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Unraveling Oxidative Stress in Moyamoya Disease: Exploring Thiol-Disulfide Dynamics and Ischemia-Modified Albumin

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ABSTRACT

This study aimed to explore the potential association between oxidative stress markers and Moyamoya Disease (MMD), a complex cerebrovascular disorder characterized by vascular constriction and collateral vessel formation. The study focused on thiol-disulfide homeostasis and ischemia-modified albumin (IMA) levels as indicators of oxidative stress. A total of 23 MMD patients and 23 control subjects were included in the study. Clinical assessments and comprehensive blood analyses were conducted to evaluate factors including age, gender, disease duration, treatment history, and biochemical parameters. Thiol-disulfide homeostasis parameters were measured using an automated method. Ischemia-modified albumin levels were also analyzed. Statistical analyses, including chi-square tests and ROC curve analysis, were performed to determine differences and potential diagnostic cut-off points. Elevated levels of native thiol, total thiol, and disulfide were observed in the MMD patient group compared to the control group, statistically significant. Ischemia-modified albumin levels were notably higher in the patient group, corroborating the association between oxidative stress and ischemic events. ROC curve analysis identified potential diagnostic cut-off points for these markers. The study also highlighted clinical differences, including BMI, CRP levels, and the frequency of various symptoms, between the patient and control groups. Our study offers insights into the intricate interplay between oxidative stress and Moyamoya Disease. The statistically significant elevated levels of thiol-disulfide markers and ischemia-modified albumin suggest potential links to oxidative stress dynamics within MMD. These findings contribute to our understanding of oxidative stress in cerebrovascular diseases and open avenues for further research.

Keywords: Moyamoya Disease, Oxidative Stress, Thiol-Disulfide Homeostasis, Ischemia-Modified Albumin, Cerebrovascular Disorder

Introduction

Moyamoya Disease (MMD) stands as a perplexing cerebrovascular ailment characterized by progressive vascular constriction, internal carotid artery (ICA) occlusion, and the emergence of intricate collateral vessels termed "Moyamoya vessels " (1,2). These delicate, mist-like vessels unfortunately fail to furnish adequate cerebral perfusion, consequently giving rise to an array of symptoms including ischemic or hemorrhagic stroke, seizures, cognitive decline, and in severe cases, debilitation or fatality (1). Notably prevalent in East Asian populations, especially in countries like Japan, China, Taiwan, and Korea, MMD's regional and ethnic predilection strongly implicates genetic factors as key contributors (2,3).

Regrettably, a panacea remains elusive, as progressive cases lack preventive strategies or medically validated interventions. In instances of ischemic MMD, surgical revascularization assumes

