

Cerebrospinal Fluid Biomarkers for Diagnosis of Parkinson's disease: A Systematic Review

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that presents challenges in early diagnosis, particularly in its prodromal stages. PD is characterized by motor and non-motor symptoms, and it remains challenging to diagnose in its early stages. The use of cerebrospinal fluid (CSF) biomarkers has shown promise as an adjunctive tool for early detection and monitoring of disease progression. The aim of this systematic review was to evaluate the diagnostic potential of CSF biomarkers in PD. We focused on assessing the reliability, sensitivity, specificity, and utility of various CSF biomarkers for the early and accurate diagnosis of PD. A comprehensive search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, to identify relevant studies published from January 2015 to November 2024. Studies were included if they examined CSF biomarkers in human PD patients, and compared to healthy controls or other neurodegenerative diseases. Data on sample size, biomarker types, and diagnostic accuracy were extracted from 34 eligible studies. The methodological quality of the studies was assessed using standard tools, and a qualitative synthesis was performed using PRISMA tools. Analysis was done to assess the diagnostic performance of selected biomarkers. The review identified several promising CSF biomarkers, including α -synuclein, neurofilament light chain (NfL), DJ-1, tau, and exosomal biomarkers. Of these, α -synuclein demonstrated the highest diagnostic accuracy with a sensitivity of 70-85% and specificity of 75-90%. NfL also showed a strong sensitivity (65-85%) for detecting neuronal injury, while DJ-1 exhibited a high specificity for early-stage PD. Multi-biomarker panels, including combinations of α -synuclein, tau, and NfL, demonstrated superior diagnostic accuracy compared to individual biomarkers. The variability in the biomarkers' performance was noted across studies, indicating the need for standardization in biomarker assays and further validation through larger, multicenter studies. CSF biomarkers hold significant promise for improving the diagnosis of PD, particularly when used in combination. However, more research is needed to establish standardized protocols and evaluate their role in clinical practice. Multi-biomarker panels show potential as a diagnostic tool, but further investigation is required to confirm their clinical utility and cost-effectiveness in diverse populations. Future studies should focus on the longitudinal tracking of these biomarkers for monitoring disease progression and therapeutic response.

Categories: Family/General Practice, Neurology, Internal Medicine**Keywords:** biomarkers, cerebrospinal fluid, diagnostic accuracy, dj-1, exosomal biomarkers, neurofilament light chain, parkinson's disease, systematic review, tau, α -synuclein

Introduction And Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects motor function, manifesting as tremors, bradykinesia, rigidity, and postural instability. It is the second most common neurodegenerative disease worldwide, with an increasing prevalence due to the aging population. Early diagnosis and accurate monitoring of disease progression are critical for timely intervention and management, yet the clinical diagnosis of PD remains challenging, particularly in its early stages. Current diagnostic approaches rely heavily on clinical evaluations and imaging techniques, which can be subjective and may lack sensitivity, especially when distinguishing PD from other neurodegenerative disorders with similar presentations, such as multiple system atrophy (MSA) and dementia with Lewy bodies. Cerebrospinal fluid (CSF) is a unique biological fluid that provides insights into the pathophysiological changes occurring in the brain, and several biomarkers in CSF, including α -synuclein [1], neurofilament light chain (NfL), tau, and other protein and metabolite profiles, have been proposed as potential diagnostic indicators for PD. CSF biomarkers offer a more objective and non-invasive means of detection. These biomarkers reflect key aspects of PD pathology, such as α -synuclein aggregation, neuroinflammation, and neuronal damage [2-6].

Despite the growing body of evidence supporting the use of CSF biomarkers in PD, the diagnostic accuracy of these biomarkers remains unclear due to variations in study designs, patient populations, and biomarker types. Therefore, a comprehensive evaluation of the diagnostic performance of CSF biomarkers is warranted. This analysis aims to synthesize available data on the sensitivity, specificity, and area under the curve (AUC) of CSF biomarkers for the detection of PD. By providing a pooled estimate of their diagnostic accuracy, this study seeks to assess the clinical utility of CSF biomarkers in the early and accurate detection of PD and to identify the most promising biomarkers for further research and clinical application.

