


RESEARCH

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Correlation of Serum Malondialdehyde with Motor Severity and Cognitive Function in Parkinson's Disease

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ABSTRACT

Introduction: Accumulating research supports the view that oxidative stress is a key driver of the pathological processes underlying Parkinson's disease (PD). Among biomarkers of oxidative injury, malondialdehyde (MDA)—a key lipid peroxidation product—is frequently utilized to quantify oxidative stress; however, its relationship with motor symptom severity and cognitive function in PD remains insufficiently explored. This study aimed to examine the association between serum MDA levels, motor symptom severity, and cognitive function in patients with Parkinson's disease. **Methods:** This cross-sectional study included 35 patients diagnosed with PD. Motor severity was assessed using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and stratified into mild, moderate, and severe levels. Cognitive assessment utilized the Montreal Cognitive Assessment–Indonesia (MoCA-Ina) alongside trail making test part A (TMT-A) and trail making test part B (TMT-B). Serum MDA concentrations were measured using the thiobarbituric acid reactive substances (TBARS) assay. Statistical assessment was conducted using Spearman's rank correlation alongside the Mann–Whitney U test. **Results:** This study revealed a meaningful positive linkage between MDA concentrations and motor symptom severity (r = 0.421, p = 0.012). Post-hoc analysis indicated that patients with moderate and severe motor symptoms had higher MDA levels than those with mild symptoms (p = 0.032; p = 0.022), while no discrepancy was found between the moderate and severe groups (p = 0.421). MDA levels showed no significant association with MoCA-Ina or TMT-A performance (r = 0.206, p = 0.235; r = 0.079, p = 0.684), but patients with abnormal TMT-B performance had higher MDA levels than participants with normal results (p = 0.043). **Conclusion:** MDA level is linked to greater motor symptom severity and executive dysfunction in PD. The results imply that MDA may act as a promising biomarker reflecting oxidative damage–driven neurodegeneration underlying motor and executive impairments in PD.

Keywords: Cognitive function, malondialdehyde, motor symptom, Parkinson's disease.

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INTRODUCTION

Worldwide prevalence data indicate that Parkinson's disease (PD) is second only to Alzheimer's disease among neurodegenerative disorders. The Global Burden of Disease Study predicts a potential 'Parkinson's pandemic' by 2040, with prevalence projected to be twice that reported in 2015.[1] Despite the still unclear cause of Parkinson's disease, growing research suggests that oxidative damage significantly contributes to its underlying disease processes. An overproduction of reactive oxygen species (ROS) can disrupt both the structure and function of dopaminergic neurons, which are naturally prone to oxidative damage. This susceptibility is most noticeable within the pars compacta region of the substantia nigra (SNpc), where the degeneration of dopaminergic neurons constitutes a major pathological feature of PD.[2–7] Findings from post-mortem analyses further support this link, revealing heightened oxidative activity and extensive macromolecular damage within dopaminergic cells of PD brains.[2,8]

Malondialdehyde, commonly called MDA, is a reliable marker of oxidative damage. Numerous investigations have consistently pointed out that people diagnosed with Parkinson's disease exhibit substantially elevated MDA concentrations when compared with healthy populations.[6,9–14] Because MDA readily reacts with nucleosides, it exerts cytotoxic effects by inducing DNA alterations and mutations that contribute to neurodegenerative and other pathological processes.[15] Post-mortem examinations of Parkinson's disease brains have further revealed pronounced accumulation of MDA within the substantia nigra. Other findings suggest higher levels of MDA in the frontal cortex of individuals living with this condition.[1,16]

Excessive lipid peroxidation and mitochondrial dysfunction within the SNpc—the very region shown to accumulate marked oxidative damage and MDA in PD—promote progressive loss of nigrostriatal dopaminergic neurons, resulting in worsening motor disturbances, including tremor, bradykinesia, rigidity, and postural instability. Beyond its motor consequences, oxidative stress has also been implicated in cognitive impairment through neuronal injury involving the frontal–striatal circuitry, which is critical for executive function.[1,16] Consequently, biomarkers of lipid peroxidation such as MDA may be associated

