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Potential biofluid markers for cognitive impairment in Parkinson's disease

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From the Contents

Abstract

Cognitive impairment is a particularly severe non-motor symptom of Parkinson's disease that significantly diminishes the quality of life of affected individuals. Identifying reliable biomarkers for cognitive impairment in Parkinson's disease is essential for early diagnosis, prognostic assessments, and the development of targeted therapies. This review aims to summarize recent advancements in biofluid biomarkers for cognitive impairment in Parkinson's disease, focusing on the detection of specific proteins, metabolites, and other biomarkers in blood, cerebrospinal fluid, and saliva. These biomarkers can shed light on the multifaceted etiology of cognitive impairment in Parkinson's disease, which includes protein misfolding, neurodegeneration, inflammation, and oxidative stress. The integration of biofluid biomarkers with neuroimaging and clinical data can facilitate the development of predictive models to enhance early diagnosis and monitor the progression of cognitive impairment in patients with Parkinson's disease. This comprehensive approach can improve the existing understanding of the mechanisms driving cognitive decline and support the development of targeted therapeutic strategies aimed at modifying the course of cognitive impairment in Parkinson's disease. Despite the promise of these biomarkers in characterizing the mechanisms underlying cognitive decline in Parkinson's disease, further research is necessary to validate their clinical utility and establish a standardized framework for early detection and monitoring of cognitive impairment in Parkinson's disease.

Key Words: amyloid-β; biomarkers; cognitive impairment; dementia; metabolomics; neurodegeneration; neuroinflammation; Parkinson's disease; proteomics; tau; α-synuclein

Introduction

Parkinson's disease (PD) is a neurodegenerative condition primarily known for its motor symptoms, such as tremors, stiffness, and bradykinesia (slowed movements). Additionally, patients with PD exhibit a variety of non-motor symptoms, among which cognitive impairment in PD (PD-CI) is the most significant. PD-CI can manifest as either PD with mild cognitive impairment (PD-MCI) or progress to PD dementia (PDD). The incidence of PD-MCI is considerable, with approximately 30% of patients with PD experiencing this condition (Wojtala et al., 2019). PD-MCI has been recognized as a precursor to PDD, and its presence is a firmly established risk factor for progression to PDD. PD-MCI represents an intermediate state between PD with normal cognitive function (PD-NC) and PDD, with the potential to transition in both directions over time. Studies have suggested that within 5 years, approximately 39%–50% of individuals with PD-MCI may progress to PDD, while 11%–27.8% may return to their baseline cognitive function (Cammisuli et al., 2019). The progression from PD-MCI to PDD significantly affects patients' quality of life, increases the caregiving burden (Szeto et al., 2020), and may even be associated with risk factors for early death. Early diagnosis and intervention for PD-MCI are clinically significant, necessitating identification of the mechanisms driving PD-MCI progression and new therapeutic targets. This approach can effectively delay or even prevent the occurrence of PDD, ultimately leading to enhanced quality of life and improved prognosis for patients.

PD-MCI subtypes have been also shown to exhibit significant heterogeneity, presenting with various types and degrees of cognitive impairment (CI), including challenges with executive functions, memory, language skills, and visuospatial capabilities. Patients with PD-MCI have a distinct cognitive profile in comparison with those showing Alzheimer's disease (AD) with mild cognitive impairment (AD-MCI). Impairment of executive functions is the most characteristic cognitive deficit in patients with PD-MCI, and is related to the disruption of the frontal–striatal circuit (Kalbe et al., 2016). Clinically, this impairment mainly manifests as impaired cognitive flexibility, planning, formation of concepts, working memory, and learning ability. Memory impairment in patients with PD-MCI mainly presents as deficits in short-term and immediate memory, among which long-term memory deficits are less apparent. Furthermore, memory functions related to digits, such as digit sequence memory and digit calculation ability, remain relatively intact (Brandão et al., 2020). Patients with PD-MCI may exhibit visuospatial impairment, which is characterized by reduced visual motor speed, decreased visual memory, and reduced visual analysis, motor coordination, and spatial abstraction abilities. Language naming and semantic comprehension abilities in patients with PD-MCI can remain intact in the early stages of the disease. However, the patients' language organization skills and fluency may be affected to a certain extent (Andrade et al., 2023). Currently, the diagnosis of PD and its progression to PDD are dependent on clinical and neuropsychological assessments. However, some challenges related to the homogeneity of the results of neuropsychological tests remain unresolved, and the testing process is time-consuming and labor-intensive. In contrast, changes in biomarker levels may reflect the degenerative process that can begin years before the onset of CI or dementia in both AD and PD. Therefore, objective and accurate biomarkers to gauge the severity of PD-CI are urgently needed.

The characteristic pathological features of PD include α-synuclein (α-Syn) aggregation and Lewy body formation (Schulz-Schaeffer, 2010), which are prevalent in the limbic and cortical brain regions and are accompanied by ubiquitin markers (Braak et al., 2003). While the exact pathological mechanisms underlying PD-CI remain unclear, research indicates a correlation between the occurrence of neurofibrillary tangles, amyloid-β

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(Aβ)-plaques, and Lewy bodies in the cortex and limbic system and the onset of PD-MCI (Jellinger, 2010) and PDD (Irwin et al., 2013). α-Syn, a central element of Lewy bodies, has garnered significant attention for its role in PD-related cognitive dysfunction. Moreover, the shared pathological features between PD-CI and cognitive impairment in AD (AD-CI) indicate that biomarkers such as tau phosphorylated at Thr181 (p-tau), total tau (t-tau), and $A\beta_{42}$, which are commonly linked to AD, hold potential for assessing the progression of cognitive decline in PD (Olsson et al., 2016). A biomarker-based model originally used for the diagnosis of AD, which categorized AD pathology into amyloid deposition (A), Tau pathology (T), neuronal degeneration (N), and other factors (X), has enhanced diagnostic precision and established a common research framework for AD (Jack et al., 2016; Huang et al., 2022). Efforts are underway to adapt this model for diagnosing other neurodegenerative diseases like PD. Höglinger et al. (2024) proposed a biological classification of PD termed SynNeurGe that is based on the presence or absence of pathological α-Syn (S) in tissues or body fluids, the manifestation of neuronal degeneration (N), and genetic factors (G); this classification has facilitated progress in both basic and clinical research and brought the field nearer to the precision medicine required to develop disease-modifying therapies . The co-occurrence of AD in individuals with PD can profoundly impact their prognosis and cognitive deterioration. The study by Cousins et al. (2024) underscored this point, suggesting that patients with PD showing the biomarkers of AD, specifically cerebrospinal fluid (CSF) beta-amyloid 42 (CSF-β_{42}), phosphorylated Tau 181 (p-tau181), and serum neurofilament light chain (NfL), experienced accelerated cognitive deterioration. The Alzheimer's Treatment in Neurodegenerative Disorders of the Peripheral and Central Nervous System (ATNPD) strategy aims to enhance prognostic assessment for patients with PD and highlights the importance of investigating the comorbidities of AD within the PD population. By learning from the biomarker framework conventionally used for the diagnosis and SynNeurGe classification of AD, researchers may gain new insights that could potentially revolutionize the diagnosis and treatment of PD-CI patients. This paper provides a comprehensive overview of the biomarkers found in biological fluids (**Figures 1** and **2**), focusing on their value for the early diagnosis and prognosis of PD-CI patients. Additionally, it discusses prospective research directions to further enhance the understanding of the mechanism and management of PD-CI.

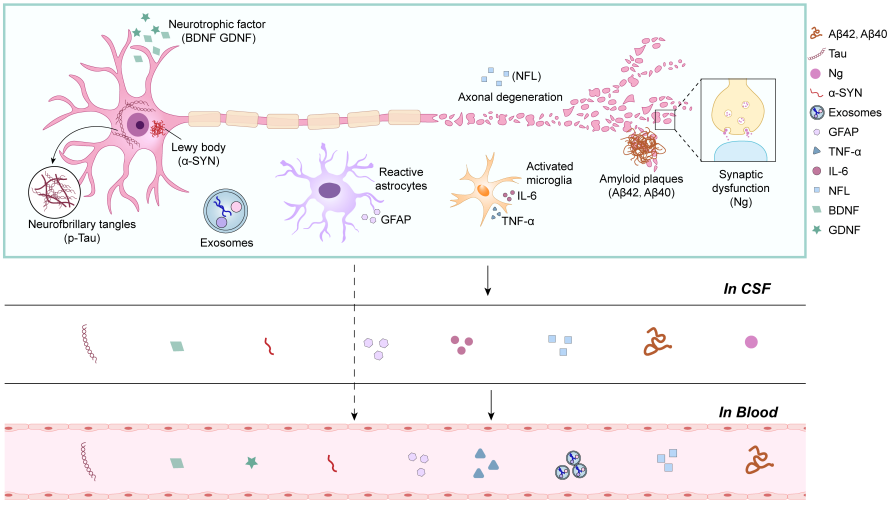

Figure 1 | **Mechanisms underlying the pathology of Parkinson's disease and biofluid-based biomarkers associated with cognitive impairment in Parkinson's disease.**
High-reliability biomarkers in both cerebrospinal fluid and blood include amyloid-β, Tau, NfL, exosomes, GFAP, IL-6, TNF-α, NfL, and neurogranin. Aβ: Amyloid-β; BDNF: brain-derived neurotrophic factor; CSF: cerebrospinal fluid; GDNF: glial cell line-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; IL-6: interleukin-6; NfL: neurofilament light chain; Ng: neurogranin; TNF-α: tumor necrosis factor-α; α-Syn: α-synuclein.

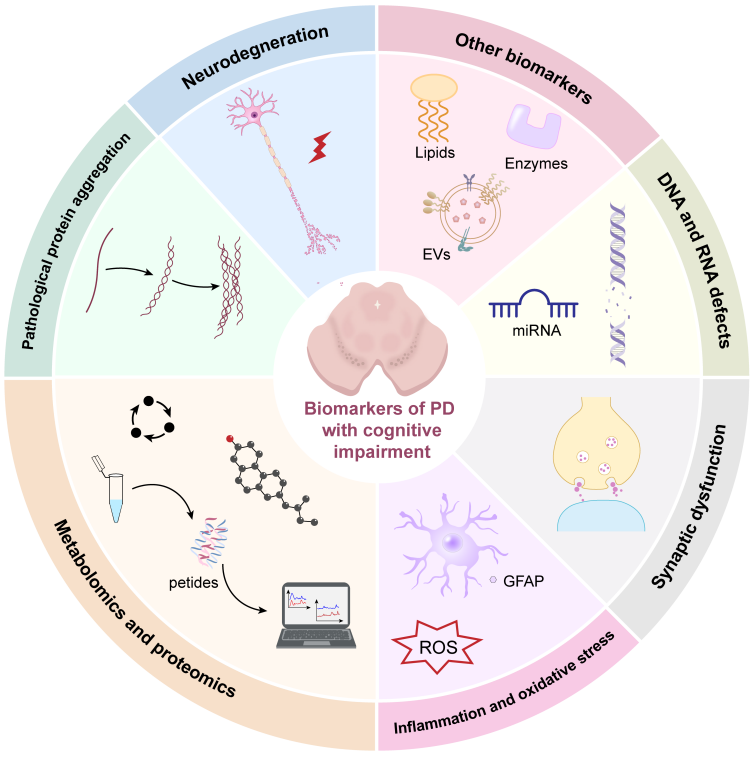

Figure 2 | **Biomarkers of PD with cognitive impairment.**
A comprehensive overview of the biomarker landscape in PD-related cognitive impairment is effectively presented in the diagram, illustrating the diverse mechanisms involved. EVs: Extracellular vesicles; GFAP: glial fibrillary acidic protein; miRNA: microRNA; PD: Parkinson's disease; ROS: reactive oxygen species.

