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Biofluid biomarkers for Alzheimer's disease

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Alzheimer's disease (AD) is a multifactorial neurodegenerative disease, with a complex pathogenesis and an irreversible course. Therefore, the early diagnosis of AD is particularly important for the intervention, prevention, and treatment of the disease. Based on the different pathophysiological mechanisms of AD, the research progress of biofluid biomarkers are classified and reviewed. In the end, the challenges and perspectives of future research are proposed.

KEYWORDS

Alzheimer's disease, diagnosis, biofluid, biomarkers, neurodegenerative diseases

1 Introduction

Alzheimer's disease (AD) is the most common type of dementia, which accounts for 60~80% of all cases (Gauthier et al., 2022). According to the "World Alzheimer' Report in 2019," there were about 55 million dementia patients in the world, and this number was expected to reach 152 million by 2055 (Alzheimer's Disease International, 2019). In 2019, the global societal cost of dementia was around 1.3 trillion US dollars, of which 50% was from the economic value of unpaid care. The 2017 World Health Assembly (WHA) recognized dementia as a public health priority (World Health Organization, 2017). Nowadays, dementia has become one of the biggest public health challenges in the world.

AD can be divided into early-onset AD (EOAD) and late-onset AD (LOAD) at the age boundary of 60 or 65. It could also be classified into familial AD (FAD) and sporadic AD (SAD) based on the family history (Xie et al., 2022). LOAD is mainly SAD, accounting for around 95% of all cases. EOAD is relatively rare, which accounts for less than 5% of AD (Alzheimer's Disease International, 2019). Jia et al. (2022) reported a 19-year-old AD patient with the memory impairment occurring at the age of 17, which was the youngest probable AD case in the world.

The amyloid plaques and the neurofibrillary tangles (NFT) are the two main pathological characteristics of AD (Blennow et al., 2006; Kang et al., 2022; Mahaman et al., 2022). The amyloid plaques are formed by deposition of extracellular β -amyloid protein (β), and the NFT is induced by intracellular tau hyperphosphorylation. The etiology of AD is still unclear. However, it is generally believed that AD is induced by multiple factors, e.g., genetics, biology, environment, and social psychology (Vermunt et al., 2019; Kulichikhin et al., 2021). The potential mechanism of β -induced neurodegeneration is always the research focus. Human soluble β dimers and trimers induce progressive loss of hippocampal synapses. When exposes to picomolar level of soluble β oligomers, pyramidal neurons in rat brain slice significantly reduce the density of dendritic spines and the number of electrophysiologically active synapses (Shankar et al., 2007). β could directly incorporate into neuronal membranes

of hypothalamic neurons, and participate in the formation of calcium-permeable pores, leading to an increase in intracellular calcium concentration of GT1-7 cells. Therefore, the disruption of calcium homeostasis by “ $A\beta$ -channels” is recognized as the molecular basis for $A\beta$ neurotoxicity. Previous studies indicated that the lipid composition of cell membrane played an important role in the formation of this channel (Kawahara and Kuroda, 2000). Normally, tau proteins bind to microtubules for maintaining the stability of cytoskeleton. The hyperphosphorylated tau aggregates to form paired helical filaments, which have fewer binding sites and unable to attach to microtubules, thus forming NFT (Liu et al., 2019). NFT disintegrates the microtubule network of nerve cells, resulting in the inhibition of cell biochemical communication, the destruction of the cytoskeleton, and ultimately the production of neurotoxicity (Srivastava et al., 2021). Research data showed that $A\beta$ induced the spread of tau pathology in an unknown way leading to neuronal death (Long and Holtzman, 2019; Karran and De Strooper, 2022). Once $A\beta$ accumulation exceeding a specific threshold, the spread of tau pathology was significantly accelerated (Karran and De Strooper, 2022). However, the hypothesis that the interaction between $A\beta$ and tau leads to cytopathology is still required further investigation.

Since the conceptual framework of preclinical AD was officially proposed by the National Institute of Aging and the Alzheimer's Association (NIA-AA) in 2011, accumulating data suggested that cognitive decline occurred continuously and progressively over a long period (Jack et al., 2018). For example, the whole course of AD for a 70-year-old person could take approximately 15–25 years, including ~10-year asymptomatic stage (preclinical stage), 4-year mild cognitive impairment, and 6-year for ultimately developing into dementia (Scheltens et al., 2021). Therefore, the measurement of AD biomarker should be a continuous process that begins before symptom appearance (Fleisher et al., 2015; Jack et al., 2018).

Cerebrospinal fluid (CSF) directly reflects pathological changes in brain. Core CSF biomarkers of AD include $A\beta_{42}$, total tau protein (T-tau) and P-tau. $A\beta_{42}$ reflects cortical amyloid deposition. T-tau indicates the density of neurodegeneration, and P-tau links to the pathological changes in NFT. The increased concentration of CSF T-tau and P-tau was found in AD patients (Reitz and Mayeux, 2014), and their diagnostic accuracy was around 85–90% (Visser et al., 2009). However, the CSF or imaging analysis of AD biomarkers is either invasive or expensive (e.g., 10,000 RMB/per time for positron emission tomography (PET), 1,500 RMB/per time for magnetic resonance imaging (MRI), 300 RMB/per time for computed tomography (CT), 1,000–3,000 RMB/per time for CSF examination), or both (Teunissen et al., 2022).

Based on the characteristics of accessibility, sampling technology, repeatability and cost-effectiveness, blood biomarkers have more advantages than CSF and imaging analysis (Blennow and Zetterberg, 2018). However, the detection of AD biomarkers in blood is much more complex than in CSF (Kulichikhin et al., 2021). First, there is a blood–brain barrier (BBB) in the human body. The capillary endothelium in BBB lacks pores (Ueno et al., 2016), and therefore ions and polar molecules could only cross the BBB in the presence of some transport proteins (Haas, 2018). However, the transporters that are responsible for transporting tau through BBB have not yet been identified (Ueno et al., 2016). When the axon is damaged, proteins are released from the extracellular space of the brain and only a small fraction could enter the bloodstream. These brain proteins are cleaved,

modified, and degraded before or after passing through BBB (Kulichikhin et al., 2021). Second, the blood-cerebrospinal fluid barrier (BCB) is another important barrier. BCB is porous, so small peptides and hydrophilic molecules could pass through it. Due to the death of neuronal cells and intracellular high concentration, tau is firstly released to CSF (Tarasoff-Conway et al., 2015), and then enters the blood through the barrier (Haas, 2018). Because of the existence of BBB and BCB, there is a difference on the concentration between CSF and blood biomarkers. Third, plasma contains multiple background proteins. Some of them are at high levels. Therefore, the analytical techniques of blood samples should have a high sensitivity and specificity in order to detect a small quantity of biomarkers in the complex backgrounds (Kulichikhin et al., 2021).

In this review, the traditional and emerging AD biomarkers are summarized and categorized according to main AD pathologies such as amyloidosis, NFT, neurodegeneration, synaptic dysfunction, neuroinflammation, and BBB breakdown (Figure 1). The physiological function and the biofluid level of these markers are described. In addition, the research of some biomarkers on the other neurodegenerative diseases are also reviewed in this article.

