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Review article

Circulating biomarkers of inflammaging and Alzheimer's disease to track age-related trajectories of dementia: Can we develop a clinically relevant composite combination?

Angela Marie Abbatecola a,b

Angelica Giuliani c,*

Leonardo Biscetti d

Lucia Scisciola e

Petronilla Battista f

Michelangela Barbieri e

Jacopo Sabbatinelli g,h,1

Fabiola Olivieri g,h,1

a Alzheimer's Disease Day Clinic, Azienda Sanitaria Locale, Frosinone, Italy

b Univesita ` degli Studi di Cassino e del Lazio Meridionale, Dipartimento di Scienze Umane, Sociali e della Salute, Cassino, Italy

c Istituti Clinici Scientifici Maugeri IRCCS, Cardiac Rehabilitation Unit of Bari Institute, Italy

d Unit of Neurology, IRCCS INRCA, Ancona 60127, Italy

e Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

f Istituti Clinici Scientifici Maugeri IRCCS, Laboratory of Neuropsychology, Bari Institute, Italy

g Department of Clinical and Molecular Sciences, DISCLIMO, Universita ` Politecnica delle Marche, Ancona, Italy

h Clinic of Laboratory and Precision Medicine, IRCCS INRCA, Ancona, Italy

Abstract

Alzheimer's disease (AD) is a rapidly growing global concern due to a consistent rise of the prevalence of dementia which is mainly caused by the aging population worldwide. An early diagnosis of AD remains important as interventions are plausibly more effective when started at the earliest stages. Recent developments in clinical research have focused on the use of blood-based biomarkers for improve diagnosis/prognosis of neurodegenerative diseases, particularly AD. Unlike invasive cerebrospinal fluid tests, circulating biomarkers are less invasive and will become increasingly cheaper and simple to use in larger number of patients with mild symptoms or at risk of dementia. In addition to AD-specific markers, there is growing interest in biomarkers of inflammaging/neuro-inflammaging, an age-related chronic low-grade inflammatory condition increasingly recognized as one of the main risk factor for almost all age-related diseases, including AD. Several inflammatory markers have been associated with cognitive performance and AD development and progression. The presence of senescent cells, a key driver of inflammaging, has also been linked to AD pathogenesis, and senolytic therapy is emerging as a potential treatment strategy. Here, we describe blood-based biomarkers clinically relevant for AD diagnosis/prognosis and biomarkers of inflammaging associated with AD. Through a systematic review approach, we propose that a combination of circulating neurodegeneration and inflammatory biomarkers may contribute to improving early diagnosis and prognosis, as well as providing valuable insights into the trajectory of cognitive decline and dementia in the aging population.

Keywords: Alzheimer's disease; blood biomarkers; inflammaging biomarkers; dementia

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and is rapidly increasing on a worldwide scale. The constantly rising number of persons reaching advanced age is associated with a significant rise in dementia cases, currently estimated in 50 million individuals worldwide, a number expected to almost triple by 2050 (Long et al., 2023).

Over the last decade, there has been an increasing number of clinical trials investigating the potential usefulness of blood-based biomarkers for the diagnosis of neurodegenerative diseases and, in particular, AD (NCT04733989, NCT05020106, and NCT05187819). Considering that the first cerebrospinal fluid (CSF) biomarkers that typically reflect main AD pathogenetic mechanisms (amyloidosis and taupathy), i.e. β -amyloid, total tau (t-tau), and phosphorylated tau (p-tau), are detectable 20 years prior to clinical onset of AD, biomarker-based diagnosis at the earliest opportunity is imperative (Barthelemy et al., 2020). The CSF confirmation of AD pathology provides significant advantages to patients. The Alzheimer's Association recently published criteria for the use of lumbar puncture and CSF testing, underlining that clinical indications for the use of CSF are considered appropriate in those less than 65 years of age with an early onset of dementia or in an early stage of disease, namely Mild Cognitive Impairment (MCI) or Dementia (Shaw et al., 2018). The authors underlined that CSF biomarkers may also be useful in those over 65 years of age especially if there is a clinical uncertainty regarding an AD diagnosis. The use of CSF puncturing is a quite invasive procedure and limitations in the CSF puncturing underline that this technique is contraindicated for patients with coagulation issues, including those with severe thrombocytopenia and those taking anticoagulant medications. CSF use also holds limitations due to different quantifying measures across clinical centers (Delaby et al., 2022). In addition to CSF biomarkers, positron emission tomography (PET) using amyloid or tau tracers is considered as a valid tool to make AD diagnosis according to current AD diagnostic criteria (Dubois et al., 2014; Jack et al., 2018). However, PET is expensive and not universally available, thus it has limited feasibility for screening purposes. In this framework, the use of blood biomarkers could offer potential benefits for AD screening or diagnosis

in primary care settings worldwide, significantly less invasive and, overall, less costly than CSF. Now, there is substantial data supporting the use of diverse blood biomarkers capable of distinguishing AD dementia from other dementias, as well as predicting the development of AD in non-demented adults with cognitive complaints (Cullen et al., 2021). In the near future, blood biomarkers might also be used to monitor the efficacy of AD treatment.

Aging and prevalent diseases in older persons, the so-called age-related diseases, including AD, share some pathophysiological mechanisms (Lopez-Otin et al., 2013; Pezone et al., 2023). Inflammaging, the age-related chronic, low-grade, systemic proinflammatory condition, is today recognized as one of the main mechanisms increasing the risk of developing the most common age-related diseases (ARDs) (Lopez-Otin et al., 2013). Numerous potential biomarkers of inflammaging have been proposed, but a universally acceptable single-measurement biomarker has still not been identified, most likely due to the complexity of the aging process itself (Moqri et al., 2023). Chronic inflammation represents a crucial link between the immune and nervous systems along with advancing age, since increased levels of inflammaging predispose to the development of various diseases, including the spectrum of neurodegenerative diseases (Franceschi et al., 2000). The chronic low-grade inflammatory process in the central nervous system (CNS), mainly driven by glial cells, has been defined as neuro-inflammaging, and it was associated with increased AD risk (Mohapatra et al., 2023; Soraci et al., 2024; Stephenson et al., 2018). The main culprits of inflammaging are chronically activated innate immune cells and the increased burden of senescent cells acquiring senescence-associated proinflammatory secretory phenotype (SASP) (Fulop et al., 2018). Consequently, among the circulating biomarkers of inflammaging, those reflecting neuroinflammation and cellular senescence have been significantly associated with age-related diseases (Saavedra et al., 2023).

In this review, we will highlight the role and diagnostic value specific biomarkers of neuronal damage in AD and diverse biomarkers related to inflammaging and neuroinflammaging. Through a systematic

review approach, we will propose that a composite blood-based biomarker signature may contribute to tracking the trajectories of neurodegeneration and dementia during aging.

2. Blood-based clinically relevant biomarkers in AD dementia

There is rapidly growing clinical evidence regarding the use of blood-based biomarkers for AD diagnosis and prognosis and the identification of individuals for dedicated intervention trials. In the search for early markers of neurodegeneration and AD, research on blood-based measures has been emerging, given their advantages in accessibility and cost-effectiveness compared to CSF procedure and neuroimaging techniques (Teunissen and Middeldorp, 2022). Ultrasensitive assays have been developed, allowing reliable measure concentrations of AD and neurodegeneration blood biomarkers, including amyloid- β_{40} ($A\beta_{40}$) and amyloid- β_{42} ($A\beta_{42}$), hyperphosphorylated tau (p-tau181, p-tau217, p-tau231), and neurofilament light chain (NfL) (Blennow and Zetterberg, 2019). Also, glial fibrillary acidic protein (GFAP), measurable in blood and reflecting astrocytic inflammation, was associated with neurodegenerative diseases (Gaur et al., 2023). Clinically relevant biomarkers in AD diagnosis are listed in Table 1.

The most common studied biomarker, Amyloid β ($A\beta$) is the core pathological hallmark of AD. Both CSF and PET biomarkers of $A\beta$ have been shown to alter before clinical onset (Hansson et al., 2018). Interestingly, the use of plasma $A\beta$ as an AD biomarker has been identified as a tool for detecting AD amyloid plaques (Nakamura et al., 2018).

Numerous investigations continue to test plasma $A\beta$ pathology concentrations using different technologies for plasma $A\beta_{42}/A\beta_{40}$ ratio measurements. In the past, there was a lack of sufficient precision regarding plasma $A\beta$ levels which may be explained by the type of technology used for measurements. A recent report underlined that Immunoprecipitation mass spectrometry technology may be superior to other technologies; however, assays need to be tested in similar cohorts for greater assessment (Brand et al., 2022). At the moment, there is no diagnostic application in clinical practice to differentiate AD from non-AD dementia using plasma $A\beta_{42}/A\beta_{40}$ (Nakamura et al., 2018).

Neurofilament light chain (NfL) is one of the three components of the intermediate filaments (Nfs) of neurons, including neurofilament heavy chain (NFH) and neurofilament middle chain (NFM), abundantly expressed in large caliber myelinated axons (Barro et al., 2020). NfL is the best candidate among the three Nfs subunits to be measured because of its greater solubility and detectability in several biofluids, including CSF and blood (Gafson et al., 2020). When neuronal cells or their axonal membranes are damaged, NfL are released into the interstitial fluid (IF), CSF, and blood, thus levels of NfL in the blood can be used for diagnosis, prognosis, monitoring disease progress, treatment response, or drug toxicity.

Identifying biomarkers capable of predicting initial cognitive impairment in individuals at high risk of cognitive decline and AD is imperative. A recent study reported that measurement of classical biomarkers ($A\beta_{42}/A\beta_{40}$ and NfL) in both CSF and in plasma (in this latter case with mass spectrometry) predicted cognitive decline in older persons at risk of dementia in similar manner (Aschenbrenner et al., 2022). Specifically, this study allowed for a head-to-head comparison of plasma and CSF biomarkers with respect to the prediction of cognitive decline. The authors found that both plasma and CSF biomarkers are independently associated with cognitive decline and that a clinical trial where enrolment is based on plasma assessment would require only a marginally larger cohort compared to one based on CSF biomarkers measures.

In an additional study involving people aged 65 years or older, neuronal injury during acute illness and delirium, measured by NfL, was also associated with greater cognitive decline (Krogseth et al., 2023).

