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# Traces of Aging and Oxidative Stress in Essential Tremor: An Investigation of Sirtuin and Thiol Levels: A Case-Control Study

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## Abstract

# Background

This study aimed to evaluate serum SIRT1 levels and thiol/disulfide homeostasis parameters among patients with Essential Tremor (ET) to investigate the potential roles of oxidative stress in the pathogenesis of the disease.

# Methods

Forty-five patients diagnosed with ET and 45 age- and sex-matched healthy controls were included in the study. Serum SIRT1 levels were measured using ELISA. In the same samples, total thiol, native thiol, and disulfide levels were assessed, and the thiol/disulfide ratio was calculated.

# Results

ET patients demonstrated significantly higher SIRT1 levels compared to controls (5.73 [3.54–18.89] vs. 4.63 [0.86–25.92] ng/mL; $p = 0.02$). Native thiol levels were significantly reduced in the ET group (357.20 [225.50–446.00] vs. 374.10 [244.20–485.80] µmol/L; $p = 0.03$). Total thiol was also reduced in ET patients (408.80 [260.60–518.20] vs. 436.30 [295.10–555.30] µmol/L; $p = 0.02$). Disulfide levels did not differ significantly between groups ($p = 0.24$), nor did disulfide/native thiol or disulfide/total thiol ratios ($p = 0.84$ for both).

# Conclusions

Our findings indicate alterations in oxidative stress markers in ET patients, suggesting that the increased SIRT1 levels may represent a compensatory response to neurodegenerative processes. Additionally, disruption in thiol/disulfide homeostasis may reflect redox imbalances involved in ET pathophysiology. SIRT1 and thiol parameters may serve as potential biomarkers in ET.

## Background

Essential tremor (ET) is a progressive neurological disease [1]. Patients typically manifest rhythmic involuntary movements at 4–12 Hz during voluntary actions [1, 2] predominantly affecting the upper extremities initially, with potential progression to cranial structures in advanced disease stages [3]. Essential tremor (ET) is among the most common movement disorders with adult onset. Although essential tremor can begin at any age, the majority of cases are diagnosed in later life, with pediatric cases being reported only rarely. More than one-third of epidemiological studies have reported a gender difference, with most showing a higher prevalence of ET in men [4].

Structural cerebellar changes have been reported even in some ET patients without detectable brain pathology. These include a decrease in the number of Purkinje cells (PC), an increase in torpedo and feathered basket cells, and brainstem-level changes such as Lewy body (LB) accumulation in the locus coeruleus [5]. Furthermore, it has been shown that the linear density of Purkinje cells is inversely proportional to age. During healthy aging, it is estimated that these cells are lost at a rate of 2.5–5.0% per decade [6]. The term 'neurodegeneration' indicates the presence of neuron cell death. Despite the widespread belief that essential tremor (ET) is a functional disorder, studies on ET pathology have been limited, even though its prevalence is high. Pioneering findings in this field were described in a series of 20 ET cases followed for 32 years until 2004 [7].

Sirtuins are class III histone deacetylases homologous to the yeast-derived "silent information regulator 2" (SIR2) gene and are involved in fundamental biological processes such as transcriptional regulation, DNA repair, metabolism, and cellular stress responses [8]. The sirtuin family consists of seven members (SIRT1–SIRT7) that share a similar catalytic domain and utilize nicotinamide adenine dinucleotide ($NAD^+$) as a co-substrate. Each sirtuin is differentiated by its unique intracellular localization and biological function, playing potential roles in aging and neurodegenerative processes [9]. Members of the sirtuin family play roles in different biological processes depending on their intracellular localization. SIRT1, SIRT6, and SIRT7 are primarily localized within the nucleus and regulate mechanisms associated with aging, such as transcriptional regulation, genome stability, DNA repair, and cell cycle control. In contrast, SIRT3 functions in the mitochondria and plays an important role in regulating oxidative phosphorylation and antioxidant defense mechanisms. [10]. In recent years, SIRT1 has been increasingly studied, particularly in the context of neurodegenerative diseases. The current literature has revealed that SIRT1 has regulatory effects on many pathological processes associated with Alzheimer's disease (AD), such as the cleavage of the amyloid-β precursor protein (APP), neuroinflammation, neurodegeneration, and mitochondrial dysfunction. Furthermore, it has been reported that SIRT1 promotes the growth of neuronal extensions and improves synaptic plasticity by increasing the expression of nerve growth factors. Recent experimental studies have shown that various agents, such as cystatin C, genipin, cinnamaldehyde, resveratrol, the adiponectin plant homolog osmotin, and fuzhisan from traditional Chinese medicine, suppress Aβ production via SIRT1. These data make it worthwhile to investigate the neuroprotective potential of SIRT1 not only in Alzheimer's dementia but also in other neurodegenerative diseases [11].

SIRT1 is the most extensively studied member of the Sirtuin family, widely distributed in the central nervous system and highly expressed in the hippocampus, prefrontal cortex, and basal ganglia regions. SIRT1 supports the development of axonal and dendritic development by regulating neurogenesis; it has been shown to increase both axon length and dendritic branching in hippocampal neurons. Activation of SIRT1 through genetic overexpression or pharmacological activation has provided neuroprotective effects in various neurodegenerative disease models, including Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and prion disease [12]. Furthermore, it has been reported that SIRT1 interacts with the DJ-1 protein, enhancing its deacetylase activity and further suppressing the transcriptional activity of p53 [13].

Clinical studies have demonstrated that serum levels of SIRT1 vary in patients with acute ischemic stroke, and these alterations may be associated with stroke severity. Moreover, it has been proposed that SIRT1 activators, such as resveratrol, may reduce risk factors linked to ischemic stroke and potentially extend the therapeutic window. These findings indicate that SIRT1 may exert neuroprotective effects in pathological conditions such as cerebral ischemia and may play a critical role in maintaining brain homeostasis under physiological conditions [14].

It has also been shown that SIRT1 supports learning and memory processes by enhancing the expression of neurotrophic factors such as cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF), whereas SIRT2 modulates synaptic transmission by regulating AMPA receptor deacetylation. The literature highlights the neuroprotective roles of sirtuins in neurodegenerative diseases such as Alzheimer's disease and cerebral ischemia. In particular, SIRT1 is reported to slow disease progression by reducing amyloid-β (Aβ) aggregation and tau protein hyperphosphorylation. These findings suggest that the sirtuin family plays essential roles in cognitive functions and represents promising therapeutic targets for neurodegenerative disorders [15].

Studies conducted in patients with Parkinson's disease have shown that plasma SIRT1 levels are negatively correlated with age, severity of motor symptoms, anxiety, depression, daytime sleepiness, and quality of life. Conversely, higher SIRT1 levels have been positively associated with cognitive performance, particularly in visual-spatial and executive functions, memory, and language domains. According to magnetic resonance imaging (MRI) data, plasma SIRT1 levels also exhibit a positive correlation with total gray matter volume, and these two parameters combined demonstrate high diagnostic accuracy in identifying cognitive impairment. Patients with lower SIRT1 levels presented with higher scores on the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III), reflecting more severe motor dysfunction, and significantly lower scores on the Mini-Mental State Examination (MMSE), indicating reduced cognitive function. These findings suggest that SIRT1 levels are closely linked to both motor and cognitive symptoms in Parkinson's disease [16]. Furthermore, considering the regulatory effects of SIRT1 on energy metabolism and vascular function, non-pharmacological activation strategies —such as intermittent hypoxic training and remote ischemic preconditioning—have been proposed as potential therapeutic approaches [17].