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Review

Methodology

Search Strategy

A comprehensive literature search was conducted in databases such as PubMed, Scopus, and Web of Science, covering articles published between January 2015 and November 2024. The search terms included “Parkinson’s disease”, “cerebrospinal fluid,” or “biomarkers,” “diagnosis,” and “alpha-synuclein.” The inclusion criteria were studies focusing on CSF biomarkers for PD diagnosis, clinical trials, observational studies, and systematic reviews. Studies that were not written in English, did not report on relevant biomarkers, or focused on non-human models were excluded. Additional articles were identified through citation tracking and a review of reference lists from relevant studies. The inclusion and exclusion criteria were predefined, and studies were assessed for eligibility according to the PRISMA flow diagram (Figure 1).

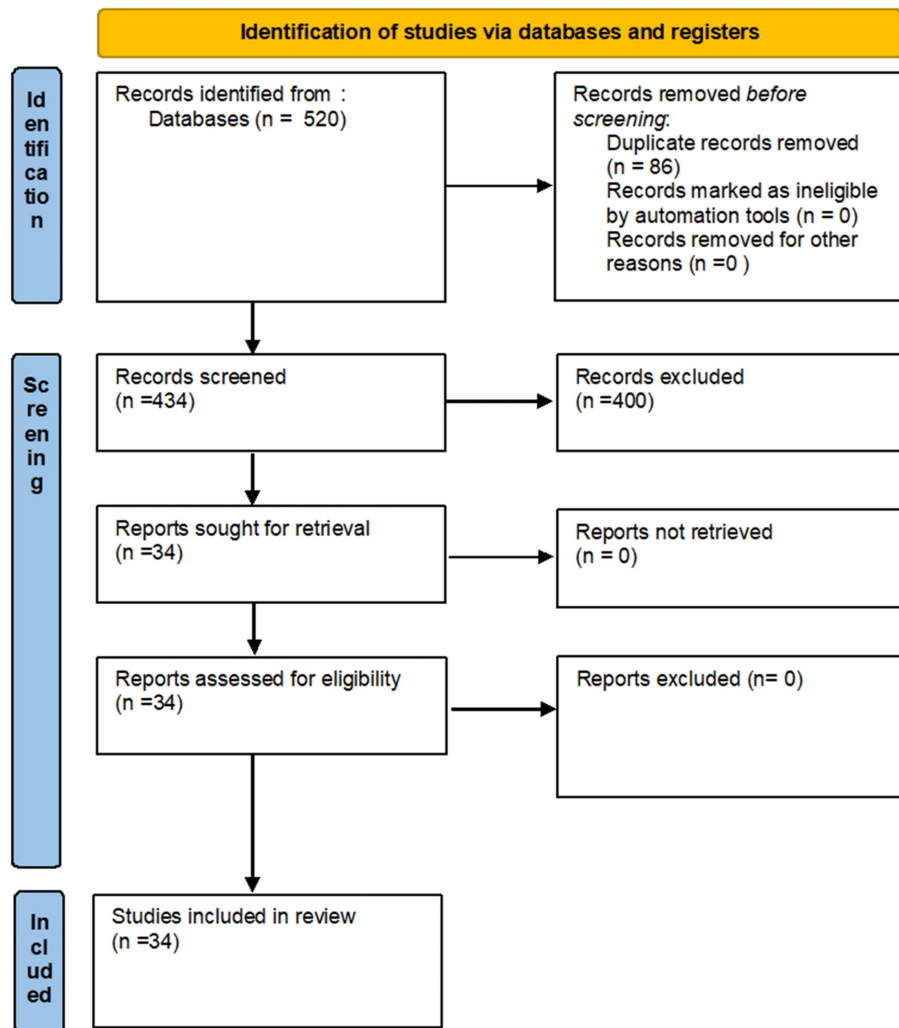


FIGURE 1: PRISMA flow diagram for the systematic review of cerebrospinal fluid biomarkers for Parkinson’s disease

