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Clinical significance of plasma candidate biomarkers of Alzheimer's Disease

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ABSTRACT

The number of patients with Alzheimer's Disease (AD) has increased rapidly in recent decades. AD is a complex progressive neurodegenerative disease affecting c.14 million patients in Europe and the United States. The hallmarks of this disease are neurotic plaques composed of the amyloid-β (Aβ) peptide and neurofibrillary tangles formed of hyperphosphorylated tau protein (pTau). To date, four CSF biomarkers: amyloid beta 42 (Aβ42), Aβ42/40 ratio, Tau protein, and Tau phosphorylated at threonine 181 (pTau181) have been validated as core neurochemical AD biomarkers. Imaging biomarkers are valuable for AD diagnosis, although they suffer from limitations in their cost and accessibility, while CSF biomarkers require lumbar puncture. Thus, there is an urgent need for alternative, less invasive and more cost-effective biomarkers capable of diagnosing and monitoring AD progression in a clinical context, as well as expediting the development of new therapeutic strategies. This review assesses the potential clinical significance of plasma candidate biomarkers in AD diagnosis. We conclude that these proteins might hold great promise in identifying the pathological features of AD. However, the future implementation process, and validation of the assays' accuracy using predefined cut-offs across more diverse patient populations, are crucial in establishing their utility in daily practice.

Keywords: Alzheimer's Disease, amyloid beta, tau, plasma biomarkers

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Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that leads to a gradual decline in cognitive abilities and behavioural changes. Currently, more than 55 million people have dementia worldwide, and every year there are nearly 10 million new cases. The cumulative expenses linked to healthcare, long-term care, and hospice care for AD and other forms of dementia was estimated in 2019 to cost economies globally 1.3 trillion US dollars [1]. Furthermore, given that AD occurrence escalates with age, the prevalence of the disease is inexorably on the rise as the population ages. An estimated 44 million individuals worldwide currently live with dementia, a figure projected to triple by 2050 owing to an ageing population. The most significant increase in dementia prevalence is anticipated in low and middle-income countries [1–3]. The onset of AD is associated with pathological changes that begin in the medial temporal lobe and then spread to areas of the neocortex, and these changes start decades before any clinical symptoms appear [3, 4].

AD progresses through three stages: a pre-symptomatic phase, a prodromal phase marked by cognitive symptoms, and finally a symptomatic phase leading to dementia [5]. Additionally, mild cognitive impairment (MCI) is often a precursor to cognitive dysfunction in AD dementia. Each year, c.10-20% of individuals with MCI will develop AD [6].

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The clinical presentation of AD typically follows a predominantly symptom-free preclinical phase, making early diagnosis especially challenging [5–8]. Therefore, early detection of AD is crucial for effective treatment.

The pathophysiology of AD is centred on the buildup of amyloid beta (Aβ) plaques and neurofibrillary tangles formed by Tau fibrils, alongside glial activation, neuronal and synaptic degeneration, and neuroinflammation. The presence of extracellular senile plaques made up of Aβ peptides and intracellular neurofibrillary tangles that contain a hyperphosphorylated form of Tau (pTau) proteins are two of the most frequent neuropathological characteristics observed in the brains of patients with AD. It is widely accepted that the most reliable biomarkers of AD are these two categories of molecules [5–8].

Cerebrospinal fluid (CSF) biomarkers

Aβ peptides

Amyloid plaques consist of peptides formed from the enzymatic breakdown of β-amyloid precursor protein (APP). Consequently, the generation of Aβ occurs through the successive cleavage of APP by β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and γ-secretase, resulting in the liberation of multiple forms of Aβ peptides, the most abundant being 40 amino acids in length (Aβ40) [9]. Furthermore, α-secretase may also process APP, leading to the release of soluble APPα via a pathway that does not produce amyloid. Moreover, the cleavage site of γ-secretase within the transmembrane domain of APP lacks precision, leading to the production of Aβ peptides varying in length [9, 10]. AD-associated Aβ is present in the central nervous system (CNS) in many different isoforms, having both N- and C-terminal variants. The most hydrophobic and longest Aβ consists of 42 amino acids (Aβ42) and is the major constituent of senile plaques in AD brains. Aβ42 is also present in cerebrospinal fluid (CSF), but at a lower concentration compared to the shorter and more hydrophilic Aβ40 and Aβ38 isoforms [10].

Some studies have shown that the levels of Aβ42 in CSF are inversely related to the amount of plaque in the brain. This has been observed both through *in vivo* imaging with positron emission tomography (PET) and in post mortems [11]. The reduction in CSF Aβ42 levels among AD patients has been confirmed by numerous studies, consistently demonstrating an average fold change of 0.56 for CSF Aβ42 compared to cognitively intact older individuals [12]. It has been proved that the measurement of CSF Aβ42 is characterised by sensitivity of 78% and specificity of 81% in distinguishing AD patients from elderly controls [13]; similar results have been presented by other authors [14]. Moreover, it has been estimated that CSF Aβ42 measurements aid in the accurate classification of 87% of individuals when distinguishing between non-Alzheimer's (non-AD) dementia patients and non-demented individuals [15]. Furthermore, it is suggested that a decrease in CSF Aβ42 serves as an early indicator of clinically 'silent' brain amyloidosis [16].

Several investigators have shown improved diagnostic accuracy of CSF Aβ42/40 ratio compared to Aβ42 alone [17]. The usefulness of Aβ42/Aβ40 values across the spectrum of AD can be grouped into three main categories. The first category includes diagnostic studies for AD, which use clinical diagnosis as a reference (case control design) and compare their results to amyloid PET as an indicator of AD pathology. The second category focuses on differential diagnosis between AD and other types of neurodegenerative disorders. The third category comprises prognostic studies that test the ability of the Aβ42/Aβ40 ratio to predict progression from pre-clinical to dementia stages of the disorder.

CSF biochemical markers such as Aβ42, total Tau (tTau) and Tau phosphorylated at threonine 181 (pTau181) have proven diagnostic accuracy for MCI and dementia due to AD [7, 17–18]. It is important to be able to distinguish between AD and other types of dementia. Previously, we compared the accuracy of CSF Aβ42 and Aβ40 as well as tTau concentrations in discriminating between patients with AD, non-AD, and control subjects using the enzyme-linked immunosorbent assay (ELISA) method [17].

The concentrations of CSF Aβ42 have been shown to be significantly lower, while CSF tTau levels are significantly higher, in AD patients compared to controls and non-AD [17]. CSF levels of Aβ40 did not differ significantly among the analysed groups. Moreover, receiver operating characteristic (ROC) analysis was assessed to define cut-off values for maximised sensitivity and specificity. For all analysed groups, the Aβ42/Aβ40 ratio classified more patients correctly than did the concentration of Aβ42 alone (AD vs controls, 94% and 86.7%; AD vs non-AD, 90% and 85%; and AD vs non-AD and controls, 90.8 and 87%) [17]. In addition, the percentage of correctly classified patients was further improved when the Aβ42/Aβ40 ratio was combined with the analysis of the CSF tTau levels [17].