Thiols are potent antioxidant compounds that play a critical role in maintaining the cellular redox balance. Under oxidative stress conditions, thiol groups are oxidized to form disulfide bonds, serving as a fundamental defense mechanism against the harmful effects of reactive oxygen species (ROS). Thiol/disulfide homeostasis reflects the organism's capacity to manage oxidative stress, and this balance is evaluated by measuring native thiol, total thiol, disulfide levels, and their respective ratios. Numerous studies have demonstrated that alterations in the thiol/disulfide balance are associated with a wide range of systemic diseases, including coronary artery disease [18], diabetes mellitus [19], and respiratory system diseases [20]. However, the role of this antioxidant system in neurological diseases such as essential tremor has not yet been sufficiently investigated [21]. The thiol/disulfide balance serves as a key indicator of cellular redox homeostasis and plays a critical regulatory role in maintaining

the structural integrity and functional activity of proteins. Under oxidative stress conditions, protein thiols undergo reversible oxidation to form disulfide bonds, thereby modulating redox-sensitive signaling pathways. The current literature indicates that disturbances in the thiol redox system contribute to the pathogenesis of various conditions, including neurodegenerative diseases, cardiovascular disorders, and metabolic syndromes [22].

Studies on central nervous system disorders, such as multiple sclerosis, have demonstrated that both native and total thiol levels are significantly reduced, with these alterations correlating with clinical disease severity. These findings suggest that thiol/disulfide homeostasis may serve not only as an indicator of redox balance but also as a potential biomarker for disease progression [23].

In neurodegenerative disorders such as Alzheimer's disease, oxidative stress has been shown to play a central role in pathogenesis through various biochemical pathways. Research has revealed a marked disruption in both the intracellular glutathione system and extracellular thiol/disulfide homeostasis. In these patients, levels of glutathione and native thiols are significantly diminished, while levels of disulfides and oxidized glutathione are elevated. This redox imbalance becomes more pronounced with advancing disease severity and shows a strong correlation with cognitive decline [24].

These findings suggest that the thiol/disulfide balance may serve not only as a marker of oxidative stress but also as a potential biomarker reflecting the progression of neurodegenerative processes. In light of this, evaluating thiol/disulfide homeostasis as a potential biomarker in neurological conditions such as essential tremor (ET) represents a promising avenue for future research.

The primary contribution of this study to the existing literature lies in its evaluation of oxidative stress in conjunction with SIRT1 and thiol-based biomarkers in ET, an area that remains underexplored. To our knowledge, this is the first study to demonstrate that these biochemical parameters may offer potential clinical utility in both the diagnosis and longitudinal monitoring of ET. Our aim was to investigate the association between these parameters and processes of oxidative stress and neurodegeneration, and to assess their potential as biomarkers in the pathogenesis of essential tremor.

# Methods

# Study Population

Patients with essential tremor included in this study were recruited from the Neurology Clinic of Ankara Bilkent City Hospital between February 2020 and December 2020. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (30/01/2020; Ethics Code: E1-19-149). Written informed consent was obtained from all study participants. This study was conducted in accordance with the Declaration of Helsinki.

### Inclusion criteria

Patients aged 18–70 years diagnosed with ET according to the Movement Disorder Society criteria, with no accompanying chronic diseases (including diabetes mellitus, cardiovascular disease, chronic kidney disease, autoimmune disorders, or active malignancy), no history of medication use (including antioxidant supplements, statins, or anti-inflammatory drugs) within the past 3 months, and no smoking or alcohol consumption history.

### Exclusion criteria

Patients with other movement disorders, secondary causes of tremor, neurological comorbidities, acute or chronic inflammatory conditions, history of cerebrovascular events, or laboratory evidence of hepatic or renal dysfunction were excluded.

## Clinical Evaluation

All patients underwent comprehensive neurological examination by a neurologist specializing in movement disorders. Tremor severity was assessed using the Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS)[25], a previously validated and widely used clinical scale for essential tremor severity assessment. Disease duration was defined as the time from first tremor symptom to study enrollment. Tremor distribution (upper limbs, head, voice) and functional disability were systematically documented.

The control group consisted of age- and sex-matched healthy volunteers with no known chronic diseases, neurological disorders, or family history of tremor or neurodegenerative diseases. All controls underwent screening neurological examination to exclude subclinical tremor.

Physical examination included measurement of body mass index (BMI), blood pressure, and general health assessment to ensure absence of systemic illness.

## Blood Sample Collection and Processing

Blood samples were collected from 45 ET patients (22 men and 23 women) and 45 healthy controls (20 men and 25 women) for biochemical analysis. Fasting blood samples (10 mL) were collected between 08:00–10:00 AM to minimize circadian variation effects. Patients were instructed to fast overnight (minimum 8 hours) and avoid strenuous physical activity 24 hours prior to sampling. All samples were collected during a period when patients were at rest and had not experienced recent tremor exacerbation.

Blood samples were collected into serum separator tubes (BD Vacutainer®, Becton Dickinson, USA) and allowed to clot at room temperature for 30 minutes. Samples were then centrifuged at 3500 rpm (2000 × g) for 10 minutes at 4°C within 1 hour of collection. Serum was carefully separated and aliquoted into two separate sterile Eppendorf tubes (1.5 mL each) and immediately stored at -80°C until analysis. All samples underwent a single freeze-thaw cycle to preserve biomarker integrity.

## Biochemical Analyses

SIRT1 levels were quantified using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (Human SIRT1 ELISA Kit, Catalog No. E-EL-H1150, Elabscience®, Houston, TX, USA). The assay was performed according to the manufacturer's protocol. The detection range was 0.16-10 ng/mL with a sensitivity of 0.1 ng/mL. Intra-assay coefficient of variation (CV) was < 5% and inter-assay CV was < 10%. All samples were measured in duplicate, and the mean value was used for analysis.

Thiol and disulfide levels were measured using the automated method developed by Erel and Neselioglu [26]. This method allows dynamic and specific measurement of both thiol and disulfide concentrations. Briefly, disulfide bonds are reduced to functional thiol groups by sodium borohydride. Unused reductant is consumed by formaldehyde, and all thiol groups (both native and reduced) are determined using 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB). Dynamic disulfide amount is calculated as half of the difference between total and native thiol. Results are expressed in μmol/L. Intra-assay CV was < 3% and inter-assay CV was < 5%.

# Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. For non-normally distributed variables, the Mann-Whitney U test was employed for between-group comparisons. Correlations between variables were analyzed using Spearman's rank correlation coefficient. A p-value < 0.05 was considered statistically significant.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the biomarkers. Area under the curve (AUC), sensitivity, and specificity values were reported accordingly. A post-hoc power analysis was conducted to determine the adequacy of the sample size and the effect size.

Binary logistic regression analysis was used to assess the predictive value of SIRT1 levels in relation to essential tremor. In this model, the SIRT1 level was treated as the independent variable, and group status (patient vs. control) was designated as the dependent variable. Model fit and predictive accuracy were evaluated using the Hosmer-Lemeshow goodness-of-fit test and the − 2 log-likelihood statistic. Results were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

Post-hoc statistical power analysis was conducted using G*Power software version 3.1.9.4 to determine the adequacy of the sample size. Power was calculated based on observed effect sizes (Cohen's d) and AUC values using the formula: Power = (AUC − 0.5)/0.25, with α = 0.05 (two-tailed).

