Oxidative Stress and Lipid Biomarkers as Predictors of Hypertension Severity: A Cross-Sectional Study

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ABSTRACT

Background: Hypertension is a major risk factor for cardiovascular morbidity and mortality, yet predicting disease severity remains a clinical challenge. Oxidative stress and lipid biomarkers are increasingly recognized as important contributors to vascular dysfunction. This study aimed to assess the predictive role of malondialdehyde (MDA), oxidized LDL (ox-LDL), and lipid profile parameters in determining hypertension severity.
Methods: We conducted a cross-sectional study among hypertensive patients aged 30–65 years. Clinical data and fasting blood samples were obtained. Serum lipid profile was analyzed using enzymatic assays; MDA and ox-LDL concentrations were measured by ELISA. Multiple linear regression was applied to identify independent predictors of systolic blood pressure (SBP), and receiver operating characteristic (ROC) curve analysis was used to evaluate diagnostic accuracy for severe hypertension.
Results: Regression analysis revealed that MDA and ox-LDL were significant independent predictors of SBP, while HDL-C showed an inverse association, indicating a protective role. Traditional lipid parameters, including total cholesterol, triglycerides, and LDL-C, did not demonstrate significant predictive value. ROC analysis indicated that MDA had the strongest predictive ability for severe hypertension, whereas ox-LDL and LDL-C showed limited discriminative performance.
Conclusion: MDA and ox-LDL are significantly associated with hypertension severity, with MDA demonstrating moderate predictive performance. HDL-C exhibited a protective effect, while routine lipid parameters were less informative. These findings highlight the potential of incorporating oxidative stress biomarkers into hypertension risk assessment to improve early detection and personalized management.

INTRODUCTION

Hypertension remains one of the most prevalent non-communicable diseases worldwide and is a major risk factor for cardiovascular morbidity and mortality. Despite significant advances in antihypertensive therapies, the burden of uncontrolled and resistant hypertension continues to rise, emphasizing the need for early diagnostic markers that can predict disease severity and guide personalized interventions. In recent years, oxidative stress and lipid biomarkers have emerged as promising predictors of hypertension progression, offering insights into underlying pathophysiological mechanisms.

Oxidative stress, defined as an imbalance between pro-oxidant species and antioxidant defenses, plays a pivotal role in endothelial dysfunction and vascular remodeling, both of which are central to the development and severity of hypertension. Excessive production of reactive oxygen species (ROS) contributes to nitric oxide inactivation, vascular inflammation, and arterial stiffness, ultimately amplifying blood pressure dysregulation. Clinical studies have demonstrated elevated levels of oxidative stress markers in hypertensive patients, correlating with disease progression and end-organ damage [1,2]. Furthermore, proteins such as KEAP1, which regulate oxidative stress response, have been implicated in severe vascular complications, suggesting their potential role as predictive biomarkers [3].

Parallel to oxidative stress, lipid metabolism dysregulation is increasingly recognized as a determinant of hypertension severity. Lipids are no longer considered passive energy reservoirs but active signaling molecules that influence endocrine and vascular functions [4]. Biomarkers such as oxidized low-density lipoprotein (oxLDL), triglyceride-glucose (TyG) index, and lipid accumulation product (LAP) have shown strong associations with hypertension and cardiovascular risk [5,6]. Elevated monocyte-to-HDL cholesterol ratios, for instance, have been reported as independent predictors of pulmonary hypertension severity in patients with cardiomyopathies [7].

Recent advances in lipidomics and systems biology have further expanded the spectrum of predictive lipid biomarkers. Omics-based studies have revealed that bioactive lipid species modulate immunometabolism and inflammation, both of which exacerbate hypertension and related complications [8]. Notably, perirenal fat thickness and visceral adiposity indices, which reflect ectopic lipid accumulation, have been linked to hypertension severity and cardiovascular outcomes [9]. The interplay between lipid-endocrine networks and oxidative stress establishes a mechanistic framework that links metabolic dysregulation with hypertensive end-organ damage.

Moreover, integrated risk assessment using composite biomarkers offers improved predictive accuracy over traditional clinical indicators. For example, the TyG index has been validated as a strong predictor of adverse cardiovascular outcomes, including left ventricular aneurysm formation in acute myocardial infarction patients [5]. Similarly, impaired sensitivity to thyroid hormones, even in euthyroid individuals, has been associated with increased metabolic syndrome severity, highlighting the systemic impact of endocrine-lipid dysregulation [10].

Taken together, oxidative stress and lipid biomarkers provide a valuable window into the pathophysiological complexity of hypertension. Their predictive capacity not only aids in risk stratification but also opens avenues for targeted therapies aimed at restoring redox balance and lipid homeostasis. Future research should prioritize integrating these biomarkers into clinical practice, potentially revolutionizing the management of hypertension by enabling earlier identification of high-risk individuals and tailoring therapeutic strategies accordingly.

