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Original Article

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Comparison of Multiple Equations for Low-Density Lipoprotein Cholesterol Calculation Against the Direct Homogeneous Method

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Due to the nature of the research, supporting data is not available.

ABSTRACT

Objective: Several equations have been proposed as alternatives for the reference method of measuring low-density lipoprotein cholesterol (LDL-C). This study aimed to evaluate these alternatives in comparison to the homogeneous method and validate their clinical utility.
Methods: Data on the lipid profiles of 1,006 Sudanese individuals were analyzed. The paired t-test was used to compare the results of direct and calculated LDL-C. Bland-Altman plots were used to demonstrate the differences between the measured and calculated LDL-C against the mean values. Linear regression was conducted, using the correlation coefficient (r) to quantify the relationship between methods. The bias between measured and calculated LDL-C was compared to the National Cholesterol Education Program Laboratory Standardization Panel criteria (i.e., accuracy within ±4% of expected values).
Results: The Martin and Anandaraja equations showed no significant difference compared to directly measured LDL-C (p>0.05). The DeLong equation indicated an insignificant difference only with a 99% confidence interval (p>0.01). The Martin, DeLong, and Teerakanchana equations exhibited the smallest limits of agreement, with data points concentrated closely around the mean difference line. Linear regression analysis revealed strong positive correlations (r>0.8) for most equations, except for the Ahmadi equation. The DeLong, Rao, and Martin equations demonstrated superior performance for LDL cutoff points (bias within ± 4%). The DeLong formula also showed superior performance at different lipid levels, closely followed by the Martin equation (bias within ±4%).
Conclusion: The DeLong and Martin equations outperformed others, such as the widely used Friedewald equation, in calculating LDL-C. Further validation studies are needed.

Keywords: Low density lipoprotein cholesterol; Coronary heart disease; Methodological study

INTRODUCTION

An elevated level of low-density lipoprotein cholesterol (LDL-C) is a significant risk factor for coronary heart disease (CHD), which is currently the primary cause of morbidity and mortality worldwide. The National Cholesterol Education Program Adult Treatment Panel III

Author Contributions

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(NCEP-ATP III) has outlined the primary goals of therapy and the cutoff points for initiating treatment for hypercholesterolemia based on LDL-C levels.[1]

Accurate estimation of LDL-C is essential for the correct diagnosis and monitoring of patients with CHD. β-quantification is regarded as the reference method for estimating LDL-C because it avoids potential interferences from other lipoproteins. However, β-quantification, which involves ultracentrifugation and chemical precipitation, presents several challenges. It is labor-intensive, time-consuming, and necessitates the use of an ultracentrifuge.[2]

The Friedewald equation is recommended as a suitable alternative for calculating LDL-C in cases where triglyceride (TG) levels are below 400 mg/dL in routine clinical practice globally.[3] This equation presumes a constant ratio of 5 between TG and very low-density lipoprotein cholesterol (VLDL-C); however, this ratio can fluctuate. Therefore, the accuracy of LDL-C measurements may be compromised in patients with conditions such as diabetes mellitus, alcoholic liver disease, and chronic renal failure, particularly those undergoing dialysis.[4-6]

To overcome these limitations, several alternative equations have been proposed for calculating LDL-C. These equations use varying constant ratios of TG to VLDL-C[7] or different fixed factors between total cholesterol (TC), TG, and high-density lipoprotein cholesterol (HDL-C).[8-14]

A novel equation developed by Martin et al.[15] applies an adjustable factor determined as the N-strata-specific median TG: VLDL-C ratio based on TG and non-HDL-C concentrations to calculate LDL-C. This equation has proven to provide a more accurate estimation of LDL-C than the Friedewald equation.[16,17]

This study aimed to compare the performance of 10 published equations with the routinely accepted homogeneous method for estimating LDL-C, in order to validate their application not only in hospitalized patients but also in the general Sudanese population.

MATERIALS AND METHODS

1. Study subjects

In total, 1,006 lipid profile reports were analyzed from patients over 18 years old who had their TC, TG, HDL-C, and LDL-C levels tested between January and May 2018 at Alaml National Hospital and Alribat University Hospital in Khartoum, Sudan.