CSF levels of Aβ peptides ending at the amino acid position of 42 are widely accepted biomarkers of AD. However, a neurochemical dementia diagnostics (NDD) interpretation of subjects with constitutively high or low CSF levels of total Aβ peptides, could lead to erroneous conclusions, because these biomarkers seem to correlate better with the total Aβ load than with the pathological status.

In our previous study, we reported significantly increased CSF concentrations of phosphorylated Tau (pTau181) and tTau in subjects with high CSF Aβ40 concentrations and decreased Aβ42/Aβ40 ratio compared to those with a low CSF Aβ40 and a normal Aβ42/Aβ40 ratio [18]. Furthermore, we found a significantly decreased Aβ42/Aβ40 ratio in the group of subjects with apolipoprotein E epsilon 4 (APOEε4) allele compared with the group of subjects without this allele. Surprisingly, patients with low Aβ40 and decreased Aβ42/Aβ40 ratio were characterised by decreased pTau181 and unaltered tTau compared

to subjects with high Aβ40 and a Aβ42/Aβ40 ratio within the normal range.

We suggest that the Aβ concentration ratio should replace the 'raw' concentrations of corresponding Aβ peptides to improve reliability of the neurochemical dementia diagnosis [18]. In addition, based on the body of evidence, we suggest that the CSF Aβ42/40 ratio, rather than the absolute value of CSF Aβ42, should be used when analysing CSF AD biomarkers to improve the percentage of appropriately diagnosed patients [7]. Furthermore, it is worth emphasising that the empirical findings of a better diagnostic performance of Aβ42/40 ratio, compared to Aβ42 alone, is grounded in fundamental principles of mathematical stochastics and theory of distributions, as was derived in our previous study [19]. With this derivation, it was proven that under particular conditions, a quotient of two variables (in our case, Aβ42/40) has always more compacted and less dispersed distribution than has the numerator (Aβ42), which leads to less overlapping of the distributions from two populations e.g. subjects with and without disease [19].

Research involving AD patients and cognitively normal individuals highlighted a strong agreement between CSF Aβ42 levels and amyloid-β PET imaging [11, 20]. The concentration of CSF Aβ42 decreases before the detection of amyloid-β using PET imaging, implying that Aβ42 may serve as a more sensitive marker of AD during its very early stages, while Aβ PET could provide better at grading the severity of early AD [11, 20]. Palmqvist et al. [21] found that both amyloid PET and CSF biomarkers accurately identify early AD in patients with MCI-AD, with no enhanced accuracy when combining CSF and PET amyloid measures compared to using either CSF Aβ42 or tTau alone [21]. Therefore, the decision about using CSF or Aβ PET biomarkers for early AD identification may currently depend on PET scanner availability, physician/patient preference, and associated costs [22, 23].

Research has been conducted to investigate the potential of various Aβ peptides as biomarkers for AD. Peptides longer than 42 or shorter than 40 amino acid residues have been assessed for their diagnostic accuracy. For instance, the Aβ43 isomer is decreased in AD and has a similar diagnostic accuracy to that of CSF Aβ42. Clinical investigations have revealed that there is no significant difference between CSF Aβ38 levels in AD patients and control subjects. However, there is a correlation between CSF Aβ38 and PET Aβ [24]. The authors concluded that the CSF Aβ42/Aβ38 and CSF Aβ42/Aβ40 ratios are better indicators than CSF Aβ42 alone in detecting brain amyloid deposition in prodromal AD and in distinguishing AD dementia from non-AD dementias [25]. Additionally, the CSF Aβ42/Aβ38 ratio may aid in differentiating between AD and other non-AD dementias [21] e.g. dementia with Lewy bodies (DLB) [26]. It seems that an initial stage in the development of AD is the oligomerisation of Aβ monomers, especially those ending at the C-terminal 42. Therefore, Aβ oligomers may have a diagnostic role in AD [28–31], something we will look at in the next section.

Tau protein and its phosphorylated forms

Tau proteins are a type of microtubule-associated molecule that can be found in both neuronal and non-neuronal cells. There are six different isoforms of this protein, varying in length from 352 to 441 amino acid residues [32]. The primary function of Tau proteins is to promote stability and growth of neuronal microtubules. tTau protein concentration is a non-specific marker of neuronal destruction in neurodegenerative diseases. Various studies have demonstrated that tTau concentrations are elevated in the CSF of AD patients [33].

The pTau molecules play a crucial role in the regulation of Tau-microtubule interactions. It is thought that hyperphosphorylated Tau or oligomeric Tau may contribute to synaptic degeneration, while granular Tau oligomers could be responsible for neuronal loss. There is a suggestion that adding the measurement of soluble oligomers of Tau protein (TauOs) to the panel of CSF biomarkers might enhance the diagnosis of AD. It is believed that the toxicity of TauOs could be a potential factor in the pathogenesis of this disease, acting in the initial stages and seeding Tau pathology within the brains of individuals with AD. It has been identified that there are multiple phosphorylated tau residues in the mid-domain, including pTau181, threonine 231 (pTau231), serine 235 (pTau235), serine 199 (pTau199) as well as for the C-terminal residues serine 396 and 404 [34]. Studies have shown that CSF levels of pTau181, pTau199, and pTau231 are effective in distinguishing AD from other neurodegenerative disorders and non-demented controls [35]. In AD patients, CSF concentrations of pTau181 were significantly higher, especially in those with neurochemically supported clinical diagnoses with decreased Aβ42 in the CSF [15]. According to a study by Parnetti et al. [36], pTau181 could potentially serve as a biomarker to differentiate between AD and DLB. Furthermore, patients with MCI who progressed to AD during the study showed elevated levels of Tau protein phosphorylated at threonine 231 and serine 235 positions [37]. It has been assessed that levels of CSF pTau217 and pTau231 show pathological changes earlier than CSF pTau181. Thus, studies have reported that CSF pTau 217 correlates more strongly with amyloid PET and tau PET positivity than other forms of tau [38,39]. Buchhave et al. [40] examined the predictive capability of CSF pTau in forecasting the development of AD within 10 years in individuals with MCI. They compared CSF biomarkers between those who converted to AD early and late during follow-up. Initially, patients who progressed to AD had notably higher pTau levels compared to nonconverters. Additionally, early converters exhibited significantly elevated pTau levels compared to late converters. Some authors claim that so-called 'Tau/Aβ' quotients have the potential to upgrade diagnostic performance or, to put it more precisely, improve its interpretation. Such approaches must be taken with caution.

