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The fluid biomarkers of Alzheimer's disease

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REVIEW ARTICLE

The fluid biomarkers of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disorder. However, it still has no available disease-modifying therapies. Its pathology cascade begins decades before symptomatic presentation. For these reasons, highly sensitive and highly specific fluid biomarkers should be developed for the early diagnosis of AD. In this study, the well-established and emerging fluid biomarkers of AD are summarized, and recent advances on their role in early diagnosis and progression monitoring as well as their correlations with AD pathology are highlighted. Future prospects and related research directions are also discussed.

1 Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common cause of dementia among people with old age. It is characterized by progressive cognitive dysfunction and behavioral impairments. More than 50 million patients have dementia worldwide, and this figure will have increased to 152 million by 2050 [1]. The diagnostic criteria of AD are constantly updated, especially the importance of biomarkers in disease diagnosis. However, few hospitals or research institutions in China can perform AD-related molecular imaging and cerebrospinal fluid (CSF) examination. Specific drugs that can effectively modify the development of AD pathology have yet to be developed. Most relevant clinical trials in developing new drugs have failed because initiating treatment is too late when patients show dementia. Thus, biomarkers that can facilitate the early diagnosis of AD should be developed.

AD has two major pathological characteristics

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[2]: the extraneuronal neuritic plaques (NP) composed of amyloid β (Aβ) and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau. Neuronal loss, glial cell proliferation, and coexistence of other pathologies, such as TDP-43 or α-synuclein proteinopathies, occur in the brain of a patient with AD. AD pathologies exist many years before the appearance of the clinical symptoms of dementia. Hence, AD can be diagnosed at early stages by detecting the relevant biomarkers reflecting AD pathology. Currently, the generally recognized biomarkers used in AD diagnosis include PET (Aβ and tau) and core markers [Aβ, total tau (t-tau), and p-tau] in the CSF [3]. However, they are not widely applied in clinical practice because of their high cost and invasive procedures. Therefore, further studies have been performed to identify reliable, reproducible, inexpensive, noninvasive, sensitive, and specific fluid biomarkers to certain pathology.

This review is performed to summarize the established and emerging fluid biomarkers in different body fluids and highlight recent advances on their role in early diagnosis, progression monitoring, and correlations with AD pathology. Future prospects and related research direction are also discussed.

Relevant articles in English were identified for this review by searching PubMed without language restrictions for articles published before August 30, 2020. The following search terms were used: "Alzheimer Disease" "biomarker" "Aβ" "tau" "BACE1" "NF-L" "TREM2" "YKL-40" "neurogranin" "exosome (or EVs)" and "miRNA".

2 Biomarkers in the CSF

The CSF directly associates with brain tissues. As such, biomarkers in the CSF can dynamically and sensitively reflect pathological changes. A cohort study has shown that the measured CSF biomarkers may be a reliable substitution for PET in AD diagnosis, and CSF tau/Aβ ratios are as precise as PET image evaluation in predicting outcomes read via a visual approach [4].

2.1 Aβ

Amyloid beta 42 (Aβ42), t-tau, and tau phosphorylated at threonine 181 (p-tau181) in the CSF are recognized as the core biomarkers in AD diagnosis. Aβ42, not p-tau181, in the CSF can differentiate amnestic mild cognitive impairment from subjective cognitive impairment; it can also predict progression from amnestic mild cognitive impairment to Alzheimer's disease dementia [5, 6]. A comprehensive study has confirmed the discriminative performance of CSF Aβ42 between AD and other neurodegenerative diseases in the Chinese population [7]. Other studies have confirmed the CSF Aβ42/Aβ40 ratio can be used to predict the AD pathology with a higher accuracy than that of Aβ42 alone [8, 9], and it has a high reproducibility under different conditions of laboratory analysis [10]. The ratio has also been utilized to predict the progression from mild cognitive impairment (MCI) to AD [11]. Therefore, it shows a good performance in reducing quantitative variability caused by preanalytical factors, such as nonspecific sample tube adsorption, which can enhance the accuracy of CSF Aβ1-42 measurements [12].