This study was reviewed and approved by the research committee of the faculty of Medical Laboratory Sciences at the University of Khartoum, Sudan (UofK/FMLS/M.Sc.ByCourses/2018).

2. Measurement of lipid profile

TC and TG were measured using enzymatic spectrophotometric methods, while HDL-C and LDL-C were estimated using the direct homogeneous method with a Mindray autoanalyzer (Mindray BS-380). The analytical performance of the direct LDL-C method used in the study was as follows: The assay range of the method was 0–370 mg/dL, and the sensitivity was 0.627 mg/dL. The within-run imprecision coefficient of variation (%) was 1.7 for both low and high results. The within-run imprecision coefficient of variation (%) for another set of results was 3.3 for low results and 2.0 for high results. Accuracy, when compared to other

instruments, was demonstrated with a regression analysis yielding Y=1.017x +1.7, and a correlation coefficient (*r*) of 0.990.

An internal quality control system was implemented to ensure the reliability of results, utilizing both normal and pathological biochemistry control serum (human) (Biosystems). The system employed Levey-Jennings charts along with Westgard's Multi-Rules, and all results remained within the established control limits.

LDL-C was calculated using the equations shown in **Table 1** with Microsoft Office Excel 2007. The Martin equation for LDL-C was determined using an LDL-C calculator instead of the N-strata-specific median TG:VLDL-C ratio (http://www.ldlcalculator.com).

3. Statistical analysis

Statistical analysis was performed using SPSS version 16 (SPSS Inc.). The selection of statistical tests was guided by Westgard's comparison of methods experiment.[18] Average values are reported as mean ± standard deviation (SD). The paired *t*-test was employed to compare direct and calculated LDL-C, with a *p*-value <0.05 indicating significant difference between the results of calculated and measured LDL-C. A Bland-Altman plot illustrates the differences between directly measured and calculated LDL-C plotted against the mean of the measured and calculated LDL-C. It also shows the limits of agreement (LOA), which represent the range within which 95% of the differences between the two methods fall. A narrow LOA suggests a high level of agreement between the methods. The closer the data points are to the mean difference line and the narrower the LOA, the better the agreement between the direct and calculated LDL-C values. Linear regression was employed to illustrate the relationship between calculated and directly measured LDL-C, and to compute the correlation coefficient as a numerical value for this relationship. The regression formula for each equation was calculated as $Y_c=A+bX_c$. The expected values were determined at LDL-C cutoffs designated by NCEP-ATP III at 100, 130, 160, and 190 mg/dL. Subsequently, the difference between the expected and calculated LDL-C, termed "bias," was calculated. This bias was then compared to the criteria specified by the NCEP Laboratory Standardization Panel, which requires accuracy within ±4% of the expected values.

TG and HDL-C were categorized into subgroups based on cutoff values defined by NCEP-ATP III: <150, 150–199, 200–399, and >400 mg/dL for TG, and <40, 40–59, and >60 mg/dL for HDL-C. The accuracy of equations within these subgroups was assessed by examining the bias between the expected and calculated LDL-C. This bias was then evaluated against the

Table 1. Equations for LDL-C calculations

Formula	Equation
Friedewald	TC – HDL-C – TG/5
De Cordova	0.7541 (TC – HDL-C)
Hattori	(0.94 TC) – (0.94 HDL-C) – (0.19 TG)
Anandaraja	(0.9 TC) – (0.9 TG/5) – 28
Chen	0.9 (TC – HDL-C) – (0.1 TG)
Teerakanchana	(0.91 TC) – (0.634 HDL-C) – (0.111 TG) – 6.755
Ahmadi	(TC/1.19) – (HDL-C/1.1) + (TG/1.9) – 38
DeLong	TC – (HDL-C + 0.16 TG)
Rao	(4.7 TC – 4.364 HDL-C – TG)/4.487
Martin	TC – HDL-C – TG/Adjusted Factor

LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

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criteria set by the NCEP Laboratory Standardization Panel, which stipulates that acceptable performance is achieved when accuracy is within ±4% of expected values.

