Meta-analysis of ICU Delirium Biomarkers and Their Alignment with the NIA-AA Research Framework

Carol K Chan, MBBCh MSc[1],[*], **Yiqing Song, MD, ScD**[2],[*], **Ryan Greene, PsyD**[3], **Heidi Lindroth, PhD, RN**[4],[5],[6], **Sikandar Khan, DO, MS**[4],[5],[6], **Gabriel Rios, MLIS**[8], **Babar Khan, MD, MS**[4],[5],[6], **Sophia Wang, MD**[3],[7]

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD

[2]Fairbanks School of Public Health, Indiana University, Indianapolis, IN

[3]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN

[4]Division of Pulmonary, Critical Care, Sleep and Occupational Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

[5]Indiana Center of Aging Research, Regenstrief Institute, Indianapolis, IN

[6]Center for Health Innovation and Implementation Science, Indianapolis, IN

[7]Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine, Indianapolis, IN

[8]Ruth Lilly Medical Library, Indiana University School of Medicine, Indianapolis, Indiana

INTRODUCTION

30–80% of survivors of critical illness acquire post-intensive care unit (ICU) cognitive impairment (1–3). The mechanisms underlying this association are still uncertain but growing evidence suggests that ICU delirium is a major risk factor for post-ICU cognitive impairment (4,5). A crucial step in understanding this relationship is to examine how the biomarker profile of ICU delirium compares to well-characterized dementia subtypes (e.g. Alzheimer's disease). The National Institute on Aging and Alzheimer's Association (NIA-AA) have recently proposed a research framework for biomarkers related to Alzheimer's disease and other related dementias (ADRD) (6). The framework groups biomarkers into those of β amyloid deposition (A), pathologic tau (T), neurodegeneration (N), and other (X; e.g. markers of inflammation, vascular changes etc), known collectively as AT(N)-X. To examine whether ICU delirium has a comparable biomarker profile to ADRD, we conducted

Corresponding Author Contact Information: Carol Chan, MBBCh MSc, Cchan46@jhmi.edu, Telephone: 410-550-0000 (Work), 443-343-2060 (Home), Fax: 619-393-1088, Address: 600 N Wolfe St, Baltimore, MD 21287.
[*]Both authors contributed equally.

a meta-analysis of ICU delirium biomarker studies to determine their alignment with disease state biomarkers of the AT(N)-X framework.

METHODS

Search Criteria and Strategy

These systematic review and meta-analyses were conducted in accordance with the Preferred Reporting Items for Reviews and Meta-Analyses (PRISMA) guidelines. The search strategy and full inclusion/exclusion criteria were previously described in detail (7). Briefly, Ovid MEDLINE, PsycInfo, Embase, and the Cochrane Library were searched for citations published between January 1st, 2000 through February 20th, 2020 using a combination of controlled vocabulary, keywords, and MeSH terms pertaining to the concepts of delirium and biomarkers in the AT(N)-X framework (6). Inclusion criteria of the search were: 1) age 18 years old, 2) used standardized delirium screening tools or diagnostic assessments, and 3) biomarker measurements listed in AT(N)-X categories (regardless of the modality used). Study exclusion criteria, in brief, were: 1) primary focus on delirium in the following contexts: 1a) premorbid or comorbid ADRD; 1b) psychiatric disorders 1c) central nervous system disorders other than ADRD; 1d) terminal illness; 1e) persistent delirium; 1f) long-term care settings; 1g) risk of delirium; and 2) non-English articles. The aim of excluding studies focused on delirium in 1a – 1f was to eliminate potentially confounding factors. Persistent delirium, terminal delirium, and delirium in central nervous system disorders other than ADRD may have a different etiology from delirium in the general hospital setting, and individuals in the long-term care setting and premorbid/comorbid ADRD likely have abnormal AT(N)-X biomarkers at baseline.

Study Selection

Study selection was conducted by two independent, blinded reviewers, and discrepancies were evaluated by consensus panel. Citations were first reviewed for selection criteria based on title and abstract, followed by full-text review. If multiple articles were published from the same cohort, we included data from the study with the most detailed report of biomarker quantities.

