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REVIEW PAPER

Harnessing Statistical and Machine Learning Approaches to Analyze Oxidized LDL in Clinical Research

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Abstract

Oxidized low-density lipoprotein (OxLDL) is increasingly recognized as a critical mediator in the pathogenesis of atherosclerosis and several chronic diseases, including type 2 diabetes, metabolic syndrome, Alzheimer's disease, and chronic kidney disease. Given the biochemical heterogeneity of OxLDL, its accurate quantification remains a significant analytical challenge for precise statistical and Machine Learning (ML) methods. The paper examines statistical and computational methodologies used to assess OxLDL levels in clinical studies, highlighting strengths, limitations, and clinical relevance. This contribution provides current insights on standardizing analytic pipelines using statistical and machine learning tools for reproducibility, interpretability, and translational impact in clinical research. Traditional statistical methods have provided a foundational understanding of OxLDL's clinical implications. Meta-analyses, regression models, and survival analyses have consistently demonstrated associations between elevated OxLDL levels and increased disease risk, severity, and mortality. Comparative analyses (t-tests, ANOVA) and correlation studies further reveal its links with inflammation, lipid profiles, and cardiac function. Emerging ML and Artificial Intelligence (AI) approaches offer powerful tools to advance OxLDL research. Predictive models using ML algorithms enhance disease risk stratification, while deep learning facilitates automated image analysis to assess OxLDL-induced vascular changes. AI-integrated diagnostic platforms now combine clinical, biochemical, and imaging data to improve outcome prediction in CVD.

Keywords Atherosclerosis · Lipoproteins · Cardiovascular disease · Machine learning

The Significance of Oxidized Low-density Lipoprotein (OxLDL)

Background on Lipoproteins and LDL

Lipoproteins are essential complexes responsible for the transport of lipids, including cholesterol and triglycerides, throughout the body [1]. Among these, low-density lipoprotein (LDL) serves as the primary carrier of cholesterol, delivering it to peripheral and liver cells through receptor-mediated endocytosis [2]. However, LDL particles can undergo oxidative modification, a process thought to be initiated by free radicals and enzymatic reactions within the body [1]. This oxidation is not a singular, uniform event but rather a spectrum of chemical alterations that can occur under various physiological and pathological conditions. Different methods employed in vitro to induce LDL oxidation, such as incubation with copper ions or through enzymatic reactions, can result in OxLDL with varying characteristics. This heterogeneity in the oxidized LDL particle is an important consideration for research, as the specific type of modification may influence the outcomes of analyses and their interpretation [3]. This contribution provides current insights on standardizing analytic pipelines using statistical and machine learning tools for reproducibility, interpretability, and translational impact in clinical research.

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The Role of OxLDL in Pathophysiology

Oxidized LDL plays a significant role in the development of atherosclerosis, a chronic inflammatory disease of the arteries [4]. The process begins with endothelial dysfunction, where the inner lining of the arteries becomes impaired, facilitating the entry and retention of LDL in the arterial wall. Once in the subendothelial space, LDL can become oxidized. This OxLDL then triggers a cascade of events, including the recruitment of monocytes, which differentiate into macrophages. These macrophages possess scavenger receptors that avidly take up OxLDL, leading to the accumulation of lipids within them and their transformation into foam cells, a hallmark of atherosclerotic plaques [4]. The continued accumulation of foam cells, along with other cellular components and extracellular matrix, contributes to plaque growth and instability, eventually leading to adverse cardiovascular events such as myocardial infarction and stroke [4]. Beyond cardiovascular disease, OxLDL has also been implicated in the pathophysiology of other conditions, including diabetes mellitus, metabolic syndrome, Alzheimer's disease, and kidney disease [5]. This suggests that OxLDL acts as a central mediator in a variety of disease processes, indicating its broad relevance as both a biomarker and a potential therapeutic target [6]. The specific mechanisms through which OxLDL exerts its effects may differ across these various diseases, highlighting the need for targeted research to elucidate these pathways [6].

Despite its well-established mechanistic involvement in atherogenesis, translating OxLDL biology into clinical interventions has proven challenging. While numerous studies have demonstrated associations between circulating OxLDL levels and cardiovascular risk, therapeutic strategies specifically targeting OxLDL or its pathways have yielded mixed results [7].

Circulating OxLDL has also been implicated in the pathophysiology of Alzheimer's disease through both mechanistic and observational evidence [8]. Likewise, in chronic kidney disease, studies have shown that OxLDL levels are markedly elevated (up to ten-fold higher than in healthy individuals) [9]. These findings underscore the broad relevance of OxLDL beyond cardiovascular disease and highlight the need for targeted research to distinguish observational correlations from causal mechanistic links.

Importance of Robust Analytical Methods

Given the significant role of OxLDL in various diseases, the development and application of accurate and reliable methods to measure and analyze its levels and effects in biological systems are of paramount importance. This is particularly challenging due to the inherent heterogeneity of

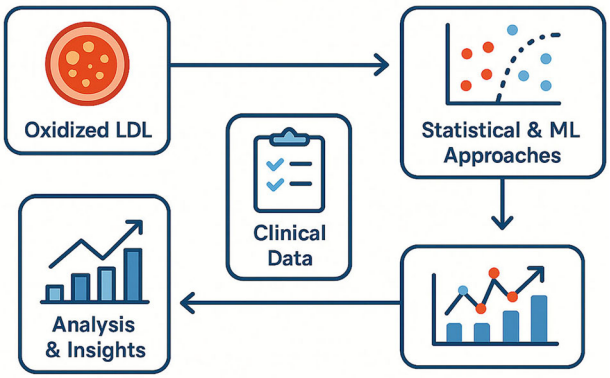

Fig. 1 From OxLDL Particles to Clinical Reporting

OxLDL particles and the complexity of their interactions with cells and other molecules [1]. The fact that "OxLDL" is a broad term encompassing a range of oxidation states and modifications implies that different assays or analytical techniques might detect different aspects of OxLDL. This can lead to variability in research findings and underscores the need for careful consideration of the specific methods employed and their limitations [1]. Therefore, research focusing on characterizing specific oxidative modifications or subfractions of OxLDL, rather than treating it as a single entity, may yield more precise and clinically relevant insights (Fig. 1) [10].