2 Biomarkers of amyloidosis

2.1 $A\beta_{42}$

$A\beta_{40}$ and $A\beta_{42}$ are the most common subtypes in human. Due to the expanded C-terminal, $A\beta_{42}$ is highly hydrophobic and easier to aggregate than $A\beta_{40}$ (Long and Holtzman, 2019). The level of CSF $A\beta_{42}$ in preclinical stage, mild cognitive impairment (MCI), and AD with dementia symptoms was lower than those in control groups (Bateman et al., 2012). It could decrease to around 50% of the healthy individuals (Table 1; Olsson et al., 2016). A neuropathological examination showed that a decrease in CSF $A\beta_{42}$ was associated with an increase in brain amyloid plaques (Strozyk et al., 2003). Elderly persons with a decrease of CSF $A\beta_{42}$ were also $A\beta$ -PET positive, and vice versa (Fagan et al., 2006). The studies indicated that a reduction in CSF $A\beta_{42}$ preceded the formation of plaques (Palmqvist et al., 2016; Kulichikhin et al., 2021). Thus, CSF $A\beta_{42}$ is considered as a robust biomarker of early AD diagnosis. A decrease in CSF $A\beta_{42}$, coupled with an increase in T-tau and P-tau could help to identify the symptomatic AD (Blennow and Hampel, 2003). Low level of CSF $A\beta_{42}$, rather than high level of T-tau, could predict cognitive decline (Stomrud et al., 2007). In addition, a significant decrease in CSF $A\beta_{42}$ was observed in Creutzfeldt-Jakob disease (CJD), multiple system atrophy (MSA), and amyotrophic lateral sclerosis (ALS) (Holmberg et al., 2003), which indicated that CSF $A\beta_{42}$ could be influenced by other factors besides plaque formation (Mahaman et al., 2022).

Plasma $A\beta$ analysis is one of the most widely applied peripheral biomarker tests of AD (Mahaman et al., 2022). Plasma and CSF $A\beta_{42}$ had a weak positive correlation, while plasma $A\beta_{42}$ levels and brain $A\beta$ deposition had a negative correlation (Janelidze et al., 2016b). The research results regarding the relationship between plasma $A\beta_{42}$ and cognitive impairment were not consistent. Some studies showed decreased plasma $A\beta_{42}$ in MCI and AD (Nakamura et al., 2018), while others reported increased $A\beta_{42}$ level and following decreased trend before or at the beginning of cognitive decline (Mayeux et al., 2003). The inconsistent results are probably caused by differences in sample

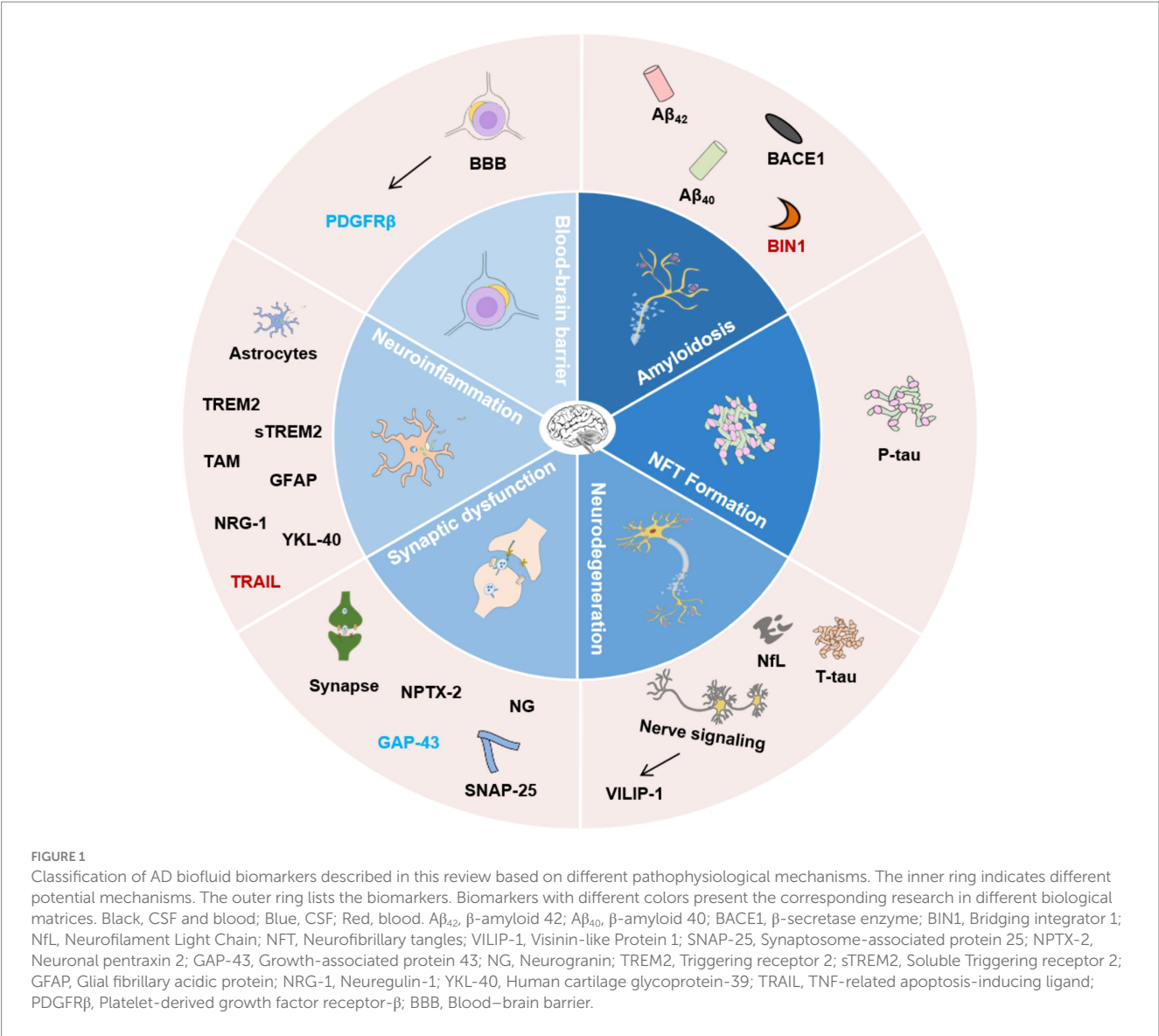


TABLE 1 Summarized information of AD amyloidosis biofluid biomarkers presented in this review.

