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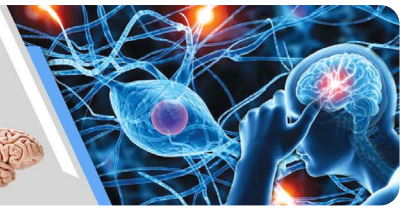

Panel of Plasma Protein Biomarkers for Diagnosing Chronic Traumatic Encephalopathy in Adults

Umema Zafar[1], Syed Hamid Habib[2*], Shahid Bashir[3]

Abstract

Background: Chronic Traumatic Encephalopathy (CTE) is a neurodegenerative disorder often associated with repeated head trauma, yet its clinical diagnosis remains challenging. This scoping review aims to identify a panel of plasma protein biomarkers that may serve as diagnostic tools for CTE in adults.

Methods: Following PRISMA-ScR guidelines, a predefined search strategy was employed to systematically screen the literature and identify relevant plasma biomarkers. Plasma protein biomarkers were identified through a comprehensive review of databases such as MEDLINE and Google Scholar. These biomarkers were evaluated and ranked based on a rubric with criteria including brain tissue specificity, sensitivity of quantification, detectability in blood, and their utility for CTE diagnosis. Each biomarker was scored on a scale from 1 to 3, where 1 represented the least suitable and 3 the most feasible for CTE screening.

Results: Out of the 38 biomarkers, Neurofilament light chain (NfL), phosphorylated tau (p-tau), and neuron-specific enolase (NSE) achieved the highest scores, receiving 12, 12, and 11 points, respectively (out of a maximum of 12).

Conclusion: According to this scoring system, NfL, p-tau, and NSE exhibit optimal characteristics for the diagnosis of CTE, demonstrating superior diagnostic potential when compared to other biomarkers. These findings suggest that a targeted biomarker panel could improve the clinical diagnosis of CTE in adult patients.

Keywords: Chronic Brain Injury; Traumatic Brain Injury; Panel of Biomarkers; Protein Biomarkers; Scoping Review.

Introduction

Mild traumatic brain injury (mTBI) or concussion occurs when the brain collides with the skull, often leading to repeated injuries that can progress into tauopathy over time, potentially resulting in disability and contributing to the economic burden [1]. To date, the only definitive method for diagnosing Chronic Traumatic Encephalopathy (CTE) is through post-mortem brain autopsy. However, emerging evidence suggests that blood biomarkers could offer a viable method for assessing disease severity and predicting outcomes [2,3]. This research aims to recommend a panel of plasma biomarkers identified in the literature that are associated with CTE in adults.

Pathology of CTE

CTE is a progressive neurodegenerative disorder linked to repetitive

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head trauma, originally observed in boxers nearly a century ago and termed "dementia pugilistica" or "punch-drunk syndrome." [4]. More recently, it has been connected with athletes participating in contact sports, military personnel, and individuals exposed to blasts [5] The first comprehensive description of CTE pathology was provided by Corsellis et al. in 1973, who examined post-mortem brains of fifteen former boxers. These brains exhibited atrophy, enlarged ventricles, fenestrations in the septum pellucidum, a thin corpus callosum, and depigmentation of the substantia nigra. Histological analysis revealed neurofibrillary tangles (NFTs), gliosis, blood-brain barrier (BBB) disruption, and senile plaques [6,7] The precise pathophysiology of CTE remains unclear, but one hypothesis suggests that axonal damage following head trauma triggers these changes [8]

The National Institute of Neurological Disorders and Stroke (NINDS) has defined CTE's pathognomonic lesion as p-tau aggregates in neurons, astrocytes, and cell processes surrounding small vessels, predominantly at the depths of cortical sulci [9]. Given that these criteria necessitate post-mortem biopsy, there is a critical need for developing serological diagnostic tools for CTE [10].

Stages and Symptoms of CTE

CTE typically develops gradually, with symptoms progressing through early, late, and advanced stages. Early symptoms often include mood disturbances, intermittent headaches, and motor dysfunction [12] As the disease advances, cognitive and motor impairments become more pronounced, leading to dementia, psychiatric disorders, and motor abnormalities, including parkinsonism, ataxia, and dysarthria [13-16] McKee classified CTE into four stages [17] Stage I involves subtle microscopic changes without gross brain abnormalities, presenting with headaches, memory issues, and depression. In Stage II, gross changes appear, such as ventricular enlargement and tau deposits at cortical sulci. Stages III and IV involve brain atrophy, extensive NFT deposition, and significant neurodegeneration, with symptoms ranging from explosive anger to severe dementia [17].