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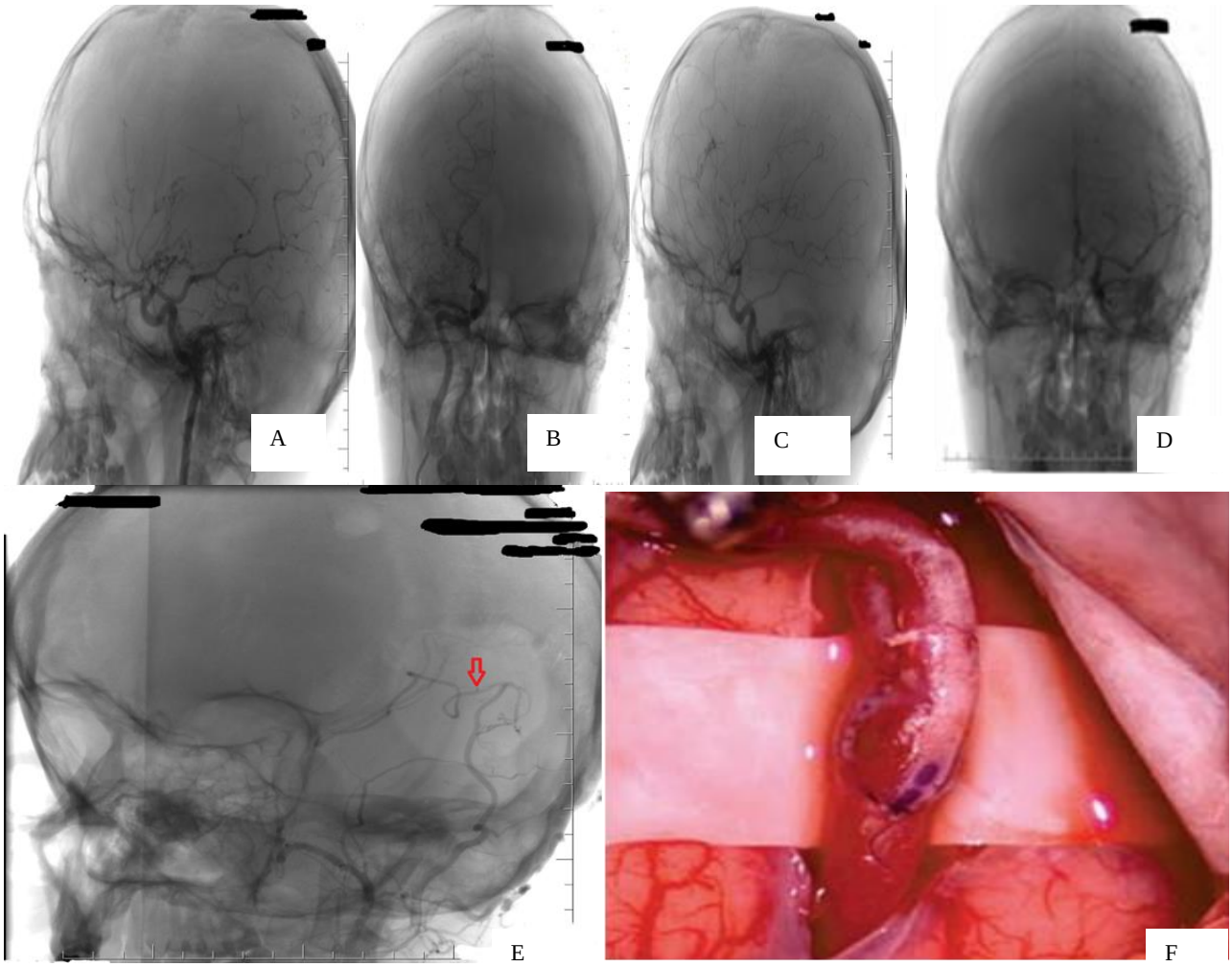

Fig. 1. Preoperative, intraoperative and postoperative Moyamoya Disease (MMD) imaging. A,B,C,D) preoperative MMD digital subtraction angiography (DSA) images, E) Postoperative STA-MCA bypass DSA image (red arrow points to bypass), F) Intraoperative side to end bypass photo

the mantle, seeking to augment cerebral blood flow, manage symptoms, and avert future ischemic strokes. Conversely, hemorrhagic scenarios take a divergent route. The postulation here rests on mitigating long-term hemodynamic stress within collateral branches, a strategy aimed at inducing regression in the precarious vasculature and, by extension, curtailing the likelihood of hemorrhagic recurrence (3,4).

The persistent vascular insufficiency inherent to MMD begets a chronic ischemic milieu within the cerebral tissue. In this setting, an influx of leukocyte series is triggered, along with the accumulation of reactive oxygen species (ROS) and other potent free radicals (5,6). This assembly of leukocyte series, ROS, and radicals coalesces within the brain tissue over time, propelling the emergence of a physiological equilibrium between oxidant and antioxidant mechanisms. Disturbing this balance marks the advent of oxidative stress (7).