Pathophysiological mechanism	Biomarker	Biological matrices	Trend	Purpose
Amyloidosis	Aβ ₄₂	CSF	Decrease (Olsson et al., 2016)	Diagnosis (Jack et al., 2018)
		Blood	Controversial (Mayeux et al., 2003; Nakamura et al., 2018)	Research (Wang J. et al., 2018)
	Aβ ₄₀	CSF	No significant change (Kulichikhin et al., 2021)	Research (Janelidze et al., 2016b; Kulichikhin et al., 2021)
		Blood	Decrease (Janelidze et al., 2016b)	
	Aβ ₄₂ /Aβ ₄₀	CSF	Decrease (Schindler et al., 2019)	Diagnosis (Jack et al., 2018)
		Blood	Decrease (Janelidze et al., 2016b)	Research (Schindler et al., 2019)
	T-tau/Aβ ₄₂	CSF	Increase (Kaplow et al., 2020)	Research (Kaplow et al., 2020)
	P-tau181/Aβ ₄₂	CSF		
	APP669-711/Aβ ₄₂	Blood	Increase (Nakamura et al., 2018)	Research (Nakamura et al., 2018)
	BACE1	CSF	Increase (Cervellati et al., 2020)	Research (Decourt and Sabbagh, 2011)
	BIN1	Blood	Increase (Sun et al., 2013)	Research (Sun et al., 2013)

inclusion and exclusion criteria, as well as the analytical methods (Wang J. et al., 2018). Elevated levels of plasma $A\beta_{42}$ and $A\beta_{40}$ were also associated with other diseases, such as hypertension, diabetes and ischemic heart disease, indicating significant differences in metabolic process of amyloid proteins between blood and brain (Janelidze et al., 2016b). Despite these differences, all studies confirmed the changes of blood amyloid proteins at the early stages of AD. In the future, the association between AD pathology and blood amyloid protein is required further exploration to promote its clinical application.

2.2 $A\beta_{40}$

$A\beta_{40}$ is the most abundant protein fragment hydrolyzed from APP. The concentration of CSF $A\beta_{40}$ had no significant difference during the development of AD (Kulichikhin et al., 2021). Similar to $A\beta_{42}$, there was a weak positive correlation between plasma and CSF $A\beta_{40}$ (Janelidze et al., 2016b). Although $A\beta_{40}$ does not have the same strong cytotoxicity as $A\beta_{42}$, $A\beta_{40}$ aggregates could be detected in cerebral amyloid vasculopathy (Attems et al., 2011). The decreased plasma concentration of $A\beta_{40}$ was observed in AD patients compared with controls (Janelidze et al., 2016b). Biochemical and molecular simulation showed that $A\beta_{40}$ inhibited the aggregation of $A\beta_{42}$ (Jan et al., 2008).

2.3 $A\beta_{42}/A\beta_{40}$

The impact of total $A\beta$ variation could be neutralized through normalization of $A\beta_{42}$ by $A\beta_{40}$ (Lewczuk et al., 2004). Several studies showed that CSF $A\beta_{42}/A\beta_{40}$ could better diagnose, differentiate, and monitor AD than CSF $A\beta_{42}$ (Hansson et al., 2019). CSF $A\beta_{42}/A\beta_{40}$ and $A\beta$ -PET positive had a good correlation (Kulichikhin et al., 2021). Compared to negative $A\beta$ -PET population, the CSF $A\beta_{42}/A\beta_{40}$ level of positive $A\beta$ -PET individuals decreased (Schindler et al., 2019). PD and dementia with Lewy body (DLB) had higher level of CSF $A\beta_{40}$. Therefore, $A\beta_{42}/A\beta_{40}$ could help to distinguish AD from these diseases (Nutu et al., 2013; Mahaman et al., 2022). The combined application of CSF $A\beta_{42}/A\beta_{40}$ and other CSF biomarkers, e.g., T-tau or P-tau, gave a better prediction of AD (Baldeiras et al., 2018) and the conversion from MCI to AD (Baldeiras et al., 2018; Mahaman et al., 2022). Thus, CSF $A\beta_{42}/A\beta_{40}$ is proposed as a promising biomarker for preclinical AD diagnosis (Hansson et al., 2019; Kulichikhin et al., 2021).

In a 719-person cohort study, the plasma concentration of $A\beta_{42}/A\beta_{40}$ significantly decreased in MCI and AD patients (Janelidze et al., 2016b). Ovod et al. (2017) reported that plasma $A\beta_{42}/A\beta_{40}$ was decreased in patients with cerebral amyloidosis. Cognitive decline and the risk of AD progression were associated with low plasma $A\beta_{42}/A\beta_{40}$ levels (Verberk et al., 2020). Plasma $A\beta_{42}$ alone was not an accurate biomarker for AD brain pathology, while $A\beta_{42}/A\beta_{40}$ could give a better prediction (Ovod et al., 2017; Schindler et al., 2019). Moreover, plasma $A\beta_{42}/A\beta_{40}$ was associated with $A\beta$ -PET (Schindler et al., 2019). Cognitively normal individuals with declined $A\beta_{42}/A\beta_{40}$ were observed within $A\beta$ -PET-negative groups, indicating the early stage of AD before plaque formation (Schindler et al., 2019). A mathematical simulation study suggested that the risk of positive $A\beta$ -PET for the above population was 15 times higher than those with normal plasma $A\beta_{42}/A\beta_{40}$ in the next 6 years (Schindler et al., 2019). Additionally, plasma $A\beta_{42}/A\beta_{40}$ and $A\beta_{42}/A\beta_{38}$ had higher accuracy than $A\beta_{42}$ in

distinguishing AD from DLB, PD, or subcortical vascular dementia (VaD) (Janelidze et al., 2016c).

2.4 Other $A\beta$ ratios

Elevated CSF T-tau/ $A\beta_{42}$ or P-tau181/ $A\beta_{42}$ indicated an obvious AD brain pathology (Kaplow et al., 2020). CSF $A\beta_{42}/P$ -tau181 showed high accuracy in predicting the progression from MCI to AD (Buchhave et al., 2012; Mahaman et al., 2022). A study based on mass spectrometry suggested that the plasma levels of APP669-711/ $A\beta_{42}$ and $A\beta_{40}/A\beta_{42}$ in $A\beta$ -PET-positive individuals were higher than those with negative $A\beta$ -PET scan (Nakamura et al., 2018). These two ratios were associated with the levels of CSF $A\beta_{42}$ (Kaneko et al., 2014; Nakamura et al., 2018), and they could be used to predict the brain $A\beta$ burden (Nakamura et al., 2018).

2.5 BACE1

BACE1, also known as β -secretase or β -site APP-lyase 1, is encoded by *BACE1* gene, which is primarily expressed in neurons of brain and responsible for $A\beta$ production (Vassar et al., 1999). It was reported that the increase of *BACE1* gene expression or the abnormal function of β -secretase was one of the earliest processes in AD (Yang et al., 2003). Knocking out *BACE1* in mice resulted in a significant decrease in $A\beta$ and CTF β concentration (a 99-amino acid fragment starting with the N-terminal aspartic acid residue of $A\beta$) in the brain (McConlogue et al., 2007). In the SAD brain, the expression of BACE1 significantly increased (Yang et al., 2003). The CSF level of BACE1 protein of AD patients were significantly elevated (Cervellati et al., 2020). The activity of CSF BACE1 was higher in the individuals with the conversion from MCI to AD than those without (Zetterberg et al., 2008). A recent research (Hampel et al., 2021) and two large-scale cohort studies (Zuliani et al., 2020) presented similar trend of CSF BACE1 in peripheral blood, with a 30% increase in serum of AD compared to the control group. In *APP/PS-1* transgenic mice, abnormal BACE1 expression in the retina predated behavioral defects. Therefore, BACE1 could be used as a sensitive biomarker for the early diagnosis of AD (Decourt and Sabbagh, 2011; Haas, 2018). However, the application of CSF BACE1 as a clinical AD biomarker is limited by its inter-subject variability and technical difference of assay in the lab (Hampel et al., 2020). The research focus is mainly on the *BACE1* gene rather than the level of BACE1 protein in the other neurodegenerative diseases such as PD (Li et al., 2020).