## Results

# Clinical and Demographic Characteristics

A total of 45 ET patients and 45 age- and sex-matched healthy controls were enrolled. The groups were well-balanced for age (58.3 ± 10.2 vs. 56.7 ± 11.1 years, p = 0.47), sex distribution (p = 0.64), and BMI (26.4 ± 3.8 vs. 25.9 ± 3.2 kg/m², p = 0.52). The mean disease duration was 8.5 ± 5.3 years, with a mean FTM-TRS total score of 24.6 ± 8.7 (Table 1).

Table 1
Clinical and Demographic Characteristics of Study Participants

| Parameter | Patients (n = 45) | Controls (n = 45) | p value |
|---|---|---|---|
| Age (years), mean ± SD | 58.3 ± 10.2 | 56.7 ± 11.1 | 0.47 |
| Sex (Male/Female), n | 22/23 | 20/25 | 0.64 |
| BMI (kg/m²), mean ± SD | 26.4 ± 3.8 | 25.9 ± 3.2 | 0.52 |
| Disease-Related Parameters | | | |
| Disease duration (years), mean ± SD | 8.5 ± 5.3 | — | — |
| FTM-TRS total score, mean ± SD | 24.6 ± 8.7 | — | — |
| Part A (tremor rating), mean ± SD | 18.3 ± 6.4 | — | — |
| Part B (handwriting), mean ± SD | 4.2 ± 2.1 | — | — |
| Part C (functional disability), mean ± SD | 2.1 ± 1.4 | — | — |

Independent samples t-test for continuous variables; Chi-square test for categorical variables.

FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale; BMI: Body mass index; SD: Standard deviation

## Biomarker Comparisons

Patients with essential tremor (ET) had significantly higher serum SIRT1 levels compared to the control group (median: 5.73 ng/mL [3.54–18.89] vs. 4.63 ng/mL [0.86–25.92]; $p = 0.024$). Conversely, levels of native thiol (357.2 µmol/L [225.5–446.0] vs. 374.1 µmol/L [244.2–485.8]; $p = 0.031$) and total thiol (408.8 µmol/L [260.6–518.2] vs. 436.3 µmol/L [295.1–555.3]; $p = 0.022$) were significantly lower in the ET group. Although disulfide levels were also lower in ET patients (23.5 µmol/L [7.35–44.8] vs. 26.85 µmol/L [3.65–50.45]), the difference was not statistically significant ($p = 0.240$) (Table 2, Figs. 1–2).

Table 2
Serum SIRT1 and thiol parameters in essential tremor patients and controls

| Parameter | Patients (n = 45) | Controls (n = 45) | Total (n = 90) | |
|---|---|---|---|---|
| | Median (Min-Max) | Median (Min-Max) | Median (Min-Max) | p |
| SIRT1 (ng/mL) | 5.73 (3.54–18.89) | 4.63 (0.86–25.92) | 5.37 (0.86–25.92) | 0.02 |
| Native THIOL | 357.20 (225.50–446.00) | 374.10 (244.20–485.80) | 368.30 (225.50–485.80) | 0.03** |
| Total THIOL | 408.80 (260.60-518.20) | 436.30 (295.10-555.30) | 424.30 (260.60-555.30) | 0.02** |
| Disulfide | 23.50 (7.35–44.80) | 26.85 (3.65–50.45) | 25.45 (3.65–50.45) | 0.24** |
| Disulfide/Native Thiol x100 | 7.30 (2.07–14.41) | 7.41 (0.92–14.17) | 7.32 (0.92–14.41) | 0.84 |
| Disulfide/Total Thiol × 100 | 6.37 (1.99–11.18) | 6.45 (0.90–11.04) | 6.38 (0.90–11.18) | 0.84 |
| *Mann-Whitney U Test, **Independent Samples T Test | | | | |

These findings suggest a reduction in antioxidant capacity and a possible increase in oxidative stress in patients with essential tremor. However, no significant differences were observed between the groups in disulfide/native thiol (7.30 vs. 7.41; $p = 0.84$) and disulfide/total thiol ratios (6.37 vs. 6.45; $p = 0.84$). This suggests that although absolute thiol levels are reduced, the dynamic balance between thiols and disulfides remains relatively intact in ET pathophysiology.

# Diagnostic Performance

According to the ROC curve analysis, SIRT1 demonstrated a statistically significant diagnostic discriminatory power, with an AUC of 0.638 ($p = 0.024$). A low threshold value of ≤ 3.542 ng/mL yielded 100% sensitivity and 44.4% specificity, indicating its potential utility as a highly sensitive screening biomarker, although the limited specificity restricts its diagnostic precision (Table 3, Fig. 3).

Table 3
ROC curve analysis of biomarker diagnostic performance

| Measure | SIRT1 | Native Thiol | Total Thiol | Disulfide |
|---|---|---|---|---|
| AUC (95% CI) | 0.638* | 0.620** | 0.624*** | 0.590**** |
| Cut-off Value | ≤ 3.542* | < 366.9 | < 381.2 | < 23.9 |
| Sensitivity (%) | 100.0 (92.1–100.0) | 60.0 | 40.0 | 53.0 |
| Specificity (%) | 44.4 (30.9–58.8) | 62.0 | 82.0 | 78.0 |
| PPV (%) | 64.3 (52.6–74.5) | 61.5 | 69.2 | 70.5 |
| NPV (%) | 100.0 (83.9–100.0) | 60.5 | 57.8 | 62.5 |
| Accuracy (%) | 72.2 (62.2–80.4) | 61.0 | 66.5 | 66.0 |

p=*0.02, **0.05, ***0.04, ****0.14, AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

The AUC values for native thiol and total thiol were 0.620 and 0.624, respectively, suggesting modest but meaningful diagnostic contributions (Fig. 4). While their sensitivity and specificity were not as robust as SIRT1's sensitivity at the low cut-off, their inclusion reinforces the biological plausibility of oxidative imbalance in ET pathogenesis.

Post-hoc power analyses were performed based on the observed AUC values using the formula *(AUC − 0.5)/0.25* and a total sample size of 90 (45 ET patients and 45 controls). The calculated statistical power was 0.980 for SIRT1 (AUC = 0.638), 0.942 for native thiol (AUC = 0.620), 0.954 for total thiol (AUC = 0.624), and 0.779 for disulfide (AUC = 0.590). These results indicate that SIRT1 and thiol parameters possess sufficient discriminative capacity, with power values exceeding 94% for all but disulfide. The findings support the reliability of the observed diagnostic performance, despite the moderate sample size, and underscore the clinical relevance of SIRT1 and thiol homeostasis in essential tremor.

# Correlation Analysis

Correlation analyses were performed to examine relationships between biochemical parameters and clinical disease variables (Table 4). SIRT1 levels showed a significant positive correlation with disease duration (ρ = 0.312, p = 0.037), suggesting progressive upregulation over time. Native thiol (ρ=-0.318, p = 0.033) and total thiol (ρ=-0.305, p = 0.042) levels were inversely correlated with FTM-TRS scores, indicating that lower antioxidant

capacity associates with greater tremor severity.

