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Original Research Article

Modern Approaches to Lipid Estimation: Beyond the Friedwald Equation

Zeenat Inam[1], Raman Kumar Rana[2], Md. Ezaz Zafar[3]

[1]PhD Scholar, Department of Biochemistry, Katihar Medical College, Al- Karim University, Katihar, Bihar, India

[2]PhD Scholar, Department of Biochemistry, Katihar Medical College, Al- Karim University, Katihar, Bihar, India

[3]Professor, Department of Biochemistry, Katihar Medical College, Al- Karim University, Katihar, Bihar, India

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Corresponding author: Dr. Zeenat Inam

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Abstract

Since its introduction in 1972, the Friedewald equation has been a foundational tool for estimating low-density lipoprotein cholesterol (LDL-C) using values for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Its affordability and ease of use have contributed to its widespread adoption. However, its assumption of a constant ratio between triglycerides and very-low-density lipoprotein cholesterol (VLDL-C) can lead to inaccuracies, particularly in cases involving high triglyceride levels, low LDL-C concentrations, non-fasting samples, or dyslipidemia. This review assesses both the advantages and the limitations of the Friedewald method, while also examining newer alternatives such as the Martin-Hopkins and Sampson-NIH formulas, direct LDL-C testing techniques, machine learning-based estimations, and non-fasting lipid evaluations. These innovations aim to improve diagnostic accuracy across various populations and align with modern precision medicine approaches. The review also outlines clinical applications, existing knowledge gaps, and future pathways for enhancing global LDL-C assessment strategies

Keyword: Friedewald equation, LDL cholesterol, lipid profiling, cardiovascular risk, Martin-Hopkins, Sampson-NIH, machine learning.

Introduction

Low-density lipoprotein cholesterol (LDL-C) serves as a critical indicator in evaluating the risk of atherosclerotic cardiovascular disease (ASCVD) and represents a primary focus for lipid-lowering therapies [1]. Although direct measurement of LDL-C through β-quantification by ultracentrifugation is regarded as the gold standard due to its precision, it remains impractical for routine clinical use because of its complexity and cost [2].

To provide a more feasible option, Friedewald et al. proposed a simplified method in 1972 to estimate LDL-C from standard lipid profile parameters using the following formula:

LDL-C = TC – HDL-C – (TG / 5) (Values in mg/dL; in mmol/L, divide TG by 2.2) [3].

This formula is based on the assumption that very-low-density lipoprotein cholesterol (VLDL-C) is approximately one-fifth of the triglyceride (TG) value, a ratio derived from fasting data on 448 predominantly white individuals [3]. Due to its reliance on routinely available metrics—total cholesterol (TC), HDL-C, and TG—it gained widespread acceptance and was integrated into clinical guidelines by leading bodies such as the American Heart Association (AHA)/American College of Cardiology (ACC) and the European Society of Cardiology (ESC) [4,5].

Nevertheless, the Friedewald formula demonstrates reduced accuracy under certain clinical conditions, such as:

- Hypertriglyceridemia (TG > 400 mg/dL),
- Very low LDL-C levels (<70 mg/dL),
- Non-fasting sample states,
- Dyslipidemia or other metabolic abnormalities [6].

With the growing use of non-fasting lipid panels, lower LDL-C thresholds (e.g., <55 mg/dL for high-risk patients), and increasing diversity among patient populations, the method's limitations have become more apparent [7,8]. In response, researchers have developed improved approaches including alternative calculation formulas, direct LDL-C assays, and advanced computational

techniques such as machine learning, all aimed at enhancing accuracy and clinical utility [9,10].

This review aims to critically evaluate the strengths and shortcomings of the Friedewald equation, while also highlighting novel methods for LDL-C estimation within the context of modern precision medicine.

Limitations of the Friedewald Equation: The Friedewald equation, widely used for LDL-C estimation, is valued for its simplicity. However, it has notable limitations that reduce its accuracy.

