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Concordance between LDL Cholesterol estimated by various formulas and directly measured LDL cholesterol

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Abstract
Background: Low density lipoprotein cholesterol (LDL-C) has been established as a major risk factor for cardiovascular diseases. Numerous algorithms have been developed for LDL-C calculation; nonetheless, the precision of these equations varies across different ethnicities. This study aimed to quantify the discordance in LDL-C levels between (the DeLong's, Friedewald, Sampson and Martin/Hopkins equations) and compare them with direct LDL-C (dLDL-C).
Materials and Methods: A total of 1020 patients, aged between 18-65 years were included in the study. LDL-C measured by friedewald's formula, deLong's formula, sampson's formula, de Cordova's formula, anandaraja formula and martin's formula were compared with directly measured LDL-C. Comparison of calculated LDL-C with directly measured LDL-C was done at Triglyceride (TG) range of 400 mg/dL. Statistical analysis was done utilizing Lin's concordance coefficient (CCC) and two paired t-test.
Results: Of the total 1020 samples, there were 619 males and 401 females. The mean age observed was 40.9±8.0 years. The formulas with the best CCC were DeLong (0.962) and Sampson (0.960) with no relevant differences. The extended Martin/Hopkins formula (0.935) and the Friedewald formula (0.949) also executed well. The Anandaraja (0.887) and de Cordova (0.924) equations exhibited inferior performance. The mean differences observed was in the range of 1.6 to 9.68 mmol/L.
Conclusion: In the present study, DeLong's and Sampson formula showed highest concordance and low percentage of errors compared to Frieldwald's, Martin/Hopkins, Anandaraja and de Cordova's formula.

Keywords: Low-density lipoprotein cholesterol (LDL-C), Lin's Concordance Coefficient, Triglycerides, dyslipidemia

Introduction

Low-density lipoprotein cholesterol (LDL-C) is a well-established biomarker for evaluating cardiovascular risk and conducting lipid-lowering therapy. It serves as a pivotal therapeutic target in the prevention and management of atherosclerotic cardiovascular disease (ASCVD) [1]. While direct measurement methods, such as homogeneous enzymatic assays, are available, they are often cost-prohibitive and not routinely used in all clinical settings due to higher cost, limited availability and technical complexity [2].

Consequently, LDL-C is frequently estimated using mathematical formulas based on total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). The Friedewald formula, is the most prevalently utilized method for calculating LDL-C [3]. However, its accuracy diminishes significantly in cases with elevated TG levels (>400 mg/dL), low LDL-C concentrations or non-fasting samples [4]. To address these limitations, alternative formulas such as the Martin/Hopkins equation and the more recent Sampson equation have been developed, offering improved precision, particularly in patients with dyslipidemia or hypertriglyceridemia [5].

Despite these advancements, discrepancies continue to exist between estimated and directly measured LDL-C values, which may lead inappropriate therapeutic interventions. Therefore, understanding the concordance between calculated and directly measured LDL-C levels is crucial for ensuring optimal clinical management. This study aims to evaluate the agreement

between LDL-C values derived from multiple estimation formulas and those obtained through direct measurement in a clinical population.

Materials and Methods

Study design: A prospective study

Study site: Department of Biochemistry, Yashoda Hospital, a multi-super specialty hospital in Secunderabad, Telangana, India.

Study duration: This study was conducted from 01 Feb 2025 to 28 Feb 2025

Inclusion criteria: The study includes patients of age above 18 years, who had complete lipid profiles.

Exclusion criteria: The study excludes patients with diabetes mellitus, hypothyroidism, liver cirrhosis, chronic hepatitis, chronic kidney disease, pancreatitis, patients on active medication including steroids, statins, omega-3 fatty acids.

Subsequent to enrolment, an elaborate demographic attributes and anthropometric parameters was meticulously conducted. Blood samples were taken by venipuncture to assess the participants' lipid profiles, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Lipid profiles were directly determined by the standard homogenous enzymatic technique using an automatic chemistry analyzer. LDL-C was calculated utilizing the following equations: DeLong's, friedewald's, sampson's, anandaraja, de cordova and extended Martin hopkin's formula. Bland altman plots were also created to determine the levels of agreement These limits define the range within which the differences in data between one method and another are found. The narrower the range, better the agreement.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0. Pearson correlation coefficients were used to assess the linear relationship between calculated and directly measured LDL-C values. Concordance was further assessed using intraclass correlation coefficients and mean absolute differences. $p<0.05$ was considered statistically significant.

Results

Table 1 presents, a total of 1,020 subjects were included in the study, comprising 619 males (60.68%) and 401 females (39.32%). The mean age of the participants was 40.9 ± 8.0 years. The average body weight was 60.42 ± 10.2 kg, while the mean height was 158.86 ± 8.6 cm. The mean body mass index (BMI) was 23.96 ± 3.98 kg/m², indicating that the study population largely fell within the normal weight range.

