Diagnostic Utility of Selected Serum Dementia Biomarkers: Amyloid β-40, Amyloid β-42, Tau Protein, and YKL-40: A Review

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Abstract: Introduction: Dementia is a group of disorders that causes dysfunctions in human cognitive and operating functions. Currently, it is not possible to conduct a fast, low-invasive dementia diagnostic process with the use of peripheral blood biomarkers, however, there is a great deal of research in progress covering this subject. Research on dementia biomarkers in serum validates anticipated health and economic benefits from early screening tests. Biomarkers are also essential for improving the process of developing new drugs. Methods: The result analysis, of current studies on selected biomarker concentrations (Aβ40, Aβ42, t-tau, and YKL-40) and their combination in the serum of patients with dementia and mild cognitive disorders, involved a search for papers available in Medline, PubMed, and Web of Science databases published from 2000 to 2020. Results: The results of conducted cross-sectional studies comparing Aβ40, Aβ42, and Aβ42/Aβ40 among people with cognitive disorders and a control group are incoherent. Most of the analyzed papers showed an increase in t-tau concentration in diagnosed Alzheimer’s disease (AD) patients’ serum, whereas results of mild cognitive impairment (MCI) groups did not differ from the control groups. In several papers on the concentration of YKL-40 and t-tau/Aβ42 ratio, the results were promising. To date, several studies have only covered the field of biomarker concentrations in dementia disorders other than AD. Conclusions: Insufficient amyloid marker test repeatability may result either from imperfection of the used laboratorial techniques or inadequate selection of control groups with their comorbidities. On the basis of current knowledge, t-tau, t-tau/Aβ42, and YKL-40 seem to be promising candidates as biomarkers of cognitive disorders in serum. YKL-40 seems to be a more useful biomarker in early MCI diagnostics, whereas t-tau can be used as a marker of progress of prodromal states in mild AD. Due to the insignificant number of studies conducted to date among patients with dementia disorders other than AD, it is not possible to make a sound assessment of their usefulness in dementia differential diagnostics.

Keywords: Alzheimer’s disease; vascular dementia; mixed dementia; serum; biomarkers; amyloid beta; tau protein; YKL-40

1. Introduction

1.1. Dementia

Dementia is a group of multiple etiology cognitive disorders that result in daily life impediments. The most common cause of dementia is Alzheimer’s disease (AD) which is chronic, progressive, and leads to death of the neurodegenerative process [1].

There are two main groups of pathologies that cause dementia, i.e., neurodegenerative diseases and secondary dementias [1]. The cause of neurodegenerative diseases (proteinopathies) is accumulation
and aggregation of proteins with abnormal conformation [2], which results in death of neurons and supporting cells, leading to cognitive and motor dysfunctions [3]. Death of cells results in activation of glial cells and secretion of cytokine and chemokine by them, which leads to the chronic inflammatory process interfering with brain tissue homeostasis. Moreover, neurotoxicity of some inflammatory response products intensifies the neurodegenerative process [4]. Neurodegenerative dementia includes the following: dementia in Alzheimer’s disease, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), dementia in Parkinson’s disease (PDD), Huntington’s disease (HD), and dementia in prion diseases.

The most common secondary dementia is vascular dementia. Approximately 10–15% of patients are only diagnosed with vascular-only dementia (VD). VD consists of subtypes of different etiology and clinical features, such as multi-infarct dementia, small vessel disease, strategic infarct dementia, hypoperfusion dementia, haemorrhagic dementia, hereditary cerebral autosomal dominant arteriopathy with subcortical infarction, and leukoencephalopathy (CADASIL) [1,5].

The observed symptoms of dementia such as depression, delirium, thyroid hormone abnormalities, vitamin deficiencies, or normotensive hydrocephalus are in potentially reversible states [1]. Chronic alcohol use is also a very common cause of dementia. In contrast to Wernicke–Korsakoff syndrome associated primarily with memory impairment, in alcoholic dementia, there are disorders in many other cognitive functions. Alcoholic dementia constitutes approximately 10% of early-onset cases and slightly more than 1% of late-onset dementia cases [6].

Dementia can be of mixed etiology, in up to half of patients, especially in senior age groups [1]. Vascular lesions occur in 40% of demented patients and usually coexist with other dementia causes. Changes caused by microinfarcts were found in around half of the patients with AD [7]. Contrary to previous diagnostic recommendations considering cerebral vascular lesions as an exclusion criterion of AD, the American Alzheimer’s Association currently takes the view that dementia often results from both neurodegenerative and vascular pathologies and suggests classifying such conditions as mixed dementias [1]. An autopsy study by Schneider et al. revealed that subjects with multifactorial etiology of dementia found in the autopsy were more frequently diagnosed with dementia during life as compared to those with only one type of neuropathological change [8]. It suggests that mixed dementia (despite its heterogeneous etiology) may be a category for underdiagnosed cases, and it also has an important clinical and prognostic value. Other relatively common forms of mixed dementia include the coexistence of AD and DLB or PDD [8].

1.2. Amyloid Beta and Its Role in Dementia Process

Amyloid is a group of insoluble beta-sheet proteins that form filamentous structures. They may play a role in the pathogenesis of various diseases when accumulating as deposits in the extracellular space. Each amyloid type is formed from its specific precursor protein-like amylin, derived from the precursor islet amyloid polypeptide (IAPP), involved in the pathogenesis of insulin-dependent diabetes, or AL and AH proteins composed of light and heavy chains of immunoglobulin, resulting in primary systemic amyloidosis [9]. Except for brain tissue, the amyloid precursor protein (APP) has been identified in the thymus, heart, lungs, kidneys, muscles, adipose tissue, liver, spleen, skin, and the intestine [10].

Amyloid beta (Aβ) refers to oligopeptides composed of 40–42 amino acid residues, originating from the amyloid precursor protein (APP). The APP protein family includes two similar peptides, i.e., amyloid precursor-like proteins 1 and 2 (APLP1 and APLP2) [11]. The APP protein encoding gene is located on chromosome 21q21. Most of the many APP mutations exist around sequences encoding secretase splitting sites and they are responsible for early-onset, familial forms of the disease [12]. The amyloid precursor protein is transformed to oligopeptides by three enzymes, i.e., α-, β- and γ-secretase. The C-terminal fragment of APP is always cut off by γ-secretase, but the forming of Aβ is determined by enzyme activity cutting off the N-terminus of either α- or β-secretase precursor peptides. Formation of Aβ happens when an N-terminus fragment is cleaved by β-secretase, while the
activity of secretase $\alpha$ results in making a so-called secreted form of APP (s-AAP$\alpha$) [13], a signal protein which is a neuron growth factor that promotes synaptogenesis and has a positive role in memory and learning processes [10]. Another factor contributing to A$\beta$ formation are mutations of the $\gamma$-secretase subunits, i.e., presenilins. On the one hand, presenilins of correct structure regulate intracellular calcium balance, lysosome, and proteasome activity and counteract the effects of oxidative stress. On the other hand, presenilin mutations contribute to the formation of longer A$\beta$ chains, which are more prone to aggregate into insoluble A$\beta$ forms [14].

A$\beta$ oligopeptides vary in the number of amino acids in the molecule. Most scientific research has focused on the fragment with 42 amino acid residues, i.e., A$\beta$42. It is the main component of amyloid plaques found in the brain of patients with AD. A second dominant isoform of A$\beta$ is peptide with a length of 40 amino acid residues. A$\beta$40 is a less amyloidogenic form. Researchers have also suggested their role in preventing formation of A$\beta$ deposits. Calculation of the A$\beta$42/A$\beta$40 ratio can be found in many scientific papers. A high value of this ratio is used as a predictor of cerebral amyloidopathy. Other forms of A$\beta$ were also considered to be potential biomarkers, mainly A$\beta$38 [15].

In addition to previously described overproduction, accumulation, and aggregation of A$\beta$ in the brain tissue, the impaired pathological protein degradation also contributes to dementia pathogenesis. Peroxidation of the cell membrane lipids under oxidative stress results in 4-hydroxynonenal (HNE) secretion, which has an ability to modify protein structure and function. HNE lowers the catalytic activity of neprilysin, a metallopeptidase preventing the deposition of A$\beta$ through degradation of mono- and oligomeric A$\beta$ forms [16]. Apolipoproteins E2 and E3 (but not E4 which is one of the main AD risk factors) are capable of binding HNE through cysteine, lysine, and histidine residue, preventing the damage of other proteins [17]. HNE also increases the synthesis of A$\beta$ by its binding with nicastrin, part of the gamma-secretase complex, increasing activity of this enzyme [18].

The role of A$\beta$ in AD pathogenesis is described in the so-called amyloid cascade hypothesis. This theory suggests that the disease process begins with overproduction and accumulation of A$\beta$ as amyloid plaques. Their presence leads to mitochondrial and synaptic damage, disrupting the homeostasis of brain tissue. This process is accompanied by microglia and astrocytes activation, which results in inflammation and oxidative stress, eventually causing the death of neurons. Furthermore, A$\beta$ is considered to be a factor that activates hyperphosphorylation of tau proteins. In addition to the amyloid cascade hypothesis, there are other possible explanations of the AD pathogenesis, such as the “prion-like” action of the A$\beta$ hypothesis [19]. More and more reports have shown that the amyloid cascade hypothesis has not fully explained the pathogenesis of AD. It has recently been demonstrated that amyloid-dependent memory and synaptic plasticity impairments could occur without tau [20].

On the basis of current knowledge, pathologies tied with A$\beta$ are not specific for AD dementia. The existence of amyloid deposits have also been identified by PET scan in dementias other than AD, especially among seniors who have been carriers of the APOE4 allele. Ossenkoppele et al. obtained positive amyloid-PET results in as many as 83% of 80-year-old APOE4 gene carriers with DLB, 43% with FTD and 64% with VD. Among a younger group of people (around 60 years old), who were not carriers of APOE4, those percentages were respectively 29%, 5%, and 7% [21]. It is not easy to state whether those observations might result from incorrectly established clinical diagnosis or rather amyloid deposition is secondary to neuropathology of other dementia types [22]. Among non-AD dementias, the clearest relationship occurs between A$\beta$ and VD. It is known that apart from the predominant atherosclerotic etiology, other angiopathies such as congophilic amyloid angiopathy (CAA) can initiate the disease process [5]. Contrary to AD, where amyloid deposits locate mainly (but not exclusively) into intercellular space, in CAA subjects, the lesions are predominately in the blood vessel walls [3]. It has been proven that the density of congophilic vascular lesions increased with the severity of cognitive impairment [7]. On the one hand, overproduction or impaired elimination of A$\beta$ can also occur in other diseases. Increased amyloid peptide concentrations were found in patients diagnosed with liver tumors [23], kidney [24] and liver [25] failure, Parkinson’s disease [26], obesity
and insulin resistance [27], or Down Syndrome [28]. On the other hand, a decrease in Aβ42 levels in the serum has been observed in depression [29]. An increased level of Aβ in many conditions results in serious limitations of its use as a biomarker, especially in a multimorbid old age group. Meta-analysis published by Zhang et al. indicated that the lack of proper screening for comorbidities among the control group resulted in minor differences in the amyloid marker concentrations among groups in studies [30].

1.3. Tau Protein and Its Role in Dementia

Tau protein is a product of the MAPT gene, located on chromosome 17. It is expressed predominantly in the central nervous system [31]. This protein is found mainly inside neurons (especially in microtubule-rich axons), but also, to a lesser extent, in glial cells (astrocytes and oligodendrocytes) [32], as well as in extracellular space [33]. It locates primarily in the cytoskeletal structures of the cell, but it has also been identified in the nuclei and centrosomes [32]. The MAPT gene product undergoes alternative splicing into six different, tissue-specific tau proteins. Depending on the number of 29-amino acid inserts (0, 1 or 2), there are three isoforms, i.e., 0 N, 1 N, and 2 N. Each isoform contains three or four microglobulin binding domain repeats (3R or 4R) [32,33]. In normal conditions, the tau protein is soluble and unfolded [33].

The physiological functions of the tau protein include stabilization and polymerization of microtubules, regulation of axonal transport, neuron polarization, axon growth and elongation, protection of DNA and RNA integrity, formation of cytoskeleton actin filaments, regulation of synaptic plasticity (dendritic tau protein), as well as cell cycle regulation via tyrosine kinase, membrane interactions, synaptic transmission, and regulation of NMDA transmission through interactions with the Fyn protein [32–34]. The tau protein undergoes post-translational modifications such as phosphorylation, O-glycosylation, advanced glycation, Maillard reaction, ubiquitination, nitration, sumoylation, proline isomerization, acetylation, and truncation. The most important one of the above is the kinase-induced phosphorylation process regulating tau distribution within the cell, the transport of organelles to the somatodendritic compartment, and enabling interactions with neurotransmitters and enzymes. Under physiological conditions, tau phosphorylation occurs in response to stressors such as insulin imbalance, hunger, hypothermia, anesthesia, glucocorticoids, opiates, or alcohol [32].

