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VEGFA Gene Expression Levels in Patients with Parkinson's Disease and First-Degree Relatives

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Abstract

Background: Vascular endothelial growth factor A (VEGFA) contributes to angiogenesis and exerts neurotrophic and neuroprotective effects. Altered *VEGFA* expression has been implicated in neurodegenerative processes, including Parkinson´s disease (PD), yet findings from peripheral transcriptomic studies remain inconsistent. Data on individuals at increased risk, particularly first-degree relatives (FDRs), are limited.

Objective: To evaluate peripheral blood *VEGFA* mRNA expression in patients with PD and their asymptomatic FDRs compared with healthy controls, and to assess age-related patterns and diagnostic performance.

Methods: Peripheral blood *VEGFA*expression was analyzed in 123 participants (PD patients, FDRs, healthy controls) using one-step RT-qPCR normalized to *B2M*. Relative expression values were log-transformed (logVEGFA). Group differences, age correlations, and diagnostic discrimination were assessed using ANOVA, Pearson correlation, and receiver operating characteristic (ROC) analysis.

Results: Both PD patients and FDRs showed significantly higher logVEGFA levels than healthy controls ($p = 0.004$), with the most pronounced differences observed in participants aged ≤ 60 years ($p < 0.001$). A positive correlation between age and logVEGFA was detected only in healthy controls. In participants aged ≤ 60 years, logVEGFA demonstrated excellent discrimination between PD patients and healthy individuals (AUC 0.897; 95% CI 0.771–1.000; sensitivity 100%, specificity 73.3%).

Conclusions: Peripheral *VEGFA* expression is elevated in both PD patients and FDRs, particularly in younger individuals. Age-stratified *VEGFA* assessment may support early identification of individuals at risk of PD and complement existing prodromal biomarkers, pending longitudinal validation.

Introduction

Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis and also exerts important neurotrophic and neuroprotective functions within the central nervous system. Among the VEGF isoforms, *VEGF-A* is the most extensively studied and has been linked to neuronal survival, inhibition of apoptosis, and neural regeneration, making it a molecule of interest in neurodegenerative disorders such as Parkinson's disease (PD) (3–5).

PD is a progressive neurodegenerative condition characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta. Its multifactorial pathogenesis involves mitochondrial dysfunction, oxidative stress, neuroinflammation, and impairment of endogenous neuroprotective mechanisms (6,7). Several transcriptomic studies have examined peripheral *VEGFA* expression in PD, though their findings remain inconsistent (8–10). Protein-level studies also report heterogeneous results: *VEGF-A* is often elevated in post-mortem brain tissue or cerebrospinal fluid, whereas peripheral protein concentrations are frequently unchanged (11–13). These discrepancies may reflect

methodological variability, central–peripheral compartment differences, or weak mRNA–protein correlation driven by post-transcriptional and translational regulation (14,15). Demographic factors, particularly age, may further contribute to variability in measured VEGFA levels (16).

Despite growing interest in molecular biomarkers of preclinical neurodegeneration, little is known about peripheral *VEGFA* expression in individuals at elevated risk of PD, particularly first-degree relatives (FDRs) (17,18). FDRs represent a key population for biomarker studies not only because of their higher lifetime risk, but also because subtle motor and non-motor abnormalities - including hyposmia, anxiety, or REM sleep behavior disorder - have been reported even in asymptomatic relatives. Such early alterations suggest underlying biological changes that precede clinical onset (19–22). Experimental data further support a potential role of VEGF signaling in early neurodegenerative processes (5).

In this study, we investigated peripheral blood *VEGFA* expression in patients with PD, their asymptomatic first-degree relatives, and healthy controls. We also examined age-related expression patterns to determine whether *VEGFA* may serve as an early biomarker of neurodegeneration in at-risk individuals.