These findings highlight the urgent need for a serological diagnostic approach to detect CTE in its earliest stages, allowing timely intervention to halt disease progression.

Consequences of "Getting Dinged"

In American football, the term "getting dinged" refers to temporary cognitive symptoms following a head impact. Approximately 100,000 to 300,000 concussions are reported annually among football players [18] Other high-contact sports such as soccer, boxing, and hockey are similarly implicated in CTE development.18 CTE may also contribute to the pathogenesis of other neurodegenerative diseases, including Alzheimer's and Parkinson's disease [18].

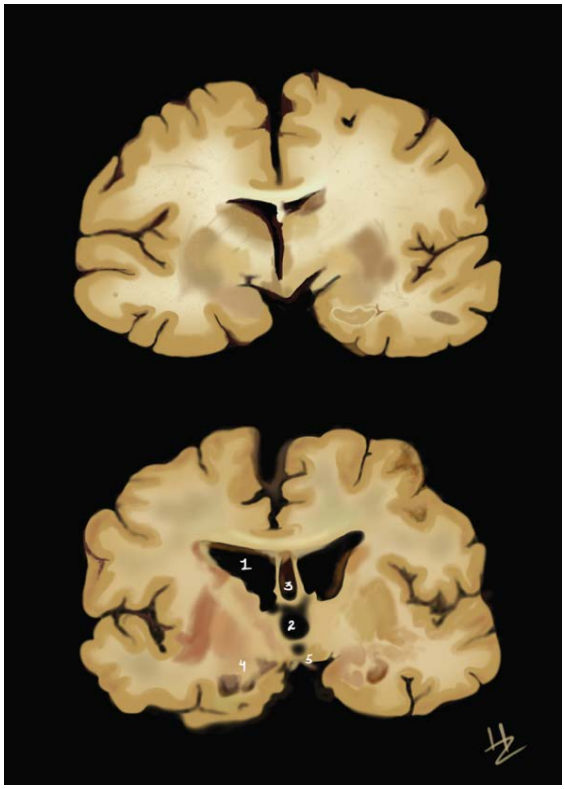

Figure 1: Macroscopic picture of Chronic Traumatic Encephalopathy (CTE). The top brain section is that of a normal brain. The bottom brain section is showing the characteristic gross pathology of CTE with dilatation of ventricles (1 & 2), cavum septum pellucidum (3), atrophy of the medial temporal lobe structures (4), and shrinkage of the mammillary bodies (5). (Illustration done by Dr. Hamna Zafar, from Stern et al.s', research paper 1)

Symptoms of CTE generally appear years after the initial trauma. For example, Rob Kelly, an American football player who retired at 28 after sustaining numerous concussions, later suffered from extreme mood changes, sleeplessness, and disability [19] Kelly's case, along with others, has intensified public awareness of the possible link between contact sports and CTE [19].

Long-term consequences of TBI include significant disability, as illustrated by Hillier et al., who found that 30% of TBI patients experienced arm dysfunction, 9% required assistance for daily activities, and 24% had gait impairments [20]. Such disabilities contribute to early frailty and add to the overall healthcare burden [21].

Protein Biomarkers

A protein biomarker is a molecule measurable in biological fluids such as blood, cerebrospinal fluid (CSF), or urine, and can be utilized for diagnostic or prognostic purposes [3]. Ideally, biomarkers should be specific to a condition, safe, easy to measure, and provide accurate information [22]. Blood biomarkers are preferable due to their minimally invasive collection method. However, blood's protein complexity