Firstly, in contrast to Aβ42/40 ratio, which is a measure for normalisation of Aβ42 for the total CSF amount of Aβ (of which Aβ40 is the most abundant isoform), Tau/Aβ attempts

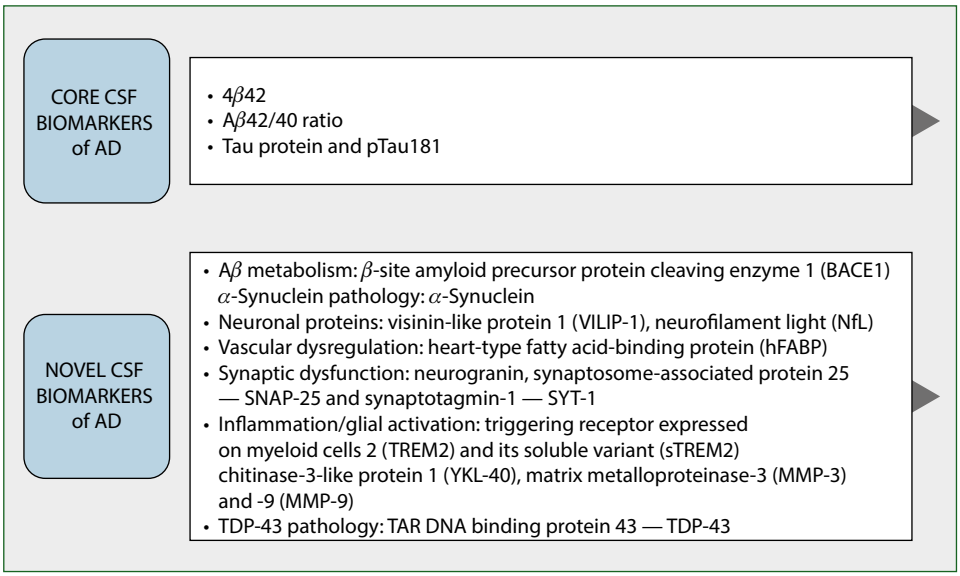

Figure 1. Core and novel cerebrospinal fluid (CSF) biomarkers of Alzheimer's Disease (AD) [17–19, 34–58]

to normalise a biomarker of one pathophysiological process (amyloidosis) for a biomarker of another process (neurodegeneration). This is methodologically questionable. Secondly, any quotient, by its mathematical definition, explicitly assumes that the relation of the two quantities (here, a biomarker of amyloidosis and a biomarker of neurodegeneration) is linear, which is simply incorrect [41]. An example will clarify this.

Let us imagine a patient with an early stage of disease (and note that such patients are the ultimate target population for early AD diagnostics) whose Aβ42 just starts declining but who has constitutively low concentrations of Tau and/other pTau. Such a patient will have a normal Aβ/Tau ratio until a much later stage, when Tau starts increasing, and will be diagnosed falsely negatively. In an even worse scenario, consider a patient with physiologically low Aβ42 (due to a low total Aβ amount) who has Tau larger than the median, albeit within the normal range. Such a patient will have a decreased Aβ/Tau quotient, and will be diagnosed falsely positively.

Potential further CSF biomarkers for AD

Potential CSF biomarkers have been categorised according to the underlying pathophysiological mechanisms of AD, encompassing various domains such as Aβ metabolism (Aβ38, BACE1), inflammation and glial activation (triggering receptor expressed on myeloid cells 2 – TREM2 and its soluble variant – sTREM2, chitinase-3-like protein 1 – YKL-40, vascular dysregulation (heart-type fatty acid-binding protein – hFABP), α-Synuclein pathology (α-Syn), synaptic dysfunction (neurogranin, synaptosome-associated protein 25 – SNAP-25 and synaptotagmin-1 – SYT-1), TDP-43 pathology (TAR DNA binding protein 43 – TDP-43), and other neuronal proteins (visinin-like protein 1 – VILIP-1 and neurofilament light – NfL) [42-58]. While alterations in Aβ metabolism are recognised as the earliest detectable events in AD, interventions based on the Aβ hypothesis have to date yielded disappointing results [59,60]. This underlines the need for a broader exploration of alternative hypotheses, with particular interest in those related to Tau [61]. This is reinforced by the observation that cognitive symptoms in AD correlate more directly with biomarkers of neurodegeneration than with Aβ deposition. Following this rationale, a novel assay designed to specifically measure non-phosphorylated forms of Tau molecules (Non-pTau) has been developed [62]. Intriguingly, it significantly improved the accuracy of patient classification (99%) compared to routinely used assays: Tau (90%), pTau181 (62%) [63]. Additionally, the Non-pTau assay is extensively employed in the differential diagnosis of other dementias, particularly those with substantial Tau pathology, although definitive conclusions have yet to be drawn [62-63]. Well-established, and candidates for novel, CSF biomarkers of AD are set out in Figure 1.

Compared to non-soluble forms in Aβ plaques, soluble Aβ oligomers (AβOs) are more toxic [28]. Clinical investigations have demonstrated a notable increase in CSF AβOs and/or the AβOs/Aβ42 ratio in AD patients compared to age-matched controls, along with an inverse correlation between AβO levels and mini-mental state examination (MMSE) score, suggesting the significance of oligomers as a diagnostic marker for AD [29]. Authors have concluded that AβOs could serve as a test to differentiate between AD and MCI patients and cognitively normal controls, suggesting that elevated AβO levels may predict progression from MCI to AD [30] and might serve as a potential biomarker for AD diagnosis, with diagnostic sensitivity and specificity of more than 95% and 90% respectively [31].

Many papers have indicated that total αSyn levels tend to be higher in AD patients than in controls [64–67]. The increased levels of CSF αSyn in AD and the moderate correlation

between αSyn and Tau/pTau181 support the findings of previous research suggesting that increased CSF αSyn in AD is due to general neurodegeneration, rather than any process specific to AD. As the primary source of αSyn in the brain is presynaptic neuronal terminals, it seems reasonable to suggest that degenerating neurons release αSyn molecules, which can then diffuse into the CSF at a higher rate. Further studies are needed to determine the relationship between biomarkers and clinical presentation, such as cognitive measures, as well as the impact of patient variables such as sex, APOEε4 status, and comorbidities [66, 67]. This is currently being looked at for several other candidates, such as selected metalloproteinases (MMPs) and their tissue inhibitors [56]. For instance, compared to elderly individuals without cognitive deficits, AD patients have significantly lower CSF concentrations of matrix metalloproteinase 9 (MMP-9), and significantly higher levels of matrix metalloproteinase 3 (MMP-3). These biomolecules might contribute to the pathophysiology and diagnosis of AD, indicating the need for further studies involving larger patient cohorts to determine their potential diagnostic value [56].

The Erlangen Score

The combination of reduced CSF Aβ42 levels and/or Aβ42/40 ratio, along with elevated levels of Tau and/or pTau, as discussed previously, signifies the dual pathological processes of AD i.e. amyloidosis and neurodegeneration. Despite the high accuracy of these CSF biomarkers for diagnosis, their global acceptance has been hampered by challenges related to result comparability across different laboratories (or even within the same lab) using different analytical methods. Efforts have been made to standardise procedures for sample collection, measurement protocols, and assay calibrators to address this issue, but widespread adoption of these new approaches will require time [68–71]. Furthermore, with the increasing use of AD CSF biomarkers in routine clinical settings, interpreting the results requires expertise and caution. The challenge lies in deciphering the frequently heterogeneous information these biomarkers provide, which might not always fit neatly into clear normal/abnormal categories. Various approaches have been proposed to standardise the diagnostic interpretation of CSF biomarker profiles. The ES interpretation algorithm was introduced in 2009 [71], and this has been followed by other methods such as logistic regression models, classification scales like the Paris-Lille-Montpellier (PLM) scale [72], or a descriptive nominal-scale A/T/N system [73].