Analytical Methods for the Determination of OxLDL

The measurement of OxLDL in human plasma is crucial for understanding its role in atherogenesis and cardiovascular diseases. Multiple methods, each with its strengths and limitations, have been developed or are under investigation to quantify OxLDL, assess its oxidation products, or capture OxLDL-containing complexes. The biochemical heterogeneity of OxLDL poses a major barrier to its development as a reliable clinical biomarker. OxLDL exists as a complex and variable mixture of particles with differing degrees and sites of oxidation, involving both lipid and protein components such as oxidized phospholipids, cholesterol derivatives, and apoB-100 modifications. This heterogeneity results from diverse oxidative pathways (e.g., enzymatic vs. non-enzymatic) and is influenced by individual metabolic and inflammatory states. As a consequence, different assays may detect distinct OxLDL epitopes or subsets, leading to variability in measurements and poor cross-study comparability. Without standardized definitions and detection platforms, translating OxLDL into a robust, reproducible biomarker for cardiovascular risk remains challenging.

Here are some examples of these methods for the measurement and assessment of OxLDL in human serum and plasma samples:

Table 1 Key Laboratory Methods used for the Determination of OxLDL

Method	Sensitivity	Specificity	Throughput	Clinical Use
Commercial ELISA	Moderate	Moderate	High	Common
LC-MS/MS	High	High	Low to Moderate	Research
Electrophoresis	Low	Low	Low	Rare
Flow Cytometry	High	Moderate	Low	Research
SPR	High	High	Low	Experimental
Biosensors	Emerging	Potentially High	High	Developmental
Immunoprecipitation + MS	High	High	Low	Research
OxLDL-IC Assays	Moderate	Moderate	Moderate	Limited clinical trials

Immunoassays (ELISA-based Methods): Several commercial ELISA kits are currently available for the measurement of OxLDL in human plasma and serum samples. OxLDL ELISA assay is the most popular method due to its high throughput and ease of use. The assay mainly targets Oxidized apoB-100 epitopes, MDA-modified LDL, or Cu2+-oxidized LDL. However, the variability in antibody specificity, epitope masking, and lack of standardization across kits represent the main limitations [11].

Mass Spectrometry-Based Techniques: LC-MS/MS methods are less commonly used for the measurement of OxLDL. However, most commonly used for the detection and measurement of oxidation products, such as detecting oxidized phospholipids (oxPL), oxysterols (e.g., 7-keto-cholesterol), and protein carbonylation products related to LDL particle cholesterol. LCMS methods demonstrate a high sensitivity, specificity, and ability to profile multiple oxidation products as indirect measurements of OxLDL. However, the major limitation is linked to the technically demanding, time-consuming sample preparation and costly instrumentation [12].

Lipidomics Approaches: These comprehensive lipid profiling methods enable a thorough profiling of oxidized lipid species on LDL particles and other contributing lipid components. These methods are mainly used for biomarker discovery and mechanistic insights. Standardization, biological variability, and interpretation of data and the need for LCMS and or GCMS systems represent the main limitations [13].

Other Less-used Methods

These techniques include the use of electrophoresis-based techniques, which use agarose gel electrophoresis to compare the mobility of native LDL vs OxLDL (which is more negatively charged) [14]. Western blotting is also used for the detection of specific oxidized protein epitopes using monoclonal antibodies. The method is not commonly used for clinical samples OxLDL measurement; however, it is mainly used for research and validation of OxLDL detections by other methods, including ELISA [15]. The use of flow cytometry-based detection, which utilizes antibodies against oxidized LDL epitopes to detect OxLDL bound to monocytes or endothelial cells, is commonly seen in molecular research [16]. This assay provides functional cellular assays and evaluation of immune complexes. Another method mainly used for OxLDL validation is known as surface plasmon resonance (SPR) [17]. This method detects real-time binding of OxLDL to specific receptors or antibodies, which allows label-free and kinetic profiling of OxLDL-antibody or OxLDL-receptor interactions. This method is more research-focused and not widely used in clinical diagnostics. In addition to these methods, several other techniques such as the use of nanotechnology-based biosensors (Emerging methods) and an electrochemical sensor to detect redox-active moieties on OxLDL or its components. The use of immunoprecipitation coupled to analytical methods and the detection of circulating immune complexes (OxLDL–ICs), which involves the quantification of OxLDL bound to IgG or IgM autoantibodies, is also considered [18–20] summarizsed in Table 1.

Statistical Methods in the Analysis of OxLDL

Meta-analysis

Meta-analysis is a powerful statistical technique used to systematically combine the results from multiple independent studies that address a similar research question [21]. By pooling data from various studies, meta-analysis can provide a more precise and reliable estimate of an effect than any individual study alone, as well as assess the consistency of findings across different contexts.

In the realm of OxLDL research, meta-analysis has been applied to synthesize the growing body of evidence regarding its association with various diseases. For instance, a meta-analysis was conducted to evaluate the correlation between different lipid metabolism levels, including total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL), and endometriosis [22]. Although this

specific meta-analysis did not focus solely on OxLDL, it demonstrated the utility of this method in examining the role of lipid-related biomarkers in disease etiology, using Review Manager 5.4 for the analysis [22]. This suggests that similar meta-analyses could be and have been conducted to specifically investigate the relationship between OxLDL and various health conditions.