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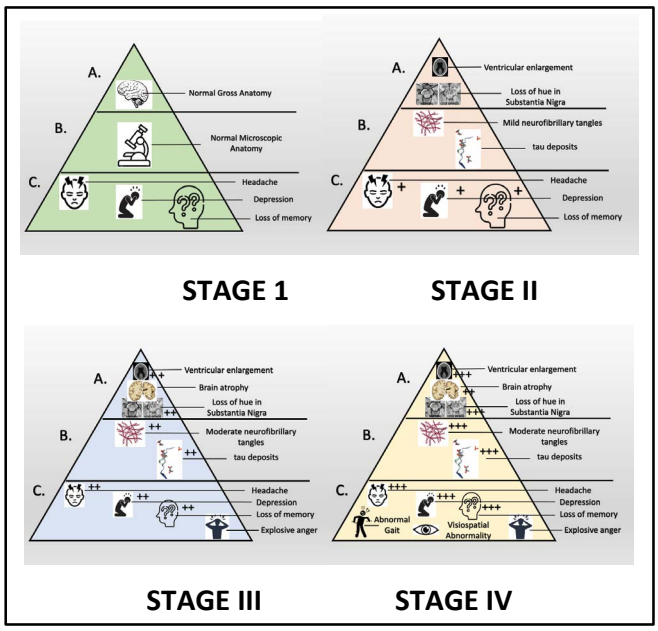

Figure 2: Staging of CTE A. This row shows Gross changes in the brain in each stage, B. Microscopic changes in the brain are shown in these rows in each stage, C. Clinical signs and symptoms of each stage of CTE shown in row C.

(Taken from McKee's categorization of CTE 17)

can complicate detection, and the presence of proteases may degrade target proteins. CSF biomarkers, though more specific, require invasive collection methods and carry a higher risk of infection [23] Urine biomarkers, like cystatin (a GFAP by-product), are less reliable due to degradation, providing limited insight into injury severity [24]. Since brain biopsies are not feasible in living subjects, there is an urgent need for a reliable biomarker panel for diagnosing CTE [25].

The use of a biomarker panel could yield more accurate diagnostic results than individual biomarkers [25]. For example, in Alzheimer's disease, amyloid-β levels are used in conjunction with imaging techniques to improve diagnostic accuracy [26]. Identifying a similar panel for CTE could provide a holistic approach to diagnosis and prognosis.

Methods

This scoping review adheres to the methodological framework established by Arksey and O'Malley (2005) [27]. The review was conducted and reported in accordance with PRISMA-ScR guidelines [28]. The study was registered with the Open Science Framework (https://doi.org/10.17605/OSF.IO/VPD7B).

Data Charting

The data charting process for this scoping review consisted of two main steps:

- **Step 1:** Identification of biomarkers
- **Step 2:** Scoring of biomarkers

Data Charting for Step 1

Data charting was conducted independently by one researcher, with all extracted data subsequently verified by a second researcher.

Search Strategy

The goal of the review was to identify a panel of blood-based protein biomarkers that could be utilized for diagnosing traumatic brain injury (TBI). A comprehensive search was conducted in MEDLINE and Google Scholar, spanning publications from as early as the 1930s, when the term "punch drunk" was first coined. A combination of free text and MeSH terms was employed, including: "serum biomarkers," "blood protein neuro biomarkers," "plasma neuro biomarkers," "traumatic brain injury," "chronic brain injury," and "chronic traumatic encephalopathy." Boolean operators AND and OR were applied. The specific search string used was: "serum biomarkers" OR "blood protein neuro biomarkers" OR "plasma neuro biomarkers" AND "traumatic brain injury" OR "chronic brain injury" OR "chronic traumatic encephalopathy."

Study Selection

The initial search yielded 16,324 articles. Of these, the first 200 most relevant articles were screened for potential neuro biomarkers, as after reviewing 170 articles, the biomarkers began to appear repetitively. Thus, a cutoff of 200 was established to identify all possible neuro biomarkers related to CTE detection. Articles that discussed chronic traumatic brain injury and neuro biomarkers were included, as were studies addressing both acute and chronic brain injury. Papers solely focused on acute brain injury and related biomarkers were excluded.

Biomarker Identification

A total of 38 biomarkers were identified for further analysis. The application of the rubric occurred in Step 2.