Currently, the Erlangen Score provides a system based on CSF biomarkers, but its flexibility allows its easy adaptation to other biomarkers e.g. those derived from the blood or neuroimaging [71]. The sole prerequisite is that there is at least one biomarker of amyloidosis and at least one biomarker of neurodegeneration, and that the biomarkers are validated in terms of a centre-specific reference range. A score of 0 is given if all biomarkers are normal, which equates to 'no neurochemical evidence for AD'. If there are border zone alterations in one biomarker group (either Aβ or Tau/pTau but not both), the score is 1, and this is referred to as 'neurochemically improbable AD'. A score of 2 is given if there are evident alterations in either Aβ metabolism (decreased Aβ42 concentration or Aβ42/Aβ40 ratio) or tau metabolism (increased concentrations of Tau and/or pTau181), but not in both, or if there are border zone alterations in the CSF biomarkers of both groups. When there are noticeable changes in either Aβ or Tau biomarkers group along with border zone changes in the other group, a score of 3 points is assigned. These cases, when ES = 2 or 3, are referred to as 'neurochemically possible AD' (see Tab. 1). If there are noticeable changes in both Aβ and Tau groups, it results in 4 points, known as 'neurochemically probable AD'. In cases where there is isolated, very high concentration of tTau, it is interpreted as suspected rapidly progressing neurodegeneration with unlikely AD. However, if this same concentration of Tau is accompanied by pathological Aβ42 concentrations/ratio, then the interpretation would shift to possible or even probable AD depending on the normality of pTau. The ES pattern can be presented graphically for clinicians to review.

This concept offers distinct advantages over alternative methods. It facilitates the classification of CSF results into five classes on a graded scale (0-4), indicating increasing deviations in AD CSF biomarkers. Additionally, it introduces the novel concept of border zone results, enhancing the interpretation of CSF AD biomarkers. ES is straightforward and does not require computer-based support in routine laboratory operations, although it can be easily adapted for automated systems in high-throughput labs. In contrast to the A/T/N classification, ES categorises subjects on a graded scale, facilitating semi-quantitative correlation of CSF findings with other metrics such as progression hazards, odds ratios, or time to progression from MCI to dementia. Moreover, as an ordinal-scale system, ES accommodates border-zone laboratory results, seamlessly integrating them into the interpretation algorithm. Furthermore, compared to the PLM approach, which focuses on the number of abnormal CSF biomarkers [72], ES is more adaptable, allowing for the inclusion of additional potential biomarkers reflecting amyloid pathology or neurodegeneration without the need to adjust the categories. Regardless of the number of biomarkers considered, ES consistently categorises CSF patterns into five ordinal categories. ES has undergone thorough validation using cohorts from various expert centres and a wide range of predefined endpoints. Initially, ES demonstrated accurate classification of individuals with non-demented/mild cognitive impairment who were at higher risk of dementia development in two separate, large-scale, multicentre studies (the German Competence Network Dementias and the US-ADNI). Notably, these studies used distinct sample handling protocols, laboratory analytical platforms, and centre-specific reference ranges. Nonetheless, ES exhibited consistent performance across both [71, 74].

Table 1. Interpretation of Erlangen Score [71]

Score	Interpretation of amyloid β results	Interpretation of Tau/ /pTau results	Interpretation of Erlangen Score
0	Aβ42 — normal Aβ42/Aβ40 ratio — normal	Tau — normal pTau — normal	No neurochemical evidence for AD
1	Levels in border zone alterations in one biomarker group (either Aβ or Tau/pTau, but not both)		Neurochemically improbable AD
2	Evident alterations in either Aβ metabolism (decreased Aβ42 concentration or Aβ42/Aβ40 ratio) or tau metabolism (increased concentrations of Tau and/or pTau181) but not both, or if there are border zone alterations in CSF biomarkers of both groups		Neurochemically possible AD
3	Notable changes in either Aβ or Tau biomarkers group along with border zone changes in other group		Neurochemically possible AD
4	Notable changes in both Aβ and Tau groups		Neurochemically probable AD

Note that this does not cover cases with extremely large concentrations of Tau, which may point at rapidly progressing neurodegenerative conditions like Creutzfeldt-Jakob Disease rather than at AD, and which need special consideration

A separate investigation revealed that individuals diagnosed with MCI and categorised as 'neurochemically probable AD' had an 8-12 times greater risk of dementia onset compared to those classified as 'neurochemically improbable AD', even after accounting for age, gender, MMSE score, and APOEε4 genotype. Importantly, these hazard ratios remained consistent regardless of time. Conversely, the ES fully accounted for the risks associated with demographic, cognitive, and genetic factors [75]. When examining neuropsychological and neuroimaging outcomes, it has been observed that a greater ES correlates with accelerated disease progression in individuals with MCI. Those with higher ES scores exhibit swifter declines in both whole brain and hippocampal volumes, as well as more rapid decreases in MMSE scores [76].

Ultimately, the ES algorithm has facilitated accurate prediction of post-mortem neuropathological outcomes based on *in vivo* CSF results of three core AD biomarkers. The likelihood of having AD pathology post mortem, as opposed to non-AD pathologies such as DLB, vascular dementia (VaD), or frontotemporal dementia (FTLD), increases nearly linearly with higher ES ordered categories. Interestingly, less than 3% of neuropathologically confirmed AD patients (3/106) were classified as 'probable AD' (ES = 0 or 1) [77].

It has been proved that neuropathological assessment of the amount and distribution of plaques and neurofibrillary tangles is the most crucial criterion for the diagnosis of AD [78, 79]. In daily practice, PET and the analysis of CSF biomarkers have been widely used to detect and monitor AD-related amyloid and tau pathologies [80]. However, recent investigators have focused on developing blood tests for AD because blood sample collection is less invasive and more cost- and time-effective.

Therefore, the aim of the next section is to critically evaluate the potential significance of plasma candidate biomarkers, such as plasma amyloid beta (Aβ), plasma pTau, inflammatory plasma candidate biomarkers including YKL-40, glial fibrillary acidic protein (GFAP), monocyte chemoattractant protein-1 (MCP-1) and eotaxin-1, as well as other plasma candidate biomarkers of AD (e.g. NfL) in the diagnosis of AD. Many investigators have confirmed that plasma candidate biomarkers that would be useful in early diagnosis, stratification, prediction of disease course, or monitoring response to therapy in AD are sorely needed. However, technical challenges with the measurement of these molecules in the blood, and a lack of validation and cutoff values, have limited their use in daily practice. Recent technological advances have improved assay sensitivity, delivering ultrasensitive assays capable of measuring specific plasma biomarkers. The potential significance of plasma candidate biomarkers of AD is set out in Table 2.

