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OXIDATIVE STRESS MARKERS AND LIPOPROTEIN(A) LEVELS IN STROKE PATIENTS: INSIGHTS FROM A TERTIARY CARE PERSPECTIVE

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ABSTRACT

Background: Stroke remains a leading cause of morbidity and mortality worldwide. Oxidative stress and lipoprotein(a) [Lp(a)] have emerged as critical biomarkers in the pathophysiology of stroke. This systematic review aims to explore the role of oxidative stress markers and Lp(a) levels in stroke patients within tertiary care settings. We analyze recent studies highlighting the interplay between oxidative damage and lipid abnormalities, their diagnostic and prognostic implications, and the potential for targeted interventions. Findings underscore the need for further research to standardize biomarker use in clinical practice.

Materials and Methods: A systematic search of PubMed, Scopus, Web of Science, and Cochrane Library was conducted for articles published between 2015 and 2025. Keywords included "oxidative stress markers," "lipoprotein(a)," "stroke," "biomarkers," and "tertiary care." Inclusion Criteria: Studies assessing oxidative stress markers and/or Lp(a) levels in stroke patients, conducted in tertiary care settings, and published in peer-reviewed journals. Exclusion Criteria: Non-human studies, reviews without original data, and studies focusing on other neurological disorders. Data Extraction and Analysis: Data on study design, population characteristics, biomarker levels, diagnostic accuracy, and clinical outcomes were extracted. The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS).

Results & Discussion: Malondialdehyde (MDA): Elevated levels of Malondialdehyde (MDA), a lipid peroxidation marker, were consistently reported in ischemic and hemorrhagic stroke patients. MDA correlates with infarct size and neurological deficits. Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx): Stroke patients exhibited reduced activity of antioxidant enzymes, highlighting impaired oxidative defense mechanisms. 8-Hydroxy-2'-Deoxyguanosine (8-OHdG): This DNA damage marker is significantly elevated in acute stroke and correlates with poor outcomes. Lipoprotein(a) Levels in Stroke**:** Elevated Lp(a) levels were associated with an increased risk of ischemic stroke, particularly in patients with concurrent cardiovascular risk factors Lp(a) contributes to pro-inflammatory and pro-thrombotic pathways, exacerbating vascular damage in stroke. Studies highlighted the genetic regulation of Lp(a) levels, suggesting variability in susceptibility among different populations.

Conclusion: Thorough systematic analysis of studies revealed decrease in level of Glutathione peroxidase(GPx) and superoxide dismutase(SOD). In case of Malondialdehyde(MDA) and Lipoprotein(a), levels were higher in stroke patients in golden period i.e. first 60 minutes as well as in first 24 hours. This

shows promising role of reduced Glutathione peroxidase(GPx) and Superoxide dismutase(SOD) in assessing oxidative stress in early ischaemic period of stroke. Similar analysis of studies using Lipoprotein(a) biomarker further gave corroborative evidences of increased levels in stroke patients. On the basis of these studies and findings we can conclude that measurement of these biomarkers give an important clue in identifying risk factors for stroke.
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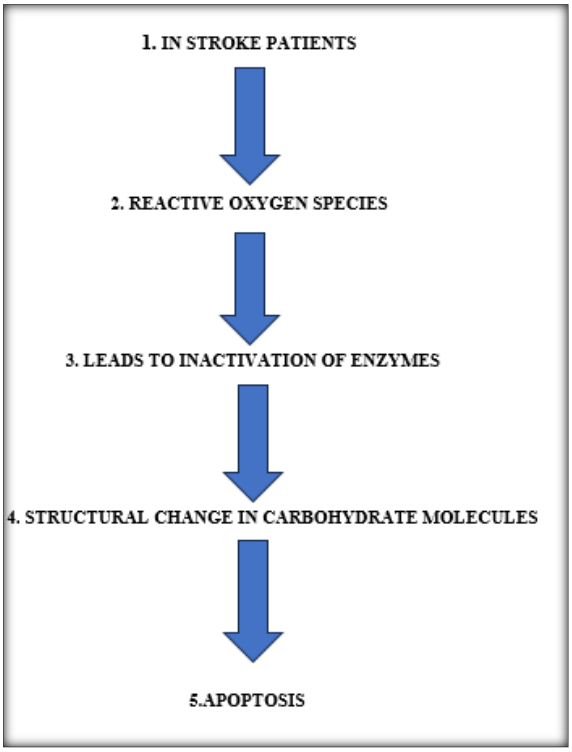
Key words: Oxidative stress, Lipid peroxidation, Lipoprotein(a), Stroke.