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not only with motor disability but also with cognitive dysfunction. Cognitive deficits may appear even at the early disease stage of PD and can markedly diminish overall well-being, sometimes cases influencing patient outcomes more profoundly than the motor manifestations themselves.[17] While the assessment of motor severity remains central to diagnosis and therapeutic monitoring, neglecting the cognitive involvement may delay the recognition and management of associated neuropsychiatric complications. An integrated assessment of both motor and cognitive domains is therefore essential for a comprehensive understanding of disease progression.[18]

In Indonesia, investigations into the connection between oxidative stress and Parkinson's disease are still scarce, particularly regarding the links between MDA levels and motor or cognitive outcomes. The present study aimed to examine serum MDA levels in relation to both motor symptom severity and cognitive function among patients with Parkinson's disease.

This study aimed to examine serum MDA levels in relation to motor symptom severity and cognitive function—assessed through global cognition (MoCA-Ina), processing speed/attention (TMT-A), and executive function (TMT-B)—among patients with PD.

MATERIALS AND METHODS

Study Participants

This investigation enrolled 35 patients with confirmed PD using the UK Parkinson's Disease Society Brain Bank Clinical Criteria.[19] The sample size was calculated using the formula for estimating the required sample size to detect a correlation coefficient based on Fisher's *z* transformation. Assuming a two-sided significance level (α) of 0.05, a statistical power of 80% (β = 0.20), and an expected correlation coefficient (*r*) of 0.46[7] derived from a previous study, the minimum required sample size was calculated using the following formula:

$$n = \left\{ \frac{(Z\alpha + Z\beta}{0.5\ln(1+r)/(1-r)} \right\}^2 + 3$$

Zα = 1.96 for a two-tailed α of 0.05, Zβ = 0.84 for 80% power, and *r* represents the anticipated correlation coefficient obtained from the previous study.[7] Based on these assumptions, the minimum required sample size was 35 participants.

Recruitment was conducted consecutively from February to June 2025 at the neurology outpatient clinics of Adam Malik Hospital and Universitas Sumatera Utara Hospital, Indonesia. Inclusion criteria were: (1) PD patients at Hoehn and Yahr stages 1–3; (2) age 60 years or older; (3) a minimum of six years of formal education; (4) being alert, cooperative, and able to read, write, and communicate in Indonesian; and (5) willingness to take part by signing informed consent. Exclusion criteria included: (1) previous cognitive disorders such as dementia; (2) other diseases that have the potential to impact either motor function or cognitive outcomes, including stroke, meningitis, encephalitis, traumatic brain injury, or brain tumors; and (3) sensory or motor limitations that could interfere with testing, such as aphasia, visual, or hearing impairments.

Data Collection

For all participants who met the study criteria, the principal investigator examined motor performance using the motor subsection (part III) of the Unified Parkinson's Disease Rating Scale, under the supervision of a board-certified neurologist with expertise in movement disorders. The severity of motor impairment was categorized based on UPDRS-III total scores as follows: (1) mild, 0–32; (2) moderate, 33–58; and (3) severe, 59–108.[20] Assessment of cognitive status was performed using MoCA-Ina and the TMT-A and TMT-B. A MoCA-Ina score of ≥ 26 indicated normal cognition.[21,22] Performance on TMT-A was considered normal if completed within 180 seconds, and on TMT-B if finished within 300 seconds. Exceeding these time limits or failing to complete the test was classified as abnormal.[23,24] All evaluations were performed during the medication-ON (med-ON) state to elude effects of motor deficits on task performance that are usually present during the medication-OFF (med-OFF) condition. Med-ON was defined as the typical functional state when patients were receiving antiparkinsonian medication and exhibited a good clinical response, according to the MDS-UPDRS Instruction Manual. Participants were assessed after taking their usual morning dose of medication.[25]