Literature Retrieval Strategy

Using the PubMed database, an extensive literature review was performed to collect relevant full-text articles published in English up to March 31, 2024. To refine the scope and enhance the specificity and sensitivity of the search results, a combination of keywords, including "Parkinson's disease," "biomarkers," "Alzheimer's disease," "cognitive decline," and "cognitive impairment," was used in the search strategy. The titles and abstracts of the retrieved references were systematically reviewed to select potentially relevant studies. Older papers published 10 years ago were included only when they were considered indispensable for a comprehensive understanding of the topic under discussion.

Biomarkers Associated With the Pathology of Protein Misfolding

α-Synuclein

α-Syn is an intrinsically disordered protein that is predominantly expressed in presynaptic nerve terminals, and its pathological aggregates are considered key hallmarks of PD (De Bartolo et al., 2024; Yang and Zhang, 2024). As the disease progresses, pathological α-Syn fibers can spread between neurons via membrane receptors on the neuronal surface, ultimately contributing to CI in cortical systems. Postmortem pathological studies have indicated that the presence of Lewy bodies (misfolded α-Syn) in limbic and cortical regions is strongly associated with the occurrence of PDD

(Halliday et al., 2014). The existing research has not established a significant correlation between oligomeric or total α-Syn (o-α-Syn/t-α-Syn) levels and cognitive abilities in patients with PD (Førland et al., 2018). A large-cohort study conducted over 8 years suggested that elevated levels of t-α-Syn in the CSF may predict cognitive decline, particularly in patients with delayed recall and new dot test performance, while lower levels of t-α-Syn could indicate better cognitive preservation (Stewart et al., 2014). Similarly, Hall et al. (2015) found that patients showing PD with higher initial levels of t-α-Syn in the CSF experienced worsening cognitive processing speed over the subsequent 2 years. Conversely, in the Parkinson's Progression Markers Initiative study, Skogseth et al. (2015) observed that reduced t-α-Syn levels in the CSF among untreated patients with PD were significantly associated with decreased composite cognitive scores and lower scores in the executive-attention domain, with a trend toward decreased scores in memory and visuospatial domain. Research on the o-α-Syn levels in the CSF has been limited. However, initial findings have indicated higher levels in patients with PDD than in controls (Compta et al., 2015).

Due to the presence of the blood–brain barrier, blood levels of α-Syn are significantly lower than those in CSF, making its detection more complicated. However, using an ultrasensitive immunoassay, Lin et al. (2017) reported that plasma α-Syn levels were significantly higher in patients with PDD than in those with PD-MCI or PD-NC, and elevated plasma α-Syn levels were negatively correlated with Mini-Mental State Examination (MMSE) scores. Similarly, Chen et al. (2020b) found that α-Syn could effectively distinguish individuals with PD-NC from those with PD-CI. In contrast, Wang et al. (2022) utilized an ultrasensitive single-molecule array (Simoa) and found no significant differences in plasma α-Syn levels between patients with PD-MCI and those with PD-NC. These conflicting results may be attributable to the different assays used to measure α-Syn levels in plasma and the presence of undefined sources of the protein. The concentration of synaptic nuclear proteins in plasma can be heavily influenced by red blood cells, since approximately 99% of these proteins is contained within the cells, leaving only about 1% in plasma. The pathological forms of α-Syn, including phosphorylated, ubiquitinated, nitrated, truncated, and oligomeric variants, have received particular focus and may provide deeper insights into disease progression and PD-associated cognitive decline. However, few cross-sectional or longitudinal studies have examined the relationship of the nitrated, phosphorylated, and ubiquitinated forms of α-Syn with the cognitive decline in PD (Gao et al., 2015). Future research should aim to develop more precise immunoassays for detecting post-translationally modified forms of α-Syn and establish standardized protocols for identifying specific forms of α-Syn associated with the cognitive decline in PD. Interestingly, the use of parameters that combine biomarkers, such as the plasma α-Syn/$A\beta_{40}$ ratio, may enhance the accuracy for the prediction of cognitive decline in PD (Chan et al., 2022).

Amyloid-β

Aβ, a crucial component of amyloid plaques and a central biomarker in AD (Abyadeh et al., 2024; Lozupone and Panza, 2024), has also been implicated in PD-CI. The role of Aβ biomarkers in the diagnosis and monitoring of cognitive decline in PD remains an area of active research. In clinical practice, assays for $A\beta_{42}$ and $A\beta_{40}$ in the CSF, their ratio, and the findings of amyloid positron emission tomography have primarily been used for diagnosing AD (Blennow et al., 2015). In the context of PD, variations in the $A\beta_{42}$, $A\beta_{40}$, and $A\beta_{38}$ levels in the CSF have been observed in patients with early-stage PD and are correlated with memory impairments (Alves et al., 2010). Research has shown that $A\beta_{42}$ levels in the CSF can predict cognitive decline to PDD when compared to the levels in both healthy controls (Bäckström et al., 2015) and PD patients without cognitive impairment (Alves et al., 2014). Terrelonge et al. (2016) found that medication-naïve PD patients without cognitive impairment who had lower baseline CSF $A\beta_{42}$ levels were more likely to develop CI on the basis of the findings of neuropsychological assessments after two years of follow-up. Similarly, longitudinal studies indicated that lower CSF $A\beta_{42}$ levels could predict a faster rate of cognitive decline in PD (Parnetti et al., 2014). Moreover, various cognitive dysfunctions in PD, including dysfunctions in phonetic memory (Compta et al., 2009), visual memory (Yarnall AJ, 2014), attention and working memory (Leverenz et al., 2011), executive function (Stav et al., 2015), and verbal learning (Leverenz et al., 2011), have been associated with low $A\beta_{42}$ levels in the CSF. A recent study by Tufekcioglu et al. (2023) found no significant differences in most cognitive domains, with the exception of the visuospatial domain, between PDD patients with diminished and normal baseline $A\beta_{42}$ levels in the CSF. These findings, coupled with the observed high sensitivity and negative predictive value, underscore the potential of the $A\beta_{42}$ level in the CSF as an independent predictor and early prognostic biomarker for the progression from PD-MCI to PDD, despite variations in study methodologies and durations.

Although $A\beta_{42}$ levels in the CSF have demonstrated potential as predictive biomarkers, the invasiveness associated with CSF collection via lumbar puncture presents significant challenges. Advances in ultrasensitive technologies, such as immunomagnetic reduction-based immunoassays and the Simoa digital immunoassays, have improved the sensitivity of these assessments and enabled accurate quantification of biomarkers in peripheral blood (Yang et al., 2011). However, the findings for plasma $A\beta_{40}$ and $A\beta_{42}$ levels in PD-CI patients have been inconsistent. An enzyme-linked immunosorbent assay-based study has suggested that plasma $A\beta_{42}$ levels may not serve as reliable markers for PD-CI (Chojdak-Łukasiewicz et al., 2020). In contrast, Chen et al. (2020b) utilized an ultrasensitive IMR method and found that decreased plasma $A\beta_{40}$ levels were significantly correlated with cognitive decline in patients with PD. Conversely, a study by Tsai (2021) revealed that elevated plasma $A\beta_{40}$ levels were associated with cognitive decline in PD. Additionally, a recent analysis identified elevated baseline levels of plasma $A\beta_{40}$ as a predictive factor for accelerated cognitive deterioration in PD, particularly among carriers of the APOE-ε4 allele (Lin et al., 2023a). The plasma $A\beta_{42}/A\beta_{40}$ ratio has demonstrated good consistency with the occurrence of amyloidosis and is associated with cognitive decline as well as an increased likelihood of progression to AD dementia, indicating its potential as a more reliable early screening marker for dementia (Schindler et al., 2019). Using the Simoa platform, Wang et al. (2022) found that patients with PD-MCI exhibited a lower $A\beta_{42}/A\beta_{40}$ ratio than those without CI, and a higher $A\beta_{42}/A\beta_{40}$ ratio was correlated with better executive function scores. However, no significant differences were observed in the plasma levels of $A\beta_{42}$ and $A\beta_{40}$ between the PD-MCI and PD-NC groups. In conclusion, validating the significance of plasma Aβ levels in predicting PD-MCI and PDD is essential and could facilitate the identification of individuals with newly diagnosed PD who are at a higher risk of developing early PDD, especially when cognitive symptoms are mild or not yet apparent. Early identification is vital, since it allows for timely interventions, which are believed to be most effective during the initial stages of cognitive decline. These findings underscore the importance of targeting Aβ brain pathology early in cognitive decline, since such an approach could potentially halt or prevent further deterioration of cognitive function and the onset of PDD. Furthermore, integrating Aβ biomarkers with amyloid imaging and comprehensive cognitive assessments could enhance our understanding of the role of amyloid pathology in the cognitive aspects of PD.

Tau protein

The Tau protein plays a crucial role in promoting the aggregation of tubulin proteins into microtubules and binds to newly polymerized microtubules to prevent their disassembly, thereby maintaining structural stability (Chu et al., 2024; Ye et al., 2024; Zheng et al., 2024a). Abnormal modifications of tau, such as hyperphosphorylation, lead to its accumulation as neurofibrillary tangles within neurons. These tangles impair cellular function and contribute to cognitive decline and neuronal death, which are major pathological features of AD. The levels of p-tau and t-tau have been shown to serve as markers for neuronal degeneration and tau pathology, playing a critical role in predicting AD-related dementia (Olsson et al., 2016). Most studies have indicated that baseline t-tau levels in the CSF do not predict cognitive decline in patients with PD (Compta et al., 2013; Parnetti et al., 2014). However, longitudinal studies have identified a significant correlation between a rapid increase in p-tau levels in the CSF and accelerated cognitive decline in patients with PD (Liu et al., 2015; Hall et al., 2016). Several studies have reported elevated levels of p-tau181 in the CSF in patients with PD-CI in comparison with those in patients with PD-NC, indicating a relationship between p-tau181 levels and cognitive status and highlighting its potential as a biomarker for cognitive deterioration in PD (Vranová et al., 2014; Liu et al., 2015). One study examining the relationship between biomarkers in the CSF and cognitive function over time in patients with PD found that an elevated p-tau181/$A\beta_{42}$ ratio and increased p-tau181 levels were predictive of impending cognitive decline, particularly decline involving memory and executive function (Liu et al., 2015).