RESULTS

The mean ± SD values of TC, TG, HDL-C, and directly measured LDL-C were 164±44.7, 120±66.4, 44.1±12.1, and 99.2±36.7 mg/dL, respectively. The mean ± SD values for calculated LDL-C are shown in **Table 2**.

The paired *t*-test was used to compare the results of direct and calculated LDL-C (**Table 2**). The results from the Martin and Anandaraja equations showed no significant difference between directly measured and calculated LDL-C ($p>0.05$). The DeLong results would be considered insignificant if a 99% confidence interval were chosen ($p=0.0203$, which is >0.01).

A Bland-Altman graphical plot was used to visually present the results, as shown in **Fig. 1**. The Martin, DeLong, and Teerakanchana equations demonstrated the smallest LOA, with data points concentrated closely around the mean difference line.

The relationship between direct and calculated LDL-C is illustrated through linear regression plotting in **Fig. 2**. All the equations demonstrated a strong positive correlation between measured and calculated LDL-C ($r>0.8$), with the exception of the Ahmadi equation, which exhibited only a moderate positive correlation ($r>0.664$).

Linear regression formulas were used to evaluate the performance of each equation at LDL-C cutoff values determined by the NCEP-ATP III. The bias for each equation was evaluated at ±4, 5.2, 6.4, and 7.6 mg/dL for the 100, 130, 160, and 190 mg/dL cutoff values, respectively, as shown in **Table 3**. The DeLong, Rao, and Martin equations demonstrated superior performance across the various LDL-C cutoff values. The Teerakanchana equation also showed acceptable performance at all cutoff values except for LDL-C 190 mg/dL. The Friedewald, Anandaraja, and Chen equations only performed acceptably at the LDL-C 100 mg/dL cutoff. In contrast, the performance of the De Cordova, Hattori, and Ahmadi equations was deemed unacceptable across the different LDL-C cutoff values.

Table 2. Comparison of calculated LDL-C using equations against direct LDL-C, using the *t*-test

Formula	Mean ± SD (mg/dL)	Standard error of mean	t	df	Sig. (2-tailed)	Mean of difference (mg/dL)	Standard error of difference (mg/dL)	95% CI (mg/dL)
Friedewald	95.9±39.45	1.24	5.31	1,005	<0.0001	3.341	0.629	2.104 to 4.577
De Cordova	90.4±32.71	1.03	15.09	1,005	<0.0001	8.797	0.583	7.652 to 9.942
Hattori	89.9±37.06	1.17	15.43	1,005	<0.0001	9.34	0.605	8.150 to 10.529
Anandaraja	98.0±37.70	1.19	1.77	1,005	0.0774*	1.187	0.672	−0.132 to 2.507
Chen	95.9±36.65	1.16	5.65	1,005	<0.0001	3.267	0.578	2.131 to 4.403
Teerakanchana	101.2±37.09	1.17	3.46	1,005	0.0006	−2.002	0.579	−3.139 to −0.866
Ahmadi	123.0±60.64	1.91	16.68	1,005	<0.0001	−23.808	1.433	−26.624 to −20.991
DeLong	100.6±39.92	1.26	2.33	1,005	0.0203†	−1.440	0.619	−2.656 to −0.223
Rao	102.1±41.28	1.30	4.37	1,005	<0.0001	−2.886	0.660	−4.183 to −1.589
Martin	98.0±39.05	1.23	1.91	1,005	0.0565*	1.149	0.602	−0.034 to −2.331

LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; t, the test statistic (denoted t); df, degrees of freedom; Sig. (2-tailed), the *p*-value corresponding to the given test statistic t with degrees of freedom; CI, confidence interval of the difference.
*The *p*-value is >0.05, indicating an insignificant difference between calculated and direct LDL-C; †The *p*-value is >0.01, indicating an insignificant difference between calculated and direct LDL-C.