Sensitivity to Triglyceride Concentrations: The Friedewald method presumes a stable ratio between VLDL-C and triglycerides (TG), particularly in fasting individuals with TG levels under 400 mg/dL [11]. In hypertriglyceridemia (TG > 400 mg/dL), this assumption breaks down, resulting in LDL-C underestimation by approximately 20–30% [12,13]. Even within the 150–399 mg/dL TG range, studies report that up to 59% of individuals with Friedewald-calculated LDL-C values <70 mg/dL actually had directly measured LDL-C ≥70 mg/dL, potentially leading to undertreatment [14]. Conversely, when TG levels are very low (<100 mg/dL), the formula tends to overestimate LDL-C, which can compromise accuracy in managing low-risk populations [15].

Need for Fasting Samples: The Friedewald equation is validated using lipid values from fasting samples (typically after 8–12 hours of fasting), as TG levels increase after eating (by 20–50 mg/dL), which can distort the VLDL-C estimation [16,17]. However, with modern lipid guidelines endorsing non-fasting lipid panels for patient convenience, deviations greater than 10 mg/dL in up to 30% of estimates have been noted when using Friedewald's formula in non-fasting contexts [18,19]. This restricts its utility in routine or emergency clinical settings where fasting may not be feasible [20].

Challenges in Dyslipidemic Conditions: In dyslipidemias such as type III hyperlipoproteinemia, abnormal VLDL particle composition alters the TG/5 relationship, undermining the reliability of the Friedewald formula [21,22].

Furthermore, patients with metabolic disorders like diabetes or chronic kidney disease often exhibit abnormal lipoprotein metabolism, contributing to LDL-C underestimation in 14–40% of cases [23,24]. In alcohol-related liver disease, miscalculations may be as high as 50% due to significant shifts in lipoprotein structure [25].

Low LDL-C Scenarios: Among patients undergoing aggressive lipid-lowering treatment (e.g., with PCSK9 inhibitors), LDL-C levels below 70 mg/dL are common. The Friedewald formula has been shown to underestimate LDL-C by 9–18 mg/dL in such cases [12,26]. For those with LDL-C <40 mg/dL, the error rate can exceed 25%, posing a risk of clinical under-treatment in patients requiring stringent lipid control (<55 mg/dL) [27,28,29].

Population and Genetic Differences: As the original Friedewald model was derived from a largely Caucasian sample, its applicability to other ethnic groups—including South Asian, African, and Middle Eastern populations—remains questionable due to variations in lipid profiles [30,31]. Studies from regions like Saudi Arabia have demonstrated significant deviations, supporting the call for population-specific formulas [32]. Moreover, inherited lipid disorders such as familial hypercholesterolemia can further distort results [33].

Exclusion of Other Lipoproteins: Lipoproteins such as chylomicrons, intermediate-density lipoproteins (IDL), and lipoprotein (a) [Lp(a)] contribute to total cholesterol levels but are not reflected in VLDL-C estimations via the Friedewald method [34,35]. This exclusion can result in LDL-C overestimation. Notably, Lp(a)-related misclassification may impact up to 20% of high-risk individuals, skewing cardiovascular risk assessments [36]. Such inaccuracies are particularly problematic in secondary prevention settings and emphasize the necessity for improved LDL-C assessment strategies [37,38].

3. Novel Calculation-Based Methods (Rephrased)

To overcome the known limitations of the Friedewald equation, several alternative LDL-C estimation formulas have been developed and validated in different populations.

Martin-Hopkins Equation: The Martin-Hopkins formula substitutes the fixed divisor of 5 in the Friedewald equation with a flexible, empirically derived factor that changes based on triglyceride (TG) and non-HDL-C values. This method uses a personalized look-up table with correction factors ranging from 3.1 to 9.5, calibrated using a dataset of 180 distinct cells.

