 patients (83.33%) developed postoperative delirium. The average Aß42 CSF concentration for a dementia patient who did not develop delirium was 317 pg/mL while those who developed delirium had an average Aß42 CSF concentration of 283pg/mL. As shown in both the dementia and non-dementia groups, there was an overall lower average Aß42 CSF concentration between patients who did and did not develop delirium in each group. However, there was clearly a larger difference between average Aß42 CSF concentration between patients who developed delirium against those who did not in the non-dementia group. Thus, interpretation of this raw data can suggest Aß42 CSF concentration as a predictor of postoperative delirium in non-dementia patients but cannot be reported as an independent predictor since statistical significance tests were not performed to determine this.

When evaluating the integrity of this study utilizing the CASP questionnaire (Appendix E, Table E3), the study did report data that was pertinent to this systematic review. However, there were limitations to be noted in this study. As the research group reported, their small sample size limits the generalizability of results to the entire older adult surgical population. Another limitation of this study was that delirium was not officially assessed preoperatively and similar to the previous study, those undergoing

elective surgery are usually prevented from undergoing a procedure if they demonstrate signs and symptoms of delirium preoperatively. For this reason, the study remained accepted and incorporated in this systematic review.

The exploratory study by Idland et al. (2017) (Appendix D, Table D-4) investigated whether CSF biomarkers Aß42, T-tau, and P-tau are associated with delirium in hip fracture patients with and without dementia. The study enrolled 129 patients that included 65 patients without dementia and 64 patients with dementia. In the dementia group, there were 64 patients, 17 males, 47 females, with an average age of 85 years old. In the non-dementia group, 65 patients were enrolled which included 17 males, 48 females, and an average age of 84 years old. CSF samples were taken by the anesthesiologist prior to injection of anesthetic agent. CSF biomarkers Aß42, T-tau, and P-tau were quantified and analyzed using ELISA. Subjects were classified as Aß42+ (< 530 ng/L) or Aß42- (≥ 530 ng/L), T-tau+ (> 350 ng/L) or T-tau- (≤ 350 ng/L), and P-tau+ (≥ 60 ng/L) or P-tau- (<60 ng/L). Dementia was assessed upon admission by a psychiatrist and geriatrician using medical records and diagnoses that fulfilled ICD-10 criteria. They were allowed to extract information from clinical records (previous dementia diagnoses, cognitive test results, IQCODE scores, CDR scores, and NEADL at admission. Delirium was assessed preoperatively using CAM by study physician or study nurse until the fifth postoperative day or, in cases where delirium status was positive, delirium was assessed until hospital discharge. Chi-Square tests or Fisher's Exact tests were used for analyses of categorical variables. Ratios of Aß42 to T-tau and P-tau were calculated due to the potential increase in the predictive value of CSF biomarkers to delirium. In the non-dementia group, logistic regression analyses were conducted to

adjust for potential confounders in the association between biomarker concentration and delirium.

Outcomes of this study by Idland et al. (2017) reported that overall that CSF Aß42 concentration as well as CSF Aß42 expressed as a ratio with T-tau or P-tau (i.e. Aß42/T-tau and Aß42/P-tau) serve as independent predictors for postoperative delirium in the non-dementia older adult surgical population. In the dementia group, 51 study subjects (79.68%) developed delirium. There was no significant difference in the Aß42 concentration and Aß42/biomarker ratios between those who developed delirium and those who did not in the dementia group. In contrast, there was a statistically significant difference among participants in the non-dementia in Aß42 concentration, Aß42/T-tau, and Aß42/P-tau for those who developed delirium and those who did not develop delirium. Overall, there were 16 participants that developed delirium (24.61%) out of the 65 non-dementia patients and displayed and overall lower median CSF Aß42 concentration of 310 ng/L compared to 489 ng/L in the non-dementia patients who did not develop delirium ($p = .006$). In addition to Aß42 concentration, researchers also found that there was a higher median CSF T-tau concentration of 505 ng/L compared to a median of 351 ng/L in patients who did not develop delirium although this concentration was not found to be statistically significant ($p = .02$). Lastly, in the non-dementia group, patients with delirium also had lower Aß42/T-tau ratios ($p < .001$) and Aß42/P-tau ratios ($p = .001$) relative to those without delirium. The overall outcome of this study suggests Aß42 concentration, Aß42/T-tau, and Aß42/P-tau are independent predictors of postoperative delirium in non-dementia older adult surgical patients.

When evaluating the integrity of this study utilizing the CASP questionnaire (Appendix E, Table E4), the study addressed a clear relationship using tests which showed statistical significance and clearly answered the question addressed in this systematic review. Limitations of this study, as mentioned by the research group, include the small sample size. A small sample size makes generalizability to entire older adult surgical population difficult as it may not be as applicable as a larger study sample would be. Another limitation of this study mentioned was retrospective dementia diagnoses performed for all subjects, meaning that there was no cognitive assessment upon hospital admission but rather the diagnoses were made based on prior documentation in subjects' medical records. However, the researchers reported that their consensus cognitive diagnosis minimize this limitation as it was "more accurate" than solely basing an individual's cognitive diagnosis on IQCODE cut-offs.

Cross-Study Analysis

All four studies compared dementia and non-dementia patients and postoperative delirium outcomes. Two of the four studies, Cunningham et al., (2019) and Idland et al., (2017), demonstrated Aß42 concentration as an independent predictor for postoperative delirium in non-dementia older adult surgical population utilizing tests for statistical significance. These two studies also reported significant findings for Aß42 as a ratio with other dementia-associated biomarkers as independent predictors of postoperative delirium in the non-dementia older adult surgical population. The remaining two studies by Chan et al., (2021) and Henjum et al., (2018) did not implement tests for statistical significance for Aß42 concentration or Aß42 as a ratio in predicting postoperative delirium. However, Aß42 was included among the other variables examined in both studies and thus the

outcomes can only suggest a possible relationship between Aß42 and postoperative delirium but not as a predictor for postoperative delirium. Chan et al., (2021) reported Aß42/T-tau ratio as the third highest predictor after the GDS-10 and the MMSE for postoperative delirium in non-dementia patients using their KappaTree analysis.