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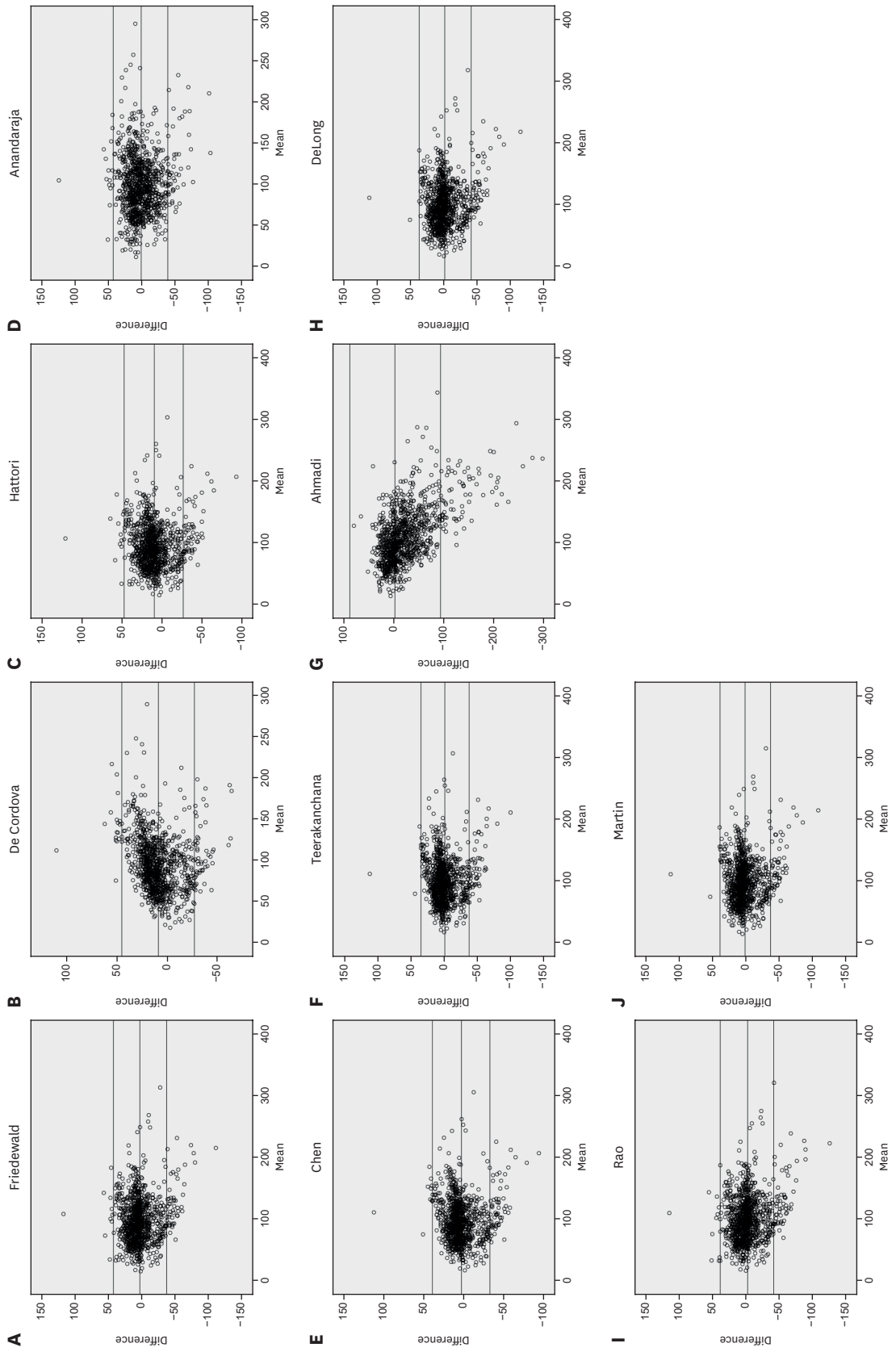

Fig. 1. Bland Altman plotting for calculated LDL-C values against directly measured LDL-C values.
(A) Friedewald, (B) De Cordova, (C) Hattori, (D) Anandaraja, (E) Chen, (F) Teerakanchana, (G) Ahmadi, (H) DeLong, (I) Rao, and (J) Martin formulas.
LDL-C, low-density lipoprotein cholesterol.