In this intricate interplay, compounds harboring the thiol group emerge as stalwart defenders against oxidative stress by virtue of their reductive attributes. Notably, as thiol groups undergo oxidation, they engage in a reversible dance to form disulfide bonds. This reversible nature lends itself to the dynamic thiol-disulfide homeostasis, enabling a continuous restoration of equilibrium. A crucial facet of this equilibrium is the interception of ROS and free radicals, a task that unfolds through both enzymatic and nonenzymatic avenues. A hallmark marker of oxidant onslaught, ischemia-modified albumin (IMA), takes form when oxidative stress or ischemia alters the N-terminal of albumin (5,8). Noteworthy elevations in serum IMA levels have been observed in various maladies, including but not limited to pulmonary embolism, cerebral hemorrhage, acute coronary syndrome, and stroke.

As the tapestry of oxidative stress in Moyamoya Disease unravels, the intricate choreography of these molecular actors comes to light, opening

doors to potential therapeutic interventions and a deeper comprehension of this intricate cerebrovascular enigma.

Material and Methods

Patient Selection: The study adhered rigorously to ethical principles and received the requisite approval from the Institutional Review Board under code TUEK E1-23-3467. Prior to participation, informed consent was acquired from all patients, ensuring their comprehensive understanding of potential risks.

The study involved 23 patients with a confirmed diagnosis of MMD using the gold standard digital subtraction angiography (DSA). DSA was performed both pre- and post-surgery for MMD. Surgical options included combination of direct superficial temporal artery to middle cerebral artery side-to-end bypass and a combined indirect encephalo-duro-arterio-myo-synangiosis (Figure 1). Blood samples were obtained from MMD patients during the preoperative period, excluding those who had previously undergone intracranial surgery. To establish a comparative baseline, 23 individuals without cranial disorders were carefully chosen as the control group.

Systematic clinical assessments, both in clinical and outpatient settings, were administered to all participants by the investigative team. These assessments delved into intricate facets including detailed medical histories, comprehensive neurological examinations, age, gender, disease duration, and treatment backgrounds. Notably, none of the study participants had a history of smoking, alcohol, or drug usage.

Stringent exclusion criteria were implemented. Patients grappling with progressive cerebral ailments, chronic systemic conditions, or comorbidities were excluded. Likewise, those adhering to specialized diets or chronic medication regimens were also omitted from the study. The control group was meticulously screened, revealing no instances of malignancy, systemic ailments, or neurological disorders.

Furthermore, both patients and control group individuals were devoid of acute medical issues, such as trauma or infection, at the time of blood collection. A baseline of health was established through comprehensive assessments including lipid profiles, blood glucose levels, complete blood counts, renal function tests, blood electrolyte levels, and iron profiles, all of which revealed normal results.

The meticulous procedure for plasma sampling and analysis involved the collection of venous blood samples from participants' antecubital veins. These samples were procured in the morning following a 12-hour fast and stored in ethylene diamine tetra acetic acid (EDTA) tubes. Swift centrifugation of the plasma blood samples at 1500 rpm for 10 minutes, within half an hour of collection, ensured their integrity. The subsequent storage of these samples at -80°C preserved their quality until the time of utilization.

The Method of Laboratory: This study delves into the intricate interplay of dynamic thiol-disulfide homeostasis and IMA within serum samples, juxtaposing patients diagnosed with MMD against healthy individuals. A cutting-edge automated methodology, pioneered by Erel et al., forms the bedrock of this investigation (9). To elucidate the thiol landscape, the concentrations of total thiol (TT, comprising both -SH and -S-S-) as well as native thiol (NT, -SH) were gauged utilizing the renowned Ellmann's reagent and its modified variant. The procedure involved pivotal calculus, where the native thiol content was subtracted from the total thiol content. Half of the resulting difference revealed the quantity of active disulfide bonds (-S-S-). This innovative approach allowed the computation of several vital ratios, including (–S-S-) 100/(–SH), –SH 100/(–SH + –S-S-) , and (–S-S-) 100/(–SH + –S-S-) (10). This web of indices was meticulously woven using these distinctive parameters.