To summarize the dementia groups among all studies, 3 out of the 4 studies showed no difference in Aß42 concentration for dementia subjects that developed postoperative delirium compared to dementia subjects who did not. Only 1 study showed that there was a slightly lower average Aß42 concentration in the dementia subjects who developed postoperative delirium compared to the dementia subjects who did not develop postoperative delirium. In addition, the dementia groups in 3 out of the 3 studies that analyzed Aß42 as a ratio with another dementia-associated biomarker found there was no difference in values between dementia patients who developed delirium and those who did not.

To summarize the non-dementia groups among all studies, 3 of the 4 studies reported a difference in average Aß42 concentration between non-dementia patients that developed postoperative delirium compared to non-dementia patients who did not develop postoperative delirium. Of these 3 studies, 2 studies were able to report Aß42 concentration as an independent predictor of postoperative delirium in non-dementia patients using tests for statistical significance. In addition, there were 3 out of the 4 studies that analyzed Aß42 as a ratio with another dementia-associated biomarkers. Lower average Aß42/T-tau ratios were reported in 3 out of the 3 studies and lower average Aß42/P-tau ratios were reported in 2 of the 3 studies for non-dementia patients who developed postoperative delirium compared to those who did not.

Summary and Conclusions

Prior research has demonstrated that among the entire older adult surgical population, individuals with dementia are at a higher risk for developing postoperative delirium (POD), a complication that leads to increased hospital length of stay (LOS) and increased short-term mortality (Fick, 2013; Kassahun, 2018). Unfortunately, the neuropathology of POD still remains unclear making predicting and preventing this complication in the older adult surgical population difficult. Knowing that dementia patients are at higher risk for developing POD allows healthcare providers to tailor treatment to individuals with dementia to prevent this complication. However, predicting POD in the entire older adult surgical population becomes more difficult since alterations in dementia-associated biomarkers are present in the brain and CSF up to ten years prior to the emergence of clinical signs or symptoms of the disease (Olsson et al, 2016). The lack of apparent signs and symptoms of dementia in older adult surgical patients with underlying clinical pathologies puts them at the same risk level for developing POD as a patient with dementia.

Efforts by scientists have been made towards discovering whether there is a relationship between the neuropathology of postoperative delirium and dementia pathology since dementia patients present most frequently with this complication in the older adult surgical population (Kassahun, 2018). Amyloid-42 (Aß42), a biomarker commonly associated with Alzheimer's disease, has demonstrated that lower cerebrospinal fluid (CSF) Aß42 reflects the accumulation of Aß42 in the brain and is seen before the clinical emergence of the disease (Fagan, 2006). More recent studies have evaluated multiple dementia-associated biomarkers as concentrations (Tolboom et. al,

2009; Blom et. al, 2009) as well as in ratios (Xie et. al, 2014) to increase the value of dementia pathologies to postoperative delirium.

The purpose of this systematic review was to investigate whether the preoperative CSF concentration of Aß42 in non-dementia older adult surgical patients predicts the incidence of postoperative delirium. A comprehensive literature review was completed using CINAHL and MEDLINE/PubMed databases for articles focusing on postoperative delirium, evidence for a potential relationship between dementia and postoperative delirium, and the presence of dementia biomarkers and postoperative delirium occurrence. PRISMA as the framework chosen to assist in the identification and evaluation of articles incorporated into this systematic review which consists of a 27-item checklist and four-phase flow diagram.

Individual study analysis was completed on the final four studies incorporated into this systematic review. Data that was pertinent to addressing this systematic review was extracted and organized into data collection tables. Critical Appraisal Skills Programme (CASP) checklists were utilized to evaluate the integrity of each individual study. Finally, a cross-study analysis table was developed to analyze and compare outcomes across the four studies.

In the overall cross-study analysis, findings from the studies in this systematic review suggest that there is involvement of CSF Aß42 in postoperative delirium pathology in the non-dementia older adult surgical population. The purpose of this systematic review was to investigate whether the preoperative CSF concentration of Aß42 in non-dementia older adult surgical patients predicts the incidence of postoperative delirium. Findings suggest that CSF Aß42 as concentration or as a

combined ratio with another dementia-associated biomarker was either a predictor for postoperative delirium (based on statistical significance) or suggestive of involvement based on data trends and averages in the non-dementia older adult surgical patient. Although only two of the four included studies utilized tests for statistical significance, all of the studies reported at least dementia-biomarker involvement or trend that supports future research to determine whether the preoperative CSF concentration of Aß42 of a non-dementia older adult can predict the incidence of postoperative delirium.

There were several limitations to this systematic review. First, the small sample size of patients enrolled in each study and thus the small amount of dementia and non-dementia patients limits the generalizability of these findings to the entire older adult surgical population. A second limitation was the variety of methods used for diagnosing preoperative cognitive status, e.g., the ICD-10 criteria and the MMSE. Furthermore, some studies had differing MMSE cut-off values for what was considered to be a dementia patient versus a non-dementia patient. The lack of standardization in assessment tools and their baseline values could have affected overall outcome and findings for this systematic review. A third limitation is the lack of statistical significance testing among some of the studies. Without statistical significance, the final answer for Aß42 as a predictor in the non-dementia older adult surgical patients is inconclusive.