Several meta-analyses have focused on the association between OxLDL levels and cardiovascular disease (CVD) in various settings [4]. These meta-analyses pooled data from multiple observational studies and employed random effects models to account for potential heterogeneity between studies. They consistently demonstrated that OxLDL levels are significantly increased in participants with CVD in the presence of chronic inflammation [4]. These studies often assessed for publication bias using methods like the Egger or Begg test and funnel plots to evaluate the reliability of the overall findings [4]. The consistent finding of elevated OxLDL in CVD patients with chronic inflammation strengthens the argument for OxLDL as a useful biomarker in risk-stratifying cardiovascular disease in this population.

Another meta-analysis reassessed the circulating levels of OxLDL in patients with obstructive sleep apnea (OSA) compared to controls [23]. This study also utilized a random effects model to determine the overall impact of OSA on OxLDL levels. Interestingly, subgroup analysis revealed that studies matching OSA patients and controls for age or body mass index (BMI) showed no significant difference in OxLDL levels, while unmatched studies did show higher levels in OSA patients [23]. This finding suggests that the previously observed association between OSA and elevated OxLDL levels might be confounded by these factors, highlighting the importance of carefully controlling for potential confounders in OxLDL research.

Overall, meta-analysis serves as a critical tool in synthesizing the expanding literature on OxLDL, providing more robust estimates of its association with various diseases. However, it is essential to consider the quality of the individual studies included in the meta-analysis and to assess for potential biases, such as publication bias, to ensure the reliability of the conclusions.

Several meta-analyses have systematically quantified the relationship between circulating OxLDL and cardiovascular risk, demonstrating the value of pooled estimates in this field. By aggregating data from multiple independent cohorts, these studies achieve greater precision and statistical power than individual reports, while formally evaluating between-study heterogeneity and publication bias. An early meta-analysis of observational studies demonstrated a clear association between circulating OxLDL and atherosclerotic cardiovascular disease [24]. Another systematic review and meta-analysis of three observational studies (1,060 participants) confirmed that OxLDL levels are significantly elevated in individuals with cardiovascular disease amidst chronic inflammatory conditions [4]. A recent work has shown that higher serum OxLDL (and the OxLDL/LDL-C ratio) is associated with a greater risk of cardiovascular events, particularly in patients with type 2 diabetes and coronary atherosclerosis [25]. In 2025, a meta-analysis of twelve high-quality studies evaluated soluble LOX-1, the primary receptor for OxLDL, and found that elevated sLOX-1 levels significantly predict major adverse cardiovascular or cerebrovascular events (HR ≈ 1.47) [26]. Collectively, these meta-analyses affirm OxLDL as a robust biomarker of oxidative stress and vascular injury, while underscoring that rigorous assessment of study quality, covariate control, and heterogeneity is essential to derive reliable, clinically meaningful conclusions.

An overview of these meta-analyses (including study designs, participant characteristics, and pooled effect estimates) is provided in Table 2. The ensuing principal clinical implications and areas for future research are:

- OxLDL as a Biomarker: Strong evidence supports using OxLDL (and the OxLDL/LDL-C ratio), especially in patients with inflammation or diabetes, as an adjunct CVD risk marker.
- sLOX-1 Potential: With a consistent hazard ratio of ≈ 1.47 across studies, sLOX-1 is emerging as a promising prognostic biomarker in both acute and chronic cardiovascular disease.

Comparative Studies (t-tests and ANOVA)

Comparative statistical methods, such as t-tests and analysis of variance (ANOVA), are fundamental tools for examining differences in OxLDL levels between distinct groups or under varying conditions.

Table 2 Overview of Recent Meta-analysis Studies

Study / Biomarker	Population & Sample Size	Outcome & Insight
Hong et al. [4] OxLDL	3 studies, n = 1,060	OxLDL is elevated in CVD with chronic inflammation
OxLDL/LDL-C meta-analysis	Multiple observational	Elevated ratios linked to CVD risk, esp. with diabetes
sLOX-1 meta-analysis (2025)	12 studies	sLOX-1 predicts major adverse CVD events (HR ≈ 1.47)

The independent samples t-test is used to compare the means of two independent groups to determine if there is a statistically significant difference between them [27]. This method has been employed in OxLDL research to establish associations with various conditions. For example, an independent Student's t-test was used to compare the mean levels of circulating OxLDL between patients with premature myocardial infarction (MI) and a control group [27]. The analysis revealed a significant elevation of Ox-LDL levels in the premature MI group compared to the controls, with a p-value of 0.002, indicating that this difference was statistically significant [27]. This finding directly supports the role of OxLDL in the pathogenesis of premature MI and suggests its potential as a marker for risk assessment in younger individuals.

Analysis of variance (ANOVA) is utilized to compare the means of three or more groups or to analyze the effects of multiple independent variables on a dependent variable [28]. The application of ANOVA in this context reveals the complex interplay between OxLDL, age, sex, and vascular function, highlighting the importance of considering these factors in future studies on OxLDL's vascular effects. The identification of differential effects based on these variables could have implications for personalized medicine approaches.

ANOVA has been used to compare plasma lipid profiles and valvular OxLDL content in patients with aortic stenosis [29]. This analysis revealed that patients with higher valvular OxLDL content had significantly higher triglyceride levels and a greater proportion of small dense LDL particles in their plasma compared to those with lower valvular OxLDL [29] This suggests a link between circulating lipid profiles, particularly the presence of small dense LDL which is more prone to oxidation, and the local accumulation of OxLDL in atherosclerotic lesions, providing insights into the mechanisms of plaque formation and progression.

In summary, t-tests and ANOVA are essential statistical methods for comparing OxLDL levels and their effects across different groups and conditions, contributing significantly to our understanding of OxLDL's role in both health and disease.