Plasma candidate biomarkers for AD

Plasma amyloid beta (Aβ)

First of all, it needs to be emphasised that currently (June 2024) there is no validated 'plasma biomarker' that could be used for an individual-level diagnostic. Neurochemical assessment of AD patients relies on identifying pathology through Aβ aggregates via brain scans or CSF analysis, typically performed at specialised medical centres. Consequently, the quest for blood biomarkers accurately reflecting abnormal Aβ accumulation is paramount for enhancing AD diagnosis [81–83]. The recent focus has been on blood-based biomarkers facilitating early AD detection via cost-effective, minimally invasive methods. However, plasma Aβ concentrations are notably lower (50–100 times) than in CSF [84–88]. Due to insufficient precision and conflicting outcomes, distinguishing between an AD and a non-AD individual poses significant challenges [89]. Consequently, research is increasingly focusing on correlating plasma AD biomarkers with PET imaging, core CSF biomarkers, and cognitive staging.

In recent years, research into mass spectrometry (MS) has witnessed significant advances in sensitivity and precision, enabling the detection of protein concentrations at femtomolar levels with a coefficient of variation (CV) of below 4% [84]. Consequently, numerous investigators have used immunoprecipitation-mass spectrometry (IP-MS) to assess plasma Aβ levels, aiming to differentiate between individuals with

Table 2. Potential significance of plasma candidate biomarkers of AD

Pathophysiological mechanism	Plasma biomarker	Alterations in AD	References
Aβ metabolism	Aβ42	– significantly lower in amyloid PET-positive individuals than in PET negative cases	[26, 87, 94–95]
	Aβ42/40 ratio	– significantly lower in MCI and AD cases compared to cognitively healthy controls – best biomarker for discriminating Aβ-positive vs Aβ-negative individuals	
Intracellular neurofibrillary tangles formed by hyperphosphorylated form of Tau (pTau) proteins	pTau181	– higher in AD patients compared to CU and strongly correlated with both Aβ and Tau PET – strong correlation with CSF pTau181 – differentiated AD dementia from non-AD neurodegenerative diseases with an accuracy similar to that of Tau PET and CSF ptau181	[107–111]
	pTau217	– differentiated clinically diagnosed AD dementia from non-AD neurodegenerative disorders, with accuracy comparable to CSF pTau and tau PET – significantly better performance than all other plasma pTau biomarkers when detecting abnormal Aβ status or progression to Alzheimer's dementia – more useful biomarker than tau PET in earliest stages of AD	[78, 114, 116]
	pTau231	– distinguished AD patients from patients with non-AD neurodegenerative disorders as well as from Aβ-negative MCI patients	[94, 118]
Inflammation/microglial activation	chitinase-3-like protein 1 (YKL–40)	– significantly different levels between preclinical AD based on pTau181/Aβ1-42 ratio and healthy elderly individuals	[127]
	glial fibrillary acidic protein (GFAP)	– significantly elevated in patients with preclinical AD compared to healthy elderly – significantly higher in Aβ-positive group compared to Aβ-negative group – correlated with increased risk of progression to dementia and steeper cognitive decline (valuable prognostic biomarker predicting incident dementia)	[127, 130, 132]
Neuronal proteins	Neurofilament light (NfL)	– increased levels in MCI and AD Aβ-positive individuals compared to cognitively unimpaired and AD Aβ-negative group – strong correlation with CSF levels – significant increase in AD cases, comparable to core AD CSF biomarkers – elevated levels in MCI cases with positive amyloid PET scans – screening test at first clinical evaluation of patients with cognitive disturbance – novel biomarker for early neurodegeneration in AD	[122, 123, 145] [16, 135, 139, 143, 144, 146]

amyloidosis and those without, with reference to amyloid PET and CSF Aβ measurements [84, 86]. The IP-MS approach employs selected reaction monitoring (SRM) for plasma Aβ42 and Aβ40 quantification, incorporating stable isotope-labelled Aβ peptides into samples prior to analysis (simultaneous assessment), and using octyl glucopyranoside detergent to disrupt Aβ-protein complexes in plasma [90]. Ovod et al. employed an IP-MS technique involving LysN proteolytic digestion of Aβ peptides prior to analysis. They found that plasma Aβ42 levels and the Aβ42/40 ratio were notably lower in individuals with positive amyloid PET scans compared to those with negative scans [87]. Furthermore, the plasma Aβ42/40 ratio exhibited a 14% decrease in the amyloid PET-positive group compared to amyloid PET-negative participants, demonstrating a high ROC value of 0.89 [87]. Several clinical studies have suggested that currently available plasma Aβ42/40 tests using IP-MS technologies could serve as valuable screening tools, potentially reducing the necessity for amyloid PET scans in c.49-64% of patients [91–93]. Additionally, researchers have also observed a correlation between the plasma levels of Aβ42/40 [91, 94–97] and cerebral amyloidosis detected by PET imaging, with the area under the ROC curve (AUC) ranging from 0.7–0.8 or even higher in studies incorporating age and APOE genotype into the analysis [94].

In the extensive Swedish BioFINDER study cohort, significant correlations were observed between plasma Aβ42 levels, the Aβ42/40 ratio, and corresponding CSF biomarkers, as well as cortical 18 F-florbetapir amyloid PET retention. These findings were achieved using an ultra-sensitive immunoassay platform (SIMOA, single molecule array for protein detection), which employs a single-molecule array based on immunocapture of protein biomarkers on magnetic beads [98]. Furthermore, markedly lower plasma Aβ42/40 ratios were detected in individuals with both MCI and AD compared to cognitively healthy controls [98]. Smirnov et al. similarly reported the relationship between plasma AD biomarkers and post mortem brain findings, employing the SIMOA platform to validate longitudinal plasma candidate biomarkers against PM-confirmed diagnoses, and they investigated specific associations with AD. Notably, subjects with significant amyloid AD pathology were shown to exhibit lower plasma Aβ42/40 levels, with a diagnostic accuracy of AUC = 0.601 [94].

Keshavan et al. conducted a comparative analysis of various blood-based methodologies, including liquid

chromatography mass spectrometry (LC-MS) and SIMOA assays, to ascertain plasma Aβ levels and their ability to detect cortical 18 F-florbetapir amyloid PET positivity in individuals without dementia [95]. Thus, they assessed the potential utility of blood biomarkers as predictors of amyloid PET status using logistic regression models [95]. The authors found that while the AUC for amyloid PET status using a base model incorporating age, sex, and APOEε4 status was 0.695, the two most effective SIMOA plasma candidate biomarkers were Aβ42/40 (AUC = 0.620) and phospho-tau181 (AUC = 0.707), neither of which surpassed the base model. In contrast, MS plasma measures such as Aβ42/40 (AUC = 0.817) and Aβ composite (AUC = 0.820) performed significantly better. Additionally, MS measures of Aβ42/40 exhibited 86.6% sensitivity and 71.9% specificity in detecting amyloid PET positivity.

These findings suggest that the LC-MS platform is superior to SIMOA assay for plasma Aβ and pTau181 analysis when screening a large population of dementia-free individuals for concurrent PET amyloid status. Furthermore, the authors propose that plasma screening could reduce the need for amyloid PET scans in identifying Aβ-positive individuals for clinical trial recruitment or anti-amyloid therapy administration, which may be feasible even in preclinical cohorts [95].