Materials and Methods

Participants and study design

Patients with a clinically confirmed diagnosis of Parkinson's disease (PD) were recruited according to the Movement Disorder Society (MDS) diagnostic criteria (23). Disease severity was evaluated using the Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the modified Hoehn and Yahr scale (24). Asymptomatic first-degree relatives (FDRs), defined as siblings or children of PD patients, with no history of neurological disease were included. Healthy controls had no personal or family history of PD or other neurological disorders. Inclusion and exclusion criteria for all study groups are listed in Table 1.

Sample collection and processing

Peripheral venous blood samples were collected into K_3EDTA tubes (SARSTEDT AG & Co. KG, Nümbrecht, Germany) and immediately stored at −80°C until processing to minimize RNA degradation. After thawing, total RNA was isolated from 200 µL of frozen whole blood using the NucleoSpin® RNA Blood Kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany) according to the manufacturer's instructions. RNA purity and quantity were determined spectrophotometrically using a NanoDrop 2000 instrument (Thermo Fisher Scientific, Waltham, MA, USA). Samples with an A260/280 ratio outside the 1.8–2.0 range were excluded.

RT-qPCR analysis

Quantification of *VEGFA* expression was performed using reverse transcription quantitative polymerase chain reaction (RT-qPCR) with the KAPA PROBE FAST Universal One-Step qRT-PCR Master Mix (2X) Kit

(Roche Diagnostics GmbH, Mannheim, Germany). TaqMan probes were used for the target gene *VEGFA* (Assay ID: Hs03929054_s1) and the reference gene *B2M* (Assay ID: Hs00984230_m1).

Each reaction had a total volume of 20 µL, including 2 µL of isolated RNA. Amplification was performed on a qTOWER³ touch/qTOWER³ G touch Real-Time PCR Thermal Cycler (Analytik Jena GmbH+Co. KG, Jena, Germany) using qPCRsoft 4.1 software.

The thermal cycling protocol consisted of:

- reverse transcription at 42 °C for 5 min,
- polymerase activation at 95 °C for 3 min,
- followed by 40 cycles of 95 °C for 3 s and 60 °C for 30 s.

Each sample was analyzed in two to four technical replicates. Samples with a Ct standard deviation > 0.25 across replicates were excluded.

In this study, '*VEGFA* expression" denotes peripheral blood mRNA quantified by one-step RT-qPCR and normalized to the reference gene *B2M*. The results were expressed as the relative expression of *VEGFA* to *B2M*, calculated using the 2^-ΔΔCt method (25,26). All relative expression values were natural-log transformed (logVEGFA) for subsequent analysis.

Statistical analysis

For each participant, the geometric mean of the technical replicates of relative *VEGFA* expression was calculated (due to proportional data). These values were then **natural-log transformed (the variable logVEGFA)** to follow normal distribution as confirmed by the **Shapiro–Wilk** test. Subsequent analyses used logVEGFA as specified below.

The baseline characteristics were analyzed using descriptive statistics. Continuous variables are presented as the mean ± standard deviation, categorical variables as absolute and relative frequencies (%). Between-group differences for continuous variables were analyzed with the analysis of variance (ANOVA) with the Games-Howell or Tukey post-hoc test. Differences between groups for categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate.

The correlation between age and logVEGFA was assessed using Pearson's correlation coefficient. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value for *VEGFA* expression distinguishing PD patients. The cut-off was selected by maximizing Youden's index.

All statistical analyses were performed using IBM SPSS 30.0 statistical software. Two-tailed p-values < 0.05 were considered statistically significant.

Ethics

Participants were recruited between January 2023 and December 2024 at the Faculty of Medicine, University of Ostrava, and collaborating neurology outpatient clinics. The study was approved by the Ethics Committee of the Faculty of Medicine, University of Ostrava (Approval No. SGS02/LF/2023) and conducted in accordance with the Declaration of Helsinki (2013 revision). Written informed consent was obtained from all participants. Data processing complied with the EU General Data Protection Regulation (GDPR, 2016/679).