Table 4
Correlation Between Biomarkers and Clinical Parameters in ET Patients

| Variable | Disease Duration | | FTM-TRS Total Score | |
|---|---|---|---|---|
| | ρ | p | ρ | p |
| SIRT1 (ng/mL) | 0.312 | 0.037* | 0.287 | 0.056 |
| Native thiol (µmol/L) | -0.245 | 0.104 | -0.318 | 0.033* |
| Total thiol (µmol/L) | -0.238 | 0.115 | -0.305 | 0.042* |
| Disulfide (µmol/L) | -0.089 | 0.558 | -0.176 | 0.247 |
| Disulfide/Native thiol ratio (×100) | 0.198 | 0.192 | 0.241 | 0.110 |
| Disulfide/Total thiol ratio (×100) | 0.201 | 0.184 | 0.238 | 0.116 |
| *p < 0.05; Spearman rank correlation coefficient (ρ); FTM-TRS: Fahn-Tolosa-Marin Tremor Rating Scale | | | | |

Since SIRT1 levels were not normally distributed in either group, Spearman's rank correlation was used for the correlation analyses. The results showed no significant correlation between SIRT1 levels and native thiol (ρ = 0.161, $p = 0.129$), total thiol (ρ = 0.146, $p = 0.170$), or disulfide levels (ρ = -0.031, $p = 0.772$). In contrast, a very strong positive correlation was observed between native thiol and total thiol levels (ρ = 0.959, $p < 0.001$), while a moderately significant positive correlation was found between total thiol and disulfide levels (ρ = 0.453, $p < 0.001$) (Fig. 5). These findings suggest that thiol/disulfide homeostasis plays a significant role in oxidative stress mechanisms. Moreover, the absence of correlation between SIRT1 and thiol parameters implies that SIRT1 may be involved in alternative, oxidative stress-independent pathways in the pathogenesis of essential tremor. The strong associations among thiol parameters indicate that the thiol/disulfide system may offer greater sensitivity as a biochemical marker of oxidative stress.

* p < 0.05),** p ≥ 0.05

**Figure 5.** Spearman correlation matrix of SIRT1 and thiol-disulfide parameters.

# Logistic Regression Analysis

In the univariate logistic regression analysis, native thiol (p = 0.03) and total thiol (p = 0.02) levels emerged as significant protective factors (Table 5, Fig. 6). However, their statistical significance was lost when included in the multivariate model, likely due to high collinearity between these variables, indicating their limited independent predictive value. Although SIRT1 levels did not reach statistical significance in either model, their potential biological relevance cannot be excluded and may become more apparent in studies with larger sample sizes.

Table 5
Logistic regression analysis of SIRT1 and thiol parameters

| Variable | Univariate OR (95% CI) | p | Multivariate[1] OR (95% CI) | p |
|---|---|---|---|---|
| SIRT1 (ng/mL) | 1.031 (0.95–1.119) | 0.46 | 1.045 (0.959–1.140) | 0.31 |
| Native thiol | 0.992 (0.985–0.999) | 0.03 | 0.999 (0.929–1.019) | 0.93 |
| Total Thiol | 0.992 (0.986–0.999) | 0.02 | 0.993 (0.929–1.019) | 0.46 |

[1]Enter Method; OR, odds ratio; CI, confidence interval

# Discussion

Recent studies have provided compelling evidence supporting the role of oxidative stress in the pathogenesis of essential tremor (ET). Given that disease progression in ET often varies over time and remains clinically unpredictable, the need for reliable biomarkers is steadily increasing. In our study, elevated SIRT1 levels and decreased thiol levels in ET patients are consistent with previous findings that highlight oxidative stress as a key mechanism in neurodegenerative diseases. These alterations in SIRT1 and thiol-disulfide balance suggest that redox imbalance may be involved in ET pathogenesis.

Recent research has emphasized the involvement of sirtuin family members—particularly SIRT1 and SIRT2—in aging and neurodegenerative processes [27]. Our findings corroborate this and further suggest that SIRT1 and thiol/disulfide parameters may serve as potential biomarkers for ET. Although SIRT1 showed only moderate discriminative power in ROC analysis, it demonstrated high sensitivity, indicating its promise as a potential screening tool. However, the relatively low specificity limits its standalone diagnostic value.

This study demonstrated that serum SIRT1 levels were significantly elevated in patients with essential tremor (ET), whereas total and native thiol levels were significantly decreased. These findings provide important insights into the potential involvement of oxidative stress in the pathogenesis of ET. The elevated SIRT1 levels may reflect a compensatory cellular response aimed at limiting oxidative damage and preserving cellular homeostasis. In contrast, reduced thiol levels point to a diminished antioxidant defense capacity, indicating a vulnerability to oxidative stress.

Correlation analysis revealed no significant association between SIRT1 levels and thiol/disulfide homeostasis, suggesting that SIRT1 may exert its effects through alternative molecular mechanisms independent of redox balance. On the other hand, the strong correlation observed between total thiol and disulfide levels may represent a more consistent biochemical indicator of oxidative stress.

Given the neuroprotective functions of SIRT1 and SIRT3 within the central nervous system (CNS), the upregulation of these sirtuins in ET may be interpreted as a compensatory neuroadaptive mechanism

[28]. Conversely, considering the documented neurotoxic effects of SIRT2, future studies evaluating SIRT2 expression and activity in ET could provide deeper insights into disease progression. The observed increase in SIRT1 may, therefore, reflect both ongoing neurodegeneration and an intrinsic protective cellular response. Previous studies have shown that SIRT1 supports dopaminergic neuron survival by modulating mitochondrial biogenesis and maintaining redox homeostasis via the PGC-1α pathway [29]. Moreover, the reduction in thiol levels may be indicative of increased reactive oxygen species (ROS) production and subsequent depletion of antioxidant reserves.

The imbalance between oxidative stress and antioxidant defenses is a key contributor to neuronal damage in Parkinson's disease. SIRT3, a protective protein that regulates mitochondrial function and provides resistance against aging, has been shown to be reduced in Parkinson's patients. This decrease may reflect both age-related changes and disease progression [30].

The neuroprotective effects of SIRT1 have been demonstrated in various models of neurodegenerative diseases. Singh et al. [31] showed that overexpression of SIRT1 in the SH-SY5Y cell line enhances cell survival under oxidative stress and reduces α-synuclein aggregation. Similarly, studies by Tang [12] and Takahashi-Niki [13] emphasized that SIRT1 can modulate Parkinson's disease pathology through mechanisms such as autophagy, mitochondrial biogenesis, and redox homeostasis. Xu [32] further highlighted the central role of SIRT1 in regulating energy balance and mitochondrial function in the hypothalamus. Additionally, Leite [10] proposed that sirtuins may serve as pharmacological targets in the treatment of neurodegenerative disorders. Collectively, these findings suggest that SIRT1 may also exert protective effects in neurodegenerative diseases such as essential tremor (ET).

A recently published study reported elevated serum neurofilament light chain protein (sNfL) levels in patients with essential tremor (ET), suggesting that neurodegenerative mechanisms may already be active in the early stages of the disease. This finding aligns with our results based on oxidative stress markers and further supports the notion that ET is not merely a functional or benign condition, but one that involves structural and neurobiological alterations [33].

Recent studies have emphasized the pivotal roles of the sirtuin family in the pathogenesis of neurodegenerative disorders. As highlighted by Dhiman et al. [34], sirtuins—particularly SIRT1 and SIRT2—play essential roles in regulating oxidative stress, mitochondrial dysfunction, and neuroinflammation through modulation of protein acetylation and deacetylation. Activation of SIRT1 enhances antioxidant defense mechanisms and supports neuronal survival, whereas excessive SIRT2 activity has been implicated in promoting neurotoxicity. Accordingly, the observed elevation in SIRT1 levels in patients with essential tremor (ET) may reflect an underlying neurodegenerative process or represent a compensatory cellular adaptation aimed at mitigating oxidative damage. Conversely, the reduction in thiol levels may indicate increased free radical activity and a compromised antioxidant defense system.