Glial fibrillary acidic protein (GFAP), an intermediate filament-III protein uniquely found in astrocytes in the CNS, non-myelinating Schwann cells in the peripheral nervous system (PNS), and enteric glial cells, is another promising blood-based biomarker for neurodegeneration and dementia. Emerging evidence suggests that, following traumatic brain and spinal cord injuries and stroke, GFAP protein and its breakdown products are rapidly released into biofluids, making them strong candidate biomarkers for such neurological disorders (Yang and Wang, 2015).

Hyperphosphorylated tau has been identified as a major constituent of neurofibrillary tangles, the major pathological hallmark of AD, in addition to amyloid plaque (Grundke-Iqbal et al., 1986). Even though tau has numerous phosphorylation sites, studies have found that plasma concentrations of p-tau181, p-tau217, and p-tau231 are strongly associated with AD diagnosis compared to those controls (Brickman et al., 2021) as well to non-AD dementias (Ossenkoppele et al., 2022; Palmqvist et al., 2020). p-tau181 has gained attention since plasma p-tau181 concentrations were associated to AD clinical severity and with tau-PET (Mielke et al., 2018). Interestingly, p-tau217 plasma concentrations showed a strong correlation with cognitive decline in A β -positive cognitively unimpaired (CU) individuals (Mielke et al., 2018), a higher diagnostic accuracy than all other plasma p-tau biomarkers for AD diagnosis (Janelidze et al., 2023), and a comparable diagnostic performance in plasma and CSF (Mendes et al., 2024).

Even though there have been substantial advances to the potential use of plasma biomarkers for diagnosing AD dementia, no single biomarker can be used to predict cognitive decline in pre-clinical AD cases and differentiate AD cases from other type of dementia (Pais et al., 2023). An interesting approach emerged from a recent study which aimed to integrate plasma p-tau217, age, and APOE ϵ 4 status into a workflow to identify patients at high risk of AD (Brum et al., 2023). In this framework, the authors proposed that only patients with borderline levels of the biomarker should be forwarded for further testing, thus reducing the burden of unnecessary CSF and imaging exams. Recent reports highlighted the significance of using combined assessments of plasma markers than single biomarkers on differentiating neurodegenerative dementia from healthy aging, as well as identifying AD from other conditions, such as frontotemporal lobar degeneration (FTLD) (Benussi et al., 2022). According to a recent study, when A β ₄₂/A β ₄₀, NfL, p-tau181, and GFAP were analyzed as diagnostic biomarkers, NfL was the best single biomarker to distinguish between healthy aging and dementia, while the cluster of multiple biomarkers increased diagnostic accuracy (Benussi et al., 2022). In addition, this study identified the best biomarkers combination for distinguishing between AD and FTLD, such as A β ₄₂/A β ₄₀, p-tau181, and other markers related to transcranial stimulations. A prospective cohort

study in cognitively unimpaired elderly examining the prognostic and monitoring capabilities of biomarkers of neurodegeneration (ND) through their quantification in serum showed that GFAP, NfL and A β ₄₂/A β ₄₀ were valuable prognostic and/or monitoring tools in asymptomatic stages providing complementary information in a time- and pathology-dependent manner (De Meyer et al., 2023).

Combinations of CSF and blood biomarkers were also investigated in the dementia framework. Neuronal pentraxins (NPTXs), a family of proteins involved in homeostatic synapse plasticity, is emerging as novel CFS biomarkers to characterize different type of dementia (Shao et al., 2020). The combination of CSF NPTX2, serum NfL, and serum GFAP was proposed to differentiate different types of dementia with good accuracy (Bolssewig et al., 2022).

During the preclinical stage, biomarkers of AD disease, including those of A β , tau, and neurodegeneration, are thought to have prognostic value regarding the identification of individuals at risk of developing AD dementia in the coming years. The National Institute on Aging–Alzheimer's Association Research Framework was developed to provide a staging model called the AT(N) (Jack et al., 2018). This framework classes individuals into groups based on three types of biomarkers: amyloid (A), tau (T), and neurodegeneration (N), which are theorized to drive symptomatic AD (Jack et al., 2018). The AT(N) system is flexible in that new biomarkers can be added to the three existing AT(N) groups, and new biomarker groups beyond AT(N) can be added when they become available. In this framework, innovative biomarkers of aging could be characterized by potential crosstalk with dementia. The need to understand the power of aging itself on changes related to AD blood biomarkers may hold significant clinical awareness, especially for well-designed clinical trials.

Higher levels of these above-described markers have been shown to be associated with neurodegenerative processes and AD brain pathology suggesting that monitoring these biomarkers in clinical settings may provide important insight into underlying early brain changes and neurodegeneration (Merten et al., 2023; Teunissen et al., 2022).

In this context, a recent investigation compared the correspondence of CSF and plasma core AD core biomarkers with AD pathological change at post-mortem examination, which still represents the

diagnostic gold standard (Wang et al., 2023). In this study, CSF accurately predict AD neuropathological changes, while plasma AD biomarkers can predict the results of neuropathological examination only when combined to APOE ϵ 4 genotype, which is the strongest genetic risk factor for sporadic AD. These findings suggested that CSF biomarkers have a relatively higher accuracy than plasma biomarkers in prediction of AD pathological changes, but plasma biomarkers together with APOE genotype can represent a valid and less invasive alternative.

3. Blood-based Biomarkers of inflammaging and Alzheimer's Disease

In recent years, technological innovation has allowed the analysis of multiple biomarkers, increasing the knowledge of inflammaging over the aging process. Specific aging clocks have been developed based on blood proteins modulating inflammation and have been defined as Inflammatory clocks (Alpert et al., 2019; Lehallier et al., 2020; Murabito et al., 2018; Sayed et al., 2021). The limitation in designating these models is due to the large dimensionality of input data with poor effectiveness in clinical terms. Increasing efforts are devoted to developing small clocks based on a limited number of immunological biomarkers (Kalyakulina et al., 2023; Yusipov et al., 2022). Interestingly, these inflammatory clocks have confirmed the role played by circulating cytokines, mainly IL-6, the key cytokine of inflammaging, as an age predictor, and highlighted interesting roles for a variety of chemokines, including CXCL8, CXCL9, CXCL10, and the Platelet Derived Growth Factor Subunit A (PDGFA) (Kalyakulina et al., 2023).

Interestingly, IL-6, CXCL9, and PDGFA were found to be associated singly or in combination with cognitive performance and AD (Bradburn et al., 2018; Lyra et al., 2021; Pagoni et al., 2022; Sil et al., 2018; Wang et al., 2018). Recent reports confirmed that higher levels of circulating IL-6 were associated with cognitive impairment in an older adult population of Southern Italy (Griseta et al., 2023).

The chemokines CXCL9 and CXCL10 share CXCR3 as a common receptor, which is expressed not only on T and NK cells, but also on neurons. CXCL10 was found to be expressed in astrocytes and

to be localized around A β plaques in AD animal models (Krauthausen et al., 2015). A recent meta-analysis of chemokines in CSF and blood (plasma or serum) suggested that CXCL9 and CXCL10 might also be useful as tau-independent and A β -independent blood-based candidate biomarkers for AD (Zhou et al., 2023). CXCL8, also called IL-8, is expressed in neurons, astrocytes, and microglia, and blood CXCL8 levels were associated with long-term cognitive function (Teoh et al., 2023). Although evidence on circulating chemokines suggest a possible role as biomarkers of AD progression, data on their specificity to discriminate among different forms of dementia is limited. Growth differentiation factor-15 (GDF15) is recently emerging not only as a marker of inflammation and oxidative stress, but also as a key player in the aging process, being one of the most up-regulated protein with age and associated with a variety of age-related diseases, and therefore recognized as biomarkers of inflammaging (Conte et al., 2022).

Numerous reports have indicated a potential diagnostic role of specific cytokines and chemokines during AD pathogenesis (Park et al., 2020). Immune-related pathophysiological mechanisms of senescence may be related to AD pathogenesis (Guerrero et al., 2021) since age is the main risk factor for neurodegenerative diseases. Several basic and animal research studies suggested that lower senescent cell abundance could improve the health span (Musi et al., 2018). The findings on animal models supported the idea that reducing senescent cell burden in the brain may reduce neurodegeneration in humans, thus leading to new therapeutic interventions, such as drugs targeting senescent cells called senolytics (Gonzales et al., 2021; Kirkland and Tchkonja, 2020; Lee et al., 2021; Rolland et al., 2023). Recently, an open-label, proof-of-concept, phase I clinical trial of orally delivered senolytic therapy, Dasatinib (D) and Quercetin (Q), was conducted in early-stage symptomatic patients with AD to assess CNS penetrance, safety, feasibility, and efficacy (NCT04063124 and NCT04685590) (Gonzales et al., 2023). Preliminary results demonstrated CNS penetrance of senolytics with outcomes supporting safety, tolerability, and feasibility in patients with AD and suggested that biomarker data could contribute to monitoring senolytic effects (Gonzales et

al., 2023). This is the first pilot study that has provided evidence for proceeding to a multisite Phase II clinical trial to investigate the safety and feasibility of senolytic therapy in AD.

Some studies have highlighted cytokine secretion associated with the SASP to quantify senescent cells. Common SASP factors secreted by senescent cells include signaling molecules such as interleukins (e.g., IL-6 and IL-8) and many chemokines (Basisty et al., 2020). The burden of SASP factors on the brain is determined by the local production and the rate of mediators crossing the blood-brain barrier (BBB) and penetrating the CNS. Crucial to the integrity of the BBB are endothelial cells which, upon reaching the senescent state, release SASP factors themselves and determine an increase in BBB permeability, thus facilitating systemic factors that may elicit an inflammatory response in the brain (Guerrero et al., 2021; Sabbatinelli et al., 2021).

However, the confirmation of senescence based on these markers alone is very challenging because the proinflammatory molecules are also secreted by non-senescent cells. In this framework, it is reasonable that combinations of biomarkers related to inflammaging/cellular senescence and specific biomarkers of dementia may have diagnostic/prognostic clinical relevance for neurodegenerative diseases (Gonzales et al., 2022).