Phosphorylation also enables the tau protein to aggregate [31]. Excessive aggregation of the tau protein leads to formation of neurofibrillary tangles and it occurs in medical conditions called tauopathies and in the physiological aging process [32]. The presence of tau protein inclusions in neurons or glia causes tauopathies-progressive diseases associated with cognitive, behavioral, and motor impairment. Hyperphosphorylated tau protein and its isoforms, such as p-tau-217, measured in the peripheral blood are also promising AD biomarker candidates [35].

The pathological changes caused by the hyperphosphorylated tau protein (p-tau) can be divided into the following:

1. Resulting from the loss of its physiological properties:
   a. Axonal transport disturbance;
   b. Actin cytoskeleton abnormalities leading to increased susceptibility of the cell to oxidative stress;
   c. Disturbed structure and function of mitochondria, disrupting their metabolism and increasing susceptibility to oxidative stress, which leads to the death of the cell.

2. Resulting from the toxic effect of the abnormal isoform:
   a. Activation of astrocytes and microglia to secrete proinflammatory mediators;
   b. Disruption of synaptic transmission through the accumulation of pathological tau in postsynaptic spines;
   c. Disturbances in proteasome degradation and autophagy [30,32].
Formation of tau protein deposits is the key pathophysiological process in primary tauopathies, while in secondary tauopathies, its origin is from other pathologies. Primary tauopathies include the subtypes of frontotemporal dementia, atypical parkinsonian syndromes, argyrophilic grain disease, and globular glial tauopathy. Considering complex (dependent also from amyloid beta) aetiopathogenesis, AD is qualified as a secondary tauopathy [36]. Other conditions, secondary to the tau protein pathology are the aging process (primary tauopathy related to age, astriogliopathy related to age), Down syndrome, prion diseases, post-traumatic encephalopathy (dementia pugilistica), amyotrophic lateral sclerosis, parkinsonism-dementia complex, postencephalitic parkinsonism, and some rare diseases such as progressive subcortical gliosis, diffuse neurofibrillary tangles with calcification, “tangle-only dementia”, Hallervorden–Spatz disease, Niemann–Pick type C disease, subacute sclerosing panencephalitis, myotonic dystrophy, non-guanamian motor neuron disease with neurofibrillary tangles, meningoangiomatosis, and tuberous sclerosis [32]. Neurofibrillary changes have also been identified post mortem in subjects without any dementia characteristics. There is an assumption that in such cases the disease was present in an asymptomatic state [7].

It is believed that the concentration of tau protein in CSF relates to the degree of brain cells damage [37]. Tau protein is secreted from neurons to the cerebrospinal fluid, where it penetrates through the blood-brain barrier and the arachnoid granules to the bloodstream, which is why it can be identified in peripheral blood [38]. Results of studies show the correlation between total tau protein (t-tau) concentration in serum and its brain tissue levels assessed by PET scan [39,40].

1.4. YKL-40: An Inflammatory Marker in Dementia

More and more data show the key role of the inflammatory process (neuroinflammation) in AD pathogenesis. Most of all, microglia cells and astrocytes are present in the CNS inflammatory response. These cells are activated by proinflammatory cytokines, as well as Aβ and APP, causing the release of neurotoxic proinflammatory cytokines and reactive oxygen forms, and resulting in intensification of the inflammatory process and oxidative stress [41]. This knowledge resulted in taking the interest of inflammatory mediators as potential AD biomarkers.

Chitinase 3-like protein 1 (CHI3L1), also named YKL-40, human cartilage glycoprotein-39 (hcgp-39), or breast regression protein (BRP-39), is ranked among the chitinase family (glycosidic hydrolases). It is an acute-phase protein secreted into extracellular matrix through connective tissue cells (neutrophils, monocytes, macrophages, coming from monocytes, dendritic cells, osteoclasts, chondrocytes, synovial cells), vascular smooth muscle cells, glandular epithelium, and also thru other cells within an inflammatory state in response to inflammatory cytokines such as TNF-alpha, INF-gamma, IL-1beta, and IL-6 [42,43]. Some cancerous cells also have the ability of YKL-40 secretion [44].

In the inflammatory process, YKL-40 acts as an acute-phase protein that regulate proliferation, adhesion, migration, and cells differentiation. To date, the known functions of YKL-40 are the following:

- connective tissue repair process, i.e., connective tissue growth stimulation, bonding and fibrillogenesis of collagen, modulating of inflammatory cytokines impact on fibroblasts;
- stimulation of epithelial cells migration;
- modulation, adhesion, and migration of vascular smooth muscle cells;
- stimulation of alveoli macrophages to metalloproteinases and chemokines secretion;
- increase in auxiliary lymphocytes Th2 response caused by antigens;
- regulation of oxidative stress response;
- regulation of apoptosis process (i.e., prevention of epithelial cells apoptosis);
- stimulation of M2 macrophages differentiation;
- suppression of mammary gland epithelial cells differentiation [42,43,45].

Studies have described the relationship between YKL-40 and AD (occurrence of increased YKL-40 expression areas, concentrating mainly on astrocytes surface, around amyloid plaques and blood vessels, with amyloid angiopathy in patients with AD brain [46]), and the relationship between APOE4
genotype and YKL-40 concentration in cerebrospinal fluid (CSF) [47]. This was also supported by an experiment conducted by Choi et al., who found, in mice disease model, decreased APP expression and an improvement of rodents’ cognitive functions after administration of substance suppressing CHI3L1 activity [48]. The relationship between neuroinflammation and described biomarkers in AD are shown on Figure 1.

**Figure 1.** The role of neuroinflammation and neurodegeneration processes in the formation of dementia protein biomarkers, i.e., amyloid, tau, and YKL-40. IL-1\(\beta\), interleukin 1 beta; IL-6, interleukin 6; TNF-\(\alpha\), tumor necrosis factor alpha.

YKL-40 diagnostic utility is limited by its non-specificity. An increased concentration of this protein was found in various types of cancer, inflammatory and autoimmune diseases [43], bacterial, viral, and parasitic infections [44]. An increase in serum YKL-40 concentration was also documented in VD and mixed dementia with vascular risk factors, such as metabolic syndrome [49], coronary heart disease [50], atrial fibrillation [51], and obstructive sleep apnea [52]. Xu et al. concluded, in a group of patients with prehypertensive state, that the disease could be preceded by an increase in YKL-40 concentration [53]. In the first days after an ischaemic stroke, an increase in this marker was proportional to the volume of the stroke site and the severity of symptoms [54].

An increase in YKL-40 expression was observed in tissues and bodily fluids other than serum, for example, in motor cortex and spinal cord of patients with atrophic lateral sclerosis [55], in hippocampus of schizophrenia patients [56], or in CSF of elderly woman with suicidal thoughts [57]. On the one hand, increased YKL-40 immunoreactivity in brain, correlating with tau protein, was observed in tauopathies other than AD [58]. On the other hand, studies conducted by Isgren et al. have shown that decreased concentration of YKL-40 in CSF of patients with bipolar disorders was preceded by episodes of mania or hypomania [59].
1.5. Practical Aspects of Using Dementia Biomarkers

Many studies conducted, to date, have proven that brain lesions precede the occurrence of clinical symptoms of disease even by 20 years [1], which gives hope to use these observations for development of early detection and prevention methods. Efforts that have been undertaken to use proteins involved in disease pathogenesis as biomarkers have proven that they can inform about disease existence even in the asymptomatic stage and they also correlate with disease intensification when neuropathological changes buildup [60].

Considering potential application, the following can be singled out:

- predictive biomarkers for estimating disease in the preclinical stage, and for estimating clinical prognosis;
- diagnostic biomarkers in precise differential diagnosis;
- biomarkers for healing response and assessing the effectiveness of therapy;
- surrogate markers for estimating the influence of therapeutic intervention on selected pathophysiological processes;
- trait markers, strictly tied to disease characteristics (e.g., mutations);
- condition markers (e.g., enzymes) for monitoring progression of disease [22].

Diagnosis and monitoring of dementia are carried out mainly by clinical assessment and neuropsychological tests. It is only possible to diagnose the disease in the symptomatic stage, and the given diagnosis is considered to be probable [22]. Regular neuropsychological assessment, which is recommended as an early dementia diagnosis tool, is not fulfilling its role. The main causes of this situation are (among others) the long waiting time for an appointment and very short duration of visits. In standard healthcare, a common problem is also inaccurate screening performance and interpretation of cognitive functioning of patients. This results from insufficient training and experience of primary care staff. The key step is the referral of a patient to a specialist by a general medical practitioner. Adequate biochemical markers could be an inestimable tool in the hands of family physicians, facilitating selection of patients in need of specialist treatment [61]. Regardless of health benefits, early AD diagnosis could significantly reduce treatment and care costs generated by patients [1].

Usage of biomarkers in dementia diagnostics could aid early diagnosis, monitoring of disease severity, and recovery prognosis. It could also help in the development of more personalized pharmacotherapy by adequate recruiting and grouping of subjects, as well as assessment, in clinical trials, of test drug effectiveness and dosage [15]. The role of biomarkers in the development process of new drugs is crucial because of verification of patients included in clinical trials, for example, the PET amyloid test showed that many of the patients were falsely classified as AD patients [62]. In the future, proper selection and use of biomarkers may enable the development of personalized therapy for every individual patient, such as in modern oncological treatment standards [15,61]. However, the current goal, in studies on AD biomarkers, is to achieve a cost-efficient screening test with high negative (not necessarily high positive) predictive value, which should have the ability to identify AD cases on a large scale [61].

An ideal diagnostic marker should be characterized by at least moderate sensitivity and high specificity (>85% [22]), ease of obtaining research material, easy determination method, repeatability, and low cost [60]. It should also have the ability to identify disease in the early stage and differentiate it from other dementias, reflecting the neuropathology of the examined disease. Another important characteristic of a valuable biomarker is the absence of concentration changes due to the influence of the used symptomatic treatment [22]. Currently, on the one hand, biomarker identification in cerebrospinal fluid (Aβ42, t-tau, p-tau) requires qualified personnel that can use a more invasive, expensive, and often non-refundable procedure for material extraction [60,63]. Use of the CSF extraction procedure is limited to a wide-range population and its repeatability, which calls in to question its usability in standard healthcare or in clinical trials [15]. Survival assessment of the occurrence of Aβ deposits
with the PET method is very costly and often non-refundable, moreover it is associated with exposure to a radioactive substance [63]. On the other hand, collecting a blood sample and its analysis is a routine procedure that does not require additional personnel training and it is repeatable and possible to perform in various conditions [61].

Imprecise measurement of the concentration of marker in peripheral blood due to its low blood-brain barrier (BBB) permeability [60], possible proteolysis of tested protein in peripheral blood, and its fast elimination by liver or kidneys are the main elements that limit the capability of using biomarkers from peripheral blood. Moreover, blood is a fluid with a high concentration of various proteins, posing a risk of obtaining false-positive results with insufficient specificity of applied tests [61,64]. Therefore, imperfections of available markers may be minimalized by application of several different test panels [60].

The aim of this review is to gather and summarize studies conducted to date, on using selected proteins that can act as dementia biomarkers in blood material, for example, Aβ40 and Aβ42 amyloids, tau protein, as well as its phosphorylation products (p-tau) and YKL-40 protein.

2. Experimental Section

For the analysis of acquired studies and their results on concentrations of selected biomarkers in the blood of dementia patients, the search for works about human research published in English scientific journals in Medline, Pubmed, and Web of Science databases was conducted with the use of keywords such as “amyloid beta”, “tau protein”, “YKL-40 OR CHI3L1” AND “dementia OR alzheimer*” AND “plasma OR serum or blood”. Considering the possibility of outdated laboratory techniques influencing results, the search was limited only to studies from 2000 to 2020. Among the acquired search results, only cross-sectional studies with a control group and a test group with dementia and mild cognitive impairments (MCI) were qualified for comparison. Review articles and prospective studies were excluded. Studies on biomarkers in other than plasma or serum biological material, as well as studies on specific isoforms of the markers, were excluded. We also did not qualify research made on specific groups, i.e., corpses, children, patients with concomitant diseases (e.g., Down syndrome), or patients with undefined dementia etiology. Some groups of patients were investigated in more than one article, in such cases, only one methodologically best study was taken into account. Papers with no significance level “p” value for comparison among groups and in which test or control groups consisted of less than 10 people were also excluded. The results obtained in groups other than dementia and MCI were not included in the tables. The number of search results in each database is listed in the Table 1.

| Biomarker | Database  | Found | Qualified | Qualified Total |
|-----------|-----------|-------|-----------|-----------------|
| Amyloid beta | Medline | 1698  | 41 | 50 |
|           | PubMed  | 1709  | 40 |  |
|           | Web of Science  | 7133  | 48 |  |
| T-tau    | Medline | 405   | 15 | 20 |
|           | PubMed  | 397   | 16 |  |
|           | Web of Science  | 1547  | 14 |  |
| YKL-40   | Medline | 14    | 4  |  |
|           | PubMed  | 11    | 3  |  |
|           | Web of Science  | 38    | 5  |  |
| Amyloid beta and t-tau combination | Medline | 281 | 5 |  |
|           | PubMed  | 255   | 5  |  |
|           | Web of Science  | 960   | 5  |  |
3. Results

3.1. Amyloid Markers $A\beta_{40}$, $A\beta_{42}$, and $A\beta_{40}/42$ Ratio

According to the adopted criteria, 50 studies comparing concentrations of $A\beta_{40}$, $A\beta_{42}$, and their ratio were selected from the search results. A total number of 7303 patients with dementia or MCI and people from control groups without any cognitive disorders were examined in these studies. In 31 studies, the ELISA method was used for identification; in eight studies, the immunomagnetic reduction method (IMR) was used; in six studies, the fluorescence in multiplex immunology test method (xMAP) was used; and in two studies, the single molecular array method (Simoa) was used. In one study, identification was made using the immunoblot method [65]. The most recent from the covered studies [66] was conducted by carbon nanotubes array (CNT).