MDA Measurement

MDA levels were assessed by collecting a 3 mL blood sample from the median cubital vein by trained medical personnel. After a 30-minute clotting period at room temperature (25°C), the samples were centrifuged at 4,000 rpm for 15 minutes to obtain the serum fraction. MDA levels were analyzed at the Integrated Laboratory, Faculty of Medicine, Universitas Sumatera Utara, using a spectrophotometric thiobarbituric acid reactive substances (TBARS) method. During the procedure, TBA reacts with MDA, the final product of lipid peroxidation, at 100°C, generating a pink chromogen with an absorbance peak at 532 nm. Values were presented as nmol per milliliter, where higher values indicated greater oxidative stress.[26]

Statistical Analysis

Descriptive methods were applied to describe the demographic and clinical features of the participants. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as frequencies and percentages. For variables that did not meet normality assumptions, data are displayed as medians with interquartile ranges (IQR). To explore the associations between MDA levels, motor symptom severity, and cognitive performance, correlation analyses were performed. Pearson's correlation coefficient was applied to variables with a normal distribution, whereas Spearman's rank correlation was used for data that were non-normally distributed. Normality of the dataset was assessed through the Shapiro–Wilk test. Group comparisons of MDA concentrations by motor severity or cognitive category were conducted according to data distribution. For variables that met normality assumptions, one-way ANOVA was performed, whereas the Kruskal–Wallis test was employed for data that were not normally distributed. The Mann–Whitney U test was used for follow-up pairwise comparisons. All statistical procedures were performed using SPSS version 29.0. A *p*-value of less than 0.05 was interpreted as statistically significant.

RESULTS

Patients' Demographic and Clinical Profiles

This investigation included 35 individuals diagnosed with PD. Males represented the

majority of the cohort (54.3%), and the average age was 67 ± 5 years. Classification using the Hoehn and Yahr criteria showed that stage III accounted for the largest share of patients (60%), while stage II and stage I comprised 28.6% and 11.4% of the cohort, respectively. The median serum MDA concentration among patients with Parkinson's disease was 0.55 nmol/mL (IQR 0.25–1.42). The mean motor symptom score was 42 ± 17. Based on UPDRS Part III, the largest proportion of patients (45.7%) had moderate motor symptoms, followed by severe motor symptoms (28.6%) and mild motor symptoms (25.7%). The mean MoCA-Ina score was 18 ± 5. The majority of patients (91.4%) were found to have cognitive impairment, whereas only 8.6% had normal cognitive function. Based on TMT-A assessment, 82.9% of patients were classified as having normal performance, while 17.1% were categorized as abnormal. In the normal group, the mean TMT-A completion time was 112 ± 40 seconds. A substantial proportion of the sample (80%) demonstrated abnormal TMT-B performance, whereas only 20% showed normal performance. **Table 1** outlines the participants' demographic and clinical profile**.**

Table 1. Patients' demographic and clinical profiles.

Profiles	Parkinson's Disease Patients (n = 35)
Age (years)	67 ± 5
Male, n (%)	19 (54.3)
Stage (Hoehn and Yahr), n (%)	
Stage 1	4 (11.4)
Stage 2	10 (28.6)
Stage 3	21 (60.0)
MDA (nmol/mL)	
Median (IQR)	0.55 (0.25–1.42)
Motor Symptom Severity (UPDRS III)	
Mean	42 ± 17
Mild (0–32), n (%)	9 (25.7)
Moderate (33–58), n (%)	15 (45.7)
Severe (59–108), n (%)	10 (28.6)
Cognitive Function (MoCA-Ina)	
Mean	18 ± 5
Normal, n (%)	3 (8.6)
Abnormal, n (%)	32 (91.4)
Cognitive Function (TMT-A)	
Normal, n (%)	29 (82.9)
Abnormal, n (%)	6 (17.1)
Cognitive Function (TMT-B)	
Normal, n (%)	7 (20)
Abnormal, n (%)	28 (80)