IL-1 family cytokines, including IL-33, as key players in the field of inflammaging field, were recently associated with neurodegeneration, since they ameliorate microglial damage associated molecular profiles (DAMP) clearance and promote microglial chemotaxis toward A β plaque-associated ApoE, finally leading to A β clearance (Lau et al., 2023). A recent meta-analysis confirmed that serum IL-33 and its soluble receptor (sST2) have potential clinical application value as biomarkers for identifying AD (Jiang et al., 2023).

Several studies have suggested a pivotal role for Interleukin-17 family in human autoimmune diseases and neurodegenerative disorders, including AD, Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) (Chen et al., 2020). Elevated levels of IL-17A in plasma and CSF have been reported in patients with AD (Fu et al., 2022). Although the specific mechanism of IL-17 in neurodegenerative diseases is still controversial, it is generally accepted that this cytokine

can cause diseases by activating glial cells (Chen et al., 2020). Notably, IL-17Ab reduced neuroinflammation and behavioral symptoms induced by A β in animal models, suggesting a possible future therapeutic approach in patients with AD (Cristiano et al., 2019).

Recently, chemokine platelet factor 4 (PF4), also called CXCL4, was identified as a pro-youthful factor that attenuates age-related neuroinflammation, elicits synaptic-plasticity-related molecular changes and rescues hippocampal-dependent learning and memory in aged mice, while CXCR3 mediates the cellular, molecular and cognitive benefits of systemic PF4 on the aged brain (Leiter et al., 2023; Schroer et al., 2023). Interestingly, common signatures were also identified between AD and PD at transcriptional levels by analyzing mRNA sequencing data, highlighting the relevance of C-X-C chemokine receptor type 4 (CXCR4), and these signatures were used to identify putative therapeutic agents for these diseases through computational analysis (Tripathi and Kumar, 2023).

The simultaneous analysis of more than 50 inflammatory proteins in elderly control, mild cognitive impairment, and AD subjects from AddNeuroMed, ten analytes, including cytokines CCL11 (eotaxin-1), CCL2 (MCP-1), and MIP-1 β , were able to differentiate AD, MCI and CTL (Morgan et al., 2019).

When the associations between a panel of inflammatory biomarkers, cognitive function and incident dementia outcomes were analyzed in the Framingham Heart Study Offspring cohort, several proteins including IL-10, LIF-R, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), CCL19, IL-17C, MCP-4, and TGF-alpha, resulted to be associated with more than one cognitive domain (Chen et al., 2023). Higher levels of both TNFB and CDCP1 were associated with higher risks of incident all-cause and AD dementia. TWEAK concentration correlated with cognitive function and risks for AD dementia (Chen et al., 2023). Moreover, when the intrinsic capacity (IC), i.e. the composite of physical and mental capacities, was analyzed longitudinally in community-dwelling older people from the Multidomain Alzheimer Preventive Trial (MAPT), elevated levels of plasma IL-6, tumor necrosis factor receptor-1 (TNFR-1), and GDF-15 reported to be associated with a higher risk of low level of cognitive, locomotion, psychology, and vitality performances (Lu et al., 2023).

The most relevant inflammatory circulating biomarkers related to AD degeneration are summarized in Table 2.

4. Potential composite blood-based biomarkers of inflammaging and Alzheimer's disease to track trajectories of dementia

Until now, comprehensive and exhaustive analyses of blood-based biomarker signatures involving both specific biomarkers of AD or neurodegeneration and inflammation biomarkers are not available, thus studies are rapidly needed. We suggest investigating correlations among blood biomarkers listed in Table 1 in association with those listed in Table 2 to validate their clinical potential role in dementia trajectories.

To this end, we performed a systematic search through the PubMed database of experimental studies simultaneously evaluating the circulating levels of biomarkers related to AD neurodegeneration (Table 1) and systemic inflammation (Table 2). We adhered to the PRISMA guidelines for carrying out this systematic search, using the following terms in the PubMed database: “(Alzheimer[Mesh] OR "Alzheimer's disease"[tw]) AND ("chemokines"[tw] OR "chemokine"[tw] OR "cytokines"[tw] OR "cytokine"[tw] OR "inflammatory biomarker"[tw] OR "inflammatory biomarkers"[tw] OR "inflammatory marker"[tw] OR "inflammatory markers"[tw]) AND ("A β "[tw] OR "Amyloid β "[tw] OR "neurofilament light chain" OR "nfl" OR "tau" OR "p-tau" OR "gfap") ("circulating"[tw] OR "plasma"[tw] OR "serum"[tw]) NOT (Review[Publication Type]) NOT ("Systematic Review"[Publication Type]) NOT ("Clinical Trial"[Publication Type]) NOT ("mice"[tw] OR "mouse"[tw]) NOT "rats"[tw]”. The following exclusion criteria applied: (I) studies performed in in vitro, ex vivo, and animal model; (II) assessment of neurodegenerative markers exclusively in CSF; (III) studies that did not assess circulating inflammatory markers; (IV) studies in which the outcome did not match the aim of the review. Information on the data extraction process is presented in the Supplemental Material. The PRISMA flow diagram reported in Figure 1 provides a visual summary of the study selection process.

Of the 147 articles initially retrieved, we included 18 original studies in our final analysis. The characteristics of the included studies, i.e. study design, study population, sample type, analytical platform, evaluated biomarkers, and information on significant associations with disease are summarized in Supplementary Table 1. Scoring of each study for methodological quality for bias and applicability was performed using the QUADAS-2 tool (Whiting et al., 2011), as detailed in the Supplemental Material. The quality assessment (results in Supplementary Figure 2) led to the exclusion of one study (Schmidt-Morgenroth et al., 2023), which raised important concerns in terms of applicability of the findings.

Most of the studies explored the association of ND and inflammation biomarkers in cross-sectional studies comparing AD and MCI patients and healthy controls. Five studies evaluated the correlations between the biomarkers and cognitive decline in prospective cohorts of healthy patients or in patients with AD or MCI. Biomarkers were evaluated on serum or plasma using immunoenzymatic or multiplex assays, such as SIMOA or Bio-Plex. Regarding the sample size, only four studies included at least 100 cases of AD/MCI. All the included studies found significant differences or associations between the disease phenotype and the levels of circulating ND markers. There was a general agreement on higher circulating t-tau and p-tau and lower $A\beta_{42}/A\beta_{40}$ ratio in AD vs. control subjects. Remarkably, a number of studies reported alterations of circulating levels of ND biomarkers also in subjects with MCI (Foley et al., 2023; Giannisis et al., 2022; Kleinschmidt et al., 2016). Among the most frequently assessed biomarkers of systemic inflammation were TNF- α (12 studies), IL-6 (11 studies), IL-10 (8 studies), and IL-1 β (6 studies). Despite the availability of high-sensitivity methods capable of detecting very low amounts of cytokines, only a relatively small number of studies were capable of highlighting significant associations with presence of either AD or MCI, or with the progression of AD, even though we did not report any situation of clear disagreement between assessments, except for the chemokine RANTES. In a number of studies where inflammatory biomarkers did not show the ability to discriminate between control subjects and patients with AD/MCI, significant correlations emerged between their levels and blood-based markers of ND. The

most frequently observed pattern of correlation was among $A\beta_{42}$, $A\beta_{40}$, (and their ratio) and the cytokines IL-6, IL-8, and IL-10 (Foley et al., 2023). Similarly, two studies observed a positive correlation between TNF- α and t-tau or p-tau181 (Deniz et al., 2021; Foley et al., 2023). Interestingly, the correlations between inflammatory and ND markers varied among the study groups (Foley et al., 2023; Startin et al., 2019), suggesting a complex interaction effect of systemic inflammation on neurodegeneration, which deserves further attention.

We then focused our interest on those studies that included a group of patients with MCI, or that prospectively evaluated healthy controls or patients with MCI for the conversion to AD. We observed that changes in IL-8, IL-10 (Foley et al., 2023), IL-1Ra, CCL4 (Liang et al., 2021), and IL-33 (Liang et al., 2020) were already evident in subjects with MCI and that levels of these cytokines displayed variable association with cognitive function in AD.

In Table 3, we summarized evidence from the qualitative synthesis for each inflammatory biomarker. Overall, generalizability of the findings is limited by relatively small sample sizes and heterogeneity in terms study design, diagnostic criteria, and analytical methods. Moreover, the additive value of inflammation biomarkers over the assessment of circulating ND markers has not been fully investigated and thus, there are inconclusive results. The limited data regarding this issue underlines the need for prognostic and monitoring capabilities relating to cognitive decline, $A\beta$ accumulation, and grey matter loss in cognitively unimpaired older persons over extended time periods. Based on the number of supporting evidences, the ability of intercepting early cognitive impairment, and availability of automated in vitro diagnostics (IVD)-cleared assays, we propose the integration of the assessment of circulating ND markers that showed the most robust evidence, i.e. $A\beta_{42}/A\beta_{40}$ ratio, t-tau, p-tau181, Nfl, and GFAP, with that of IL-6, IL-10, IL-1Ra, IL-33, and CCL4. This signature could be further expanded with the assessment of other inflammatory biomarkers, such as those reported in Table 2, that showed significant associations with AD/MCI but to date were not tested in conjunction with ND biomarkers.

The proposed combination may be clinically appealing, however only long-term clinical trials and studies designed with the specific aim of assessing the incremental diagnostic accuracy of multiple biomarkers will be able to identify which combinations can define early diagnosis and provide information on disease prognosis.

5. Conclusions

There is a rapidly rising interest in identifying specific blood biomarkers capable of identifying an early diagnosis of AD. Indeed such biomarkers may also provide an important role in future clinical trial use, in terms of monitoring the potential use of new drugs on cognition and AD biomarkers, especially in older adults. Importantly, chronic inflammation during to the aging process may strongly impact circulating biomarkers. Increased concentrations of inflammatory molecules, indicative of increased inflammaging level, are associated with increased risk of developing several ARDs, including diabetes, cardiovascular diseases, neurodegenerative diseases, and cancers. The association of circulating biomarkers of inflammaging with specific CNS-derived blood biomarkers could increase the predictive power of a composite signature related to AD. This type of composite signature approach could be applied into the clinical setting to improve pharmacological and non-pharmacological management of cognitive decline. More specifically, plasma inflammatory biomarkers, in addition to core AD biomarkers, may improve the early diagnosis of neurodegenerative disorders with typical evolution to dementia (both AD and non-AD). This could be crucial in the view of enrolment of patients with subtle cognitive decline, as well as high risk asymptomatic subjects, in clinical trials aimed to test disease-modifying therapies.

