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Biomarker Mild Cognitive Impairment in Older Adults: A Review

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ABSTRACT

Dementia and other neurodegenerative diseases are on the rise due to an ageing population; moderate cognitive impairment (MCI) is a precursor to the more serious illness. Measurable cognitive impairments that do not meet the dementia diagnostic criteria characterise mild cognitive impairment (MCI), with an annual conversion rate to dementia of 10–15%. Early detection is critical to mitigating this progression, yet standardized diagnostic criteria are lacking. This review investigates the role of plasma biomarkers, including BDNF, vascular endothelial growth factor (VEGF), microRNA (miRNA), and neurofilament light chain (NfL), in the detection and prediction of MCI in elderly populations.

A systematic literature search identified 11 studies published between 2014 and 2024 that met inclusion criteria. Evidence suggests that BDNF, a neurotrophin essential for synaptic plasticity, learning, and memory, is downregulated in MCI patients, though compensatory elevation in preclinical stages of dementia has been observed. VEGF, implicated in neuroprotection and angiogenesis, demonstrated inconsistent levels in MCI. Circulating miRNAs, including miR-206 and miR-132, were significantly upregulated in MCI, disrupting neuroprotective pathways through BDNF and SIRT1 downregulation. NfL, a biomarker of axonal injury, was consistently elevated in MCI patients and showed improved diagnostic specificity when combined with phosphorylated tau.

These findings underscore the potential of plasma biomarkers in improving early diagnostic precision for MCI. Integration of molecular markers into clinical frameworks could enhance screening efficacy and therapeutic targeting, though further research is necessary to standardize their application in routine medical practice.

Keywords: Biomarkers; Mild Cognitive Impairment

INTRODUCTION

Population aging is a global phenomenon experienced by almost every country worldwide. In 2019, there are 703 million individuals worldwide who are 65 or older, and experts predict that number will reach 1.5 billion by the year 2050.[1] Assuming the ageing population maintains its current levels of health, activity, and productivity, this growth might have beneficial effects. However, population aging also presents numerous challenges, particularly in the health sector. The increasing trend in life expectancy is accompanied by a rise in the

prevalence of non-communicable diseases, including dementia.[2,3] The prevalence of dementia is higher in low- and middle-income countries compared to high-income countries, making it one of the leading causes of death among the elderly population, especially women.[3]

MCI refers to cognitive deficits that do not meet the criteria for dementia.[4] MCI represents a transitional stage between normal cognitive function and dementia. A key outcome of MCI is the increased risk of progression to dementia. In some cases, individuals with MCI may regain normal cognitive function; however, in most cases, MCI either remains stable or progresses to dementia. The progression rate from MCI to dementia ranges between 20–40% (10–15% per year).[5] Thus, early detection of cognitive impairment in the elderly is crucial to prevent progression to dementia.

To date, there is no standardized criterion for diagnosing MCI. In addition to cognitive assessments using tools such as the Brief Interview for Mental Status, Mini-Mental State Examination (MMSE), and Brief Cognitive Assessment Tool, several criteria have been developed to facilitate the early detection of MCI. These include criteria from the National Institute on Aging-Alzheimer's Association for detecting MCI related to Alzheimer's disease and Mayo Clinic criteria.[4,5] These diagnostic frameworks rely on symptomatology and cognitive function assessments.

In recent decades, various biological substances and imaging modalities with potential as biomarkers for diagnosing MCI have been extensively investigated. These efforts have yielded promising results in improving early detection and diagnosis of MCI in the elderly population. This review aims to further explore the role of several biomarkers, particularly plasma biomarkers such as BDNF, VEGF, microRNA (miRNA), and neurofilament light chain (NfL), in predicting MCI in the elderly population.

MATERIALS & METHODS

This article reviews data from previously published studies on biomarkers for MCI. A literature search was carried out using a variety of databases, one of which being PubMed, Google Scholar, ScienceDirect, and EBSCO, using search terms such as "biomarker and MCI," "brain-derived neurotrophic factor/BDNF and MCI," "vascular endothelial growth factor/VEGF and MCI," "microRNA/miRNA and mild cognitive impairment," and "neurofilament light chain/NfL and MCI," along with other relevant phrases. Inclusion criteria include: 1) articles written in English, 2) studies comparing plasma biomarker levels in elderly individuals with cognitive impairment (MCI and/or Alzheimer's disease) to a control group (without cognitive impairment), and 3) published from 2014-2024. Exclusion criteria include: 1) articles that were not accessible in full text, 2) systematic reviews, meta-analyses, case reports, or case series, and 3) articles with incomplete data.