Statistics: The data analysis was carried out using the IBM SPSS 25.0 statistical package programs in Armonk, NY, by IBM Corp. Various descriptive statistical methods were employed, including frequency, percentage, mean, standard deviation, median, and the range. To compare qualitative data, the Chi-Square test ($\chi 2$) was applied. The normality of the data distribution was assessed using the Shapiro-Wilk test, skewness, kurtosis, and graphical techniques such as histograms, Q-Q Plots, Stem-and-Leaf plots, and Boxplots. For comparisons of normally distributed quantitative data between groups, Independent Samples t Test was used, while comparisons of non-normally distributed quantitative data between groups were conducted using the Mann-Whitney U test. The ROC curve (Receiver Operating Characteristic) method was employed to determine the discriminatory power of variables, and the statistical significance level was set at $\alpha=0.05$.

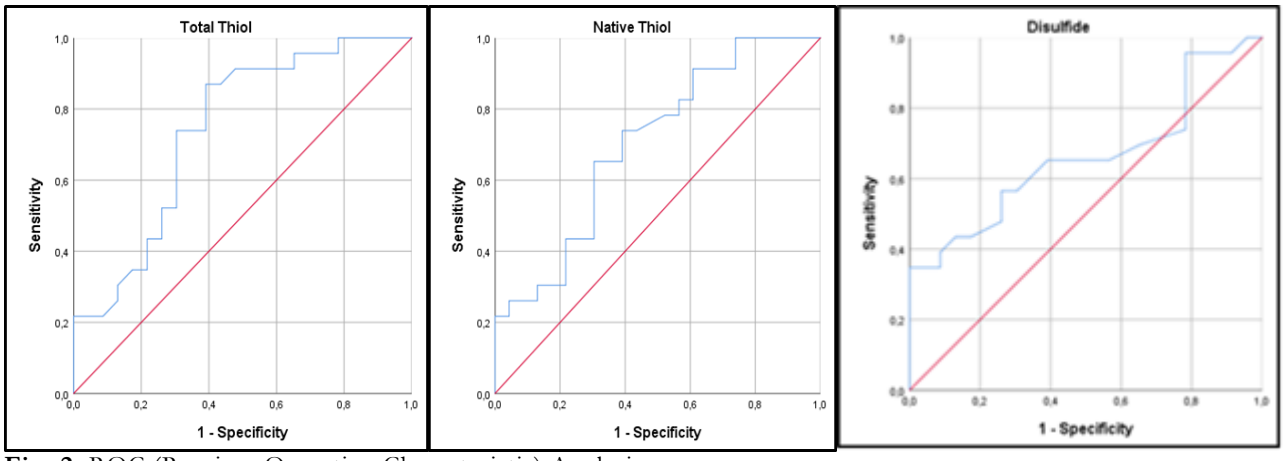

Fig. 2. ROC (Receiver Operating Characteristic) Analysis

Power analysis was performed using the G*Power 3.1.9.7 statistical package program developed by Franz Faul at the University of Kiel, Germany. The sample sizes for the two groups were n1=23 (with a mean of 519.4±70.1) and n2=23 (with a mean of 581.6±61.2). The significance level (α) was set at 0.05, and the Effect Size (d) was 0.95, yielding a statistical power of 88%.

Results

Table 1 provides a comparison of the clinical characteristics between the patient group and the control group. In Table 2, the distribution of blood values and biochemical parameters in both the MMD patient and control groups is presented. Notably, a statistically significant difference ($p<0.05$) was observed between these groups with respect to BMI, Ischemic Stroke, Other Ischemic Findings/Transient Ischemic Attack (TIA), Sensory Disturbances, Speech Disturbance, Syncope, Seizure, CRP, Native Thiol, Total Thiol, and Disulfide values. These findings point to significant distinctions between the patient and control groups.