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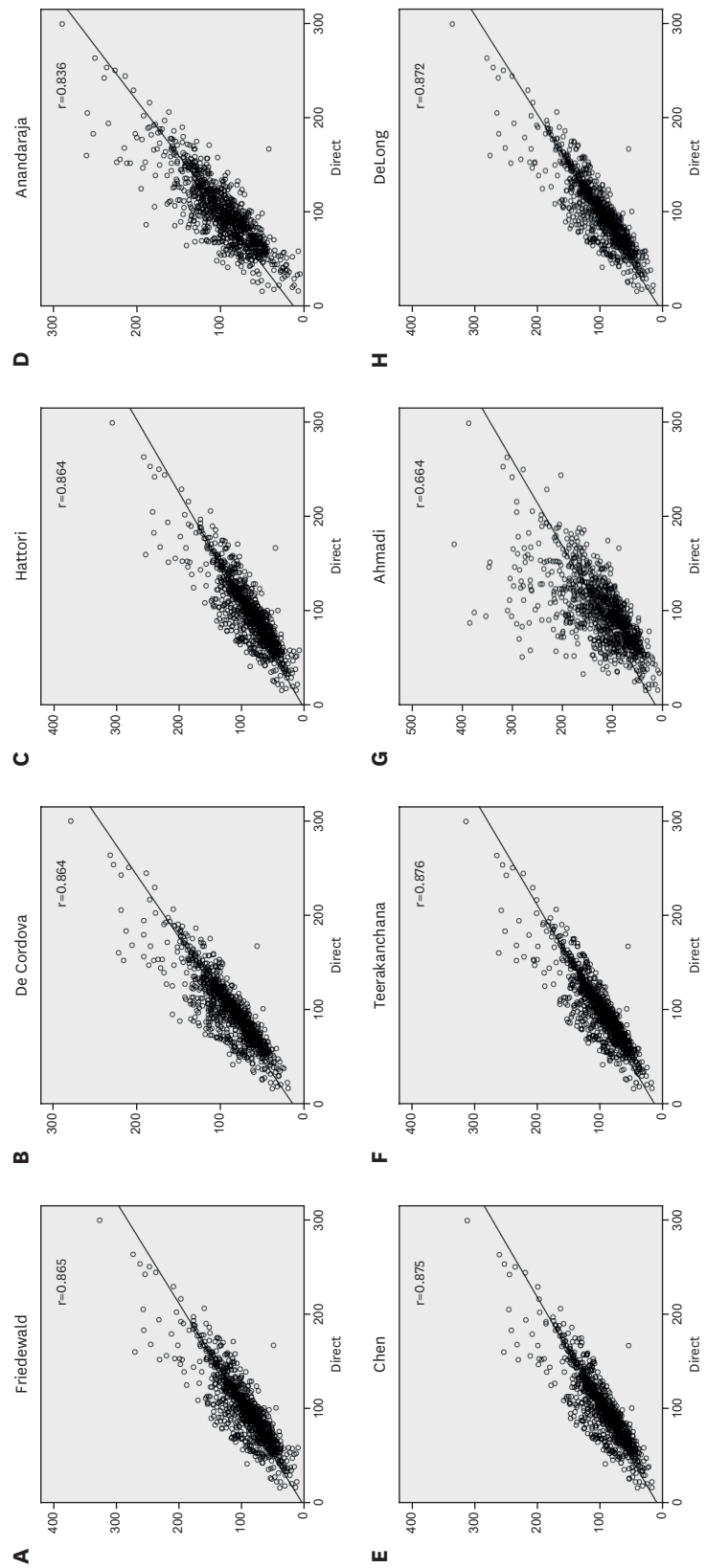

Fig. 2. Linear regression plots for calculated LDL-C values using 10 equations against directly measured LDL-C values.
(A) Friedewald, (B) De Cordova, (C) Hattori, (D) Anandaraja, (E) Chen, (F) Teerakanchana, (G) Ahmadi, (H) DeLong, (I) Rao, and (J) Martin formulas.
LDL-C, low-density lipoprotein cholesterol.