Consequently, a widespread use of combined plasma biomarkers of neurodegeneration and inflammation would contribute to reduce economic and social burden related to the overwhelming and rising costs associated to the management of patients with cognitive impairment. However, there are some limitations still hampering the use of this blood-based biomarker signatures. First of all, if on one hand, it is well known that neuroinflammation is relevant in the pathophysiology of many

neurodegenerative disorders, on the other hand we do not know in detail which specific neuroinflammatory process is implicated in each disease and which biomarkers can specifically reflect each pathophysiological mechanism. This lack of evidence limits the use of these tools in the view of a differential diagnosis. A second limitation is linked to the fact that there is a lack of universal standardization of plasma biomarkers measurement and some relevant pre-analytical and analytical factors still hinder the definition of internationally validated cut-offs.

In conclusion, there is current and increasing need to identify a specific combination of proinflammatory biomarkers of both systemic and CNS inflammation to assess the interindividual variability in the aging trajectories in older persons. We strongly believe that future investigations are warranted.

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Declaration of Competing Interest

The authors report no declarations of interest.

Author contributions

Conceptualization, A.A. and F.O; Methodology, J.S. and A.G.; Writing - original draft, A.A., A.G., L.B., J.S., and F.O.; Writing - review & editing, A.A., L.S., B.P. and M.B.

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram of study selection.

Table 1. Circulating biomarkers related to AD neurodegeneration

Groups of AD Biomarkers	Biomarkers	Measurements related to AD	Applicability	References
Amyloid	A β ₄₂ /A β ₄₀	extracellular buildup of brain A β plaque	Potential clinical use for measuring AD degeneration in terms of cognitive decline and PET quantification	(Schindler et al., 2019)
Tau	p-tau181, p-tau217, p-tau231	phosphorylated tau (p-tau) protein at epitopes 181, 217, and 231	Potential clinical use for measuring AD degeneration in terms of cognitive decline and PET quantification	(Sarto et al., 2023)
Neurodegeneration	NfL	neuroaxonal injury and neurodegeneration	Strong potential future clinical use, Strong Research application in AD	(Mullard, 2023)
Neurodegeneration	GFAP	product of astroglial activation and astrocytosis	Strong potential future clinical use, Strong Research application in AD	(Chatterjee et al., 2021)

Glial fibrillary acidic protein (GFAP); neurofilament light (NfL); phosphorylated tau protein (p-tau).

Table 2. Inflammatory circulating biomarkers related to AD degeneration

Blood inflammatory biomarkers	Description	Relevance to AD pathophysiology	Evidence in human studies	References
CRP	Acute phase protein	Propagates vascular damage and neurodegeneration by triggering complement-mediated responses	Variable association, influenced age, BMI, MMSE and APOE genotype	(Shen et al., 2019) (Tao et al., 2018) (Gabin et al., 2018) (Gong et al., 2016) (Gong et al., 2016)
IL-6	Proinflammatory cytokine	-Released by microglia and astrocytes following A β deposition	↑ in AD and MCI vs control -Associated with severity of cognitive impairment	(Shen et al., 2019) (Lyra et al., 2021) (Quillen et al., 2023) (Singh-Manoux et al., 2014)
IL-1 β	Proinflammatory cytokine	-Mediates neurodegeneration following A β deposition	↑ in AD vs control	(Shen et al., 2019) (Ng et al., 2018)
IL-33/ST2 axis	Cytokine	- Neuroprotective -Promotes microglial clearance of A β -Mitigates neuroinflammation	↑ soluble sST2 in AD vs control	(Jiang et al., 2023)
CXCL8 (IL-8)	Chemokine	-Released by CNS cells upon A β stimulation -Exerts paracrine/autocrine neuroprotective effects	↓ in MCI vs control	(Shen et al., 2019)
sTNFR1	Soluble receptor	TNFR-1 required for in A β -induced neuronal death	↑ in AD and MCI vs control ↑ in AD vs MCI	(Shen et al., 2019) (Buchhave et al., 2010) (Diniz et al., 2010)
sTNFR2	Soluble receptor	Activation of TNFR-2 promotes uptake and degradation of A β	↑ in AD vs control ↑ in AD vs MCI	(Shen et al., 2019) (Buchhave et al., 2010)
TNF- α	Proinflammatory cytokine	Pleiotropic, receptor-dependent effect	↑ in AD and MCI vs control	(Balldin et al., 2012) (Alvarez et al., 2007)
TNFB	Proinflammatory cytokine	Unknown	↑ in AD vs control	(Chen et al., 2023)
TWEAK	Proinflammatory cytokine	Unknown	↑ in AD vs control	(Chen et al., 2023)
α 1-ACT	Acute phase protein	-binds to β -amyloid peptide (ApP) and induces the polymerization of A β P into amyloid filaments - induces abnormal tau phosphorylation	↑ in AD vs control	(Shen et al., 2019) (Lieberman et al., 1995)
IL-1ra	Receptor antagonist	-reduces leukocyte infiltration induced by IL-1 β	↑ in AD vs control	(Italiani et al., 2018)
sCD40L	Costimulatory molecule	Induces reactive gliosis	↑ in AD vs control -negatively correlated with MMSE	(Shen et al., 2019) (Desideri et al., 2008)
CXCL4 (PF4)	Chemokine	Attenuated age-related neuroinflammation	↓ in AD vs control ↓ in young vs old	(Schroer et al., 2023)
CXCL9 (MIG)	Chemokine	Unknown	↑ in AD vs control ↑ in AD vs MCI	(Shen et al., 2019) (Zhou et al., 2023)

CXCL10	Chemokine	Released by hippocampal astrocytes in response to A β stimulation	↑ in AD vs control	(Zhou et al., 2023)
CCL27	Chemokine	Inflammation and endothelial dysfunction.	↑ in AD vs control	(Zhou et al., 2023)
CCL15	Chemokine	Inflammation and endothelial dysfunction.	↑ in AD vs control	(Zhou et al., 2023)
CX3CL1	Chemokine	-Secreted by neurons -modulates glial activation	↑ in MCI vs control	(Zhou et al., 2023)
MCP-1 (CCL2)	Chemokine	Enhances glial activation and accelerates tau pathology	↑ in MCI vs control	(Shen et al., 2019) (Morgan et al., 2019) (Bettcher et al., 2016)
TGF- β	Growth factor	Neuroprotective effects, reduces microglial reactivity and promotes A β clearance	Unclear	(Shen et al., 2019) (Park et al., 2021)
GDF-15	Mytokine	-Promotes neuron regeneration and axonal elongation -Enhances A β clearance by microglia	Associated with reduced cognition	(Beydoun et al., 2023)
Eotaxin-1 (CCL11)	Chemokine	Associated with lowered neurogenesis and neurodegenerative processes	↑ in AD vs control ↑ in AD vs MCI	(Morgan et al., 2019) (Bettcher et al., 2016)
Factor B (FB)	Component of the alternative pathway of complement	Unclear, component complement colocalize with A β plaques	↑ in AD vs control	(Morgan et al., 2019)
Factor H (FH)	Soluble complement regulator	Unclear, component complement colocalize with A β plaques	↑ in AD vs control	(Morgan et al., 2019)
sCR1	Inhibitor of complement activation	Unclear, expressed by microglia and astrocytes	↑ in AD vs control ↑ in AD vs MCI	(Morgan et al., 2019) (Bettcher et al., 2016)

α 1 -antichymotrypsin (ACT); C-C Motif Chemokine Ligand (CCL); C reactive protein (CRP) Growth Differentiation Factor 15 (GDF-15); Interleukin-1 receptor antagonist (IL-1ra); Monokine induced by gamma (MIG); Monocyte Chemoattractant Protein-1 (MCP-1); Platelet-derived growth factor subunit A (PDGFA); platelet factor 4 (PF4); soluble complement receptor 1 (sCR1); soluble CD40 ligand (sCD40L); Transforming Growth Factor- β (TGF- β); Tumor Necrosis Factor (TNF); soluble tumour necrosis factor receptor (sTNFR); TNF-related weak inducer of apoptosis (TWEAK); visinin-like protein-1 (VILIP-1).

Table 3. Summary of the evidence supporting the implementation of circulating biomarkers of neurodegeneration and inflammation for the diagnosis of AD and MCI.

Variable	Number of studies	MCI vs CTR	AD vs CTR	AD vs MCI	Evidence against	Availability of IVD-cleared methods	Adoption supported
Neurodegeneration biomarkers							
A β ₄₂	15	↓↑	↓↓↓↓↓↑		4		
A β ₄₀	11	↑↓	↑↑↑↑↓	↑↓	3		
A β _{42/40}	6		↓↓↓↓	↓	3		√
t-tau	8	↑↑	↑↑↑↑	↑	3		√
p-tau181	7	↑	↑↑↑	↑↑	2		√
Nfl	4	↑	↑↑	↑↑	-	√	√
GFAP	2	↑	↑		-	√	√
Inflammatory biomarkers							
TNF- α	12		↑↑		10	√	
IL-6	11		↑↑↑		8	√	√
IL-10	8	↓		↓	6	√	√
IL-1 β	6		↑		5	√	
IL-8	4	↓			3	√	
INF- γ	3		↑		2		
MCP-1 (CCL2)	3		↓		2		
IL-1Ra	2	↑	↑		-		√
RANTES	2		↑↓		-		
sCD40	2		↑		1		
CRP	1				1	√	
IL-9	1		↓		-		
IL-33	1	↑	↑	↑	-		√
MMP-3	1		↑		-		
IL-18BP	1		↓		-		
IL-18	1		↑		-		
ICAM-1	1		↑		-		
sCD40	2		↑		1		
CD40	1		↑		-		
CCL4 (MIP-1 β)	1	↓	↓		-		√

Each arrow indicates the direction of change in a single study. AD, Alzheimer's disease; CTR, healthy subjects without cognitive impairment; MCI, mild cognitive impairment; IVD, in vitro diagnostics.

Circulating biomarkers of inflammaging and Alzheimer's disease to track age-related trajectories of dementia: can we develop a clinically relevant composite combination?