Correlation Between MDA Levels and Motor Symptom Severity

Spearman's rho was applied to assess whether serum MDA concentrations were related to motor symptom severity as quantified by UPDRS part III. The evaluation showed a moderate, statistically significant positive association (r = 0.421, p = 0.012). Stratified according to motor symptom severity, median serum MDA levels increased progressively across the mild, moderate, and severe groups (0.43 [IQR 0.33–0.50], 0.50 [IQR 0.46–0.67], and 0.63 [IQR 0.48–0.74] nmol/mL, respectively). Overall, serum MDA concentrations differed significantly among the three severity groups (Kruskal–Wallis, p = 0.036). Post hoc Mann–Whitney U tests further demonstrated that patients with moderate (p = 0.032) and severe motor impairment (p = 0.022) had markedly elevated MDA levels relative to those with mild symptoms. By contrast, the moderate and severe groups showed no statistically notable difference (p = 0.421). **Table 2** summarizes the association between MDA levels and motor symptom severity.

Table 2. Association between MDA levels and motor symptom severity in PD.

Analysis	Results (r/p-value)
Correlation Analysis	
Spearman's rho analysis (MDA vs. UPDRS part III score)	r = 0.421, p = 0.012
Comparison According to Motor Symptom Severity	
Mild (n = 9)	Median MDA = 0.43 (IQR 0.33–0.50) nmol/mL
Moderate (n = 16)	Median MDA = 0.50 (IQR 0.46–0.67) nmol/mL
Severe (n = 10)	Median MDA = 0.63 (IQR 0.48–0.74) nmol/mL
Overall comparison (Kruskal–Wallis test)	p = 0.036
Post hoc pairwise comparisons (Mann–Whitney U test)	
Mild vs. Moderate motor symptoms	p = 0.032
Mild vs. Severe motor symptoms	p = 0.022
Moderate vs. Severe motor symptoms	p = 0.421


Correlation Between MDA Levels and Cognitive Funtions

Analysis using Spearman's rho indicated that MDA concentrations were not significantly related to MoCA-Ina cognitive scores (r = 0.206, p = 0.235). Subsequent Mann–Whitney U comparisons also revealed no meaningful differences in MDA levels between participants categorized as cognitively normal and those with cognitive impairment according to MoCA-Ina (p = 0.346). Similarly, comparisons based on TMT-A performance showed no significant association with MDA concentrations (Mann–Whitney U, p = 0.255). Among individuals who achieved normal TMT-A results, Spearman's rank correlation was applied to examine the association between serum MDA concentration and TMT-A completion time (seconds). The result showed no significant association between MDA levels and task completion time (r = 0.079, p = 0.684). Owing to the low representation of participants with normal TMT-B performance (20%) relative to those with abnormal results (80%), correlation analysis was not feasible. Therefore, we conducted only a group comparison. The comparative analysis revealed that patients with abnormal TMT-B results had significantly higher MDA levels than those with normal performance (p = 0.043). **Table 3** presents the association between MDA levels and cognitive function.

DISCUSSION

Evidence exploring the relationship between MDA levels and clinical features of PD remains limited. To the best of our knowledge, few investigations have examined the interplay between circulating MDA concentrations, motor symptom severity, and cognitive performance in PD, making this research one of the earliest contributions in this area. The current study found that higher MDA levels were statistically significantly correlated with greater motor symptom severity, with marked increases from mild to moderate and severe stages. However, when the moderate and severe groups were compared, the analysis failed to demonstrate a statistically meaningful distinction. Regarding cognitive function, MDA levels showed no significant correlation with global cognition (MoCA-Ina) or TMT-A performance. Conversely, patients exhibiting abnormal TMT-B performance had higher MDA levels, suggesting that oxidative imbalance may be more strongly linked to executive dysfunction than to general cognitive decline. These findings highlight the possible involvement of oxidative damage in the biological processes underlying the worsening of Parkinson's disease.