Specifically, the patient group exhibited elevated levels of Body Mass Index (BMI), C-Reactive Protein (CRP), as well as values related to Native Thiol, Total Thiol, and Disulfide in comparison to the control group. Furthermore, in several categories, including Ischemic Stroke, Other Ischemic Findings/Transient Ischemic Attack (TIA), Sensory Disturbances, Speech Disturbance, Syncope, and Seizure, the frequency of occurrences marked as "yes" was notably higher in the patient group compared to the control group. It's worth noting that there were no statistically significant differences between the groups in terms of other variables ($p>0.05$).

Following a comprehensive analysis of variables that displayed distinct differences through pairwise comparisons utilizing ROC (Receiver Operating Characteristic) analysis, noteworthy cut-off points were identified for several parameters. Notably, a BMI value exceeding 25.6 emerged as a significant threshold (AUC=0.694, p=0.015, 95% CI: 0.540 - 0.821). Similarly, for CRP values, a cut-off point of >0.5 was underscored (AUC=0.674, p=0.028, 95% CI: 0.520 - 0.805). Furthermore, in the case of Native Thiol values, a threshold of >497 was discerned (AUC=0.701, p=0.010, 95% CI: 0.548 - 0.827). Likewise, Total Thiol values revealed a significant cut-off point of >524 (AUC=0.742, p=0.001, 95% CI: 0.592 - 0.860). Conversely, the identified cut-off point for Disulfide values did not attain statistical significance ($p>0.05$). These distinctive thresholds offer valuable insights into the potential diagnostic utility of these parameters in distinguishing between different groups (Table 3, Figure 2).

Discussion

MMD, a significant neurovascular disorder affecting young adults, currently poses challenges in terms of early diagnosis and effective treatment. Diagnosis of MMD remains provisional, relying on clinical criteria, with treatment primarily focused on symptom management and slowing disease progression. The underlying pathophysiology of MMD remains elusive, with neurobiological changes observed years before symptoms manifest (3). While substantial research has explored fundamental cellular changes occurring at the onset of MMD, there remains a dearth of comprehensive data. Presently, much research is directed towards identifying non-invasive biomarkers that could facilitate early

Table 1: Comparison of the Clinical Characteristics of The Patients With The Control Group

		Control (n=23)	Patients (n=23)	P
Sex	Female	13 (56,5%)	13 (56,5%)	1,000 †
	Male	10 (43,5%)	10 (43,5%)	
Age		34,4 ± 12,2	31,9 ± 10,2	0,443 ‡
BMI (kg/m2)		25,7 ± 3,5	28,1 ± 4,3	0,044 ‡
Follow-up (Month)		--	21,4 ± 12,1	--
Suzuki Degree	3	(0,0)	5 (21,7%)	
	4	(0,0)	8 (34,8%)	--
	5	(0,0)	10 (43,5%)	
Ischemic Stroke	No	23 (100,0%)	18 (78,3%)	0,049 †
	Yes	0 (0,0%)	5 (21,7%)	
Other Ischemic Findings/TIA	No	23 (100,0%)	8 (34,8%)	0,000 †
	Yes	0 (0,0%)	15 (65,2%)	
Intracranial Hemorrhage	No	23 (100,0%)	19 (82,6%)	0,109 †
	Yes	0 (0,0%)	4 (17,4%)	
Related Aneurysm	No	23 (100,0%)	23 (100,0%)	1,000 †
	Yes	0 (0,0%)	(0,0%)	
Motor Disturbances	No	23 (100,0%)	20 (87,0%)	0,233 †
	Yes	0 (0,0%)	3 (13,0%)	
Sensory Disturbances	No	23 (100,0%)	13 (56,5%)	0,001 †
	Yes	0 (0,0%)	10 (43,5%)	
Speech Disturbance	No	23 (100,0%)	18 (78,3%)	0,049 †
	Yes	0 (0,0%)	5 (21,7%)	
Consciousness Disturbance	No	23 (100,0%)	23 (100,0%)	1,000 †
	Yes	0 (0,0%)	(0,0%)	
Visual Disturbance	No	23 (100,0%)	19 (82,6%)	0,109 †
	Yes	0 (0,0%)	4 (17,4%)	
Movement Disorders	No	23 (100,0%)	20 (87,0%)	0,233 †
	Yes	0 (0,0%)	3 (13,0%)	
Syncope	No	23 (100,0%)	18 (78,3%)	0,049 †
	Yes	0 (0,0%)	5 (21,7%)	
Seizure	No	23 (100,0%)	16 (69,6%)	0,009 †
	Yes	0 (0,0%)	7 (30,4%)	
PsychiatricSymptoms	No	19 (82,6%)	13 (56,5%)	
	Depression	3 (13,0%)	5 (21,7%)	0,219 †
	Anxiety	1 (4,3%)	4 (17,4%)	
	Anxiety-Depression	0 (0,0%)	1 (4,3%)	
Other Symptoms	No	23 (100,0%)	3 (13,0%)	
	Anxiety-Depression	0 (0,0%)	1 (4,3%)	
	Headache	0 (0,0%)	13 (56,5%)	--
	Headache +Vertigo	0 (0,0%)	5 (21,7%)	
	Headache +Vertigo + Dizziness	0 (0,0%)	1 (4,3%)	