2.6 BIN1

Bridging integrator 1 (BIN1) is a member of amphiphysin proteins family. It is associated with the cytoskeleton and cell membrane. BIN1 plays an important role in the nervous system (Sudwarts et al., 2022). BIN1 is widely expressed in mice and human brain (Miyagawa et al., 2016). It participates in the regulation of endocytosis (Wechsler-Reya et al., 1998), and it is important in intracellular vesicles sorting (Pant et al., 2009).

Previous study showed that BIN1 affected the AD molecular pathobiology through the regulation membrane trafficking of AD-related proteins (Miyagawa et al., 2016). BIN1 dependent pathophysiological process is possibly associated with tau pathology through various mechanisms (Thomas et al., 2019). However, there is no further evidence to clarify whether this effect is regulated through the modulation of tau phosphorylation (Thomas et al., 2019), the influence of BIN1-tau interactions (Malki et al., 2017; Sartori et al., 2019), or directly facilitating the propagation of pathogenic tau (Crotti et al., 2019). Genome-wide association studies demonstrated that *BIN1* was a genetic risk factor of LOAD (Tan et al., 2013). The depletion of *BIN1* enhanced the level of cellular BACE1 by impairing endosomal trafficking and decreased BACE1 lysosomal degradation, leading to the overproduction of A β (Miyagawa et al., 2016). A cohort study including 112 AD and 200 control subjects showed significantly elevated levels of BIN1 mRNA and protein in the plasma of ADs. However, this trend is required further investigation in the larger-scale cohort (Sun et al., 2013).

3 Biomarkers of NFT formation

3.1 P-tau

AD-related NFT are composed of P-tau (Grundke-Iqbal et al., 1986). CSF P-tau was elevated at the preclinical stage of AD (Sato et al., 2018), and it continued to rise during the early clinical stage (Palmqvist et al., 2019). Higher CSF T-tau and P-tau indicated faster disease progression (Wallin et al., 2010). The elevated CSF T-tau reflected CNS degeneration, while increased P-tau was specific to AD (Blennow and Hampel, 2003; Skillbäck et al., 2014). Therefore, P-tau could help to distinguish AD from other neurodegenerative diseases (Hampel et al., 2004). The correlation between CSF P-tau and A β was stronger than that between CSF P-tau and tau-PET (La Joie et al., 2018). This is probably because A β pathology is the reason for the increased CSF P-tau, while tau-PET measures NFT (Sato et al., 2018; Smirnov et al., 2022).

Several CSF P-tau proteins were reported to increase at the preclinical stage of AD. Both P-tau181 and P-tau217 began to increase at the early stage of AD, which were around 20 years before the detection of tau aggregation in the brain (Barthélemy et al., 2020b). Compared to the control groups, the CSF P-tau217 increased by 5 times in AD patients, while P-tau181 only increased by 1.3 times (Barthélemy et al., 2019). CSF or plasma P-tau217 could identify patients with A β -PET positive but tau-PET negative, which indicated the changes of CSF P-tau before the detection of tau aggregates (Barthélemy et al., 2020a; Kulichikhin et al., 2021). CSF P-tau205 increased in the advanced AD, and it was related to the increase of T-tau and brain atrophy (Barthélemy et al., 2020b). Studies reported that P-tau231 was the earliest increasing biomarker in AD (Ashton et al., 2021; Smirnov et al., 2022). There are few studies about comparison of different CSF P-tau biomarkers. One study showed that the levels of CSF P-tau181, P-tau199 and P-tau231 were strongly associated with each other (Hampel et al., 2004). By combining the application of two or more biomarkers, higher diagnostic accuracy could be obtained (Hansson et al., 2006). The fragments of the microtubule binding region (MTBR) where tau was much easier to aggregate (Blennow et al., 2020) were more reliable indicators for tau aggregation (Simrén et al., 2023). A mass spectrometry study investigating the role of MTBR showed that CSF MTBR-tau, such as

MTBR-tau243, MTBR-tau299 or MTBR-tau354, was a promising biomarker for monitoring target participation in the clinical trials (Horie et al., 2021).

Plasma P-tau was suggested to be the most promising analyte as a screening tool in clinical application. The increase of plasma P-tau was closely related to amyloid plaques and tau tangles (Mattsson-Carlgren et al., 2021). The validity of plasma P-tau as AD biomarker has been verified in neuropathologically confirmed cases (Lantero Rodriguez et al., 2020; Palmqvist et al., 2020), which was not affected by common co-pathologies (such as TDP-43 or α -synuclein pathology) (Smirnov et al., 2022). Studies proved that plasma P-tau could predict the progression from cognitively unimpaired individuals to MCI and eventually to AD (Janelidze et al., 2020). Plasma P-tau had excellent accuracy in distinguishing AD from non-AD tau proteinosis (e.g., progressive supranuclear paralysis or cortical basal degeneration) or non-AD neurodegenerative diseases [e.g., DLB or frontotemporal dementia (FTD)] (Palmqvist et al., 2020; Ashton et al., 2021; Thijssen et al., 2021). Several P-tau proteins such as P-tau181, P-tau217 and P-tau231 have been proposed as AD blood biomarkers (Palmqvist et al., 2020; Ashton et al., 2021; Smirnov et al., 2022). With the progression of the disease, plasma P-tau181 increased steadily (Suárez-Calvet et al., 2020; Thijssen et al., 2020), and it could accurately distinguish AD from non-AD neurodegenerative diseases (Janelidze et al., 2020). Plasma P-tau 217 was at a high level before detection of tau pathology by PET.

The concentrations of P-tau181, T-tau and A β ₄₂ in exosomes of AD were associated with the corresponding CSF biomarkers. They were significantly higher than those in MCI and healthy controls (Jia et al., 2019). Compared to the control groups, P-tau, A β ₄₂ and phosphorylated insulin receptor substrate 1 (IRS-1) of neuronal derived extracellular vesicles (NDEVs) in ADs showed high accuracy in predicting and distinguishing AD (Kapogiannis et al., 2019).

4 Biomarkers of neurodegeneration

In 2018, NIA-AA guideline proposed neurodegeneration as the third biomarker of AD (Table 2; Jack et al., 2018). Although neurodegeneration alone was not enough as a diagnostic marker, its change rate could accurately predict the progression of the disease (Frisoni et al., 2010).

4.1 T-tau

In AD patients, the level of CSF T-tau increased (Shui et al., 2018). Similar to CSF P-tau181, CSF T-tau began to increase after the formation of amyloid plaques (Schindler, 2022). This happened 10 ~ 15 years earlier before NFT (Bateman et al., 2012; Fleisher et al., 2015). Therefore, CSF T-tau and P-tau181 probably reflected neuron dysfunction caused by A β plaques, rather than tau tangles. The level of CSF T-tau also increased in other diseases, such as stroke, acute neuronal injury, and CJD (Skillbäck et al., 2014). It increased within a few days after acute brain injury, and continued to elevate for several weeks until it finally fell back to the normal range (Zetterberg et al., 2006). Previous studies reported that the highest level of CSF T-tau was observed in the most serious neurodegenerative diseases. For example, CSF T-tau level in CJD patients was 10 to 20 times higher than that in AD (Skillbäck et al., 2014).