Angela Marie Abbatecola^{1,2}, Angelica Giuliani³, Leonardo Biscetti⁴, Lucia Scisciola⁵, Petronilla Battista⁶, Michelangela Barbieri⁵, **Jacopo Sabbatinelli^{7,8*}** and Fabiola Olivieri^{7,8*}

¹ Alzheimer's Disease Day Clinic, Azienda Sanitaria Locale, Frosinone, Italy

² Univesità degli Studi di Cassino e del Lazio Meridionale, Dipartimento di Scienze Umane, Sociali e della Salute, Cassino, Italy

³ Istituti Clinici Scientifici Maugeri IRCCS, Cardiac Rehabilitation Unit of Bari Institute, Italy

⁴ Unit of Neurology, IRCCS INRCA, 60127 Ancona, Italy

⁵ Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

⁶ Istituti Clinici Scientifici Maugeri IRCCS, Laboratory of Neuropsychology, Bari Institute, Italy

⁷ Department of Clinical and Molecular Sciences, DISCLIMO, Università Politecnica delle Marche, Ancona, Italy

⁸ Clinic of Laboratory and Precision Medicine, IRCCS INRCA, Ancona, Italy

* These authors equally contributed to the manuscript.

Corresponding author:

Angelica Giuliani

angelica.giuliani@staff.univpm.it

Istituti Clinici Scientifici Maugeri IRCCS
Cardiac Rehabilitation Unit of Bari Institute
Via Generale Bellomo, 73/75
70124 Bari, Italy

Abstract

Alzheimer's disease (AD) is a rapidly growing global concern due to a consistent rise of the prevalence of dementia which is mainly caused by the aging population worldwide. An early diagnosis of AD remains important as interventions are plausibly more effective when started at the earliest stages. Recent developments in clinical research have focused on the use of blood-based biomarkers for improve diagnosis/prognosis of neurodegenerative diseases, particularly AD. Unlike invasive cerebrospinal fluid tests, circulating biomarkers are less invasive and will become increasingly cheaper and simple to use in larger number of patients with mild symptoms or at risk of dementia. In addition to AD-specific markers, there is growing interest in biomarkers of inflammaging/neuro-inflammaging, an age-related chronic low-grade inflammatory condition increasingly recognized as one of the main risk factor for almost all age-related diseases, including AD. Several inflammatory markers have been associated with cognitive performance and AD development and progression. The presence of senescent cells, a key driver of inflammaging, has also been linked to AD pathogenesis, and senolytic therapy is emerging as a potential treatment strategy. Here, we describe blood-based biomarkers clinically relevant for AD diagnosis/prognosis and biomarkers of inflammaging associated with AD. **Through a systematic review approach**, we propose that a combination of circulating **neurodegeneration** and inflammatory biomarkers may contribute to improving early diagnosis and prognosis, as well as providing valuable insights into the trajectory of cognitive decline and dementia in the aging population.

Keywords: Alzheimer's disease; blood biomarkers; inflammaging biomarkers; dementia

1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and is rapidly increasing on a worldwide scale. The constantly rising number of persons reaching advanced age is associated with a significant rise in dementia cases, currently estimated in 50 million individuals worldwide, a number expected to almost triple by 2050 (Long et al., 2023).

Over the last decade, there has been an increasing number of clinical trials investigating the potential usefulness of blood-based biomarkers for the diagnosis of neurodegenerative diseases and, in particular, AD (NCT04733989, NCT05020106, and NCT05187819). Considering that the first cerebrospinal fluid (CSF) biomarkers that typically reflect main AD pathogenetic mechanisms (amyloidosis and taupathy), i.e. β -amyloid, total tau (t-tau), and phosphorylated tau (p-tau), are detectable 20 years prior to clinical onset of AD, biomarker-based diagnosis at the earliest opportunity is imperative (Barthelemy et al., 2020). The CSF confirmation of AD pathology provides significant advantages to patients. The Alzheimer's Association recently published criteria for the use of lumbar puncture and CSF testing, underlining that clinical indications for the use of CSF are considered appropriate in those less than 65 years of age with an early onset of dementia or in an early stage of disease, namely Mild Cognitive Impairment (MCI) or Dementia (Shaw et al., 2018). **The authors underlined that CSF biomarkers may also be useful in those over 65 years of age especially if there is a clinical uncertainty regarding an AD diagnosis. The use of CSF puncturing is a quite invasive procedure and limitations in the CSF puncturing underline that this technique is contraindicated for patients with coagulation issues, including those with severe thrombocytopenia and those taking anticoagulant medications. CSF use also holds limitations due to different quantifying measures across clinical centers (Delaby et al., 2022).** In addition to CSF biomarkers, positron emission tomography (PET) using amyloid or tau tracers is considered as a valid tool to make AD diagnosis according to current AD diagnostic criteria (Dubois et al., 2014; Jack et al., 2018). However, PET is expensive and not universally available, thus it has limited feasibility for screening purposes. In this framework, the use of blood biomarkers could offer potential benefits for AD screening or diagnosis

in primary care settings worldwide, significantly less invasive and, **overall**, less costly than CSF. Now, there is substantial data supporting the use of diverse blood biomarkers capable of distinguishing AD dementia from other dementias, as well as predicting the development of AD in non-demented adults with cognitive complaints (Cullen et al., 2021). In the near future, blood biomarkers might also be used to monitor the efficacy of AD treatment.

Aging and prevalent diseases in older persons, the so-called age-related diseases, including AD, share some pathophysiological mechanisms (Lopez-Otin et al., 2013; Pezone et al., 2023). Inflammaging, the age-related chronic, low-grade, systemic proinflammatory condition, is today recognized as one of the main mechanisms increasing the risk of developing the most common age-related diseases (ARDs) (Lopez-Otin et al., 2013). Numerous potential biomarkers of inflammaging have been proposed, but a universally acceptable single-measurement biomarker has still not been identified, most likely due to the complexity of the aging process itself (Moqri et al., 2023). Chronic inflammation represents a crucial link between the immune and nervous systems along with advancing age, since increased levels of inflammaging predispose to the development of various diseases, including the spectrum of neurodegenerative diseases (Franceschi et al., 2000). The chronic low-grade inflammatory process in the **central nervous system (CNS)**, mainly driven by glial cells, has been defined as neuro-inflammaging, and it was associated with increased AD risk (Mohapatra et al., 2023; **Soraci et al., 2024**; Stephenson et al., 2018). The main culprits of inflammaging are chronically activated innate immune cells and the increased burden of senescent cells acquiring senescence-associated proinflammatory secretory phenotype (SASP) (Fulop et al., 2018). Consequently, among the circulating biomarkers of inflammaging, those reflecting neuroinflammation and cellular senescence have been significantly associated with age-related diseases (Saavedra et al., 2023).

In this review, we will highlight the **role and diagnostic value** specific biomarkers of neuronal damage in AD and diverse biomarkers related to inflammaging **and** neuroinflammaging. **Through a systematic**

review approach, we will propose that a composite blood-based biomarker signature may contribute to tracking the trajectories of neurodegeneration and dementia during aging.

2. Blood-based clinically relevant biomarkers in AD dementia

There is rapidly growing clinical evidence regarding the use of blood-based biomarkers for AD diagnosis and prognosis and the identification of individuals for dedicated intervention trials. In the search for early markers of neurodegeneration and AD, research on blood-based measures has been emerging, given their advantages in accessibility and cost-effectiveness compared to CSF procedure and neuroimaging techniques (Teunissen and Middeldorp, 2022). Ultrasensitive assays have been developed, allowing reliable measure concentrations of AD and neurodegeneration blood biomarkers, including amyloid- β_{40} ($A\beta_{40}$) and amyloid- β_{42} ($A\beta_{42}$), hyperphosphorylated tau (p-tau181, p-tau217, p-tau231), and neurofilament light chain (NfL) (Blennow and Zetterberg, 2019). Also, glial fibrillary acidic protein (GFAP), measurable in blood and reflecting astrocytic inflammation, was associated with neurodegenerative diseases (Gaur et al., 2023). Clinically relevant biomarkers in AD diagnosis are listed in Table 1.

The most common studied biomarker, Amyloid β ($A\beta$) is the core pathological hallmark of AD. Both CSF and PET biomarkers of $A\beta$ have been shown to alter before clinical onset (Hansson et al., 2018). Interestingly, the use of plasma $A\beta$ as an AD biomarker has been identified as a tool for detecting AD amyloid plaques (Nakamura et al., 2018).

Numerous investigations continue to test plasma $A\beta$ pathology concentrations using different technologies for plasma $A\beta_{42}/A\beta_{40}$ ratio measurements. In the past, there was a lack of sufficient precision regarding plasma $A\beta$ levels which may be explained by the type of technology used for measurements. A recent report underlined that Immunoprecipitation mass spectrometry technology may be superior to other technologies; however, assays need to be tested in similar cohorts for greater assessment (Brand et al., 2022). At the moment, there is no diagnostic application in clinical practice to differentiate AD from non-AD dementia using plasma $A\beta_{42}/A\beta_{40}$ (Nakamura et al., 2018).

Neurofilament light chain (NfL) is one of the three components of the intermediate filaments (Nfs) of neurons, including neurofilament heavy chain (NFH) and neurofilament middle chain (NFM), abundantly expressed in large caliber myelinated axons (Barro et al., 2020). NfL is the best candidate among the three Nfs subunits to be measured because of its greater solubility and detectability in several biofluids, including CSF and blood (Gafson et al., 2020). When neuronal cells or their axonal membranes are damaged, NfL are released into the interstitial fluid (IF), CSF, and blood, thus levels of NfL in the blood can be used for diagnosis, prognosis, monitoring disease progress, treatment response, or drug toxicity.

Identifying biomarkers capable of predicting initial cognitive impairment in individuals at high risk of cognitive decline and AD is imperative. A recent study reported that measurement of classical biomarkers ($A\beta_{42}/A\beta_{40}$ and NfL) in both CSF and in plasma (in this latter case with mass spectrometry) predicted cognitive decline in older persons at risk of dementia in similar manner (Aschenbrenner et al., 2022). Specifically, this study allowed for a head-to-head comparison of plasma and CSF biomarkers with respect to the prediction of cognitive decline. The authors found that both plasma and CSF biomarkers are independently associated with cognitive decline and that a clinical trial where enrolment is based on plasma assessment would require only a marginally larger cohort compared to one based on CSF biomarkers measures.