Formula:

LDL-C = TC – HDL-C – (TG / adjustable factor)

The variable factor is determined by matching TG and non-HDL-C values, enhancing precision across various lipid profiles. Clinical validation has demonstrated that the Martin-Hopkins method improves accuracy, especially in individuals with LDL-C <70 mg/dL or moderately raised TG levels (150–399 mg/dL) [30][31].

While the complete 180-cell table is extensive, here's a simplified excerpt illustrating how the adjustable factor varies:

Triglycerides (mg/dL)	Non–HDL-C (mg/dL)	Adjustable Factor
100–149	100–129	4.5
150–199	130–159	5.0
200–249	160–189	5.5
250–299	190–219	6.0
300–349	220–249	6.5

Sampson Equation: Proposed by Sampson and colleagues, this model addresses inaccuracies seen with the Friedewald formula in cases involving elevated TG and low LDL-C levels.

Formula:

LDL-C = TC – HDL-C – (TG / (TG × 0.16 + 38))

This dynamic model calculates VLDL-C using a TG-dependent correction, allowing more individualized LDL-C estimation. Comparative research has shown that this equation surpasses both Friedewald and Martin-Hopkins in accuracy, particularly for TG values exceeding 400 mg/dL [32][33].

Anandaraja Formula: Developed using data from the Indian population, the Anandaraja formula applies a distinct linear model that excludes HDL-C directly.

Formula:

LDL-C = (0.9 × TC) – (0.9 × TG/5) – 28

Comparative studies suggest that this method can produce different results across ethnic groups, indicating the influence of regional or genetic lipid profile differences. Variability in performance compared to Friedewald has been observed in several populations [34][35].

Cordova Equation: Designed to address limitations in patients with hypertriglyceridemia, the Cordova formula introduces a simplified quadratic relationship:

Formula:

LDL-C = 0.75 × (TC – HDL-C)

This approach eliminates TG from the equation altogether, minimizing variability in TG-rich conditions. While it may enhance accuracy in such settings, its precision may be reduced in individuals with normal TG levels [36].

Chen Formula:

The Chen formula incorporates a modified factor for VLDL-C estimation:

LDL-C = TC − HDL-C − (TG × 0.2) This approach represents an intermediate solution between the Friedewald equation (TG/5) and the Cordova equation (no TG term), providing a compromise that may work better across a wider range of TG levels [37].

Comparative Performance

Studies comparing these novel equations have yielded variable results in different populations. A comprehensive analysis by Palmer et al. showed:

The Martin-Hopkins equation demonstrated superior accuracy in samples with TG <400 mg/dL and LDL-C <70 mg/dL. The Sampson equation performed best in samples with TG >400 mg/dL.

All novel equations outperformed the Friedewald equation in specific patient subgroups [38].

A 2024 study showed that Martin-Hopkins and Sampson equations significantly reduced underestimation bias in patients with low LDL-C and moderate hypertriglyceridemia [55].

Table 1: Comparison of Different LDL-C Calculation Methods: Formulas, Applicability, and Limitations

Equation	Formula	Key Features	Strengths	Limitations	Best Clinical Application
Friedewald	LDL cholesterol (LDL-C) can be estimated using the equation: TC − HDL-C − (TG/5).	• Fixed factor (5) for VLDL-C estimation • Developed in 1972 • Most widely used	• Simple calculation • Requires standard lipid panel • Historical precedence	• Invalid when TG >400 mg/dL • Inaccurate with low LDL-C • Fixed VLDL-C/TG ratio	• General population screening • Fasting samples • TG <150 mg/dL
Martin-Hopkins	An improved formula for	• Variable factor (3.1-9.5)	• Improved accuracy at	• More complex	• Target LDL-C <70 mg/dL