Data Extraction and Quality Assessment

Data extraction was conducted by independent, blind reviewers. Discrepancies were resolved via consensus. Only studies that examined delirium in the ICU setting and fluid biomarkers were included in these analyses. For all studies suitable for meta-analysis, we extracted the means and errors (standard deviations [SD], standard errors [SE], or confidence intervals [CIs]) and sample sizes of each biomarker for delirium cases and non-delirium controls. If SD was not reported, it was calculated from SEs or CIs. For studies that reported the median, the minimum and maximum values, and/or the first and third quartiles, we estimated the sample mean and SD from these quantities. When a study presented estimates in the figures/graphs without providing numerical values, data were obtained from graphs using ImageJ software (http://imagej.nih.gov).

Statistical Analysis

Standardized mean differences (SMDs) and 95% CIs were calculated using DerSimonian and Laird random-effects models. SMDs were chosen as the main outcome because different assays and units were used for biomarkers. Between-study heterogeneity was assessed by a Q-statistic and I^2 Index. The A-Q-statistic was calculated using a chi-squared test to quantify the heterogeneity among combined results. Inconsistency was calculated using the I^2 Index. I^2 of 25%, 50%, and 75% indicate low, medium, and high heterogeneity. All statistical significance was defined as two-sided ($\alpha < 0.05$). All statistical analyses were performed with Stata statistical software version 12 (STATA Corp, College Station, TX). Significance was set at $p<0.05$.

RESULTS

A detailed flow diagram for inclusion and exclusion of studies per PRISMA guidelines is shown in Supplemental figure 1. Methods and results of study quality assessment has previously been published (7).

From the initial 113 studies, 38 studies examined the relationship between ICU delirium and fluid biomarkers. All studies focused on serum biomarkers. Nine included both medical and surgical patients, 11 included only medical patients, and 18 included only surgical patients. CAM-ICU (25 studies) and CAM (8 studies) were the most common methods of delirium assessment. No study assessed the association between "T" (pathologic tau) biomarkers and ICU delirium. 3 studies included "A" (β amyloid deposition) biomarkers. Seven studies examined "N" (neurodegeneration) biomarkers, including neuron-specific enolase (NSE) (4), t-tau (2), and neurofilament light (NFL) (1). Thirty-seven studies included "X" biomarkers, all of which examined inflammatory biomarkers.

Biomarkers that met criteria for meta-analysis included serum $A\beta_{1-40}$, $A\beta_{1-42}$, t-tau, NSE, CRP, IL-1β, IL-RA, IL-6, IL-8, IL-10, IL-17, S100β, TNF-α, and MCP-1. Table 1 and Figure 1 show meta-analysis of biomarkers studied in association with ICU delirium. There was a significant association between ICU delirium and $A\beta_{1-40}$ (SMD = 0.42, 95% CI = 0.09 – 0.75), IL-RA (SMD = 0.58, 95% CI = 0.21 – 0.94) and IL-6 (SMD = 0.31, 95% CI = 0.06 – 0.56). The mean age of participants in studies included in meta-analyses are in Supplemental table 1.

DISCUSSION

To our knowledge, this is the first study to conduct a meta-analysis of AT(N) and inflammatory biomarkers in ICU delirium. We found a modest relationship between ICU delirium and elevated $A\beta_{1-40}$, IL-RA and IL-6, consistent with previously reported patterns of serum amyloid and inflammatory biomarkers in ADRD (8,9). Few studies examined neurodegenerative biomarkers in the context of ICU delirium, and no studies focused on pathological tau were found. Though we were not able to evaluate biomarkers in the "T" and "N" categories in pooled analyses, a significant positive relationship was observed between Aβ1-40 and ICU delirium.