The most important limitation to the outcome of this systematic review is the scarce amount of published literature that was available to include in answering the purpose of this systematic review. The relationship between the neuropathology of delirium and dementia is currently a popular area of interest in which multiple government-funded studies are actively enrolling subjects into study trials. Thus, a

limited amount of completed or published studies were available to compare in a cross-study analysis. Future research findings from these studies will hopefully be able to address the relationship between dementia and postoperative delirium in the older adult surgical population. Results could either support or oppose CSF biomarker analysis for the older adult surgical population in efforts to decrease the outcome of postoperative delirium.

In conclusion, results for this systematic review are inconclusive but suggest that Aß42 may be a potential independent predictor of postoperative delirium in the older adult surgical population. Additional research with larger sample sizes of dementia and non-dementia patients that investigate the relationship between dementia biomarkers need to be conducted in order to confirm whether dementia biomarkers are a strong sole predictor for postoperative delirium regardless of preoperative cognitive status or clinical signs and symptoms of dementia. Prescreening for dementia pathologically by obtaining values for CSF dementia biomarkers and analyzing individual concentrations or together as ratios could potentially decrease the outcome for postoperative delirium in the older adult surgical population. Incorporating dementia biomarker analysis of CSF into a preoperative or perioperative assessment could alert healthcare providers of a patient's potential to develop postoperative delirium and allow providers to optimize the quality of care for an at-risk individual.

Recommendations and Implications for Advanced Nursing Practice

An important theme among the studies presented in this systematic review is that the realm of neuroscience demonstrates a potential correlation between dementia biomarkers and postoperative delirium pathogenesis. Future studies will include randomized controlled trials rather than observational or retrospective studies of the older adult surgical population with dementia and non-dementia patients. Overall outcomes from these studies could report that dementia-associated biomarkers are independent predictors of postoperative delirium in the non-dementia older adult surgical population. If future clinical trials are able to confirm a relationship or correlation between dementia pathophysiology by analyzing CSF biomarker concentration and postoperative delirium, preoperative or perioperative CSF biomarker analysis would be beneficial as a prescreening intervention to predict and prevent postoperative delirium in the older adult surgical population.

Currently, preoperative evaluation does not routinely include prescreening for dementia pathologies for non-dementia patients. Prescreening for dementia biomarkers along with preoperative cognitive evaluation of an older adult surgical candidate followed by early postoperative delirium assessment could allow for better care of the older adult surgical population as care would be tailored to the individual with existing dementia pathologies rather than implementing a generalized plan of care for the older adult surgical population. Furthermore, the global “precision medicine” healthcare initiative would be supported, which focuses on treatments developed according to individual variability such as genes, environment, and lifestyles. As a result, there may be a decreased incidence and severity of postoperative delirium among the older adult

surgical population resulting in decreased hospital stays, morbidity and mortality rates and overall healthcare costs. More importantly, implementing interventions based on these findings would improve patient care and promote patient safety.

The advanced practice nurse can play a role in prescreening for dementia pathology by obtaining values for CSF dementia biomarkers and analyzing individual concentrations or ratios which could potentially decrease the outcome for postoperative delirium in the older adult surgical population. Incorporating dementia biomarker analysis of CSF into a preoperative or perioperative assessment could alert healthcare providers of a patient's potential to develop postoperative delirium and allow providers to optimize the quality of care for an at-risk individual. This offers the advanced practice nurse the opportunity to change a medication regimen or for a certified registered nurse anesthetist to change their anesthetic management in an effort to prevent postoperative delirium. Advanced practice nurses can also encourage patient participation in and recruitment for ongoing clinical trials involving findings for postoperative delirium in the older adult surgical patient.

Plans to disseminate the findings of this systematic review include publication as the Master of Science in Nursing Major Paper required of all graduate students at the Rhode Island College School of Nursing (RICSON) upon graduation. A presentation to faculty and graduate students of RICSON as well patient advocacy communities are among the plans to share findings from this research study and to encourage prescreening preoperatively for dementia in the older adult surgical population. Efforts will be made to alert healthcare providers of underlying dementia pathologies in this population which will encourage providers to alter their practice, provide quality care, optimize outcomes,

and prevent postoperative delirium. Presentation of these systematic review findings at conferences attended by anesthesia providers, geriatricians, neurologists, and advanced practice nurses would be of interest to them as these findings may benefit their patients. Finally, disseminating findings of this systematic review to the principal investigators currently researching the relationship between postoperative delirium and pre-existing dementia biomarkers funded by the National Institute on Aging could be beneficial for future research proposals.