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Table 3. Comparison between equations and the direct method for LDL-C estimation at LDL-C cutoff points

Formula	$Y_c = A + bX_c$							
	X_c 100 mg/dL		X_c 130 mg/dL		X_c 160 mg/dL		X_c 190 mg/dL	
	Y_c (mg/dL)	Bias (mg/dL)	Y_c (mg/dL)	Bias (mg/dL)	Y_c (mg/dL)	Bias (mg/dL)	Y_c (mg/dL)	Bias (mg/dL)
Friedewald	96.6	−3.4*	124.5	−5.5	152.4	−7.6	180.3	−9.7
De Cordova	91.1	−8.9	114.2	−15.8	137.3	−22.6	160.4	−29.6
Hattori	90.5	−9.5	116.7	−13.3	142.9	−17.1	169.1	−20.9
Anandaraja	98.7	−1.3*	124.4	−5.6	150.2	−9.8	176.0	−14.0
Chen	96.6	−3.4*	122.8	−7.2	149.1	−10.9	175.3	−14.7
Teerakanchana	101.9	1.9*	128.5	−1.5*	155.1	−4.9*	181.6	−8.4
Ahmadi	123.8	23.8	156.8	26.8	189.7	29.7	222.7	32.7
DeLong	101.4	1.4*	129.9	−0.1*	158.3	−1.7*	186.8	−3.2*
Rao	102.8	2.8*	131.9	1.9*	161.0	1.0*	190.1	0.1*
Martin	98.8	−1.2*	126.7	−3.3*	154.6	−5.4*	182.5	−7.5*

LDL-C, low-density lipoprotein cholesterol; Y_c, corresponding value from regression line; A, intercept; b, slope; X_c, LDL-C cutoff values.
*Acceptable, as bias is within ±4% of X_c.

The performance of 10 equations in calculating LDL-C across various levels of TG and HDL-C is detailed in **Tables 4** and **5**. Except for the TG >400 mg/dL subgroup, the DeLong equation consistently demonstrated acceptable performance. The Teerakanchana and Martin equations performed acceptably in the TG 150–199 mg/dL and 200–399 mg/dL subgroups. Meanwhile, the Rao equation only showed acceptable performance in the TG 150–199 mg/dL subgroup.

Table 4. Comparison between equations and the direct method for LDL-C estimation in different TG subgroups

Formulas	TG range															
	<150 mg/dL (n=794)				150–199 mg/dL (n=112)				200–399 mg/dL (n=91)				≥400 mg/dL (n=9)			
	Bias when X_c (mg/dL)				Bias when X_c (mg/dL)				Bias when X_c (mg/dL)				Bias when X_c (mg/dL)			
	100	130	160	190	100	130	160	190	100	130	160	190	100	130	160	190
Friedewald	−2.5*	−5.1*	−7.7	−10.4	−5.9	−5.3	−4.7*	−4.2*	−10.7	−10.6	−10.4	−10.3	−23.8	−27.4	−30.9	−34.5
De Cordova	−12.0	−20.2	−28.4	−36.6	−3.7*	−10.5	−17.2	−24.0	6.4	−1.3*	−8.9	−16.5	25.2	16.7	8.2	−0.3*
Hattori	−8.5	−12.7	−17.0	−21.3	−11.9	−13.1	−14.4	−15.6	−16.6	−18.3	−20.0	−21.7	−29.0	−34.0	−38.9	−47.8
Anandaraja	1.2*	−3.1*	−7.4	−11.7	−9.2	−9.8	−10.4	−11.1	−15.3	−16.5	−17.7	−18.9	−28.4	−32.5	−36.5	−40.6
Chen	−4.5	−9.2	−14.0	−18.7	−1.9*	−4.2*	−6.6	−9.0	1.1*	−2.0*	−5.0*	−8.1	4.5	−0.8*	−6.2*	−11.5
Teerakanchana	1.5*	−2.7*	−7.0	−11.2	1.3*	−0.2	−1.7*	−3.2*	2.9*	0.6*	−1.6*	−3.8*	3.8*	−0.7*	−5.1*	−9.6
Ahmadi	6.9	5.2*	3.5*	1.7*	54.8	51.2	47.5	43.8	115	109	102	96	236	234	234	233
DeLong	1.4*	−0.9*	−3.2*	−5.5*	−0.8*	1.4*	2.1*	2.7*	−0.5*	−0.4*	−0.3*	−0.3*	−5.9	−8.9	−11.9	−15.0
Rao	4.4	3.0*	1.7*	0.3*	0.8*	1.4*	3.7*	5.9*	−7.3	−5.6	−3.9*	−2.1*	−23.8	−26	−28.1	−30.3
Martin	−2.4*	−5.2*	−8.1	−10.9	0.4*	−0.5*	−1.3*	−2.2*	3.8*	1.7*	−0.5*	−2.7*	12.7	5.6	−1.4*	−8.5

LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; n, number of individuals within the subgroup.
*Acceptable, as bias is within ±4% of the LDL-C cutoff value.

Table 5. Comparison between equations and the direct method for LDL-C estimation in different HDL-C subgroups

Formulas	HDL-C range											
	<40 mg/dL (n=354)				40–59 mg/dL (n=558)				≥60 mg/dL (n=94)			
	Bias when X_c (mg/dL)				Bias when X_c (mg/dL)				Bias when X_c (mg/dL)			
	100	130	160	190	100	130	160	190	100	130	160	190
Friedewald	−2.3*	−3.5*	−4.7*	−5.9*	−4.3	−7.3	−10.3	−13.3	−2.2*	−2.8*	−3.4*	−4.0*
De Cordova	−4.4	−10.2	−17.2	−23.6	−11.5	−18.6	−25.8	−33.0	−11.2	−17.5	−23.2	−28.9
Hattori	−8.4	−11.3	−14.3	−17.2	−10.2	−14.9	−19.6	−24.3	−8.2	−10.6	−13.0	−15.4
Anandaraja	−10.7	−13.7	−16.6	−19.6	1.1*	−5.0*	−10.9	−16.8	21.5	17.2	12.9	8.6
Chen	−0.3*	−3.4*	−6.5	−9.6	−5.1	−9.5	−13.8	−18.2	−4.4	−6.8	−9.2	−11.6
Teerakanchana	1.6*	−1.0*	−3.5*	−6.1*	1.3*	−3.1*	−7.4	−11.7	7.8	5.4	3.0*	0.5*
Ahmadi	43	45.8	48	51	14.7	18.9	23.1	27.0	5.7	10.9	15.0	19.7
DeLong	3.5*	2.9*	2.28	1.5*	0.1*	−2.2*	−4.6*	−6.9*	1.6*	1.6*	1.6*	1.6*
Rao	2.8*	2.9*	3.0*	3.1*	2.4*	0.4*	−1.5*	−3.5*	6.2	6.8	7.3	7.8
Martin	2.0*	0.7*	−0.7*	−2.1*	−3.1*	−5.8	−8.5	−11.2	−2.3*	−2.7*	−3.2*	−3.6*

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; n, number of individuals within the subgroup.
*Acceptable, as bias is within ±4% of LDL-C cutoff value.

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Across the HDL-C subgroups, the DeLong equation outperformed other equations, showing acceptable results in all subgroups. The Friedewald and Martin equations performed acceptably at HDL-C levels below 40 mg/dL and above 60 mg/dL. The Rao equation was acceptable in subgroups with HDL-C levels below 40 mg/dL and 40–59 mg/dL. In contrast, the Teerakanchana equation only showed acceptable performance in the subgroup with HDL-C levels below 40 mg/dL.