The $A\beta_{40}$ concentration was tested in 43 trials, listed in Table 2. The obtained results are highly incoherent. Statistically significant differences among groups were found in only 24 trials, whereas, in 10 of the trails, the concentrations of $A\beta_{40}$ were (contrary to general trend) higher in the control group. In 39 trials, AD patients were investigated. Twenty trials compared MCI subjects to cognitively normal controls. The inconsistency of results did not depend on the method used. A large part of research gave statistically not significant results (12 out of 20 for ELISA, three out of eight for IMR, two out of five for xMAP).

In 48 of the selected studies, there was a comparison of $A\beta_{42}$ among groups. In 32 of them, the results were statistically significant. In most of the comparisons, the $A\beta_{42}$ concentrations were higher in control groups, but in as many as 13 cases higher concentrations of $A\beta_{42}$ were identified in patients with dementia or MCI rather than in the control group. Among the methods repeated in several studies, it was noteworthy that, in all seven studies conducted using the IMR method, the $A\beta_{42}$ levels were significantly higher in the AD or MCI groups than in the controls. In addition, studies based on ELISA or xMAP method gave very inconsistent results.
Table 2. Studies on Aβ40, Aβ42, and Aβ40/Aβ42 in serum.

| Study | N   | Groups (n) | Aβ40 Concentration [pg/mL] (SD or CI) | p   | Aβ42 Concentration [pg/mL] (SD or CI) | p   | Aβ42/Aβ40 (SD or CI) | p   | Method       |
|-------|-----|------------|--------------------------------------|-----|--------------------------------------|-----|----------------------|-----|--------------|
| Mehta et al., 2000 [67] | 65  | AD (36), HC (29) | AD 272 (100–770) HC 219 (35–490) | 0.005 | AD 73 (25–880) HC 81 (25–905) | >0.05 | - | - | ELISA |
| Sobóew et al., 2005 [68] | 158 | AD (54), MCI (39), HC (35) | AD 168.7 (32.2) MCI 160.1 (20.2) HC 160.1 (17.2) | >0.05 | AD 37.8 (10.3) MCI 56.8 (9.3) HC 36.3 (6.3) | <0.001 (MCI vs. AD + HC) | AD 4.6 (0.9) MCI 2.9 (0.6) HC 4.5 (0.6) | <0.001 (MCI vs. AD + HC) | ELISA |
| Pesaresi et al., 2006 [69] | 324 | AD (146), MCI (89), HC (89) | - | - | AD 38 MCI 52 HC 54 | <0.01 (AD vs. MCI + HC) | - | - | ELISA |
| Fagan et al., 2007 [70] | 114 | AD CDR1 (16), AD CDR0.5 (33), HC-CDR0 (65) | AD CDR 1 AD CDR 0.5 CDR 0 191 (61.3) | 0.51 | AD CDR 36 (37.2) AD CDR0.5 41 (38.9) CDR0 36 (29.4) | 0.76 | - | - | ELISA |
| Abdullah et al., 2007 [71] | 213 | AD (67), HC (146) | Serum AD 183.01 (6.23) HC 134.33 (2.79) Plasma AD 103.38 (4.27) HC 80.66 ± 1.86 | <0.05 | Serum AD 9.87 (0.82) HC 9.02 (0.40) Plasma AD 4.53 (0.52) HC 5.66 (0.31) | >0.05 | - | - | ELISA |
| Baranowska-Bik et al., 2008 [72] | 124 | mildAD (29), m-sAD (28), HC (67) | Serum AD 112 (39.51) pmol/L HC 95.38 (32.30) | <0.0002 | AD 10.29 (13.80) pmol/L HC 12.13 (12.29) | <0.0001 | AD 0.064 (0.011) HC 0.076 (0.005) Plasma AD 0.053 (0.008) HC 0.061 (0.006) | <0.05 | ELISA |
| Xu et al., 2008 [73] | 268 | AD (113), HC (155) | AD 112 (39.51) pmol/L HC 95.38 (32.30) | <0.0002 | AD 10.29 (13.80) pmol/L HC 12.13 (12.29) | <0.0001 | - | - | ELISA |
| Ait-ghezala et al., 2008 [74] | 175 | AD (73), HC (102) | AD 91.99 (5.02) HC 81.04 (2.94) | <0.05 | AD 1.91 (0.14, 6.84) HC 2.82 (0.59, 5.38) | >0.05 | AD 0.015 (0.002, 0.097) HC 0.022 (0.008, 0.065) | >0.05 | ELISA |
| Rober et al., 2009 [75] | 38  | AD (17), HC (21) | AD 424.06 (147.73) HC 344.41 (132.43) | 0.088 | AD 139.91 (77.82) HC 124.71 (42.34) | 0.448 | AD 0.35 (0.16) HC 0.44 (0.30) | 0.292 | ELISA |
| Sedaghat et al., 2009 [76] | 35  | AD (29), HC (16) | - | - | AD 16.2 (2.6) HC 13.4 (1.4) | >0.05 | - | - | ELISA |
| Luis et al., 2009 [77] | 78  | AD (25), MCI (13), HC (40) | AD 181 (13.78) MCI 158 (17.55) HC 158 (7.65) | >0.05 | AD 13.89 (2.00) MCI 25 (9.31) pmol/L HC 10 (3.64) | 0.015 (MCI vs. HC) | AD 0.086 (0.013) MCI 0.161 (0.045) HC 0.071 (0.014) | 0.021 | ELISA |
| Cammarata et al., 2009 [78] | 293 | MCI (191), HC (102) | MCI 294.7 (20.86) HC 315.6 (23.64) | >0.05 | MCI 26.62 (2.68) HC 16.46 (1.46) | <0.01 | MCI 0.12 (0.02) HC 0.09 (0.03) | <0.01 | ELISA |
| Lui et al., 2010 [79] | 1032 | AD (186), MCI (122), HC (724) | AD 155.1 (44.2) MCI 152.9 (51.5) HC 153.4 (40.2) | 0.877 | AD 30.0 (10.2) MCI 30.2 (11.9) HC 32.4 (9.7) | <0.001 | AD 0.199 (0.056) MCI 0.216 (0.120) HC 0.221 (0.097) | 0.001 | ELISA |
Table 2. Cont.