The neuroprotective potential of sirtuin modulators has garnered increasing attention in recent literature. Specifically, SIRT1 activators such as resveratrol, SRT1720, and cilostazol have demonstrated the ability

to enhance cognitive function and may hold therapeutic potential for neurodegenerative diseases [13], [32].

The ROC curve and post-hoc power analyses conducted in this study demonstrated that SIRT1 and, to a lesser extent, thiol parameters possess notable diagnostic discriminatory power. In particular, the statistical power of 98% calculated for SIRT1 supports its potential as a reliable biomarker in essential tremor. Conversely, the relatively lower power observed for disulfide levels (approximately 78%) suggests that while disulfide alone may not serve as a strong standalone marker, it could still contribute as a supportive parameter in combination with other oxidative stress indicators.

Thiol/disulfide homeostasis has gained importance in recent years as an indirect marker of oxidative stress. The novel measurement method developed by Erel and Neselioglu allows for the dynamic assessment of thiol and disulfide levels, thereby increasing the clinical applicability of these parameters in various diseases. Thiol levels have been shown to decrease and disulfide levels to increase in conditions such as urolithiasis [35] and gastritis [36]. Similar alterations observed in ET patients in our study suggest that systemic oxidative burden may contribute to ET pathogenesis. The disruption of thiol/disulfide homeostasis found in our ET cohort parallels previous findings in Graves' disease [39]. Elmas et al. [21] associated significant impairment in thiol/disulfide homeostasis, indicative of oxidative stress, with increased inflammation in obese individuals. Furthermore, Ertürk et al. [37]demonstrated that elevated serum disulfide levels and standard inflammatory markers at baseline in patients with septic arthritis are associated with oxidative stress. Taken together, these findings support the notion that oxidative stress may represent a common mechanistic pathway in the pathophysiology of neurological disorders.

Specifically, SIRT1 exhibits a neuroprotective effect by supporting cell survival under oxidative stress and contributes to the maintenance of protein homeostasis. Decreased SIRT1 levels in neurodegenerative disorders such as Alzheimer's disease (AD) have been associated with the progression of these diseases [38]. Additionally, SIRT1 offers a protective mechanism against neurodegenerative pathologies through pathways such as deacetylation of tau proteins, regulation of transcription of enzymes involved in amyloid precursor protein (APP) metabolism, and improvement of mitochondrial functions [27].

The changes in sirtuin levels detected in ET patients in our study may reflect the effects of aging and oxidative stress. These alterations support the emerging perspective that essential tremor (ET) may be part of the neurodegenerative disease spectrum. Furthermore, the thiol levels measured in our study, as indicators of oxidative stress, align with the known regulatory roles of SIRT1 in maintaining redox balance. SIRT1 helps reduce oxidative damage by enhancing antioxidant enzyme activity, suppressing inflammation, and promoting mitochondrial biogenesis. It also supports neuronal survival through the activation of anti-apoptotic pathways and modulation of transcription factors involved in stress response. These mechanisms offer valuable insights into the pathophysiological processes underlying ET [39].

Additionally, an experimental study conducted in 2024 demonstrated that the combination of resveratrol and vitamin D3 improved motor and cognitive functions in a harmaline-induced essential tremor (ET) rat model [40]. This improvement was associated with increased SIRT1 expression, suggesting a mechanistic link between enhanced sirtuin activity and neurofunctional recovery. These findings support the potential neuroprotective role of SIRT1 in ET. Collectively, accumulating evidence emphasizes that therapeutic strategies targeting the sirtuin pathway, particularly SIRT1, warrant further investigation as promising candidates in the management of ET.

Our study demonstrates that thiol/disulfide homeostasis is significantly altered in patients with ET, suggesting a possible association with oxidative stress mechanisms. These findings align with current literature emphasizing the pivotal role of thiol groups in redox biology and cellular antioxidant defense. The observed imbalance supports the hypothesis that thiol/disulfide homeostasis may serve as a potential biomarker in ET. Future investigations integrating thiol parameters into broader biomarker panels may enhance our understanding of ET pathophysiology and contribute to biomarker development in other neurodegenerative diseases as well [22].

The applicability of these biomarkers in early diagnosis, disease progression monitoring, and personalized treatment strategies warrants further investigation through longitudinal and large-scale studies. Given the clinical heterogeneity and often subtle progression of ET, the identification of reliable and accessible biomarkers remains a clinical priority.

SIRT1 and thiol-based oxidative stress markers demonstrate promising potential as auxiliary tools for early detection and follow-up assessments in ET. Their integration into clinical workflows may support individualized patient management, particularly in distinguishing subtypes, monitoring therapeutic response, and tailoring neuroprotective interventions.

Future research should focus on validating these biomarkers across diverse ET cohorts and evaluating their sensitivity and specificity in different stages of the disease. Furthermore, their predictive value in assessing treatment efficacy or forecasting disease trajectory could significantly enhance personalized medicine approaches in neurodegenerative disorders.

This study has several limitations that should be acknowledged. First, the cross-sectional design precludes the ability to establish causal relationships between oxidative stress markers and ET pathogenesis. Second, the relatively small sample size may limit the generalizability of the findings, and statistical power for detecting smaller effect sizes could be insufficient. Third, the use of serum-based biomarkers may not fully reflect underlying central nervous system (CNS) alterations, as peripheral measurements do not always correspond with central biochemical changes. Fourth, potential confounding factors, such as dietary habits, physical activity, or undetected subclinical inflammation, were not controlled for and may have influenced the biomarker levels. Fifth, SIRT1 expression levels and functional activity within the CNS were not directly measured, limiting mechanistic insights. Additionally, biomarker validation using cerebrospinal fluid (CSF) analysis or neuroimaging techniques was not conducted, which would have strengthened the biological relevance of the findings.

Future research should focus on larger, well-powered, longitudinal studies incorporating CSF biomarkers, advanced neuroimaging modalities, and comprehensive evaluation of confounding variables to more accurately elucidate the role of oxidative stress in ET and validate the clinical utility of the proposed biomarkers.

# Conclusions

This study contributes to the current understanding of oxidative stress in ET pathogenesis by demonstrating increased SIRT1 levels and decreased thiol levels in ET patients. These findings support the hypothesis that oxidative imbalance may play a role in ET and suggest that SIRT1 and thiol parameters could serve as accessible and non-invasive biomarkers.

The potential of these biomarkers to assist in early diagnosis, disease monitoring, and treatment response tracking should be further evaluated in prospective, large-scale studies. Their clinical integration may provide new tools for personalized management, especially in the context of the heterogeneous clinical presentation of ET.

By addressing a gap in the literature concerning the role of SIRT1 and thiol/disulfide balance in ET, this study sets the foundation for future research exploring redox biology in neurodegeneration. Translational studies focusing on sirtuins and redox modulation may advance therapeutic development not only in ET but also in broader neurodegenerative disease contexts.

# Abbreviations

ET
Essential tremor
SIRT1
Sirtuin 1
$NAD^+$
Nicotinamide adenine dinucleotide
ROS
Reactive oxygen species
ELISA
Enzyme-linked immunosorbent assay
FTM-TRS
Fahn-Tolosa-Marin Tremor Rating Scale
BMI
Body mass index
ROC
Receiver operating characteristic
AUC

Area under the curve
CNS
Central nervous system
CSF
Cerebrospinal fluid
AD
Alzheimer's disease
BDNF
Brain-derived neurotrophic factor
CREB
cAMP response element-binding protein
APP
Amyloid-β precursor protein
PPV
Positive predictive value
NPV
Negative predictive value
OR
Odds ratio
CI
Confidence interval

# Declarations

### Ethics approval and consent to participate

This study was approved by the Ankara Bilkent City Hospital Ethics Committee (30/01/2020; Ethics Code: E1-19-149). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

### Consent for publication

Not applicable.