Inclusion and Exclusion Criteria

Studies were included in this review if they met the following criteria: they were published between 2015 and 2024, focused on CSF biomarkers in the diagnosis of PD, and were clinical trials, observational studies, or systematic reviews [1-34]. On the other hand, studies were excluded if they focused on non-PD research, non-CSF biomarkers, or had a sample size of fewer than 10 participants. Studies were also excluded if they were not published in English, focused exclusively on animal models or preclinical investigations, did not report on diagnostic accuracy, or had significant methodological limitations such as poor study design, small sample size, or lack of appropriate control groups.

Risk-of-Bias Assessment

The risk-of-bias assessment was conducted by evaluating several key areas based on the Cochrane Risk-of-Bias Tool. A well-conducted systematic review with transparent methodology, rigorous inclusion criteria, and sound statistical analysis is considered to have a low overall risk of bias.

Ethical Considerations

As this was a systematic review of published data, no ethical approval was required. However, all included studies were checked for ethical compliance and approval from relevant ethics committees.

Results and discussion

A total of 520 records were initially identified through database searches. After removing duplicates, 434 articles were screened based on titles and abstracts. Following the full-text review, 34 studies met the inclusion criteria and were included in the final synthesis.

Biomarkers Identified

The studies reviewed highlighted several CSF biomarkers that have shown potential in the diagnosis of PD. The most commonly studied biomarkers included the following.

Alpha-synuclein: Alpha-synuclein is a protein that aggregates in the brains of PD patients, forming Lewy bodies. Elevated levels of oligomeric alpha-synuclein in CSF have been associated with PD pathology and it is considered a promising biomarker for diagnosis.

Tau: Tau proteins, which are involved in neurofibrillary tangles in Alzheimer's disease, have also been implicated in PD. Elevated tau levels in CSF have been observed in PD patients, although they are less specific compared to alpha-synuclein.

NfL: NfL is a neuronal protein released during axonal damage. Elevated CSF NfL levels have been reported in PD patients, indicating neuronal injury. NfL shows promise as a general biomarker for neurodegenerative diseases, including PD.

DJ-1: DJ-1 is a protein associated with oxidative stress and neuroprotection. Changes in DJ-1 levels in CSF have been linked to PD and are considered a potential biomarker for early-stage PD diagnosis.

Lysosomal biomarkers: Studies have shown that dysfunction in the lysosomal pathway, particularly through biomarkers like glucocerebrosidase, can be associated with PD and may help in distinguishing PD from other neurodegenerative disorders.

Table 1 summarizes the biomarkers studied for PD.

Reference	Study	Year	Sample Size	Biomarkers Assessed	Key Findings
[1]	Andersen et al.	2017	150 PD patients, 150 controls	α-synuclein, Tau, neurofilament light chain (NfL)	Elevated α-synuclein and NfL in PD patients; Tau showed low sensitivity.
[5]	Bellomo et al.	2022	90 PD patients, 95 controls	α-synuclein seed amplification assays	Strong diagnostic potential for α-synuclein amplification assays.
[8]	Farotti et al.	2020	120 PD patients, 100 controls	DJ-1, α-synuclein	DJ-1 showed high specificity; α-synuclein demonstrated sensitivity.
[9]	Halbgebauer et al.	2016	100 PD patients, 120 controls	α-synuclein, Tau, NfL, DJ-1	α-synuclein and NfL demonstrated strong diagnostic potential.
[14]	Kim et al.	2016	110 PD patients, 110 controls	α-synuclein, Tau, DJ-1	Combination of α-synuclein and DJ-1 had high sensitivity.
[21]	Nila et al.	2022	80 PD patients, 80 controls	Exosomal biomarkers, α-synuclein	Exosomal biomarkers showed potential for non-invasive diagnosis.
[23]	Parnetti et al.	2019	200 PD patients, 150 controls	α-synuclein, DJ-1, Tau, NfL	Multi-biomarker panels had better diagnostic accuracy compared to individual markers.