†: ChiSquare Test (n / %), ‡: IndependentSamples t Test (Mean ± SD), c: Mann-Whitney U Test (Median (Min-Max)

Table 2: The Distribution of Blood Values and Biochemical Parameters In Mmd Patient and Control Groups

	Control (n=23)	Patients (n=23)	P
Creatinine (mg/dL)	0,6 (0,4 – 1,0)	0,6 (0,4 – 1,1)	0,627 ‡
ALT (IU/L)	26,0 (7,0 – 49,0)	22,0 (7,0 – 49,0)	0,708‡
AST (IU/L)	24,0 (12,0 – 55,0)	22,0 (7,0 – 54,0)	0,355 ‡
Albumin (g/L)	43,4 ± 7,0	39,6 ± 6,2	0,059 †
Neutrophils (109/L)	5,4 ± 1,4	5,4 ± 1,5	0,979 †
Lökosit (109/L)	1,77 (1,01 – 3,40)	2,16 (1,05 – 3,51)	0,404 ‡
Platelet (109/L)	285,52 ± 68,03	280,91 ± 79,42	0,834 †
CRP (mg/dL)	0,50 (0,12 – 10,00)	3,00 (0,12 – 10,00)	0,037 ‡
ESR(mm/h)	11,00 (5,00 – 16,00)	12,00 (4,00 – 53,00)	0,223 ‡
NativeThiol	485,26 ± 68,36	538,96 ± 57,04	0,006 †
Total Thiol	519,39 ± 70,08	581,65 ± 61,19	0,002 †
Disulfide	16,61 ± 5,13	21,30 ± 7,39	0,017 †
(Disulfide/NativeThiol)*100	3,47 ± 1,11	3,98 ± 1,42	0,180 †
(Disulfide/Total Thiol)*100	3,22 ± 0,96	3,65 ± 1,21	0,179 †
(NativeThiol/Total Thiol)*100	93,37 ± 2,30	92,69 ± 2,41	0,337 †
IMA	0,69 ± 0,04	0,71 ± 0,03	0,152 †

†: IndependentSamples t Test (Mean ± SD), ‡: Mann-Whitney U Test (Median (Min-Max)), IMA: ischemia-modified albumin

MMD diagnosis, shedding light on the disease's pathophysiology, enabling preventive measures, and enhancing therapeutic strategies. Among the potential factors implicated in MMD's etiopathogenesis, oxidative stress emerges as a prominent contender (2,4).