INTRODUCTION

Stroke is a multifaceted cerebrovascular condition that poses a significant global health challenge. Oxidative stress is a key factor in the development of stroke, as it worsens neuronal injury and disrupts the integrity of the blood-brain barrier. At the same time, elevated lipoprotein(a) [Lp(a)] levels have been linked to vascular inflammation and thrombosis, which are known to increase the risk of stroke. This review explores the connection between oxidative stress markers and Lp(a) levels, highlighting their potential role as biomarkers for early detection, risk assessment, and monitoring treatment outcomes in specialized healthcare settings. The clinical manifestations of stroke are influenced by various factors, including the location of the injury in the brain's vasculature and parenchyma.[1] If neurological symptoms resolve within 24 hours, regardless of whether there is evidence of lasting brain damage on imaging, this is classified as a transient ischemic attack (TIA)1. Stroke is diagnosed if symptoms persist for more than 24 hours.[1] High blood pressure is the leading preventable cause of stroke.[2] Other modifiable risk factors include smoking, obesity, high cholesterol, diabetes, prior TIAs, and atrial fibrillation.[2] Numerous cerebrovascular studies have highlighted the critical role of oxidative stress in worsening brain injury.[3] The brain, which uses about 20% of the body's total oxygen consumption, is particularly vulnerable to oxidative damage due to the high susceptibility of neuronal cells compared to other cell types. The brain accounts for approximately 2% of the body's total weight.[4]

From 1990 to 2010, significant changes were observed in the incidence of stroke. In developing countries, stroke cases increased by 10%, while developed countries saw a 10% decrease in the number of patients.[5] The average age of patients with acute ischemic stroke in developed nations is around 73 years.[6] In India, the percentage of younger individuals experiencing stroke is higher compared to developed countries, with major contributing factors including rheumatic heart disease, ischemic strokes during the peripartum period, and vascular issues related to central nervous system infections such as bacterial and tuberculous meningitis.[7]

In 2013, stroke was the second leading cause of death, following coronary artery disease, accounting for 6.4 million deaths (12% of the total).[8] Of these, 3.3 million deaths were attributed to ischemic stroke, while 3.2 million were due to hemorrhagic stroke.[8] Reactive oxygen species (ROS) also contribute to other forms of cellular damage, such as the inactivation of enzymes, alterations in carbohydrate structures, and ultimately, apoptosis.[9,10,11]



MATERIALS AND METHODS

2.1 Search Strategy

A comprehensive and systematic literature search was conducted to identify relevant studies from a variety of databases, including PubMed, Scopus, Web of Science, and the Cochrane Library. The search was restricted to articles published within the past decade, specifically from 2015 to 2025, in order to ensure the inclusion of the most up-to-date research findings. The search terms used included a combination of keywords such as “oxidative stress markers,” “lipoprotein(a),” “stroke,” “biomarkers,” and “tertiary care,” which were selected to capture studies addressing the relationship between oxidative stress, lipoprotein(a) levels, and stroke, particularly in clinical settings where specialized

care is provided. This approach aimed to gather a comprehensive set of data on the role of oxidative stress and lipid markers in stroke, focusing on studies that assessed the biochemical and clinical outcomes in tertiary care environments.

2. Inclusion and Exclusion Criteria

To ensure the relevance and quality of the studies selected, specific inclusion and exclusion criteria were established.

- **Inclusion Criteria:** Only studies that assessed oxidative stress markers and/or lipoprotein(a) levels in patients diagnosed with stroke were included. Additionally, studies conducted in tertiary care hospitals or research centers, where specialized medical care is typically available, were prioritized. Only peer-reviewed journal articles were considered, ensuring that the studies met rigorous academic and scientific standards.
- **Exclusion Criteria:** Non-human studies, including those conducted on animals, were excluded from this review, as the focus was on human clinical outcomes. Review articles that did not present original research data were also excluded, as well as studies focused on neurological disorders other than stroke, to maintain the focus of the review on stroke and its associated biomarkers. By setting these criteria, the search aimed to collect high-quality, clinically relevant data specific to stroke patients in specialized care settings.