TABLE 2 Summarized information of AD neurodegeneration biofluid biomarkers presented in this review.

Pathophysiological mechanism	Biomarker	Biological matrices	Trend	Purpose
Neurodegeneration	T-tau	CSF	Increase (Shui et al., 2018)	Diagnosis (Jack et al., 2018)
		Blood	Increase (Chen et al., 2019)	Research (Mahaman et al., 2022)
	NfL	CSF	Increase (Zetterberg et al., 2016)	Research (Mattsson et al., 2017; Bridel et al., 2019)
		Blood	Increase (Mattsson et al., 2017)	
	VILIP-1	CSF	Increase (Braunewell, 2012; Halbgebauer et al., 2022b)	Research (Mroczko et al., 2015; Halbgebauer et al., 2022b)
		Blood		

A two-year longitudinal study involving 152 people showed that plasma T-tau and T-tau/A β_{42} could predict the deposition of abnormally folded proteins in the brain (Sutphen et al., 2018). There was a correlation between high plasma T-tau and AD (Chen et al., 2019). Although the plasma T-tau concentration in MCI or AD increased, the research data showed that the range of plasma T-tau in AD overlapped with that in normal population. This hinders the application of plasma T-tau as a diagnostic biomarker (Mahaman et al., 2022).

metabolism (Mattsson et al., 2017). Weston et al. pointed out that serum NfL increased in asymptomatic FAD, and it was associated with the stage and severity of the disease (Weston et al., 2017). Due to the concomitant pathologies of axons and peripheral axons, big difference in plasma NfL levels among healthy elderly population limited its specificity (Simrén et al., 2023). Nevertheless, the plasma NfL was more specific in autosomal dominant AD (ADAD) and Down syndrome because of the younger onset age of these disease process (Simrén et al., 2023).

4.2 Neurofilament light chain (NfL)

Neurofilament plays an important role in maintaining the neuronal integrity and regulating the transport of intracellular components (Liu et al., 2004; Wagner et al., 2007; Yan et al., 2007; Bruno et al., 2012). Because of the imbalance of tau kinase and phosphatase activity, abnormal hyperphosphorylation of neurofilaments occurred leading to the loss of their stability and axonal injury in the white matter and brain (Gong et al., 2000). Axonal injury released neurofilament proteins into interstitial fluid, and they could be detected in CSF (Bruno et al., 2012). The concentration of NfL in CSF rose at the early clinical stages of AD, correlating with cognitive decline and the changes of brain structure (Zetterberg et al., 2016). A longitudinal study involving 389 subjects showed the elevated CSF NfL level in ADs than healthy controls (Mattsson et al., 2016). The lack of correlation between increased CSF NfL and A β pathology indicated that NfL was not specific to AD. Higher concentration of CSF NfL indicated the existence of axonal injury (Bridel et al., 2019). Although CSF NfL was not a specific biomarker for a disease, it could help clinicians to investigate whether cognitively impaired patients had neurological causes (Schindler, 2022). Studies showed that combined application of NfL with other biomarkers could greatly improve the accuracy of dementia diagnosis (de Jong et al., 2007; Mattsson et al., 2016). For example, the combination of CSF A β_{42} and P-tau181 with CSF NfL improved the diagnosis accuracy of early AD and FTD (de Jong et al., 2007).

Blood NfL was closely related to CSF NfL (Hansson et al., 2017), and it has become an easy-to-obtain biomarker for reflecting the intensity of neuronal damage and neurodegeneration (Simrén et al., 2023). Some studies proposed that blood NfL was an effective tool for the early diagnosis of AD (Fortea et al., 2018). Elevated plasma NfL concentrations were observed in SAD (Ashton et al., 2021). Compared to the healthy controls, the plasma NfL level of AD increased by nearly 150% (Mattsson et al., 2017). The increased NfL was related to the cognitive decline, brain atrophy and low

4.3 VILIP-1

Visinin-like Protein 1 (VILIP-1) is a new biomarker for reflecting the pathological changes of AD. It is a calcium-binding protein of neuronal calcium sensor (NCS), which plays an important role in neuronal signaling cascades (Burgoyne and Weiss, 2001). In AD and other neurodegenerative diseases, neurons showed abnormal Ca²⁺ homeostasis, which resulted in the aberrant regulation of Ca²⁺ ion channels and reduction of Ca²⁺ buffering capacity (Marambaud et al., 2009). VILIP-1 participated in calcium-mediated neuronal injury through regulation of Ca²⁺ ions. The expression of VILIP-1 was closely related to A β plaque and NFT in ADs (Braunewell et al., 2001; Braunewell, 2012). CSF VILIP-1 could predict the change rate of global and focal brain atrophy which was similar as T-tau and P-tau181 (Luo et al., 2013). The CSF VILIP-1 level of ApoE ϵ 4 carriers was significantly increased, and it was positively correlated with tau and P-tau levels (Wang et al., 2020). A meta-analysis indicated enhanced levels of CSF VILIP-1 in AD compared to the control group. In addition, the CSF VILIP-1 level was higher in MCI patients who progressed to AD than stable MCIs (Mavroudis I. A. et al., 2021). Similarly, several longitudinal studies pointed out that the concentration of VILIP-1 and/or VILIP-1/A β_{42} in CSF could be applied to diagnose diseases at an early stage, and predicted the future cognitive impairment of normal individuals (Luo et al., 2013). For example, the VILIP-1/A β_{42} and VILIP-1 in the CSF could help to differentiate AD from CJD (Halbgebauer et al., 2022b). No significant difference of VILIP-1 was observed between AD and DLB (Mavroudis I. A. et al., 2021). Serum VILIP-1 could not discriminate AD from PD, ALS, and behavioral variant frontotemporal dementia (bvFTD) (Halbgebauer et al., 2022b). It was reported that serum VILIP-1 was correlated with acute ischemic stroke (Stejskal et al., 2011; Liu D. et al., 2020) and the neuronal injury caused by epileptic seizures (Tan et al., 2020). To date, there is no convincing data supporting the correlation between plasma VILIP-1 and AD or other neurodegenerative diseases.

5 Biomarkers of synaptic dysfunction

Synaptic dysfunction is closely correlated with the loss of synaptic integrity and neuropathological changes in the brain, which is another important pathophysiological mechanism of cognitive decline in AD. Synaptic dysfunction is largely driven by A β and tau pathology, and/or by the indirect consequence of neuroinflammatory response (Jackson et al., 2019). Therefore, synaptic alterations are considered as an early pathological event of AD (Scheff et al., 2007). Biomarkers indicating synaptic integrity and plasticity are helpful for early diagnosis and prognosis monitoring of AD (Table 3; Marambaud et al., 2009).