| Study                  | N   | Groups (n)                      | Aβ40 Concentration [pg/mL] (SD or CI) | p      | Aβ42 Concentration [pg/mL] (SD or CI) | p      | Aβ42/Aβ40 (SD or CI) | p      | Method     |
|------------------------|-----|---------------------------------|---------------------------------------|--------|---------------------------------------|--------|----------------------|--------|------------|
| Kornm et al., 2011 [80]| 49  | AD (39), HC (21)                | AD 378 (113) HC 254 (63)              | <0.0001| AD 321 (3.0) VH 37.3 (5.1) OD 37.2 (5.5) HC 37.7 (7.4) | <0.001 | AD 0.29 (0.07) VH 0.4 (0.09) OD 0.4 (0.08) HC 0.41 (0.09) | <0.001 | ELISA      |
| Han et al., 2012 [81]  | 343 | AD (112), VD (85), other dementia—OD (30), HC (116) | AD 90.7 (8.7) VH 93.6 (12.3) OD 93.1 (13.0) HC 92.4 (13.0) | <0.05  | AD 11.5 (2.9) VH 13.2 (3.1) OD 13.3 (3.7) | <0.001 | AD 0.12 (0.03) VH 0.14 (0.02) OD 0.14 (0.01) | <0.001 | ELISA      |
| Zhang et al., 2013 [82]| 326 | AD (153), VD (53), HC (120)     | AD 97.7 (30.6) VH 98.2 (20.5) VH 92.6 (26.7) | <0.05  | AD 10.8 (7.5) VH 14 (9) VH 13 (12) | <0.002 | AD 0.12 (0.03) VH 0.14 (0.02) OD 0.14 (0.01) | <0.001 | ELISA      |
| Huang et al., 2013 [83]| 34  | AD (18), MCI + HC (16)          | -                                     | -      | AD 17.19 (21.9) VH 7.31 (5.3) | 0.079  | -                    | -      | ELISA      |
| Ruiz et al., 2013 [84] | 140 | AD (51), MCI (36), HC (53)      | AD 51 (16) MCI 58.9 (16) VH 44.4 (14) | <0.02  | AD 10.8 (7.5) VH 14 (9) VH 13 (12) | <0.002 | AD 0.12 (0.03) VH 0.14 (0.02) OD 0.14 (0.01) | <0.001 | ELISA      |
| Wang et al., 2014 [85] | 273 | AD 97 MCI 54 VH 122             | AD 59.10 (20.30) MCI 51.66 (26.03) VH 43.14 (22.57) | MCI vs. HC 0.027 MCI vs. AD 0.063 AD vs. HC <0.001 | AD 47.10 (2.29) MCI 47.49 (0.93) VH 47.53 (1.97) | 0.944 MCI vs. VH 0.474 MCI vs. AD 0.468 AD vs. HC | -      | ELISA      |
| Tzikas et al., 2014 [86]| 55  | AD (28), HC (27)                | AD 39.65 (6.08) HC 36.30 (6.68)       | 0.171  | AD 3.38 (2.34) HC 3.39 (2.64) | 0.849  | -                    | -      | ELISA      |
| Krishnan et al., 2014 [87]| 105 | AD (30), VH (35), HC (40)       | -                                     | -      | AD 164.66 (66.76) VH 148.17 (60.24) HC 86.10 (43.75) | <0.001 | AD 0.01 (AD vs. VH) HC 0.01 (AD vs. HC) | >0.05  | ELISA      |
| Kleinschmidt et al., 2015 [88]|94  | AD (15), MCI (14), HC (18–30 years (13), HC 40–65 (13), HC 66–85 (19) | HH 66–85 > AD > HC 40–65 > MCI > HC 18–30 | <0.05 for AD vs. MCI <0.01 for MCI vs. HC | HH 66–85 > HC 40–65 > MCI > AD | <0.05 for AD vs. HC HH 66–85 and MCI vs. HC 66–85 | <0.01 (AD vs. HC 66–85) 0.05 (MCI vs. HC 66–85) | ELISA  |
| Jiao et al., 2015 [89] | 285 | AD (156), HC (129)              | AD 86.2 (55.5) HC 60.2 (34.7)         | <0.001 | AD 68.4 (61.9) HC 49.3 (27.7) | 0.001  | -                    | -      | ELISA      |
| Study                      | N   | Groups (n)               | Aβ40 Concentration [pg/mL] (SD or CI) | p       | Aβ42 Concentration [pg/mL] (SD or CI) | p       | Aβ42/Aβ40 (SD or CI) | p       | Method           |
|----------------------------|-----|--------------------------|---------------------------------------|---------|---------------------------------------|---------|----------------------|---------|-------------------|
| Igarashi et al., 2015      | 153 | AD (70), MCI (50), HC (33) | Median AD 51.0 pmol/L MCI 50.0 HC 51.4 | >0.05   | Median AD 6.4 pmol/L MCI 6.2 HC 6.9   | >0.05   |                      |         | ELISA             |
|                            |     |                          | AD vs. HC p = 0.01 MCI vs. HC p = 0.14 |         | AD 18.34 (32.10) MCI 37.58 (74.38) HC 65.63 (177.04) | <0.001 (AD vs. HC) 0.005 (MCI vs. HC) |         |                   |
| Poljak et al., 2016        | 251 | AD (39), MCI (93), HC (129) | Median AD 155.82 (20.25) MCI 104.58 (20.24) HC 103.33 (14.77) | AD vs. HC p = <0.001 MCI vs. HC p = 0.14 |         | AD 18.34 (32.10) MCI 37.58 (74.38) HC 65.63 (177.04) | <0.001 (AD vs. HC) 0.005 (MCI vs. HC) |         |                   |
| Grewal et al., 2016        | 75  | 3 groups of 15 (aMCI) and 10 (HC) women of different races | Median LA aMCI 127.63 (23.76) CA aMCI 160.51 (25.91) AA aMCI 106.28 (9.57) | LA p = <0.05 CA p = 0.001 all groups p = 0.0001 |         | LA aMCI 40.38 (4.76) CA aMCI 33.21 (2.61) AA aMCI 26.48 (2.61) LA HC 23.69 (2.34) CA HC 34.82 (4.00) AA HC 26.95 (4.05) | <0.005 (LA) >0.05 (CA, AA) |         |                   |
| Yamashita et al., 2016     | 36  | AD (18), HC (18)         | Median AD 103.6 (11.8) fmol/mL HC 81.2 (9.8) | >0.05   | Median AD 25.0 (5.3) HC 18.5 (2.8)   | >0.05   | AD 0.3 (0.1) HC 0.3 (0.0)  | >0.05   | ELISA             |
| Rani et al., 2017          | 90  | AD (45), HC (45)         | -                                      | -       | AD 174.87 (62.15) HC 90.62 (42.35)   | <0.001  | -                    | -       | ELISA             |
| Sun et al., 2018           | 137 | AD (76), HC (61)         | Median AD 215.25 (54.26) HC 144.62 (47.20) | <0.001  | Median AD 123.48 (45.89) HC 91.35 (36.39) | <0.001  | -                    | -       | ELISA             |
| Chen et al., 2018          | 126 | AD (96), HC (30)         | Median AD 649.68 (132.21) HC 423.32 (100.99) | <0.001  | Median AD 322.25 (76.04) HC 219.21 (62.51) | <0.001  | AD 40/42 AD 2.13 (0.66) HC 2.15 (0.95) | >0.05   | ELISA             |
| Biber et al., 2007         | 85  | AD (15), AD-CVD (20), HD (15), PD/PDD (20), HC (15) | Median AD 0.199 (0.099) AD-CVD 0.197 (0.063) HD 0.270 (0.103) PD/PDD 0.185 (0.069) HC 0.209 (0.087) | <0.05 (VD vs. HC) remaining p > 0.05 | Median AD 0.022 (0.007) AD-CVD 0.023 (0.013) HD 0.002 (0.008) PD/PDD 0.023 (0.007) HC 0.025 (0.007) | >0.05   | -                    | -       | immunoblot         |
| Study                        | N  | Groups (n) | Aβ40 Concentration [pg/mL] (SD or CI) | p   | Aβ42 Concentration [pg/mL] (SD or CI) | p   | Aβ42/Aβ40 (SD or CI) | p   | Method |
|-----------------------------|----|------------|----------------------------------------|-----|--------------------------------------|-----|---------------------|-----|--------|
| Le Bastard et al., 2009 [98]| 162| AD (48), non-AD (46), MCI (39), HC (29) | - | - | AD 40.5 (32.8–50.9) | 0.174 | - | - | xMAP |
| Le Bastard et al., 2010 [99]| 147| AD (50), non-AD (50), HC (47) | AD 306.8 (268.7–336.8) | 0.347 | AD 40.4 (32.1–50.8) | 0.174 | - | - | xMAP |
| Sundelöf et al., 2010 [100] | 213| AD (101), MCI (84), HC (28) | AD 145.9 (64.3) | <0.05 (AD vs. HC and MCI vs. HC) | AD 28.5 (10.7) | <0.05 (AD vs. HC and MCI vs. HC) | - | - | xMAP |
| Chou et al., 2016 [101]    | 781| AD (592), MCI (119), HC (170) | AD 173.1 (79.3) | 0.807 (AD vs. MCI) | AD 23.8 (15.1) | 0.899 (AD vs. MCI) | 0.001 (AD vs. HC) | 0.01 | xMAP |
| Hsu et al., 2017 [102]     | 335| AD (177), MCI (60), HC (108) | AD 170.3 (63.9) | 0.001 (AD vs. HC) | AD 37.2 (14.1) | 0.025 (AD vs. HC) | 0.14 (AD vs. HC) | 0.02 | xMAP |
| Hanen et al., 2018 [103]   | 1040| AD (501), aMCI (417), naMCI (122) | AD 263.6 (80) | 0.04 | AD 36.9 (11.7) | 0.09 | - | - | xMAP |
| Uslu et al., 2012 [104]    | 60 | AD (18), MCI (16), HC (26) | AD 53.2 (34.6) | >0.05 | AD 34.2 (31.6) | 0.001 (AD vs. HC) | AD 0.6 (0.3) | 0.001 (AD vs. HC) | IMR |
| Chiu et al., 2012 [105]    | 60 | AD (18), MCI (16), HC (26) | AD 53.2 (34.6) | >0.05 | AD 34.2 (31.6) | 0.001 (AD vs. HC) | AD 0.6 (0.3) | 0.001 (AD vs. HC) | IMR |
| Tzen et al., 2014 [106]    | 45 | AD (14), MCI (11), HC (20) | AD 36.9 (1.6) | <0.001 | AD 18.9 (0.3) | <0.001 | AD 0.5 (0.2) | <0.001 | IMR |
| Lee et al., 2017 [107]     | 140| AD (62), HC (78) | AD 43.9 (22.1) | <0.001 | AD 23.2 (18.4) | <0.001 | AD 0.5 (0.2) | <0.001 | IMR |
| Study                        | N     | Groups (n)                  | Aβ40 Concentration [pg/mL] (SD or CI) | p    | Aβ42 Concentration [pg/mL] (SD or CI) | p    | Aβ42/Aβ40 (SD or CI) | p    | Method |
|-----------------------------|-------|----------------------------|--------------------------------------|------|--------------------------------------|------|---------------------|------|--------|
| Teunissen et al., 2018 [108]| 106   | AD 63, HC 43               | AD 17.9 (4.3)                        | < 0.001 | AD > VD > HC                        | < 0.05 (AD vs. HC) | -       | -     | IMR    |
| Tang et al., 2018 [109]     | 79    | AD (21), VD (34), HC (24)  | HC > VD > AD                        | < 0.01 (AD vs. HC) | AD > VD > HC                        | < 0.01 (AD vs. VD) | -       | IMR    |
| Fan et al., 2018 [110]      | 80    | AD (16), MCI (25), HC (39) | AD 39.5 (5.8) MCI 41.5 (3.9) HC 59.2 (11.1) | < 0.001 (AD vs. HC, MCI vs. HC) | AD 19.0 (2.7) MCI 17.0 (2.0) HC 16.1 (1.8) | < 0.001 (AD vs. MCI, MCI vs. HC) | -       | IMR    |
| Tsai et al., 2019 [111]     | 90    | AD (37), MCI (40), HC (13) | AD 51.7 (3.7) MCI 51.9 (4.9) HC 51.8 (5.1) | > 0.05 | AD 17.4 (1.0) MCI 17.0 (0.7) HC 16.7 (0.7) | < 0.05 (AD + MCI vs. HC) | AD 0.338 (0.032) MCI 0.330 (0.035) HC 0.326 (0.035) | > 0.05 | IMR    |
| Startin et al., 2019 [28]   | 54    | AD (27), HC (27)           | AD 160.80 (43.60–420.00) HC 144.40 (26.88–355.60) | 0.506 | AD 13.32 (4.28–18.84) HC 14.76 (2.00–45.62) | 0.710 | AD 0.08 (0.04–0.11) HC 0.10 (0.07–0.17) | < 0.001 | Simoa |
| Janelidze et al., 2016 [112]| AD (57), MCI (214), HC (274) | AD 244.3 (105.8) MCI 287.6 (77.0) HC 276.7 (66.1) | < 0.001 (AD vs. HC) | AD 13.2 (7.3) MCI 18.8 (6.1) HC 19.6 (5.2) | < 0.0001 (AD vs. HC) | AD 0.057 (0.022) MCI 0.066 (0.015) HC 0.073 (0.023) | 0.0001 (AD vs. HC) | Simoa |
| Shi et al., 2009 [113]      | 155   | MCI (68), HC (87)          | MCI 157.65 (64.50) HC 183.76 (61.87) | 0.011 | MCI 5.95 (2.60) HC 8.14 (3.12) | 0.000 | -                   | -     | Simoa |
| Kim et al., 2020 [66]       | 40    | AD (20), HC (20)           | AD 184 (67.8) HC 159 (78.0) | 0.26 | AD 6.49 (5.02) HC 19.3 (15.5) | < 0.001 | AD median approx. 0.1 HC median approx. 0.05 (from the graph) | < 0.000001 | CNT |

SD, standard deviation; CI, confidence interval; AD, Alzheimer’s disease; MCI, mild cognitive impairments; HC, control group; CDR, clinical dementia rating; VD, vascular dementia; PD, Parkinson’s disease; mildAD, AD in mild level; m-sAD, moderate and severe AD; non-AD, dementia of etiology other than AD; aMCI, amnestic MCI subtype; naMCI, non-amnestic MCI subtype; ELISA, immunoenzymatic method; IMR, immunomagnetic reduction method; CNT, carbon nanotube array.
The amyloid peptide concentration ratio was assessed in 29 studies. In nine cases, the results were not statistically significant. Among the comparisons that were statistically significant, in 11 cases, the Aβ42/Aβ40 concentration ratio was higher in the control groups and, in seven cases, it was higher in the study groups. In two of the studies, the Aβ42/Aβ40 ratio was similar in the AD and control groups and significantly higher than in the MCI groups [68,102]. The results varied depending on laboratory methods use. None of the three studies using xMAP gave statistically significant results, while, in four out of five IMR studies, the Aβ42/Aβ40 ratio was significantly higher in the AD or MCI groups than in the controls. The results obtained in ELISA studies were highly inconsistent.

### 3.2. Tau Protein

Twenty cross-sectional tests, conducted to date, on t-tau concentration in patients with dementias and MCI serum, and which meet the search criteria, are listed in Table 3. One work included separately examined cohorts [114]: 16 patients with AD and 12 patients with MCI were examined. Single tests referred to FTD (t-tau significantly higher than in control group [115]) and VD (t-tau significantly lower than in AD and higher than control group [87,109]). The identification of tau protein was conducted in seven studies by the Simoa method, in six studies by the ELISA method, in six studies by the IMR method, and in one study by CNT. The absolute values of t-tau concentration identified by the single molecule array (Simoa) method were lower by one to two orders of magnitude than values acquired by other methods.

**Table 3. Studies on t-tau concentration in serum.**

| Study                        | N    | Groups (n)             | Tau Concentration in Serum (SD or CI) [pg/mL] | p             | Method |
|------------------------------|------|------------------------|----------------------------------------------|---------------|--------|
| Chiu et al., 2014 [116]      | 60   | AD (10), MCI (20), HC (30) | AD 53.9 (11.7), MCI 32.7 (5.8), HC 15.6 (6.9) | <0.01 (MCI vs. AD) >0.05 (MCI vs. HC) | IMR    |
| Tzen et al., 2014 [106]       | 45   | AD (14), MCI (11), HC (20) | AD 46.7 (2.0), MCI 33.5 (2.2), HC 13.5 (5.5) | <0.001        | IMR    |
| Lee et al., 2017 [107]        | 140  | AD (62), HC (78)        | AD 47.5 (18.9), HC 15.0 (7.3) and 14.9 (5.5) | <0.001        | IMR    |
| Tang et al., 2018 [109]       | 79   | AD (21), VD (34), HC (24) | AD > VD > HC | <0.001 (AD vs. HC) <0.01 (AD vs. VD) <0.05 (VD vs. HC) | IMR    |
| Yang et al., 2018 [117]       | 73   | AD (21), MCI (29), HC (23) | AD 37.54 (12.29), MCI 32.98 (16.18), HC 18.85 (10.16) | <0.001 (AD vs. HC) <0.01 (AD vs. VD) <0.05 (VD vs. HC) | IMR    |
| Tsai et al., 2019 [111]       | 90   | AD (37), MCI (40), HC (13) | AD 27.1 (4.8), MCI 24.5 (4.0), HC 22.5 (3.4) | <0.05        | IMR    |
| Wang et al., 2014 [105]       | 273  | AD (97), MCI (54), HC (122) | AD 213.95 (44.57), MCI 209.61 (39.65), HC 214.94 (43.23) | 0.457 (MCI vs. HC) remaining comparisons p > 0.05 | ELISA  |
| Krishnan et al., 2014 [87]    | 105  | AD (30), VD (35), HC (40) | AD 458.62 (253.82), VD 718.3 (326.24), HC 879.19 (389.53) | <0.05 (AD vs. VD) <0.001 (AD vs. HC) | ELISA  |
| Jiao et al., 2015 [109]       | 285  | AD (156), HC (129)      | AD 227.1 (102.2), HC 181.0 (103.2) | <0.001        | ELISA  |
| Shekhar et al., 2016 [118]    | 113  | AD (39), MCI (37), HC (37) | AD 47.49 (9.00), MCI 39.26 (7.78), HC 34.92 (6.58) | <0.001 (AD vs. HC) <0.001 (AD vs. MCI) 0.059 (MCI vs. HC) | ELISA  |
| Rani et al., 2017 [85]        | 90   | AD (45), HC (45)        | AD 451.76 (240.82), HC 836.93 (369.31) | <0.001        | ELISA  |
### Table 3. Cont.