Using an immunomagnetic reduction-based immunoassay, one study demonstrated that plasma t-tau levels could help distinguish between patients with PD-NC and those with PD-CI (area under the curve [AUC] = 0.726, sensitivity = 67.5%, specificity = 77.1%) (Chen et al., 2020b). Another study found that higher plasma t-tau levels were associated with lower cognitive performance, especially for attention and executive functions (Lin et al., 2022). A recent investigation indicated that plasma p-tau species may serve as useful markers for the co-pathology of AD in PDD, with higher plasma p-tau181 concentrations linked to more rapid cognitive decline over time. Lin et al. (2023a) reported significant associations of plasma p-tau181 levels and the p-tau181/$A\beta_{42}$ ratio with Montreal cognitive assessment (MoCA) scores, with higher baseline plasma p-tau181 levels predicting a more rapid cognitive decline over a 5-year follow-up, especially in APOE-ε4 carriers. Consistent these findings, Wang et al. (2022) demonstrated that the PD-MCI group had significantly higher plasma p-tau181 levels than the PD-NC group. Increased plasma p-tau181 levels and an elevated p-tau181/$A\beta_{42}$ ratio were associated with reduced working memory function and attention. However, Batzu et al. (2022) suggested that while plasma p-tau181 levels were elevated in patients with PD, no correlation with cognitive performance was observed, either cross-sectionally or longitudinally. They proposed that p-tau181 may be more suitable for assessing cognitive progression in patients with more pronounced AD-like pathology, such as PDD. Additionally, the levels of p-tau231 and p-tau217 in peripheral blood have shown strong specificity for the pathophysiology of AD. Among the proposed blood tau biomarkers, p-tau217 has demonstrated significant effectiveness in identifying the pathology of AD in patients with mild cognitive impairment (MCI) (Ossenkoppele et al., 2022; Janelidze et al., 2023). However, research on the predictive utility of these biomarkers for cognitive function in PD remains limited.

Markers of Neurodegeneration: Neurofilament Light Chain

As a cytoplasmic protein, NfL plays a crucial role in providing structural support, regulating axon diameter, and facilitating nerve signal transmission in large-caliber myelinated axons. After axonal injury or neuronal death, NfL can leak into the extracellular space and subsequently enter the CSF and bloodstream (Gaetani et al., 2019). Blood levels of NfL can effectively distinguish PD from atypical parkinsonian disorders with a high accuracy, thereby serving as a diagnostic marker (AUC = 0.91) (Hansson et al., 2017). Furthermore, NfL has emerged as a promising biomarker for monitoring and predicting the severity of cognitive decline in PD. Lerche et al. (2020) reported that PD-CI patients exhibited higher baseline CSF NfL levels than those who did not experience cognitive decline, although CSF NfL levels did not predict the onset of CI. Plasma NfL levels in Chinese PD patients were negatively correlated with MMSE scores and could distinguish between patients with PDD and those with PD-NC or PD-MCI (Zhu et al., 2021b). Similarly, another study demonstrated that serum NfL levels could effectively distinguish patients with PDD from those showing PD-NC and PD-MCI with a high accuracy (Mao et al., 2023). Plasma NfL levels also demonstrated potential in predicting clinical conversion to PD-MCI or PDD (Aamodt et al., 2021). Increased plasma NfL levels correlated with a significant decline in MoCA scores in PD patients during follow-up visits (Ou et al., 2024). Additionally, higher serum NfL levels have been shown to predict greater declines not only in global cognition but also in episodic memory, visuospatial functioning, executive function/working memory, language, and processing speed/attention in untreated "*de novo*" PD patients (Ma et al., 2021). In a study by Sampedro et al. (2020), based on data from the Parkinson's Progression Markers Initiative study, untreated "*de novo*" PD patients showed a correlation of significantly elevated serum NfL levels with poorer cognitive performance and cortical structural changes in both cross-sectional and longitudinal analyses. Pagonabarraga et al. (2022) analyzed plasma NfL and p-tau181 levels in a cohort of patients with PD, finding that only baseline plasma NfL levels were significantly associated with progression to PDD. Specifically, higher NfL levels were significantly correlated with lower scores in semantic verbal fluency, action verbal fluency, alternating verbal fluency, delayed recall, and Benton facial recognition. In contrast, p-tau181 levels did not show significant differences in relation to the scores. Furthermore, elevated NfL levels were predictive of the development of dementia within a four-year monitoring period. While the evidence supporting NfL as a biomarker for early cognitive decline in PD is growing, an important consideration is that NfL is a sensitive but non-specific indicator, potentially influenced by factors such as age. Chen et al. (2020a) proposed a comprehensive model integrating plasma α-Syn and NfL levels, along with neuroimaging biomarkers and key clinical indicators, as a viable strategy for assessing the severity of PD and predicting the risk of PDD.

Biomarkers of Inflammation and Oxidative Stress

Biomarkers of neuroinflammation

Astrocytes, the primary cell type in the human central nervous system, predominantly express glial fibrillary acidic protein (GFAP), which serves multiple functions. This protein provides structural support for the integrity of the astrocyte cytoskeleton and plays a vital role in regulating neuronal physiology (Zheng et al., 2024b). In response to injury or disease, astrocytes can undergo reactive changes, leading to the release of GFAP into both CSF and blood. Elevated levels of GFAP are indicative of astrogliosis, a process commonly observed in neurodegenerative diseases such as PD and AD (Benedet et al., 2021). GFAP has emerged as a promising biomarker in PD, particularly for evaluating CI and predicting disease progression. Bartl et al. (2021) observed that GFAP levels in the CSF of newly diagnosed, unmedicated patients with PD were potentially associated with lower MoCA scores at the six-year follow-up. Similarly, Liu et al. (2023) investigated the relationship between the GFAP levels in the CSF and CI, as well as the changes in the CSF biomarkers in patients with early-stage PD. Their results indicated that higher GFAP levels in the CSF were correlated with a more pronounced decline in overall cognitive function over time (MoCA scores). Additionally, increased GFAP concentrations in the CSF were associated with a greater likelihood of dementia over an 8-year period in patients showing PD-NC (Liu et al., 2023). Interestingly, plasma GFAP levels have been reported to be an even more sensitive biomarker than their CSF counterpart. Patients with PDD and PD-MCI show higher plasma GFAP levels than those with PD-NC, and these levels have been shown to be negatively correlated with MMSE scores. Thus, plasma GFAP levels may be useful for distinguishing between patients with PDD and those with PD-NC and for predicting the transition from MCI to PDD (Tang et al., 2023). In a prospective cohort study, elevated plasma GFAP levels were linked to a more rapid decline in MoCA and Frontal Assessment Battery scores over a 5-year period in patients with PD (Lin et al., 2023b). These findings indicate that plasma GFAP may be valuable for patient classification in clinical trials and for monitoring disease progression.

Uric acid

Uric acid (UA) may play a protective role in PD by effectively scavenging reactive nitrogen and oxygen free radicals. An earlier study indicated that lower plasma UA levels are associated with poorer cognitive performance in individuals with PD, reinforcing the neuroprotective potential of UA (Annanmaki et al., 2008). A meta-analysis conducted by Khan et al. (2016) showed that patients with PDD exhibited lower serum UA levels, while higher serum UA levels in PD patients were linked to a decreased risk of developing dementia. Additionally, Shi et al. (2022) reported that serum UA levels were correlated with various non-motor symptoms, including cognitive dysfunction, anxiety, depression, dysphagia, and apathy. Recent studies have suggested that a reduced UA-to-serum creatinine ratio may serve as a predictor for the decline in cognitive function over time in patients with PD (Qu et al., 2023) Future studies involving diverse patient populations, extended follow-up periods, and varying dosages of urate-lowering therapies are necessary to gain a more comprehensive understanding of their impact on cognitive function within the context of PD.

Silent information regulator 1

Silent information regulators (SIRTs) are a family of proteins that play a crucial role in regulating cellular functions vital for aging, metabolic regulation, and other essential biological processes. Among these, SIRT1 has been extensively investigated for its diverse roles in maintaining cellular health (Manjula et al., 2021). In the context of PD, SIRT1 is involved in the degradation of α-Syn oligomers (Ubaid et al., 2022), management of oxidative stress, and modulation of inflammatory responses (Guo et al., 2016), thereby exerting neuroprotective effects (Feng et al., 2015). Recent studies have suggested a potential link between SIRT1 and cognitive decline in PD (Zhu et al., 2021a). For instance, Li et al. (2024) found a correlation between plasma SIRT1 levels and various non-motor symptoms of PD, including CI. Furthermore, the combination of plasma SIRT1 levels with total gray matter

volume has shown promise as a diagnostic tool for identifying PD-CI. The potential for SIRT1 to serve as both a biomarker and a therapeutic target is particularly exciting, since it may lead to the development of innovative diagnostic methods and treatments for cognitive decline in PD. Nevertheless, the precise mechanisms through which SIRT1 operates in PD require elucidation, and its application as a biomarker and therapeutic target needs to be refined. This understanding could facilitate the development of more effective strategies for addressing cognitive decline in PD patients, ultimately enhancing their quality of life.

Homocysteine

Homocysteine (Hcy) is a critical intermediate in the metabolic pathway of methionine, an essential amino acid (Mattson and Shea, 2003). Disorders in Hcy metabolism are linked to various pathological mechanisms for PD-CI, including the deposition of α-Syn and Aβ, oxidative stress injury, and dysregulation of lipid metabolism (Kruman et al., 2000; Jara-Prado et al., 2003; Tjiattas et al., 2004). Research examining Hcy levels as a biomarker for PD-CI patients has yielded inconsistent findings. Sleeman et al. (2019) reported that elevated serum Hcy levels predicted declining MoCA scores over a 54-month period in newly diagnosed PD patients, and their findings suggested that Hcy may serve as a useful biomarker for predicting cognitive decline in the early stages of PD. However, their study included participants both on and off levodopa therapy, which may have influenced the results since levodopa has been shown to raise Hcy levels (Müller and Muhlack, 2010). The impact of levodopa-induced changes on Hcy levels in PD-CI patients remains a topic of ongoing debate (Zoccolella et al., 2010; Song et al., 2013). A recent cross-sectional study indicated that for every 1 unit increase in Hcy levels above 17.7 μM, the risk of PD-CI increased 1.6 times, suggesting that Hcy could be a modifiable factor for cognitive decline in the early stages of the disease (Ouyang et al., 2024). Nevertheless, some cross-sectional and longitudinal studies have not found a direct correlation between plasma Hcy levels and PD-CI (Camicioli et al., 2009; Rodriguez-Oroz et al., 2009). A meta-analysis by Xie et al. (2017) further explored the relationship between Hcy levels and PD-CI, indicating that higher Hcy levels, along with lower levels of folate and vitamin B12, may be associated with cognitive deficits in this population. Clinical trials have shown that reducing Hcy levels through supplementation with folate and vitamin B12 may alleviate PD-CI (Durga et al., 2007; Cacciapuoti, 2013), providing a novel perspective for treatment. Additionally, a recent study highlighted the value of combining assessments of periventricular white-matter hyperintensities—a brain imaging marker for small-vessel disease—with Hcy levels to more accurately predict PD-MCI in comparison with individual assessments. This integrated approach could enhance the prediction of cognitive decline and offer insights into disease progression and prognosis (Zhang et al., 2023). Further research is necessary to clarify the precise relationship between Hcy levels and CI, confirm the clinical significance of Hcy as a biomarker, and investigate the potential benefits of folate and vitamin B12 supplementation in managing cognitive deficits in PD.