In an additional study involving people aged 65 years or older, neuronal injury during acute illness and delirium, measured by NfL, was also associated with greater cognitive decline (Krogseth et al., 2023).

Glial fibrillary acidic protein (GFAP), an intermediate filament-III protein uniquely found in astrocytes in the CNS, non-myelinating Schwann cells in the peripheral nervous system (PNS), and enteric glial cells, is another promising blood-based biomarker for neurodegeneration and dementia. Emerging evidence suggests that, following traumatic brain and spinal cord injuries and stroke, GFAP protein and its breakdown products are rapidly released into biofluids, making them strong candidate biomarkers for such neurological disorders (Yang and Wang, 2015).

Hyperphosphorylated tau has been identified as a major constituent of neurofibrillary tangles, the major pathological hallmark of AD, in addition to amyloid plaque (Grundke-Iqbal et al., 1986). Even though tau has numerous phosphorylation sites, studies have found that plasma concentrations of p-tau181, p-tau217, and p-tau231 are strongly associated with AD diagnosis compared to those controls (Brickman et al., 2021) as well to non-AD dementias (Ossenkoppele et al., 2022; Palmqvist et al., 2020). p-tau181 has gained attention since plasma p-tau181 concentrations were associated to AD clinical severity and with tau-PET (Mielke et al., 2018). Interestingly, p-tau217 plasma concentrations showed a strong correlation with cognitive decline in A β -positive cognitively unimpaired (CU) individuals (Mielke et al., 2018), a higher diagnostic accuracy than all other plasma p-tau biomarkers for AD diagnosis (Janelidze et al., 2023), and a comparable diagnostic performance in plasma and CSF (Mendes et al., 2024).

Even though there have been substantial advances to the potential use of plasma biomarkers for diagnosing AD dementia, no single biomarker can be used to predict cognitive decline in pre-clinical AD cases and differentiate AD cases from other type of dementia (Pais et al., 2023). An interesting approach emerged from a recent study which aimed to integrate plasma p-tau217, age, and APOE ϵ 4 status into a workflow to identify patients at high risk of AD (Brum et al., 2023). In this framework, the authors proposed that only patients with borderline levels of the biomarker should be forwarded for further testing, thus reducing the burden of unnecessary CSF and imaging exams. Recent reports highlighted the significance of using combined assessments of plasma markers than single biomarkers on differentiating neurodegenerative dementia from healthy aging, as well as identifying AD from other conditions, such as frontotemporal lobar degeneration (FTLD) (Benussi et al., 2022). According to a recent study, when A β ₄₂/A β ₄₀, NfL, p-tau181, and GFAP were analyzed as diagnostic biomarkers, NfL was the best single biomarker to distinguish between healthy aging and dementia, while the cluster of multiple biomarkers increased diagnostic accuracy (Benussi et al., 2022). In addition, this study identified the best biomarkers combination for distinguishing between AD and FTLD, such as A β ₄₂/A β ₄₀, p-tau181, and other markers related to transcranial stimulations. A prospective cohort

study in cognitively unimpaired elderly examining the prognostic and monitoring capabilities of biomarkers of neurodegeneration (ND) through their quantification in serum showed that GFAP, NfL and A β ₄₂/A β ₄₀ were valuable prognostic and/or monitoring tools in asymptomatic stages providing complementary information in a time- and pathology-dependent manner (De Meyer et al., 2023).

Combinations of CSF and blood biomarkers were also investigated in the dementia framework. Neuronal pentraxins (NPTXs), a family of proteins involved in homeostatic synapse plasticity, is emerging as novel CFS biomarkers to characterize different type of dementia (Shao et al., 2020). The combination of CSF NPTX2, serum NfL, and serum GFAP was proposed to differentiate different types of dementia with good accuracy (Bolssewig et al., 2022).

During the preclinical stage, biomarkers of AD disease, including those of A β , tau, and neurodegeneration, are thought to have prognostic value regarding the identification of individuals at risk of developing AD dementia in the coming years. The National Institute on Aging–Alzheimer's Association Research Framework was developed to provide a staging model called the AT(N) (Jack et al., 2018). This framework classes individuals into groups based on three types of biomarkers: amyloid (A), tau (T), and neurodegeneration (N), which are theorized to drive symptomatic AD (Jack et al., 2018). The AT(N) system is flexible in that new biomarkers can be added to the three existing AT(N) groups, and new biomarker groups beyond AT(N) can be added when they become available. In this framework, innovative biomarkers of aging could be characterized by potential crosstalk with dementia. The need to understand the power of aging itself on changes related to AD blood biomarkers may hold significant clinical awareness, especially for well-designed clinical trials.

Higher levels of these above-described markers have been shown to be associated with neurodegenerative processes and AD brain pathology suggesting that monitoring these biomarkers in clinical settings may provide important insight into underlying early brain changes and neurodegeneration (Merten et al., 2023; Teunissen et al., 2022).

In this context, a recent investigation compared the correspondence of CSF and plasma core AD core biomarkers with AD pathological change at post-mortem examination, which still represents the

diagnostic gold standard (Wang et al., 2023). In this study, CSF accurately predict AD neuropathological changes, while plasma AD biomarkers can predict the results of neuropathological examination only when combined to APOE ϵ 4 genotype, which is the strongest genetic risk factor for sporadic AD. These findings suggested that CSF biomarkers have a relatively higher accuracy than plasma biomarkers in prediction of AD pathological changes, but plasma biomarkers together with APOE genotype can represent a valid and less invasive alternative.

3. Blood-based Biomarkers of inflammaging and Alzheimer's Disease

In recent years, technological innovation has allowed the analysis of multiple biomarkers, increasing the knowledge of inflammaging over the aging process. Specific aging clocks have been developed based on blood proteins modulating inflammation and have been defined as Inflammatory clocks (Alpert et al., 2019; Lehallier et al., 2020; Murabito et al., 2018; Sayed et al., 2021). The limitation in designating these models is due to the large dimensionality of input data with poor effectiveness in clinical terms. Increasing efforts are devoted to developing small clocks based on a limited number of immunological biomarkers (Kalyakulina et al., 2023; Yusipov et al., 2022). Interestingly, these inflammatory clocks have confirmed the role played by circulating cytokines, mainly IL-6, the key cytokine of inflammaging, as an age predictor, and highlighted interesting roles for a variety of chemokines, including CXCL8, CXCL9, CXCL10, and the Platelet Derived Growth Factor Subunit A (PDGFA) (Kalyakulina et al., 2023).

Interestingly, IL-6, CXCL9, and PDGFA were found to be associated singly or in combination with cognitive performance and AD (Bradburn et al., 2018; Lyra et al., 2021; Pagoni et al., 2022; Sil et al., 2018; Wang et al., 2018). Recent reports confirmed that higher levels of circulating IL-6 were associated with cognitive impairment in an older adult population of Southern Italy (Griseta et al., 2023).

The chemokines CXCL9 and CXCL10 share CXCR3 as a common receptor, which is expressed not only on T and NK cells, but also on neurons. CXCL10 was found to be expressed in astrocytes and

to be localized around A β plaques in AD animal models (Krauthausen et al., 2015). A recent meta-analysis of chemokines in CSF and blood (plasma or serum) suggested that CXCL9 and CXCL10 might also be useful as tau-independent and A β -independent blood-based candidate biomarkers for AD (Zhou et al., 2023). CXCL8, also called IL-8, is expressed in neurons, astrocytes, and microglia, and blood CXCL8 levels were associated with long-term cognitive function (Teoh et al., 2023).

Although evidence on circulating chemokines suggest a possible role as biomarkers of AD progression, data on their specificity to discriminate among different forms of dementia is limited.

Growth differentiation factor-15 (GDF15) is recently emerging not only as a marker of inflammation and oxidative stress, but also as a key player in the aging process, being one of the most up-regulated protein with age and associated with a variety of age-related diseases, and therefore recognized as biomarkers of inflammaging (Conte et al., 2022).

Numerous reports have indicated a potential diagnostic role of specific cytokines and chemokines during AD pathogenesis (Park et al., 2020). Immune-related pathophysiological mechanisms of senescence may be related to AD pathogenesis (Guerrero et al., 2021) since age is the main risk factor for neurodegenerative diseases. Several basic and animal research studies suggested that lower senescent cell abundance could improve the health span (Musi et al., 2018). The findings on animal models supported the idea that reducing senescent cell burden in the brain may reduce neurodegeneration in humans, thus leading to new therapeutic interventions, such as drugs targeting senescent cells called senolytics (Gonzales et al., 2021; Kirkland and Tchkonja, 2020; Lee et al., 2021; Rolland et al., 2023). Recently, an open-label, proof-of-concept, phase I clinical trial of orally delivered senolytic therapy, Dasatinib (D) and Quercetin (Q), was conducted in early-stage symptomatic patients with AD to assess CNS penetrance, safety, feasibility, and efficacy (NCT04063124 and NCT04685590) (Gonzales et al., 2023). Preliminary results demonstrated CNS penetrance of senolytics with outcomes supporting safety, tolerability, and feasibility in patients with AD and suggested that biomarker data could contribute to monitoring senolytic effects (Gonzales et

al., 2023). This is the first pilot study that has provided evidence for proceeding to a multisite Phase II clinical trial to investigate the safety and feasibility of senolytic therapy in AD.

Some studies have highlighted cytokine secretion associated with the SASP to quantify senescent cells. Common SASP factors secreted by senescent cells include signaling molecules such as interleukins (e.g., IL-6 and IL-8) and many chemokines (Basisty et al., 2020). The burden of SASP factors on the brain is determined by the local production and the rate of mediators crossing the blood-brain barrier (BBB) and penetrating the CNS. Crucial to the integrity of the BBB are endothelial cells which, upon reaching the senescent state, release SASP factors themselves and determine an increase in BBB permeability, thus facilitating systemic factors that may elicit an inflammatory response in the brain (Guerrero et al., 2021; Sabbatinelli et al., 2021).

However, the confirmation of senescence based on these markers alone is very challenging because the proinflammatory molecules are also secreted by non-senescent cells. In this framework, it is reasonable that combinations of biomarkers related to inflammaging/cellular senescence and specific biomarkers of dementia may have diagnostic/prognostic clinical relevance for neurodegenerative diseases (Gonzales et al., 2022).