| Study            | N    | Groups (n) | Tau Concentration in Serum (SD or CI) [pg/mL] |   | Method  |
|------------------|------|------------|-----------------------------------------------|---|---------|
| Jiang et al., 2019 [119] | 238  | AD (110), HC (128) | AD 26.14 (11.52)
HC 15.02 (9.04) | <0.001 | ELISA |
| Dage et al., 2016 [120] | 439  | MCI (161), HC (378) | MCI 4.34
HC 4.14 | 0.078 | Simoa |
| Mattson et al., 2016 [114] | 563 + 547 (two cohorts) | I: AD (179), MCI (195), HC (189),
II: AD (61), MCI (212), HC (274) | AD 3.12 (1.50) and 5.37 (2.56)
MCI 2.71 (1.32) and 5.46 (2.71)
HC 2.58 (1.19) and 5.58 (2.51) | 0.0017 and 0.58 (AD vs. MCI + HC) | Simoa |
| Mielke et al., 2017 [121] | 458  | MCI (123) HC (335) | MCI 4.5 (1.8)
HC 4.2 (1.5) | 0.28 | Simoa |
| Deters et al., 2017 [122] | 508  | AD (168), MCI (174), HC (166) | AD 3.13 (1.3)
MCI 2.81 (1.2)
HC 2.71 (1) | 0.002 (AD vs. MCI + HC) | Simoa |
| Mielke et al., 2018 [39] | 267  | AD (40), MCI (57), HC (172) | AD 7.2 (2.8)
MCI 5.9 (2.8)
HC 5.9 (1.9) | 0.029 (AD vs. MCI)
0.001 (AD vs. HC)
>0.05 (MCI vs. HC) | Simoa |
| Foiani et al., 2018 [115] | 176  | BvFTD (71), PPA (83), HC (22) | BvFTD 1.96 (1.07)
PAA 2.65 (2.15)
HC 1.67 (0.50) | <0.05 (FTD vs. HC) | Simoa |
| Shi et al., 2019 [113] | 155  | MCI (68), HC (87) | MCI 3.71 (2.3)
HC 3.56 (1.84) | 0.865 | Simoa |
| Kim et al., 2020 [66] | 40   | AD (20), HC (20) | AD 32.2 (16.4)
HC 13.4 (13.2) | <0.001 | CNT |

SD, standard deviation; CI, confidence interval; AD, Alzheimer’s disease; MCI, mild cognitive impairments; HC, control group.

In 14 studies, t-tau concentration was higher as compared with a control group; in five studies, there was no significant difference; and in two studies [87,95], t-tau concentration was higher in the control group. A significantly higher concentration of t-tau protein in AD as compared with a control group was identified in 13 out of 16 studies, and AD as comparing with MCI in eight of nine studies. In addition, in studies comparing t-tau concentration between MCI and the control group, results indicating diagnostic usability of this marker were achieved in only two out of 12 comparisons.

In all six studies using the IMR method and in five out of six studies performed with ELISA determination, tau levels were significantly higher in AD/MCI patients. Simoa gave less consistent results, i.e., in three out of eight cohorts the differences among groups did not reach the statistical significance.

### 3.3. Amyloid Markers and Total Tau Protein Combinations

In database searches, there were four studies on t-tau/Aβ42 ratio as a dementia biomarker in serum. The results are listed in Table 4. In three studies, the t-tau/Aβ42 concentration ratio was higher in the control group than in the AD group, but, in one of them, this difference was not statistically relevant. The age gap between the AD groups and control groups could have influenced the obtained results from this study [28]. In the Krishnan et al. study, the combination of both markers was characterized by significantly higher diagnostic sensitivity in differentiation of AD from healthy subjects (90.3%, AUC 0.991), than each separate marker (80.6%), but specificity for t-tau, Aβ42, and markers ratio hovered around 67% [87]. Kim et al. acquired a higher t-tau to Aβ42 concentration ratio level in the test group, using a new identification technique [66]. Assessment of t-tau/Aβ42 in serum was also conducted by Park et al. Authors of this study did not provide a comparison among groups (AD, MCI, HC), but they were searching for a correlation of acquired biomarkers ratio to existence or non-existence of tau protein deposits by the use of PET. The researchers managed to show a relation between biomarkers concentration ratio and occurrence of tauopathy within cingulate gyrus, temporal, prefrontal, and orbitofrontal cortex [40].
Moreover, diagnostic usability of the t-tau/β42 ratio identified by IMR method was assessed in two other studies. The results obtained by Chiu et al. pointed to 80% sensitivity and 82% specificity of the biomarker ratio in AD as compared with MCI, as well as 96% sensitivity and 97% specificity for the cognitive impairments group (AD and MCI) as compared with healthy subjects. The authors did not provide the $p$ value for comparisons among groups [123]. In the Tsai et al. study, the difference between a cognitively impaired group and a control group was statistically relevant ($p < 0.05$), but in the AD and MCI groups the acquired values of the biomarker ratio overlapped (respectively 473.2 ± 107.4 and 418.3 ± 80.3) [111].

### 3.4. YKL-40

The adopted search criteria were met by five studies that focused on diagnostic and prognostic usability assessment of YKL-40 in MCI and dementia in serum of patients. Their results are listed in Table 5.

| Study                                      | N     | Groups (n)                                      | YKL-40 Concentration in Serum (SD or CI) [ng/mL] | $p$            | Method |
|--------------------------------------------|-------|------------------------------------------------|------------------------------------------------|----------------|--------|
| Craig-Schaprio et al., 2010 [45]           | 237   | AD (CDR1 and CDR0.5), HC                        | AD (CDR1): 91.9 (15) AD (CDR 0.5): 81.1 (8) HC (CDR 0): 62.5 (3.4) | 0.031 (AD CDR1 vs. HC) 0.046 (AD CDR0.5 vs. AD) | ELISA  |
| Choi et al., 2011 [124]                    | 141   | AD (61), MCI (41), HC                           | AD: 376.86 (54.1) MCI:176.49 (25.69) HC: 96.91 (11.02) | 0.014 (AD vs. HC) 0.008 (AD vs. MCI) | ELISA  |
| Grewal et al., 2016 [93]                   | 75    | 15 (aMCI) and 10 (HC) women of white race (CA), | LA aMCI 114.08 (30.02) CA aMCI 93.39 (12.70) AA aMCI 54.26 (10.12) LA HC 54.2 (8.37) CA HC 70.92 (15.96) AA HC 54.66 (14.42) | 0.033 (LA) 0.418 (CA) 0.988 (AA) | ELISA  |
| Surendranatan et al., 2018 [125]          | 35    | DLB (19), HC (16)                               | DLB 64.350 (46.616) HC 43.034 (28.357)            | 0.115          | ELISA  |
| Villar-Pique et al., 2019 [126]            | 315   | CJD (78), AD (50), DLB (34), FTD (17), VD (22), | DLB: 167 (157) CJD: 189 (167) FTD: 125 (108) VD: 140 (150) AD: 133 (110) ND: 95 (61) HC: 84 (84) | $<0.001$ (CJD vs. HC) remaining $p > 0.05$ | ELISA  |

SD, standard deviation; CI, confidence interval; AD, Alzheimer’s disease; MCI, mild cognitive impairments; HC, control group; CDR, clinical dementia rating; CA, Caucasian race; AA, African American race; LA, Latino-American race; aMCI, amnestic MCI subtype; VD, vascular dementia; CJD, Creutzfeld–Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; ND, neurological diseases other than dementia.
Briefly, the findings of these five studies were the following:

1. Craig-Schapiro et al. found a statistically relevant increase in YKL-40 concentration in serum with disease progress which corresponded with results from CSF [45].

2. Choi et al. suggested that YKL-40 could be highly useful in the diagnostic of MCI progression to mild AD. This was supported by the highest marker increase among these groups and the correlation of acquired results with patient functioning, measured by the CDR scale at this stage of disease progression diagnosis [127]. The results of this study do not clearly reinforce the prognostic value of YKL-40 in serum, but they suggest its diagnostic usability in combination with other markers (Aβ42, tau, and p-tau) [124].

3. Grewal et al. examined women with amnestic MCI subtype from various ethnicity groups. Statistically significant concentration differences of YKL-40 among subgroups were identified only in the Latin American group. In addition, other measured biomarkers showed the differences of sensitivity among ethnic groups [93]. Amnestic type MCI is a state highly predisposing to AD, contrary to non-amnestic types which are the bases for developing other dementias. The results of prospective studies show that, every year, dementia is developed in 10–15% of patients with MCI [128].

4. Surendranathan et al. did not show any statistically significant YKL-40 concentration differences between patients with DLB and a control group [125].

5. Villar-Pique et al. did not obtain any statistically relevant differences between AD patients and a control group. The acquired results were significantly divergent across groups. Among the tested groups, highly increased YKL-40 concentrations were observed in patients with CJD (p < 0.001) and to a lesser degree in patients with LBD (p < 0.05). The authors hypothesized that the crucial factor influencing the concentration of the marker in peripheral blood may be the damage level of the blood-brain barrier in the course of primary disease [126].

4. Discussion

In dozens of studies, conducted to date, comparing the concentrations of Aβ40, Aβ42, and Aβ42/Aβ40 in blood of dementia and MCI patients, the results have been incoherent. This constitutes a fairly surprising observation regarding the crucial role of Aβ in AD pathogenesis and proven diagnostic value of amyloid markers in CSF. The incoherence of the observed results suggest that Aβ concentration in serum does not reflect its level in brain tissue and CSF. It is equally probable that not enough restrictive selection of a control group regarding comorbidities or imprecision of used laboratorial methods could have had an influence on these results.

Tau protein is characterized by higher specificity than other markers. In common, typically for the elderly somatic disorders, there was no increase in its concentration. The concentration of tau protein increases mainly in tauopathies, from which many of them are rare diseases. Therefore, t-tau may be the preferred marker in patients with somatic ailments. The most common tauopathy, other than AD, is FTD. The t-tau concentration in serum is increased in both of these diseases, however it seems that regarding specific FTD symptoms (behavioral problems preceding dementia and distinctive aphasia) differentiation of these diseases may not be a major diagnostic problem. According to many experts, tau protein hyperphosphorylation and its accumulation in the form of neurofiber tangles is secondary to amyloidopathy. The results of studies have highlighted that the lack of an increase in t-tau, in patients with MCI, could possibly be confirmation of this theory. T-tau may, thus, serve as a marker of progression from MCI to AD. However, it seems useless in asymptomatic stages and MCI diagnostics.

The past failure to identify a single, sensitive, and specific dementia serum marker implies attempts using combinations of more than one biomarker. In several studies, conducted to date, comparing values of t-tau and Aβ indicator, the acquired results were promising, and therefore this seems to be a good reason for further studies.
There are not many works on using YKL-40 in dementia diagnostics. Studies by Craig-Schapiro et al. [45], Choi et al. [124], and Grewal et al. [93] have given hope for its use in diagnostics of early stage dementias (MCI and mild stage AD). Less promising results were acquired by Villar-Pique et al. [126]. Due to the increase in this marker in many other diseases, there is an assumption that its usage may be limited only to the patients without any somatic comorbidity.

Considering the results of amyloid markers separately for individual laboratory methods, we noticed some differences. In the case of amyloid markers, on the one hand, almost all tests performed with the IMR method gave consistent, statistically significant results, in contrast to the determinations by ELISA or xMAP. On the other hand, the Simoa method, often used for the determination of tau protein concentrations, in the analyzed works, gave much less consistent results as compared with ELISA and IMR. Therefore, it seems that the laboratory method used may influence the obtained results.