Table 2 presents the concordance analysis of various LDL-C estimation formulas compared to directly measured LDL-C values. For formulas restricted to triglyceride (TG) levels ≤400 mg/dL, the DeLong formula showed the highest concordance with a Lin's Concordance Correlation Coefficient (CCC) of 0.962, the narrowest limits of agreement (22 to 18 mg/dL), and a minimal mean difference (-1.6 mg/dL). The Sampson and Friedewald formulas also demonstrated high concordance (CCC = 0.960 and 0.949, respectively), though with slightly wider limits of agreement and greater mean differences. Among formulas applicable without TG restriction, the Cordova formula outperformed the Anandaraja formula, showing higher concordance (0.924 v/s. 0.887) and narrower agreement limits. The Extended Martin/Hopkins formula, though restricted to TG ≤400 mg/dL, showed a moderate CCC (0.935) with the largest mean difference (9.68 mg/dL) among all formulas.

Discussion

This study assessed the concordance between various LDL-C estimation formulas and directly measured LDL-C values, using Lin's concordance correlation coefficient (CCC), limits of agreement (LoA), and mean difference. Among the formulas restricted to triglyceride (TG) levels ≤400 mg/dL, the DeLong formula demonstrated the highest concordance (CCC = 0.962), with narrow LoA and minimal bias, suggesting superior agreement with direct measurement. These findings are consistent with previous research by David-Pardo *et al*, the DeLong method's robustness across a wide range of lipid profiles [6].

The Sampson formula also showed excellent concordance (CCC = 0.960) in our study, supporting prior findings by Shi *et al*., who validated the formula in a large, diverse cohort and demonstrated improved accuracy over Friedewald in patients with both normal and elevated triglyceride levels [7].

The Friedewald equation account for the prime methodological paradigm for the quantification of low-density lipoprotein cholesterol (LDL-C) across most clinical laboratories on a global scale. However, many studies reported that the accuracy of Friedewald's equation was prone to decrease in some conditions, such as in low LDL-C and/or high TG levels [8]. The Friedewald formula, despite widespread clinical use, showed relatively lower concordance (CCC = 0.949) and wider LoA in our study. Numerous studies have reported clinically significant underestimation of LDL-C by Friedewald in patients with metabolic syndrome, diabetes, and cardiovascular disease [9]. Further studies with various ranges of TG and LDL-C are needed to generalize the results of our study.

The extended Martin-Hopkins formula, developed using a stratified median TG: VLDL-C ratio derived from a large clinical database, showed moderate concordance (CCC = 0.935) in our cohort. Although this formula has demonstrated superior accuracy over Friedewald, particularly in patients with low LDL-C and varying TG levels, but its performance in our population was suboptimal, with an outstanding positive bias (mean difference = 9.68 mg/dL) [10].

Among the unrestricted formulas, the de Cordova and Anandaraja equations showed lesser concordance (CCC = 0.924, 0.887) respectively compared to other equations. While Cordova *et al*. reported acceptable performance of their equation in general populations [11]. The Anandaraja formula, despite being derived from an Indian population and designed for broad applicability, showed wide LoA (36/35 mg/dL) and weaker concordance, consistent with other evaluations indicating its limited accuracy in high TG contexts [12]. Current study results on concordance of de Cordova and Anandaraja equations were similar with the study done by Rerksuppaphol *et al* with lesser concordance compared with other equations [13].

This is one of the finest studies to evaluate all six formulas simultaneously in India, allowing us to compare their performance. It is noteworthy that the DeLong formula, in spite of having the arithmetically highest CCC within our population, remains among the least extensively validated or scrutinized in international research settings. Collectively, our results support the growing body of evidence favoring DeLong and Sampson formulas for estimating LDL-C with greater fidelity to direct measurement, especially in populations with moderate-to-elevated triglyceride levels. While Friedewald remains widely used, its known limitations reinforce the need for adopting more accurate alternatives in clinical decision-making. Crucially, the extrapolation of LDL-C estimation equations should be validated in local populations, as performance may influenced by ethnicity, comorbidities and laboratory assessment.

Table 1: Baseline characteristics of study population

Parameter	Mean ±SD
Age (Years)	40.9±8.0
Male (%)	619 (60.68%)
Female (%)	401 (39.32%)
Weight (kg)	60.42±10.2
Height (cm)	158.86±8.6
BMI (kg/m^2)	23.96±3.98

Table 2: Mean differences, Lin's Concordance Coefficient, and Limits of agreement between the estimated LDL-C and directly measured LDL-C

LDL-C formula	TG Limit	Lin's Concordance Coefficient	Limits of Agreement	Difference
DeLong	400 mg/dL	0.962	22/18	-1.6
Friedewald	400 mg/dL	0.949	-18/26	3.82
Sampson	400 mg/dL	0.960	-18/22	1.89
Anandaraja	Unrestricted	0.887	36/35	-0.24
deCordova	Unrestricted	0.924	-24/28	1.95
Martin Hopkin's	400 mg/dL	0.935	-9/28.38	9.68

Conclusion

The outcomes of the present analysis revealed that the DeLong and Sampson formulas exhibited better concordance for estimating directly measured LDL-C. Additionally, the Friedewald and extended Martin/Hopkins equations also exhibit commendable accuracy. In disparity, the Anandaraja and de Cordova formulas performance was not up-to mark and are not suggested.

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Declarations

- **Funding:** No funding sources
- **Conflict of interest:** None declared
- **Ethical approval:** Not required

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