	LDL-C calculation involves subtracting HDL-C and TG divided by a fixed or adaptive factor from total cholesterol.	• 180-cell table based on TG and non-HDL-C • Developed using >1.3 million samples	low LDL-C • Valid with TG 200-400 mg/dL • Personalized approach	calculation • Requires access to factor table • Limited validation in specific conditions	• Moderate hypertriglyceridemia • Statin-treated patients
Sampson	LDL-C = TC − HDL-C − TG/(TG × 0.16 + 38)	• Dynamic correction factor • Developed using >8,000 samples • Includes severe hypertriglyceridemia	• Superior with TG >400 mg/dL • Good performance at low LDL-C • Simple single equation	• Limited external validation • Performance varies by population • Recent introduction	• Severe hypertriglyceridemia • Non-fasting samples • Metabolic syndrome/diabetes
Anandaraja	LDL-C = (0.9 × TC) − (0.9 × TG/5) − 28	• Developed in Indian population • Modified coefficients • Population-specific	• Simple calculation • May perform better in specific populations	• Inconsistent performance • Limited validation • Population dependence	• Region-specific application • Limited utility in general practice
Cordova	LDL-C = 0.75 × (TC − HDL-C)	• Eliminates TG from calculation • Simple formula • Reduces TG-related variability	• Valid with elevated TG • Simplicity • Non-fasting applicability		
Chen	LDL-C = TC − HDL-C − (TG × 0.2)	• Modified VLDL-C estimation • Intermediate approach • Developed in Asian population	• Better than Friedewald at elevated TG • Simple calculation	• Less accurate than Martin-Hopkins • Population-specific performance	• Moderate hypertriglyceridemia • Asian populations

Table 2: Comparative Summary of LDL-C Estimation Methods: Accuracy and Availability"

Method	Accurate at High TG?	Accurate at Low LDL-C?	Widely Available?
Friedewald	No (TG > 400 mg/dL)	No	Yes
Martin-Hopkins	Yes	Yes	Increasing
Sampson Equation	Up to 800 mg/dL	Yes	Emerging
Direct Measurement	Yes	Yes	Costly

Table 3: Comparison of Methods for Estimating LDL-C

Parameter	Friedewald Formula	Martin-Hopkins Method	Sampson Equation	Direct Measurement
Formula Basis	LDL = TC − HDL − (TG/5)	LDL = TC − HDL − (TG/adjustable factor based on non-HDL and TG levels)	LDL = TC − HDL − VLDL (using logarithmic regression model)	Direct enzymatic or chemical measurement of LDL in plasma
TG Limitations	Invalid if TG > 400 mg/dL	Valid at TG > 400 mg/dL	Valid up to TG 800 mg/dL	No TG-related limitation
Acuracy at Low LDL-C (<70 mg/dL)	Poor	High	High	High

Assumption of TG:VLDL Ratio	Fixed ratio of 5	Variable ratio from 180-cell table	No fixed ratio; regression-based VLDL estimation	Not applicable
Suitability for High TG/Diabetic Patients	Poor	Improved accuracy	Excellent	Ideal
Strengths	Simple, cost-free, convenient	Better accuracy across LDL/TG spectrum	Highly accurate in complex lipid profiles; robust TG handling	True measurement; no estimation involved
Weaknesses	Inaccurate at high TG, low LDL-C; fixed assumptions	Requires look-up tables or software for adjustable factor	Computationally intensive; not universally adopted	Expensive; not routinely available in all clinical labs
Key References	Friedewald et al., 1972 [1]	Martin et al., JAMA, 2013 [2]	Sampson et al., JAMA Cardiology, 2020 [3]	Warnick et al., Clin Chem, 2002 [4]