Vitamin D

Vitamin D has been linked to both the onset and progression of PD. Although elevated vitamin D levels have been shown to be positively correlated with enhanced memory and semantic fluency (Mayne and Burne, 2019), the relationship between serum 25-hydroxyvitamin D (25(OH)D), the primary metabolite used to assess vitamin D status, and CI in patients with PD remains unclear. The mechanisms underlying this association may involve inflammatory oxidative stress (Li et al., 2018) and the deposition of Aβ (Lin et al., 2020). A prospective longitudinal study conducted by Santangelo et al. (2021) on drug-naïve PD patients suggested that lower levels of 25(OH)D could potentially act as a biomarker for the development of PD-MCI over time. Supporting these findings, Wu et al. (2022) reported reduced serum 25(OH) D levels in patients with PD-CI in comparison with healthy controls. However, a study by Sleeman et al. (2017), which included an 18-month follow-up, did not find a significant association between initial vitamin D levels and the risk of developing PD-MCI, thereby challenging the notion that early-stage vitamin D deficiency could predict MCI. Randomized controlled trials are needed to assess the potential neuroprotective effects of vitamin D supplementation and its capacity to prevent cognitive decline in PD.

Other inflammatory markers

Neuroinflammation and immune responses play critical roles in the pathogenesis of PD. Serum C-reactive protein (CRP) serves as a key marker of systemic inflammation. Lawton et al. (2020) observed no significant correlations between CRP levels and the intercept or slope of the MoCA score. In contrast, Mollenhauer et al. (2019) reported that elevated baseline serum CRP levels may be predictive of cognitive decline in PD. Moreover, Shen et al. (2022) developed a predictive model incorporating the levels of three proteins—melanoma inhibitory activity (MIA) protein, albumin, and CRP—to identify individuals at a higher risk for rapid cognitive decline. Notably, MIA protein has demonstrated a causal role in cognitive decline in PD through Mendelian randomization analyses, positioning it as a valuable biomarker for predicting cognitive deterioration. Pathways related to MIA may contribute to the development of cognitive symptoms in PD. Furthermore, increased levels of other inflammatory markers, such as tumor necrosis factor (Menza, 2010), interleukin (IL)-6 (Yu SY, 2014), and interferon gamma-induced protein 10 (Rocha et al., 2014), may also play roles in cognitive decline among PD patients. Specifically, elevated tumor necrosis factor levels have been linked to impairments in language and executive functions; higher interferon gamma–induced protein 10 levels are associated with decreased mental flexibility and inhibitory control; and a negative linear relationship has been reported between MoCA scores and IL-6 levels. These findings highlight the significance of investigating neuroinflammatory pathways in PD, which is essential for enhancing our understanding of PD-CI and for developing potential therapeutic interventions.

Markers of Metabolic Response

Lipid metabolism

Triglycerides (TG) may influence cognitive functions, potentially by inducing resistance to leptin and insulin receptors at the blood–brain barrier (Banks et al., 2018). Huang et al. (2018) found a correlation between elevated TG levels and the presence of PD-MCI, particularly visuospatial and executive functions. Additionally, Deng et al. reported that individuals with PD-MCI exhibited higher levels of apolipoprotein A1, total cholesterol, triglycerides, and apolipoprotein B than those with PD-NC, suggesting that these lipids could serve as valuable biomarkers for PD-MCI (Deng et al., 2022). Moreover, Mollenhauer et al. (2019) observed that increased baseline serum levels of high-density lipoprotein could act as a biochemical marker for predicting cognitive decline in patients with PD. Interestingly, Bakeberg et al. (2021) identified a relationship between elevated serum high-density lipoprotein levels and decreased cognitive function, specifically in female patients with PD, indicating a potential sex-specific biomarker for PD-CI patients.

Ceramide metabolism

Ceramides, essential components of sphingolipids, play important roles in various cellular processes, including growth arrest, apoptosis, senescence, adhesion, and migration (Hannun and Obeid, 2008). Disruptions in ceramide metabolism have been associated with the pathogenesis of PD, contributing to the deposition of α-Syn and the formation of Lewy bodies, which are hallmark features of PD pathology. Mutations in the glucocerebrosidase (*GBA*) gene, which are responsible for encoding the enzyme that breaks down glucosylceramide into glucose and ceramide, have been linked to an earlier onset of PD and an increased risk of cognitive decline and dementia (Brockmann et al., 2011). These findings highlight the importance of glucosylceramide and ceramide metabolism in the progression of PD and its cognitive complications.

Despite the established connection between GBA mutations and PD, research on ceramide metabolism in patients with PD without GBA mutations remains limited. Blum et al. found that patients with PD without GBA mutations exhibited higher levels of various ceramides, including monohexosylceramides and lactosylceramides, than control individuals, with the highest levels observed in patients in PD-CI, such as MCI or dementia. Thus, alterations in ceramide metabolism may play an important role in the cognitive deficits seen in patients with PD without GBA mutations (Blum et al., 2013). Supporting this, a study by Xing et al. (2016) demonstrated a correlation between elevated ceramide levels and diminished memory function, further implicating ceramides in the cognitive decline associated with PD. However, these studies were constrained by small sample sizes and did not specifically focus on the process by which GBA mutations influenced the relationship between ceramides and PD symptoms. To gain a comprehensive understanding of the effects of ceramide metabolism on PD, particularly in individuals without GBA mutations, more extensive and focused research is needed.

Other Biomarkers

Neurotrophic factors

Neurotrophic factors are essential proteins associated with the growth, survival, and differentiation of neurons, thus playing critical roles in neuronal plasticity, learning, memory, and various cognitive functions. A widely accepted hypothesis suggests that deficiencies in neurotrophic factors may be a contributing factor for the onset of CI (Nikolac Perkovic et al., 2023). Brain-derived neurotrophic factor (BDNF) is a key neurotrophic factor that significantly influences neuroplasticity, particularly in the hippocampus, a region crucial for learning and memory (Egan et al., 2003). Leverenz et al. (2011) found that BDNF concentrations in the CSF were significantly correlated with Digit Symbol performance. Wang et al. (2016) reported that decreased BDNF levels were extensively observed in PD-CI patients, affecting attention, delayed memory, language, visuospatial/constructional skills, and immediate memory. Similarly, Costa et al. (2015) identified a strong positive correlation between serum BDNF levels and cognitive abilities, including attention and executive functions, in individuals with PD-MCI. A genetic study has also linked the BDNF Val66Met polymorphism to PD-CI (Ramezani et al., 2021). Notably, Angelucci et al. (2015) observed an increase in plasma BDNF levels following cognitive rehabilitation in patients with PD-MCI, indicating its potential therapeutic benefits.

Glial cell line–derived neurotrophic factor (GDNF), recognized for its support of dopaminergic neurons, has also been investigated for its potential association with CI in both AD and PD (Sharif et al., 2021). Gao et al. (2021) suggested that serum GDNF levels could serve as a diagnostic marker for PD-MCI. Furthermore, a multivariable prediction model that combined serum GDNF levels, imaging indicators, and MoCA scores demonstrated enhanced diagnostic accuracy for cognitive dysfunction in PD (Tang et al., 2024). Liu et al. (2020) observed a correlation between lower GDNF levels and increased severity of PD-CI, suggesting that GDNF may influence cognitive functions such as executive skills, memory, and attention, either independently or in conjunction with neurotransmitters. Collectively, these findings indicate that GDNF may serve as an effective diagnostic marker for PD-CI and holds promise as a therapeutic intervention for PD-related cognitive issues. Clinical trials are expected to evaluate the safety and efficacy of GDNF as a potential treatment for patients with PD.

Growth factors

Epidermal growth factor (EGF) and insulin-like growth factor 1 (IGF-1) function also as neurotrophic factors for dopaminergic nigrostriatal neurons in PD (Iwakura et al., 2005). IGF-1 is particularly crucial for enhancing the clearance of Aβ, preventing α-Syn aggregation, and mitigating the harmful effects of both Aβ and α-Syn. Lower baseline plasma EGF levels have been shown to be linked to unfavorable long-term cognitive outcomes in individuals with PD (Lim et al., 2016). Pellecchia et al. (2013) evaluated patients with early-stage PD and found that those with diminished EGF levels performed poorly on semantic fluency tasks and color perception tests, indicating that EGF levels may act as an early indicator of PD-CI.

These findings highlighted a relationship between declining EGF levels and a decrease in both neurotrophic function and cognitive abilities. A reduction in EGF levels may weaken its neurotrophic effects, potentially leading to cognitive decline in patients with PD. Pellecchia et al. (2014) also demonstrated positive correlations of IGF-1 levels with verbal episodic memory (immediate recall and delayed recall), visuo-perceptual skills, and attention/executive functions in untreated PD patients after a 2-year follow-up. Subsequently, Shi et al. (2023) reported positive associations of IGF-1 levels and EGF levels with total MMSE scores.

Enzymes

Ubiquitin C-terminal hydrolase (UCH-L1) is a neuron-specific deubiquitinating enzyme that accounts for 1%–5% of the total soluble protein content in the brain. It has emerged as a potential marker for post-traumatic brain injury and cognitive decline in both AD and PD (Bishop et al., 2016). Zhang et al. (2022) demonstrated a correlation between serum UCH-L1 levels and various cognitive domains in patients with AD, including performance on the MMSE, attention, calculation skills, and language abilities. Furthermore, a cross-sectional study found an inverse relationship between serum UCH-L1 and plasma NfL levels in patients with PD, indicating that lower UCH-L1 levels were associated with higher NfL levels and poorer cognitive function (Dong et al., 2023). Nevertheless, the specific relationship between UCH-L1 and NfL within the pathological framework still requires further investigation. UCH-L1 is vital for the ubiquitin-proteasome system, which is crucial for the selective degradation of proteins in cells. Dysfunction in UCH-L1 may prevent the clearance of α-Syn, a key protein implicated in the pathology of PD (Webb et al., 2003; Setsuie and Wada, 2007), potentially leading to CI.