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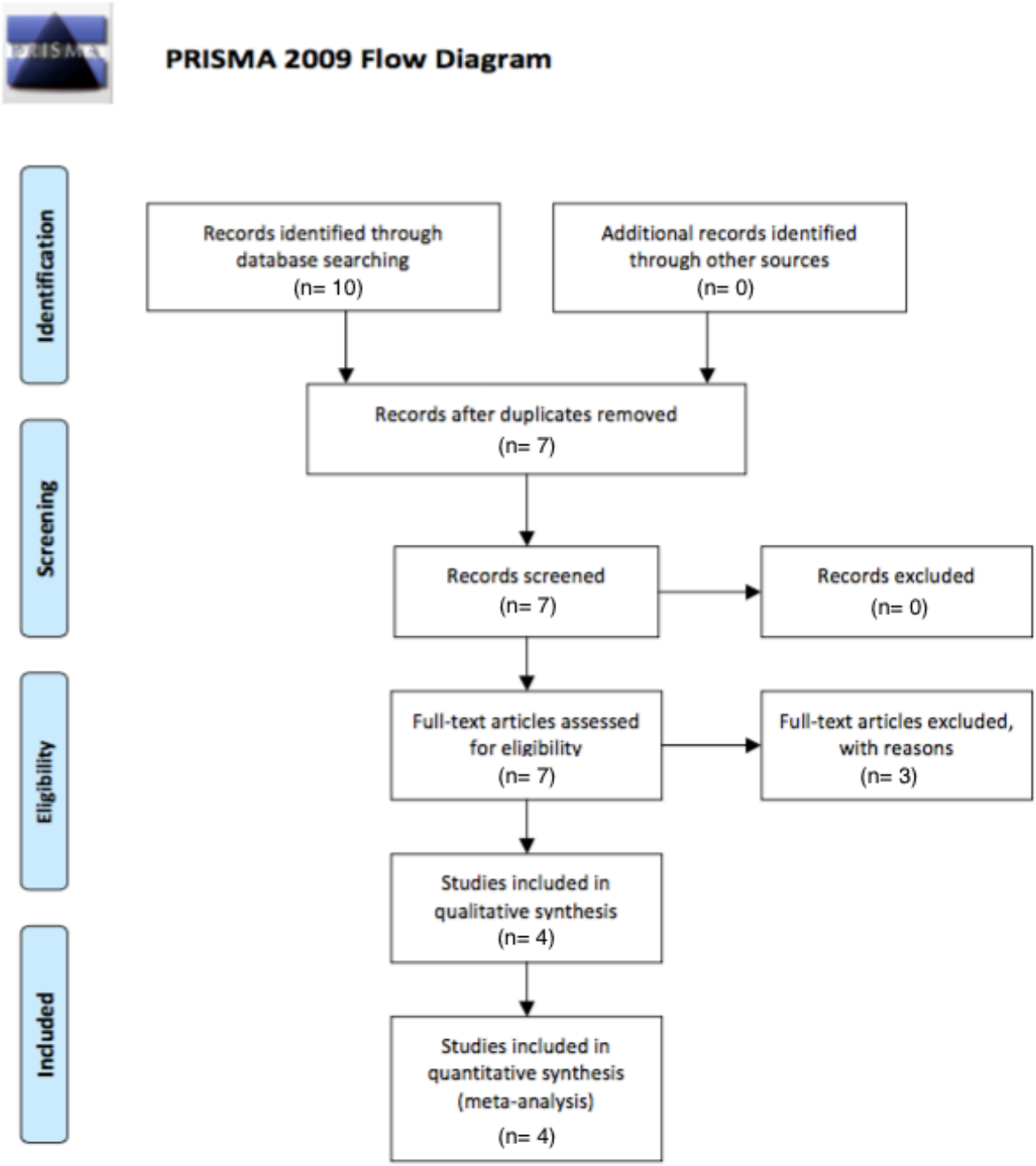
Appendix A

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Four Phase Flow Diagram



Appendix B

PRISMA Check List

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Appendix C

Critical Appraisal Skills Programme (CASP) Cohort Study Checklist

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?			
2. Was the cohort recruited in an acceptable way?			
3. Was the exposure accurately measured to minimized bias?			
4. Was the outcome accurately measured to minimized bias?			
5. (a) Have the authors identified all important cofounding factors?			
5. (b) Have they taken into account of the cofounding factors in the design and/or analysis?			
6. (a) Was the follow up of subjects complete enough?			
6. (b) Was the follow up of subjects long enough?			
Section B: What are the results?			
7. What are the results of this study?			
8. How precise are the results?			
9. Do you believe the results?			
Section C: Will the results help locally?			
10. Can the results be applied to the local population?			
11. Do the results of this study fit with other available evidence?			
12. What are the implications of study for this practice?			

Appendix D

Descriptive Data Tables

D-1

Chan, CK, Sieber, F.E., Blennow, K., Inouye, SK., Kahn, G., Leoutsako, JMS, Marcantonio, ER., Neufeld, K.J., Rosenburg, Wang, N-Y., Zetterberg, H., Lyketsos, Oh, E.S. (2021). Association of depressive symptoms with postoperative delirium and CSF biomarkers for Alzheimer's disease among hip fracture patients. *American Journal of Geriatric Psychiatry*. Advance online publication. https://doi.org/10.1016./j.jagp.2021.02.001

Purpose	Design	Site/Sample	Methods	Outcomes Measured	Results	Limitations
To determine whether depression is associated with postop delirium and AD biomarkers and to determine whether depressive symptoms a major finding with postoperative delirium biomarkers and CSF AB biomarkers.	Prospective cohort study enrolled patients from prior RCT "STRIDE" trial "A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients."	199 participants (Male: 56 Female: 143 Mean Age: 82) Dementia: 80 Non-Dementia: 119 Preoperative MMSE score ≥ 15 undergoing hip fracture repair with spinal anesthesia. Exclusion criteria: POD	CSF was obtained during onset of anesthesia and were analyzed for AB-40 and AB42 using MSD electrochemiluminescence assay. T-tau and P-tau were assayed using INNOTEST ELISA. Dementia: Patients completed MMSE and a consensus panel of 2 psychiatrists and 1 geriatrician scored Clinical Dementia Rating Sum of Boxes (CDR-SB) based on assessment of all available clinical cognitive data, the Short IQCODE. Global score of 0-3 (none, mild, moderate, severe dementia). Delirium: Diagnostic and Statistical Manual of Mental Disorders (4th edition) including CAM, DRS-98, digit span, medical records, and family/nursing staff interviews. (Additional depression assessed from GDS-15 scale)	Primary: POD Variables: • Age, sex, race, education, MMSE, GDS-15, CCI, vascular index, ADA physical status classification, ADLs, IADLs • Fracture type • APOE status, • CDR global scale, CDR-S • AB42/T-tau, and AB42/P-tau ratio Statistical analysis: • STATA 16 software and R package KappaTree. • Significance was set at two-sided $p < .05$.	POD: Dementia: 47 (58.75%) Non-Dementia: 26 (21.85%) POD and Aß42 concentration: Dementia: No difference Non-Dementia: No difference Aß42 as a biomarker ratio and POD: Dementia: No difference Non-Dementia: 9 of 26 with Aß42/T-tau ratio ≤1.2	Small secondary analysis of a single site clinical randomized trial. Primary goal of research question was depression as a dementia prodrome for POD. Dementia biomarkers were assessed as secondary variables.