Data Extraction and Rubric Formulation

A simple rubric was devised to meet the research objective. The existing literature was reviewed to determine the qualities of biomarkers that could specifically and sensitively diagnose CTE. These qualities were incorporated into the rubric (Table 1) [29]. Subsequently, PubMed was searched to identify studies relevant to the selected biomarkers. Abstracts were scanned, and full texts were reviewed when necessary. The following characteristics were used to build the rubric:

1. Biomarker is of protein origin
2. Detectable in blood/serum and/or cerebrospinal fluid (CSF)
3. Associated with Chronic Traumatic Encephalopathy [30,31]

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Rubric Application

The data extraction focused on key characteristics, including:

1. Detection of biomarkers in blood
2. Brain origin of the biomarker
3. Sensitivity of quantification
4. Detection of acute or chronic brain injury

The rubric was then applied to the identified biomarkers, and the biomarkers were scored accordingly. Those with the highest scores were deemed most suitable for diagnosing CTE.

Table 1: Biomarkers' rubric

CRITERIAS	Poor indicator	Average indicator	Good indicator
	1 point	2 points	3 points
Detection in blood	Only CSF	CSF detection is more than blood	Both serum and CSF with almost equal sensitivity
Origin	Originates majorly from body organs other than brain	Originates from brain and other body organs on almost equal basis	Originates majorly from brain
Quantification sensitivity	micro level	nano level	pico level
Acute and/or chronic brain injury detection	Short term damage	Short term and long-term damage	Long-term injury

Results

From the literature search, 38 biomarkers were identified. These biomarkers were then scored using the rubric after doing thorough literature search. The rubric contains four criteria namely; Detection in blood, Origin, Quantification sensitivity and acute and/or chronic brain injury detection. The lowest possible score was four, and the highest was 12. Of the 38 identified biomarkers, 14 scored ten or higher on the rubric. Another 24 biomarkers scored between six and nine; none of the identified biomarkers scored lower than six. (Figure 3) Based on these scores, the biomarkers were divided into three categories: category 1 includes biomarkers with scores higher than 11 (total 3 biomarkers), category 2 includes biomarkers with a score of ten (total 10 biomarkers), and category 3 includes biomarkers with scores of nine and below (total 25 biomarkers).

The three biomarkers with the highest scores were Neurofilament Light chain (NfL), Phosphorylated forms of tau (P-Tau), and Neuron specific enolase (NSE) with 12, 12, 11 scores respectively. (Table 3, Figure 3) Based on the rubric score these three can be used as a panel for detecting.

Table 2: Score wise categorization of biomarkers

Score on the rubric	Biomarkers
12	NfL, P-Tau
11	NSE
10	S100B, GFAP, AM, SBDP, ACA, p-NF, BDNF, Aβ42, serum netrin-1, Pannexin-1
9	Aβ4, VILIP-1, MAP-2
8	Apelin-13, YKL-40
	AMPAR, PrPc, synaptogyrin-3, IL-6, MBP, NE, B-FABP, UCH-L1, C-tau, MM,
	serum sST2, Ado
7	Occludin, IL-8, LDH
6	SAAP, PCT
5 and below	None

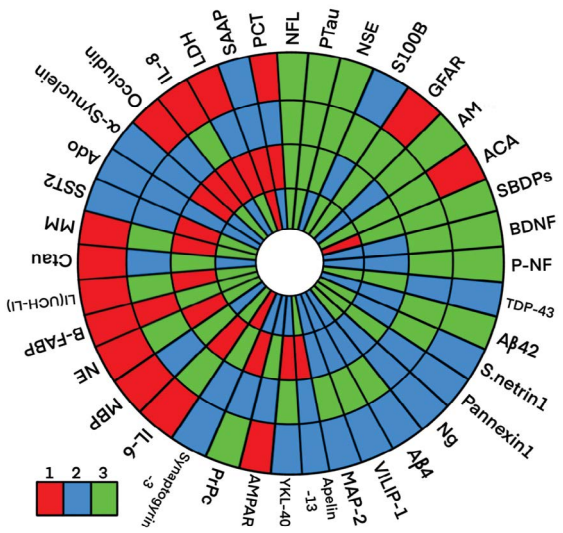

Figure 3: Scoring scheme of biomarkers. Red colour represents score 1, blue is score 2 and green is score 3. The four rings in the circle represent the four criteria in Table 1. The inner most ring shows Criterion 1: Detection in blood, the second ring shows Criterion 2: Origin, the third ring shows Criterion 3: Quantification sensitivity and the outermost ring shows Criterion 4: Brain injury detection.