2.3 Data Extraction and Analysis

Data extraction was performed systematically, capturing essential information from the selected studies. This included details on the study design, population characteristics (such as age, gender, and stroke type), as well as the specific biomarkers measured, including oxidative stress markers and lipoprotein(a) levels. In addition, the diagnostic accuracy of these biomarkers and their potential correlations with clinical outcomes were examined. This allowed for an in-depth analysis of how these biomarkers can be used to predict stroke severity, prognosis, and recovery. The risk of bias in each study was evaluated using the Newcastle-Ottawa Scale (NOS), a well-established tool for assessing the methodological quality of non-randomized studies. This step ensured that the findings were derived from reliable and scientifically rigorous research.

RESULTS AND DISCUSSION

3.1 Oxidative Stress markers in stroke

Oxidative stress, a condition characterized by an imbalance between reactive oxygen species (ROS) production and the body's ability to neutralize them, has long been implicated in the pathophysiology of stroke. Various biomarkers of oxidative stress have been studied for their potential to predict stroke outcomes and to serve as therapeutic targets. The following markers have been consistently associated with stroke:

- **Malondialdehyde (MDA):** Malondialdehyde, a key marker of lipid peroxidation, has been found to be significantly elevated in both ischemic and hemorrhagic stroke patients. MDA levels correlate closely with infarct size, which refers to the extent of brain tissue damage, as well as with the degree of neurological deficits experienced by patients following stroke. Higher MDA concentrations suggest greater oxidative damage to cellular membranes, which may contribute to stroke-related tissue injury and poor recovery outcomes.
- **Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx):** These are antioxidant enzymes that play a critical role in mitigating oxidative damage by neutralizing superoxide radicals and hydrogen peroxide, respectively. In stroke patients, particularly those who experience severe neurological deficits, activity levels of both SOD and GPx are typically reduced. This decrease in antioxidant activity suggests that the body's natural defense mechanisms against oxidative stress are impaired, which may exacerbate stroke-related damage. The reduced enzyme activity further highlights the importance of understanding oxidative stress in stroke pathogenesis and the potential for antioxidant therapies.
- **8-Hydroxy-2'-Deoxyguanosine (8-OHdG):** As a biomarker of DNA damage caused by oxidative stress, 8-hydroxy-2'-deoxyguanosine has been shown to be significantly elevated in the acute phase of stroke. Its levels are positively correlated with poor clinical outcomes, such as larger infarct size and greater neurological impairment. Elevated 8-OHdG suggests that oxidative stress not only affects cellular membranes but also directly impacts genetic material, leading to cellular dysfunction and death. This biomarker has potential utility in predicting long-term recovery and could be a valuable tool for monitoring the effectiveness of treatments aimed at reducing oxidative damage.

3.2 Lipoprotein(a) Levels in Stroke

Elevated Lp(a) levels were associated with an increased risk of ischemic stroke, particularly in patients with concurrent cardiovascular risk factors Lp(a) contributes to pro-inflammatory and pro-thrombotic pathways, exacerbating vascular damage in stroke. Studies highlighted the genetic regulation of Lp(a) levels, suggesting variability in susceptibility among different populations.

A study by Antonio Cherubini and colleagues,[12] found that both ischemic and hemorrhagic strokes lead to an increase in free radical production, which results in oxidative stress and contributes to brain injury. Measuring oxidative stress in stroke could

provide valuable insights into its underlying mechanisms and help identify patient subgroups that may benefit from targeted treatments. However, since it is challenging to directly measure free radicals and oxidized molecules within the brain in humans, various peripheral biomarkers have been explored as potential indicators. Among the products of lipid peroxidation, malondialdehyde, despite some methodological challenges, has been shown to correlate with ischemic stroke size and patient outcomes. F2-isoprostanes are another promising marker, though they have not yet been thoroughly assessed. Additionally, 8-hydroxy-2-deoxyguanosine, a marker for oxidative DNA damage, has been extensively studied, but no research has been conducted specifically in stroke patients. Both enzymatic and nonenzymatic antioxidants have also been proposed as indirect markers. Compounds like ascorbic acid, alpha-tocopherol, uric acid, and superoxide dismutase have been associated with brain injury and clinical outcomes. After reviewing existing literature, the authors concluded that while an ideal biomarker for stroke is still lacking, focusing on the balance between antioxidants and oxidative stress by-products may provide the most reliable method for assessing oxidative stress in stroke patients.

Cojucaru IM et al,[13] reportedly observed significantly lower level of plasma GPx and SOD while high level of MDA in cases with acute ischemic stroke.