D-2

Cunningham, E. L., McGuinness, B., McAuley, D. F., Toombs, J., Mawhinney, T., O'Brien, S., Beverland, D., Schott, J.M., Lunn, M.P., Zetterberg, H., Passmore, A. P. (2019). CSF beta-amyloid 1-42 concentration predicts delirium following elective arthroplasty surgery in an observational cohort study. *Annals of Surgery, 269*(6), 1200-1205. https://doi.org/10.1097/SLA.0000000000002684						
Purpose	Design	Site/Sample	Methods	Outcomes Measured	Results	Limitations
To determine whether APOE €4 status and CSF fluid Aß42, T-tau, and P-tau will independently predict the risk of postoperative delirium.	Observational cohort study	279 participants Dementia: 42 (Male: 23 Female: 19 Mean Age: 74) Non-Dementia: 237 (Male: 100 Female: 137 Mean Age: 74) Admitted for primary elective hip or knee arthroplasty admitted to a single surgical center.	All patients completed an MMSE preoperatively. CSF levels were obtained upon spinal anesthesia prior to surgery. CSF levels of T-tau, P-tau, and Aß42 biomarkers were quantified and analyzed using ELISA. Delirium: Patients were assessed postoperatively for delirium once daily for the first 3 days using CAM. CAM was utilized at additional times if a nursing staff reported signs or symptoms of delirium. Dementia: MMSE administered preoperatively by nursing staff. *Belief that they may have included patients with prior dementia they analyzed as a total cohort versus those with MMSE > or equal to 24 (no dementia) and the results for delirium.	Primary: CSF AB42 and POD. Additional variables: age, comorbidities, baseline functional abilities, additional dementia-associated biomarkers.	POD: Dementia: 8 (19.05%) Non-Dementia : 32 (13.5%) POD and Aß42 concentration: Dementia: No difference Non-Dementia: Lower average Aß42 496.0 ng/L vs was 637.2 ng/L ($p < .001$) Aß42 as a biomarker ratio and POD: Dementia: No difference Non-Dementia: Assumed lower	Pts were not assessed for delirium preoperatively. May have possibly included patients with undiagnosed dementia.

D-3

Henjum, K., Quist-Paulsen, E., Zetterberg, H., Blennow, K., Nilsson, L. N., Watne, L. O. (2018). CSF sTREM2 in delirium-relation to Alzheimer's disease CSF biomarkers Aß42, t-tau, and p-tau. *Journal of Neuroinflammation, 304*(15), 1-15. https://doi.org/10.1186/s12974-018-1331-1						
Purpose	Design	Site/Sample	Methods	Outcomes Measured	Results	Limitations
To determine a relationship between CSF sTREM2 and/or Alzheimer's Disease biomarkers CSF Aß42, T-tau, and P-tau and delirium in hip fracture patients with and without dementia.	Prospective controlled trial	117 participants Dementia: 60 (Male: 16 Female: 44 Mean Age: 84) Non-Dementia: 57 (Male: 16 Female: 41 Mean Age: 86)	CSF was collected at the onset of spinal anesthesia before administering anesthetic agents for their surgery. CSF levels of T-tau, P-tau, and Aß42 were quantified and analyzed using ELISA. Delirium: CAM assessment by a study physician or study nurse preoperatively until the fifth POD or in case of delirium until discharge. Pre-existing dementia: based on ICD-10 dementia criteria and consensus by geriatrician and psychologist on clinical data and medical records.	POD	POD: Dementia: 50 (83.33%) Non-Dementia: 13 (22.81%) Dementia: Slightly lower average Aß42 268 pg/mL vs. 317 pg/mL Non-Dementia: Lower average Aß42 283 pg/mL versus 479 pg/mL Aß42 as a biomarker ratio and POD: Not analyzed	Small sample size Dementia was assessed pre-op but delirium was not.

D-4

Idland, A., Wyller, T. B., Støen, R., Eri, L. M., Frihagen, F., Ræder, J., Chaudhry, F.A., Hansson, O., Zetterberg, H., Blennow, K., Bogdanovic, N., Braekhus, A., Watne, L.O. (2017). Preclinical amyloid-b and axonal degeneration pathology in delirium. *Journal of Alzheimer's Disease, 55*, 371-379. https://doi.org/10.3233/JAD-160461						
Purpose	Design	Site/Sample	Methods	Outcomes Measured	Results	Limitations
Whether CSF biomarkers AB42, T-tau, and P-tau are associated with delirium in hip fracture patients with and without dementia.	Exploratory patient cohort from an RCT	129 participants Dementia: 64 (Male: 17 Female: 47 Mean Age: 85) Non-Dementia: 65 (Male: 17 Female: 48 Mean Age: 84)	Exploratory study on a patient cohort from RCT. CSF samples were taken by the anesthesiologist prior to injection of anesthetic agent. CSF biomarkers Aß42, T-tau, and P-tau were quantified and analyzed using ELISA. Subjects were classified as Aß42+ (<530ng/L) or Aß42- (>530 ng/L). Delirium: CAM method by study physician or study nurse pre-op and until the 5th POD or in case of delirium until discharge. Dementia: upon admission by a psychiatrist and geriatrician using medical records and diagnoses that fulfilled ICD-10 criteria. They were allowed to extract information from clinical records (previous dementia diagnoses, cognitive test results, IQCODE scores, CDR scores, and NEADL at admission.	POD	POD: Dementia: 51 (79.69%) Non-Dementia: 16 (24.62%) Dementia: No difference Non-Dementia: Lower median Aß42 310 ng/L vs. 489 ng/L (p = .006) Aß42 as a biomarker ratio and POD: Dementia: No difference Non-Dementia: Lower Aß42/T-tau and Aß42/P-tau ratios (p < .001, p = .001)	Small sample size Dementia diagnoses were retrospective and upon admission to hospital.