Arylsulfatase A (ARSA) is a lysosomal enzyme with molecular chaperone functions that may play a role in inhibiting the secretion, clustering, and propagation of α-Syn (Lee et al., 2019). Li et al. (2022) used an enzyme-linked immunosorbent assay to establish the relationships of low plasma ARSA levels with elevated α-Syn concentrations and CI in patients with PD. Furthermore, plasma ARSA levels were significantly lower in the PD-CI group than in the PD-NC group (Li et al., 2022). However, no correlation was found between the total MMSE score and plasma ARSA levels in patients with either early or late-stage PD (Yoo et al., 2020). Given its potential involvement in the mechanisms underlying PD-CI, further research on ARSA is warranted.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is mainly produced by inflammatory cells and may contribute to the development of CI, likely through mechanisms involving inflammation and oxidative stress (Ridker et al., 2022), given its potential role in the pathogenesis of cognitive deficits in neurodegenerative diseases such as AD (Doody et al., 2015). Wu et al. (2024) indicated that Lp-PLA2 exhibited relatively high specificity but low sensitivity in distinguishing between PD-CI and PD-NC. Additionally, the activity of Lp-PLA2 was identified as an independent risk factor for PD-CI. Overall, these findings suggest that elevated serum Lp-PLA2 activity could serve as a promising biomarker for predicting PD-CI.

MicroRNAs

MicroRNAs (miRNAs) are short, single-stranded non-coding RNAs that typically consist of approximately 21–25 nucleotides (O'Brien et al., 2018). They can bind to complementary sequences on target messenger RNAs (mRNAs), resulting in the inhibition of translation or degradation of the mRNA molecule and thereby regulating the expression of the corresponding proteins. Although miRNAs are primarily located in the cytoplasm of cells, recent studies have identified their presence in extracellular environments such as CSF and blood. Due to their regulatory roles, miRNAs have been explored as potential biomarkers for PD (Alkhazaali-Ali et al., 2024), particularly in relation to PD-CI. Their involvement in processes such as synaptic plasticity and memory formation, along with their capacity to regulate proteins associated with neurodegenerative disorders (such as α-Syn, Aβ, and tau), makes them significant candidates for biomarkers in PD-CI patients (Nadim et al., 2017; Fan et al., 2021). Han et al. (2020) observed that the levels of miR-29b could effectively distinguish PDD from non-PDD, achieving an AUC of 0.859, while the AUCs for miR-29a and miR-29c were moderate (0.689 and 0.701, respectively). This finding underscored the specific association of miR-29b with CI, making it a promising candidate biomarker for PDD. Further analysis of cognitive domains indicated that all three members of the miR-29 family (miR-29a, miR-29b, and miR-29c) were associated with memory performance in patients with PD. Additionally, the levels of miR-29a and miR-29b were linked to language function, while miR-29b levels were related to executive function (Han et al., 2020). Hsu et al. (2024) reported that the plasma levels of miR-203a-3p were significantly elevated in the PDD group in comparison with the PD-MCI or non-PDD groups. Furthermore, the ratio of miR-203a-3p to miR-16-5p showed an inverse correlation with the total MoCA score, particularly affecting the visuospatial, language, and orientation domains. A logistic regression model that incorporated age, the miRNA ratio, and Unified Parkinson's Disease Rating Scale III scores achieved an AUC of 0.883, facilitating the differentiation of PDD patients from non-PDD patients. miR-203a-3p belongs to the miR-203 family. Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated that the multiple target genes of this miRNA are involved in pathways such as the dopaminergic synapse, apoptosis, and nuclear factor-kappa B signaling (Hsu et al., 2024). Moreover, miR-203a-3p has been shown to bind to the 3′ untranslated region of synuclein alpha, the gene encoding α-Syn, leading to its overexpression and promoting the aggregation and spread of α-Syn. These effects have been implicated in the pathogenesis of PDD. Therefore, targeting miRNA-based therapies for PD-CI may represent a novel and largely unexplored treatment strategy.

Biomarkers for synaptic dysfunction

Neurogranin (Ng) is a calmodulin-binding protein primarily found in the dendritic spines of postsynaptic neurons, where it plays a crucial role in memory, learning, long-term potentiation, and synaptic plasticity. Ng has emerged as a potential CSF biomarker for synaptic injury in patients with AD (Agnello et al., 2021). Research has indicated that elevated Ng levels in the CSF can predict the progression from MCI to AD and are associated with accelerated cognitive decline in amyloid-positive prodromal AD (Kvartsberg et al., 2015). However, studies examining Ng levels in the CSF among patients with PD are limited, with findings showing either reduced or stable levels of Ng in comparison with control groups (Portelius et al., 2018; Hall et al., 2020). Investigations into the Ng levels in the CSF among patients with PD experiencing cognitive decline are scarce and have yielded mixed results. The relationship between baseline Ng levels in the CSF and the subsequent development of PDD remains unclear due to a lack of consensus in the literature (Hall et al., 2020). Nonetheless, some studies have demonstrated that higher postsynaptic Ng levels in the CSF are correlated with diminished cognitive performance, as assessed by the MoCA and MMSE, in patients with PD (Bereczki et al., 2017; Sancesario et al., 2020). Sancesario et al. (2020) reported that the CSF $A\beta_{42}$/Ng ratio had greater accuracy in distinguishing patients with PD-CI than the Ng level alone, highlighting its potential as an indicator of global synaptic dysfunction and a valuable biomarker for monitoring PD-CI. Selnes et al. showed that the concentrations of Aβ, α-Syn, and Ng in the CSF were linked to cortical metabolism and cognitive decline, indicating that dysregulation of synaptic function due to Aβ and α-Syn may significantly contribute to the progression of PD-CI (Selnes et al., 2017). YWHAG, a gene essential for encoding the 14-3-3 gamma protein, plays a vital role in maintaining synaptic plasticity, which is crucial for memory and learning (Han et al., 2022). The 14-3-3 gamma protein has been found to be involved in cell signaling pathways related to cell survival and apoptosis, indicating its potential role in cognitive processes. Recent studies have also highlighted the clinical potential of YWHAG as a novel diagnostic biomarker for distinguishing patients with PD-NC from those with PDD, achieving an AUC of 0.95. Furthermore, the AUC for distinguishing between PD-NC and PD-CI was 0.76, demonstrating the effectiveness of this biomarker in assessing cognitive decline in PD (Peng et al., 2024).

Biomarkers in extracellular vesicles

Plasma extracellular vesicles (EVs) play a crucial role in intercellular communication within the brain, facilitating the transfer of proteins, nucleic acids, and lipids. Recent studies have emphasized the potential of plasma EV biomarkers, particularly cytokines and proteins associated with neurodegenerative pathology, as indicators of PD-CI. Elevated levels of pro-inflammatory cytokines in plasma EVs, such as tumor necrosis factor-α, IL-6, pro-IL-1β, and IL-10, have been associated with PD-CI, underscoring the significance of inflammation in disease progression (Chan et al., 2021). One study demonstrated higher levels of $A\beta_{42}$ and tau in the plasma EVs from patients with PD-CI than in those with preserved cognitive function. The combined evaluation of α-Syn, tau, and $A\beta_{42}$ levels in plasma EVs, along with demographic factors, has demonstrated potential for effectively predicting PD-CI (Chung et al., 2021). Additionally, another investigation indicated that an increase in plasma EV tau levels, either alone or in combination with increased α-Syn and $A\beta_{42}$ levels, could serve as a predictor for the progression of PD-CI over a 1-year follow-up period (Chan et al., 2023). However, these biomarkers were neuron-specific, and α-Syn found in blood EVs likely originates from the CNS (Shi et al., 2014). Neuronal origin-enriched EVs (NEVs) can be isolated from peripheral blood using immunocapture techniques, providing a valuable resource for identifying biomarkers for clinical and preclinical diagnosis, prognosis, and exploration of disease mechanisms in neurodegenerative disorders like AD and PD (Athauda et al., 2019; Kapogiannis et al., 2019; Eren et al., 2020). Plasma NEVs may also offer insights into cognitive prognosis in patients with PD, with α-Syn in NEVs proving to be more informative than plasma α-Syn levels. A study by Blommer et al. (2023) revealed lower levels of NEV α-Syn, α-Syn/Tau181, and tyrosine-phosphorylated insulin receptor substrate-1, but higher Tau181 levels in PD-CI patients in comparison with PD-NC patients. This finding underscored the involvement of α-Syn and tau, along with impaired insulin signaling, in PD-CI. To enhance understanding of the timeline of biomarker changes in PD, future studies should prioritize longitudinal studies of NEV biomarkers in patients transitioning from PD-NC to PD-MCI or PDD. Exosomes, which are nano-sized EVs, have been demonstrated to contribute to the dissemination of misfolded proteins such as α-Syn. A study reported that increased plasma exosome levels in patients with PD may correlate with cognitive decline (Alamri et al., 2016). The cellular prion protein, a glycosylphosphatidylinositol-anchored protein located in lipid rafts on presynaptic and postsynaptic membranes, was released into the extracellular space via exosomes, where it was abundantly expressed on their surface (Linden et al., 2008). These exosomes not only carried the cellular prion protein (Leng et al., 2020), which was linked to cognitive decline in PD, but also transported mRNA and miRNA. This dual function of exosomes provides valuable insights into the molecular mechanisms underlying PD-CI. For instance, significant differences in serum exosomal miR-135a levels have been noted between patients with PDD and healthy controls (Yang et al., 2018). The role of exosomes as biomarkers and therapeutic targets in PD has attracted increasing interest. Furthermore, recent studies have suggested that exosomes derived from mesenchymal stem cells may help mitigate CI in PD models, potentially by influencing cholesterol metabolism and phospholipid composition in hippocampal neurons (Xu et al., 2022). This highlights the potential of exosomes in developing innovative therapeutic strategies for PD-CI.