Our findings suggest that there may be overlap in the biomarker profile of ICU delirium and ADRD, and support prior observations that delirium is associated with persistent cognitive dysfunction in survivors of critical illness (5), including a large observational case-control study (n=21,000) (4). It remains unclear whether delirium (1) accelerates cognitive decline in at-risk individuals with premorbid ADRD pathology or (2) causes de-novo ADRD pathology. Further studies directly examining post-ICU cognitive dysfunction and ADRD biomarkers are needed. In contrast to a recent systematic review (8) which noted that in critically ill patients, S100β and CRP were associated with delirium in most studies, we did not find a significant association between ICU delirium and S100β or CRP in our pooled analyses. This discrepancy may be explained by differences in included studies. As an example – for S100B, only 1 of the 6 studies from Michels et al was included in our meta-analysis, while the other 2 studies in our meta-analysis were not reported in their systematic review. Similarly, for CRP only 1 study was included in both Michels et al and our meta-analysis. These differences may be explained by differences in search strategy, including our exclusion of non-English articles and inclusion of studies that did not use the CAM or CAM-ICU to assess delirium, as well as limiting our meta-analysis to studies that were methodologically comparable..

Although the number of studies were limited for the "T" and "N" category, we found a significant relationship between Aβ1-40 and ICU delirium. It should be noted, however, that while we excluded studies with premorbid or comorbid ADRD (a known risk factor for delirium), one of the studies included in the meta-analysis of Aβ1-40 and Aβ1-42 comprised of a delirium group that was older than the non-delirious controls (mean (SD) age = 73 (9.9) vs. 67 (10), p=0.03). This could potentially have introduced bias as amyloid is known to increase with age, even in individuals with normal cognition (10). Though Aβ1-42 is more specific to the pathophysiology of Alzheimer's disease (AD) (11), Aβ1-40 is the most abundant form of Aβ in the brain, and the concentration ratio of Aβ1-42/Aβ1-40 has also been proposed to be a superior biomarker of AD than Aβ1-42 alone (12). Aβ has been associated with increased proinflammatory cytokines in AD (13), though to our knowledge this relationship in the context of delirium has not been investigated. Further study is needed to investigate whether this relationship has implications for the elevated risk of cognitive decline following critical illness.

These findings should be interpreted in the context of their limitations. As a meta-analysis of observational studies, the influence of confounding variables cannot be ruled out or fully assessed. There were few studies that met criteria for meta-analysis, resulting in only 2 studies being included in the meta-analysis of 7 biomarkers. Heterogeneity was high in the meta-analysis of several biomarkers, including CRP and IL-8.