Appendix E

Completed Critical Appraisal Skills Programme (CASP) Cohort Study Checklist

E-1 Chan, CK, Sieber, F.E., Blennow, K., Inouye, SK., Kahn, G., Leoutsako, JMS, Marcantonio, ER., Neufeld, K.J., Rosenburg, Wang, N-Y., Zetterberg, H., Lyketsos, Oh, E.S. (2021). Association of depressive symptoms with postoperative delirium and CSF biomarkers for Alzheimer's disease among hip fracture patients. *American Journal of Geriatric Psychiatry*. Advance online publication. https://doi.org/10.1016./j.jagp.2021.02.001

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue? The primary question asked if depression was associated with POD and AD biomarkers and to explore the association between depression and POD while examining AD pathology as a possible link.	X		
2. Was the cohort recruited in an acceptable way? The cohort was recruited in an acceptable way from a prior RCT in which consent was obtained.	X		
3. Was the exposure accurately measured to minimized bias? Yes, the consensus panel of two psychiatrists and one geriatrician were blinded to the intervention scored on the CDR-SB.	X		
4. Was the outcome accurately measured to minimized bias? Study team that evaluated CSF in lab were blinded to patient information as well as the study team who evaluated POD were blinded to GDS-15 scores and prior patient information.	X		
5. (a) Have the authors identified all important cofounding factors? Yes, other baseline characteristics that were considered included age, sex, race, education and CCI along with MMSE and AD biomarkers.	X		
5. (b) Have they taken into account of the cofounding factors in the design and/or analysis? Yes, multiple logistic regression models were performed to examine covariates that could have affected results.	X		
6. (a) Was the follow up of subjects complete enough? Yes, the follow up of the subjects was complete enough with a POD assessment 1-5 or up until discharge if the patient continued with delirium.	X		
6. (b) Was the follow up of subjects long enough? Yes, please refer to 6a.	X		
Section B: What are the results?			
7. What are the results of this study? 73/199 (37% developed POD). Findings were mixed for biomarkers and were primarily analyzed in conjunction with depressive symptoms. In those with GDS-15 < or equal to 2 and MMSE >20 (no dementia or depression pre-op), 9 (or 60%) had an AB42/T-tau ratio of < or equal to 1.2 (abnormal). Biomarkers were not associated with delirium; however, were a strong predictor of delirium when adjusting for covariates. Shown as strong predictor for non-dementia and POD.			
8. How precise are the results? Variables considered were age, sex, race, education, MMSE, GDS-15, CCI, vascular index, ADA physical status classification, ADLs, IADLs, fracture type, APOE status, CDR global scale, CDR-SB, AB42/T-tau, and AB42/P-tau ratio. Statistical analyses were performed with STATA 16 software and R package KappaTree. Significance was set at two-sided $p<0.05$.			
9. Do you believe the results? Yes, when comparing this research studies with other studies that support this finding of AD biomarkers and POD pathology.	X		
Section C: Will the results help locally?			
10. Can the results be applied to the local population? Yes, the results can be applied to the local population and the study population for this systematic review.	X		
11. Do the results of this study fit with other available evidence? Yes, additional studies support the CSF AD biomarkers and linkage to POD in both dementia and non-dementia patients.	X		
12. What are the implications of study for this practice? Implications of study show that AD biomarkers could potentially serve as a predictor for POD in patients with no dementia as they demonstrate pathology for this disease based on CSF findings.	X		

E-2 Cunningham, E. L., McGuinness, B., McAuley, D. F., Toombs, J., Mawhinney, T., O'Brien, S., Beverland, D., Schott, J.M., Lunn, M.P., Zetterberg, H., Passmore, A. P. (2019). CSF beta-amyloid 1-42 concentration predicts delirium following elective arthroplasty surgery in an observational cohort study. *Annals of Surgery, 269*(6), 1200-1205. https://doi.org/10.1097/SLA.0000000000002684

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue? To determine whether APOE €4 status and CSF fluid Aß42, T-tau, and P-tau will independently predict the risk of postoperative delirium.	X		
2. Was the cohort recruited in an acceptable way? Yes, the patients were recruited in an acceptable way where consent was obtained by patient in accordance with local ethical committee procedures.	X		
3. Was the exposure accurately measured to minimized bias? Yes, equal exposure for MMSE and postoperative assessment were the same for all subjects.	X		
4. Was the outcome accurately measured to minimized bias? The study group (in attempts to eliminate when they felt as though they may have included patients with pre-existing dementia) they re-ran analyses with MMSE > or equal to 24 in accordance with STROBE guidance.	X		
5. (a) Have the authors identified all important cofounding factors? Potential confounding operative and anesthetic factors including surgical duration intraoperative blood loss, and hypotension and use of sedatives, opioids and general anesthesia were recorded from medical charts when possible.	X		
5. (b) Have they taken into account of the cofounding factors in the design and/or analysis? Yes, univariate analyses of baseline characteristics and anesthetic factors between the delirium and no delirium groups utilized t-tests.	X		
6. (a) Was the follow up of subjects complete enough? Yes, Patients were assessed postoperatively for delirium once daily for the first 3 days using CAM. CAM was utilized at additional times if a nursing staff reported signs or symptoms of delirium.	X		
6. (b) Was the follow up of subjects long enough?	X		
Section B: What are the results?			
7. What are the results of this study? Total cohort and POD: 282 patients, 40 developed delirium, 242 did not. The average AB42 concentration in the total cohort was 601.7, delirium = 496, and no-delirium = 619.2. Non-dementia > or equal to 24 on MMSE and POD: Similar findings as there were in the total cohort group where CSF AB42 was 618, delirium = 496.0, and no delirium was 637.2. P values in both cohorts was significant at P=<0.001. CSF AB42 concentration was found to be significant at the 5% level for p-values when compared to other independent predictors of age, ASA status, CCI, IQR, IQ, CSF T-tau, CST P-tau, type of surgery, and IV opioids.			
8. How precise are the results? P values in both cohorts was significant at P=<0.001 for CSF AB42 (results for independent predictors were considered when p was at 5% level).			
9. Do you believe the results? I do believe the results given results from other studies that support these findings; however, this research group did not assess the patients for pre-operative delirium although this would have most likely been apparent when assessing patients at the time of the MMSE.	X		
Section C: Will the results help locally?			
10. Can the results be applied to the local population? Yes, the results can be applied to the local population studied in this systematic review.	X		
11. Do the results of this study fit with other available evidence? Yes, the results of this study fit with the other studies in this systematic review where CSF AB42 can serve as a predictor for postoperative delirium in the non-dementia population.	X		
12. What are the implications of study for this practice? This study was the first to show an independent association between CSF AB42 and delirium which raises the possibility that delirium is indicative of an underlying dementia pathology,	X		