2.2 tau

In a study on 322 participants from the ADNI cohort, an increase in CSF p-tau levels can indicate AD pathology and cognitive decline before tau PET abnormality occurs [13]. At the early stages of AD, increases in CSF t-tau and p-tau181 levels can reliably reflect pathological abnormalities and neuronal injury, but changes

in these two biomarkers have failed to show correlation with the pattern of brain atrophy and neurodegeneration at later disease stages [14]. In another study based on a large cohort, the correlation of tau PET with CSF p-tau217 is significantly stronger than that with CSF p-tau181 in brain regions corresponding to the Braak stage; this finding suggests that CSF p-tau217 is a more significantly accurate predictor of an aberrant tau PET status than CSF p-tau181. CSF p-tau217 can also be used to distinguish AD from other neurodegenerative diseases. Moreover, the longitudinal increase in CSF p-tau217 is higher than that in CSF p-tau181 and better interrelated with tau PET in Aβ-positive individuals. Another cohort study has provided consistent evidence supporting the better performance of CSF p-tau217 in the differential diagnosis of AD [15, 16].

In a study on three independent cohorts, a tangle-enriched fragment of tau generated by the cysteine protease asparagine endopeptidase is introduced and named tauN368; its qualitative analysis in the CSF via a novel Simoa method suggests the fragmentation patterns change in AD, as indicated by a higher CSF tauN368 level but a lower CSF tau368/t-tau in patients with AD than in the controls [17]. In another large cohort study by Dr. Blennow and his team, t-tau/Aβ42 and p-tau/Aβ42 are used to predict the risk of clinical decline and conversion to dementia in patients without dementia [18]. Interestingly, vascular risk factors are correlated with longitudinal changes in CSF tau markers [19]. Accordingly, a more sensitive, fast, and simple technique for tau detection should be developed. And it is noteworthy that a transistor-based biosensor with the direct label-free detection of tau is presented [20].

2.3 BACE1

β-site amyloid precursor protein cleaving enzyme 1 (BACE1) mediates the rate-limiting step during Aβ production. It is widely expressed in the brain, particularly in neurons, oligodendrocytes, and astrocytes [21–23]. It is the major β-secretase that participates in the sequential proteolytic processing of amyloid precursor protein (APP) and the generation of Aβ [24]. Several studies have focused on BACE1 levels in the CSF. The BACE1 activity in patients with MCI-AD is higher than that in controls and MCI-non-AD [25]. The ratio of neurogranin and BACE1 in the CSF has also been studied as a potential marker of synapse loss in early AD. Neurogranin is linked to postsynaptic signal transduction, and BACE1 is associated with presynaptic APP metabolism. A cohort study has demonstrated that a higher level of CSF neurogranin/BACE1 in preclinical AD is related not only to the reduction of hippocampal volume and memory function at baseline but also to the cognitive decline during follow-up [26]. Besides, the neurogranin/BACE1 ratio in CSF can be used to discriminate patients diagnosed with a major depressive disorder and cognitive impairments from patients with mild AD [27].

2.4 NF-L

Neurofilament light chain (NF-L), which is an abundant cytoskeletal protein exclusively expressed by central and peripheral neurons, is a prospective biomarker of active neuroaxonal damage and neurodegeneration [28, 29]. In a research involving 467 subjects from a multicenter study, CSF NF-L levels increase with age, and this result is independent of diagnosis, but it is contrary to the trajectory of CSF tau markers that decrease at the late stage of AD [30]. Importantly, CSF NF-L is a strong predictor of cognitive decline in the AD spectrum [31, 32]. Increased CSF NF-L levels may be correlated with damage to the white matter in prodromal

AD [33, 34]. In another research based on 221 participants, CSF NF-L levels are significantly elevated in patients with AD compared with that in healthy controls and could differentiate individuals with AD from controls with a sensitivity of 81.5%. In particular, CSF NF-L levels can be utilized to predict volume loss in the cortical gray matter and cognitive decline; therefore, it is a promising biomarker of neurodegeneration during disease progression [32]. However, NF-L may be a nonspecific biomarker of axonal degeneration because its level increases in a majority of neurodegenerative diseases [35–37]. Thus, CSF NF-L should be combined with other disease-specific biomarkers in the analysis of AD diagnosis.