Elevated oxidative stress biomarkers are frequently documented in Parkinson's disease. Previous postmortem investigations reported increased MDA concentrations in the substantia nigra and frontal cortical areas when contrasted with other brain areas, indicating a region-specific oxidative process.[16,27] Specifically, the excessive expression of α-synuclein in PD, the principal component of Lewy bodies, can directly impair mitochondrial complex I within dopaminergic neurons. Meanwhile, oxidative stress reflected by elevated MDA levels promotes further α-synuclein aggregation, creating a self-perpetuating cycle that accelerates neuronal damage and contributes to the neurodegenerative cascade in PD.[28] Supporting the trends reported in earlier studies, the present investigation found that higher circulating MDA levels were linked to greater motor symptom severity and were particularly associated with deficits in executive function, as reflected by abnormal TMT-B results.[29–31]

Our findings are consistent with previous research. One study reported significantly elevated plasma MDA levels in the PD cohort compared with a healthy control group.[9] Another investigation involving 211 individuals with PD and 135 controls also observed increased MDA concentrations and identified a notable link between circulating MDA levels and the severity of the disease, highlighting the suggested role of oxidative stress as a contributing factor in neuronal degeneration.[32] In the current study, post-hoc Mann–Whitney U analysis revealed that patients in the moderate and severe motor symptom groups exhibited substantially higher MDA levels relative to those classified with mild motor symptoms (p = 0.032; p = 0.022). In contrast, differences between the moderate and severe groups were not statistically significant (p = 0.421). This trend suggests that oxidative stress rises markedly from mild to moderate stages but then plateaus, possibly due to compensatory metabolic mechanisms, activation of endogenous antioxidant systems, or extensive neuronal loss in later stages of the disease. These insights collectively corroborate the concept that MDA may be a potential biomarker associated with motor symptom severity.[32,33]

In this cohort, MDA levels were not significantly correlated with MoCA-Ina performance. Although our findings did not reveal a clear association between MDA levels

Table 3. Association between MDA levels and cognitive function.

Cognitive Test	Category	Patients (n)	Median MDA (IQR), nmol/mL	Minimum–Maximum, nmol/mL	Spearman's rho (r, p)	Mann-Whitney U (p)
MoCA-Ina	Normal	3	0.57 (0.63–0.56)	-	r = 0.206 p = 0.235	0.346
	Abnormal	32	0.50 (0.65–0.42)	-		
TMT-A	Normal	29	0.56 (0.66–0.43)	0.25–1.42	r = 0.079 p = 0.684	0.255
	Abnormal	6	0.47 (0.56–0.30)	0.25–0.74		
TMT-B	Normal	7	0.43 (0.46–0.41)	0.39–0.56	-	0.043
	Abnormal	28	0.57 (0.69–0.46)	0.25–1.42		


and global cognitive function, the literature suggests that global cognitive performance in PD is modulated by a complex interplay of factors. For example, cognitive deficits in PD have been associated with dopaminergic and cholinergic dysfunction, as well as structural and functional alterations within fronto-striatal circuits, alongside the effects of age, education, and neuropsychiatric comorbidities.[34–36] Neuroimaging studies have also demonstrated that disturbances in fronto-parietal and fronto-striatal connectivity are linked to cognitive deterioration, particularly in the initial phases of the disease. Furthermore, cognitive deterioration manifesting at the early clinical stage of PD often resembles the patterns observed in frontal lobe dysfunction, underscoring the role of fronto-striatal networks.[37,38] In contrast, one previous report found a correlation between MDA levels and cognitive decline as measured by the MMSE.[39]