Results

A total of 123 subjects (64 males, mean age: 57.5 ± 14.6 years) were enrolled in the study: 41 patients with clinically established PD (29 males; mean age: 66.3 ± 9.6 years), 52 asymptomatic FDRs (22 males; mean age: 50.2 ± 13.9 years), and 30 healthy controls (13 males, mean age: 58.1 ± 14.8 years). All details pertaining to the studied sample are available in Table 2. Given the observed correlation with age and statistically significant differences between the groups, the cohort was subsequently stratified into two age categories: < 60 and > 60 years.

Comparison of logVEGFA values across all groups revealed significant differences ($p = 0.004$, ANOVA Welch test), with the lowest expression observed in the group of healthy controls (Table 2). Post hoc testing using the Games-Howell test showed significant differences between healthy controls and patients with PD ($p = 0.003$), as well as between healthy controls and FDRs ($p = 0.011$). No significant differences were observed between patients with PD and their relatives ($p = 0.773$; Table 3, Figure 1a).

When analyzing age-stratified subgroups, differences in logVEGFA expression between groups persisted only in younger participants ($p < 0.001$), whereas they were no longer statistically significant among older individuals ($p = 0.643$; Tables 2 and 3, Figure 1b).

The healthy control group exhibited a moderate linear trend of increasing logVEGFA with age (Pearson's correlation coefficient $r = 0.571$, $p < 0.001$), whereas no such significant correlation was observed in patients with PD or FDRs (Figure 2).

Based on the previous results, ROC analysis was conducted to assess the diagnostic performance of logVEGFA (i.e., relative *VEGFA* expression) in distinguishing patients with PD from healthy controls. In participants aged ≤ 60 years, where the differences between groups were most pronounced, *VEGFA* expression (logVEGFA) showed an excellent ability to distinguish patients with PD from healthy individuals. The area under the ROC curve (AUROC) reached 0.897 (95% confidence interval: 0.771–1.000, $p < 0.001$). According to the maximal Youden's index, the optimal cut-off value was determined to be logVEGFA = –1.346 (i.e., 0.260 for relative expression *VEGFA*), with 100% sensitivity, 73.3 % specificity, and an overall accuracy of 84.6% (Figure 3).

Discussion

In this study, we demonstrated that peripheral *VEGFA* expression is elevated not only in patients with PD but also in asymptomatic FDRs compared with healthy controls (Tables 2 and 3). Age-stratified analysis revealed that these group differences in *VEGFA* expression were most pronounced in individuals aged ≤ 60 years.

In healthy controls, age-related decline is well documented for several non-motor domains relevant to prodromal PD, including olfaction and sleep (27–30). In contrast, olfactory abnormalities tend to persist across age strata in PD and at-risk cohorts (31,32). We observed an age-associated increase in peripheral *VEGFA* expression exclusively among healthy controls, a trend consistent with age-linked low-grade inflammation and leukocyte compositional changes rather than endothelial expression shifts (33). The absence of this association in PD patients and FDRs suggests that early neurodegenerative processes may interfere with physiological, age-associated compensatory mechanisms. These findings underscore the importance of incorporating age stratification when evaluating molecular biomarkers in prodromal or early PD (32,34).

Prior studies assessing circulating VEGF-A protein levels have shown heterogeneous results, with several reporting no significant differences between PD patients and controls (13). Such variability may reflect heterogeneity in cohorts, methodological differences, or the inherently limited correlation between mRNA expression and protein abundances due to post-transcriptional and translational regulation. Our study specifically focused on *VEGFA* transcript levels in a relatively younger population (≤ 60 years), which may yield better sensitivity for detecting early disease-related molecular changes.

The dual role of VEGF-A in the central nervous system adds biological plausibility to these findings. VEGF-A supports angiogenesis, enhances regional cerebral blood flow, and promotes dopaminergic neuron survival, all of which have demonstrated protective effects in experimental PD models (5). Conversely, dysregulated VEGF-A signaling has been linked to blood-brain barrier dysfunction and neuroinflammatory processes implicated in PD pathogenesis (3,12). Whether the elevated *VEGFA* expression observed in FDRs represents an adaptive compensatory response or an early molecular hallmark of neurodegeneration remains unclear.