2.5 TREM2

Triggering receptor expressed on myeloid cell 2 (TREM2), which is expressed abundantly by microglia in the central nervous system (CNS), is an important microglial regulator. It enables microglial responses by sustaining energetic and biosynthetic metabolism in cells in AD [38]. High levels of CSF sTREM2 are correlated with the biomarkers of tau and neuronal injury in CSF but not in amyloidosis [39–41]. Interestingly, high CSF sTREM2 levels at baseline are associated with slow rates of Aβ accumulation (assessed with amyloid PET for more than 2 years); this result suggests that high CSF sTREM2 levels play a protective role in the progression of amyloid pathology [42]. Another study has proposed similar protective effects of TREM2 at the preclinical stage of AD and provided evidence that blood TREM2 levels in patients with MCI and particularly those with MCI-AD are higher than those in healthy controls [43]. A longitudinal study has confirmed that CSF sTREM2 at baseline is associated with longitudinal volumetric and diffusivity changes in AD-related regions [44].

2.6 YKL-40

CSF chitinase-3-like protein 1 (YKL-40) is a secreted glycoprotein expressed by microglia and astrocytes in the CNS [45, 46] and considered one of the most promising biomarkers of neuroinflammation in AD. In a longitudinal study, CSF YKL-40 increases with age [30]. In a study on participants from the ADNI database, YKL-40 can be used to reflect neurodegeneration and is associated with hippocampal atrophy at baseline and follow-up in Aβ-positive patients [47]. In another study on participants from two Norwegian cohorts, CSF YKL-40 levels increase in patients with dementia-related AD compared with Aβ-positive MCI individuals and healthy controls [48]. A large cohort study has confirmed that CSF YKL-40 levels increase in preclinical AD. It is associated with tau pathology in Aβ-positive individuals. A high YKL-40 level is correlated with cognitive impairment and a high risk of progression to AD [49]. CSF YKL-40 is related to progression from presymptomatic to symptomatic AD [50].

2.7 Neurogranin

Neurogranin is a calmodulin-binding post-synaptic protein that plays a critical role in synaptic plasticity and long-term potentiation [51]. The trajectory of CSF neurogranin increases with aging in Aβ-positive individuals [52]. It is also significantly associated with AD pathology [31, 53]. In a study based on patients from the ADNI database, CSF neurogranin levels are associated with CSF core biomarkers, and the diagnostic efficiency of neurogranin in differentiating AD from controls is comparable with that of core biomarkers in the CSF. Neurogranin levels also increase in MCI and AD groups compared with those in the control group, and this increase can be used to predict the conversion from cognitively normal to MCI.

Importantly, high levels of CSF neurogranin are correlated with longitudinal cognitive decline [54]. Other studies have also confirmed the correlation of CSF neurogranin with cognitive decline in AD [55, 56].

3 Biomarkers in the blood

Undergoing an invasive lumbar puncture in CSF collection is not widely acceptable among patients. Instead, collecting blood specimens is preferred because this procedure is noninvasive, convenient, reproducible, and cost effective. Some molecules can pass the blood–brain barrier, so some biomarkers in the blood can reflect the AD pathology.

3.1 Aβ

Notably, a novel measurement of plasma Aβ biomarkers via immunoprecipitation coupled with mass spectrometry has demonstrated the potential clinical practicality of blood biomarkers in predicting brain Aβ burden [57]. Plasma Aβ 40/42 ratio can also predict cerebral amyloidosis in cognitively normal individuals at risk of AD [58]. The plasms Aβ42/Aβ40 ratio also shows a good performance in the differential diagnosis [59] and identification of AD pathology in cognitively normal individuals with SCD [60]. Many studies have demonstrated that a low Aβ42/Aβ40 ratio is associated with diagnosis and PET Aβ positivity in AD, indicating that this ratio can be utilized to predict cerebral Aβ deposition [61, 62]. In another cohort study, plasma Aβ42/Aβ40 is applied to identify individuals suffering from amnestic MCI and predict its progression to dementia [63].