Discussion

We conducted an extensive review of biomarkers potentially useful in diagnosing Chronic Traumatic Encephalopathy (CTE). Some of these biomarkers are already in use for assessing brain injuries, while others remain in the early stages of research and discovery [148,149]. The biomarkers that best met our rubric's criteria were categorized based on their scores (Table 3). The top-scoring biomarkers were neurofilament light chain (NfL), neuron-specific enolase (NSE), and phosphorylated tau (p-tau).

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Table 3: Overall scoring of biomarkers using criteria given in Table 1

S no.	Biomarkers	References	Criterion 1: Detection in blood	Criterion 2: Origin	Criterion 3: Quantification sensitivity	Criterion 4: Brain injury detection	Total score
1.	Neurofilament Light chain (NfL)	[32 33]	3	3	3	3	12
2.	Phosphorylated forms of tau (P-Tau)	[34 35 36]	3	3	3	3	12
3.	Neuron specific enolase (NSE)	[37 38]	2	3	3	3	11
4.	S100 calcium-binding protein B (S100B)	[39 40 41 42]	3	2	3	2	10
5.	Glial Fibrillary Acidic Protein (GFAP)	[40 43 44 45]	3	3	3	1	10
6.	Adrenomedullin (AM)	[46 47]	2	2	3	3	10
7.	Activin A (ACA)	[40 48]	3	3	3	1	10
8.	α-II-spectrin breakdown products (SBDPs)	[43 49]	1	3	3	3	10
9.	Brain-derived neurotrophic factor (BDNF)	[50 51]	2	2	3	3	10
10.	Hyperphosphorylated neurofilaments (p-NF)	[32 33]	2	2	3	3	10
11.	TDP-43	[52 53 54]	3	3	2	2	10
12.	Aβ42	[55 56]	2	2	3	3	10
13.	serum netrin-1	[57 58 59]	3	2	3	2	10
14.	Pannexin-1	[60 61 62 63]	3	3	2	2	10
15.	Neurogranin (Ng)	[64 65]	3	2	2	2	9
16.	β-amyloid peptide 4 (Aβ4)	[66 67 68 69]	2	2	3	2	9
17.	Visinin-like protein 1 (VILIP-1)	[70 71 72 7374]	2	2	3	2	9
18.	microtubule-associated-protein-2 (MAP-2)	[75 76 77 78]	2	2	3	2	9
19.	Apelin-13	[79 80 81 82]	3	1	2	2	8
20.	chitinase-3-like protein 1 (YKL-40)	[83 84 85 86]	2	1	3	2	8
21.	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor peptide (AMPAR)	[87 88 89]	2	3	2	1	8
22.	cellular prion protein (PrPc)	[90 91 92 93]	2	1	2	3	8
23.	synaptogyrin-3	[94 95 96]	1	3	2	2	8
24.	interleukin (IL-6)	[97 98 99 100]	3	1	3	1	8
25.	Myelin basic protein (MBP)	[101 102]	2	3	2	1	8
26.	Norepinephrine (NE)	[103 104 105 106]	3	1	3	1	8
27.	Brain fatty-acid binding protein (B-FABP)	[107 108]	3	3	1	1	8
28.	Ubiquitin carboxy-terminal hydrolase L1(UCH-L1)	[40 109 39 110]	3	1	3	1	8
29.	Cleaved tau (C-tau)	[111 112 113 114]	2	3	2	1	8
30.	Matrix Metalloproteinases (MM)	[115 116 117 118]	3	1	3	1	8
31.	serum sST2	[119 120 121]	3	1	2	2	8
32.	Adenosine (Ado)	[122 123 124 125 126]	2	2	2	2	8
33.	alpha-synuclein	[127 128 129 130]	2	1	2	2	7
34.	Occludin	[131 132 133 134]	3	1	2	1	7
35.	Interleukin-8 (IL-8)	[135 136 137]	2	1	3	1	7
36.	Lactate dehydrogenase (LDH)	138 139 140 141	3	1	2	1	7
37.	Serum Amyloid A Protein (SAAP)	[142 143 144 145]	1	1	2	2	6
38.	procalcitonin (PCT)	[146 147]	2	1	2	1	6