A study conducted by Branislav Kollár and colleagues,[14] investigated lipid and lipoprotein profiles, as well as oxidative stress (OS) markers, in patients within the first 24 hours following an acute ischemic stroke (AIS). The study aimed to examine differences between patients with and without coronary artery disease (CAD) and to explore the relationship between these factors and clinical scales (NIHSS, mRS) post-stroke. The sample included 27 AIS patients without CAD (AIS group) and 37 AIS patients with CAD (CAD-AIS group). Plasma LDL and HDL subfractions were analyzed using polyacrylamide gel electrophoresis (Lipoprint system), while oxidative stress parameters, including plasma antioxidant capacity, lipoperoxides, homocysteine (HC), paraoxonase 1 activity, and catalase activity, were measured through spectrophotometric methods. Additionally, urinary isoprostanes and antioxidant enzyme activities (SOD, GPx) were assessed using commercial kits.

Results revealed that CAD-AIS patients had higher HC levels, but there were no significant differences in lipoprotein subfractions or OS markers between the two groups. In the AIS group, mRS scores were negatively correlated with catalase and GPx activities, as well as total cholesterol levels. In contrast, the CAD-AIS group showed a significant positive correlation between atherogenic lipoproteins (IDL, LDL2, LDL3–7) and mRS scores. The study highlights the role of dyslipidemia and oxidative stress in the development of both AIS and CAD and underscores the complex interactions between specific biomarkers and clinical outcomes following stroke. It also suggests that CAD treatment affects lipid profiles but does not significantly impact homocysteine levels. These findings challenge the conventional view of high cholesterol as the primary risk factor for cardiovascular diseases, particularly with respect to neurological outcomes.

Although some oxidative stress markers showed trends toward statistical significance (e.g., lipoperoxides, protein carbonyls, paraoxonase A activity), none of these differences reached significance. This suggests that a larger sample size may be needed to fully explore these potential relationships. Polyacrylamide gel electrophoresis (Lipoprint LDL and HDL System; Quantimetrix, Redondo Beach, CA, USA) was used to assess the lipoprotein subfractions, but no significant differences in these subfractions were found between the two groups of patients.

Table[14]: Oxidative stress markers in plasma of patients within 24 hours after an acute ischaemic stroke

PARAMETER	CAD-AIS GROUP	AIS GROUP	P Value	Significance
Lipoperoxides (nmol/ml)	36.41	68.48	0.06	Close to sig.
Protein Carbonyls (mol/mg)	0.28	0.16	0.07	Close to sig.
Paraoxonase (U/ml)	83.39 ± 28.03	101.03 ± 38.43	0.05	Close to sig
Lipoprotein subfractions (LDL/HDL)	No significant change	No significant change	NA*	Not significant

***Not Available**

Jaspreet kaur et al,[15] detected a significant increase total cholesterol, triglycerides, LDL cholesterol and MDA in stroke patients whereas a significant decrease in erythrocyte Superoxide dismutase and vitamin E levels was observed while comparing the control group.

Dhamija et al,[16] carefully observed the part of homocysteine and Lp(a) in ischemic stroke. They decided to calculate plasma Lp(a) concentration in 66 patients with ischemic stroke and 72 controls and found that these two parameters are independently associated with ischemic stroke with a significant positive correlation between them.

Many retrospective studies have assessed lipoprotein(a) as a risk factor for stroke.

Lindgren and colleagues,[17] assessed lipid profiles in 131 patients six months following a stroke. These individuals showed elevated triglyceride (TG) and lipoprotein(a) [Lp(a)] levels, along with reduced total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) compared to healthy controls.

Vavernova and colleagues,[18] examined Lp(a) concentrations in 45 stroke patients under 55 years old, along with their first-degree relatives.

Regarding the genetic regulation of plasma Lp(a) levels, Jurgens and his team,[19] analyzed Lp(a) levels and apo(a) phenotypes in 265 patients with ischemic stroke, comparing them to 288 controls. They found that increased Lp(a) levels were a key risk factor linked to the development of ischemic stroke. Additionally, low molecular weight apo(a) isoforms (< 580 kDa) were found to be more prevalent in stroke patients (42.65%) compared to controls (16.73%; $p < 0.001$).

Peynet and colleagues,[20] studied Lp(a) concentrations and apo(a) isoform sizes in 90 young adults (average age 37.4 years) who had acute cerebral ischemia. They observed a significant rise in Lp(a) levels among the stroke patients ($p = 0.009$), though no differences were noted in apo(a) isoform distribution between the two groups.