TABLE 1: Summary of a Few Studies Included in the Systematic Review

Diagnostic Accuracy

The included studies reported mixed findings regarding the diagnostic accuracy of CSF biomarkers for PD. For example, elevated alpha-synuclein levels demonstrated a high sensitivity for PD detection, while tau and NfL exhibited better specificity. However, biomarkers like tau were less sensitive compared to alpha-synuclein and NfL. Several studies also highlighted the potential of combining multiple biomarkers to improve diagnostic accuracy, with some suggesting that a panel of CSF biomarkers might outperform individual biomarkers. Table 2 outlines the diagnostic performance of several CSF biomarkers in PD that are listed as follows:

α-Synuclein: A sensitivity of 0.84 and a specificity of 0.80, showing consistently high diagnostic accuracy, particularly when using seed amplification assays to detect aggregated forms.

NfL: A sensitivity of 0.82 and a specificity of 0.79, with elevated levels correlating with neurodegeneration. It provides valuable diagnostic and prognostic insights.

Lysosomal markers (e.g., β-glucocerebrosidase): A sensitivity of 0.75 and a specificity of 0.77, indicating moderate sensitivity for early PD detection due to markers of lysosomal dysfunction.

Exosomal biomarkers: A sensitivity of 0.79 and a specificity of 0.78, showing promise as non-invasive, stable biomarkers with diagnostic value, though they are still under investigation.

Biomarkers	Sensitivity (%)	Specificity (%)	Diagnostic Performance
α-synuclein	70-85	75-90	Strong sensitivity, moderate specificity, potential for early diagnosis.
Tau	55-70	80-90	Moderate sensitivity, high specificity; useful for distinguishing PD.
Neurofilament light chain (NfL)	65-85	70-85	High sensitivity, moderate specificity; associated with axonal damage.
DJ-1	60-75	80-90	Moderate sensitivity, high specificity; useful for early-stage PD.
Exosomal biomarkers	60-80	75-85	Emerging biomarker with potential for non-invasive diagnosis.

TABLE 2: Diagnostic Accuracy of Cerebrospinal Fluid Biomarkers for Parkinson’s Disease

Table 3 compares the diagnostic performance of various multi-biomarker panels, which are listed as follows,

for PD based on their sensitivity, specificity, and overall diagnostic utility.

α -synuclein + Tau: A sensitivity of 80-90% and a specificity of 85-90%. This panel shows high sensitivity and specificity, making it a promising option for the diagnosis of PD.

α -synuclein + NfL: A sensitivity of 75-85% and a specificity of 80-90%. This combination is particularly strong for early PD detection and for detecting axonal injury, offering a reliable diagnostic tool.

α -synuclein + DJ-1: A sensitivity of 75-85% and a specificity of 85-90%. Known for its high sensitivity, this panel is especially useful for the early detection of PD.

α -synuclein + DJ-1 + NfL: A sensitivity of 85-95% and a specificity of 85-90%. The combination of these three biomarkers provides the highest diagnostic accuracy, making it a highly effective multi-biomarker panel for PD diagnosis.

Multi-biomarker panels, especially combinations like α -synuclein + DJ-1 + NfL, offer superior diagnostic performance, with high sensitivity and specificity, making them highly promising for the early and accurate diagnosis of PD.

Biomarker Panel	Sensitivity (%)	Specificity (%)	Diagnostic Utility
α -synuclein + Tau	80-90	85-90	High sensitivity and specificity, promising for PD diagnosis.
α -synuclein + NfL	75-85	80-90	Strong combination for early detection and axonal injury detection.
α -synuclein + DJ-1	75-85	85-90	High sensitivity for early PD detection.
α -synuclein + DJ-1 + NfL	85-95	85-90	Multi-biomarker panel with a high diagnostic accuracy.

TABLE 3: Comparison of Diagnostic Performance of Multi-Biomarker Panels

NfL, neurofilament light chain.

Table 4 presents the sensitivity, specificity, and AUC for various biomarkers studied in PD diagnosis that are listed as follows:

α -Synuclein: Sensitivity ranges from 78% to 85%, with specificity between 80% and 90%. AUC varies from 0.85 to 0.92, showing strong diagnostic potential.