Numerous studies have examined alterations resulting from the imbalance between oxidant and antioxidant systems, aiming to elucidate the role of hypoxia-induced oxidative damage in the initiation and progression of MMD(11). Neurological changes precede clinical diagnosis, prompting investigations into biomarkers that may predict MMD development before overt symptoms emerge. These studies have indicated heightened cerebral oxidative damage in individuals who later develop MMD, suggesting the potential utility of these molecules as predictive markers for the disease. While oxidative stress is acknowledged as a significant contributor to MMD, whether it serves as the primary instigator or merely a consequence of the neurodegenerative process remains an open question.

In MMD, our study stands as an inaugural endeavor to illuminate the intricacies of IMA levels and thiol disulfide homeostasis. Through meticulous exploration, the authors have ushered to the forefront a fresh understanding of biochemical dynamics that may hold significance in MMD pathology. Remarkably, we unveil a distinct profile within MMD patients, revealing elevated NT, TT, and Disulfide values compared to the control group. This robust discrepancy underscores the potential involvement of these markers in the multifaceted tapestry of MMD. Intriguingly, though not statistically significant, our study identifies heightened (Disulfide/NT)*100, (Disulfide/TT)*100, (NT/TT)*100, and IMA ratios in the MMD group. These trends, while warranting further exploration, hint at potential alterations in oxidative stress dynamics in the context of MMD.

Oxidative stress has become increasingly important due to the disruption between reactive oxidant radicals and the body's protective antioxidant mechanisms. Recent literature has underscored its role in chronic inflammation and mitochondrial dysfunction in the context of brain ischemia, a pertinent consideration in the realm of MMD (5,7). Of particular note is the significance of thiol-disulfide homeostasis, a parameter intricately woven into several biochemical processes. It regulates protein function, stabilizes protein structures, and safeguards proteins from irreversible oxidation. During oxidative stress, thiol molecules valiantly combat free oxygen radicals, converting into disulfide bonds, thereby

Table 3: ROC (Receiver Operating Characteristic) analysis

	AUC	%95 GA	CutOff	Sensitivity	Specificity	Youden index	+PV	-PV	P†
BMI (kg/m2)	0,694	0,540 – 0,821	>25,6	78,3	56,5	0,348	64,3	72,2	0,015
CRP (mg/dL)	0,674	0,520 – 0,805	>0,5	73,9	60,9	0,348	65,4	70,0	0,028
NativeThiol	0,701	0,548 – 0,827	>497	73,9	60,9	0,348	65,4	70,0	0,010
Total Thiol	0,742	0,592 – 0,860	>524	87,0	60,9	0,478	69,0	82,4	0,001
Disulfide	0,661	0,506 – 0,794	>25	34,8	100,0	0,348	100,0	60,5	0,054

†: RocCurve Analysis

averting tissue damage. This phenomenon is a testament to the remarkable protective mechanism orchestrated by thiol molecules.

Interestingly, the study did not find a statistically significant cut-off point for Disulfide values. This could indicate that Disulfide levels alone may not be a reliable biomarker for MMD. However, the elevation in NT and TT levels in MMD patients may still signify an imbalance in oxidative stress mechanisms.

Yet, under circumstances of persistent oxidative stress, serum thiol levels can diminish, giving rise to an elevation in the disulfide/thiol ratio. This phenomenon, indicative of a disrupted balance, has been observed in various diseases characterized by intense inflammation and oxidative stress, as reported by Erel et al (9). Notably, conditions spanning stress, prediabetes, metabolic syndrome, hypertension, myocardial infarction, type 1 diabetes, and even burns have showcased impaired thiol-disulfide equilibrium.