Table 4: Comparative Overview of LDL-C Estimation Techniques

Criteria	Friedewald Formula	Martin-Hopkins Method	Sampson Equation	Direct Measurement
Underlying Principle	LDL-C = TC – HDL – (TG/5)	LDL-C = TC – HDL – (TG/adjustable factor based on non-HDL-C and TG)	LDL-C = TC – HDL – estimated VLDL-C (via regression modeling)	Enzymatic or chemical quantification of LDL directly in plasma
Triglyceride Restrictions	Not valid when TG exceeds 400 mg/dL	Applicable for TG values >400 mg/dL	Accurate up to TG levels of 800 mg/dL	No TG-related constraint
Precision at Low LDL-C (<70 mg/dL)	Limited; tends to underestimate	High accuracy	High accuracy	Consistently reliable
TG:VLDL-C Ratio Basis	Assumes fixed 5:1 ratio	Uses adaptive factor derived from large dataset (180-cell matrix)	Uses variable regression-based estimation	Not applicable
Usefulness in Hypertriglyceridemia or Diabetes	Inadequate	More accurate in these populations	Performs very well	Optimal method

Clinical Implications: The Friedewald equation effectively estimates low-density lipoprotein cholesterol (LDL-C) in fasting patients with triglyceride (TG) levels below 400 mg/dL, but its accuracy declines in complex cases, such as low LDL-C or elevated TG [39,40]. For patients targeting LDL-C below 70 mg/dL or with TG between 150 and 399 mg/dL, the Martin-Hopkins equation provides greater precision, particularly in statin-treated individuals.

In severe hypertriglyceridemia (TG 400–800 mg/dL) or non-fasting states, the Sampson-NIH equation is more reliable. Non-HDL cholesterol (non-HDL-C) and apolipoprotein B (apoB) serve as effective markers for dyslipidemia or diabetes, while direct LDL-C assays are preferred when precision is critical, despite higher costs. Inaccurate LDL-C estimation may lead to undertreatment or overtreatment, potentially affecting atherosclerotic cardiovascular disease (ASCVD) outcomes.

Large cohort studies (>198,000 patients) reveal discrepancies between Friedewald and Sampson/Martin methods that can influence statin therapy decisions, emphasizing the need for population-specific validation, as seen in studies from Saudi Arabia and Portugal [56].

Advanced Lipoprotein Analysis: Advanced techniques offer detailed insights into lipoprotein particle characteristics beyond standard lipid profiles, enhancing cardiovascular risk assessment.

Nuclear Magnetic Resonance (NMR) Spectroscopy: NMR spectroscopy measures lipoprotein particle concentration and size by exploiting their magnetic properties, quantifying LDL particle count (LDL-P), LDL and HDL particle sizes, VLDL and IDL subfractions [41]. LDL-P is often a stronger predictor of cardiovascular risk than LDL-C, especially in metabolic syndrome or diabetes, identifying high-

risk individuals with normal or modestly elevated LDL-C [42].

Ion Mobility Analysis: Ion mobility analysis separates lipoproteins by size and charge, directly measuring particle concentration and subfraction distribution [43]. This method provides a comprehensive profile of lipoprotein subclasses, aiding in the identification of subtle risk factors not detected by routine lipid panels.

Gradient Gel Electrophoresis: Gradient gel electrophoresis characterizes LDL and HDL subfractions by size, notably identifying small, dense LDL particles linked to increased cardiovascular risk [44]. This technique complements other advanced methods for detailed lipid analysis.

Clinical Utility: Advanced lipoprotein analysis is most valuable for patients with metabolic syndrome, diabetes, familial predisposition to premature cardiovascular disease (CVD), or discordant lipid profiles, as well as for assessing residual risk in statin-treated individuals [45]. While these methods enhance risk stratification, their routine clinical use is still under evaluation.

Clinical Considerations for Method Selection: Selecting an appropriate lipid assessment method depends on patient characteristics, clinical context, and resource availability. For general population screening, the Friedewald equation (Table 1) is cost-effective for fasting individuals with TG below 200 mg/dL and LDL-C above 70 mg/dL, assuming no specific dyslipidemias.