RESULT

The initial search yielded a total of 383 articles. After removing duplicates and screening abstracts, 293 articles were selected for eligibility assessment. Ultimately, 11 research articles were included in the review, as shown in Table 1. These studies evaluated biomarkers for diagnosing or predicting MCI in elderly individuals compared to healthy controls (without cognitive impairment).

Table 1. Studies Investigating Biomarkers for Detecting or Predicting MCI

Author and year of publication	Sample	Measurement/Comparison	Result	Conclusion
Ng et al[14], 2021	160 participants: 56 healthy controls (HC) 40 MCI cohort 64 CP cohort Health control: participants in the Montreal Cognitive Assessment (MoCA) MCI cohort who are 60–85 years old and have a minimum score of 22 points: people who are 65 and older who meet the DSM-V operational criteria for mild cognitive impairment.	Blood samples were collected from each participant, and plasma biomarkers (BDNF, hs-CRP, and DHEA-S) levels were measured using ELISA kits. We assessed cognitive processes using neurocognitive tests with established content validity; higher scores indicate superior cognitive ability.	• Plasma BDNF was significantly increased in MCI (3.19±0.51 pg/mL) compared to HC (2.34±0.51, p<0,001) • Cognitive test scores were shown to be considerably lower in those with greater plasma BDNF levels. • For all-cause MCI, plaque BDNF showed fair accuracy (AUC=0.84, 95% CI=0.74-0.95, p<0.001), and for non-amnestic MCI, it demonstrated outstanding discriminative accuracy (AUC=0.92, 95% CI=0.84-1.00, p<0.001).	• It seems that plasma BDNF is a good biomarker for differentiating between MCI and non-aMCI, and it's also an excellent biomarker. • In preclinical dementia, a rise in BDNF is seen as a compensatory strategy.
Siuda et al[12], 2017	134 individuals with Alzheimer's disease 115 people with amnestic mild cognitive impairment There were 129 controls in all, with 80 categorised as cognitively normal and 49 as neurodegenerative. The Mayo Clinic Group criteria for MCI, the DSM-IV criteria for dementia (AD), and the NINCDS-ADRDA criteria for Alzheimer's disease (AD) were used for diagnosis.	Cognitive evaluation: the Sunderland approach was used to grade the Clock Drawing Test and the Mini-Mental State Exam, both of which measure general cognitive state. A battery of comprehensive cognitive evaluations was also conducted. An ELISA kit was used to assess the serum BDNF level from blood samples that were obtained.	• The BDNF serum levels of MCI patients were noticeably lower than those of the CN control group (P<0.05). • The BDNF blood levels of AD patients were noticeably lower (p<0.001) in comparison to the controls, who were MCI, CN, and ND.	Like Alzheimer's disease, BDNF serum level is likely influenced by a neurodegenerative process.
Forlenza et al[11], 2015	134 older adults: 26 with mild to moderate AD; 62 with MCI; 46 cognitively healthy older adults (control)	Blood samples were taken, and serum biomarkers (BDNF, GDNF, NGF) levels were measured using ELISA kits	• Control: BDNF (pg/ml): 844.6±688.5 NGF (pg/ml): 45.0±37.1 GDNF (pg/ml): 50.0±63.2 • Patients with MCI:	As potential indicators of disease progression, measuring blood concentrations of BDNF and NGF may aid in the