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**References**

1. Alzheimer’s Association. 2018 Alzheimer’s Disease Facts and Figures. *Alzheimers Dement.* 2018, 14, 367–429. [CrossRef]
2. Katsnelson, A.; De Strooper, B.; Zoghbi, H.Y. Neurodegeneration: From cellular concepts to clinical applications. *Sci. Transl. Med.* 2016, 8, 364ps18. [CrossRef] [PubMed]
3. Smith, E.E. Cerebral amyloid angiopathy as a cause of neurodegeneration. *J. Neurochem.* 2018, 144, 651–658. [CrossRef] [PubMed]
4. Dichev, V.; Kazakova, M.; Sarafian, V. YKL-40 and neuron-specific enolase in neurodegeneration and neuroinflammation [published online ahead of print, 2020 Feb 11]. *Rev. Neurosci.* 2020. [CrossRef]
5. O’Brien, J.T.; Thomas, A. Vascular dementia. *Lancet* 2015, 386, 1698–1706. [CrossRef]
6. Cheng, C.; Huang, C.L.; Tsai, C.J.; Chou, P.H.; Lin, C.C.; Chang, C.K. Alcohol-related dementia: A systemic review of epidemiological studies. *Psychosomatics* 2017, 58, 331–342. [CrossRef]
7. Fernando, M.S.; Ince, P.G.; MRC Cognitive Function and Ageing Neuropathology Study Group. Vascular pathologies and cognition in a population-based cohort of elderly people. *J. Neurol. Sci.* 2004, 226, 13–17. [CrossRef]
8. Schneider, J.A.; Arvanitakis, Z.; Bang, W.; Bennett, D.A. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007, 69, 2197–2204. [CrossRef]
9. Rambaran, R.N.; Serpell, L.C. Amyloid fibrils: Abnormal protein assembly. *Prio* 2008, 2, 112–117. [CrossRef]
10. Puig, K.L.; Combs, C.K. Expression and function of APP and its metabolites outside the central nervous system. *Exp. Gerontol.* 2013, 48, 608–611. [CrossRef]
11. van der Kant, R.; Goldstein, L.S. Cellular functions of the amyloid precursor protein from development to dementia. *Dev. Cell* 2015, 32, 502–515. [CrossRef]
12. Bekris, L.M.; Yu, C.E.; Bird, T.D.; Tsuang, D.W. Genetics of Alzheimer disease. *J. Geriatr. Psychiatry Neurol.* 2010, 23, 213–227. [CrossRef] [PubMed]
13. Nigam, S.M.; Xu, S.; Kritikou, J.S.; Marosi, K.; Brodin, L.; Mattson, M.P. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. *J. Neurochem.* 2017, 142, 286–296. [CrossRef] [PubMed]
14. Duncan, R.S.; Song, B.; Koulen, P. Presenilins as drug targets for Alzheimer’s disease—recent insights from cell biology and electrophysiology as novel opportunities in drug development. *Int. J. Mol. Sci.* 2018, 19, 1621. [CrossRef] [PubMed]
32. Castellani, R.J.; Perry, G. Tau Biology, Tauopathy, Traumatic Brain Injury, and Diagnostic Challenges. *Acta Neuropathol.* 2018, 136, 821–853. [CrossRef]

16. Wang, R.; Wang, S.; Malter, J.S.; Wang, D.S. Effects of HNE-modification induced by Abeta on nepilysin expression and activity in SH-SYSY cells. *J. Neurochem.* 2009, 108, 1072–1082. [CrossRef] [PubMed]

17. Butterfield, D.; Mattson, M. Apolipoprotein E and oxidative stress in brain with relevance to Alzheimer’s disease. *Neurobiol. Dis.* 2020, 138, 104795. [CrossRef]

20. Puzzo, D.; Argyrousi, E.K.; Staniszewski, A.; Zhang, H.; Calcagno, E.; Zuccarello, E.; Acquarone, E.; Fa’, M.; et al. New insights into the pathogenesis of Alzheimer’s disease. *Front. Neurol.* 2020, 10, 1312. [CrossRef]

21. Ossenkoppele, R.; Jansen, W.J.; Rabinovici, G.D.; Knol, D.L.; van der Flier, W.M.; van Berckel, B.N.M.; Scheltens, P.; Visser, P.J. Prevalence of amyloid PET positivity in dementia syndromes: A meta-analysis. *JAMA* 2015, 313, 1939–1949. [CrossRef][PubMed]

22. Lewczuk, P.; Riederer, P.; O’Bryant, S.E.; Staniszewski, A.; Zhang, H.; Calcagno, E.; Zuccarello, E.; Acquarone, E.; Fa’, M.; Puma, D.D.L.; Grassi, C.; et al. Tau is not necessary for amyloid-beta-induced synaptic and memory impairments. *J. Clin. Investig.* 2020, 130, 4831–4844. [CrossRef]

23. Jin, W.S.; Bu, X.L.; Liu, Y.H.; Shen, L.L.; Zhuang, Z.Q.; Jiao, S.S.; Zhu, C.; Wang, Q.H.; Zhou, H.D.; Zhang, T.; et al. Plasma amyloid-beta levels in patients with different types of cancer. *Neurotox. Res.* 2017, 31, 283–288. [CrossRef]

24. Gronewold, J.; Klafki, H.W.; Baldelli, E.; Kaltwasser, B.; Seidel, U.K.; Todica, O.; Volsek, M.; Haussmann, U.; Wiltfang, J.; Kriiben, A.; et al. Factors responsible for plasma β-amyloid accumulation in chronic kidney disease. *Mol. Neurobiol.* 2016, 53, 3136–3145. [CrossRef]

25. Wang, Y.R.; Wang, Q.H.; Zhang, T.; Liu, Y.H.; Yao, X.Q.; Zeng, F.; Li, J.; Zhou, F.Y.; Wang, L.; Yan, J.C.; et al. Associations between hepatic functions and plasma amyloid-beta levels-implications for the capacity of liver in peripheral amyloid-beta clearance. *Mol. Neurobiol.* 2017, 54, 2338–2344. [CrossRef][PubMed]

26. Chojdak-Lukasiewicz, J.; Malodobra-Mazur, M.; Zimny, A.; Noga, L.; Paradowski, B. Plasma tau protein and Aβ42 level as markers of cognitive impairment in patients with Parkinson’s disease. *Adv. Clin. Exp. Med. Off. Organ Wrocl. Univ.* 2020, 29, 115–121. [CrossRef][PubMed]

27. Lee, Y.H.; Martin, J.M.; Maple, R.L.; Tharp, W.G.; Pratley, R.E. Plasma amyloid-beta peptide levels correlate with adipocyte amyloid precursor protein gene expression in obese individuals. *Neuroendocrinology* 2009, 89, 383–390. [CrossRef]

28. Startin, C.M.; Ashton, N.J.; Hamburg, S.; Hithersay, R.; Wiseman, F.K.; Mok, K.Y.; Hardy, J.; Lleó, A.; Lovestone, S.; Parnetti, L. Plasma biomarkers for amyloid, tau, and cytokines in Down syndrome and sporadic Alzheimer’s disease. *Alzheimers Res. Ther.* 2019, 11, 26. [CrossRef]

29. Yasuda, S.; Baba, H.; Maeshima, H.; Shimano, T.; Inoue, M.; Ichikawa, T.; Shukuzawa, H.; Suzuku, T.; Arai, H. Serum levels and mutual correlations of amyloid β in patients with depression. *Geriatr. Gerontol. Int.* 2020, 20, 125–129. [CrossRef]

30. Zhang, S.; Huang, S.Y.; An, X.B.; Zeng, L.; Ai, J. Medical histories of control subjects influence the biomarker potential of plasma Aβ in Alzheimer’s disease: A meta-analysis. *J. Mol. Neurosci.* 2020, 70, 861–870. [CrossRef]

31. Zhang, C.C.; Xing, A.; Tan, M.S.; Tan, L.; Yu, J.T. The role of MAPT in neurodegenerative diseases: Genetics, mechanisms and therapy. *Mol. Neurobiol.* 2016, 53, 4893–4904. [CrossRef][PubMed]

32. Castellani, R.J.; Perry, G. Tau Biology, Tauopathy, Traumatic Brain Injury, and Diagnostic Challenges. *J. Alzheimers Dis.* 2019, 67, 447–467. [CrossRef][PubMed]

33. Wu, X.L.; Piña-Crespo, J.; Zhang, Y.W.; Chen, X.C.; Xu, H.X. Tau-mediated neurodegeneration and potential implications in diagnosis and treatment of Alzheimer’s disease. *Clin. Med.* 2017, 130, 2978–2990. [CrossRef]
34. Tapia-Rojas, C.; Cabezas-Opazo, F.; Deaton, C.A.; Vergara, E.H.; Johnson, G.V.W.; Quintanilla, R.A. It’s all about tau. *Prog. Neurobiol.* 2019, 175, 54–76. [CrossRef]

35. Barthélémy, N.R.; Horie, K.; Sato, C.; Bateman, R.J. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer’s disease. *J. Exp. Med.* 2020, 217, e20200861. [CrossRef]

36. Irwin, D.J. Tauopathies as clinicopathological entities. *Parkinsonism Relat. Disord.* 2016, 22 (Suppl. 1), S29–S33. [CrossRef]

37. Llorens, F.; Villar-Piqué, A.; Candelise, N.; Ferrer, I.; Zerr, I. Tau protein as a biological fluid biomarker in neurodegenerative dementias. In *Cognitive Disorders*; Foyaca Sibat, H., Ed.; IntechOpen: London, UK, 2019. [CrossRef]

38. Choi, J.Y.; Yeo, I.J.; Kim, K.C.; Choi, W.R.; Jung, J.K.; Han, S.B.; Hong, J.T. K284-6111 prevents the... implications of YKL-40: Answers may lie in ‘outside-in’ signaling. *Cell Signal.* 2013, 25, 1567–1573. [CrossRef] [PubMed]

39. Di Rosa, M.; Malaguarnera, L. Chitinase 3 like-1: An emerging molecule involved in diabetes and diabetic complications. *Pathobiology* 2016, 83, 228–242. [CrossRef] [PubMed]

40. Park, J.C.; Han, S.H.; Yi, D.; Byun, M.S.; Lee, J.H.; Jang, S.; Ko, K.; Jeon, S.Y.; Lee, Y.S.; Kim, Y.K.; et al. Plasma tau/amyloid-β1-42 ratio predicts brain tau deposition and neurodegeneration in Alzheimer’s disease. *Brain* 2019, 142, 771–786. [CrossRef]

41. Calsolaro, V.; Edison, P. Neuroinflammation in Alzheimer’s disease: Current evidence and future directions. *Alzheimers Dement.* 2016, 12, 719–732. [CrossRef]

42. Mielke, M.M.; Hagen, C.E.; Xu, J.; Chai, X.; Vemuri, P.; Lowe, V.J.; Airey, D.C.; Knopman, D.S.; Roberts, R.O.; Machulda, M.M. Plasma phospho-tau181 increases with Alzheimer’s disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimers Dement.* 2018, 14, 989–997. [CrossRef]

43. Gispert, J.D.; Monté, G.C.; Suárez-Calvet, M.; Falcon, C.; Tucholka, A.; Rojas, S.; Rami, L.; Sánchez-Valle, R.; Lladó, A.; Kleinberger, G. The APOE ε4 genotype modulates CSF YKL-40 levels and their structural brain correlates in the continuum of Alzheimer’s disease but not those of sTREM2. *Alzheimers Dement.* 2016, 6, 50–59. [CrossRef] [PubMed]

44. Prakash, M.; Bosas, M.; Prakash, D.; Nawani, N.; Khetmalas, M.; Mandal, A.; Eriksson, C. Diverse pathological implications of YKL-40: Answers may lie in ‘outside-in’ signaling. *Cell Signal.* 2013, 25, 1567–1573. [CrossRef] [PubMed]

45. Craig-Schapiro, R.; Perrin, R.J.; Roe, C.M.; Xiong, C.; Carter, D.; Cairns, N.J.; Mintun, M.A.; Peskind, E.R.; Li, G.; Galasko, D.R. YKL-40: A novel prognostic fluid biomarker for preclinical Alzheimer’s disease. *Biol. Psychiatry* 2016, 88, 903–912. [CrossRef]

46. Llorens, F.; Thiüne, K.; Tahir, W.; Kanata, E.; Diaz-Lucena, D.; Xanthopoulos, K.; Kovatsi, E.; Pleschka, C.; Garcia-Esparcia, P.; Schmitz, M.; et al. YKL-40 in the brain and cerebrospinal fluid of neurodegenerative dementias. *Mol. Neurodegener.* 2017, 12, 83. [CrossRef] [PubMed]

47. Gispert, J.D.; Monté, G.C.; Suárez-Calvet, M.; Falcon, C.; Tucholka, A.; Rojas, S.; Rami, L.; Sánchez-Valle, R.; Lladó, A.; Kleinberger, G. The APOE ε4 genotype modulates CSF YKL-40 levels and their structural brain correlates in the continuum of Alzheimer’s disease but not those of sTREM2. *Alzheimers Dement.* 2016, 6, 50–59. [CrossRef] [PubMed]

48. Choi, J.Y.; Yeo, I.J.; Kim, K.C.; Choi, W.R.; Jung, J.K.; Han, S.B.; Hong, J.T. K284-6111 prevents the amyloid beta-induced neuroinflammation and impairment of recognition memory through inhibition of NF-κB-mediated CHI3L1 expression. *J. Neuroinflamm.* 2018, 15, 224. [CrossRef]

49. Akboğa, M.K.; Yalçın, R.; Şahinarslan, A.; Yılmaz Demirtaş, C.; Paşaoğlu, H.; Abaci, A. Increased serum YKL-40 level is associated with the presence and severity of metabolic syndrome. *Anatol. J. Cardiol.* 2016, 16, 953–958. [CrossRef] [PubMed]

50. Jia, Y.; Cao, J.N.; Wang, C.X.; Huan, X.H.; Xu, X.; Yang, C.J. High serum YKL-40 level positively correlates with coronary artery disease. *Biomark. Med.* 2017, 11, 133–139. [CrossRef] [PubMed]

51. Marott, S.C.; Benn, M.; Johansen, J.S.; Jensen, G.B.; Tybjærg-Hansen, A.; Nordestgaard, B.G. YKL-40 levels and atrial fibrillation in the general population. *Int. J. Cardiol.* 2013, 167, 1354–1359. [CrossRef]

52. Mutlu, L.C.; Tülbüş, F.; Alp, R.; Kaplan, G.; Yildiz, Z.D.; Gürel, A. Serum YKL-40 level is correlated with apnea hypopnea index in patients with obstructive sleep apnea syndrome. *Eur. Rev. Med. Pharmacol. Sci.* 2017, 21, 4161–4166. [PubMed]