Regression Analysis

Logistic regression can serve as a descriptive tool or as a predictive classifier [30]. When used descriptively, it estimates associations, such as odds ratios, between a small number of predictors and a binary outcome. In this setting, it relies on assumptions of linearity and homogeneous effects to keep results easy to interpret. When used predictively, the focus shifts to accurately classifying outcomes on new data. To boost predictive accuracy, the model can be extended with techniques like LASSO or replaced by more flexible methods (e.g., tree-based algorithms) that capture non-linearities, interactions, and high-dimensional feature spaces, though often with reduced interpretability.

Regression analysis encompasses a set of statistical techniques used to model the relationship between a dependent variable and one or more independent variables. These methods are crucial for quantifying the effect of OxLDL on various outcomes and for identifying factors that predict OxLDL levels.

Linear regression is used when the outcome variable is continuous and allows the determination of independent variables that affect this outcome [28]. Logistic regression, on the other hand, is employed when the outcome is binary, modeling the probability of an event occurring based on predictor variables [28]. Both types of regression analysis have been widely used in OxLDL research.

Multivariate logistic regression analysis was used in one study to evaluate the association between the circulating OxLDL/LDL-C ratio and the severity of coronary atherosclerosis in patients with type 2 diabetes [25]. The results showed that the OxLDL/LDL-C ratio was positively associated with the severity of coronary atherosclerosis, with an odds ratio of 2.03, suggesting that this ratio might be a valuable biomarker for assessing the extent of coronary artery disease in diabetic patients [25].

In another study, logistic regression analysis revealed that the predictive value of circulating OxLDL for coronary artery disease (CAD) was additive to that of the Global Risk Assessment Score (GRAS), a traditional risk assessment tool [31]. This indicates that measuring OxLDL levels can provide additional information beyond conventional risk factors, potentially improving the accuracy of cardiovascular risk prediction [31].

Conditional logistic regression was performed to assess the association between elevated OxLDL levels and the risk of premature myocardial infarction (MI) [27]. The analysis demonstrated that elevated OxLDL levels were associated with a 1.70-fold increased risk of premature MI compared to healthy individuals, further supporting the role of OxLDL in the development of early-onset heart attacks [27].

Multiple linear regression analysis was used to identify predictors of OxLDL concentrations in obese adolescents [32]. The study found that waist circumference and insulin sensitivity were significant independent predictors of higher OxLDL concentrations, highlighting the influence of metabolic factors on OxLDL levels in this at-risk population [32].

Cox proportional hazards models, a type of regression analysis used in survival analysis, have been employed to assess the relationship between OxLDL levels and adverse clinical events. One study used this method to show that elevated OxLDL concentrations demonstrated a potential

correlation with a heightened risk of stroke within 90 days [3].

These examples illustrate the diverse applications of regression analysis in OxLDL research, demonstrating its utility in identifying risk factors, predicting disease outcomes, and quantifying the relationship between OxLDL and various clinical conditions.

Correlation Analysis

Correlation analysis is a statistical method used to evaluate the strength and direction of the relationship between two or more variables. The correlation coefficient, such as Pearson's r for linear relationships or Spearman's rho for monotonic relationships, provides a measure of this association [28].

In OxLDL research, correlation analysis has been used to explore the relationships between OxLDL levels and other relevant biomarkers, particularly inflammatory markers. Several studies have found positive correlations between OxLDL and high-sensitivity C-reactive protein (hs-CRP), a key marker of inflammation [33]. These findings support the established role of OxLDL in promoting inflammation, a critical process in the development of atherosclerosis and other cardiovascular diseases. The observed associations suggest a potential feedback loop where OxLDL drives inflammation, which may in turn further enhance LDL oxidation.

Correlation analysis has also been used to investigate the relationship between OxLDL and cardiac function. In patients with chronic heart failure (CHF), a significant negative correlation was found between plasma levels of OxLDL and left ventricular ejection fraction (LVEF), a measure of the heart's pumping efficiency [34]. Additionally, a positive correlation was observed between OxLDL levels and plasma norepinephrine levels, indicating increased stress on the heart [34]. These correlations suggest that elevated oxidative stress, as reflected by higher OxLDL levels, is associated with poorer cardiac function in patients with CHF.

A study examining patients with aortic stenosis found a significant correlation between the proportion of small dense LDL particles in plasma and the content of OxLDL within the aortic valve [29]. This correlation suggests that the type of LDL particles circulating in the blood may influence their propensity to become oxidized and accumulate in atherosclerotic lesions. Small, dense LDL particles are known to be more susceptible to oxidation than larger, more buoyant LDL particles.

Finally, correlation analysis has shown associations between OxLDL levels and other lipid parameters, such as total cholesterol (TC), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-c) [35]. These correlations indicate that overall lipid metabolism plays a significant role in the formation and circulating levels of OxLDL. Interventions aimed at managing general lipid levels might therefore also impact OxLDL concentrations.

While correlation analysis can reveal important associations between OxLDL and other factors, it is important to remember that correlation does not imply causation. Further research, often using experimental or longitudinal study designs, is needed to establish causal relationships.

Survival Analysis

Survival analysis is a branch of statistics that deals with the analysis of time until an event occurs. Common methods in survival analysis include Kaplan-Meier curves for estimating survival probabilities over time and Cox proportional hazards models for assessing the impact of various predictors on the hazard of an event [28].

In OxLDL research, survival analysis has been used to evaluate the prognostic value of OxLDL levels in predicting long-term outcomes, particularly cardiovascular events and mortality. One study used Kaplan-Meier analysis to examine event-free survival rates in patients with very-early coronary artery disease (VECAD) based on their OxLDL levels [36]. The results revealed that VECAD patients with high OxLDL levels had significantly lower event-free survival rates compared to those with lower levels, suggesting that elevated OxLDL is associated with poorer cardiovascular outcomes in younger patients with CAD [36].