3.2 Aβ oligomers

In AD, Aβ is initially transformed into oligomers and fibrils and subsequently into amyloid plaques. Among them, oligomeric Aβ is the main toxic species. Amazingly, there are quite a few studies have developed novel effective approaches for Aβ oligomer detection in recent years[64–67]. The increased levels of oligomeric Aβ measured with a multimer detection system (also called MDS-OAβ) in the blood are negatively correlated with changes in the volume of specific brain regions, especially the typical areas of degeneration in AD [68]. Interestingly, compared with healthy controls, a stronger association between increased plasma levels of oligomeric Aβ, and deduced general cognitive level, particularly episodic memory performance is observed in patients with AD [69].

3.3 tau

In a recent prospective study, plasma t-tau is correlated with the risk of AD and the improved risk stratification of dementia after adjustments for age and sex. A marked increase in plasma t-tau levels is associated with cognitive decline, a small hippocampal volume (measured via MRI), a high burden of neurofibrillary tangles, and microinfarcts during autopsy [70]. By contrast, a clear association between plasma t-tau and AD risk is not found in two large cohort studies [60, 71]. These contradictory results may indicate that plasma t-tau is not a specific biomarker. In a longitudinal study, increased levels of tau-related biomarkers in plasma (p-tau, t-tau, p-tau/Aβ42, and t-tau/Aβ42) are significantly correlated with brain tau deposition and a high risk of tau PET positivity. Notably, the brain regions associated with increased plasma t-tau/Aβ1-42 resemble the typical region characterized by neurofibrillary tangles in AD. Particularly, plasma t-tau/Aβ1-42 can predict brain tau accumulation and neuropathological changes [72].

Plasma p-tau may serve as an accurate biomarker of AD. In four clinic-based cohorts, plasma p-tau181 gradually enhances along the AD continuum, shows a correlation with tau and Aβ pathologies (measured via PET), and plays a role in the differential diagnosis of AD from other neurodegenerative diseases [73]. These results are consistent with data from Mayo Clinic [74]. In a longitudinal cohort, plasma p-tau181 can be used to distinguish patients with AD pathology from controls without AD pathology with an AUC of 97.4% [75]. These studies have demonstrated the sensitivity and specificity of plasma p-tau181 as a biomarker of AD pathology. In addition, p-tau217 and p-tau181 in plasma are related to their concentrations in CSF. Importantly, p-tau217 has the highest specification for amyloid plaque status [76] and is used to accurately discriminate AD from other neurodegenerative diseases [77]. These studies have emphasized the importance of plasma p-tau in AD diagnosis.

3.4 BACE1

Andrea Vergallo et al. proposed the sexual dimorphism of plasma BACE1 and provided evidence that its mean concentrations are significantly higher in women than in men in cross-sectional and longitudinal aspects [78]. In a cohort of cognitively normal individuals at risk for AD, plasma BACE1 levels are associated with Aβ PET at baseline. In another study, a sensitive and specific assay is developed to detect the activity of human plasma BACE1 and quantify its protein expression [79]. In 224 individuals from three independent international academic AD research centers and memory clinics, V_{mean} of the plasma BACE1 activity in patients with MCI nonconverters (patients with MCI that has not converted to probable AD), MCI converters, and AD increases by 45.0%, 85.4%, and 97.3%, respectively, compared with those in healthy controls. Besides, the BACE1 activity is higher in MCI converters than in MCI nonconverters, indicating the utility of plasma BACE1 in predicting progression from prodromal AD to probable AD dementia [79]. Furthermore, a larger population-based study has found that the serum BACE1 activity significantly increases by around 25% in patients with late-onset AD compared with that in healthy controls [80].

3.5 NF-L

Plasma NF-L levels in patients with AD at the dementia stage and patients with MCI and a high prospect of underlying AD pathology (MCI-AD) significantly increase compared with those in controls without dementia even after adjustments for age are made [81]. Plasma NF-L concentrations are negatively correlated with cognitive status [81]. High NF-L plasma levels and low Aβ42 levels are each independently and in combination strongly correlated with the risk of all-cause and AD dementia [71].