In summary, $A\beta_{1-40}$, IL-RA and IL-6 are associated with ICU delirium, and point to potential overlapping mechanisms between delirium and ADRD. Critical care researchers and clinicians should consider integrating diagnostic approaches used in ADRD in their assessment of post-ICU cognitive dysfunction. Additional studies systematically examining the relationship between ICU delirium and biomarkers in the AT(N) framework, are needed to provide further understanding of the underlying mechanisms of ICU delirium, its relationship with post-intensive care cognitive decline and ADRD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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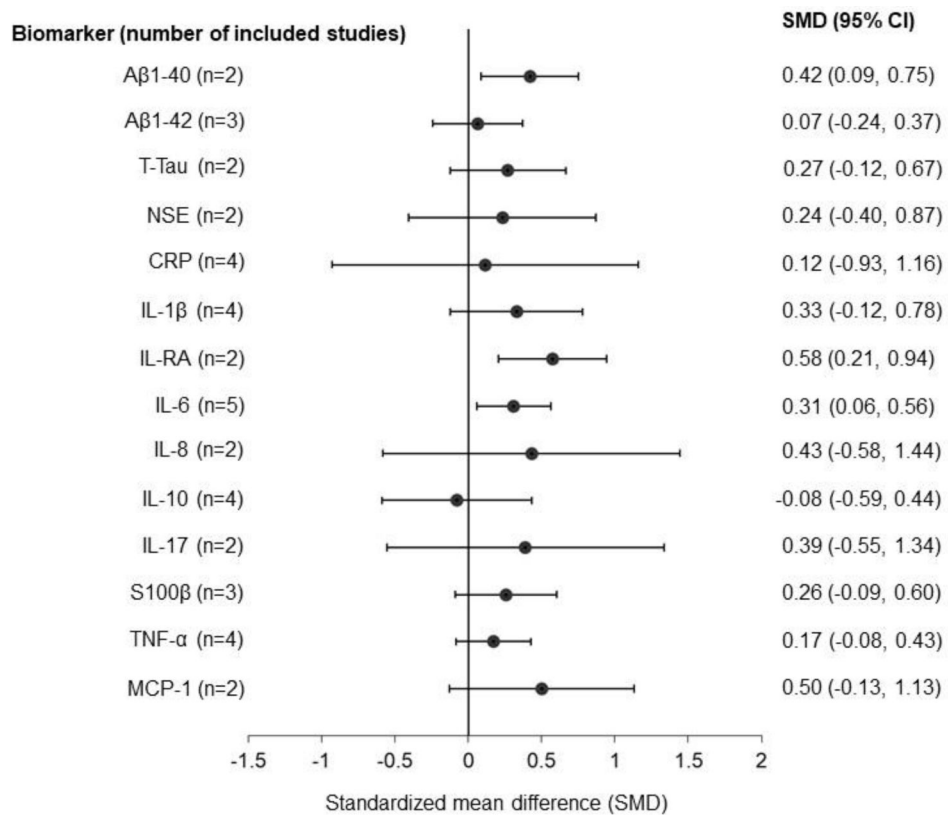
Figure 1. A summary of the results from meta-analyses of the association between biomarkers and ICU delirium. Random-effects meta-analyses were performed to calculate the pooled standardized mean difference (SMD) of each biomarker comparing ICU delirium cases to non-delirium controls. Each black circle indicates the pooled SMD per biomarker. The horizontal line represents the 95% confidence interval. The vertical line represents the null hypothesis. The number (n) in the parentheses indicate the number of included studies in the meta-analysis. Abbreviation: CI, confidence interval; Aβ1-40, amyloid beta-peptide 1–40; Aβ1-42, amyloid beta-peptide 1–42; T-tau, total tau protein; NSE, neuron specific enolase; CRP, C-reactive protein; IL, interleukin; IL-RA, interleukin-1 receptor antagonist; S100β, S100 calcium-binding protein B; TNF-α, tumor necrosis factor α; MCP-1, monocyte chemoattractant protein-1.

Table 1.

Random-effects meta-analysis of studies regarding the association between ICU delirium and biomarkers. Studies are ordered by the year of publication.