53. Xu, T.; Zhong, C.; Wang, A.; Gou, Z.; Bu, X.; Zhou, Y.; Tian, Y.; Huang-Fu, X.; Zhu, Z.; Zhang, Y. YKL-40 is a novel biomarker for predicting hypertension incidence among prehypertensive subjects: A population-based nested case-control study in China. *Clin. Chim. Acta* 2017, 472, 146–150. [CrossRef] [PubMed]
54. Park, H.Y.; Jun, C.D.; Jeon, S.J.; Choi, S.S.; Kim, H.R.; Choi, D.B.; Kwak, S.; Lee, H.S.; Cheong, J.S.; So, H.S. Serum YKL-40 levels correlate with infarct volume, stroke severity, and functional outcome in acute ischemic stroke patients. *PloS ONE* **2012**, *7*, e51722. [CrossRef] [PubMed]

55. Sanfilippo, C.; Longo, A.; Lazzara, F.; Cambria, D.; Distefano, G.; Palumbo, M.; Cantarella, A.; Malaguarnera, L.; Di Rosa, M. CHI3L1 and CHI3L2 overexpression in motor cortex and spinal cord of sALS patients. *Mol. Cell. Neurosci.* **2017**, *85*, 162–169. [CrossRef] [PubMed]

56. Chung, C.; Tallerico, T.; Seeman, P. Schizophrenia hippocampus has elevated expression of chondrex glycoprotein gene. *Synapse* **2003**, *50*, 29–34. [CrossRef]

57. Rymo, I.; Kern, S.; Bjerke, M.; Zetterberg, H.; Marlow, T.; Blennow, K.; Gudmundsson, P.; Skoog, I.; Waern, M. CSF YKL-40 and GAP-43 are related to suicidal ideation in older women. *Acta Psychiatr. Scand.* **2017**, *135*, 351–357. [CrossRef] [PubMed]

58. Park, H.Y.; Jun, C.D.; Jeon, S.J.; Choi, S.S.; Kim, H.R.; Choi, D.B.; Kwak, S.; Lee, H.S.; Cheong, J.S.; So, H.S. Serum YKL-40 levels correlate with infarct volume, stroke severity, and functional outcome in acute ischemic stroke patients. *PloS ONE* **2012**, *7*, e51722. [CrossRef] [PubMed]

59. Isgren, A.; Sellgren, C.; Ekman, C.J.; Holm

60. Keshavan, A.; Heslegrave, A.; Zetterberg, H.; Schott, J.M. Blood biomarkers for Alzheimer’s disease: Much promise, cautious progress. *Mol. Diagn. Ther.* **2017**, *21*, 13–22. [CrossRef]

61. Hampel, H.; O’Bryant, S.E.; Molinuevo, J.L.; Zetterberg, H.; Masters, C.L.; Lista, S.; Kiddle, S.J.; Battrla, R.; Blennow, K. Blood-based biomarkers for Alzheimer disease: Mapping the road to the clinic. *Nat. Rev. Neurol.* **2018**, *14*, 639–652. [CrossRef]

62. Olsson, B.; Lautner, R.; Andreasson, U.; Öhrfelt, A.; Portelius, E.; Bjerke, M.; Hölttä, M.; Rosén, C.; Olsson, C.; Strobel, G.; et al. CSF and blood biomarkers for the diagnosis of Alzheimer’s disease: A systematic review and meta-analysis. *Lancet Neurol.* **2016**, *15*, 673–684. [CrossRef]

63. Thijssen, E.H.; La Joie, R.; Wolf, A.; Strom, A.; Wang, P.; Iacarrino, L.; Bourakova, V.; Cobigo, Y.; Heuer, H.; Spina, S.; et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer’s disease and frontotemporal lobar degeneration. *Nat. Med.* **2020**, *26*, 387–397. [CrossRef] [PubMed]

64. Blennow, K.; Zetterberg, H. Biomarkers for Alzheimer’s disease: Current status and prospects for the future (Review). *J. Intern. Med.* **2018**, *284*, 643–663. [CrossRef] [PubMed]

65. Bispo, M.; Esselmann, H.; Mollenhauer, B.; Weniger, G.; Welge, V.; Liess, M.; Lewczuk, P.; Otto, M.; Schulz, J.B.; Trenkwalder, C.; et al. Blood-based neurochemical diagnosis of vascular dementia: A pilot study. *J. Neurochem.* **2007**, *103*, 467–474. [CrossRef]

66. Kim, K.; Kim, M.J.; Kim, D.W.; Kim, S.Y.; Park, S.; Park, C.B. Clinically accurate diagnosis of Alzheimer’s disease via multiplexed sensing of core biomarkers in human plasma. *Nat. Commun.* **2020**, *11*, 119. [CrossRef]

67. Mehta, P.D.; Pirttilä, T.; Mehta, S.P.; Sersen, E.A.; Aisen, P.S.; Wisniewski, H.M. Plasma and cerebrospinal fluid levels of amyloid beta proteins 1-40 and 1-42 in Alzheimer disease. *Lancet Neurol.* **2003**, *2*, 53–58. [CrossRef]

68. Sobow, T.; Flirski, M.; Kloszewska, I.; Liberski, P.P. Plasma levels of Aβ peptides are altered in amnestic mild cognitive impairment but not in Alzheimer’s disease. *Acta Neurol. Exp.* **2005**, *65*, 117–124.

69. Pesaresi, M.; Lovati, C.; Bertora, P.; Mailland, E.; Galimberti, D.; Scarpini, E.; Quadri, P.; Forloni, G.; Mariani, C. Plasma levels of beta-amyloid (1-42) in Alzheimer’s disease and mild cognitive impairment. *Neurobiol. Aging* **2006**, *27*, 904–905. [CrossRef]

70. Fagan, A.M.; Roe, C.M.; Xiong, C.; Mintun, M.A.; Morris, J.C.; Holtzman, D.M. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Arch. Neurol.* **2007**, *64*, 343–349. [CrossRef]

71. Abdullah, L.; Paris, D.; Luís, C.; Quadros, A.; Parrish, J.; Valdes, L.; Keepan, A.P.; Mathura, V.; Crawford, F.; Mullan, M. The influence of diagnosis, intra- and inter-person variability on serum and plasma Abeta levels. *Neurosci. Lett.* **2007**, *428*, 53–58. [CrossRef]

72. Baranowska-Bik, A.; Bik, W.; Wolinska-Witort, E.; Martynska, L.; Chmielowska, M.; Barcikowska, M.; Baranowska, B. Plasma beta amyloid and cytokine profile in women with Alzheimer’s disease. *Neuroendocrinol. Lett.* **2008**, *29*, 75–79. [PubMed]
73. Xu, W.; Kawarabayashi, T.; Matsubara, E.; Deguchi, K.; Murakami, T.; Harigaya, Y.; Ikeda, M.; Amari, M.; Kuvano, R.; Abe, K.; et al. Plasma antibodies to Abeta40 and Abeta42 in patients with Alzheimer’s disease and normal controls. Brain Res. 2008, 1219, 169–179. [CrossRef] [PubMed]

74. Ait-Ghezala, G.; Abdullah, L.; Volmar, C.H.; Paris, D.; Luis, C.A.; Quadros, A.; Mouzon, B.; Mullan, M.A.; Keegan, A.P.; Parrish, J.; et al. Diagnostic utility of APOE, soluble CD40, CD40L, and Abeta1-40 levels in plasma in Alzheimer’s disease. Cytokine 2008, 44, 283–287. [CrossRef] [PubMed]

75. Roher, A.E.; Esh, C.L.; Kokjohn, T.A.; Castaño, E.M.; Van Vickle, G.D.; Patton, L.; Luehrs, D.C.; Daugs, I.D.; Kuo, Y.M.; et al. Amyloid beta peptides in human plasma and tissues and their significance for Alzheimer’s disease. Alzheimers Dement. 2009, 5, 18–29. [CrossRef] [PubMed]

76. Sedaghat, F.; Dedousi, E.; Costa, V.; Dimitriadi, A.S.; Baloyannis, S.J. Plasma levels of amyloid beta1-42 are independent of neuronal function in Alzheimer’s disease. J. Alzheimers Dis. 2009, 17, 343–348. [CrossRef] [PubMed]

77. Luis, C.A.; Abdullah, L.; Paris, D.; Quadros, A.; Mullan, M.; Mouzon, M.; Ait-Ghezala, G.; Crawford, F.; Mullan, M. Serum beta-amyloid correlates with neuropsychological impairment. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 2009, 16, 203–218. [CrossRef]

78. Cammarata, S.; Borghi, R.; Giliberto, L.; Pardini, M.; Pollero, V.; Novello, C.; Fornato, M.; Vitali, A.; Bracco, L.; Caltagirone, C.; et al. Amyloid-beta42 plasma levels are elevated in amnestic mild cognitive impairment. J. Alzheimers Dis. 2009, 18, 267–271. [CrossRef]

79. Lui, J.K.; Laws, S.M.; Li, Q.X.; Villemagne, V.L. Plasma amyloid-beta as a biomarker in Alzheimer’s disease: The AIBL study of aging. J. Alzheimers Dis. 2010, 20, 1233–1242. [CrossRef]

80. Konno, T.; Hata, S.; Hamada, Y.; Horikoshi-Sakuraba, Y.; Nakaya, T.; Saito, Y.; Yamamoto, T.; Yamamoto, T.; Maeda, M.; Ikeuchi, T.; et al. Coordinated increase of γ-secretase reaction products in the plasma of some female Japanese sporadic Alzheimer’s disease patients: Quantitative analysis of p3-Alcα with a new ELISA system. Mol. Neurodegener. 2011, 6, 76. [CrossRef]

81. Han, Y.; Jia, J.; Jia, X.F.; Qin, W.; Wang, S. Combination of plasma biomarkers and clinical data for the detection of sporadic Alzheimer’s disease. Neurosci. Lett. 2012, 516, 232–236. [CrossRef]

82. Zhang, J.; Jia, J.; Qin, W.; Wang, S. Combination of plasma tumor necrosis factor receptors signaling proteins, beta-amyloid and apolipoprotein E for the detection of Alzheimer’s disease. Neurosci. Lett. 2013, 541, 99–104. [CrossRef]

83. Huang, C.W.; Wang, S.J.; Wu, S.J.; Yang, C.C.; Huang, M.W.; Lin, C.H.; Cheng, I.H. Potential blood biomarker for disease severity in the Taiwanese population with Alzheimer’s disease. Am. J. Alzheimers Dis. Other Dement. 2013, 28, 75–83. [CrossRef] [PubMed]

84. Ruiz, A.; Pesini, P.; Espinosa, A.; Pérez-Grijalba, V.; Valero, S.; Sotolongo-Grau, O.; Alegret, M.; Monleón, I.; Laufente, A.; Buendia, M.; et al. Blood amyloid beta levels in healthy, mild cognitive impairment and Alzheimer’s disease individuals: Replication of diastolic blood pressure correlations and analysis of critical covariates. PLoS ONE 2013, 8, e81334.

85. Wang, T.; Xiao, S.; Liu, Y.; Lin, Z.; Su, N.; Li, X.; Li, G.; Zhang, M.; Fang, Y. The efficacy of plasma biomarkers in early diagnosis of Alzheimer’s disease. Int. J. Geriatr. Psychiatry 2014, 29, 713–719. [CrossRef]

86. Tzikas, S.; Schlak, D.; Sopova, K.; Gatsiou, A.; Stakos, D.; Stamatelopoulos, K.; Stellos, K.; Laske, C. Increased myeloperoxidase plasma levels in patients with Alzheimer’s disease. J. Alzheimers Dis. 2014, 39, 557–564. [CrossRef] [PubMed]

87. Krishnan, S.; Rani, P. Evaluation of selenium, redox status and their association with plasma amyloid/tau in Alzheimer’s disease. Biol. Trace Elem. Res. 2014, 158, 158–165. [CrossRef] [PubMed]

88. Kleinschmidt, M.; Schoenfeld, R.; Göttlich, C.; Bittner, D.; Metzner, J.E.; Leplow, B.; Demuth, H.U. Characterizing aging, mild cognitive impairment, and dementia with blood-based biomarkers and neuropsychology. J. Alzheimers Dis. 2016, 50, 111–126. [CrossRef] [PubMed]

89. Jiao, S.; Bu, X.; Liu, Y.; Wang, Q.H.; Liu, C.H.; Yao, X.Q.; Zhou, X.F.; Wang, Y.J. Differential levels of p75NTR ectodomain in CSF and blood in patients with Alzheimer’s disease: A novel diagnostic marker. Transl. Psychiatry 2015, 5, e650. [CrossRef]