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

MM designed the study and performed neurological examinations. AK carried out the biochemical analyses. FE performed the statistical analysis. MM and AK wrote the manuscript. All authors read and approved the final manuscript.

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# Figures

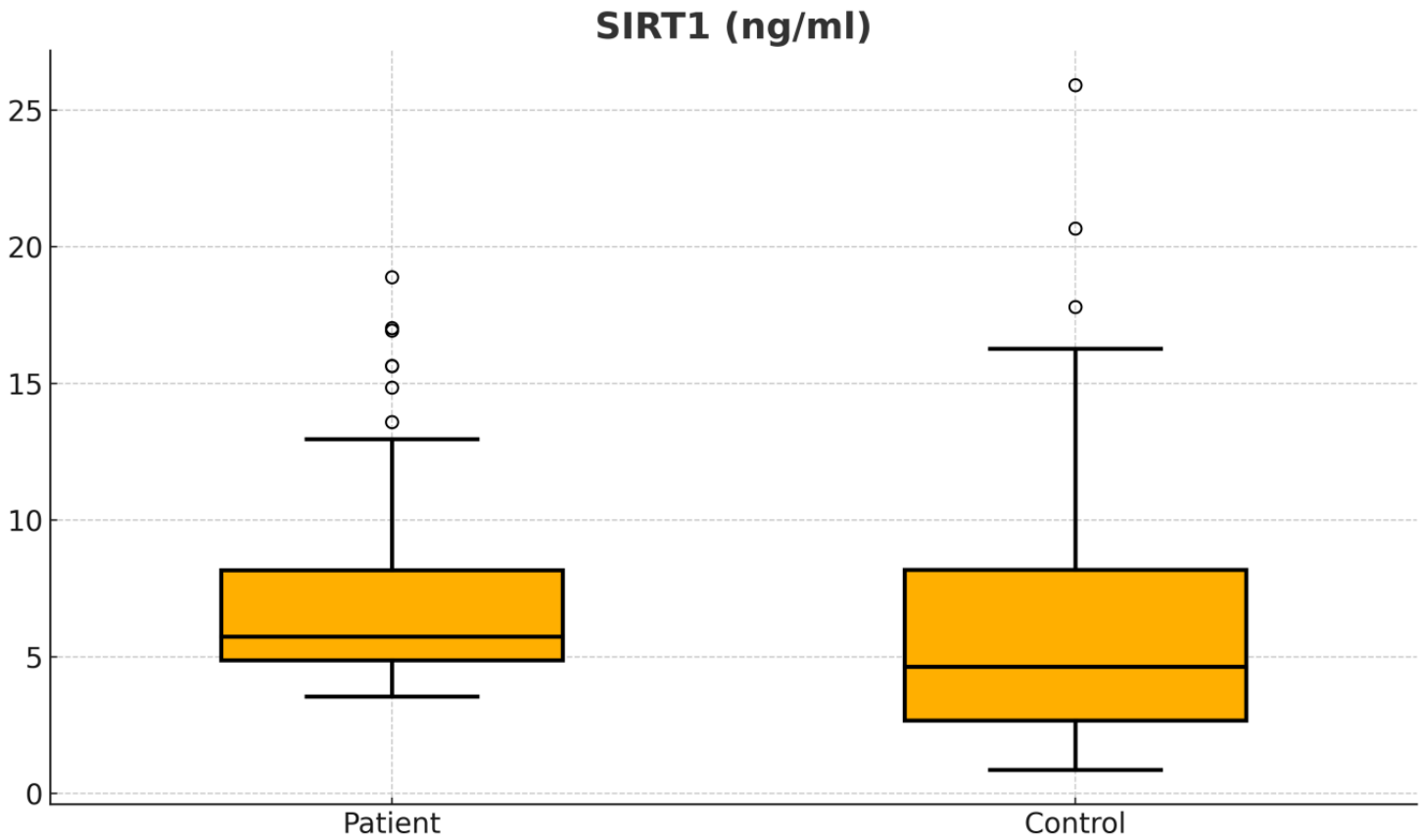
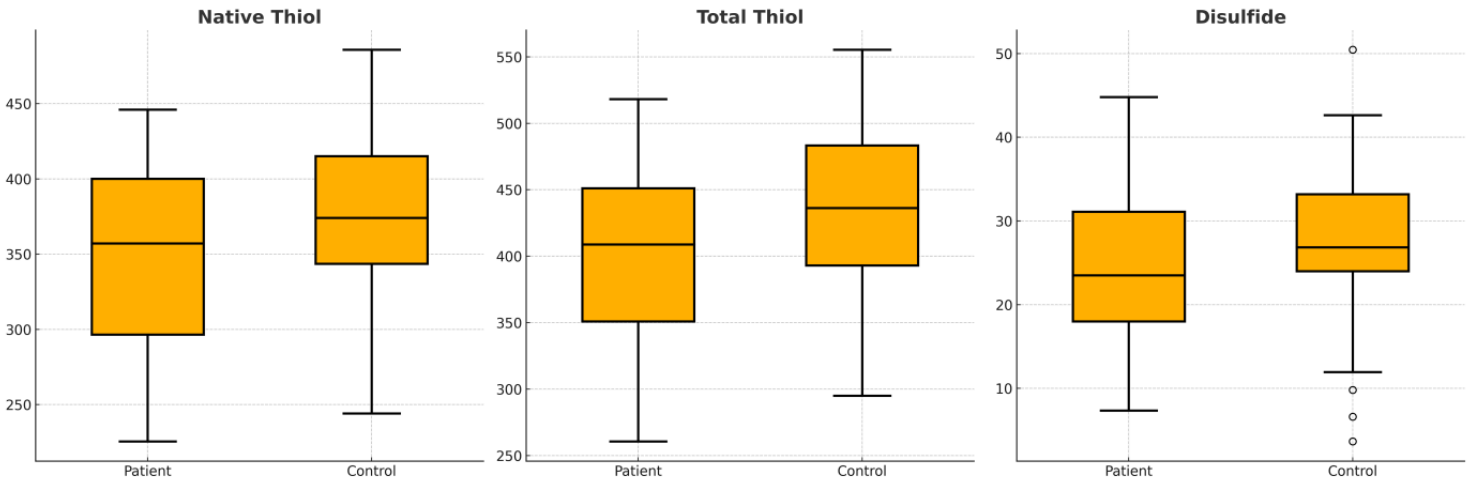