5.1 Presynaptic protein

Synaptosome-associated protein 25 (SNAP-25) exists in synaptic vesicles (Geppert et al., 1994). CSF SNAP-25 is a key participant in synaptic degeneration (Zhang et al., 2018). An increasing trend of CSF SNAP-25 was observed in the AD patients (Öhrfelt et al., 2016). The significantly reduced SNAP-25 in the cerebral cortex indicated the synaptic dysfunction (Davidsson and Blennow, 1998). It was reported that CSF SNAP-25 could differentiate AD from PD, FTD and ALS, and high concentration of CSF SNAP-25 could be applied as a biomarker for both AD and CJD (Halbgebauer et al., 2022a). CSF SNAP-25 level was correlated with APOE ϵ 4 (Wang S. et al., 2018). MCI patients carrying APOE ϵ 4 showed higher CSF SNAP-25 than non-carriers (Wang S. et al., 2018). There is few research on the correlation between blood SNAP-25 and AD. A study presented the reduced SNAP-25 in the neuron-derived exosomes (NDEs) isolated from serum, and it was associated with the cognition evaluated by Mini-Mental State Examination (MMSE) (Agliardi et al., 2019).

The increase of growth-associated protein 43 (GAP-43) was considered as another biomarker reflecting AD-related synaptic dysfunction. CSF GAP-43 increased with the cognitive decline, and it was correlated with A β plaque and NFT in hippocampus, amygdala, and cortex (Sandelius et al., 2019). CSF GAP-43 could predict the progression from MCI to AD, and this correlation was suspected to be related with APOE ϵ 4 (Zhu et al., 2023). Elevated level of CSF GAP-43 was specific to AD compared to the other neurodegenerative diseases, e.g., MCI, ALS, behavioral variant FTD (bvFTD), PD, DLB, primary progressive aphasia (PPA), progressive supranuclear palsy, corticobasal syndrome, and posterior cortical atrophy (PCA). Therefore, it was considered as a promise AD biomarker for the clinical research. However, another study reported a temporary

increase of CSF GAP-43 after ischemic stroke (Sandelius et al., 2018). A blood neuro-exosomal study presented that exosomal GAP-43 could predict MCI 5–7 years in advance (Jia et al., 2021).

Neuronal pentraxin 2 (NPTX-2) is a protein correlated with the inhibitory circuit dysfunction. NPTX-2 showed different trends from the above biomarkers. The level of NPTX-2 in AD cerebral cortex and CSF decreased, and it had a strong correlation with cognitive ability and the volume of hippocampus (Xiao et al., 2017; Nilsson et al., 2021). Reduced CSF NPTX-2 level can predict early AD in adults with Down syndrome (Belbin et al., 2020). A longitudinal CSF proteomics study found that the change rate of NPTX-2 concentration was significantly associated with cognitive decline. CSF NPTX-2 was suggested as a strong biomarker for accelerated cognitive decline (Libiger et al., 2021). NPTX-2 regulates the complement activity and the loss of microglial synapses in the brain. Reduced NPTX-2 level may exacerbate complement-mediated neurodegeneration in FTD (Zhou J. et al., 2023). Studies reported significantly reduced CSF NPTX-2 level in FTD (Das et al., 2023) and DLB (Boiten et al., 2020), indicating that CSF NPTX-2 was not a specific AD biomarker. NPTX-2/tau was closely related to the cognition of AD and MCI, and it had the best discrimination on AD (Galasko et al., 2019). The correlation between serum NPTX-2 and AD still remains unclear. There was an independent correlation between the serum NPTX-2 and cognition of VaD patients (Shao et al., 2020). Reduced NPTX-2 level was observed in the plasma NDEs of AD patients, but this change could not be detected 6–11 years before dementia (Goetzl et al., 2018).

α -syn induced hyperphosphorylation and aggregation of tau protein (Duka et al., 2006). There was a correlation between CSF α -syn and MMSE score (Korff et al., 2013). Compared to the cognitively normal population, the level of CSF α -syn in AD increased (Hall et al., 2012). CSF α -syn in AD was significantly higher than those in PD and other neurodegenerative diseases (Wang et al., 2015). More research found that α -syn was a protein associated with familial PD, and it has identified as a major protein of the neuropathological hallmark for idiopathic PD (Fayyad et al., 2019).

5.2 Postsynaptic protein

Neurogranin (NG) is the most well-studied postsynaptic protein. It is a protein composed of 78 amino acids, which is involved in synaptic dysfunction or neuronal injury (Represa et al., 1990). NG participates in the induction of synaptic plasticity by accelerating the dissociation of calmodulin, e.g., long-term potentiation (LTP) and long-term depression (LTD) (Kubota et al., 2007). High levels of CSF NG reflected the loss of

TABLE 3 Summarized information of AD synaptic dysfunction biofluid biomarkers presented in this review.

Pathophysiological mechanism	Biomarker	Biological matrices	Trend	Purpose
Synaptic dysfunction	SNAP-25	CSF	Increase (Öhrfelt et al., 2016)	Research (Öhrfelt et al., 2016; Agliardi et al., 2019)
		Blood NDEs	Decrease (Agliardi et al., 2019)	
	GAP-43	CSF	Increase (Sandelius et al., 2019)	Research (Sandelius et al., 2019)
	NPTX-2	CSF	Decrease (Goetzl et al., 2018; Nilsson et al., 2021)	Research (Goetzl et al., 2018; Nilsson et al., 2021)
		Blood NDEs		
	NG	CSF	Increase (Portelius et al., 2018)	Research (Liu W. et al., 2020)
		Blood exosome	Decrease (Liu W. et al., 2020)	

brain neurogranin protein (Saunders et al., 2023), and it was positively correlated with A β plaque and tau pathology (Pereira et al., 2017; Portelius et al., 2018). The content of CSF NG48-76 increased significantly indicating the neurodegenerative process in the brain (Kvartsberg et al., 2015). CSF NG in MCI and AD was higher than cognitive normal population, and it could help to predict the progression from MCI to AD (Kester et al., 2015). CSF NG can predict MCI 5–7 years in advance (Jia et al., 2021), but it could not differentiate MCI from FTD or DLB (Mavroudis et al., 2020). The specificity of CSF NG as a biomarker for AD diagnosis is controversial. Studies indicated that the elevation of CSF NG was highly specific to AD (Portelius et al., 2018), while others presented opposite conclusion (Willemse et al., 2021). Blood NG did not show a good trend. Plasma NG had no significant change or in a similar range between AD and healthy controls (De Vos et al., 2015; Kvartsberg et al., 2015). NG level in NDEVs of MCI and AD decreased, and it was correlated with the cognitive decline (Goetzl et al., 2016; Winston et al., 2016; Liu W. et al., 2020). A meta-analysis reported decreased NG level in plasma exosomes, and plasma NG was closely correlated with the cognitive decline (Liu W. et al., 2020). The interpretation of NDEVs biomarkers should be taken with caution because of their controversial origin (Mahaman et al., 2022).

6 Biomarkers of neuroinflammation

Neuropathologist Alois Alzheimer firstly observed lipid accumulation and fibrous structures in glial cells of dementia population's brain (Simrén et al., 2023). Glial cells in CNS include astrocytes and microglia, and they were reported to be involved in AD pathophysiology (Table 4; Simrén et al., 2023).