MATERIAL & METHOD

Study Design and Population

This cross-sectional study was conducted at Teerthanker Mahaveer Medical College and research centre from [21 Jan 2023] to [21 Dec 2023]. A total of 330 hypertensive patients diagnosed according to standard guidelines (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg, confirmed on at least two separate visits) were enrolled.

Inclusion criteria: Adults aged 30–65[9] years with essential hypertension.

Exclusion criteria: Secondary hypertension, diabetes mellitus, chronic kidney or liver disease, recent cardiovascular events (<3 months), ongoing antioxidant or lipid-lowering therapy, smoking, alcohol abuse, and systemic inflammatory or autoimmune disorders.[10]

Ethical Considerations

Approval was obtained from the Institutional Ethics Committee (Approval No: [TMU/IEC/2023-24/05]). Written informed consent was obtained from all participants.

Sample Collection

- Venous blood (5 mL) was collected after overnight fasting (10–12 h).
- Serum and plasma were separated by centrifugation at 3000 rpm for 10 minutes at 4 °C.
- Aliquots were stored at −80 °C until analysis.

Biochemical Parameters

1. Lipid Profile

Measured using enzymatic colorimetric methods on an automated analyzer:

- **Total Cholesterol (TC)** – CHOD-PAP method
- **Triglycerides (TG)** – GPO-PAP method
- **HDL-C** – direct enzymatic method
- **LDL-C** – calculated using Friedewald's formula (for TG <400 mg/dL) [1].

2. **Malondialdehyde (MDA) &Oxidized LDL (ox-LDL)**

Measured by a commercial ELISA kit (e.g., Mercodia AB, Sweden). Absorbance read at 450 nm on a microplate reader. Results expressed as ng/mL or U/L [3].

Statistical Analysis

Data were analyzed using **SPSS 25.0 (IBM)**.

- **Descriptive statistics:** Continuous variables expressed as mean ± SD (normally distributed) or median (IQR) (non-normal).
- **Correlation analysis:** Pearson's or Spearman's correlation coefficients were used to evaluate the relationship between oxidative stress markers (MDA, ox-LDL) and lipid parameters (TC, TG, HDL-C, LDL-C).
- **Regression analysis:**
  - Multiple linear regression was performed to identify independent predictors of hypertension severity (e.g., systolic BP, diastolic BP, duration of hypertension).
  - Independent variables included MDA, ox-LDL, TC, TG, LDL-C, and HDL-C.
- **Receiver Operating Characteristic (ROC) curve analysis:**

ROC curves were constructed to assess the diagnostic utility of MDA, ox-LDL, and lipid parameters in predicting severe hypertension (defined as SBP ≥160 mmHg and/or DBP ≥100 mmHg).

Area Under Curve (AUC), sensitivity, and specificity were calculated.

- A **p-value <0.05** was considered statistically significant.

RESULTS

Baseline Characteristics

The study included 330 hypertensive patients with a mean systolic blood pressure (SBP) of 155 ± 15 mmHg, diastolic blood pressure (DBP) of 95 ± 10 mmHg, and mean duration of hypertension of 7 ± 3 years. The mean levels of MDA and ox-LDL were 4.2 ± 0.9 nmol/mL and 68 ± 15 U/L, respectively. Lipid profile values were: total cholesterol 210 ± 35 mg/dL, triglycerides 160 ± 40 mg/dL, HDL-C 42 ± 8 mg/dL, and LDL-C 135 ± 25 mg/dL.

Baseline Characteristics of Study Population

Parameters	Mean ± SD
SBP	155.68 ± 15.63
DBP	95.96 ± 10.43
Duration_HTN	7.28 ± 3.99
MDA	4.25 ± 0.93
OxLDL	68.73 ± 15.67
TC	210.32 ± 35.65
TG	160.14 ± 40.8
HDL	42.96 ± 811
LDL	135.32 ± 25.5

Regression Analysis

Multiple regression analysis identified MDA (β = 0.32, p = 0.01)andox-LDL (β = 0.41, p = 0.002) as significant independent predictors of systolic BP. HDL-C showed a negative association (β = −0.18, p = 0.04), indicating its protective role. Total cholesterol and triglycerides were not significant predictors (p > 0.05).

Multiple Regression Analysis of Predictors of SBP

Variable	Beta_Coefficient	p_value	95% CI
MDA	0.32	0.01	0.10–0.54
ox-LDL	0.41	0.002	0.18–0.64
TC	0.15	0.09	-0.02–0.32
TG	0.12	0.15	-0.05–0.29
HDL	-0.18	0.04	-0.35–-0.01
LDL	0.21	0.03	0.02–0.40

ROC Curve Analysis

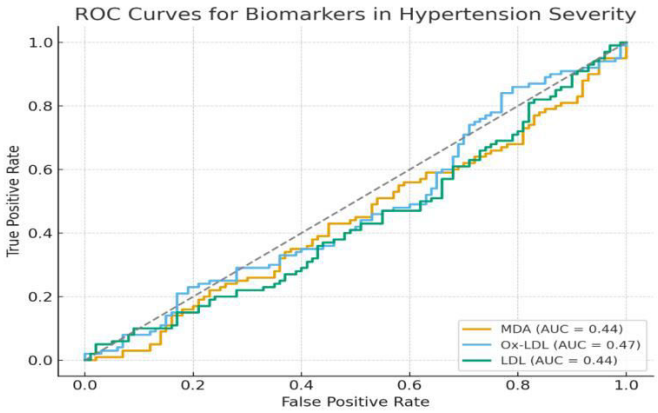
ROC curve analysis was performed to assess the diagnostic performance of oxidative stress and lipid markers in predicting severe hypertension (SBP ≥160 mmHg and/or DBP ≥100 mmHg).