FDRs constitute a biologically relevant at-risk population due to their increased lifetime risk and their tendency to exhibit subtle motor and non-motor abnormalities - such as hyposmia, anxiety, depression, or REM sleep behavior disorder - even in the absence of clinically manifest PD (19–22). Imaging studies further support early biological alterations, with dopaminergic deficits on DAT-SPECT reported in hyposmic relatives of PD patients (22,34). Family history also modifies disease risk, as siblings of patients with early-onset PD are more likely to develop PD and may present at a younger age (35).

Elevated peripheral *VEGFA* expression in FDRs, as observed in our study, raises the question of whether this pattern reflects an adaptive compensatory response or an early molecular component of the pathogenic process. A common genetic variant in *VEGFA* (rs3025039) has been identified as a risk factor for sporadic PD (5), suggesting that genetic susceptibility and regulatory dynamics of *VEGFA* expression may influence vulnerability to neurodegeneration.

From a biomarker perspective, our findings suggest that peripheral *VEGFA* expression, particularly when integrated with established prodromal markers such as hyposmia or REM sleep behavior disorder and with probability-based risk algorithms, may contribute to improved risk stratification. Previous studies have reported increased VEGF-A or VEGFR-1 levels in dopaminergic neurons and astrocytes of the substantia nigra (5,11), as well as elevated VEGF in cerebrospinal fluid (12). Our results extend these observations by demonstrating that asymptomatic FDRs also show elevated peripheral *VEGFA* levels, potentially reflecting either early compensatory activation of VEGF signaling or an early step in disease evolution.

Our findings also suggest that peripheral *VEGFA* expression has potential utility as an early biomarker of PD risk. In participants **aged ≤ 60 years**, we identified a *VEGFA* expression threshold (logVEGFA = –1.346) that distinguished patients with PD from healthy controls with high accuracy (sensitivity, 100%; specificity, ~73.3%). Because peripheral expression can be influenced by systemic variables, this biomarker is likely to be most informative when combined with additional prodromal markers or biological measures. Future longitudinal studies are needed to determine whether elevated *VEGFA* expression in at-risk individuals predicts conversion to PD and whether interventions - such as exercise or neuroprotective strategies - may modify VEGFA expression and alter disease trajectory.

Study limitations

This study has several limitations that should be considered when interpreting the results. First, the age distribution of the cohort may have influenced the findings, as early-onset PD (≤ 50 years) is relatively rare, and only a small proportion of patients with PD are diagnosed before the age of 60 (36,37). This may amplify age-related effects in subgroup analyses.

Second, the logVEGFA values reflect relative gene expression normalized to *B2M* rather than circulating VEGF-A protein levels; given that mRNA–protein correlations are typically low and gene-specific, transcript levels may not directly reflect systemic protein concentrations (14). As an additional methodological note, RT-qPCR data were normalized to a single reference gene, *B2M*. Although *B2M* showed stable expression in our dataset, the Minimum Information for Publication of Quantitative Real-Time PCR Experiments (MIQE) guidelines recommend using at least two validated reference genes to minimize normalization bias.

Finally, the genetic analysis was not comprehensive because no systematic screening was performed for known PD-related mutations. Although monogenic forms represent only approximately 5–10% of all PD cases and occur more frequently in early-onset forms, testing a broader panel of genes, such as *LRRK2*, *PRKN*, *PINK1*, or *DJ1*, could have provided further insight into the relationship between genetic predisposition and *VEGFA* expression (38–40).

Despite these limitations, the principal finding remains: both PD patients and their first-degree relatives exhibit elevated peripheral *VEGFA* expression compared with healthy controls. Taken together with age-

stratified analyses and ROC results, these findings provide preliminary support for *VEGFA* as a candidate biomarker for early PD risk.