An increased plasma NF-L may also be used to predict changes in the white matter [82, 83]. A study from the world's largest single-mutation autosomal dominant AD characterized plasma NF-L concentrations based on 2,144 presenilin 1 (PSEN1) E280A mutation carriers and noncarriers. It reported that plasma NF-L increases with age in all groups (cognitively impaired carriers, unimpaired carriers, and noncarriers). Interestingly, plasma NF-L concentrations can be used to significantly discriminate carriers from noncarriers at 22 years (22 years before the carriers' predicted age of 44 years at the MCI onset). Plasma NF-L levels are also associated with a low cognitive function at baseline and a large cognitive decline during the follow-up of approximately 6 years [84].

3.6 EVs

Extracellular vesicles (EVs), including exosomes and (shedding) microvesicles, can transport cargo (e.g., proteins and nucleic acids) between cells as a form of intercellular communication. CNS- or brain-derived extracellular vesicles likely play a critical role in biomarker research and therapeutic research because of its extraordinary characteristic of traveling between the CNS and peripheral circulation. Recently, a large longitudinal cohort study has provided evidence that the longitudinal trajectory of neuronal-enriched EV biomarkers in patients with future AD is different from those in controls with reliance on age and sex. Importantly, the cohort study also validated the usefulness of a model based on several EV biomarkers in the prediction of preclinical AD with high accuracy [85]. The levels of EV biomarkers (t-tau, p-tau181, and p-tau231) in older individuals with cognitive impairment milder than MCI are higher than those in patients with stable cognition. The annualized rates of change in insulin signaling biomarkers are also higher in individuals with cognitive decline than in patients with stable cognitive ability. These results indicate the potency of EV biomarkers in identifying the tau pathology or cognitive decline prior to clinical AD [86].

With regard to core biomarkers in EVs, a multicenter study has confirmed the correlation of exosomal biomarkers with those in the CSF and demonstrated that Aβ42, t-tau, and p-tau181 in exosomes can be used for the diagnosis of AD and aMCI considered useful as those in CSF [87]. Interestingly, the abnormal levels of APP and p-tau181/t-tau in EVs may identify patients with MCI [88]. As for exosomal synaptic proteins, Jia et al. demonstrated the robust association of some synaptic protein levels in EVs and CSF and the usefulness of the combination of exosomal GAP43, neurogranin, SNAP25, and synaptotagmin 1 in determining preclinical AD 5–7 years before cognitive impairment [89]. Furthermore, exosomal synaptic proteins are correlated with cognitive decline and may indicate the progression of AD as their levels decrease [90, 91]. In terms of exosomal microRNAs (miRNAs), the concentrations of two miRNAs (hsa-miR-451a and hsa-miR-21-5p) in AD significantly decreased compared with that in DLB with an AUC of 0.9; this result suggests its potential performance in the differential diagnosis of AD from DLB [92].

3.7 miRNA

miRNAs, as endogenous regulators of gene expression, are small noncoding RNA molecules widely expressed in the nervous system. In a large systematic review on data from 147 independent data sets, 25, 5, and 32 miRNAs have a significant differential expression in the brain, CSF, and blood-derived specimens, respectively [93]; furthermore, 36 repeatedly differential blood miRNAs may be promising components of the diagnostic panel of AD [94]. Blood miR-146b-5p and miR-15b-5p have a unanimous differential expression in AD compared with that in the controls [95]. A plasma-based panel composed of miRNAs correlated with synaptic proteins (miR-92a-3p, miR-181c-5p, and miR-210-3p) yields a high diagnosis accuracy of 0.893 for distinguishing subjects with MCI and AD from healthy controls and can be used to predict the progression of MCI to AD [96]. Hsa-mir-567 can be utilized to determine cognitive decline and predict MCI progression to AD with its higher serum expression in MCI-AD (MCI due to AD) and AD groups than in healthy controls [97]. Interestingly, Jain et al. defined a suitable panel consisting of three miRNAs to detect AD with an AUC of 0.83 in a replication cohort [98]. However, the performance of miRNAs as

biomarkers of AD is neither consistent nor validated in a longitudinal independent cohort. Thus, cohort studies with standard procedures should be performed.