Cox proportional hazards models have been employed to identify independent predictors of mortality in various patient populations. In patients with chronic congestive heart failure (CHF), high plasma levels of OxLDL were found to be an independent predictor of mortality, even after controlling for other known risk factors [34]. This highlights the potential of OxLDL as a prognostic biomarker in CHF, suggesting that monitoring OxLDL levels could aid in risk stratification and management of these patients.

Similarly, in a study of hemodialysis patients, Cox proportional hazards modeling showed that the titer of antibodies against oxidized LDL (OxLDL antibody titer) was an independent risk factor for cardiovascular mortality over a 4-year follow-up period [37]. This indicates that oxidative stress, as reflected by OxLDL antibody levels, is a significant predictor of cardiovascular death in this high-risk population.

Survival analysis has also been used to assess the relationship between OxLDL and all-cause mortality in older adults. One study found that circulating oxidized LDL lipids, when considered in proportion to high-density lipoprotein cholesterol (HDL-c), emerged as a significant risk factor for all-cause mortality in an elderly population over a 10-year follow-up [38]. This suggests that the balance

between potentially pro-atherogenic OxLDL and potentially protective HDL-c may be an important determinant of longevity in older individuals.

These applications of survival analysis underscore the prognostic significance of OxLDL levels in various cardiovascular conditions and in predicting overall mortality.

Machine Learning and Artificial Intelligence Methods in OxLDL Research

Prediction Models

Machine learning (ML) is a branch of Artificial Intelligence (AI) that focuses on enabling computers to learn from data without being explicitly programmed. ML algorithms build models based on sample data, known as "training data," to make predictions or decisions without being explicitly programmed to perform the task [39]. We consider AI to be the computational search for optimal decisions, actions, or solutions by reasoning, learning, or adapting across uncertain and complex problem spaces. ML, as an AI's subset, focuses on the computational search for optimal models or functions directly from data.

In the context of OxLDL research, ML techniques have been explored for their ability to predict various outcomes, including disease severity, mortality risk, and plaque vulnerability. For example, a study utilized a support vector machine (SVM) model to predict the severity of COVID-19 in hospitalized patients based on a panel of oxidative stress biomarkers [40]. While OxLDL was not identified as a primary predictor in this specific study, it demonstrates the potential of ML to leverage multiple oxidative stress markers, which could include OxLDL in other contexts, to predict disease progression [40]. Similarly, various ML algorithms, including SVM, Random Forest, and Neural Networks, have been developed and validated for predicting in-hospital mortality risk among patients with hyperglycemic crisis [39]. Although OxLDL was not a top predictor in this case, these studies highlight the broader applicability of ML in predicting medical outcomes, where OxLDL could be a relevant feature in different disease settings or patient populations [39].

ML models, such as Extreme Gradient Boosting (XGBoost), Logistic Regression, and AdaBoost, have also been used to predict the expression of specific biomarkers, such as Trophoblast cell surface antigen 2 (TROP2) in breast cancer models [41]. While this application is outside the direct scope of OxLDL research, it illustrates the capacity of ML to predict biomarker expression in biological systems, suggesting that similar approaches could be used to predict OxLDL levels or its impact based on other factors.

A notable application of ML in direct OxLDL research is the development of an ML-directed electrochemical impedance spectroscopy (EIS) platform to predict metabolically vulnerable atherosclerotic plaques [42]. In this approach, EIS is used to measure the electrical properties of plaques, which are influenced by their composition, including the content of metabolically active oxidized low-density lipoprotein (OxLDL), a key marker of plaque vulnerability [42]. A deep learning model called DenseNet achieved high accuracy in predicting vulnerable plaques based on the EIS data, demonstrating the potential of AI-driven diagnostic tools in cardiovascular disease [42].

ML algorithms, including Logistic Regression, Naive Bayes, Decision Tree, Random Forest, and Gradient Boosting, have been employed to predict the efficacy and safety of statin therapy [43]. While these models did not directly incorporate OxLDL levels, the fact that statins are known to affect LDL and potentially OxLDL suggests that future models could include OxLDL measurements to improve the prediction of treatment outcomes [43].

The use of ML has also extended to predicting other oxidative stress markers. One study utilized ML to predict glutathione levels based on measurements of various antioxidants [44]. This demonstrates the broader utility of ML in modeling complex relationships between different biomarkers of oxidative stress, suggesting a potential for similar models to predict OxLDL levels based on related biomarkers or clinical data [44].

Moreover, ML models, including Light Gradient Boosting Machine (LightGBM), have been used to predict the occurrence of carotid artery plaques using routine health examinations and blood markers [45]. Although OxLDL was not directly used as a predictor in this study, the identification of LDL-c as an important predictive factor suggests a potential indirect link with OxLDL, and incorporating OxLDL measurements in future models could further enhance their predictive accuracy [45].

Finally, XGBoost was identified as the best ML model for predicting osteoarthritis based on heavy metal levels [46]. While this is in a different disease context, it highlights the broad applicability of ML in diseases where oxidative stress might play a role, suggesting its potential in various OxLDL-related research areas.

These examples illustrate the growing role of ML in building predictive models involving OxLDL, with the potential to significantly enhance risk assessment, diagnosis, and the development of treatment strategies for cardiovascular and other diseases. The selection of appropriate algorithms and relevant features is crucial for optimizing the performance of these models.

All predictive metrics (e.g., AUC, accuracy, logistic loss) are computed on held-out data, either separate validation sets or via k-fold cross-validation, rather than on the

training set, to ensure true out-of-sample performance and guard against overfitting [47]. Feature selection based on a single model's accuracy without proper resampling can vary widely across splits, but aggregating importance scores over multiple cross-validation folds yields more stable, robust predictors. The application-specific workflow that employs a uniform 10-fold cross-validation scheme for hyperparameter tuning and final metric reporting ensures that all stated performance results reflect genuine generalizability on unseen data.