**Figure 1**

Serum SIRT1 levels in essential tremor patients and healthy controls




## Figure 2

Native thiol, total thiol, and disulfide levels in essential tremor and controls

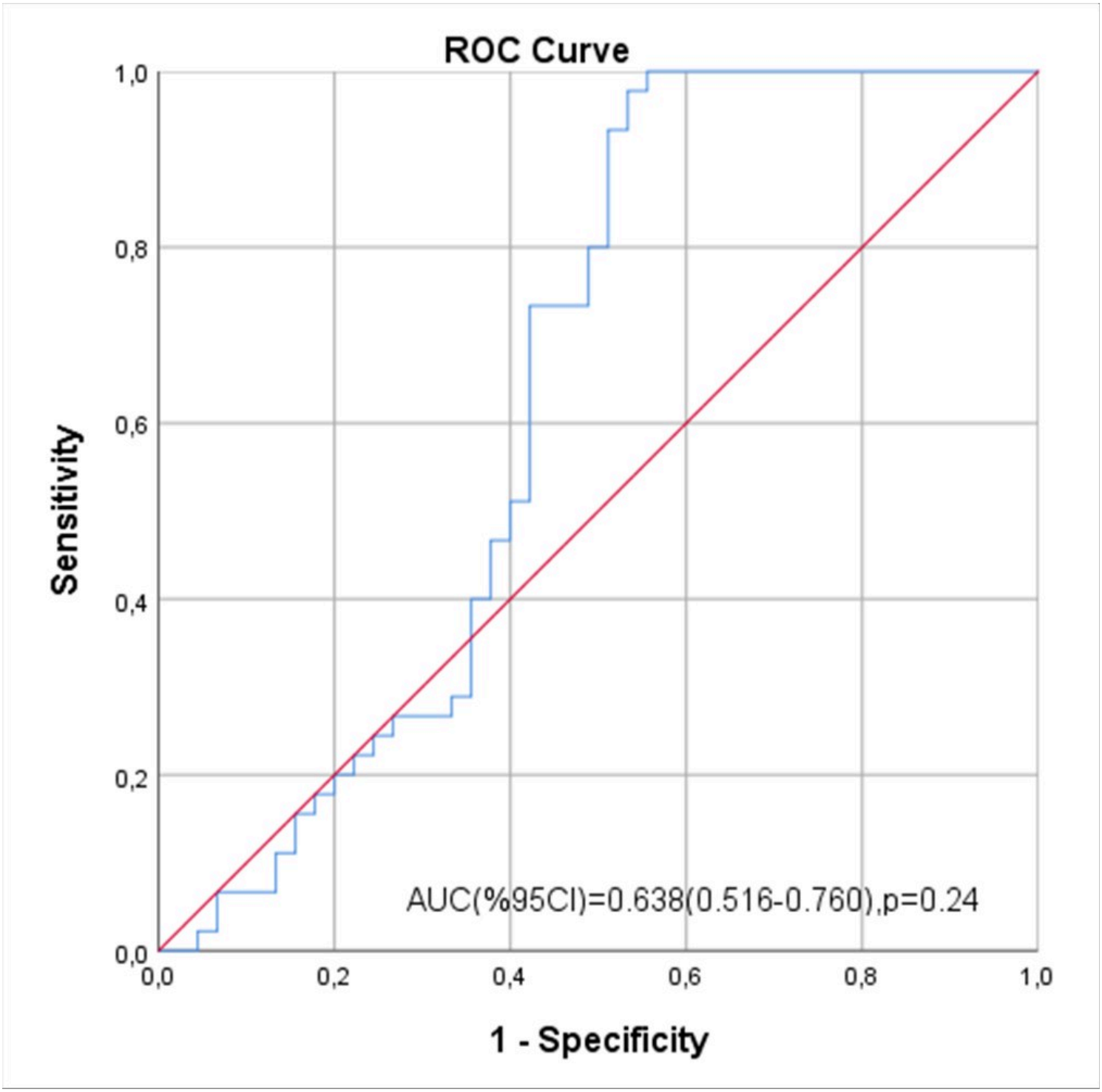



**Figure 3**

ROC curve of SIRT1 for distinguishing patients from controls (AUC = 0.638)

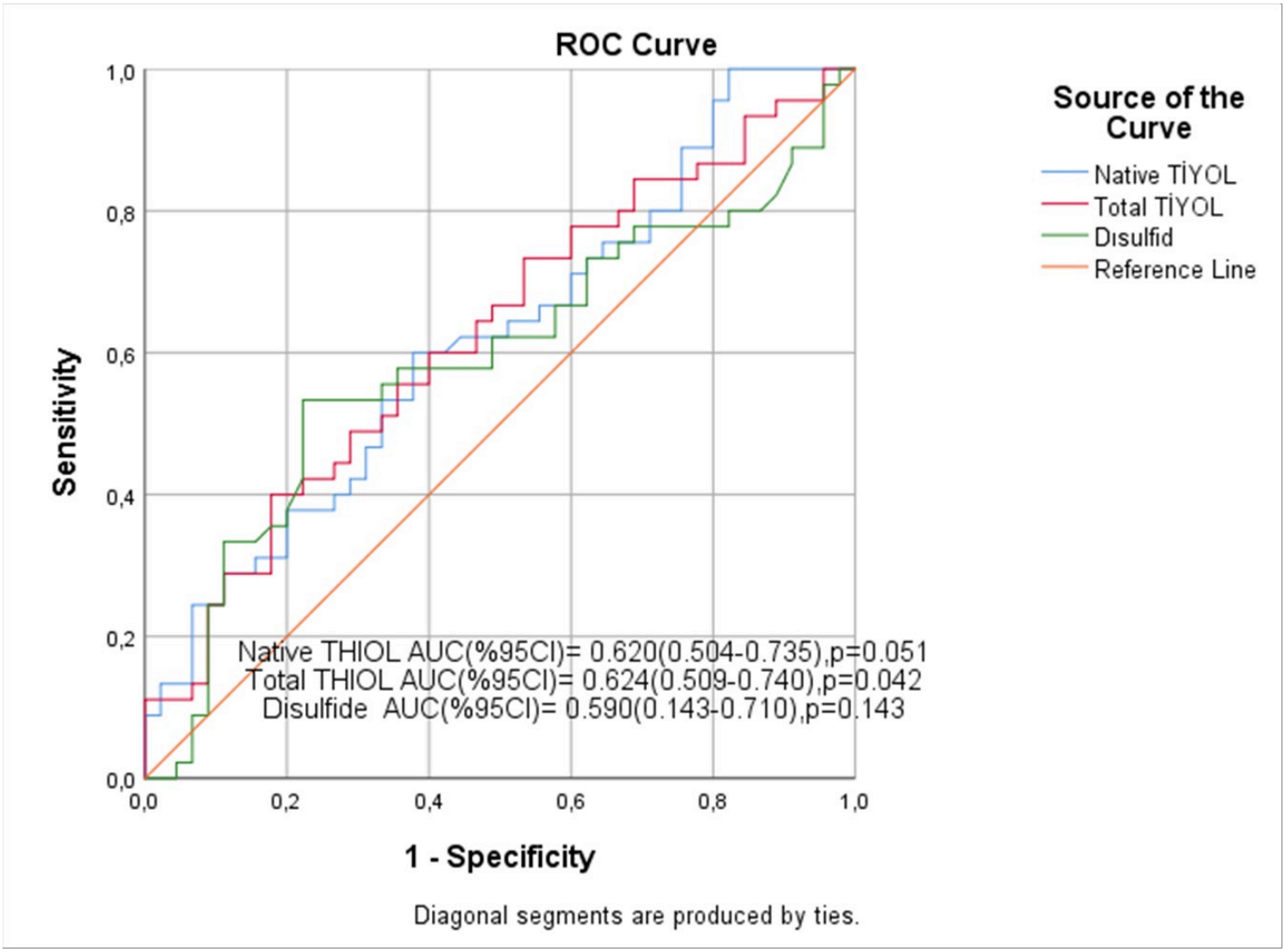
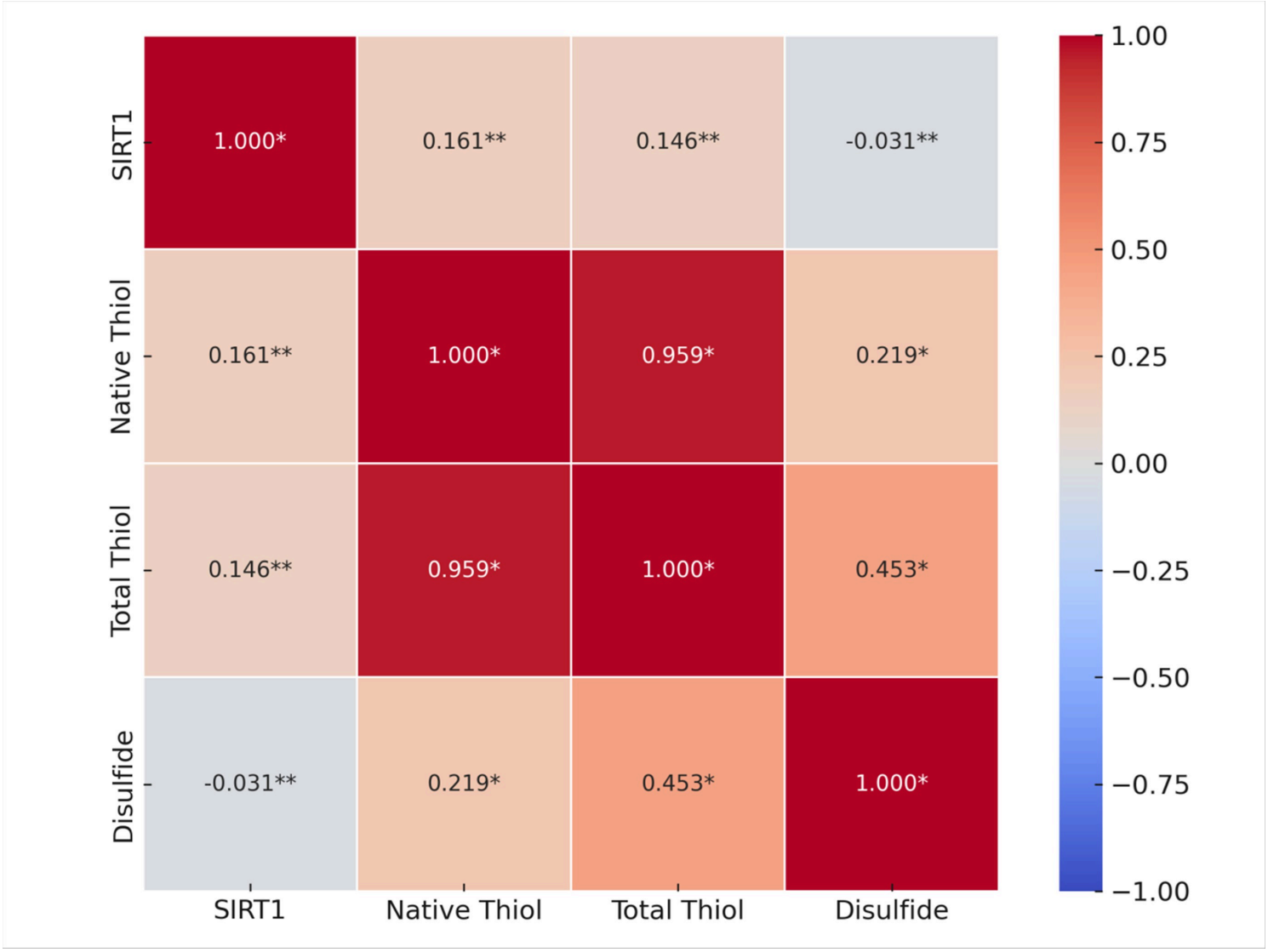