Van Kooten and colleagues,[21] evaluated Lp(a) concentrations in 151 patients hospitalized for acute cerebral ischemia. They reported that around a third of the patients had elevated Lp(a) levels, but this increase did not correlate with cardiovascular risk factors, stroke features, or prognosis.

In a recent cross-sectional study, Lp(a), PAI-1, and tPA levels were measured in 210 individuals, half of whom had a history of ischemic stroke. A link between raised Lp(a) levels and cerebral ischemia was found, particularly in patients under 70 with Lp(a) concentrations exceeding 500 mg/l.

Nagayama et al,[22] conducted a case-control study to explore Lp(a) levels in patients an average of 27 months post-stroke. They concluded that Lp(a) was an important and independent risk factor for ischemic stroke, but not for lacunar strokes (< 1 cm^2), particularly in younger adults.

Peng et al,[23] investigated the relationship between serum lipids, apoE genotypes, and ischemic stroke risk. In their study of 90 acute ischemic stroke patients compared to 90 healthy individuals, they identified Lp(a) levels and the apoE4 genotype as significant lipid predictors for ischemic stroke, alongside traditional risk factors like hypertension, family history, and smoking. Silent strokes, often detected incidentally on imaging scans (CT or MRI) without localized neurological symptoms, can precede overt stroke. Typically, these involve small lacunar infarctions (< 1 cm^2), especially in elderly individuals with hypertension, and are a major contributor to dementia.

Kario and colleagues,[24] found that silent lacunar strokes in 178 asymptomatic, high-risk elderly Japanese patients (ages 44-93) were linked to a hypercoagulable state, endothelial dysfunction, and significantly elevated Lp(a) levels. The researchers further categorized the silent lacunar group based on the number of lacunes (few: 1–2, moderate: 3–4, numerous: > 5).

In the Atherosclerosis Risk in Communities (ARIC) study, Lp(a) levels were analyzed in 15,160 participants (4,160 Black and 11,000 White individuals). This research confirmed that Lp(a) is an independent risk factor for both strokes and transient ischemic attacks (TIA) in both racial groups. The relative risk for stroke morbidity associated with Lp(a) did not differ between races. These findings suggest that higher Lp(a) concentrations may be more common in patients with atherothrombotic brain infarctions compared to those with hemorrhagic or lacunar strokes. Furthermore, individuals with ischemic heart disease (IHD) are at a higher stroke risk, which may introduce selection bias when studying the relationship between Lp(a) and stroke due to the association between IHD and elevated Lp(a).

The finding of our study and above mentioned other studies are in agreement to each other.[25,26.27,28]

3.3 Interplay Between Oxidative Stress and Lipoprotein(a)

Oxidative stress plays a crucial role in modulating the atherogenic properties of lipoprotein(a) [Lp(a)], primarily by promoting its oxidative modification. When Lp(a) undergoes oxidative changes, it becomes more harmful to the vascular system, contributing to the formation of atherosclerotic plaques and aggravating endothelial dysfunction. This oxidative modification not only increases the toxicity of Lp(a) but also intensifies the inflammatory processes within the blood vessels, further accelerating the development of cardiovascular diseases, including stroke.

Recent studies have highlighted the synergistic interaction between oxidative stress and elevated Lp(a) levels in predicting worse stroke outcomes. Patients exhibiting both high oxidative stress markers and elevated Lp(a) levels are at a significantly higher risk of experiencing severe stroke-related complications. This combination underscores the pivotal role of both factors in stroke pathophysiology, suggesting that they work together to amplify the damage to vascular structures and disrupt normal blood flow, thereby exacerbating the severity of the stroke event and potentially hindering recovery.

3.4 Clinical Utility in Tertiary Care Settings

Diagnostic Role

Markers of oxidative stress, such as malondialdehyde (MDA), along with elevated levels of Lp(a), have shown considerable promise in identifying patients at high risk for stroke in tertiary care settings. These biomarkers have demonstrated high sensitivity in detecting individuals who are more likely to experience a stroke, allowing for early intervention and timely preventive measures. Their integration into clinical practice could facilitate the development of more precise diagnostic tools, aiding healthcare professionals in distinguishing at-risk patients more effectively compared to traditional methods.

Prognostic Value

The prognostic value of oxidative stress markers and Lp(a) levels in stroke patients is significant. Studies

have consistently shown that higher concentrations of these biomarkers are associated with poorer clinical outcomes, including increased mortality and higher rates of stroke recurrence. Elevated oxidative stress and Lp(a) are linked to more severe forms of stroke and slower recovery, underlining their potential role as indicators of both short-term and long-term patient prognosis. As such, they can be valuable tools in guiding therapeutic decisions and offering patients a more individualized approach to care.