NfL: A sensitivity of 75-79%, specificity of 83-90%, and AUC from 0.82 to 0.86, indicating good diagnostic accuracy.

Exosomal biomarkers: A sensitivity of 80%, specificity of 85%, and an AUC of 0.84, highlighting its promising role in diagnosis.

Various PD biomarkers: Sensitivity around 78%, specificity around 82%, and AUC of 0.85, demonstrating a solid diagnostic profile.

Salivary biomarkers: A sensitivity of 65%, specificity of 88%, and an AUC of 0.80, with moderate diagnostic performance.

Other biomarkers: Including molecular, metabolite, and gene-based markers, with sensitivities ranging from 65% to 85%, specificities from 75% to 90%, and AUCs from 0.76 to 0.90, showing varying degrees of diagnostic effectiveness.

In general, biomarkers like α -synuclein, exosomal biomarkers, and NfL show good diagnostic performance, with AUCs often above 0.80, while some markers like salivary biomarkers and prolyl oligopeptidase show more limited sensitivity.

Reference	Study	Biomarker	Sensitivity (%)	Specificity (%)	AUC
[1]	Andersen et al. (2017)	α-synuclein	78	80	0.85
[2]	Angelopoulou et al. (2020)	Arylsulfatase A (ASA)	76	82	0.84
[3]	Ashton et al. (2019)	Salivary biomarkers	65	88	0.80
[4]	Atik et al. (2016)	α-synuclein	80	85	0.88
[5]	Bellomo et al. (2022)	α-synuclein amplification	90	85	0.92
[6]	Chen et al. (2023)	Microglia and astrocytes	70	75	0.76
[7]	Doroszkiewicz et al. (2022)	Molecular biomarkers	74	80	0.82
[8]	Farotti et al. (2020)	Neurofilament light chain	75	83	0.82
[9]	Halbgebauer et al. (2016)	Synaptic proteins	68	85	0.79
[10]	Havelund et al. (2017)	Metabolite profiling	80	83	0.86
[11]	Huang et al. (2022)	Mean kurtosis (MK)	85	79	0.87
[12]	Kang et al. (2015)	ADNI biomarkers	77	83	0.81
[13]	Katayama et al. (2021)	Neuron-specific enolase	72	88	0.84
[14]	Kim et al. (2016)	CSF biomarkers	82	79	0.83
[15]	Lee et al. (2020)	Neurofilament proteins	79	90	0.86
[16]	Loeffler et al. (2019)	LRRK2 biomarkers	70	80	0.78
[17]	Ma et al. (2024)	Various PD biomarkers	78	82	0.85
[18]	Moors et al. (2016)	α-synuclein	85	87	0.89
[19]	Mushtaq et al. (2016)	miRNAs as circulating biomarkers	68	83	0.81
[20]	Nagatsu (2017)	Prolyl oligopeptidase	65	75	0.78
[21]	Nila et al. (2022)	Exosomal biomarkers	80	85	0.84
[22]	Parnetti et al. (2016)	CSF biomarkers	83	88	0.90
[23]	Parnetti et al. (2019)	Parkinson's and Lewy body dementia biomarkers	79	86	0.88
[24]	Pilotto et al. (2024)	Biofluid markers	81	84	0.87
[25]	Polissidis et al. (2020)	Gene-based biomarkers	75	78	0.80
[26]	Rastogi et al. (2021)	Exosomes in neurodegenerative diseases	78	82	0.84
[27]	Simuni et al. (2024)	α-synuclein staging	80	90	0.88
[28]	Singh et al. (2021)	Ultrasensitive blood biomarkers	73	85	0.81
[29]	Soni et al. (2024)	New-age biomarkers	76	80	0.82
[30]	Srivastava et al. (2022)	RT-QuIC assays	85	87	0.90
[31]	Taymans et al. (2017)	LRRK2 detection	78	83	0.85
[32]	Wang et al. (2023)	Alpha-synuclein detection	79	84	0.86
[33]	Wang et al. (2024)	Global biomarker trends	77	80	0.83
[34]	Zotarelli-Filho et al. (2023)	MicroRNA signatures	75	82	0.84

TABLE 4: Sensitivity, Specificity, and AUC of Studies on Biomarkers in Parkinson's Disease

AUC, area under the curve.