In conclusion, MMD presents a complex challenge in the realm of cerebrovascular disorders, characterized by progressive vascular constriction, internal carotid artery occlusion, and the development of intricate collateral vessels. This condition can lead to severe neurological symptoms, and its underlying pathophysiology remains elusive. The study discussed here provides valuable insights into the potential role of thiol-disulfide homeostasis and oxidative stress in MMD. It is among the pioneering efforts to investigate these biochemical dynamics in MMD patients. The findings of this study reveal notable differences in markers such as NT, TT, and Disulfide levels between MMD patients and a control group. These differences suggest a potential involvement of these markers in the pathophysiology of MMD and open avenues for further research. Additionally, certain ratios related to these markers showed trends toward significance, indicating potential alterations in oxidative stress dynamics in MMD. Oxidative stress is increasingly recognized as a significant factor in various diseases, including those involving vascular dysfunction. In the context of MMD, where chronic ischemia prevails, the imbalance between oxidant radicals and antioxidant defenses can lead to detrimental effects on brain tissue. Thiol molecules, with their reductive properties, play a vital role in combating oxidative stress, and this study highlights their potential significance in MMD. However, it's important to note that the study did not find a statistically significant cut-off point for Disulfide values, suggesting that Disulfide levels alone may not be a reliable biomarker for MMD. Nonetheless, the elevation in NT and TT levels in MMD patients may still signify an imbalance in oxidative stress mechanisms, providing a direction for further investigation.

This study has certain limitations that should be acknowledged. One notable limitation is the relatively small sample size, potentially impacting the broader applicability of the results. Furthermore, the study adopts a cross-sectional design, preventing the establishment of causal relationships based on observed associations. To validate these findings and delve into the clinical implications of thiol-disulfide balance in Moyamoya Disease, it is imperative to conduct more extensive longitudinal studies with larger participant cohorts.

However, despite these limitations, this research makes valuable contributions to our comprehension of the underlying pathophysiology of Moyamoya Disease. It also offers promising directions for future developments in diagnosis and therapeutic strategies.

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References

1. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969 Mar;20(3):288–99.
2. Kuroda S, Houkin K. Moyamoya disease: current concepts and future perspectives. Lancet Neurol. 2008 Nov;7(11):1056–66.
3. Velo M, Grasso G, Fujimura M, et al. Moyamoya Vasculopathy: Cause, Clinical Manifestations, Neuroradiologic Features, and Surgical Management. World Neurosurg. 2022 Mar;159:409–25.
4. Cho WS, Kim JE, Paeng JC, et al. Can Combined Bypass Surgery at Middle Cerebral Artery Territory Save Anterior Cerebral Artery Territory in Adult Moyamoya Disease? Neurosurgery. 2017 Mar 1;80(3):431–8.
5. Yilmaz AB, Gokhan S, Sener A, Erel O. Analysis of Neutrophil/Lymphocyte ratio and Thiol/Disulfide homeostasis parameters in patients admitted to the emergency department with ischemic stroke. Pak J Med Sci. 2018;34(6):1418–23.
6. Ray S, Abugable AA, Parker J, et al. A mechanism for oxidative damage repair at gene regulatory elements. Nature. 2022 Sep;609(7929):1038–47.
7. Li J, Ge P, He Q, et al. Association between methionine sulfoxide and risk of moyamoya disease. Front Neurosci. 2023;17:1158111.
8. Karataş M, Büyükşekerci M, Gündüzöz M, et al. Alteration of thiol disulfide homeostasis and ischemia-modified albumin levels as indicators of oxidative status in patients with silicosis. Toxicol Ind Health. 2021 Jan;37(1):38–46.
9. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014 Dec;47(18):326–32.
10. Erdal H, Turgut F. Thiol/disulfide homeostasis as a new oxidative stress marker in patients with Fabry disease. J Investig Med Off Publ Am Fed Clin Res. 2023 Aug 9;10815589231191966.
11. Menon B, Ramalingam K, Krishna V. Study of Ischemia Modified Albumin as a Biomarker in Acute Ischaemic Stroke. Ann Neurosci. 2018 Dec;25(4):187–90.