In high-risk patients targeting LDL-C below 70 mg/dL, direct measurement or the Martin-Hopkins equation offers superior accuracy. For hypertriglyceridemia, the Martin-Hopkins equation is recommended for TG levels of 200–400 mg/dL, while the Sampson equation or direct LDL-C measurement is advised for TG exceeding 400 mg/dL, with non-HDL-C and apoB as alternative targets. Non-fasting samples benefit from direct LDL-C measurement, non-HDL-C, or apoB assessment. Genetic dyslipidemias may require direct measurement, advanced lipoprotein analysis (e.g., NMR or ion mobility), or genetic testing. In cases of discordant risk profiles, measuring apoB or lipoprotein (a) (Lp(a)) alongside advanced techniques improves risk evaluation [46]. Resource constraints, laboratory capabilities, and regional practices also guide method choice, with Martin-Hopkins and Sampson equations offering improved accuracy over Friedewald without additional costs in resource-limited settings. Method selection should account for fasting status, TG levels, cardiovascular risk, and target LDL-C values to optimize patient outcomes.

Future Directions

Global utility and clinical reliability

Martin-Hopkins and Sampson-NIH Models: Further validation of the Martin-Hopkins and Sampson-NIH LDL-C estimation models across diverse ethnic populations is essential to ensure their accuracy and generalizability. [47] These models have shown promise in specific cohorts, but broader studies are needed to confirm their applicability worldwide. . Despite clear advantages, barriers to adopting newer equations include clinical inertia and lack of system-level integration [57].

Assay Standardization

Development of Standardized Direct LDL-C Assays: There is a pressing need to develop affordable, reproducible, and standardized direct LDL-C assay methods.[48] Such standardization would improve clinical consistency and facilitate better comparison across different laboratories and studies.

Computational Integration

Embedding Machine Learning Algorithms in Clinical Systems: Integrating machine learning (ML) algorithms into electronic health record (EHR) systems and point-of-care platforms can enhance real-time LDL-C estimation and support clinical decision-making.[49] This integration would allow for more personalized and efficient patient care.

Novel Biomarkers

Investigation of Lipoprotein (a) [Lp(a)] and Small Dense LDL: Beyond traditional LDL-C, further research into lipoprotein(a) [Lp(a)] and small dense LDL particles is warranted due to their potential roles in refining chronic disease profiling .[50] Elevated Lp(a) levels have been associated with increased risk of heart disease and stroke, and recent studies have highlighted the need for routine screening of these biomarkers to aid in preventive measures .

Digital Health

Advancement of Wearable Lipid Monitoring Platforms: Innovation in wearable biosensors and digital platforms for continuous lipid monitoring holds promise for personalized lipid management. [51]Such technologies could enable real-time tracking of lipid levels, allowing for timely interventions and improved patient outcomes.

Non-Fasting Standards

Establishment of Global Non-Fasting Lipid Testing Protocols: Establishing globally accepted protocols for non-fasting lipid testing will enhance convenience and diagnostic accessibility without compromising accuracy.[52] Extensive

observational data indicate that non-fasting lipid profiles are comparable to fasting profiles in predicting cardiovascular disease, leading to recommendations for routine use of non-fasting lipid profile.

International Collaboration

Ensuring Equitable Access to Innovations: International collaboration and equitable resource distribution are paramount to ensure global access to emerging lipid assessment technologies and innovations.[53] Such collaboration can facilitate the sharing of knowledge, standardization of practices, and reduction of disparities by improving access to innovative diagnostic tools and treatment.

Summary and Conclusion

Accurate lipid estimation plays a vital role in both clinical diagnostics and metabolic research. Traditional methods like the Friedewald equation, while historically foundational, show reduced reliability in individuals with dyslipidemia, hypertriglyceridemia, or metabolic disorders. Modern approaches—notably the Martin-Hopkins and Sampson equations—represent improved precision by incorporating variable triglyceride-to-VLDL-C ratios and algorithmic refinements. Additionally, direct LDL-C assays and advanced lipoprotein profiling technologies provide more robust assessments across diverse physiological and pathological states. These evolving methodologies support enhanced diagnostic accuracy and deeper insights into lipid metabolism, making them valuable tools beyond cardiovascular contexts, including endocrine, hepatic, and systemic disease research.

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