IL-1 family cytokines, including IL-33, as key players in the field of inflammaging field, were recently associated with neurodegeneration, since they ameliorate microglial damage associated molecular profiles (DAMP) clearance and promote microglial chemotaxis toward A β plaque-associated ApoE, finally leading to A β clearance (Lau et al., 2023). A recent meta-analysis confirmed that serum IL-33 and its soluble receptor (sST2) have potential clinical application value as biomarkers for identifying AD (Jiang et al., 2023).

Several studies have suggested a pivotal role for Interleukin-17 family in human autoimmune diseases and neurodegenerative disorders, including AD, Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) (Chen et al., 2020). Elevated levels of IL-17A in plasma and CSF have been reported in patients with AD (Fu et al., 2022). Although the specific mechanism of IL-17 in neurodegenerative diseases is still controversial, it is generally accepted that this cytokine

can cause diseases by activating glial cells (Chen et al., 2020). Notably, IL-17Ab reduced neuroinflammation and behavioral symptoms induced by A β in animal models, suggesting a possible future therapeutic approach in patients with AD (Cristiano et al., 2019).

Recently, chemokine platelet factor 4 (PF4), also called CXCL4, was identified as a pro-youthful factor that attenuates age-related neuroinflammation, elicits synaptic-plasticity-related molecular changes and rescues hippocampal-dependent learning and memory in aged mice, while CXCR3 mediates the cellular, molecular and cognitive benefits of systemic PF4 on the aged brain (Leiter et al., 2023; Schroer et al., 2023). Interestingly, common signatures were also identified between AD and PD at transcriptional levels by analyzing mRNA sequencing data, highlighting the relevance of C-X-C chemokine receptor type 4 (CXCR4), and these signatures were used to identify putative therapeutic agents for these diseases through computational analysis (Tripathi and Kumar, 2023).

The simultaneous analysis of more than 50 inflammatory proteins in elderly control, mild cognitive impairment, and AD subjects from AddNeuroMed, ten analytes, including cytokines CCL11 (eotaxin-1), CCL2 (MCP-1), and MIP-1 β , were able to differentiate AD, MCI and CTL (Morgan et al., 2019). When the associations between a panel of inflammatory biomarkers, cognitive function and incident dementia outcomes were analyzed in the Framingham Heart Study Offspring cohort, several proteins including IL-10, LIF-R, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), CCL19, IL-17C, MCP-4, and TGF-alpha, resulted to be associated with more than one cognitive domain (Chen et al., 2023). Higher levels of both TNFB and CDCP1 were associated with higher risks of incident all-cause and AD dementia. TWEAK concentration correlated with cognitive function and risks for AD dementia (Chen et al., 2023). Moreover, when the intrinsic capacity (IC), i.e. the composite of physical and mental capacities, was analyzed longitudinally in community-dwelling older people from the Multidomain Alzheimer Preventive Trial (MAPT), elevated levels of plasma IL-6, tumor necrosis factor receptor-1 (TNFR-1), and GDF-15 reported to be associated with a higher risk of low level of cognitive, locomotion, psychology, and vitality performances (Lu et al., 2023).

The most relevant inflammatory circulating biomarkers related to AD degeneration are summarized in Table 2.

4. Potential composite blood-based biomarkers of inflammaging and Alzheimer's disease to track trajectories of dementia

Until now, comprehensive and exhaustive analyses of blood-based biomarker signatures involving both specific biomarkers of AD or neurodegeneration and inflammation biomarkers are not available, thus studies are rapidly needed. We suggest investigating correlations among blood biomarkers listed in Table 1 in association with those listed in Table 2 to validate their clinical potential role in dementia trajectories.

To this end, we performed a systematic search through the PubMed database of experimental studies simultaneously evaluating the circulating levels of biomarkers related to AD neurodegeneration (Table 1) and systemic inflammation (Table 2). We adhered to the PRISMA guidelines for carrying out this systematic search, using the following terms in the PubMed database: “(Alzheimer[Mesh] OR "Alzheimer's disease"[tw]) AND ("chemokines"[tw] OR "chemokine"[tw] OR "cytokines"[tw] OR "cytokine"[tw] OR "inflammatory biomarker"[tw] OR "inflammatory biomarkers"[tw] OR "inflammatory marker"[tw] OR "inflammatory markers"[tw]) AND ("A β "[tw] OR "Amyloid β "[tw] OR "neurofilament light chain" OR "nfl" OR "tau" OR "p-tau" OR "gfap") ("circulating"[tw] OR "plasma"[tw] OR "serum"[tw]) NOT (Review[Publication Type]) NOT ("Systematic Review"[Publication Type]) NOT ("Clinical Trial"[Publication Type]) NOT ("mice"[tw] OR "mouse"[tw]) NOT "rats"[tw]”. The following exclusion criteria applied: (I) studies performed in in vitro, ex vivo, and animal model; (II) assessment of neurodegenerative markers exclusively in CSF; (III) studies that did not assess circulating inflammatory markers; (IV) studies in which the outcome did not match the aim of the review. Information on the data extraction process is presented in the Supplemental Material. The PRISMA flow diagram reported in Figure 1 provides a visual summary of the study selection process.

Of the 147 articles initially retrieved, we included 18 original studies in our final analysis. The characteristics of the included studies, i.e. study design, study population, sample type, analytical platform, evaluated biomarkers, and information on significant associations with disease are summarized in Supplementary Table 1. Scoring of each study for methodological quality for bias and applicability was performed using the QUADAS-2 tool (Whiting et al., 2011), as detailed in the Supplemental Material. The quality assessment (results in Supplementary Figure 2) led to the exclusion of one study (Schmidt-Morgenroth et al., 2023), which raised important concerns in terms of applicability of the findings.

Most of the studies explored the association of ND and inflammation biomarkers in cross-sectional studies comparing AD and MCI patients and healthy controls. Five studies evaluated the correlations between the biomarkers and cognitive decline in prospective cohorts of healthy patients or in patients with AD or MCI. Biomarkers were evaluated on serum or plasma using immunoenzymatic or multiplex assays, such as SIMOA or Bio-Plex. Regarding the sample size, only four studies included at least 100 cases of AD/MCI. All the included studies found significant differences or associations between the disease phenotype and the levels of circulating ND markers. There was a general agreement on higher circulating t-tau and p-tau and lower $A\beta_{42}/A\beta_{40}$ ratio in AD vs. control subjects. Remarkably, a number of studies reported alterations of circulating levels of ND biomarkers also in subjects with MCI (Foley et al., 2023; Giannisis et al., 2022; Kleinschmidt et al., 2016). Among the most frequently assessed biomarkers of systemic inflammation were TNF- α (12 studies), IL-6 (11 studies), IL-10 (8 studies), and IL-1 β (6 studies). Despite the availability of high-sensitivity methods capable of detecting very low amounts of cytokines, only a relatively small number of studies were capable of highlighting significant associations with presence of either AD or MCI, or with the progression of AD, even though we did not report any situation of clear disagreement between assessments, except for the chemokine RANTES. In a number of studies where inflammatory biomarkers did not show the ability to discriminate between control subjects and patients with AD/MCI, significant correlations emerged between their levels and blood-based markers of ND. The

most frequently observed pattern of correlation was among $A\beta_{42}$, $A\beta_{40}$, (and their ratio) and the cytokines IL-6, IL-8, and IL-10 (Foley et al., 2023). Similarly, two studies observed a positive correlation between TNF- α and t-tau or p-tau181 (Deniz et al., 2021; Foley et al., 2023). Interestingly, the correlations between inflammatory and ND markers varied among the study groups (Foley et al., 2023; Startin et al., 2019), suggesting a complex interaction effect of systemic inflammation on neurodegeneration, which deserves further attention.

We then focused our interest on those studies that included a group of patients with MCI, or that prospectively evaluated healthy controls or patients with MCI for the conversion to AD. We observed that changes in IL-8, IL-10 (Foley et al., 2023), IL-1Ra, CCL4 (Liang et al., 2021), and IL-33 (Liang et al., 2020) were already evident in subjects with MCI and that levels of these cytokines displayed variable association with cognitive function in AD.

In Table 3, we summarized evidence from the qualitative synthesis for each inflammatory biomarker. Overall, generalizability of the findings is limited by relatively small sample sizes and heterogeneity in terms study design, diagnostic criteria, and analytical methods. Moreover, the additive value of inflammation biomarkers over the assessment of circulating ND markers has not been fully investigated and thus, there are inconclusive results. The limited data regarding this issue underlines the need for prognostic and monitoring capabilities relating to cognitive decline, $A\beta$ accumulation, and grey matter loss in cognitively unimpaired older persons over extended time periods. Based on the number of supporting evidences, the ability of intercepting early cognitive impairment, and availability of automated in vitro diagnostics (IVD)-cleared assays, we propose the integration of the assessment of circulating ND markers that showed the most robust evidence, i.e. $A\beta_{42}/A\beta_{40}$ ratio, t-tau, p-tau181, Nfl, and GFAP, with that of IL-6, IL-10, IL-1Ra, IL-33, and CCL4. This signature could be further expanded with the assessment of other inflammatory biomarkers, such as those reported in Table 2, that showed significant associations with AD/MCI but to date were not tested in conjunction with ND biomarkers.

The proposed combination may be clinically appealing, however only long-term clinical trials and studies designed with the specific aim of assessing the incremental diagnostic accuracy of multiple biomarkers will be able to identify which combinations can define early diagnosis and provide information on disease prognosis.

5. Conclusions

There is a rapidly rising interest in identifying specific blood biomarkers capable of identifying an early diagnosis of AD. Indeed such biomarkers may also provide an important role in future clinical trial use, in terms of monitoring the potential use of new drugs on cognition and AD biomarkers, especially in older adults. Importantly, chronic inflammation during to the aging process may strongly impact circulating biomarkers. Increased concentrations of inflammatory molecules, indicative of increased inflammaging level, are associated with increased risk of developing several ARDs, including diabetes, cardiovascular diseases, neurodegenerative diseases, and cancers. The association of circulating biomarkers of inflammaging with specific CNS-derived blood biomarkers could increase the predictive power of a composite signature related to AD. This type of composite signature approach could be applied into the clinical setting to improve pharmacological and non-pharmacological management of cognitive decline. More specifically, plasma inflammatory biomarkers, in addition to core AD biomarkers, may improve the early diagnosis of neurodegenerative disorders with typical evolution to dementia (both AD and non-AD). This could be crucial in the view of enrolment of patients with subtle cognitive decline, as well as high risk asymptomatic subjects, in clinical trials aimed to test disease-modifying therapies.