Palmqvist et al. used fully automated plasma assays, specifically Elecsys prototype immunoassays, to evaluate plasma Aβ42/Aβ40 levels across cohorts comprising cognitively unimpaired (CU), MCI, and AD individuals [81]. The authors found that the most effective biomarker for distinguishing Aβ-positive from Aβ-negative individuals was plasma Aβ42/Aβ40 ratio, with AUC values ranging from 0.83 to 0.87. Additionally, the combined measurement of plasma Aβ42/Aβ40, pTau181, and ApoE4 significantly enhanced the AUCs to 0.90–0.93 [81]. These findings suggest that a fully automated instrument capable of evaluating a combination of three biomarkers accurately identified Aβ positivity in two independent cohorts, effectively predicting the future development of AD dementia [81]. The authors proposed that blood-based biomarkers have the potential to enhance AD diagnosis, facilitate recruitment for AD trials, and monitor anti-Aβ therapies due to their high precision combined with high accuracy. Nonetheless, they emphasise that in the clinical implementation process, validation of the assays' accuracy and robustness using predefined cut-offs across more diverse patient populations is crucial to further establish the utility of plasma candidate biomarkers in daily practice [81].

The findings regarding plasma Aβ42 as a biomarker reflecting brain amyloid pathology present conflicting outcomes, attributable to the overlap in plasma Aβ42 and Aβ40 levels between AD patients and non-AD controls as assessed by various techniques [12]. This discrepancy may stem from contributions by peripheral tissues to plasma Aβ, leading to a lack of correlation between plasma and CSF Aβ concentrations [99]. Furthermore, potential interference could be mitigated through analytical enhancements like standard immunoassays [100]. Nonetheless, the reported findings are promising, underlining the importance of further investigations into plasma Aβ as a screening tool for brain amyloidosis and AD, particularly on larger clinical cohorts to compare different analytical platforms for measurement. The authors conclude that the high accuracies observed for Aβ pathology and future AD dementia using fully automated instruments offer promising prospects for integrating plasma candidate biomarkers into both clinical trials and clinical practice [84].

Plasma Phospho-Tau

CSF pTau and tau PET are established biomarkers indicative of AD-related tau pathology, showing distinct alteration patterns throughout AD progression. CSF pTau levels reflect changes in tau metabolism within the brain, with elevated concentrations observed across all stages of AD, particularly increasing in the earliest stages, whereas tau PET remains unaltered during the asymptomatic phase [101-103]. Conversely, tau PET tracers bind to insoluble paired helical tau filaments in neurofibrillary tangles, exhibiting abnormal levels primarily in symptomatic AD and correlating with brain atrophy and cognitive decline [104-105]. These findings suggest that fluid-based assessment of pTau may offer greater sensitivity than tau PET in detecting early AD stages.

Furthermore, increased plasma tau levels in AD patients have been identified using MRI and SIMOA techniques in extensive studies conducted on the ADNI and BioFINDER cohorts. The authors uncovered significant correlations between plasma tau levels and future cognitive decline, as well as increased atrophy measured by magnetic resonance imaging (MRI) and hypometabolism measured by fluorodeoxyglucose PET (FDG-PET) during a longitudinal follow-up [106]. A growing body of research suggests that blood pTau holds promise as both a diagnostic and a prognostic biomarker for AD. While CSF pTau181 has been widely validated and accepted as a core AD biomarker, recent studies have highlighted the potential of elevated plasma pTau181 in distinguishing AD patients with dementia from CU individuals [107-108]. Using the SIMOA technique, Mielke et al. demonstrated that plasma tTau and pTau181 levels were significantly higher in AD dementia patients compared to CU individuals, showing strong correlations with both Aβ and tau PET [107]. They proposed that plasma pTau181 might offer greater sensitivity and specificity as a predictor of elevated brain Aβ than tTau, serving as a valuable biomarker for AD pathophysiology and a non-invasive screening tool for elevated brain Aβ [107]. Similarly, Coolmans et al. used the SIMOA platform to compare plasma pTau181 and tau PET in predicting cognitive stage, preclinical Aβ status, and cognitive functioning [110]. They found comparable high AUC values for plasma pTau181 and tau PET in discriminating preclinical Aβ status, although tau PET outperformed plasma pTau181 in distinguishing MCI/AD from subjective cognitive decline individuals. Tau PET showed stronger correlations with cognitive decline

and a wider range of cognitive tests compared to plasma pTau181. Furthermore, while both plasma pTau181 and tau PET increased more steeply over time in MCI/AD compared to individuals with subjective cognitive decline, only tau PET annual changes were associated with cognitive decline. This may indicate its superiority in monitoring disease stage and clinical progression [110]. Moreover, Janelidze et al. revealed elevated plasma pTau181 concentrations in preclinical AD, further increasing at MCI and dementia stages, predicting positive Tau PET scans [111]. They observed a correlation between plasma and CSF pTau181, and reported that plasma pTau181 differentiated AD dementia from non-AD neurodegenerative diseases with high accuracy, like Tau PET and CSF pTau181. Elevated plasma pTau181 has also been associated with subsequent development of AD dementia in CU and MCI subjects [111]. The authors concluded that plasma pTau181 serves as a non-invasive diagnostic and prognostic biomarker for AD, with potential utility in clinical practice, trials, and predicting future progression to AD dementia in subjects without dementia [111]. Furthermore, plasma pTau181 effectively distinguishes subjects with abnormal Aβ and tau PET scans and differentiates AD dementia from non-AD neurodegenerative disorders [111].

Recent studies focusing on multiple phosphorylation sites of the tau protein have suggested that CSF tau phosphorylated at threonine 217 (pTau217) may provide a more accurate reflection of AD-related tau pathology compared to pTau181 [112, 113]. Palmqvist et al. demonstrated that plasma levels of pTau217 show changes concurrently with CSF levels, thereby better distinguishing neuropathologically confirmed AD subjects from those without neuropathological evidence of AD compared to plasma pTau181 [114]. Additionally, the authors reported that plasma pTau217 effectively differentiated clinically diagnosed AD dementia from non-AD neurodegenerative disorders, with an accuracy comparable to that of CSF pTau and tau PET [118]. Moreover, they concluded that plasma pTau217 levels begin to rise c.20 years before the onset of MCI in autosomal-dominant AD cases [114]. In their study, Palmqvist et al. compared currently available methods for determining pTau in the blood to ascertain which methods are sufficiently accurate for implementation in clinical practice [114]. Plasma pTau181, pTau217, and pTau231 levels were evaluated using immunoassays to assess abnormal brain Aβ status and predict future progression to AD [116]. The authors noted that MS pTau217 exhibited significantly better performance than all other plasma pTau biomarkers in detecting abnormal Aβ status (AUC = 0.947) or predicting progression to AD (AUC = 0.932) [116]. Despite variations in the performance of plasma pTau assays, these findings underline relatively high and consistent accuracy across several pTau immunoassays, emphasising their potential clinical utility [116].