90. Igarashi, K.; Yoshida, M.; Waragai, M.; Kashiwagi, K. Evaluation of dementia by acrolein, amyloid-β and creatinine. Clin. Chim. Acta 2015, 450, 56–63. [CrossRef]
91. Kim, H.J.; Park, K.W.; Kim, T.E.; Im, J.Y.; Shin, H.S.; Kim, S.; Lee, D.H.; Ye, B.H.; Kim, J.H.; Kim, E.J.; et al. Elevation of the plasma Aβ40/Aβ42 ratio as a diagnostic marker of sporadic early-onset Alzheimer’s disease. *J. Alzheimers Dis.* 2015, 48, 1043–1050. [CrossRef]  
92. Poljak, A.; Crawford, J.D.; Smythe, G.A.; Brodaty, H.; Slavin, M.J.; Kochan, N.A.; Trollor, J.N.; Wen, W.; Mather, K.A.; Assareh, A.A.; et al. The relationship between plasma Aβ levels, cognitive function and brain volumetrics: Sydney memory and ageing study. *Curr. Alzheimer Res.* 2016, 13, 243–255. [CrossRef] [PubMed]  
93. Grewal, R.; Haghhighi, M.; Huang, S.; Smith, A.G.; Cao, C.; Lin, X.; Lee, D.C.; Teten, N.; Hill, A.M.; Selenica, M.L.B. Identifying biomarkers of dementia prevalent among amnestic mild cognitively impaired ethnic female patients. *Alzheimers Res. Ther.* 2016, 8, 43. [CrossRef] [PubMed]  
94. Yamashita, S.; Kiko, T.; Fujiwara, H.; Hashimoto, M.; Nakagawa, K.; Kinoshita, M.; Furukawa, K.; Arai, H.; Miyazawa, T. Alterations in the levels of amyloid-β, phospholipid hydroperoxide, and plasmalogens in the blood of patients with Alzheimer’s disease: Possible interactions between amyloid-β and these lipids. *J. Alzheimers Dis.* 2016, 50, 527–537. [CrossRef] [PubMed]  
95. Rani, P.; Krishnan, S.; Rani Cathrine, C. Study on analysis of peripheral biomarkers for Alzheimer’s disease. *Front. Neurol.* 2017, 8, 328. [CrossRef]  
96. Sun, H.L.; Li, W.W.; Zhu, C.; Jin, W.S.; Liu, Y.H.; Zeng, F.; Wang, Y.J.; Bu, X.L. The correlations of plasma proteins in patients with Alzheimer’s disease compared to healthy controls. *J. Alzheimers Dis.* 2016, 50, 1223–1230. [CrossRef]  
97. Chou, C.T.; Liao, Y.C.; Lee, W.J.; Wang, S.J.; Fuh, J.L. SORL1 gene, plasma biomarkers, and the risk of Alzheimer’s disease. *Curr. Alzheimer Res.* 2012, 9, 1142–1148. [CrossRef] [PubMed]  
98. Le Bastard, N.; Aerts, L.; Leurs, J.; Blomme, W.; De Deyn, P.P.; Engelborghs, S. No correlation between time-linked plasma and CSF Aβ levels. *Neurochem. Int.* 2009, 55, 820–825. [CrossRef]  
99. Le Bastard, N.; Leurs, J.; Blomme, W.; De Deyn, P.P.; Engelborghs, S. Plasma amyloid-beta forms in Alzheimer’s disease and non-Alzheimer’s disease patients. *J. Alzheimers Dis.* 2010, 21, 291–301. [CrossRef]  
100. Hanon, O.; Vidal, J.S.; Lehmann, S.; Bombois, S.; Allinquant, B.; Trélu, J.M.; Gelé, P.; Delmaire, C.; Blanc, F.; Mangin, J.F.; et al. Plasma amyloid levels within the Alzheimer’s process and correlations with central biomarkers. *Alzheimers Dement.* 2018, 14, 858–868. [CrossRef] [PubMed]  
101. Uslu, S.; Akarkarasu, Z.E.; Ozbabalik, D.; Ozkan, S.; Colak, O.; Demirkan, E.S.; Ozkiris, A.; Demirustu, C.; Alatas, O. Levels of amyloid beta-42, interleukin-6 and tumor necrosis factor-alpha in Alzheimer’s disease and vascular dementia. *Neurochem. Res.* 2012, 37, 1554–1559. [CrossRef]  
102. Hsu, J.L.; Lee, W.J.; Liao, Y.C.; Lirng, J.F.; Wang, S.J.; Fuh, J.L. Plasma biomarkers are associated with agitation and regional brain atrophy in Alzheimer’s disease. *Sci. Rep.* 2017, 7, 5035. [CrossRef]  
103. Hanon, O.; Vidal, J.S.; Lehmann, S.; Bombois, S.; Allinquant, B.; Trélu, J.M.; Gelé, P.; Delmaire, C.; Blanc, F.; Mangin, J.F.; et al. Plasma amyloid levels within the Alzheimer’s process and correlations with central biomarkers. *Alzheimers Dement.* 2018, 14, 858–868. [CrossRef] [PubMed]  
104. Lee, N.C.; Yang, S.Y.; Chieh, J.J.; Huang, P.T.; Chang, L.M.; Chiu, Y.N.; Huang, A.C.; Chien, Y.H.; Hwu, W.L.; Chiu, M.J. Blood beta-amyloid and tau in Down syndrome: A comparison with Alzheimer’s disease. *Front. Aging Neurosci.* 2016, 8, 316. [CrossRef] [PubMed]  
105. Teunissen, C.E.; Chiu, M.J.; Yang, C.C.; Yang, S.H.; Scheltens, P.; Zetterberg, H.; Blennow, K. Plasma amyloid-β (Aβ42) correlates with cerebrospinal fluid Aβ42 in Alzheimer’s disease. *J. Alzheimers Dis.* 2018, 62, 1857–1863. [CrossRef]  
106. Tang, S.C.; Yang, K.C.; Chen, C.H.; Yang, S.Y.; Chiu, M.J.; Wu, C.C.; Jeng, J.S. Plasma β-amyloids and tau proteins in patients with vascular cognitive impairment. *Neuromol. Med.* 2018, 20, 498–503. [CrossRef]
110. Fan, L.Y.; Tzen, K.Y.; Chen, Y.F.; Chen, T.F.; Lai, Y.M.; Yen, R.F.; Huang, Y.Y.; Shiue, C.Y.; Yang, S.Y.; Chiu, M.J. The relation between brain amyloid deposition, cortical atrophy, and plasma biomarkers in amnestic mild cognitive impairment and Alzheimer’s disease. *Front. Aging Neurosci.* **2018**, *10*, 175. [CrossRef]

111. Tsai, C.L.; Liang, C.S.; Lee, J.T.; Su, M.W.; Lin, C.C.; Chu, H.T.; Tsai, C.K.; Lin, G.Y.; Lin, Y.K.; Yang, F.C. Associations between plasma biomarkers and cognition in patients with Alzheimer’s disease and amnestic mild cognitive impairment: A cross-sectional and longitudinal study. *J. Clin. Med.* **2019**, *8*, 1893. [CrossRef]

112. Janelidze, S.; Stomrud, E.; Palmqvist, S.; Zetterberg, H.; van Westen, D.; Jeromin, A.; Song, L.; Hanlon, D.; Tan Hehir, C.A.; Baker, D.; et al. Plasma β-amyloid in Alzheimer’s disease and vascular disease. *Sci. Rep.* **2016**, *6*, 26801. [CrossRef] [PubMed]

113. Shi, Y.; Lu, X.; Zhang, L.; Shu, H.; Gu, L.; Wang, Z.; Gao, L.; Zhu, J.; Zhang, H.; Zhou, D.; et al. Potential value of plasma amyloid-β, total tau, and neurofilament light for identification of early Alzheimer’s disease. *ACS Chem. Neurosci.* **2019**, *10*, 3479–3485. [CrossRef] [PubMed]

114. Mattsson, N.; Zetterberg, H.; Janelidze, S.; Insel, P.S.; Andresson, U.; Stomrud, E.; Palmqvist, S.; Baker, D.; Tan Hehir, C.A.; Jeromin, A.; et al. Plasma tau in Alzheimer disease. *Neurology* **2016**, *87*, 1827–1835. [CrossRef] [PubMed]

115. Foiani, M.S.; Woollacott, I.O.; Heller, C.; Bocchetta, M.; Heslegrave, A.; Dick, K.M.; Russell, L.L.; Marshall, C.R.; Mead, S.; Schott, J.M.; et al. Plasma tau is increased in frontotemporal dementia. *J. Neurol. Neurosurg. Psychiatry* **2018**, *89*, 804–807. [CrossRef] [PubMed]

116. Chiu, M.J.; Chen, Y.F.; Chen, T.F.; Yang, S.H.; Yang, F.P.G.; Tseng, T.W.; Chieh, J.J.; Rare Chen, J.C.; Tzen, K.Y.; Huai, M.S.; et al. Plasma tau as a window to the brain-negative associations with brain volume and memory function in mild cognitive impairment and early Alzheimer’s disease. *Hum. Brain Mapp.* **2014**, *35*, 3132–3142. [CrossRef] [PubMed]

117. Yang, C.C.; Chiu, M.J.; Chen, T.F.; Chang, H.L.; Liu, B.H.; Yang, S.Y. Assay of plasma phosphorylated tau protein (threonine 181) and total tau protein in early-stage Alzheimer’s disease. *J. Alzheimers Dis.* **2018**, *61*, 1323–1332. [CrossRef] [PubMed]

118. Shekhar, S.; Kumar, R.; Rai, N.; Kumar, V.; Singh, K.; Upadhay, A.D.; Tripathi, M.; Dwivedi, S.; Dey, A.B.; Dey, S. Estimation of tau and phosphorylated tau181 in serum of Alzheimer’s disease and mild cognitive impairment patients. *PLoS ONE* **2016**, *11*, e0159099. [CrossRef]

119. Jiang, T.; Gong, P.Y.; Tan, M.S.; Xue, X.; Huang, S.; Zhou, J.S.; Tan, L.; Zhang, Y.D. Soluble TREM1 concentrations are increased and positively correlated with total tau levels in the plasma of patients with Alzheimer’s disease. *Aging Clin. Exp. Res.* **2019**, *31*, 1801–1805. [CrossRef]

120. Dage, J.L.; Wennberg, A.M.V.; Airey, D.C.; Hagen, C.E.; Knopman, D.S.; Machulda, M.M.; Roberts, R.O.; Jack, C.R., Jr.; Petersen, R.C.; Mielke, M.M. Levels of tau protein in plasma are associated with neurodegeneration and cognitive function in a population-based elderly cohort. *Alzheimers Dement.* **2016**, *12*, 1226–1234. [CrossRef]

121. Mielke, M.M.; Hagen, C.E.; Wennberg, A.M.V.; Airey, D.C.; Savica, R.; Knopman, D.S.; Machulda, M.M.; Roberts, R.O.; Jack, C.R., Jr.; Petersen, R.C.; et al. Association of plasma total tau level with cognitive decline and risk of mild cognitive impairment or dementia in the Mayo Clinic study on aging. *JAMA Neurol.* **2017**, *74*, 1073–1080. [CrossRef]

122. Deters, K.D.; Risacher, S.L.; Kim, S.; Nho, K.; West, J.D.; Blennow, K.; Zetterberg, H.; Shaw, L.M.; Trojanowski, J.Q.; Weiner, M.W.; et al. Plasma tau association with brain atrophy in mild cognitive impairment and Alzheimer’s disease. *J. Alzheimers Dis.* **2017**, *58*, 1245–1254. [CrossRef] [PubMed]

123. Chiu, M.J.; Yang, S.Y.; Horng, H.E.; Yang, C.C.; Chen, T.F.; Chieh, J.J.; Chen, H.H.; Chen, T.C.; Ho, C.S.; Chang, S.F.; et al. Combined plasma biomarkers for diagnosing mild cognition impairment and Alzheimer’s disease. *ACS Chem. Neurosci.* **2013**, *4*, 1530–1536. [CrossRef] [PubMed]

124. Choi, J.; Lee, H.W.; Suk, K. Plasma level of chitinase 3-like 1 protein increases in patients with early Alzheimer’s disease. *J. Neurol.* **2011**, *258*, 2181–2185. [CrossRef]

125. Surendranathan, A.; Su, L.; Mak, E.; Passamonti, I.; Hong, Y.T.; Arnold, R.; Rodriguez, P.V.; Bevan-Jones, W.R.; Brain, S.A.E.; Fryer, T.; et al. Early microglial activation and peripheral inflammation in dementia with Lewy bodies. *Brain* **2018**, *141*, 3415–3427. [CrossRef] [PubMed]

126. Villar-Fiqué, A.; Schmitz, M.; Hermann, P.; Goebel, S.; Bunck, T.; Varges, D.; Ferrer, I.; Riggert, J.; Llorens, F.; Zerr, I. Plasma YKL-40 in the spectrum of neurodegenerative dementia. *J. Neuroinflamm.* **2019**, *16*, 145. [CrossRef]
127. Kim, J.W.; Byun, M.S.; Sohn, B.K.; Yi, D.; Seo, E.H.; Choe, Y.M.; Kim, S.G.; Choi, H.J.; Lee, J.H.; Chee, I.S.; et al. Clinical dementia rating orientation score as an excellent predictor of the progression to Alzheimer’s disease in mild cognitive impairment. *Psychiatry Investig.* **2017**, *14*, 420–426. [CrossRef]

128. Roberts, R.; Knopman, D.S. Classification and epidemiology of MCI. *Clin. Geriatr. Med.* **2013**, *29*, 753–772. [CrossRef]

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