4 Biomarkers in the urine and saliva

Recently, a multicenter study based on two cohorts has demonstrated that salivary lactoferrin (Lf) can discriminate prodromal AD and AD dementia from healthy controls with a high accuracy. It distinguishes AD from FTD with a sensitivity of 87% and a sensitivity of 91%. Reduced Lf levels can be used to identify subjects with positive cerebral amyloidosis [99], and this finding is consistent with a previous study [100]. Bermejo-Pareja et al. hypothesized that the reduced levels of salivary (Lf) may be related to immunological disturbances in AD, and this observation agrees with the physiopathological explanations of AD [101]. In a pilot study, a targeted and quantitative metabolomics approach is applied, and several panels composed of urinary metabolites are identified to distinguish MCI and AD from cognitively healthy controls with high sensitivity and specificity [102]. Several novel urinary biomarkers for the early diagnosis of AD have been discovered, and some of them are Alzheimer-associated neuronal thread protein (AD7c-NTP) [103–106], monocyte chemoattractant protein-1 (MCP-1) [107], and dysregulated arginine metabolism [108].

5 Conclusions

AD is a destructive neurodegenerative disorder characterized by complicated pathological changes and clinical manifestations. Patients who are pathologically confirmed to have AD only account for three-fourths of patients who are clinically diagnosed with AD [109]. As such, reliable biomarkers that can contribute to the accurate early diagnosis of AD must be developed. Currently, extensively validated core biomarkers include Aβ42, t-tau, and p-tau in the CSF. These core CSF biomarkers sensitively and reliably reflect AD pathology. However, their clinical application is less satisfactory because of invasive procedures. Conversely, biomarkers in the blood show potential for application in the early diagnosis of AD. The most promising biomarkers in the blood are plasma p-tau217, p-tau181, and NF-L. Other potential biomarkers, such as plasma BACE1, TREM2, YKL-40, neurogranin, and EVs, should be further validated. More details with those selected candidates of AD fluid biomarkers are summarized in Table 1. Conditions and protocols should be standardized to enhance the accuracy of measurements [110–112]. Larger cohort studies should also be performed to demonstrate the correlation of different biomarkers in the blood with those in the CSF and thus improve their accuracy. More longitudinal studies should be carried out to validate the clinical utility of these biomarkers.

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Conflict of interests

All contributing authors have no conflict of interests to declare.

Table 1 Summary of selected candidates of AD fluid biomarkers.

Biomarkers			Associated pathology	Levels in AD *vs.* healthy controls	Discriminative performance	Prediction of AD pathology	Correlation with neurodegeneration	Prediction of disease progression	Correlation with cognitive decline	Other
In CSF	Aβ	Aβ42	Aβ pathology	↓	aMCI *vs.* SCI [6] AD *vs.* other neurodegenerative diseases [7]			From aMCI to ADD [5]		
		Aβ42/Aβ40		↓		With higher accuracy than Aβ42 alone [8, 9]		From MCI to AD [11]		Good performance in reducing the quantitative variability [12]
	tau	p-tau	tau pathology	↑		Predict the AD pathology before tau PET abnormality [13]			√ [13]	
		p-tau217		↑	AD *vs.* other Neurodegenerative diseases [15, 16]	A better predictor of aberrant tau PET status than CSF p-tau181 [15]				
		tauN368		↑		CSF tau368/t-tau reflects tangle pathology [17]				
		t-tau/Aβ42 p-tau/Aβ42		↑				Conversion to dementia in patients without dementia [18]	√ [18]	
	BACE1			↑	Neurogranin/BACE1 ratio in CSF discriminates patients diagnosed with major depressive disorder and cognitive impairments from patients with mild AD [27]		A higher level of CSF neurogranin/BACE1 in preclinical AD was associated with the reduction of hippocampal volume [26]		√ [26]	
	NF-L		Neuroaxonal damage and neurodegeneration	↑	AD *vs.* healthy controls [32]		May correlate with damage to the white matter in prodromal AD [32–34]		√ [31, 32]	Nonspecific biomarker observed in a majority of neurodegenerative diseases [35–37]
	TREM2		Neuroinflammation response	Dynamic change [40]		Higher CSF sTREM2 levels at baseline were associated with slower rates of Aβ accumulation [42]				Early increase in sTREM2 is associated with tau-related-neurodegeneration but not with amyloid-β pathology [41] showing protective effects in the preclinical stage of AD [43]
	YKL-40		Neuroinflammation	↑		Associated with tau pathology in Aβ-positive individuals [49]	Associated with hippocampal atrophy [47]	From presymptomatic to symptomatic AD [50]	√ [49]	
	Neurogranin		Synaptic dysfunction	↑	AD *vs.* healthy controls (comparable efficiency to that of core biomarkers in CSF) [54]	Significantly associated with the degree of amyloid and tau pathology [53]		From cognitively normal to MCI [54]	√ [54–56]	