Biomarkers based on metabolomics and proteomics

Biological processes are influenced by a complex interplay of metabolism, protein function, and gene expression, reflecting both physiological and pathological conditions. Significant advancements in the fields of metabolomics and proteomics have facilitated the identification and quantification of metabolites and proteins in biological samples such as CSF, serum, and saliva (Ferrer, 2018). In the context of PD, various metabolic pathways, including those associated with oxidative stress, fatty acids, amino acids, as well as lipids, have been found to be disrupted (Paul et al., 2023; Santos et al., 2024). However, research specifically addressing PD with cognitive decline remains limited. Florence et al. identified 20 metabolites associated with PD-MCI primarily from the fatty acid oxidation pathway. Nine of these metabolites demonstrated strong predictive accuracy for the early onset of cognitive deterioration (Burté et al., 2017). Additionally, Zhang et al. (2021) performed grade-dependent proteomics and metabolomics analyses to uncover more precise biomarkers, revealing an inverse relationship between serum levels of 1-oleoyl-sn-glycero-3-phosphocholine and cognitive function in patients with PD, indicating potential clinical utility for diagnosing cognitive decline. These results implied that alterations in the metabolism of fatty acids, lecithin, long-chain fatty acids, and sphingolipids may significantly contribute to the development of PD-CI. Markaki et al. (2020) used a high-throughput antibody-based proteomics approach to highlight Kininogen-1 as a potential biomarker for cognitive decline in PD, and for predicting cognitive status on the basis of a repeatable battery for the assessment of neuropsychological status scores. Increased CSF levels of Kininogen-1 were linked to lower scores on the MoCA (Markaki et al., 2020). Jesse et al. (2012) optimized a proteomics approach for CSF and identified differentially sialylated isoforms of Serpin A1 as potential biomarkers, achieving 100% sensitivity in accurately identifying all patients with PDD. In summary, the integration of metabolomics and proteomics may provide valuable insights into cellular functions and enhance the discovery of specific biomarkers. The identification of metabolic and bacterial markers associated with various stages of PD-CI can enhance our comprehension of the disease's molecular pathways and support the development of innovative preventive or therapeutic strategies.

Biomarkers in the saliva and urine

Biomarkers in the urine and saliva are preferred over those found in blood or CSF due to the ease of sample collection and their minimally invasive nature. Saliva has shown potential as a source for identifying PD-associated biomarkers, with promising findings related to α-Syn, t-tau, p-tau, Aβ, and miRNA. However, research on salivary biomarkers specifically for PD-CI remains limited. Vivacqua et al. (2023) found that elevated levels of t-α-Syn were negatively correlated with lower scores on the MoCA. In contrast, Maria observed no significant relationship between cognitive scores and t-tau levels in the saliva of newly diagnosed PD patients, which may be attributed to the average MoCA score (≥ 26) of the study population (De Bartolo et al., 2023). As the disease progresses, salivary levels of total tau and phosphorylated tau may become associated with cognitive decline. The potential relationship between cognitive clinical status in patients with PD and the levels of tau protein and Aβ in saliva remains to be investigated.

Therefore, the predictive value of tau protein and Aβ levels in saliva for dementia progression in patients with PD remains to be clarified. Arikan et al. (2023) used a multi-omics factor analysis that integrated metaproteomics analysis and amplicon sequencing, and revealed a significant interaction between the bacterial genera Neisseria and Lactobacillus in the saliva of PD-CI patients. Additionally, urine kynurenine levels were found to be negatively correlated with the MMSE score, suggesting that urine kynurenine could serve as a valuable biomarker for monitoring the progression of PD-CI (Bai et al., 2021). Furthermore, Fraser et al. (2016) examined the levels of Ser(P)-1292 LRRK2 in urinary exosomes and observed that higher levels of Ser(P)-1292 LRRK2 were associated with the poorer MoCA scores, indicating its potential predictive value for identifying PD patients with more severe cognitive decline.

Limitations

This review had several limitations. While it provided a comprehensive overview of fluid biomarkers related to PD-CI, it did not delve deeply into the advancements in neuroimaging biomarkers. A separate article could be dedicated to exploring neuroimaging biomarkers for PD-CI in detail. Additionally, some of the included studies had small sample sizes, and certain biomarkers were not extensively studied, limiting the reliability of the findings for these biomarkers. Moreover, the review relied solely on PubMed for literature searches, which may have resulted in the omission of important studies not indexed in PubMed. Importantly, this was a narrative review rather than a systematic review or meta-analysis; thus, the conclusions may lack statistical robustness. Utilizing more stringent methodologies could produce more robust conclusions.

Conclusions

Studies on multiple biochemical markers have demonstrated the complexity and heterogeneity of the mechanisms underlying PD-CI. In this narrative review, we have summarized the main findings related to biomarkers such as α-Syn, Aβ, tau protein, and NfL, as well as the dynamic changes in the pathology of PD, including changes in the levels of lipids, metabolites, oxidative stress, inflammation, nutritional factors, and EVs (**Table 1**). However, some existing studies had significant limitations, such as relatively small sample sizes, inadequate data from cognitive assessments, unadjusted confounding variables, and unclear mechanisms. To validate the findings, further research with larger cohorts, extended follow-up periods, comprehensive neuropsychological evaluations of individual cognition, and well-matched control groups are necessary. The mechanisms underlying cognitive decline in PD are multifactorial, and likely include protein misfolding, neurotransmitter disorders, genetic risk, and neurotrophic factor deficiencies. Aggregation of misfolded proteins (α-Syn) as well as overlap with neuropathological changes in AD (Aβ and tau) are considered to be important determinants of PDD. Consequently, biomarkers such as α-Syn, Aβ42, and p-tau181 may be valuable for predicting the occurrence and severity of PD-CI. However, they should not be considered as conclusive diagnostic biomarkers for PD-CI, since some results are inconsistent, possibly due to variations in grouping and measurement methods. Combinations of biomarkers, like the $A\beta_{42}/A\beta_{40}$ ratio, could potentially serve as a more dependable early screening indicator than individual $A\beta_{42}$ and $A\beta_{40}$ levels. Additionally, a lower plasma $A\beta_{42}/A\beta_{40}$ ratio has been related to impaired executive function, while a higher p-Tau181/$A\beta_{42}$ ratio has been linked to reduced attention and working memory. Various post-translationally modified forms of α-Syn, such as phosphorylated, nitrated, and ubiquitylated variants, along with oligomers, have been identified as relatively stable indicators of disease progression in PD. However, further studies are necessary to validate their diagnostic and prognostic value as markers for PD-CI. The pathological forms of amyloid, α-Syn, and tau may interact and potentially exacerbate their aggregation, although the precise mechanisms underlying these interactions remain unclear. Targeting the common pathways involved in the aggregation of tau, α-Syn, as well as Aβ could potentially yield novel therapeutic strategies for PD, particularly for managing PD-CI. The plasma levels of GFAP and NfL are accessible and sensitive biomarkers for assessing disease severity and may act as early indicators for predicting cognitive decline in PD. However, elevated levels of GFAP and NfL are not exclusive to PD and may only be relevant for monitoring the disease in PD patients without other neurological comorbidities. Biomarkers related to oxidative stress, inflammation, nutritional factors, as well as EVs could help us better understand the complex mechanisms underlying PD-CI and present new opportunities for therapeutic intervention. Emerging biomarkers in the urine and saliva, along with exosomes and miRNAs, have shown their potential, although these preliminary results require further confirmation through future longitudinal studies. Advanced technologies, including high-throughput proteomics and metabolomics, have offered new perspectives for the recognition and development of novel biomarkers and therapeutic strategies for PD-CI patients. A detailed analysis of the global and subcellular proteome of brain regions associated with PD may elucidate the cellular basis of PD-CI and the roles of specific brain regions in the pathogenesis of PD. Given the scarcity of related findings and the relatively small sample sizes in existing studies, future large-cohort, multicenter, longitudinal investigations are warranted. The validation and implementation of unified biofluid-based biomarkers may facilitate the development of medicine. PD-CI shares similar pathological mechanisms and biomarkers with AD. Thus, we will aim to develop a composite biomarker framework that captures the various processes occurring in the brain of patients with PD-CI as dynamic phenomena throughout the progression of the disease. As disease-modifying therapies for AD become accessible, strategies guided by biomarkers may facilitate the identification of patients with PD-CI who may benefit from AD treatments. A multimodal approach, including biochemical, imaging, clinical data, and genetic biomarkers, would help enhance diagnostic sensitivity and specificity. For instance, a comprehensive model that combines various indicators (p-Tau181 levels, the $A\beta_{42}/A\beta_{40}$ ratio, specific cortical thinning, and altered functional connectivity) related to CI, has demonstrated superior diagnostic accuracy in comparison with basic clinical characteristics and individual biomarkers. The application of machine learning (Deng et al., 2023; **Figure 3**) and other methods to integrate biomarkers from different sources would help the development of a comprehensive model based on biomarkers for optimal diagnostic combinations and to explore their clinical relevance. Interactive verification across multiple omics fields and technological platforms will facilitate the construction of a comprehensive biomarker-based model, allowing researchers to identify potential biomarkers, understand their roles in disease progression, and develop targeted therapeutic interventions. Since interventions are prone to be effective during the initial stages of the disease, early detection would allow for the timely initiation of clinical trials to assess the efficacy of new neuroprotective or neurorestorative treatments.

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Table 1 | Review of the main studies evaluating fluid biomarkers for cognitive impairment in Parkinson's disease