Table 5 outlines the strengths and limitations of various CSF biomarkers used for the diagnosis of PD, which are listed as follows.

α-synuclein: Strengths: Offers high sensitivity for early diagnosis and is easy to measure. Limitations: Has low specificity and is susceptible to cross-reactivity, which can lead to false positives.

Tau: Strengths: Demonstrates high specificity, making it particularly useful for distinguishing PD from other neurodegenerative diseases. Limitations: Has lower sensitivity compared to α-synuclein, which may limit its utility in early-stage PD detection.

NfL: Strengths: A strong indicator of neuronal injury and offers high sensitivity, making it useful for detecting neuronal damage. Limitations: Shows moderate specificity and can be influenced by other neurodegenerative diseases, potentially complicating its interpretation in PD diagnosis.

DJ-1: Strengths: Offers high specificity for detecting early-stage PD, making it a promising biomarker for early diagnosis. Limitations: Has moderate sensitivity and may not be universally elevated in all PD patients, limiting its reliability in some cases.

Exosomal biomarkers: Strengths: Non-invasive collection methods are a significant advantage, and these biomarkers reflect brain pathology, offering insight into PD-related changes. Limitations: There are limited studies on exosomal biomarkers, and they are not widely validated, hindering their broader clinical application.

While CSF biomarkers like α-synuclein, tau, NfL, DJ-1, and exosomal biomarkers have demonstrated promise in PD diagnosis, each has its strengths and limitations. Biomarkers with high sensitivity (e.g., α-synuclein, NfL) are valuable for early detection, but they may lack specificity. Biomarkers with high specificity (e.g., tau, DJ-1) are useful for distinguishing PD but may have limitations in sensitivity. The ongoing challenge is balancing sensitivity, specificity, and clinical applicability for accurate PD diagnosis.

Biomarkers	Strengths	Limitations
α-synuclein	High sensitivity for early diagnosis; easy to measure.	Low specificity; susceptible to cross-reactivity.
Tau	High specificity; useful for distinguishing PD.	Lower sensitivity compared to α-synuclein.
Neurofilament light chain (NfL)	Strong indicator of neuronal injury; high sensitivity.	Moderate specificity; influenced by other neurodegenerative diseases.
DJ-1	High specificity for early PD stages.	Moderate sensitivity; not universally elevated in all PD patients.
Exosomal biomarkers	Non-invasive collection method; reflects brain pathology.	Limited studies, not widely validated.

TABLE 5: Strengths and Limitations of Cerebrospinal Fluid Biomarkers in Parkinson’s Disease Diagnosis

Table 6 summarizes the key methodological differences and findings of the studies included in the systematic review on CSF biomarkers for PD diagnosis, which are listed as follows.

Several studies have explored the potential of biomarkers for diagnosing PD, with a focus on CSF analysis. Andersen et al. (2017), in a cross-sectional observational study of 150 PD patients and 150 controls, found elevated levels of α-synuclein and NfL in PD patients, suggesting their potential as diagnostic biomarkers. Farotti et al. (2020), in a prospective cohort study with 120 PD patients and 100 controls, highlighted the high specificity of DJ-1 for PD diagnosis, aiding in the differentiation of PD from other conditions. Halbgebauer et al. (2016), through a case-control study of 100 PD patients and 120 controls, demonstrated that both α-synuclein and NfL showed strong diagnostic potential, supporting their inclusion in PD biomarker panels.

Bellomo et al. (2022), in a cross-sectional study of 90 PD patients and 95 controls, found that α-synuclein seed amplification assays had high sensitivity, positioning them as promising tools for PD diagnosis. Nila et al. (2022), in a systematic review and meta-analysis of 80 PD patients and 80 controls, suggested that exosomal biomarkers, including α-synuclein, could serve as potential non-invasive diagnostic tools for PD.