E-3 Henjum, K., Quist-Paulsen, E., Zetterberg, H., Blennow, K., Nilsson, L. N., Watne, L. O. (2018). CSF sTREM2 in delirium-relation to Alzheimer's disease CSF biomarkers Aß42, t-tau, and p-tau. *Journal of Neuroinflammation, 304*(15), 1-15. https://doi.org/10.1186/s12974-018-1331-1

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue? Yes, the authors aimed to determine a relationship between CSF sTREM2 and/or Alzheimer's Disease biomarkers CSF Aß42, T-tau, and P-tau and delirium in hip fracture patients with and without dementia.	X		
2. Was the cohort recruited in an acceptable way? Yes, the cohort was recruited in an acceptable way, Patients were recruited from the Oslo Orthogeriatric trial (OOT) between 9/2009-1/2012 where consent was obtained.	X		
3. Was the exposure accurately measured to minimized bias? Yes, pre-fracture dementia was decided upon consensus and based on ICD-10 criteria, delirium was assessed using CAM by a study physician or nurse, and CSF was obtained and collected in the same way.	X		
4. Was the outcome accurately measured to minimized bias? The outcomes were measured equally and accurately where the CSF was collected upon spinal and taken prior to administration of anesthesia.	X		
5. (a) Have the authors identified all important cofounding factors? Yes, additional cofounding factors included age, sex, time to surgery and other AD CSF biomarkers including sTREM2, T-tau, and P-tau.	X		
5. (b) Have they taken into account of the cofounding factors in the design and/or analysis? Yes, multiple linear regression was used for analysis with multiple predictor variables.	X		
6. (a) Was the follow up of subjects complete enough? Yes, I believe the follow-up was complete enough. The CAM assessment was performed by a study physician or study nurse preoperatively until the fifth POD or in case of delirium until discharge.	X		
6. (b) Was the follow up of subjects long enough? Yes, see the above question 6a.	X		
Section B: What are the results?			
7. What are the results of this study? See descriptive data table: a).Non-dementia and no POD: 44 out of 57; Average AB42 CSF = 479 pg/mL b). Dementia and no POD: 9 out of 60; Average Aß42 CSF concentration= 317 pg/mL; Lower level compared with non-dementia group. c). Non-dementia and POD: 13 out of 57; Average AB42 CSF = 283 pg/mL; Level closer to dementia versus non-dementia d). Dementia and POD: 51 out of 60 Average AB42 CSF = 258 pg/mL			
8. How precise are the results? Results are believed to be precise as p-values for CSF AB biomarkers were <0.001.			
9. Do you believe the results? I do believe the results as they were found to be significant value and based off of additional supportive research on CSF AB and postoperative delirium outcomes.	X		
Section C: Will the results help locally?			
10. Can the results be applied to the local population? Yes, the results can be applied to the local population studied in this systematic review.	X		
11. Do the results of this study fit with other available evidence? Yes, additional studies support the CSF AD biomarkers and linkage to POD in both dementia and non-dementia patients.	X		
12. What are the implications of study for this practice? A pre-operative CSF biomarker panel may help patients who may be at risk for developing POD based on their AD pathology findings.	X		

E-4 Idland, A., Wyller, T. B., Støen, R., Eri, L. M., Frihagen, F., Ræder, J., Chaudhry, F.A., Hansson, O., Zetterberg, H., Blennow, K., Bogdanovic, N., Braekhus, A., Watne, L.O. (2017). Preclinical amyloid-b and axonal degeneration pathology in delirium. *Journal of Alzheimer's Disease, 55*, 371-379. https://doi.org/10.3233/JAD-160461