Source	Biomarker	Cases and controls	Main findings	Cognitive evaluation/ diagnostic criteria	Sensitivity, specificity, and accuracy	Reference
CSF	t-α-Syn, $A\beta_{42}$	42 patients with PD, 69 controls	Patients with PD with baseline CSF $A\beta_{42}$ levels below 550 ng/L showed greater decline in delayed memory recall over 2 years than individuals with normal $A\beta_{42}$ levels (t = 3.40, P = 0.002) ↑ CSF t-α-Syn correlated with worsening in AQT over 2 years (r = 0.373, P = 0.030)	MMSE, AQT, 1-minute Animal Fluency test	/	Hall et al., 2015
	t-α-Syn, $A\beta_{42}$, p-tau 181	414 patients with PD, 189 controls	↓ $A\beta_{42}$ in PD-MCI *vs*. HC ↓ α-Syn is associated with both decreased composite cognitive score (β = 0.132, P = 0.019) and reduced score on the executive-attention domain (β = 0.137, P = 0.020), and associated at the trend level with decreased score in the memory (β = 0.109, P = 0.068) and visuospatial domains (β = 0.118, P = 0.058) No associations between $A\beta_{42}$ or p-tau 181 levels and cognitive domains	Visuospatial functions, verbal memory, executive function, attention, and MoCA scores	/	Skogseth et al., 2015
	t-α-Syn, o-α-Syn	21 patients with PD-NC, 20 patients with PDD, 13 HCs	↑ o-α-Syn levels in PDD *vs*. controls CSF total-α-Syn did not significantly differ among groups CSF o-α-Syn negatively correlated with MMSE (r = –0.31, P = 0.006)	MMSE, neuropsychological cognitive testing	/	Compta et al., 2015
	NfL	126 patients with PD, 71 controls	↑ NfL in PD-CI *vs*. PD-NC ↑ NfL in PD-NC *vs*. controls ↑NfL was associated with worse cognitive performance (lower MoCA scores)	MoCA, MMSE	Increased CSF NfL levels do not indicate the conversion to cognitive impairment beforehand	Lerche et al., 2020
	GFAP	210 patients with PD	↑ CSF GFAP predicted a more rapid decline over time not only in global cognition (MoCA, β = –0.013, P = 0.014), but also in episodic memory (HVLT Total Recall, β = –0.013, P = 0.014; HVLT Delayed Recall, β = – 0.018, P = 0.003; HVLT Retention, β = –0.015, P = 0.022), visuospatial abilities (JoLO, β = –0.015, P = 0.003), language (Semantic Fluency T est, β = –0.015, P = 0.046), as well as processing speed/ attention (SDMT, β = –0.033, P = 0.010)	MoCA, HVLT, JoLO, LNS, Semantic Fluency Test, SDMT	/	Liu et al., 2023
	Ng, $A\beta_{42}$/Ng	30 patients with PD, 30 controls	Ng and $A\beta_{42}$/Ng were correlated with MMSE scores (respectively, r = –0.644, P = 0.01, r = 0.597, P < 0.05)	MMSE, CDR	Identifying PD-CI Ng AUC = 0.8 Se = 67% Spe = 71.4% $A\beta_{42}$/Ng AUC = 0.88 Se = 92% Spe = 71.4%	Sancesario et al., 2020
	CSF Kininogen-1	74 patients with PD	KNG1 are significantly negatively correlated with RBANS (r = –0.0007, P = 0.04), but not with the MMSE score (r = –0.002; P = 0.2)	RBANS, MoCA, MMSE	AUC = 0.8. KNG1 predicting cognitive status as defined by RBANS	Markaki et al., 2020
Plasma	α-Syn	30 patients with PD-NC, 21 patients with PD- MCI, 29 patients with PDD, 34 controls	The plasma α-Syn level was significantly higher in PD patients with more severe cognitive dysfunction than in patients with PD-NC (P < 0.01) α-Syn was negatively correlated with MMSE scores (r = 0.3004, P < 0.001)	CDR, MMSE	/	Lin et al., 2017
	α-Syn, $A\beta_{40}$, t-tau	60 patients with PD, 28 controls	Plasma levels of α-Syn (r = –0.323, P = 0.002), $A\beta_{40}$ (r = 0.276, P = 0.01), and t-tau (r = –0.322, P = 0.002) were significantly correlated with MMSE scores.	CDR, MMSE	Distinguishing PD-NC from PD-CI α-Syn AUC = 0.799 Se = 95% Spe = 64.6% t-tau AUC = 0.726 Se = 67.5% Spe = 77.1% $A\beta_{40}$ AUC = 0.697 Se = 95.0% Spe = 47.9%	Chen et al., 2020b
	p-Tau181, $A\beta_{42}/A\beta_{40}$ ratio, p-Tau181/$A\beta_{42}$ ratio	26 patients with PD-MCI 23 patients with PD-NC 20 controls	↑ p-Tau181 in PD-MCI *vs*. PD-NC ↓ $A\beta_{42}/A\beta_{40}$ in PD-MCI *vs*. PD-NC ↑ p-Tau181/$A\beta_{42}$ ratio PD-MCI *vs*. PD-NC $A\beta_{42}$ levels were not significantly different among the three groups. Higher attention/working memory scores were associated with ↓ p-Tau181 (r = –0.367, P = 0.012) and ↓ p-Tau181/$A\beta_{42}$ ratio (r = –0.480, P = 0.001), and higher executive scores were correlated with ↑ $A\beta_{42}/A\beta_{40}$ ratio (r = 0.315, P = 0.033) and ↓ p-Tau181/$A\beta_{42}$ ratio (r = –0.354, P =0.016).	MMSE, MoCA	Diagnosis of PD-MCI basic variables + plasma biomarkers (p-Tau181 level and $A\beta_{42}/A\beta_{40}$ ratio) AUC = 0.849. basic variables + plasma biomarkers (p-Tau181 level and $A\beta_{42}/A\beta_{40}$ ratio) + the right lateral occipital CTh + FC value AUC = 0.987	Wang et al., 2022
	α-Syn, anti-α-Syn/$A\beta_{40}$	41 patients with PD, 106 controls	α-Syn and anti-α-Syn/$A\beta_{40}$ were positively associated with MMSE score, α-Syn/$A\beta_{40}$ were negatively associated with the MMSE score (all P values < 0.005).	MMSE	Predicting PD-CI Anti-α-Syn (AUC = 0.788) and anti-α-Syn/$A\beta_{40}$ (AUC = 0.749) were the only significant predictors of cognitive impairment	Chan et al., 2022
	NfL	57 patients with PD-NC, 34 patients with PD-MCI, 39 patients with PDD, 38 controls	↑ NfL in PDD *vs*. PD-NC or PD-MCI ↑ NfL levels were associated with lower MMSE scores (r = –0.49, P < 0.0001)	MMSE	Distinguishing PDD from PD-NC or PD-MCI (AUC = 0.7461) Se = 58.97% Spe = 86.81%	Zhu et al., 2021b

Table 1 | **Continued**

Source	Biomarker	Cases and controls	Main findings	Cognitive evaluation/ diagnostic criteria	Sensitivity, specificity, and accuracy	Reference
	GFAP	60 patients with PD-NC, 63 patients with PD-MCI, 24 patients with PDD, 15 controls	↑ GFAP in PDD *vs*. PD-MCI or PD-NC ↑ GFAP in PD-MCI *vs*. controls GFAP and MMSE scores were detected in the PD-MCI (r = –0.313, P = 0.013) and PDD groups (r = –0.506, P = 0.014), but not observed in the PD-NC group (r = –0.128, P = 0.335).	MMSE	Distinguishing PDD and PD-NC AUC = 0.79 Distinguishing PDD and PD-MCI AUC = 0.74 Distinguishing PDD and PD-NC or PD-MCI AUC = 0.77	Tang et al., 2023
	SIRT1	58 patients with PD, 91 controls	↓ Serum SIRT1 PD-CI *vs.* PD-NC Serum SIRT1 was positively related with MMSE (r = 0.301 , P < 0.05)	MMSE	Identifying PD-CI AUC = 0.739 Se: 67% Spe: 77%	Zhu et al., 2021a
	Hcy	195 patients with PD- MCI, 192 patients with PD Non-MCI	↑Hcy in PD-MCI *vs*. PD-Non-MCI ↑PWMHs in PD-CI *vs*. PD-Non-MCI	Memory, attention/ working memory visuospatial, executive, language domains	Predict PD-CI PWMHs AUC = 0.701 Hcy AUC = 0.688 Combination of PWMHs and Hcy AUC = 0.879	Zhang et al., 2023
	Ceramides	38 patients with PDD, 40 patients with PD-NC, 40 controls	↑ C24:1 PDD *vs*. PD-NC ↑ C14:0 PDD *vs*. PD-NC ↑ C14:0 PDD *vs*. controls C24:1 level was correlated with the scores of immediate verbal recall (r = –0.379 , P = 0.019) and delayed free recall (r = –0.380, P = 0.019), and C14:0 level was correlated with scores of delayed free recall (r = –0.341, P =0.036) and delayed recognition (r = –0.416, P = 0.009)	MMSE, CDR	/	Xing et al., 2016
	ARSA	59 patients with PD-CI, 61 patients with PD-NC	↓ ARSA in PD-CI *vs*. PD-NC ARSA were positively correlated with MMSE score, especially, orientation to time and place, divided attention, and delayed recall (P < 0.05)	MMSE	/	Li et al., 2022
	miR-203a-3p/ miR-16-5p	40 HCs, 37 patients with PD-NC, 23 patients with PD-MCI, 23 patients with PDD	↑ miR-203a-3p/miR-16-5p in PDD *vs*. PD-MCI No significant difference in miR-203a-3p/miR-16-5p in PD-NC *vs.* PD-MCI. the miR-203a-3p/miR-16-5p ratio showed a significant negative correlation with the total MoCA scores (r = –0.237, P = 0.024), especially the visuospatial, language, and orientation domains	MoCA	Distinguishing PDD from non-PDD (PD-MCI and PD-NC) miR-203a-3p/miR-16-5p Se: 77.77% Spe: 72.22% AUC = 0.759 miR-203a-3p/miR-16-5p + Age + UPDRS III Se: 88.89% Spe: 77.78% AUC = 0.8827	Hsu et al., 2024
	EV pro-inflammatory cytokines	113 patients with PD, 48 controls	PD-cognitive deficit (MMSE < 26) was positively associated with plasma EV pro-IL-1β, IL-6, TNF-α, and IL-10 levels and negatively with the TGF-β1 level	MMSE, MoCA	/	Chan et al., 2021
	EV tau, Aβ, and α-Syn	116 patients with PD, 46 controls	↑ EV tau PD-MCI *vs*. PD-NC ↑ EV tau PDD *vs*. PD-NC ↑ $Aβ_{42}$ PD-CI *vs*. PD-NC plasma EV tau level was negatively associated with MMSE and MoCA significantly	MMSE, MoCA	Combination of age and sex, plasma EV tau, $Aβ_{1–42}$, and α-Syn Se: 100% Spe: 60.0% AUC = 0.917	Chung et al., 2021
	NEV tau, Aβ, and α-Syn	103 patients with PD-NC, 81 patients with PD-MCI, 40 patients with PDD	↓ NEV α-Syn in PD-CI *vs*. PD-NC ↓ NEV α-Syn in PDD *vs*. PD-NC NEV $Aβ_{42}$ and NEV tTau did not differ between groups. ↑ NEV pTau181 in PD-CI *vs.* PD-NC ↓ α-Syn/pTau181 ratio in PD-CI *vs.* PD-NC	MoCA	Distinguishing PD-NC from PD-MCI α-Syn AUC = 0.65 pTau181 AUC = 0.62, $Aβ_{42}$ AUC = 0.59, Distinguishing PD-NC from PDD α-Syn AUC = 0.71 pTau181 AUC = 0.60 $Aβ_{42}$ AUC = 0.59	Blommer et al., 2023
	Exosomal prion protein	23 patients with PD-NC, 17 patients with PD-CI, 20 controls	↑ Exosomal prion protein in the PD-CI *vs*. PD-NCI group The plasma exosomal prion protein levels were also associated with visual spatial function (t = −3.816, P = 0.001), memory (t = –2.507, P = 0.017) and attention and calculation abilities. (t = –2.232, P = 0.033)	MoCA	/	Leng et al., 2020
Serum	UA	88 patients with PD, 68 controls	↓ UA PD *vs*. controls	MMSE	Identifying PD-CI UA AUC = 0.8032 Se: 61.7% Spe: 53.54%	Shi et al., 2022