	AD diagnosis was established according to NINCDS-ADRDA criteria; MCI diagnosis was made according to Mayo Clinic criteria.		BDNF (pg/ml): 510.0±270.9 NGF (pg/ml): 15.5±12.7 GDNF (pg/ml): 26.1±14.8 • Patients with AD: BDNF (pg/ml): 666.5±491.0 NGF (pg/ml): 19.3±31.9 GDNF (pg/ml): 21.0±14.2 • Patients with MCI and AD had significantly lower serum biomarkers as compared to control (P=0.003, P<0.001 and P<0.001, respectively). • Patients with MCI who eventually developing AD had significantly lower baseline serum concentrations of BDNF (p=0,02)	identification of individuals with a greater risk of developing dementia along the MCI-AD continuum.
Serrano et al[16], 2021	67 older adults with HIV divided into two groups aMCI (+) and aMCI (-) using adapted Jak/Bondi criteria	Blood samples were taken, and serum VEGF level was measured using commercial immunoassay kit (VEGF-A, VEGF-C, VEGF-D and PIGF) in duplicate in EDTA-treated plasma	The aMCI (+) group had lower VEGF-D levels compared to aMCI (-) group (P=0.01)	PWH were shown to have an association between VEFG-D and aMCI status.
Shen et al[15], 2019	114 subjects: 57 MCI patients 57 normal controls MCI was diagnosed based on criteria advocated by Peterson and colleagues. Normal control requires SM-MMSE score ≥28	A total of twenty-one biomarkers, including VEFG-A, hormones, metabolites, cytokines, and chemokines were subjected to quantitative investigations.	Among others, serum VEGF-A level was significantly lower in MCI compared to control (41.55±24.43 pg/ml vs. 56.49±37.95 pg/ml, P=0.042)	Inflammatory and meta-vascular changes involving VEFG-A contributed to the development of MCI, but further research is needed to establish whether this marker has clinical diagnostic potential and to understand the mechanism by which it works.
Callahan et al[17], 2020	49 older adults: 20 were Cognitively normal (CN); 17 were diagnosed with aMCI; 12 were diagnosed with AD	Serum angiogenesis biomarkers (VEGF, TNFα, FGF2 and amyloid-β peptide 40) were measured using ELISA kits	Serum VEGF level was higher in MCI (84.38±52.35) and AD (53.76±47.57) compared to normal subjects (43.38±25.24, P=0.0167)	VEGF might be associated with MCI, but this association still needs to be explored
Xie et al[19], 2015	142 subjects:	Micro-RNAs were detected from	• MiR-206, miR-132, miR-193b,	For a highly sensitive and

	66 with MCI 76 normal controls MCI was diagnoses according to Peterson's criteria	blood samples using quantitative real-time PCR (qPCR) Serum BDNF and sirtuin 1 (SIRT1) levels were measured by the ELISA method	miR-130b, miR-20a, miR-296, and miR-329 were among the seven microRNAs found in the two sets of samples. • In MCI patients, compared to the control group, there was a substantial upregulation of miR-206 (P<0.01) and miR-132 (P<0.01). • miR-132 had the highest AUC (0.912, 95% CI=0.853-0.953), followed by miR-206 (AUC 0.880, 95%CI=0.815-0.928), and combination of both miRNAs (AUC 0.981, 95% CI=0.942-0.996) for diagnosis MCI.	precise diagnosis of MCI, a new biomarker that combines miR-206 and miR-132 detection would be ideal.
Salama et al[20], 2020	163 adults with T2DM 102 nondiabetic apparently healthy normal cognition individuals (control) MCI was diagnosed based on the objective impairment in one or more cognitive domains assessed using Adenbrooke's Cognitive Examination (ACE) III	Serum miRNAs (miR-128, miR-132, miR-874, miR-134, miR-323 and miR-382) expressions were assessed using qPCR	• 59 (36.2%) T2DM patients had MCI. • Median miR-132 expression was noticeably greater in type 2 diabetes patients with MCI when contrasted with normal-cognitive and non-diabetic persons (P<0.05). • A 72.3% specificity rate, 56.2% specificity, and 63.8% accuracy (P<0.05) were achieved by miR-132 in distinguishing between T2DM patients with MCI and those with normal cognition.	Overexpression of miR-132 could detect MCI in T2DM individuals with sensitivity and specificity <75%
Sheinerman et al[21], 2013	50 MCI patients 50 age-matched controls (AMC)	Concentrations of 8 miRNAs (4 from miR-132 family, and 4 were from miR-134 family) measured by RT-qPCR analysis	The accuracy for differentiating MCI from AMC is 90-96% for the biomarker miRNA pairs of miR-132 and miR-134, whereas the miR-370 and miR-13 families, together with miR-491-5p, serve as	The early identification of MCI has been confirmed by two groups of plasma biomarker miRNAs: the miR-132 family and the miR-134 family.