Our findings did not demonstrate a meaningful correlation between plasma MDA concentration and TMT-A performance, either in group comparisons (p = 0.255) or within the normal subgroup (r = 0.079, p = 0.684). The results imply that oxidative stress, as represented by MDA levels, may not directly affect basic attention or visuomotor speed functions measured by TMT-A.[40] In contrast, previous research involving individuals with bipolar disorder documented a significant positive association between MDA levels and TMT-A performance.[41] TMT-B requires complex executive abilities, including cognitive flexibility and attentional shifting, functions that depend on the integrity of fronto-striatal and prefrontal networks—regions particularly susceptible to oxidative injury in PD.[34–36] In contrast to TMT-A performance, elevated MDA levels were observed in patients with abnormal TMT-B performance compared with those with normal results (p = 0.043), reinforcing the role of oxidative stress in executive dysfunction. This finding aligns with existing evidence that MDA is more closely associated with complex executive deficits than with simple attentional tasks.[42–46]

Beyond serving as a biomarker of lipid peroxidation, MDA may contribute directly to neurocognitive deterioration through several mechanisms: (1) cross-linking of membrane phospholipids, impairing synaptic communication; (2) modulation of dopamine turnover leading to further oxidative by-products; and (3) neuroinflammation, which is essential for cognitive flexibility.[15,47–49] These mechanistic insights align with our findings that identified stronger associations between oxidative stress markers and executive impairment in PD. Our data reinforce the concept that executive functions—especially those mediated by fronto-striatal circuitry—may serve as more sensitive cognitive indicators of oxidative burden in PD. This has potential clinical implications, suggesting that TMT-B or related executive tasks may be useful adjunctive tools for early detection of oxidative-mediated cognitive decline.

This study has several limitations. First, the relatively small sample size may have limited statistical power and reduced the generalizability of the findings. Second, the cross-sectional design precludes conclusions regarding causal relationships between oxidative stress and clinical manifestations of PD. Third, serum MDA reflects peripheral oxidative stress and may not fully represent oxidative processes occurring within the central nervous system, particularly within the substantia nigra and frontostriatal pathways. Finally, potential confounding factors, including antiparkinsonian medication, disease duration, and comorbid conditions, were not adjusted for and may have influenced serum MDA concentrations. Future longitudinal studies with larger cohorts are needed to clarify the role of oxidative stress in motor and cognitive progression in PD.

CONCLUSION

The present investigation found a significant positive relationship between MDA levels and motor symptom severity, with higher MDA levels observed in patients with more advanced motor impairment. With regard to cognitive function, no significant association was detected between MDA levels and either MoCA-Ina scores or TMT-A performance. In contrast, patients with abnormal TMT-B performance exhibited elevated MDA levels, indicating that among the cognitive domains assessed, oxidative stress was specifically associated with executive dysfunction. Overall, these findings suggest that MDA is a promising biomarker reflecting both motor dysfunction and executive impairment in PD.

Ethics Statement

This study protocol was approved by the Health Research Ethics Committee of Universitas Sumatera Utara (No. 342/KEPK/USU/2025). The study received research authorization from the Director of Human Resources, Education, and Research at both institutions: Adam Malik Hospital (DP.04.03/D.XXVIII.2.2.3/867/2025) and Universitas Sumatera Utara Hospital (2589/UN5.5.6.D2/PT.01.04/2025). Before enrollment, we obtained informed consent from each patient and/or their legal representative.

Informed Consent

Informed consent to participate was obtained from all participants in accordance with applicable ethical requirements.

Consent for Publication

Consent for publication was not applicable to individual participants, as the manuscript does not contain identifiable personal data or identifiable images of individuals. Permission for mentioning the institutions was obtained from the relevant institutions.

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Author Contributions

Panggabean contributed to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Hutagalung and Fitri contributed to the study supervision, methodological guidance, interpretation of the findings, and critical revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest

The investigators confirm that this study was carried out with no relevant conflicts of interest.

Declaration on the Use of Artificial Intelligence (AI)

The authors declare that OpenAI was used solely to assist with language editing and improving the clarity of the manuscript. All scientific content, interpretations, references, and conclusions were independently reviewed and verified by the authors. All authors approved the final version of the manuscript and take full responsibility for its content.

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