Monitoring

One of the major benefits of utilizing oxidative stress markers and Lp(a) in clinical settings is their utility in monitoring patient progress. After initiating treatment, a reduction in levels of oxidative stress markers and Lp(a) has been correlated with improved clinical outcomes, including better functional recovery and fewer stroke-related complications. Tracking these biomarkers during the treatment phase can provide clinicians with valuable insights into the effectiveness of therapies, allowing for adjustments and interventions when necessary. This ongoing monitoring could help optimize care strategies and ultimately improve patient outcomes.

4. Challenges and Limitations

Standardization Issues

Despite the potential of oxidative stress markers and Lp(a) as biomarkers for stroke diagnosis and management, there are significant challenges related to the standardization of measurement techniques. The variability in how these markers are measured across different laboratories and research studies complicates efforts to compare results and establish consistent clinical guidelines. Without standardized methods for measuring oxidative stress and Lp(a), it is difficult to ensure the reliability and reproducibility of results, which hinders their widespread adoption in clinical practice.

Population Differences

Another limitation in the use of these biomarkers is the influence of genetic and environmental factors on oxidative stress and Lp(a) levels. Variability in genetic predispositions, such as differences in Lp(a) gene variants, and environmental factors like diet, lifestyle, and exposure to pollutants, can affect how these biomarkers manifest in different populations. This population-specific variability may limit the generalizability of findings and make it challenging to apply these biomarkers uniformly across diverse patient groups. As a result, more research is needed to understand how these factors interact and influence the levels of oxidative stress and Lp(a) in various populations.

Lack of Longitudinal Studies

Another major limitation is the scarcity of longitudinal studies that explore the long-term implications of changes in oxidative stress and Lp(a) levels in stroke patients. While short-term studies provide valuable insights into the immediate role of these biomarkers in stroke outcomes, there is a lack of comprehensive research examining their potential as predictors of long-term recovery, recurrence, and overall cardiovascular health. Longitudinal studies are essential to better understand how fluctuations in oxidative stress and Lp(a) levels impact stroke patients over time and to evaluate their potential as markers for long-term stroke prevention.

5. Future Directions

To address the existing challenges and unlock the full potential of oxidative stress markers and Lp(a) as diagnostic and prognostic tools, several important future directions need to be explored. One of the key priorities is the development of standardized protocols for the assessment and measurement of these biomarkers. Establishing universally accepted methodologies will enhance the reliability and comparability of studies, ultimately aiding in the routine integration of these biomarkers into clinical practice.

Additionally, large-scale, multi-center studies are needed to further assess the combined diagnostic and prognostic value of oxidative stress markers and Lp(a) in stroke patients. These studies could help clarify the exact role of these biomarkers in stroke pathophysiology and their potential as predictive tools for stroke outcomes. Such research could also provide evidence to support their use in personalized treatment plans, tailoring interventions based on biomarker profiles.

Finally, there is an urgent need for the exploration of targeted therapies aimed at mitigating oxidative stress and normalizing Lp(a) levels, particularly in high-risk stroke patients. Research into pharmacological agents or lifestyle interventions that can reduce oxidative damage and regulate Lp(a) could offer promising therapeutic avenues. Such treatments could complement existing stroke management strategies and significantly improve outcomes for individuals at elevated risk.

CONCLUSION

Oxidative stress markers and lipoprotein(a) [Lp(a)] levels have emerged as highly promising biomarkers for both the diagnosis and management of stroke, particularly in tertiary care environments. These biomarkers offer significant potential for improving the accuracy and timeliness of stroke detection, enabling healthcare providers to identify at-risk patients more quickly and accurately. Additionally, they can aid in the process of risk stratification, allowing for a more tailored approach to treatment and better management of stroke outcomes. By integrating these biomarkers into clinical practice, physicians could potentially enhance the overall efficacy of stroke interventions, improving patient care and long-term prognosis. Nevertheless, while the promise of oxidative stress markers and Lp(a) levels is clear, more in-depth research is essential to overcome current limitations and challenges in their application. Further studies are needed to validate

their clinical utility and establish standardized protocols, ultimately paving the way for their routine use in stroke care and ensuring that they can be reliably incorporated into everyday medical practice.

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