DISCUSSION

International guidelines for CHD treatment consistently highlight the importance of LDL-C assays in risk assessment and patient follow-up. The current recommendations from the NCEP for cardiovascular risk assessment depend on methods that are challenging to implement in routine clinical practice, particularly in third-world countries such as Sudan.[1]

The Friedewald equation, which is the commonly used method of estimating LDL-C, has several notable limitations. These include unreliable LDL-C estimates in patients with TG levels above 400 mg/dL, as well as in those with dyslipidemia, diabetes, kidney and liver diseases, and other metabolic conditions.[4-6] Additionally, the formula tends to perform poorly in the presence of extreme TC and TG values, which are often seen in individuals on atypical diets.[19]

All 10 equations analyzed in this study, except for the Ahmadi equation, demonstrated a correlation coefficient greater than 0.80, indicating strong agreement with the direct measurement of LDL-C. The lower correlation coefficient observed with the Ahmadi equation may be attributed to its derivation solely from patients with TC levels exceeding 250 mg/dL.[12]

We assessed the analytical performance of each equation using the NCEP Laboratory Standardization Panel criteria for acceptable performance. The equations developed by DeLong, Rao, and Martin demonstrated acceptable performance, particularly at various LDL-C cutoff points. In contrast, the Friedewald equation met the criteria only at the 100 mg/dL cutoff point. Our findings align with previous research indicating that the DeLong equation, which employs a factor of 6 instead of 5 as in the Friedewald equation, and the Martin equation, which uses a variable factor for TG:VLDL-C, perform better.[7,15]

We evaluated the impact of variations in TG and HDL-C concentrations on the calculated LDL-C using different equations across various subgroups. The DeLong equation demonstrated acceptable performance across different levels of TG and HDL-C, except when TG concentrations exceeded 400 mg/dL, which contradicts findings from the DeLong et al. study. However, only 9 individuals in the study had TG concentrations over 400 mg/dL, indicating that further research is needed in the Sudanese population to address this discrepancy.[7]

Although previous studies in American and Korean populations demonstrated that the Martin equation accurately calculated LDL-C, this study found limitations with the equation at TG levels below 150 mg/dL and above 400 mg/dL, and HDL-C levels between 40 and 59 mg/dL. This discrepancy may stem from the use of the calculator recommended by the authors, rather than deriving a novel factor specifically for the Martin equation. Additionally, it is possible that the novel factor required for the Sudanese population differs from what Martin originally reported.[15-17]

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One limitation of this study is that we used the direct homogeneous method as the comparative instead of the reference method for β quantification, due to the unavailability of an ultracentrifuge in Sudan. This study initially focused on the analytical performance of equations to provide a general overview of their effectiveness in the general population, as many samples are submitted to laboratories without accompanying clinical data. Future steps will involve evaluating the performance of these equations under various medical conditions and diseases, such as diabetes mellitus, obesity, and the effects of medications. Lipoprotein(a) (LP[a]), an LDL variant containing apolipoprotein(a), may have influenced LDL-C levels. In 2014, Sudanese researchers compared Lp(a) concentrations in patients with diabetes to those without diabetes, finding concentrations of 28.49±5.5 and 23.06±4.2 mg/dL, respectively. Assuming that Lp(a) cholesterol constitutes 30% of Lp(a) mass, the contributions would be 8.5 and 6.9 mg/dL, respectively. Therefore, the corrected mean LDL-C levels in our study would be 90.7 mg/dL for people with diabetes and 92.3 mg/dL for those without diabetes in the Sudanese population.[20] Another study conducted in 1991 assessed Lp(a) levels across seven ethnic groups, including Sudanese, and reported an Lp(a) concentration of 45.7±25.9 mg/dL in the Sudanese population. However, it is important to consider that Sudan is ethnically diverse, with over 500 ethnic groups, and the sample size of only 10 black Sudanese used in the reference study is insufficient to conclusively determine the impact of Lp(a) cholesterol on measured LDL-C levels.[21]

In conclusion, by employing various statistical tools to assess and visualize the agreement between different methods of LDL-C estimation, we determined that the DeLong equation and the Martin equation outperformed other methods, including the commonly used Friedewald equation. These findings suggest that the DeLong and Martin equations should be considered for clinical use. Further research and validation studies are recommended to confirm these results across diverse patient populations and clinical settings.

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