			very sensitive biomarkers for MCI identification.	
Jing et al[23], 2024	157 subjects 97 healthy older adults with normal cognition (HC) 60 with cognitive impairment (44 in MCI group and 16 in probable AD group) Criteria for the diagnosis of MCI were based on a 2006 agreement by the Chinese Expert Group on Cognitive Impairment Prevention and Treatment. The NINCDS-ADRDA criteria were used to diagnose probable AD.	Serum NfL, IL-1β, IL-6, TNF-α, Amyloid-β40 (Aβ40), Aβ42, and phosphorylated tau protein 217 (p-tau217) were measured using ELISA kits	• Compared to the HC group, the MCI group had a much higher serum NfL level. • The MCI group had greater serum NfL levels than the AD group, however this difference was not statistically significant. • With an area under the curve (AUC) for NfL of 0.646, serum NfL, Aβ40, Aβ42, and p-tau217 were highly specific in predicting MCI. • The prediction accuracy was enhanced (AUC=0.687) when NfL and p-tau217 were combined. • With an area under the curve (AUC) of 0.732, MCI predictin was more accurate when NfL and BNT were used together.	Elevated levels of serum NfL in afflicted persons compared to healthy controls suggest that it may be used as a biomarker for the early diagnosis of MCI and AD.
Mattsson et al[24], 2019	1.583 subjek 401 had no cognitive impairment/cognitively unimpaired (CU) 855 had MCI 327 had AD dementia Dementia was determined using the NINCDS-ADRDA criteria for Alzheimer's disease; MCI was defined as a score of 24 or above on the Mini-Mental State Examination (MMSE), a CDR score of 0.5 or above, sustained ability to perform activities of daily living (ADL), and no signs of dementia.	An in-house ultrasensitive enzyme-linked immunosorbent assay (ELISA) using a platform for single molecules was used to quantify the plasma NfL level.	Various other biomarkers include Aβ42 concentrations in CSF, t-tau, and p-tau.Patients with MI (37.9 ng/l) and AD dementia (45.9 ng/l) had greater baseline NfL levels compared to the CU controls (32.1 ng/l). The NfL level rose noticeably across all categories, but it was highest among patients with MCI (2.7 ng/l per year) when contrasted with CU controls (2.4 ng/l per year), a difference that was statistically significant (P<0.001)	One noninvasive biomarker that may be used to monitor neurodegeneration in AD is plasma NfL level.

DISCUSSION

Research on biomarkers for detecting cognitive impairment is increasingly being conducted. Biomarkers in the diagnosis of cognitive impairment are closely related to the molecular pathogenesis underlying cognitive dysfunction, especially in neurodegenerative diseases. Aging can disrupt several brain functions. Studies have demonstrated an overall reduction in brain volume in older adults compared to younger adults, particularly in areas associated with cognition.[6] As aging progresses, microglia adopt a pro-inflammatory state due to decreased resting signaling from neurons and astrocytes. This condition makes the aging brain more susceptible to chronic low-grade neuroinflammation induced by external stimuli and renders it vulnerable to apoptosis signaling. These processes contribute to brain volume loss and the accompanying cognitive impairments.[6]

Neurotrophins include BDNF, which is known to have a function in neuronal plasticity, synaptic plasticity, learning, and memory.[6,7] The function and relevance of BDNF in the aetiology of cognitive impairments have made it the most investigated biomarker for this condition. A precursor to mature BDNF, proneurotrophin (pro-BDNF), is produced during translation. Apoptotic signalling cascades may be activated when pro-BDNF is released and binds to the p75 neurotrophin receptor (p75NTR). On the flip side, when BDNF reaches maturity, it binds to TrkB, which sets off a series of events that lead to increased Ca^{2+} absorption, phosphorylation of transcription factors, and the initiation of BDNF gene expression from scratch.[6] BDNF is involved in both long-term potentiation (LTP) and short-term potentiation in the hippocampus, which means it contributes to memory formation and learning processes.The structural and functional components of synaptic transmission are affected by BDNF[7–10] which improves the efficiency of neuronal signal transmission.[9] Additionally, BDNF plays a critical role in motor learning due to its contribution to synaptic plasticity in the motor cortex (M1).[8]

When exposed to stressors or pro-inflammatory signals, signaling pathways within neurons can undergo changes that trigger a cascade of events, ultimately leading to dysfunction and neuronal apoptosis. Microglia actively participate in neuroinflammatory processes by releasing neurotoxic pro-inflammatory cytokines.[6,7] This cycle can persist as long as the triggering factors remain, potentially resulting in severe consequences such as cognitive impairment, behavioral dysfunction, and neurological or psychiatric disorders. During inflammation, pro-inflammatory cytokines, particularly interleukin (IL)-1β, can downregulate BDNF expression in brain structures related to cognition. Consequently, increased levels of pro-inflammatory cytokines are associated with reduced BDNF levels, leading to diminished survival signaling and, ultimately, neuronal cell death.[6]