Table 1 | **Continued**

Source	Biomarker	Cases and controls	Main findings	Cognitive evaluation/ diagnostic criteria	Sensitivity, specificity, and accuracy	Reference
	NfL, GFAP	103 patients with PD, 37 controls	↑ NfL in PDD *vs*. PD-MCI or PD-NC ↑ GFAP in PDD *vs*. PD-MCI or PD-NC serum NfL (r = –0.472, P < 0.001) and GFAP levels (r = –0.395, P < 0.001) were negatively correlated with MoCA scores	MoCA	Distinguishing PDD from PD-NC and PD-MCI NfL AUC = 0.840, Se: 70.0% Spe: 87.7% GFAP AUC = 0.771 Se: 83.3% Spe: 58.9% combined NfL and GFAP AUC = 0.859 Se: 80.0% Spe: 80.0%	Mao et al., 2023
	Vitamin D	112 patients with PD, 70 controls	↓ 25(OH)D in PD-MCI *vs*. PD-NC ↓ 25(OH)D in PDD *vs*. PD-MCI serum 25(OH)D was positively associated with MoCA score (r = 0.489, P < 0.001)	MoCA	Diagnosing PD-CI AUC = 0.713 Se: 53.3% Spe: 86.5%	Wu et al., 2022
	Hcy	47 patients with PD, 171 controls	↑ Hcy in PD-CI *vs*. PD-NC. At Hcy levels above 17.7 μM, the risk of PD-CI increased by 1.6 times for every 1 unit elevation in Hcy levels (95% CI: 1.1–2.2, P = 0.008)	PD-CRS	/	Ouyang et al., 2024
	BDNF	97 patients with PD, 102 controls	BDNF was associated with attention (r = 0.73), delayed memory (r = 0.60), language (r = 0.58), visuospatial/ constructional (r = 0.58) and immediate memory (r = 0.57)	RBANS	/	Wang et al., 2016
	GDNF	27 patients with PD-CI, 26 patients with PD-NC	↓ GDNF in PD-CI *vs*. PD-NC. ↓ GDNF/α-pro-GDNF in PD-CI *vs*. PD-NC. GDNF levels showed positive correlations with both MMSE and MoCA scores (r = 0.610, P < 0.001 and r = 0.579, P < 0.001, respectively), and a negative correlation with CDR scores (r = –0.573, P < 0.001).	MMSE, MoCA, CDR	Distinguishing PD-NC from PD-CI GDNF AUC = 0.859 Se: 85.19% Spe: 84.62%	Gao et al., 2021
	IGF-1, EGF	100 patients with PD, 100 controls	↓ IGF-1 in PD-CI *vs*. PD-NC. ↓EGF levels in PD-CI *vs*. PD-NC. IGF-1 levels positively correlated with MMSE total scores	MMSE	/	Shi et al., 2022
	HDL, TC, TG, Apo A1	135 patients with PD, 109 controls	↑ TC, TG, and Apo A1 PD-MCI *vs*. PD-NC ↑ TC, TG, and Apo A1 levels were independent risk factors for PD-MCI	MoCA	/	Deng et al., 2022
	Lp-PLA2	100 patients with PD, 60 controls	↑ Lp-PLA2 in PD-CI *vs*. PD-NC ↑ Lp-PLA2 level was an independent risk factor for PD-CI	MMSE, MoCA	Distinguishing PD-CI from PD-NC AUC = 0.659 Se: 91.3% Spe: 37%	Wu et al., 2024
	miR-29	37 patients with PD-MCI, 22 patients with PDD, 40 HCs	↓ MiR-29a/b/c in PDD *vs*. PD-NC ↓ miR-29b/c in PDD *vs*. PD-MCI group ↓ miR-29b in PD-MCI *vs*. PD-NC	MMSE, SDMT, TMT-A, CWT, TMT-B, BNT, AFT, AVLT, Clock Drawing Test, the copy task of the Rey Osterrieth Complex Figure Test	Distinguishing PDD from non-PDD miR-29b: AUC = 0.86 miR-29a: AUC = 0.689 miR-29c: AUC = 0.701 Distinguishing PD-CI from PD-NC miR-29b: AUC = 0.726 miR-29a: AUC = 0.638 miR-29c: AUC = 0.563	Han et al., 2020
	YWHAG	87 patients with PD-NC, 91 patients with PD-MCI, 63 patients with PDD	↑ YWHAG PD-MCI and PDD *vs*. PD-NC ↑ YWHAG PDD *vs*. PD-MCI YWHAG expression levels and MoCA scores (r = –0.5490, P < 0.0001)	MoCA	Distinguishing PD-NC from PDD AUC = 0.954 PD-NC from PD-MCI and PDD AUC = 0.763	Peng et al., 2024
Saliva	Neisseria, Lactobacillus	27 HCs, 45 patients with PD-MCI, 43 patients with PDD, 8 patients with PD-NC	Neisseria exhibited a significant positive correlation with the MMSE score (P = 0.003, Spearman's ρ = 0.268) and a significant negative correlation with the CDR score (P = 0.004, Spearman's ρ = –0.27).	MMSE, CDR	/	Arikan et al., 2023
Urine	Ser(P)-1292 LRRK2	79 patients with PD, 79 controls	Ser(P)-1292 LRRK2 levels were higher in patients with PD and worse cognition and correlated with poor performance in MoCA (r = –0.2679)	MoCA	Prediction of the lower quartile of poor MoCA performance AUC = 0.731 Se: 60% Spe: 89%	Fraser et al., 2016
	kynurenine	41 patients with PD, 41 controls	KYN negatively correlated with MMSE score (r = –0.434, P = 0.005)	MMSE	Detection of PD AUC = 0.776. Se: 90.2% Spe: 65.9%	Bai et al., 2021

/: Not mentioned; AQT: cognitive processing speed; ARSA: arylsulfatase A; Aβ42: amyloid-beta 42; CDR: clinical dementia rating; CSF: cerebrospinal fluid; CTh: cortical thickness; EGF: epidermal growth factor; EV: extracellular vesicle; FC: functional connectivity; GDNF: glial cell line-derived neurotrophic factor; GFAP: glial fibrillary acidic protein; HCY: homocysteine; HVLT: hopkins verbal learning test; IGF-1: insulin-like growth factor-1; JoLO: benton judgment of line orientation; LNS: letter number sequencing; Lp-PLA2: lipoprotein-associated phospholipase A2; miRNA: microRNA; NEVs : neuronal-origin enriched extracellular vesicles; NfL: neurofilament light chain protein; Ng: neurogranin; PD: Parkinson's disease; PD-CI: PD with cognitive impairment; PD-CRS: Parkinson's Disease Cognitive Rating Scale; PDD: PD with dementia; PD-MCI: PD with mild cognitive impairment; PD-NC: PD with normal cognition; pmTOR: phosphorylated mechanistic target of rapamycin; pSer312-IRS-1:3 insulin receptor substrate-1 phosphorylated Serine312; pTau: phosphorylated tau; pTau181: phosphorylated Tau Threonine181; PWMHs: periventricular white matter hyperintensities; pY-IRS-1: insulin receptor substrate-1 4 phosphorylated Tyrosine (pan phosphor Tyrosine); RBANS: Repeatable Battery for the Assessment of the Neuropsychological Status; SDMT: symbol digit modalities test; SIRTs: silent information regulator 1; UA: uric acid; UCH-L1:ubiquitin c-terminal hydrolase; UPDRS III: part III of the Unified Parkinson's Disease Rating Scale; α-Syn: α-synuclein.

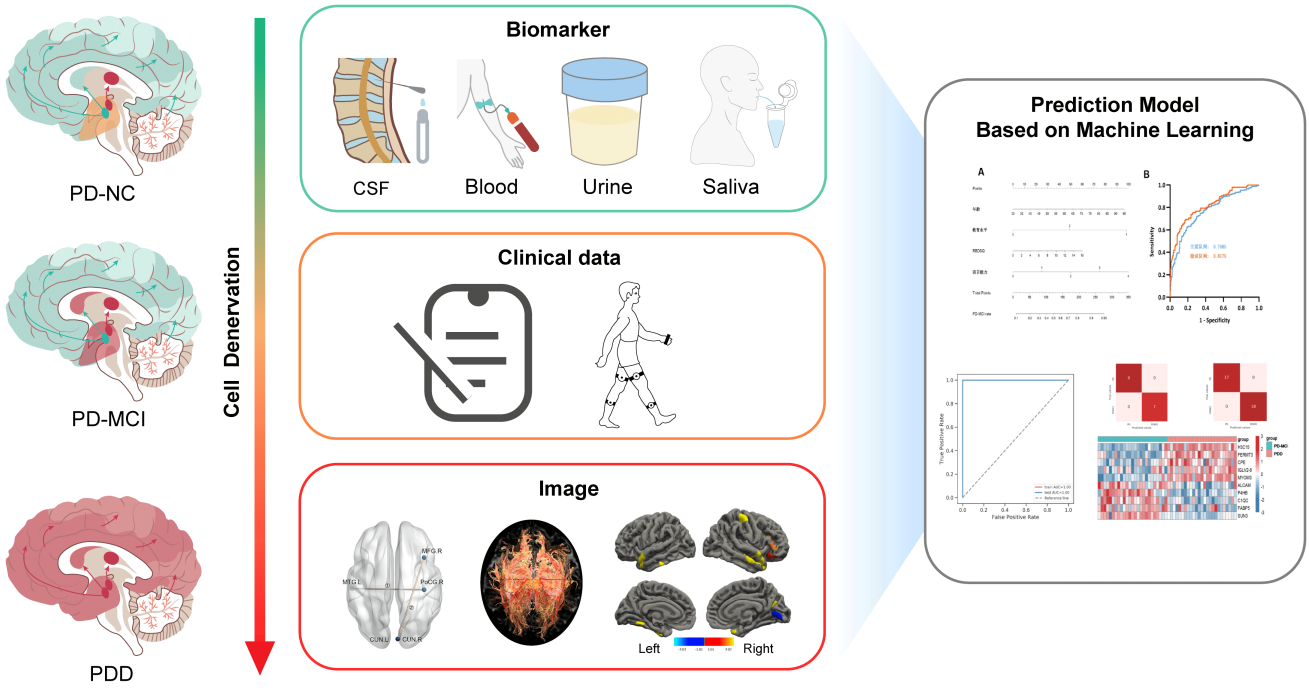

Figure 3 | **Development of a predictive model for cognitive impairment in PD.**
The development of a predictive model for individuals transitioning from PD-NC to PDD usually requires a multifaceted approach that integrates biomarkers, clinical data, and imaging techniques. A robust dataset of patients with PD-CI should be obtained by clinical physicians, including data for various biomarkers like CSF, blood, urine, saliva, and genetic markers, clinical data such as demographic information, gait, symptom severity, the degree of cognitive function, and medication history, as well as imaging data from MRI, SPECT, and PET scans. Machine learning algorithms can predict the likelihood of PD-NC progressing to PDD by analyzing a combination of factors over time based on data on various biomarkers, clinical features, cognitive assessments, neuroimaging results, and, potentially, genetic information. By identifying patterns and relationships within these data points, the algorithms can generate predictions on the probability of individuals transitioning from PD-NC to PDD, which could be integrated into clinical practice for early intervention and personalized treatment plans for patients with PD. CSF: Cerebrospinal fluid; PD: Parkinson's disease; PD-CI: cognitive impairment in PD; PDD: PD dementia; PD-NC: normal cognitive function in PD.

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