Consequently, a widespread use of combined plasma biomarkers of neurodegeneration and inflammation would contribute to reduce economic and social burden related to the overwhelming and rising costs associated to the management of patients with cognitive impairment. However, there are some limitations still hampering the use of this blood-based biomarker signatures. First of all, if on one hand, it is well known that neuroinflammation is relevant in the pathophysiology of many

neurodegenerative disorders, on the other hand we do not know in detail which specific neuroinflammatory process is implicated in each disease and which biomarkers can specifically reflect each pathophysiological mechanism. This lack of evidence limits the use of these tools in the view of a differential diagnosis. A second limitation is linked to the fact that there is a lack of universal standardization of plasma biomarkers measurement and some relevant pre-analytical and analytical factors still hinder the definition of internationally validated cut-offs.

In conclusion, there is current and increasing need to identify a specific combination of proinflammatory biomarkers of both systemic and CNS inflammation to assess the interindividual variability in the aging trajectories in older persons. We strongly believe that future investigations are warranted.

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Declaration of Competing Interest

The authors report no declarations of interest.

Author contributions

Conceptualization, A.A. and F.O; Methodology, J.S. and A.G.; Writing - original draft, A.A., A.G., L.B., J.S., and F.O.; Writing - review & editing, A.A., L.S., B.P. and M.B.

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FIGURE LEGENDS

Figure 1. PRISMA flow diagram of study selection.

Table 1. Circulating biomarkers related to AD neurodegeneration

Groups of AD Biomarkers	Biomarkers	Measurements related to AD	Applicability	References
Amyloid	A β ₄₂ /A β ₄₀	extracellular buildup of brain A β plaque	Potential clinical use for measuring AD degeneration in terms of cognitive decline and PET quantification	(Schindler et al., 2019)
Tau	p-tau181, p-tau217, p-tau231	phosphorylated tau (p-tau) protein at epitopes 181, 217, and 231	Potential clinical use for measuring AD degeneration in terms of cognitive decline and PET quantification	(Sarto et al., 2023)
Neurodegeneration	NfL	neuroaxonal injury and neurodegeneration	Strong potential future clinical use, Strong Research application in AD	(Mullard, 2023)
Neurodegeneration	GFAP	product of astroglial activation and astrocytosis	Strong potential future clinical use, Strong Research application in AD	(Chatterjee et al., 2021)

Glial fibrillary acidic protein (GFAP); neurofilament light (NfL); phosphorylated tau protein (p-tau).

Table 2. Inflammatory circulating biomarkers related to AD degeneration

Blood inflammatory biomarkers	Description	Relevance to AD pathophysiology	Evidence in human studies	References
CRP	Acute phase protein	Propagates vascular damage and neurodegeneration by triggering complement-mediated responses	Variable association, influenced age, BMI, MMSE and APOE genotype	(Shen et al., 2019) (Tao et al., 2018) (Gabin et al., 2018) (Gong et al., 2016) (Gong et al., 2016)
IL-6	Proinflammatory cytokine	-Released by microglia and astrocytes following A β deposition	↑ in AD and MCI vs control -Associated with severity of cognitive impairment	(Shen et al., 2019) (Lyra et al., 2021) (Quillen et al., 2023) (Singh-Manoux et al., 2014)
IL-1 β	Proinflammatory cytokine	-Mediates neurodegeneration following A β deposition	↑ in AD vs control	(Shen et al., 2019) (Ng et al., 2018)
IL-33/ST2 axis	Cytokine	- Neuroprotective -Promotes microglial clearance of A β -Mitigates neuroinflammation	↑ soluble sST2 in AD vs control	(Jiang et al., 2023)
CXCL8 (IL-8)	Chemokine	-Released by CNS cells upon A β stimulation -Exerts paracrine/autocrine neuroprotective effects	↓ in MCI vs control	(Shen et al., 2019)
sTNFR1	Soluble receptor	TNFR-1 required for in A β -induced neuronal death	↑ in AD and MCI vs control ↑ in AD vs MCI	(Shen et al., 2019) (Buchhave et al., 2010) (Diniz et al., 2010)
sTNFR2	Soluble receptor	Activation of TNFR-2 promotes uptake and degradation of A β	↑ in AD vs control ↑ in AD vs MCI	(Shen et al., 2019) (Buchhave et al., 2010)
TNF- α	Proinflammatory cytokine	Pleiotropic, receptor-dependent effect	↑ in AD and MCI vs control	(Balldin et al., 2012) (Alvarez et al., 2007)
TNFB	Proinflammatory cytokine	Unknown	↑ in AD vs control	(Chen et al., 2023)
TWEAK	Proinflammatory cytokine	Unknown	↑ in AD vs control	(Chen et al., 2023)
α 1-ACT	Acute phase protein	-binds to β -amyloid peptide (ApP) and induces the polymerization of A β P into amyloid filaments - induces abnormal tau phosphorylation	↑ in AD vs control	(Shen et al., 2019) (Lieberman et al., 1995)
IL-1ra	Receptor antagonist	-reduces leukocyte infiltration induced by IL-1 β	↑ in AD vs control	(Italiani et al., 2018)
sCD40L	Costimulatory molecule	Induces reactive gliosis	↑ in AD vs control -negatively correlated with MMSE	(Shen et al., 2019) (Desideri et al., 2008)
CXCL4 (PF4)	Chemokine	Attenuated age-related neuroinflammation	↓ in AD vs control ↓ in young vs old	(Schroer et al., 2023)
CXCL9 (MIG)	Chemokine	Unknown	↑ in AD vs control ↑ in AD vs MCI	(Shen et al., 2019) (Zhou et al., 2023)

CXCL10	Chemokine	Released by hippocampal astrocytes in response to A β stimulation	↑ in AD vs control	(Zhou et al., 2023)
CCL27	Chemokine	Inflammation and endothelial dysfunction.	↑ in AD vs control	(Zhou et al., 2023)
CCL15	Chemokine	Inflammation and endothelial dysfunction.	↑ in AD vs control	(Zhou et al., 2023)
CX3CL1	Chemokine	-Secreted by neurons -modulates glial activation	↑ in MCI vs control	(Zhou et al., 2023)
MCP-1 (CCL2)	Chemokine	Enhances glial activation and accelerates tau pathology	↑ in MCI vs control	(Shen et al., 2019) (Morgan et al., 2019) (Bettcher et al., 2016)
TGF- β	Growth factor	Neuroprotective effects, reduces microglial reactivity and promotes A β clearance	Unclear	(Shen et al., 2019) (Park et al., 2021)
GDF-15	Mytokine	-Promotes neuron regeneration and axonal elongation -Enhances A β clearance by microglia	Associated with reduced cognition	(Beydoun et al., 2023)
Eotaxin-1 (CCL11)	Chemokine	Associated with lowered neurogenesis and neurodegenerative processes	↑ in AD vs control ↑ in AD vs MCI	(Morgan et al., 2019) (Bettcher et al., 2016)
Factor B (FB)	Component of the alternative pathway of complement	Unclear, component complement colocalize with A β plaques	↑ in AD vs control	(Morgan et al., 2019)
Factor H (FH)	Soluble complement regulator	Unclear, component complement colocalize with A β plaques	↑ in AD vs control	(Morgan et al., 2019)
sCR1	Inhibitor of complement activation	Unclear, expressed by microglia and astrocytes	↑ in AD vs control ↑ in AD vs MCI	(Morgan et al., 2019) (Bettcher et al., 2016)

α 1 -antichymotrypsin (ACT); C-C Motif Chemokine Ligand (CCL); C reactive protein (CRP) Growth Differentiation Factor 15 (GDF-15); Interleukin-1 receptor antagonist (IL-1ra); Monokine induced by gamma (MIG); Monocyte Chemoattractant Protein-1 (MCP-1); Platelet-derived growth factor subunit A (PDGFA); platelet factor 4 (PF4); soluble complement receptor 1 (sCR1); soluble CD40 ligand (sCD40L); Transforming Growth Factor- β (TGF- β); Tumor Necrosis Factor (TNF); soluble tumour necrosis factor receptor (sTNFR); TNF-related weak inducer of apoptosis (TWEAK); visinin-like protein-1 (VILIP-1).

Table 3. Summary of the evidence supporting the implementation of circulating biomarkers of neurodegeneration and inflammation for the diagnosis of AD and MCI.

Variable	Number of studies	MCI vs CTR	AD vs CTR	AD vs MCI	Evidence against	Availability of IVD-cleared methods	Adoption supported
Neurodegeneration biomarkers							
A β ₄₂	15	↓↑	↓↓↓↓↓↑		4		
A β ₄₀	11	↑↓	↑↑↑↑↓	↑↓	3		
A β _{42/40}	6		↓↓↓↓	↓	3		√
t-tau	8	↑↑	↑↑↑↑	↑	3		√
p-tau181	7	↑	↑↑↑	↑↑	2		√
Nfl	4	↑	↑↑	↑↑	-	√	√
GFAP	2	↑	↑		-	√	√
Inflammatory biomarkers							
TNF- α	12		↑↑		10	√	
IL-6	11		↑↑↑		8	√	√
IL-10	8	↓		↓	6	√	√
IL-1 β	6		↑		5	√	
IL-8	4	↓			3	√	
INF- γ	3		↑		2		
MCP-1 (CCL2)	3		↓		2		
IL-1Ra	2	↑	↑		-		√
RANTES	2		↑↓		-		
sCD40	2		↑		1		
CRP	1				1	√	
IL-9	1		↓		-		
IL-33	1	↑	↑	↑	-		√
MMP-3	1		↑		-		
IL-18BP	1		↓		-		
IL-18	1		↑		-		
ICAM-1	1		↑		-		
sCD40	2		↑		1		
CD40	1		↑		-		
CCL4 (MIP-1 β)	1	↓	↓		-		√

Each arrow indicates the direction of change in a single study. AD, Alzheimer's disease; CTR, healthy subjects without cognitive impairment; MCI, mild cognitive impairment; IVD, in vitro diagnostics.