Conclusion

Peripheral *VEGFA* expression was significantly higher in both patients with PD and their first-degree relatives compared with healthy controls, with the clearest group differences observed in individuals aged ≤ 60 years. Only healthy controls showed an age-related increase in *VEGFA* expression, suggesting disruption of physiological regulation in PD and at-risk individuals. In younger participants, *VEGFA* expression demonstrated excellent discriminatory ability, supporting its potential utility as an early biomarker when combined with other prodromal measures. Longitudinal studies are needed to determine its predictive value for conversion to PD.

Declarations

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Competig Interests.

The authors declare no competing interests.

Author Contributions.

EA, DSk and PB conceived and designed the study. EA, FS and TM collected clinical data and samples. KTS, KF and AK performed laboratory analyses. EA and DSa conducted statistical analyses. EA, ZH, PD and DSa drafted the manuscript. All authors contributed to data interpretation, critically revised the manuscript, and approved the final version.

Data Availability Statement.

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Inclusion and exclusion criteria for subjects enrolled to the prospective study

Study group	*Inclusion criteria*	*Exclusion criteria*
Patients with Parkinson´s disease	Clinically established PD (Postuma RB et al 2015)	Diagnosed neurological or psychiatric disease except PD; known genetic mutation associated with PD; oncological treatment, ongoing infection or current tretment with immunosuppressants or corticosteroids
	Male or female	Known impairment of olfactory function (other than PD etiology)
	Age ≥ 20 years	
PD First-degree relative	Male or female	Diagnosed neurological or psychiatric disease; known genetic mutation associated with PD; oncological treatment, ongoing infection or current tretment with immunosuppressants or corticosteroids
	Age ≥ 20 years	Known impairment of olfactory functions
Healthy subjects	Subject without any known chronic disease	Diagnosed neurological or psychiatric disease; oncological treatment, ongoing infection or current tretment with immunosuppressants or corticosteroids
	Male or female	Known impairment of olfactory functions
	Age ≥ 20 years	

PD – Parkinson´s disease

Table 2. Baseline patient characteristics.

	PD	Relatives	Controls	*P* value
All participants				
Number of participants; n	41	52	30	NA
Age; mean±SD (years)	66.3 ± 9.6	50.2 ± 13.9	58.1 ± 14.8	< 0.001[a]
Male sex; n (%)	29 (70.7)	22 (42.3)	13 (43.3)	0.013 [b]
logVEGFA; mean±SD	-0.514 ± 0.590	-0.605 ± 0.687	-1.240 ± 1.024	0.004[c]
Age ≤ 60 years				
Number of participants; n	11	41	15	
Age; mean±SD (years)	53.9 ± 6.1	45.8 ± 11.9	45.5 ± 9.6	0.020[a]
Male sex; n (%)	7 (63.6)	19 (46.3)	6 (40.0)	0.471[b]
logVEGFA; mean±SD	-0.316 ± 0.534	-0.637 ± 0.703	-1.717 ± 0.991	< 0.001[c]
Age > 60 years				
Number of participants; n	30	11	15	
Age; mean±SD (years)	70.8 ± 6.0	66.6 ± 6.2	70.7 ± 4.7	0.067[a]
Male sex; n (%)	22 (73.3)	3 (27.3)	7 (46.7)	0.019[b]
logVEGFA; mean±SD	-0.587 ± 0.601	-0.484 ± 0.642	-0.762 ± 0.838	0.643[c]

[a] Kruskal-Wallis test; [b] Chi-square test; [c] ANOVA (the Welch test); PD – Parkinson´s disease; SD – standard deviation; VEGFA – vascular endothelial growth factor isoform A

Table 3. Pairwise comparisons of logVEGFA between groups (all participants and separately participats ≤60 years).