Image Analysis using Deep Learning

Deep learning, a subfield of ML, employs artificial neural networks with multiple layers to automatically learn complex features from data, including images [48]. This approach has shown significant promise in analyzing microscopy images and medical imaging data related to OxLDL studies.

One notable application is the use of a U-net convolutional neural network (CNN) to analyze the effects of OxLDL on platelet shape, spreading, and migration as observed through phase contrast microscopy [49]. This study demonstrated the power of deep learning in automating the quantification of subtle changes in cellular morphology and behavior in response to OxLDL treatment. By accurately segmenting platelets in the images and tracking their dynamics, this offers a valuable insight into the mechanisms by which OxLDL influences thrombotic processes [49].

Deep learning has also been applied to the analysis of medical imaging data, particularly carotid ultrasound images, for plaque wall segmentation and the extraction of carotid ultrasound image phenotypes (CUSIPs) [48]. Atherosclerotic plaques, in which OxLDL plays a central role in formation and progression, can be visualized and characterized using ultrasound. Deep learning algorithms can be trained to automatically segment the plaque area and extract quantitative features (CUSIPs) that serve as surrogate biomarkers for coronary artery disease [48]. This AI-driven image analysis can indirectly assess the presence and extent of OxLDL-related pathology in the arteries.

These examples highlight the transformative potential of deep learning in OxLDL research by enabling high-throughput, automated, and unbiased analysis of image data at both the cellular and tissue levels. This is particularly valuable for studying the complex interactions of OxLDL with various cell types and its role in the development of atherosclerotic plaques.

AI-enhanced Diagnostic and Risk Stratification Tools

AI is increasingly being used to develop sophisticated tools that integrate data from various sources, including OxLDL levels and other clinical parameters, to improve diagnostic accuracy and risk prediction in cardiovascular disease [48].

One example is the use of an AI-enhanced cardiac risk prediction algorithm called CaRi-Heart Risk [50]. This algorithm incorporates the Fat Attenuation Index (FAI) score, a measure of coronary inflammation derived from computed tomography angiography (CTA) that is related to the presence of OxLDL, along with traditional clinical risk factors and other CTA-derived plaque metrics [50]. By integrating these diverse data points, the AI algorithm can provide a more comprehensive and potentially accurate assessment of an individual's risk of future cardiac events.

Another area where AI is being applied is in the risk stratification of cardiovascular disease in patients with obstructive sleep apnea (OSA) [48]. OSA is known to be associated with an increased risk of cardiovascular disease, and OxLDL is implicated in the pathogenesis of both conditions. Deep learning algorithms are being explored to analyze surrogate carotid imaging data, which can reflect the presence of atherosclerotic plaques, to improve risk stratification in OSA patients. This approach leverages the link between OSA and CVD, potentially using OxLDL-related imaging biomarkers to identify individuals at higher risk.

These AI-enhanced tools demonstrate the potential to significantly improve clinical decision-making in cardiovascular disease by providing more accurate diagnoses and risk assessments, often incorporating information related to OxLDL either directly or indirectly through advanced image analysis.

Review and Comparison of Statistical and ML/AI Methods

Strengths and Limitations

Both traditional statistical methods and modern ML/AI approaches offer unique strengths and limitations when applied to the analysis of OxLDL. Statistical methods are well-established and provide a framework for hypothesis testing, often yielding interpretable results with measures of statistical significance. They are particularly suitable for understanding fundamental relationships between variables and for comparing group means [21]. However, these methods can be limited in their ability to handle complex non-linear relationships and high-dimensional datasets, and they often rely on specific assumptions about the distribution of the data [21].

In contrast, ML/AI methods excel at identifying intricate patterns and non-linear relationships within data, and they can effectively handle high-dimensional datasets [39]. These approaches often achieve high predictive accuracy,

making them valuable for tasks such as risk assessment and diagnosis [39]. However, a significant limitation of some ML/AI models is their "black box" nature, where the underlying decision-making process is not easily interpretable [42]. ML/AI models typically require large amounts of data for training and are susceptible to overfitting if not properly validated [39].

The "black box" issue arises from the prioritization of prediction accuracy over interpretability, fitting complex relationships without clearly revealing how risk factors contribute to outcomes. To address this, two main approaches exist: inherently interpretable models and post-hoc explanation methods [47]. Inherently interpretable models, such as CART decision trees, explicitly illustrate non-linear relationships and interactions between predictors and outcomes but may suffer from high variance when used individually. Alternatively, post-hoc methods like variable importance metrics, SHAP, and LIME quantify the contribution of individual variables in more complex models, aiding hypothesis generation and model understanding despite lacking direct causal interpretation.

Research Questions Approaches

The type of research question often dictates whether statistical or ML/AI methods are more appropriate for analyzing OxLDL. Statistical methods are well-suited for questions focused on comparing mean OxLDL levels between different groups (e.g., patients with and without a specific disease), assessing the independent effect of OxLDL on a particular outcome while controlling for other factors, and testing specific hypotheses about the relationship between OxLDL and other variables [4, 51–55].

On the other hand, ML/AI methods are often more effective for research questions aimed at predicting the risk of cardiovascular events or other diseases based on a combination of factors that may include OxLDL, as well as for classifying different stages of atherosclerosis or identifying vulnerable plaques based on OxLDL-related imaging data [39].

Potential for Integration

There is significant potential for integrating statistical and ML/AI methods to leverage the strengths of both approaches in OxLDL studies. For instance, statistical methods can be used for feature selection to identify the most relevant variables related to OxLDL before applying ML models for prediction [43]. Additionally, statistical analysis can play a crucial role in interpreting the results of ML models, helping to understand the significance of the identified patterns and predictions [43]. This integration could lead to the development of more robust and interpretable models that provide both accurate predictions and valuable insights into the complex role of OxLDL in disease.