6.1 TREM2 and sTREM2

Triggering receptor 2 (TREM2) is a cell surface receptor mainly expressed in CNS microglia, and it plays an important role in regulating energy metabolism and phenotypic transformation of microglia. TREM2 acts as a key regulator, allowing microglia to

switch between steady state and activated state (disease-associated microglia) (Keren-Shaul et al., 2017). Heterozygous loss-of-function variants in TREM2 were associated with the increasing AD risk (Guerreiro et al., 2013), and another study presented that they also increased the risk of the other neurodegenerative diseases, such as FTD, PD, and ALS (Carmona et al., 2018). Studies reported that TREM2 tripled the risk of AD (Guerreiro et al., 2013), probably through its influence on tau pathology (Lill et al., 2015) and A β clearance pathway (Kleinberger et al., 2014). CSF TREM2 level was deranged at the early stage of AD, and it was closely related to neurodegenerative biomarkers such as T-tau and/or P-tau (Heslegrave et al., 2016; Suárez-Calvet et al., 2016b). Compared to the healthy controls, the levels of TREM2 mRNA and protein in peripheral blood of AD were higher (Hu et al., 2014). TREM2 level in MCI-AD patients was significantly higher than that in AD or healthy controls (Casati et al., 2018).

After hydrolysis of the TREM2 protein, the soluble fragments of sTREM2 are produced outside the cell (Colonna and Wang, 2016). Transgelin-2 (TG2) is expressed on neurons. The sTREM2-TG2 interaction mediates the crosstalk between neurons and microglia (Zhang et al., 2023). The concentration of CSF sTREM2 in AD was higher than the healthy controls (Piccio et al., 2016; Suárez-Calvet et al., 2016b). Before the appearance of expected symptoms and after the increasing of A β and T-tau, the level of CSF sTREM2 in ADAD mutation carriers was higher than non-carriers (Suárez-Calvet et al., 2016a). It was suggested that sTREM2 was potential to predict the progression from MCI to AD. The MCI patients with low CSF or high plasma sTREM2 levels had a higher risk of progression to AD. In addition, the concentration of CSF sTREM2 was closely correlated with sTREM2 in plasma (Zhao et al., 2022). The dynamically changes of CSF sTREM2 was observed in preclinical AD. In the absence of neurodegeneration and tau deposition, A β pathology was correlated with the decreased CSF sTREM2. However, tau pathology and neurodegeneration are associated with the increased CSF sTREM2 (Ma et al., 2020). A meta-analysis reported that CSF sTREM2 was significantly elevated in the entire continuum of AD compared to controls. However, an increasing trend of CSF sTREM2 was also observed in PD, multiple sclerosis (MS), FTD and DLB (Zhou W. et al., 2023).

TABLE 4 Summarized information of AD neuroinflammation biofluid biomarkers presented in this review.

Pathophysiological mechanism	Biomarker	Biological matrices	Trend	Purpose
Neuroinflammation	TREM2 & sTREM2	CSF	Controversial (Ma et al., 2020)	Research (Hu et al., 2014; Suárez-Calvet et al., 2016b)
		Blood	Increase (Hu et al., 2014)	
	TAM receptor	CSF	Increase (Brosseron et al., 2022, 2023)	Research (Brosseron et al., 2022, 2023)
		Blood		
	YKL-40	CSF	Increase (Janelidze et al., 2016a)	Research (Janelidze et al., 2016a; Villar-Piqué et al., 2019)
		Blood	Increase (Craig-Schapiro et al., 2010)	
	GFAP	CSF	Increase (Benedet et al., 2021)	Research (Benedet et al., 2021; Cicognola et al., 2021; Katsipis et al., 2021)
		Blood	Increase (Benedet et al., 2021)	
		Saliva	Decrease (Katsipis et al., 2021)	
	NRG-1	CSF	Increase (Chang et al., 2016; Mouton-Liger et al., 2020)	Research (Chang et al., 2016; Mouton-Liger et al., 2020)
		Blood		
	TRAIL	Blood	Decrease (Wu et al., 2015)	Research (Wu et al., 2015)

6.2 TAM receptor

TAM receptors are widely expressed in various types of cells and tissues in the immune, neurological, vascular, and reproductive systems (Zhou S. et al., 2023). Axl and Mertk are expressed in microglia, but Tyro3 is not (Fourgeaud et al., 2016). The TAM system is an important regulator for microglia to recognize and engulfment of amyloid plaques. Axl and Mertk proteins were correlated with AD (Huang et al., 2021). Axl reduces inflammatory responses, while Mertk plays a role in the phagocytosis of aggregated proteins and cellular debris (Zhou S. et al., 2023). Research reported that A β plaque-associated microglia exhibited hyperreactivity upon systemic inflammation and upregulated phagocytic genes in the transgenic AD mouse model, including Axl (Yin et al., 2017). Microglial phagocytosis driven by TAM does not inhibit, but promotes the formation of amyloid plaques. Mertk is the major participant in this process (Huang et al., 2021). Phosphatidylserine (PtdSer) serves as the ligand decorating the plaques for TAM receptors. Mertk, expressed by activated microglia, recognized, and phagocytosed neurons exposed to PtdSer, thereby promoting tau-induced neuronal loss (Pampuscenko et al., 2020; Zhou S. et al., 2023). The increasing of soluble Axl level in CSF reflected the pathophysiology of AD and was positively correlated with P-tau181 (Brosseron et al., 2022). However, extensive clinical data showed that CSF Axl was correlated with larger brain volume and slower cognitive decline, which indicated that Axl had a protective effect on related processes (Brosseron et al., 2022). The serum Axl was significantly elevated in AD, and it was negatively correlated with cognition and structural imaging (Brosseron et al., 2023). However, the specificity of Axl as an AD biomarker is still required further investigation.

6.3 YKL-40

Human cartilage glycoprotein-39 (YKL-40) is a biomarker of inflammation, as well as the activated astrocytes (Olsson et al., 2016). It is primarily produced by astrocytes in the brain and it can predict the neurotoxicity induced by inflammation and other stress signals (Connolly et al., 2023). The research focus on the role of YKL-40 in AD is limited. It was presented that YKL-40 may promote AD progression via altering amyloid burden and neuroinflammatory processes (Connolly et al., 2023). Another study indicated a correlation between YKL-40 and tau pathology (Baldacci et al., 2017a). YKL-40 showed good performance in distinguishing tau-positive patients from controls (Baldacci et al., 2017b). A meta-analysis found that CSF YKL-40 could serve as a biomarker to predict the progression from MCI to AD, as well as for the prognosis of MCI. CSF YKL-40 was significantly elevated in AD, MCI, MCI-AD, and stable MCI compared to the controls, and it was higher in MCI-AD than in the stable MCI (Mavroudis I. et al., 2021). The level of CSF YKL-40 increased in AD and FTD, and it was relatively low in DLB (Craig-Schapiro et al., 2010; Janelidze et al., 2016a). Another study showed that the level of CSF YKL-40 in AD increased compared to non-dementia control groups, DLB and PD (Wennström et al., 2015). The above results suggested that CSF YKL-40 could be used as a non-specific neuroinflammatory biomarker to distinguish AD from PD and DLB (Wennström et al., 2015). The application of plasma YKL-40 in diagnosis of AD is controversial. It was reported that higher plasma YKL-40 in Clinical Dementia Rating (CDR) 1 and 0.5

than CDR 0 (Craig-Schapiro et al., 2010). Another study indicated the possibility of YKL-40 for predicting the progression from MCI to mild AD (Choi et al., 2011). Some studies presented no statistical difference of plasma YKL-40 between AD and controls. However, the significantly increased plasma YKL-40 was observed in CJD and LBD (Craig-Schapiro et al., 2010; Villar-Piqué et al., 2019).