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Biomarkers			Associated pathology	Levels in AD *vs.* healthy controls	Discriminative performance	Prediction of AD pathology	Correlation with neurodegeneration	Prediction of disease progression	Correlation with cognitive decline	Other
In blood	Aβ	Aβ42/Aβ40	Aβ pathology	↓	Dementia due to AD *vs.* dementia not due to AD [59]	Predict cerebral Aβ deposition [58, 61, 62]		Progression to dementia [63]		
		Aβ oligomers		↑			Negative correlation with brain volume changes of specific regions,significantly the typical areas of degeneration [68]		√ [69]	
	tau	t-tau	tau pathology	↑		Associated with a higher burden of neurofibrillary tangles [70] Elevated plasma t-tau/Aβ1-42 resembled the typical region characterized by neurofibrillary tangles [72]			√ [70]	Contradictory results in the association between plasma t-tau and AD risk [60, 70, 71]
		p-tau181		↑	AD *vs.* other neurodegenerative disease [73]	Correlated with tau and Aβ pathologies [73, 74] Accurately predicts AD pathology at least 8 years prior to post-mortem [75]			√ [75]	
		p-tau217		↑	AD *vs.* other neurodegenerative disease [77]	Showed the high specificity for amyloid plaque status [76]				
	BACE1			↑				From prodromal AD to probable AD dementia [79]		Sexual dimorphism [78]
	NF-L		Neuroaxonal damage and neurodegeneration	↑	(PSEN1) E280A mutation carriers *vs.* noncarriers when 22 years [84]		May also predict white-matter changes [82, 83]		√ [81, 84]	
	EVs	Exosomal core biomarkers			Patients with MCI *vs.* patients with AD [88]					The ability of Aβ42, t-tau, and p-tau181 in exosomes for diagnosis of AD and aMCI is as useful as those in CSF [87]
		Exosomal synaptic proteins		↓					√ [90, 91]	Robust association of some synaptic proteins levels in EVs and those in CSF [89] Determining preclinical AD 5 to 7 years before cognitive impairment [89]
	miRNA			↑	MCI and AD subjects *vs.* healthy controls [96]			Predict the progression of MCI to AD [96, 97]	√ [97]	
In urine and salivary	Salivary lactoferrin (Lf)			↓	Prodromal AD and AD dementia *vs.* healthy controls [99, 100] AD *vs.* FTD with a sensitivity of 87% and a sensitivity of 91% [99]	Reduced Lf levels could identify subjects with positive cerebral amyloidosis [99]				
	Urinary metabolites				MCI and AD *vs.* cognitively healthy controls [102]					

Note: Aβ38/40/42, amyloid beta 38/40/42; AD, Alzheimer's disease; ADD, Alzheimer's disease dementia; aMCI, amnestic mild cognitive impairment; BACE1, β-site amyloid precursor protein cleaving enzyme 1; CSF, cerebrospinal fluid; EVs, extracellular vesicles; miRNA, microRNA; NF-L, neurofilament light; p-tau, phosphorylated tau; SCI, subjective cognitive impairment; sTREM2, soluble TREM2; t-tau, total tau; TREM2, triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1.

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