The justification for integration comes from the inherent characteristics of the two methods that have significant potential to complement each other. The traditional statistical models, such as regression analyses, depend on clearly defined assumptions about the linearity, independence and distribution of variables. In contrast, machine learning approaches, which can be defined as methods conducting an automated search for optimal model structures [30], can uncover complex, nonlinear interactions without predefined functional forms. ML techniques, therefore, hold particular promise for analyzing multifaceted biological relationships, as seen in studies of OxLDL, where the interactions among metabolic, inflammatory, and genetic factors are intricate. However, ML methods demand larger datasets and meticulous validation to maintain generalizability and interpretability. A comparative summary of these methodological differences, including performance, limitations, assumptions, and data requirements, is provided in Table 3.

The useful and robust traditional regression models have certain limitations that ML methods can address. The choice often depends on the goal of the study: association analysis versus prediction analysis. Regression techniques typically struggle with datasets containing numerous predictors, particularly when predictors outnumber events, leading to instability and high variability of estimates. Machine learning approaches like regularized regression (LASSO, Ridge), tree-based methods (CART), and dimension-reduction techniques (PCR, PLS) address these challenges effectively by handling large, correlated predictor sets. Additionally, regression assumes linear and homogeneous relationships between predictors and outcomes, which may oversimplify complex biological relationships. Machine learning methods such as Generalized Additive Models (GAMs), CART, and neural networks overcome this limitation by flexibly modeling nonlinear relationships and interactions without pre-specified structures. Finally, regression's interpretability, which is valuable for association analyses, can limit predictive accuracy. ML methods prioritize prediction accuracy, often at the expense of interpretability, making them highly suitable when precise outcome prediction is the primary goal.

On a practical side, Tables 4–7 outlines the general suitability of appropriate analytical approaches in OxLDL-related studies based on the complexity of available data. The table considers key factors such as the number of predictors, linearity assumptions, interaction effects, dimensionality, and sample size, offering a straightforward framework for choosing between traditional statistical models and more advanced ML techniques.

Table 3 High-level Comparison of Traditional and ML Methods

Criterion	Regression Techniques	Machine Learning Techniques
Performance Strengths	∘ Robust and interpretable ∘ Efficient for simple (linear) relationships	∘ Improved prediction accuracy; handles complex nonlinear relationships and interactions ∘ Ensemble methods (Random Forests, Boosting) improve robustness and prediction accuracy
Performance Weaknesses	∘ Degraded performance with nonlinear data, interactions, or numerous predictors ∘ Stepwise selection methods risk overfitting	∘ "Black box" nature; difficult interpretability ∘ Risk of overfitting; balance of bias and variance critical
Limitations	∘ Assumes linearity, homogeneity of effects ∘ Limited ability to handle many predictors or rare events ∘ Requires predefined model structure; no automated "search" ∘ Requires explicit handling of missing data (e.g., imputation)	∘ Sacrifices interpretability; metrics lack a clear causal/statistical interpretation ∘ Requires careful tuning of parameters; computationally intensive ∘ Not superior if the underlying relationship is linear and simple ∘ Limited in causal inference and correlated (longitudinal) data scenarios ∘ Difficult to convert into simple, hand-calculable scores
Data Requirements	∘ Suited for small to moderate numbers of predictors ∘ Requires ≥10–20 events per predictor (rule-of-thumb) ∘ Missing data requires careful imputation	∘ Suited for large, multifaceted datasets ∘ Effective with high-dimensional data, even when predictors outnumber events ∘ Validation sets are essential; cross-validation/bootstrapping is necessary to prevent overfitting ∘ Certain methods (e.g., CART, Random Forests) can handle missing data inherently

Table 4 Generally Recommended Methods based on the Complexity of Available Data

Data Situation	Data Type & Complexity	Recommended Method
A simple comparison between two groups	The single continuous outcome, two independent groups	t-test
Simple comparison across multiple groups	Single continuous outcome, categorical predictor with >2 groups	ANOVA
Association analysis with a few predictors	The continuous or binary outcome, a limited number of predictors (low-dimensional data), and assumptions of linearity and independence are likely valid	Linear or Logistic Regression
Time-to-event outcome (survival analysis)	Event data with follow-up time, a few predictors	Cox Proportional Hazards Model
Nonlinear relationships suspected	Moderate number of predictors, potential threshold effects or curves	Generalized Additive Models (GAMs)
Multiple predictors with possible multicollinearity	Moderate/high-dimensional data, predictors correlated	Regularized Regression (LASSO, Ridge)
Many predictors, complex interactions	High-dimensional data, interactions unknown, nonlinearity likely	Tree-based Models (CART, Random Forests, Gradient Boosting)
Large, complex, multifaceted data (e.g., omics, EHRs)	Highly dimensional, mixed data types, nonlinearities, interactions	Machine Learning (Ensemble Methods, Support Vector Machines, Neural Networks, Deep Learning)
Small sample size, but many correlated predictors	Few observations and many variables	Dimension Reduction (Principal Component Analysis, Partial Least Squares)

Table 5 Summary of Key Meta-analyses on OxLDL

Study (Citation)	Condition Investigated	OxLDL Association (Direction and Significance)	Statistical Methods Used	Key Findings
[22]	Lipid metabolism levels and endometriosis	TC higher in endometriosis group (SMD = 1.70, $p = 0.003$); no significant difference in TG, LDL	Meta-analysis using Review Manager 5.4, random effects model	Meta-analysis evaluated correlation between lipid metabolism and endometriosis.
[4]	OxLDL levels and CVD in chronic inflammatory conditions	OxLDL significantly increased in participants with CVD	Meta-analysis using the random effect model, Egger/Begg test for publication bias	OxLDL may be a useful biomarker for CVD risk stratification in chronically inflamed patients.
[23]	Circulating OxLDL levels in patients with OSA	Pooled analysis showed increased OxLDL in OSA; no significant difference in age/BMI matched studies	Meta-analysis using a random effects model, subgroup analysis	Age and BMI may be confounding factors in the association between OSA and elevated OxLDL.