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NfL achieved a score of 12. Neurofilaments, which form part of the neuronal axon's cytoskeleton, consist of light, intermediate, and heavy chains [150]. NfL maintains axonal diameter and structure, which is essential for axonal conductance [151] Axonal damage causes the release of neurofilaments into cerebrospinal fluid (CSF) and eventually the bloodstream, typically within days following trauma. This makes NfL a marker of both disease severity and prognosis. Factors such as calcium-mediated cytotoxicity, mitochondrial dysfunction, and inflammatory responses contribute to elevated NfL levels post-injury [152] Conditions associated with elevated NfL levels include post-traumatic stress disorder (PTSD), Alzheimer's disease (AD), and CTE [153] Furthermore, neurodegenerative disorders such as dementia and Parkinson's disease (PD) may emerge after moderate to severe CTE [154]

P-tau also received a score of 12 in our rubric. Tau is a microtubule-associated protein that maintains neuronal structure and function by stabilizing microtubule assembly [154] In CTE, p-tau accumulates in abnormal quantities, especially near perivascular spaces and sulcal depths in the frontal cortex. Repeated head trauma initiates an inflammatory cycle, increasing astrocyte and microglial proliferation and upregulating the inflammatory marker CD68. Chronic neuroinflammation in CTE may also lead to early-onset dementia, independent of age [155] Chemokine CCL2 plays a role in tau accumulation and neurofibrillary tangle formation [156] P-tau sequesters toxic radicals and heavy metals, accumulating in viable cells for decades [157]. Like NfL, p-tau is primarily brain-derived, detectable in both blood and CSF, and associated with long-term brain injury.

Neuron-specific enolase (NSE), a glycolytic enzyme found in the cytoplasm, scored 11 in our rubric. It plays a role in glucose metabolism, catalyzing the steps involved in energy production and initiating cellular repair mechanisms.158 NSE exists in various isoforms, with enolase 2 (NSE) specifically associated with neurons and neuroendocrine cells. The γγ isoform is prevalent in neurons, while the αγ isoform is found in supportive neural cells, such as astrocytes and microglia. Elevated NSE levels are seen in tumors, including neuroendocrine tumors and small cell lung cancer, as well as in neurodegenerative conditions like Huntington's disease, Friedreich's ataxia, hereditary spastic paraplegia, PD, AD, and amyotrophic lateral sclerosis (ALS) [158]. Infections like bacterial meningitis and encephalitis can also elevate NSE levels [159]. In CTE, NSE levels rise in response to head trauma frequency and severity [159] While NSE is brain-derived and highly sensitive to quantification, it is more readily detected in CSF than in blood. Other biomarkers in our study scored lower, having met fewer criteria.

Perspectives and Significance

There is an urgent need for rapid, cost-effective, and feasible methods for detecting biomarkers at the point of care. Such advances would allow healthcare professionals to monitor treatment efficacy through serial biomarker measurements and assist in determining a patient's prognosis, ultimately helping to mitigate the progression of CTE and related disabilities [148].

Limitations

One limitation of this review is that, due to resource constraints as part of a PhD project, the workforce available was limited. Consequently, task delegation and cross-checking were less thorough. Additionally, the biomarker identification process relied on manual screening rather than automated, algorithm-driven methods.

Conclusion

In summary, NfL, p-tau, and NSE are promising biomarkers for the screening of CTE. NfL serves as an indicator of axonal damage, p-tau stabilizes microtubule assemblies, and NSE functions as a catalytic enzyme. The accurate identification of these biomarkers can provide valuable, objective insights into the early diagnosis of CTE. This advancement not only facilitates early detection but could also play a crucial role in the management of CTE, particularly in young athletes and adults at risk.

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Ethical approval

Ethical approval was obtained from Ethical Board of Institute of Basic Medical Sciences, Khyber Medical University, under letter No: KMU/IBMS/IRBE/meeting/2022/8072 dated 29/06/2022.

Disclosure statement

The authors report there are no competing interests to declare. This scoping review is part of the PhD research project of Dr Umema Zafar, titled "Developing and Validating a Novel Tool for Assessment of Brain Health".

Disclaimers: None.

Author contributions

UZ: Conceived and designed the study, Data collection, final analysis, interpretation and and final proof reading. SHH: Drafting the manuscript, paper write-up, interpretation and final proof reading. SB: Write up, drafting the manuscript, final approval.

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