	All participants	Age ≤ 60 years
	***p*-value [a]**	***p*-value [b]**
Healthy controls vs. PD patients	0.003	< 0.001
Healthy controls vs. PD relatives	0.011	< 0.001
PD patients vs. PD relatives	0.773	0.426

PD – Parkinson's disease, [a] adjusted by the Games-Howell post-hoc test, [b] adjusted by the Tukey post-hoc test

Figures

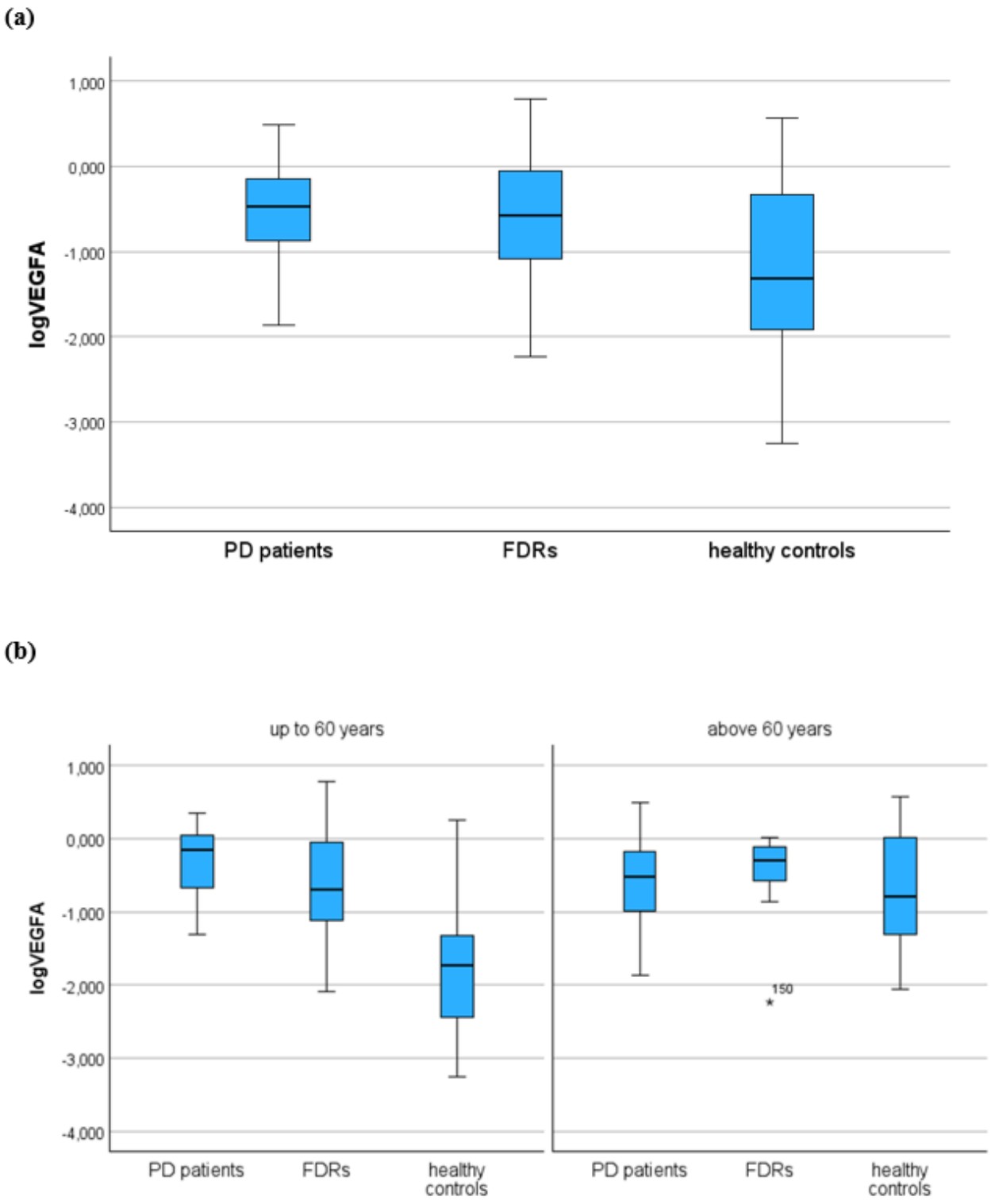


Figure 1

Distribution of logVEGFA expression across study groups.