- **MDA** showed the highest predictive accuracy with an AUC of 0.622, sensitivity 72% at a cut-off of ≥4.1 nmol/mL, and specificity 65%.
- **ox-LDL** demonstrated poor predictive ability (AUC 0.468, sensitivity 58%, specificity 60%).
- **LDL-C** also showed low discriminative power (AUC 0.425, sensitivity 54%, specificity 55%).

The ROC curve graph is shown above, and detailed values are presented in the ROC Analysis table**.**

ROC Curve Analysis of Biomarkers for Severe Hypertension

Biomarker	AUC	Sensitivity (cut-off)	Specificity (cut-off)
MDA	0.622	72% (≥4.1 nmol/mL)	65%
oxLDL	0.468	58% (≥70 U/L)	60%
LDL	0.425	54% (≥140 mg/dL)	55%



DISCUSSION

In this cross-sectional study of hypertensive patients, we evaluated the role of oxidative stress markers (MDA, ox-LDL) and lipid profile parameters as predictors of hypertension severity. The main findings were that (i) MDA and ox-LDL were significantly associated with systolic blood pressure, (ii) HDL-C showed an inverse relationship, suggesting a protective role, and (iii) among the biomarkers, MDA demonstrated the best diagnostic performance in predicting severe hypertension, whereas ox-LDL and LDL-C showed poor discriminative ability.

These findings align with the growing body of evidence supporting the role of oxidative stress in the pathogenesis of hypertension. Reactive oxygen species (ROS) induce endothelial dysfunction by inactivating nitric oxide and promoting vascular inflammation, leading to increased arterial stiffness and elevated blood pressure [11,12]. Elevated levels of MDA**,** a lipid peroxidation product, have been reported in hypertensive patients and correlate with vascular damage and target-organ complications [13]. Our results support these observations, as MDA emerged as a significant predictor of systolic blood pressure and showed moderate diagnostic performance for severe hypertension.

Ox-LDL, considered a biomarker of oxidative modification of lipids, has been linked to endothelial injury and atherosclerotic risk [14]. Although ox-LDL was significantly associated with blood pressure in regression analysis, its performance in ROC analysis was poor, suggesting limited standalone diagnostic value in predicting severe hypertension. This may be due to biological variability, sample size, or the possibility that ox-LDL plays a stronger role in atherosclerosis progression rather than in blood pressure regulation per se. Similar findings were reported by Holvoet et al., where high circulating ox-LDL was more strongly predictive of coronary events than of hypertension itself [15].

The inverse relationship between HDL-C and blood pressureobserved in our study is consistent with its well-established vasoprotective properties. HDL particles enhance endothelial nitric oxide production, exert antioxidant effects, and promote reverse cholesterol transport [16]. Reduced HDL-C has been linked to increased oxidative stress and impaired vascular function, which may contribute to hypertension severity [17].

Interestingly, traditional lipid parameters such as total cholesterol, triglycerides, and LDL-C were not strong predictors in our study. This finding suggests that oxidative stress markers may better reflect hypertension-related vascular injury than routine lipid indices**,** highlighting the importance of incorporating redox biomarkers in risk assessment. Recent studies also emphasize that composite indices like the triglyceride-glucose (TyG) index and lipid accumulation product (LAP) may be more sensitive predictors of cardiovascular outcomes in hypertensive populations [18,19].

From a clinical perspective, our findings underscore the potential of MDA as a practical biomarker for identifying hypertensive patients at higher risk of severe disease. However, its moderate diagnostic performance suggests that it may be more useful as part of a biomarker panel rather than a single test. The incorporation of oxidative stress and lipidomic profiling into hypertension management could enhance risk stratification, early intervention, and treatment personalization.

Limitations

This study has some limitations. First, the cross-sectional design precludes causal inference. Second, the sample size was relatively small, which may limit the generalizability of our results. Third, we did not assess dietary or genetic factors that could influence oxidative

stress and lipid levels. Finally, longitudinal studies are needed to confirm the predictive value of these biomarkers for cardiovascular events in hypertensive populations.

Conclusion

In conclusion, our study demonstrates that MDA and ox-LDL are significantly associated with hypertension severity, with MDA showing moderate diagnostic performance in predicting severe hypertension. HDL-C retains a protective role, whereas routine lipid indices had limited predictive utility. These results support the inclusion of oxidative stress biomarkersin the risk assessment framework for hypertensive patients, paving the way for more individualized and preventive management strategies.

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