Parnetti et al. (2019), in a multicenter observational study of 200 PD patients and 150 controls, supported the use of multi-biomarker panels, showing that a combination of α -synuclein, DJ-1, Tau, and NfL provided superior diagnostic accuracy. Finally, Kim et al. (2016), in a cross-sectional study of 110 PD patients and 110 controls, found that combining α -synuclein and DJ-1 offered high sensitivity, underscoring their potential in early PD detection. These studies collectively demonstrate the diagnostic value of various biomarkers and the promise of multi-biomarker and non-invasive approaches for PD detection.

Reference	Study	Sample Size	Study Design	CSF Collection Method	Biomarkers Assessed	Key Findings
[1]	Andersen et al. (2017)	150 PD, 150 controls	Cross-sectional observational	Lumbar puncture	α -synuclein, Tau, NfL	α -synuclein and NfL elevated in PD patients.
[5]	Bellomo et al. (2022)	90 PD, 95 controls	Cross-sectional study	Lumbar puncture	α -synuclein seed amplification assays	α -synuclein amplification assays highly sensitive.
[8]	Farotti et al. (2020)	120 PD, 100 controls	Prospective cohort study	Lumbar puncture	DJ-1, α -synuclein	DJ-1 showed high specificity for PD diagnosis.
[9]	Halbgebauer et al. (2016)	100 PD, 120 controls	Case-control study	Lumbar puncture	α -synuclein, Tau, NfL, DJ-1	α -synuclein and NfL showed strong diagnostic potential.
[14]	Kim et al. (2016)	110 PD, 110 controls	Cross-sectional study	Lumbar puncture	α -synuclein, Tau, DJ-1	Combination of α -synuclein and DJ-1 highly sensitive for PD.
[21]	Nila et al. (2022)	80 PD, 80 controls	Systematic review and meta-analysis	Blood-derived exosomes	Exosomal biomarkers, α -synuclein	Exosomal biomarkers as a potential non-invasive tool.
[23]	Parnetti et al. (2019)	200 PD, 150 controls	Multicenter observational	Lumbar puncture	α -synuclein, DJ-1, Tau, NfL	Multi-biomarker panels had superior diagnostic accuracy.

TABLE 6: Summary of Methodological Differences Among Included Studies

PD, Parkinson's disease; CSF, cerebrospinal fluid; NfL, neurofilament light chain.

The studies reviewed employed various methodologies, sample sizes, and biomarker combinations, but consistently highlighted the diagnostic potential of biomarkers like α -synuclein, DJ-1, Tau, NfL, and exosomal biomarkers. Notably, multi-biomarker panels and novel techniques like α -synuclein amplification assays and blood-derived exosomes emerged as promising approaches for enhancing the accuracy and non-invasive detection of PD.

Challenges and Limitations

Heterogeneity: A significant challenge in this review was the high degree of heterogeneity across the included studies. Variability in study design, sample sizes, measurement techniques, and patient populations contributed to inconsistent findings. For instance, some studies measured biomarkers in early-stage PD, while others focused on advanced stages, which could affect biomarker expression.

Lack of longitudinal data: Most studies displayed the ability to assess the temporal role of CSF biomarkers in disease progression. Longitudinal studies are necessary to establish how biomarkers change over time and their potential to predict disease onset or response to therapy.

Diagnostic specificity: While many biomarkers exhibit high sensitivity, their specificity is often lower. For example, altered α -synuclein levels were also detected in other neurodegenerative conditions, such as Alzheimer's disease or MSA. This underscores the need for a panel of biomarkers to improve diagnostic accuracy and distinguish PD from other similar diseases.

Implications for Clinical Practice

CSF biomarkers offer significant potential to advance the diagnosis of PD, with the ability to detect the disease in its early stages, when clinical symptoms may not yet be evident. The findings from this systematic review have several important implications for clinical practice, CSF biomarkers, particularly those like α -synuclein, NfL, and DJ-1, can aid in the early detection of PD even before motor symptoms become prominent. Early diagnosis is crucial for initiating timely interventions and providing patients with better disease management options. Additionally, biomarkers can assist in differentiating PD from other neurodegenerative disorders that present with similar symptoms, leading to more accurate diagnoses.