(a) Boxplots showing log-transformed *VEGFA*expression levels in patients with Parkinson's disease (PD), first-degree relatives (FDRs), and healthy controls (HC), across all participants regardless of age.

(b) Boxplots showing logVEGFA expression stratified by age group (≤ 60 years vs. > 60 years) across the three study groups (PD, FDRs, HC). Horizontal lines indicate median values.

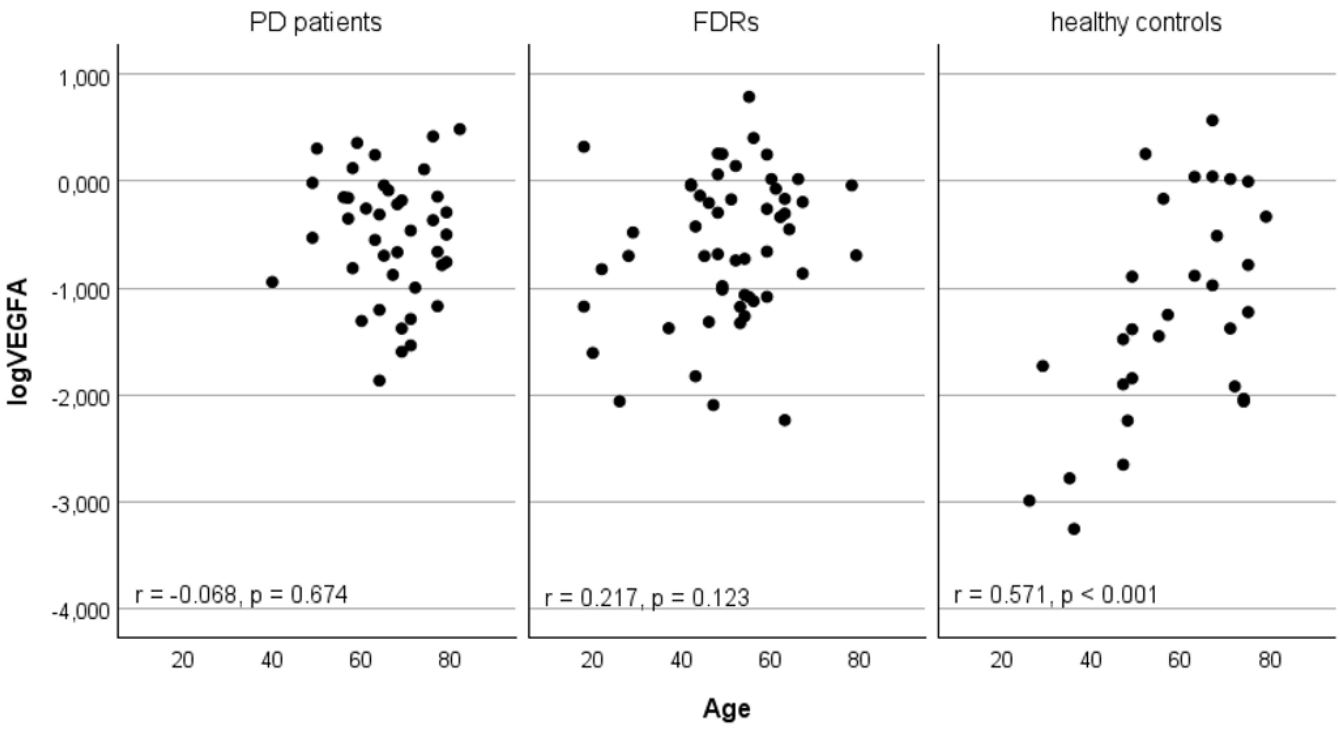


Figure 2

Association between age and logVEGFA expression.