Clinical investigations using immunoassay technology such as Meso Scale Discovery (MSD) have unveiled associations between plasma pTau217 and tau PET signals in one of the earliest regions of AD-related tau pathology in CU individuals. Through the measurement of changes in plasma pTau217, CSF pTau217, and various tau PET measures [78], researchers have assessed the correlation between plasma pTau217 and longitudinal changes in tau PET in CU and MCI patients. They observed that plasma levels of pTau217 exhibit changes early in AD compared to well-established CSF and PET biomarkers of AD pathology. Specifically, pTau217 levels were elevated in CU participants with abnormal Aβ-PET, but normal tau PET, in the entorhinal cortex and increased in the early preclinical stages of AD when insoluble tau aggregates were not yet detectable by tau PET. Moreover, similarly to CSF pTau217, the non-invasive and cost-effective nature of plasma pTau217 suggests its potential as a more practical biomarker than tau PET in the earliest stages of AD. The authors conclude that plasma pTau217 holds promise as a biomarker for early AD brain pathology, and could serve as a valuable tool for individual selection and as an outcome measure to monitor drug responses in clinical trials involving individuals with preclinical AD [78].

In Palmqvist et al.'s study, a comparison between plasma pTau181 and pTau217 assays using Elecsys prototype immunoassays revealed interesting insights [81]. The pTau217 N-terminal assay demonstrated higher accuracies for Aβ positivity than the mid-domain assay. However, it is noteworthy that in many cases, concentrations of the analysed molecules fell below the lower level of detection. Despite previous studies indicating better performance of pTau217 in identifying AD pathology, the Elecsys prototype immunoassay for pTau181 appears to be more suitable than pTau217 [82, 117–121]. Therefore, further studies are imperative to validate these findings [81].

Chatterjee et al. assessed plasma tTau, pTau181, and pTau231 levels using SIMOA assays in CU older adults, stratified based on the absence (Aβ–) or presence (Aβ+) of brain amyloidosis [122]. Their findings revealed higher plasma levels of tTau, pTau181, and pTau231 in Aβ+ CU individuals compared to Aβ– CU individuals. Moreover, longitudinal analyses showed an increase in pTau181 levels in Aβ+ CU participants over 12 months. Additionally, correlations were observed between pTau181 and pTau231 levels with cognition, although no significant associations were found with hippocampal volume [122]. The authors underlined the diagnostic and longitudinal monitoring potential of pTau for preclinical AD [122]. Furthermore, while pTau181 demonstrated equivalent or superior performance compared to other biomarkers in predicting Aβ status, a combination of biomarkers may offer enhanced predictive capability across the AD continuum [123]. Similarly, Ashton et al. assessed plasma pTau231 concentrations using the SIMOA assay and highlighted its high diagnostic value based on tau PET, CSF amyloid and tau classification, as well as findings from post mortems [118]. Plasma pTau231 effectively identified AD patients, and differentiated them from Aβ negative CU older adults, with high accuracy (AUC = 0.92–0.94). Additionally,

this biomarker distinguished AD patients from individuals with non-AD neurodegenerative disorders (AUC = 0.93) and Aβ negative MCI patients (AUC = 0.89) [118]. Furthermore, plasma pTau231 demonstrated the ability to differentiate subjects across the Braak stage spectrum, unlike plasma pTau181. The authors concluded that novel plasma pTau231 assay identifies the clinical stages of AD and increases earlier, even in the presence of subtle Aβ deposition, prior to reaching the threshold for amyloid-β PET positivity, and in response to early brain tau deposition.

Thus, plasma pTau231 could be a promising biomarker of emerging AD pathology with the potential to facilitate clinical trials targeting vulnerable populations below the PET threshold of amyloid-β positivity or apparent entorhinal tau deposition [118]. Similar findings were reported by Smirnov et al., who also observed that plasma pTau231 levels appear to increase earlier than plasma pTau181 and could be used to determine the severity of tau pathology. The investigators demonstrated that plasma pTau231 exhibited an earlier increase during intermediate stages of neuritic plaque pathology compared to plasma pTau181 [94].

Investigators have determined plasma pTau181, pTau217, pTau231 compared to tau PET in individuals from memory clinics with subjective cognitive decline, CU status, or dementia. Plasma pTau217, characterised by 95% sensitivity, resulted in nearly halving the number of tau PET scans needed. The investigators concluded that plasma pTau217 could effectively guide the selection of patients for tau PET scans [124].

Plasma markers of inflammation as candidate biomarkers of Alzheimer's Disease

The neuroinflammatory response of the immune system can potentially promote protein aggregation and interact with pattern recognition receptors on microglia and astroglia, leading to the initiation of an immune response characterised by the release of inflammatory mediators [125, 126]. The proteins involved in the neurodegeneration process are responsible for the development of AD [125]. Some authors have explored plasma levels of biomarkers associated with neuroinflammation in a cohort of preclinical AD patients, comparing these levels to those in healthy elderly individuals defined by Aβ42 CSF status. Several clinical studies have suggested that certain inflammatory biomarkers in plasma, such as GFAP, YKL-40, MCP-1, and eotaxin-1, could potentially identify preclinical AD subjects at high risk of developing AD [127].

It has been suggested that YKL-40 is a more sensitive marker of the incipient inflammatory process that occurs in response to the Aβ misfolding and aggregation, which is confirmed by the reduced Aβ1-42 levels in CSF [127]. The same authors also showed that plasma YKL-40 levels increase with age, like CSF YKL-40. Elevated plasma YKL-40 concentrations seem to be correlated with male sex, older age, APOEε4 status, and cerebral accumulation of Aβ measured with PET [128, 129].

Another inflammatory protein considered as a plasma candidate biomarker for AD is GFAP. Elevated levels of GFAP in the plasma of preclinical AD patients suggest that astrocytic damage or activation may initiate during the preclinical phase of AD [122]. Prins et al., using the SIMOA technique, found significantly increased plasma GFAP concentrations in preclinical AD patients compared to healthy elderly individuals [127]. Additionally, plasma GFAP levels were notably higher in the Aβ+ group compared to the Aβ– group. Verberk et al. suggested that plasma GFAP may serve as a valuable prognostic biomarker for predicting incident dementia [130]. Moreover, plasma GFAP demonstrated the highest impact and AUC in distinguishing between Aβ-positive cases and Aβ-negative cases CU, which was higher than AUC of plasma tTau. These findings suggest that integrating plasma GFAP into current theoretical models of AD pathogenesis could serve as a non-invasive and readily accessible method for detecting early astrocytosis secondary to Aβ pathology [127, 130, 131]. Additionally, Pereira et al. [132] concluded that plasma GFAP serves as an early indicator associated with brain Aβ pathology, though not tau aggregation, even in cognitively normal individuals with normal Aβ levels. The authors found a significant correlation between plasma GFAP concentrations and higher Aβ-PET signals in all Aβ-positive patients, as well as in cognitively normal subjects with normal Aβ values, even after adjusting for tau PET signals. They proposed that plasma GFAP should be incorporated into existing theoretical models of AD pathogenesis and used as a non-invasive and easily accessible means to detect early astrocytosis secondary to amyloid-β pathology [132].