	Delirium			Control					
Study	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**
$A\beta_{1-40}$ (pg/mL)									
Van den Boogaard 2011	170.9	73.3	50	140.3	38.2	50	69.8	0.52	0.12 – 0.92
Simons 2018	189.5	75.0	35	174.5	92.4	15	30.2	0.19	−0.42 – 0.79
Total (95% CI)			**85**			**65**	**100**	**0.42**	**0.09 – 0.75**
Heterogeneity: Tau²=0.0; Chi² = 0.83, df = 1 (p = 0.363); I²=0% Test for overall effect: Z=2.48 (p = 0.013)									
$A\beta_{1-42}$ (pg/mL)									
Van den Boogaard 2011	37.4	13.7	50	35.6	8.4	50	69.8	0.16	−0.24 – 0.55
Simons 2018	52.6	17.8	35	57.6	32.7	15	30.2	−0.215	−0.82 – 0.39
Erikson 2018	89.6	68.7	10	78.7	39.3	12	13.3	0.20	−0.64 – 1.04
Total (95% CI)			**95**			**77**	**100**	**0.07**	**−0.24 – 0.37**
Heterogeneity: Tau²=0.0; Chi² = 1.12, df = 2 (p = 0.570); I²=0% Test for overall effect: Z=0.42 (p = 0.671)									
T-Tau (pg/mL)									
Van den Boogaard 2011	52.7	51.1	50	35.2	29.8	50	65.2	0.42	0.02 – 0.81
Simons 2018	51.1	43.1	35	51.3	34.1	15	34.8	−0.01	−0.61 – 0.60
Total (95% CI)			**85**			**65**	**100**	**0.27**	**−0.124 – 0.67**
Heterogeneity: Tau²=0.02; Chi² = 1.31, df = 1 (p = 0.252); I²=23.9% Test for overall effect: Z=1.34 (p = 0.179)									
NSE (ug/L)									
Schramm 2012	22	13	23	15	5	6	46.1	0.59	−0.33 – 1.50
Erikson 2018	21.2	12.7	10	22.2	17.2	12	53.9	−0.07	−0.91 – 0.78
Total (95% CI)			**33**			**18**	**100**	**0.235**	**−0.40 – 0.87**
Heterogeneity: Tau²=0.01; Chi² = 1.07, df = 1 (p = 0.302); I²=6.3% Test for overall effect: Z=0.72 (p = 0.471)									
CRP (mg/mL)									
Pfister 2008	33.3	11.1	12	13.8	21.5	4	25.5	1.40	0.15–2.64
Tsuruta 2010	1.6	1.0	21	1.3	1.7	82	36.8	0.21	−0.27–0.69
Van den Boogaard 2011	21.2	12.7	50	54.8	54.8	50	37.6	−0.84	−1.25 – −0.434
Total (95% CI)			**83**			**136**	**100**	**0.116**	**−0.929 – 1.161**
Heterogeneity: Tau²=0.71; Chi² = 18.25, df = 2 (p = 0.0); I²=89.0% Test for overall effect: Z=0.22 (p = 0.828)									
IL-1β (pg/mL)									
Van den Boogaard 2011	4.1	2.3	50	4.4	3.1	50	31.9	−0.13	−0.52 – 0.26
Skrobik 2013	2.3	2.4	7	1.6	0.7	14	15.3	0.44	−0.47 – 1.36
Ritter 2014	76.5	86.3	31	34.6	26.8	47	29.0	0.72	0.25 – 1.19
Simons 2018	5.4	3.1	35	4.4	0.8	15	23.8	0.40	−0.21 – 1.0