6.4 GFAP

Glial fibrillary acidic protein (GFAP) is the main intermediate filament of the glial cytoskeleton (Pekny and Nilsson, 2005). GFAP mediates insulin-like growth factor 1 signaling pathway that involved in AD pathology (Wang et al., 2023). CSF GFAP increased with plaque deposition (Benedet et al., 2021), and it could be used to predict the progression from MCI to AD (Cicognola et al., 2021). In addition, studies found that CSF GFAP can effectively differentiate healthy population from preclinical ADs (Wojdała et al., 2023). Plasma GFAP is considered as an early biomarker for A β pathology, but it is not related with tau pathology (Pereira et al., 2021). Plasma GFAP was sensitive to AD pathology in LBD, especially to A β plaque accumulation (Cousins et al., 2023). Studies showed that plasma GFAP level continued to increase as the disease progression (AD dementia > MCI > cognitively normal elderly with A β positive), but CSF GFAP did not reflect the consistent trend (Verberk et al., 2020; Chatterjee et al., 2021). The reason why plasma GFAP performs better than CSF GFAP as AD biomarker is still unclear. This is probably correlated with the direct release of GFAP into the blood by astrocytic end-feet, and/or different biological degradation between these two matrices (Simrén et al., 2022). Additionally, plasma GFAP can serve as a biomarker for adult AD in Down syndrome, and it could be applied in clinical practice and trials (Montoliu-Gaya et al., 2023). Notably, significantly decreasing GFAP concentration was observed in saliva of MCI and AD compared to controls. Salivary GFAP is suggested as an excellent biomarker for distinguishing MCI or AD from the controls (Katsipis et al., 2021).

6.5 NRG-1

Neuregulin (NRG) plays an important role in the development of nervous system (Esper et al., 2006). NRG-1 is the first and best characterized NRG gene (Pankonin et al., 2009). Soluble NRG (sNRG) was preferentially accumulated on the surface of white matter astrocytes (Pankonin et al., 2009). NRG-1 signaling exerts neuroprotection through the activation of the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) pathway to prevent the neurotoxicity induced by A β ₄₂ (Baik et al., 2016). Another study presented prevention of AD via blocking NRG-1 signaling on microglia (Liu et al., 2023). Both the above studies are based on the animal models. Research found that ADs and MCI-ADs had higher CSF NRG-1 than controls and non-AD dementias, and the CSF NRG-1 was correlated with cognitive evolution (Mouton-Liger et al., 2020). Plasma sNRG-1 level in AD increased and there was a significant correlation between plasma sNRG-1 and MMSE score. The lower MMSE score was correlated with the higher plasma sNRG-1 concentration (Chang et al., 2016). In addition, plasma NRG-1 was found to be correlated with CSF GAP-43, SNAP-25, and NG (Vrillon et al., 2022). Therefore,

sNRG-1 was suggested as a sensitive plasma biomarker (Chang et al., 2016).

6.6 TRAIL

Previous study presented the involvement of TNF-related apoptosis-inducing ligand (TRAIL) in A β induced neurotoxicity in a human neuronal cell line (Cantarella et al., 2003). Blockade of the TRAIL-death receptor DR5 prevented A β -neurotoxicity (Uberti et al., 2007). It was reported that the TRAIL was specifically expressed in the brains of ADs (Uberti et al., 2004). The reduced plasma TRAIL level was observed in AD group compared to controls (Wu et al., 2015), and it was significantly associated with its level in CSF (Wu et al., 2015). No significant difference was observed in the serum TRAIL between ADs and controls. However, a negative correlation was indicated between serum TRAIL and MMSE scores of AD patients (Genc et al., 2009).

7 Biomarkers of BBB breakdown

ApoE ϵ 4 could accelerate the breakdown of BBB and damage the pericapillary cells of the brain (Halliday et al., 2016). High level of platelet-derived growth factor receptor- β (PDGFR- β) in CSF could predict the cognitive decline of *ApoE* ϵ 4 carriers (Montagne et al., 2020). Brain capillary injury and BBB breakdown occurred in the hippocampus of patients with early cognitive impairment (Nation et al., 2019). However, the BBB disruptions were not correlated with alterations in A β and/or tau levels (Nation et al., 2019; Montagne et al., 2020). BBB breakdown was proposed as an early biomarker for human cognitive impairment that was uncorrelated to A β and tau pathology (Mahaman et al., 2022).

The ratio of CSF to serum albumin was applied as a standard method to measure BBB function (Tibblin et al., 1977; Skillbäck et al., 2017; Menendez-Gonzalez and Gasparovic, 2019). The mean value of this ratio was slightly higher in AD patients with vascular factors when compared to the healthy controls, but no significant difference was observed in AD group without vascular factors (Blennow et al., 1990). It is suggested that the BBB damage in AD was associated with clinical vascular factors but not a result of the disease itself (Blennow et al., 1990). This ratio might help to exclude some of the cerebrovascular diseases and indirectly assist the diagnosis of AD (Reitz and Mayeux, 2014).

8 Outlook

The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association, and the National Institute on Aging Working Group proposed that "ideal" biomarkers for AD diagnosis should meet the following criteria (Khan and Alkon, 2015): (1) the basic characteristics of AD neuropathology could be detected; (2) the application of biomarkers should be validated in neuropathologically confirmed AD cases; (3) biomarkers could diagnose AD at the early stage with high sensitivity and specificity; and (4) the analysis should be repeatable, reliable, non-invasive, simple and cost-effective (Kulichikhin et al., 2021). Several challenges still exist. First, the diagnosis of AD mainly depends on the clinical features. Some clinical features are overlapped between AD and non-AD dementia patients, resulting in a high rate of misdiagnosis at the early stage of AD, especially in non-specialist clinical

centers (Engelborghs et al., 2008). Second, other dementias, e.g., VaD and DLB, have the pathological characteristics of AD (Schneider et al., 2009), which hinders the application of some AD biomarkers. Third, A β plaques and NFT are also presented in the elderly population without cognitive impairment (Price and Morris, 1999). Fourth, the detection of most AD biomarkers has not been standardized. Most of the results are preliminary and retrospective, and lacking comparison between patients (Sunderland et al., 2003; Mahaman et al., 2022). Finally, more meta-analysis or the correlation analysis studies among different biomarkers are insufficient. Further investigation to rank and confirm their importance is required.

In the future, the research could focus on demonstrating the accuracy of AD biomarkers, especially for the blood-based biomarkers. The relationship between AD biomarkers and the pathogenesis of AD needs further exploration. Large-scale head-to-head studies are required to determine the most appropriate application scenario of biomarkers at different stages of AD, involving diagnosis, prediction, prognosis, and clinical trial design (Ossenkoppele et al., 2019).

Author contributions

SW: Writing – review & editing, Writing – original draft. SX: Writing – review & editing, Writing – original draft. QZ: Writing – original draft. ZZ: Writing – original draft. TW: Writing – review & editing, Supervision, Conceptualization. GZ: Writing – review & editing, Supervision, Conceptualization.

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Conflict of interest

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