According to recent research, chemokines such as MCP-1 or eotaxin-1 might serve as neuromodulators and are associated with increased memory impairment in MCI and AD [133]. Morgan et al. investigated plasma concentrations of various inflammatory markers, including complement components (C3, C4, C5), complement regulators (FH, FI), a soluble form of complement receptor (sCR1), a classical inflammation marker (CRP), and three chemokines (eotaxin-1, MCP-1, and MIP-1b) in AD, MCI, and elderly controls using the ELISA and MSD methods [134]. Using logistic regression, it was found that the most effective model for distinguishing between AD and elderly controls included sCR1, FB, FH, eotaxin-1, and MCP-1, alongside covariates such as age and APOE status with AUC = 0.79, while sCR1, MCP-1, eotaxin-1 optimally differentiated between AD and MCI, with AUC = 0.74. These models were confirmed in an independent cohort with AUC = 0.81 and 0.67, respectively [134].

These findings suggest that GFAP and YKL-40 serve as more sensitive indicators of inflammation in response to Aβ misfolding and aggregation, as evidenced by decreased Aβ1-42 levels in the CSF. Using neuroinflammatory biomarkers to characterise individuals with preclinical AD is crucial for selecting subjects for new disease-modifying clinical trials. The authors suggest that evaluating these neuroimmune

response-related biomarkers during preclinical AD stages could aid in predicting which cognitively healthy elderly individuals are at higher risk of developing AD. Additionally, assessing plasma levels of GFAP and YKL-40 in individuals with preclinical AD may enhance differentiation between patients with reduced CSF Aβ42 and otherwise healthy elderly individuals, thereby refining the definition of preclinical AD status. However, further research is necessary to determine whether these inflammatory plasma candidate biomarkers are specific to (preclinical) AD.

Neurofilament light (NfL) is a component of the axonal cytoskeleton and a marker of large calibre axonal degeneration that reflects pathological alteration in neurodegenerative diseases such as AD [135–137]. Some clinical investigations have demonstrated that NfL concentrations, and its rate of change in plasma, were higher in sporadic and familial AD and correlated with clinical symptoms and progression of the disease [138]. A growing body of evidence suggests that NfL could be a novel biomarker for early neurodegeneration in AD [135, 139–144]. Researchers have reported that in Aβ-positive cognitively normal and MCI participants, baseline NfL shows a significant predictive value in assessing tau burden in the left medial orbitofrontal cortex and para-hippocampus. They demonstrated an association between plasma NfL and multi-modal neuroimaging features in AD-vulnerable regions and its predictive value for future tau deposition [135]. Chatterjee et al. investigated plasma NfL in preclinical AD patients using SIMOA assays in CU, with absence (Aβ–) or presence (Aβ+) of brain amyloidosis. Increased plasma NfL was indicated in MCI Aβ+ and AD Aβ+, compared to CU Aβ– and MCI Aβ– [123, 145]. Moreover, plasma NfL levels were found to be elevated in AD compared to CU individuals. Reduced plasma Aβ1–42/Aβ1–40 ratio and higher plasma NfL levels were correlated with a prospective cognitive decline. Increasing evidence shows that, in contrast to tau protein, the correlation between plasma and CSF levels of NfL protein is strong [146]. Mattsson et al. reported a significant increase in plasma NfL levels in AD cases, with an AUC = 0.87, which is comparable to the core AD CSF biomarkers [139]. In addition, plasma NfL levels were elevated in MCI cases with positive amyloid PET scans, and predicted faster cognitive deterioration, and higher rates of future hypometabolism and brain atrophy [139]. Moreover, blood NfL concentrations were higher in symptomatic FAD (familial AD) patients, but also in presymptomatic mutation carriers, with levels correlating with expected year of symptom onset as well as both cognitive and MRI measures of disease stage [147].

These findings suggest that plasma NfL reflects neurodegeneration also in the preclinical stage of AD. They suggest a future application for plasma NfL as a screening test at the first clinical evaluation of patients with cognitive disturbances. Thus, plasma NfL might serve as a simple, non-invasive and cheap screening tool, especially to exclude neurodegeneration [16].

Limitations

Although blood is more accessible than CSF, using a less invasive, low cost procedure, many investigators underline that measurement of blood biomarkers of AD patients has proven difficult [16]. CSF is connected with the brain extracellular fluid, via exchange of molecules from the brain to the CSF. However, only a fraction of brain proteins enters the bloodstream [16]. Furthermore, it has been proved that blood is a more challenging matrix than CSF for brain biomarkers, for several reasons. The small levels of brain proteins in the bloodstream have to be analysed in a matrix containing very high levels of plasma proteins, including albumin and immunoglobulins, entailing a high risk of interference in the analytical methods [148]. In addition, brain proteins that are released into the blood could be degraded by different proteases, and then metabolised in the liver or cleared by the kidneys. These processes are unrelated to brain changes, and are very difficult to regulate [16]. Moreover, in CSF, levels of Aβ42 and Aβ42/40 appear to decrease before amyloid PET reaches significant thresholds [22, 149, 150]. However, it is a great challenge to determine thresholds and identify cutoff points for plasma Aβ42/40, which produces a much smaller effect than CSF Aβ42/40 [101]. Additionally, this procedure could be more difficult among older patients, due to intermediate but sub-threshold amyloid pathology [98]. However, plasma candidate biomarkers useful in predicting future AD dementia are sorely needed.

Conclusions

A growing body of evidence suggests that the core AD CSF biomarkers such as tTau, pTau, Aβ42 and the Aβ42/40 ratio confirm a high diagnostic accuracy not only for AD dementia, but also for prodromal AD. Despite large strides in our understanding of AD pathogenesis, validated blood biomarkers for early detection and accurate diagnosis of AD patients are much needed. Many investigators believe that blood biomarkers may be implemented as screening tools in the initial clinical evaluation of this group of patients. Plasma Aβ42/40 ratio seems to be the best candidate biomarker for discriminating Aβ-positive from Aβ-negative individuals. In addition, pTau217 differentiates clinically diagnosed AD dementia from non-AD neurodegenerative disorders with an accuracy comparable to that of CSF pTau and tau PET, while pTau231 distinguishes AD patients from patients with non-AD neurodegenerative disorders, as well as from Aβ negative MCI patients.

Among other non-specific-for-AD biomarkers, plasma GFAP levels correlate with an increased risk of progression to dementia and steeper cognitive decline, suggesting its role as a valuable prognostic biomarker predicting incident dementia. Moreover, researchers have found a significant increase of plasma NfL levels in AD cases, comparable to the core AD

CSF biomarkers, indicating the significance of plasma NfL as a screening test at the first clinical evaluation of patients with cognitive disturbance. Some researchers suggest that plasma AD biomarkers are more suitable than CSF or PET for implementation in primary care settings worldwide, and could lessen the cost of clinical trials by improving selection and stratification of participants and monitoring of treatment response.

However, a clinical implementation process, and validation of the assays' accuracy and robustness using predefined cut-offs across more diverse patient populations is crucial to further establish the utility of plasma candidate biomarkers in routine practice.

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