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue? Whether CSF biomarkers AB42, T-tau, and P-tau are associated with delirium in hip fracture patients with and without dementia.	X		
2. Was the cohort recruited in an acceptable way? Yes, the cohort was recruited in an acceptable way, Patients were recruited from the Oslo Orthogeriatric trial (OOT) between 9/2009-1/2012 where consent was obtained.	X		
3. Was the exposure accurately measured to minimized bias? Yes, delirium was by study geriatrician or study nurse preoperatively and until the 5th POD or in case of delirium until discharge once daily using CAM method. CAM scores were based on an interview with patients, including tests of cognition, attention, and alertness (digit span test, orientation, and delayed recall), information from close relatives, nurses, and review of hospital records from previous 24 hours. Dementia assessed upon admission by an "experienced old age psychiatrist" and an experienced geriatrician using medical records and diagnoses that fulfilled ICD-10 criteria. They extracted information from clinical records (previous dementia diagnoses, cognitive test results, IQCODE scores, CDR scores, and NEADL at admission.	X		
4. Was the outcome accurately measured to minimized bias? Yes, delirium and dementia each assessed the same way for all subjects. Both independent doctors were blind to records of delirium status during hospital stay. Inter-rater agreement was very good (kappa 0.87), and disagreements were resolved with discussion.	X		
5. (a) Have the authors identified all important cofounding factors? Yes, additional cofounding factors included T-tau, P-tau, and combined AB42 ratios with these biomarkers. Demographics that were also addressed included age, gender, IQCODE score, prevalence of nursing home residency, ADL score, morbidities (stroke/TIA, DM, ischemic heart disease), APACHE, ADL, and ASA score.	X		
5. (b) Have they taken into account of the cofounding factors in the design and/or analysis? Yes, Mann-Whitney U-tests were used for analyses of continuous variables. Chi-square or Fisher's Exact Tests were used for analyses of categorical variables listed in 5a. Significance was set at $p<0.05$.	X		
6. (a) Was the follow up of subjects complete enough? Yes, dementia status of subjects was further evaluated additional information from cognitive test results, CDR score, and NEADL scores at a one-year follow-up.	X		
6. (b) Was the follow up of subjects long enough? Yes, the follow-up for delirium of subjects was daily POD 1-5 or until discharge if signs of delirium were apparent. Dementia was further assessed at one-year follow up as described in question 4 and 6b.	X		
Section B: What are the results?			
7. What are the results of this study? a).Non-dementia and no POD: 49 of 65. 28 (57%) Aß42+. Statistically significant compared with non-dementia who developed POD. b) Dementia and no POD: 10 of 64. 8 (80%) Aß42+ c) Non-dementia and POD: 16 of 65. 13 (81%) Aß42+ Statistically significant difference compared with non-dementia patients who did not develop POD. d) Dementia and POD: 54 of 64. 51 (94%) were Aß42+ (<530ng/L) All POD groups 37% lower levels compared to no POD groups.			
8. How precise are the results? Subjects were classified as AB42+ (< or equal to 530 ng/L) or AB42- (> or equal to 530 ng/L) according to cut-off values based off of prior research. All statistical analyses for CSF were performed using SPSS Statistics version 21. Mann-Whitney U-tests were used for analyses of continuous variables. Chi-square or Fisher's Exact Tests were used for analyses of categorical variables. Significance was set at $p<0.05$.			
9. Do you believe the results? I do believe the results given the authors addressed the additional cofounding factors that could have affected postoperative delirium outcomes and analyses were adjusted incorporating the additional variables.	X		
Section C: Will the results help locally?			
10. Can the results be applied to the local population? Yes, the results can be applied to the local population studied in this systematic review.	X		
11. Do the results of this study fit with other available evidence? Evidence from other research studies support AD CSF biomarker and postoperative delirium findings from this study.	X		
12. What are the implications of study for this practice? This study shows that AD pathology increases the risk of delirium before presence of measurable chronic impairment. It also shows additional studies with larger sample size need to assess the association between AD biomarkers and postoperative delirium.	X		

Appendix F

Cross-Study Analysis

Authors & Year	Total Participants	Outcome: Postoperative Delirium (POD)	Outcome: Aß42 Concentration and POD	Outcome: Aß42 as a biomarker ratio and POD	Overall Outcome: Aß42 in POD Prediction
Chan et al. (2021)	199 participants (Male: 56 , Female: 143, Mean Age: 82) Dementia: 80 Non-Dementia: 119	Dementia: 47 (58.75%) Non-Dementia: 26 (21.85%)	Dementia: No difference Non-Dementia: No difference	Dementia: No difference Non-Dementia: 9 of 26 with Aß42/T-tau ratio ≤ 1.2	Aß42/T-tau ratio ≤ 1.2 as 3rd highest predictor (1st = GDS-10 and 2nd MMSE)
Cunningham et al. (2019)	279 participants Dementia: 42 (Male: 23, Female: 19, Mean Age: 74) Non-Dementia: 237 (Male: 100 , Female: 137, Mean Age: 74)	Dementia: 8 (19.05%) Non-Dementia : 32 (13.5%)	Dementia: No difference Non-Dementia: Lower average Aß42 496.0 ng/L vs was 637.2 ng/L (< .001)	Dementia: No difference Non-Dementia: Assumed lower	Aß42 as independent predictor (Assumed ratios to be predictor driven by Aß42)
Henjum et al. (2018)	117 participants Dementia: 60 (Male: 16, Female: 44, Mean Age: 84) Non-Dementia: 57 (Male: 16, Female: 41, Mean Age: 86)	Dementia: 50 (83.33%) Non-Dementia: 13 (22.81%)	Dementia: Slightly lower average Aß42 268 pg/mL vs. 317 pg/mL Non-Dementia: Lower average Aß42 283 pg/mL versus 479 pg/mL	Not analyzed	Suggests Aß42 as potential predictor based on trends/data, but no statistical test performed
Idland et al. (2017)	129 participants Dementia: 64 (Male: 17, Female: 47, Mean Age: 85) Non-Dementia: 65 (Male: 17, Female: 48, Mean Age: 84)	Dementia: 51 (79.69%) Non-Dementia: 16 (24.62%)	Dementia: No difference Non-Dementia: Lower median Aß42 310 ng/L vs. 489 ng/L (p = .006)	Dementia: No difference Non-Dementia: Lower Aß42/T-tau and Aß42/P-tau ratios (p < .001, p = .001)	Aß42 as independent predictor Aß42/ratio as independent predictor