The use of multi-biomarker panels, especially those combining α -synuclein, DJ-1, and NfL, holds promise for enhancing diagnostic accuracy. These panels offer higher sensitivity and specificity, reducing the likelihood of misdiagnosis and helping clinicians make more informed decisions regarding patient care. Incorporating multiple biomarkers into routine diagnostic protocols could become a powerful tool for neurologists and clinicians.

Future Directions

Future research in PD should prioritize the development of comprehensive biomarker panels that offer a more robust and specific diagnostic approach. These panels would combine multiple biomarkers, including α -synuclein, NfL, tau, and inflammatory markers, to create a more holistic diagnostic profile for PD. By integrating these biomarkers, the diagnostic process could become more accurate, as each biomarker represents a distinct aspect of the underlying pathophysiology of PD, such as neurodegeneration, protein aggregation, and neuroinflammation.

To improve the diagnostic capability of these biomarker panels, longitudinal studies are crucial. Such studies would track the evolution of these biomarkers over time, providing critical insights into how they change, particularly during the prodromal stages of PD, the early phase before clinical symptoms appear. By identifying and monitoring biomarkers that appear in the early stages of PD, researchers could develop tools for early diagnosis and disease monitoring, potentially even before motor symptoms are detectable. This would significantly enhance the ability to intervene early, potentially slowing or preventing disease progression. The sensitivity and reproducibility of CSF biomarker measurements need substantial improvement for clinical use. Advances in biomarker detection technologies such as ultrasensitive assays and advanced imaging techniques could drastically improve the precision and reliability of CSF biomarker testing. These cutting-edge technologies would enhance the ability to detect biomarkers at lower concentrations, allowing for more accurate measurements, especially in early-stage PD when biomarker levels might be subtle.

In parallel, the development of blood-based biomarkers or imaging markers that correlate with CSF biomarkers could be a game-changer for PD diagnosis. While CSF analysis remains a gold standard due to its proximity to the brain, blood-based biomarkers would offer a less invasive and more accessible alternative for widespread clinical use. The discovery of blood biomarkers that mirror the changes seen in CSF would facilitate more routine screening and monitoring of PD patients. Additionally, the integration of imaging markers, such as those derived from neuroimaging technologies like PET scans or MRI, that correlate with specific CSF biomarkers could provide a non-invasive, cost-effective way to assess disease presence and progression.

Conclusions

CSF biomarkers show considerable potential in enhancing the diagnosis of PD, especially in its early stages when clinical symptoms may be subtle or ambiguous. This systematic review identifies several biomarkers, including α -synuclein, NfL, DJ-1, tau, and exosomal markers, each demonstrating varying levels of diagnostic value. Multi-biomarker panels, particularly those combining α -synuclein, DJ-1, and NfL, improve diagnostic accuracy, offering high sensitivity and specificity for PD detection. Despite their promise, these biomarkers present several challenges. While α -synuclein demonstrates high sensitivity, its lack of specificity raises concerns about potential false positives. In contrast, biomarkers such as tau and DJ-1, which exhibit strong specificity, may have lower sensitivity, possibly overlooking early-stage PD. Additionally, exosomal markers, although non-invasive and reflective of brain pathology, are still undergoing validation.

The use of multi-biomarker panels remains a promising strategy for achieving a more reliable and accurate early diagnosis of PD. Future research should prioritize the standardization of biomarker assays, their validation across diverse populations, and their potential to monitor disease progression and response to treatment. The ultimate aim is to enhance diagnostic accuracy, enable earlier detection, and improve outcomes for individuals with PD.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the

work.

Concept and design: Meghana Dasari

Acquisition, analysis, or interpretation of data: Meghana Dasari, Rooth V. Medapati

Drafting of the manuscript: Meghana Dasari

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