**Figure 4**

ROC curves of thiol parameters for essential tremor diagnosis




## Figure 5

Spearman correlation matrix of SIRT1 and thiol-disulfide parameters.

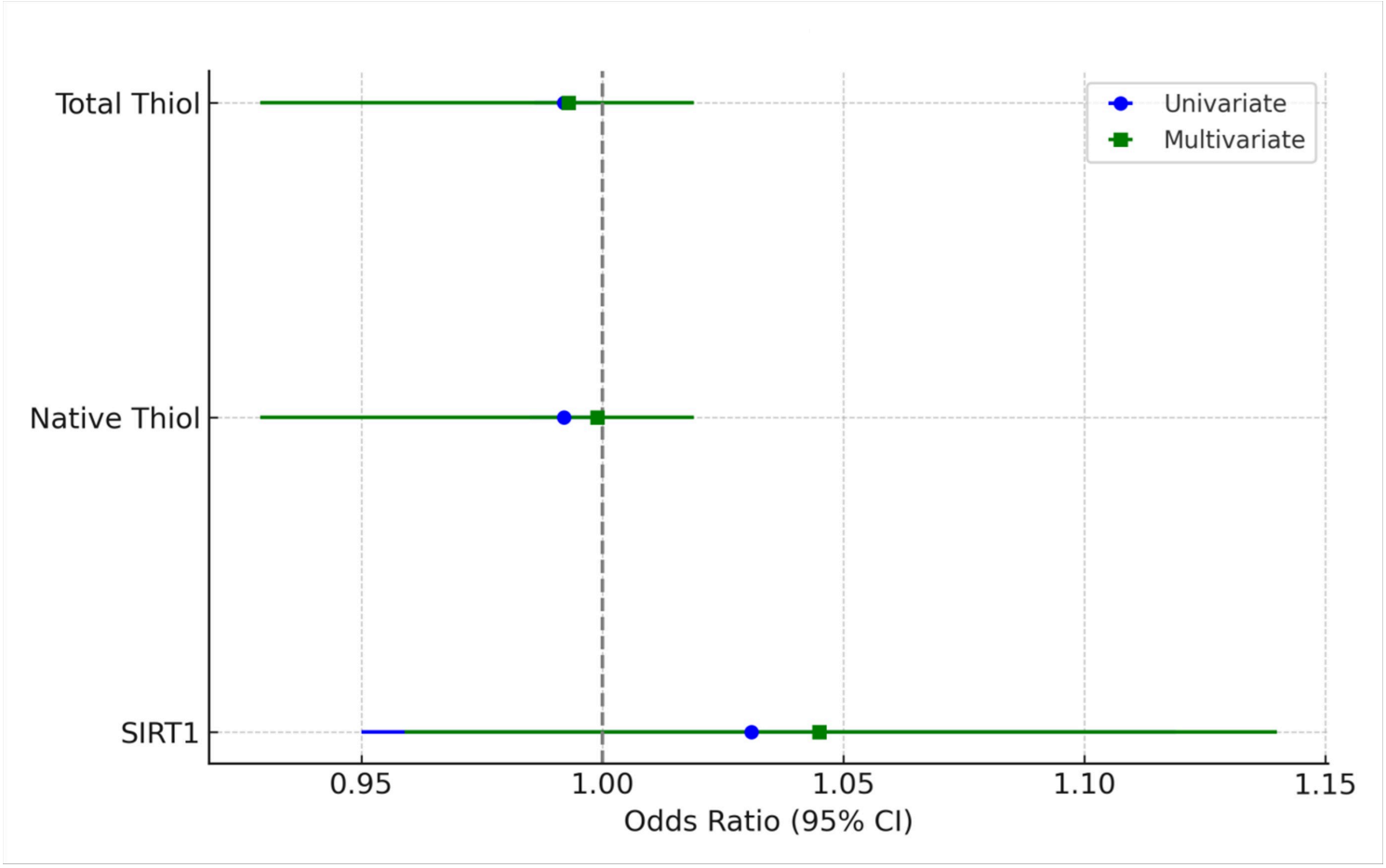



**Figure 6**

Forest plot of logistic regression analyses for SIRT1 and thiol parameters