Table 6 Examples of Regression Models Used in OxLDL Research

Study (Citation)	Outcome Variable	Predictor Variable(s) (including OxLDL)	Type of Regression	Key Findings Related to OxLDL
[25]	Severity of coronary atherosclerosis (Gensini score)	OxLDL/LDL-C ratio	Multivariate logistic regression	Positive association between OxLDL/LDL-C ratio and severity of coronary atherosclerosis in type 2 diabetes patients.
[31]	Presence of coronary artery disease (CAD)	Circulating oxidized LDL, GRAS score	Logistic regression	Predictive value of oxidized LDL was additive to that of GRAS for identifying CAD.
[27]	Premature myocardial infarction (MI)	Elevated Ox-LDL levels	Conditional logistic regression	Elevated Ox-LDL levels associated with a 1.70-fold increased risk of premature MI.
[32]	OxLDL concentrations	Waist circumference, insulin sensitivity	Multiple linear regression	Waist circumference and insulin sensitivity were significant independent predictors of higher OxLDL concentrations in obese adolescents.
[3]	Occurrence of stroke within 90 days	Elevated OxLDL concentrations	Multivariable Cox regression	Elevated OxLDL concentrations showed a potential correlation with heightened stroke risk.

Table 7 Machine Learning Algorithms Applied in OxLDL-related Research

Study (Citation)	Prediction Task	Machine Learning Algorithm(s) Used	Key Features (if OxLDL was directly used)	Performance Metrics
[42]	Metabolically vulnerable atherosclerotic plaques	DenseNet (deep learning)	EIS data (reflects OxLDL content)	Accuracy of 92.59%
[40]	Severity of COVID-19	Support Vector Machine (SVM)	Oxidative stress biomarkers (not primarily OxLDL)	7% misclassification on the training dataset
[45]	Occurrence of carotid artery plaques	LightGBM, Logistic Regression, SVM, ANN, Random Forest, XGBoost	LDL-c (indirect link to OxLDL)	LightGBM achieved the highest accuracy at 91.8%
[49]	Platelet shape, spreading, and migration	U-net (deep learning)	Phase contrast microscopy images of platelets treated with OxLDL	High accuracy in platelet segmentation (96% intersection over union)

Conclusion and Future Perspectives

Summary of Key Methods

This review has provided an overview of the diverse statistical, ML, and AI methods employed in the analysis of OxLDL. Traditional statistical techniques such as meta-analysis, comparative studies (t-tests and ANOVA), regression analysis (linear and logistic), correlation analysis, and survival analysis have been instrumental in establishing the role of OxLDL as a biomarker and in understanding its associations with various diseases, particularly cardiovascular conditions. More recently, ML and AI approaches, including prediction models, deep learning for image analysis, and AI-enhanced diagnostic and risk stratification tools, are being increasingly utilized to uncover complex patterns, improve predictive accuracy, and automate the analysis of large and intricate datasets related to OxLDL.

Future Directions

Future investigations of OxLDL should consider several key directions to better understand its contribution to disease.

Methodological innovations

Emerging machine learning approaches offer powerful tools to handle the complexity of OxLDL-related data. Deep learning, ensemble models, and explainable AI techniques such as SHAP and LIME allow researchers to capture non-linear relationships, high-dimensional interactions, and heterogeneous effects that challenge traditional regression-based approaches. Integration of multi-omic datasets, including genomics, transcriptomics, and proteomics, with OxLDL measurements can provide a more comprehensive view of atherosclerotic risk mechanisms. Additionally, dynamic modeling approaches incorporating longitudinal data and causal inference frameworks may further enhance our understanding of OxLDL's role across disease trajectories. The development of novel and more specific assays capable of distinguishing between different forms of OxLDL will be crucial for gaining a more nuanced understanding of its various roles [10].

In addition, transcriptomic data can identify gene expression patterns regulating or responding to OxLDL levels, revealing pathways involved in lipid oxidation, inflammation, and plaque progression. Epigenetic modifications, including DNA methylation and histone changes, may explain inter-individual variability in OxLDL metabolism and vascular sensitivity, offering a mechanistic context to OxLDL measurements. Causal inference frameworks can help clarify mechanistic links between OxLDL and downstream vascular outcomes, while longitudinal multi-omic time series combined with recurrent neural

networks may capture dynamic molecular shifts over time. Single-cell multi-omics, paired with ML clustering, offers the potential to dissect OxLDL-driven processes at cellular resolution, and transfer learning approaches may enhance model generalizability across diverse populations. These integrative multi-omic and ML strategies represent a promising direction for advancing OxLDL research toward clinically meaningful applications.

Clinical applications

These methodological advances hold promise for improving cardiovascular risk prediction, enabling more personalized prevention and treatment strategies. ML models integrating OxLDL-related pathways may refine patient stratification, inform early intervention, and support ongoing monitoring of disease progression. Predictive models incorporating both traditional risk factors and advanced molecular features could ultimately support more precise, individualized care for patients at risk of OxLDL-driven vascular disease.

Translational challenges

Despite these advances, several challenges remain before these models can be fully implemented in clinical practice. Large, diverse, and well-annotated datasets are needed to ensure model generalizability across populations. Rigorous external validation, careful tuning to avoid overfitting, and ongoing performance monitoring are essential to maintain clinical reliability. Addressing the challenges of interpretability and potential bias in AI models applied to OxLDL research will be critical for their successful translation into clinical practice [48]. Integrating these models into clinical workflows will also require collaboration across clinicians, data scientists, and regulatory bodies to ensure responsible and effective deployment.

Data Availability

No datasets were generated or analysed during the current study.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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