	Delirium			Control					
Study	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**
Total (95% CI)			**123**			**126**	**100**	**0.33**	**−0.12 – 0.78**
Heterogeneity: Tau^2=0.13; Chi^2 = 7.91, df = 3 (p = 0.048); I^2=62.1% Test for overall effect: Z=1.44 (p = 0.151)									
IL-RA (pg/mL)									
Van den Boogard 2011	40.6	38.9	50	22.4	15.3	50	83.9	0.61	0.21 – 1.0
Skrobik 2013	10267.2	7944.5	7	6895.3	9496.1	14	16.1	0.37	−0.54 – 1.29
Total (95% CI)			**57**			**64**	**100**	**0.58**	**0.21 – 0.94**
Heterogeneity: Tau^2=0.0; Chi^2 = 0.23, df = 1 (p = 0.635); I^2=0.0% Test for overall effect: Z=3.07 (p = 0.002)									
IL-6 (mg/mL)									
Pfister 2008	3148.3	6941.9	12	479.6	1174.0	4	4.8	−0.71	1.56 – 4.84
Van den Boogaard 2011	70.9	58.1	50	47.6	44.3	50	40.1	0.45	0.05 – 0.85
Skrobik 2013	160.2	223.1	7	352.4	740.5	14	7.6	−0.31	−1.22 – 0.61
Ritter 2014	331.5	102.6	31	232.0	298.2	47	30.1	0.41	−0.05 – 0.87
Simons 2018	195.0	242.7	35	184.0	348.4	15	17.3	0.04	−0.57 – 0.64
Total (95% CI)			**135**			**130**	**100**	**0.31**	**0.06 – 0.56**
Heterogeneity: Tau^2=0.0; Chi^2 = 3.25, df = 4 (p = 0.517); I^2=0.0% Test for overall effect: Z=2.42 (p = 0.016)									
IL-8 (pg/mL)									
Van den Boogard 2011	29.4	14.5	50	17.4	13.0	50	57.9	0.87	0.46 – 1.28
Skrobik 2013	32.4	51.0	7	42.6	63.4	14	42.2	−0.17	−1.08 – 0.73
Total (95% CI)			**57**			**64**	**100**	**0.43**	**−0.58 – 1.44**
Heterogeneity: Tau^2=0.42; Chi^2 = 4.21, df = 1 (p = 0.040); I^2=76.2% Test for overall effect: Z=0.84 (p = 0.402)									
IL-10 (mg/mL)									
Van den Boogard 2011	32.2	26.7	50	22.2	22.9	50	30.3	0.40	0.00 – 0.80
Skrobik 2013	10.3	15.3	7	7.5	9.3	14	17.0	0.25	−0.67 – 1.16
Ritter 2014	5.8	1.2	31	25.98	52.8	47	28.5	−0.49	−0.95 – −0.03
Simons 2018	14.9	13.9	35	21.7	22.9	15	24.2	−0.40	−1.01 – 0.21
Total (95% CI)			**135**			**130**	**100**	**−0.075**	**−0.59 – 0.44**
Heterogeneity: Tau^2=0.18; Chi^2 = 10.19, df = 3 (p = 0.017); I^2=70.6% Test for overall effect: Z=0.29 (p = 0.773)									
IL-17 (pg/mL)									
Van den Boogard 2011	3.4	0.8	50	3.4	0.8	50	60.3	0.0	−0.39 – 0.39
Skrobik 2013	5.0	2.7	7	3	1.7	14	39.7	0.98	0.03 – 1.94
Total (95% CI)			**57**			**64**	**100**	**0.39**	**−0.55 – 1.34**
Heterogeneity: Tau^2=0.34; Chi^2 = 3.46, df = 1 (p = 0.063); I^2=71.1% Test for overall effect: Z=0.81 (p = 0.417)									
S100β (pg/mL)									
Pfister 2008	0.19	0.12	12	0.01	0.01	4	8.5	0.23	−0.16 – 0.63
Van den Boogard 2011	178.1	148.1	50	148.8	98.5	50	76.8	0.93	−0.25 – 2.11

	Delirium			Control					
Study	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Weight (%)**	**SMD**	**95% CI**
Schramm 2012	500	800	23	500	200	6	14.7	0	−0.90 – 0.90
Total (95% CI)			**85**			**60**	**100**	**0.26**	**−0.09 – 0.60**
Heterogeneity: Tau^2=0.0; Chi^2 = 1.57, df = 2 (p = 0.455); I^2=0% Test for overall effect: Z=1.46 (p = 0.143)									
TNF-α (mg/mL)									
Van den Boogard 2011	10.6	5.3	50	8.7	6.1	50	42.2	0.34	−0.06 – 0.73
Skrobik 2013	11.2	18.0	7	8.3	9.1	14	7.9	0.23	−0.68 – 1.14
Ritter 2014	233.5	401.8	31	218.9	308.2	47	32.0	0.04	−0.41 – 0.50
Simons 2018	4.7	1.5	35	4.7	1.6	15	18.0	−0.01	−0.614 – 0.60
Total (95% CI)			**135**			**130**	**100**	**0.17**	**−0.08 – 0.43**
Heterogeneity: Tau^2=0.0; Chi^2 = 1.36, df = 3 (p = 0.716); I^2=0% Test for overall effect: Z=1.32 (p = 0.187)									
MCP-1 (mg/mL)									
Van den Boogard 2011	404.9	260.3	50	248.2	111.4	50	56.3	0.78	0.38 – 1.2
Simons 2018	327.5	412.0	35	271.7	415.5	15	43.8	0.14	−0.47 – 0.74
Total (95% CI)			**85**			**65**	**100**	**0.50**	**−0.13 – 1.13**
Heterogeneity: Tau^2=0.14; Chi^2 = 3.03, df = 1 (p = 0.082); I^2=67.0% Test for overall effect: Z=1.55 (p = 0.120)									

Abbreviations: SD = standard deviation; SMD = standardized mean difference; CI = confidence interval.