Scatterplots with fitted linear regression lines illustrating the relationship between age and logVEGFA in patients with PD, first-degree relatives (FDRs), and healthy controls (HC).

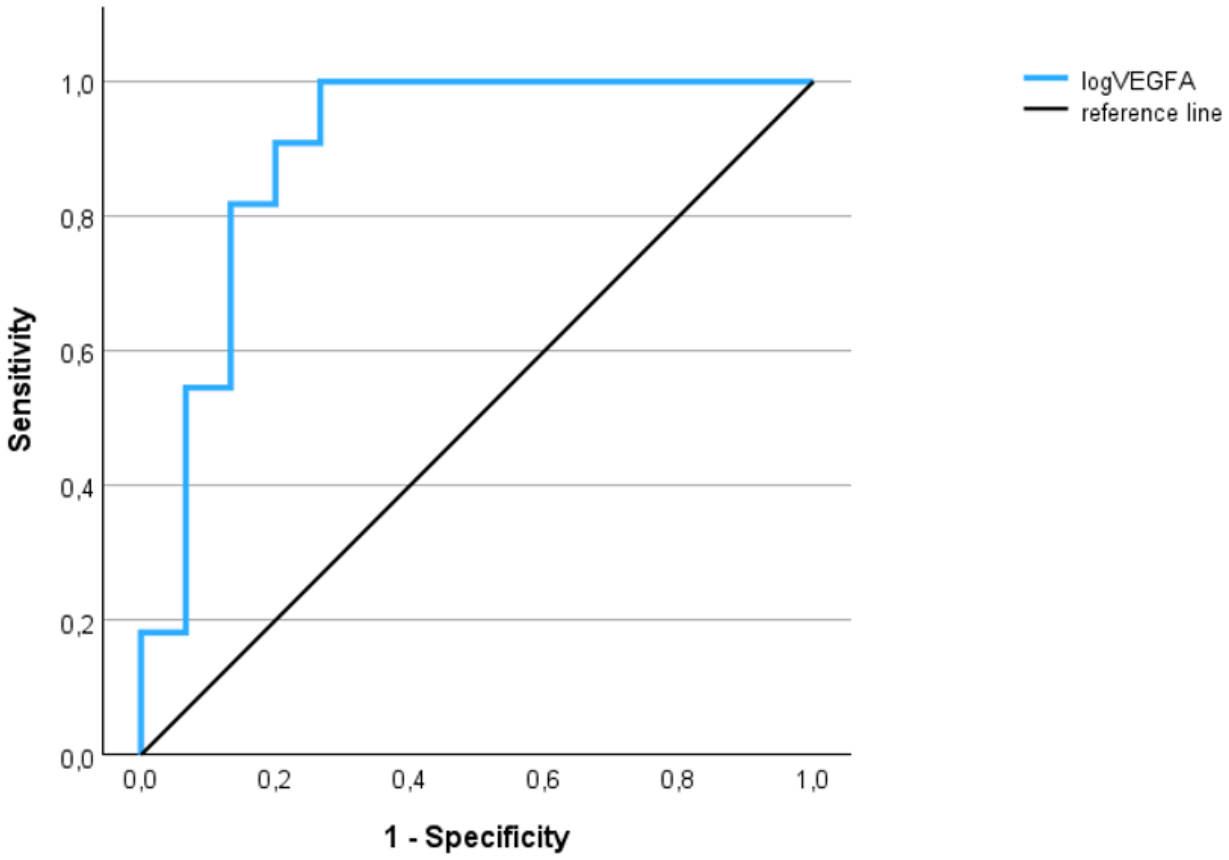


Figure 3

ROC curve for logVEGFA in distinguishing PD patients from healthy controls (≤ 60 years).

Receiver operating characteristic (ROC) curve showing discrimination performance of logVEGFA in participants aged ≤ 60 years. The area under the curve (AUC) and 95% confidence intervals are reported in the text.

Abbreviations: PD – Parkinson's disease; ROC – receiver operating characteristic.