Forlenza et al.[11] and Siuda et al.[12] demonstrated that BDNF levels were much lower in individuals with moderate cognitive impairment (MCI) compared to control groups with good cognitive function, lending credence to this notion. Furthermore, BDNF concentrations were much lower at baseline in MCI patients who developed Alzheimer's disease (AD). Accordingly, BDNF may serve as a biomarker for cognitive impairment in MCI and a predictor of patients' propensity to acquire Alzheimer's disease.[11] Patients with Alzheimer's disease had considerably lower peripheral BDNF concentrations than both healthy controls and patients with mild cognitive impairment, according to a meta-analysis.[13] Ng et al.[14] on the other hand, discovered that plasma BDNF concentrations were much higher in MCI patients than in healthy controls, which is contradictory. The correlation between elevated BDNF levels and hs-CRP levels in plasma lends credence to the idea that peripheral BDNF elevation during

preclinical dementia stages serves as a compensatory mechanism.[14]

As previously explained, numerous biochemical processes contribute to the pathogenesis of MCI and dementia, including Alzheimer's disease (AD). One hypothesis involves vascular contributions and their biomarkers, which have gained increasing research attention. However, studies on angiogenesis biomarkers and their relationship with cognitive impairment have yielded inconsistent results. Research by Shen et al.[15] and Serrano et al.[16] found lower plasma levels of VEGF in MCI patients compared to cognitively healthy controls. Despite this, studies on other VEGF family members and their association with cognitive performance are limited. VEGF's neuroprotective effects appear to be stronger when combined with other Alzheimer's-related biomarkers and are more beneficial for individuals showing early signs of Alzheimer's.[16] Contrastingly, Callahan et al. reported significantly higher plasma VEGF concentrations in MCI and Alzheimer's patients compared to healthy controls.[17] In the context of Alzheimer's disease, the role of VEGF remains unclear, as most literature on VEGF and Alzheimer's focuses on cross-sectional or post-mortem studies.[17]

MicroRNAs (miRNAs) have a role in controlling cellular growth and function; they are short non-coding RNAs that adversely affect gene expression after transcription. The use of circulating miRNAs as diagnostic biomarkers for a wide range of disorders, such as Alzheimer's, has recently attracted a lot of attention.[18] In research by Xie et al. miR-206 and miR-132 expression levels were significantly upregulated in MCI patients compared to healthy controls. Combined detection of these miRNAs showed better performance in identifying MCI than each miRNA individually.[19] Two genes involved in the development of cognitive impairment—BDNF and sirtuin-1 (SIRT1)—are the targets of these microRNAs. When miR-206 and miR-132 levels are high, the BDNF and SIRT1 proteins are downregulated.[19] Similarly, other studies have confirmed significant upregulation of miR-132 and the miRNA-134 family in MCI patients compared to normal controls. These findings emphasize the potential of miRNA-based biomarkers in diagnosing and understanding the mechanisms underlying cognitive disorders.[20,21]

Axonal cytoskeleton components that are neuron-specific and heavily phosphorylated are neurofilaments. Axonal development and stability are regulated by a number of subunits, one of which is neurofilament light chain (NfL). In a healthy state, NfL is released into the cerebrospinal fluid (CSF) by axonal cells, and it may reach the circulation at low quantities. But pathological states cause circulating NfL levels to spike, making it a sensitive indicator of axonal damage.[22] Research has shown that plasma NfL levels are much higher in individuals with MCI and AD when compared to healthy controls, which raises the possibility that it might be used as a diagnostic biomarker for MCI.[23,24] In addition, elevated levels of phosphorylated tau protein (p-tau217) enhance the diagnostic effectiveness of plasma NfL in identifying MCI.[24] Recent meta-analyses have shown that MCI patients had much greater plasma NfL concentrations than healthy controls, which is in line with our results.[25,26]

CONCLUSION

MCI is a stage between normal cognitive function and dementia; it is defined as cognitive dysfunction that does not match the criteria for dementia. Morbidity is greater in patients with MCI because they are more likely to develop Alzheimer's disease or another form of dementia.

Currently, no standardized diagnostic criteria for MCI exist. Existing criteria primarily rely on clinical symptoms, signs, and cognitive function assessments. Research has shown that molecular concentrations involved in the pathogenesis

of cognitive impairment, such as BDNF, VEGF, miRNA, and NfL, can serve as effective biomarkers for detecting MCI. These findings provide promising avenues for the development of more precise diagnostic tools and therapeutic interventions.

Declaration by Authors

Ethical Approval: Ethical approval was not required for this study as it is a review of existing literature and does not involve human or animal subjects.

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