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Original Article

Development of a Modified Friedewald's Formula to Calculate Low-Density Lipoprotein in an Iranian Population

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What's Known

- Currently, clinical laboratories estimate low-density lipoprotein cholesterol (LDL-C) based on Friedewald's formula, which cannot be used for all triglyceride levels.

What's New

- A new formula is developed for the calculation of LDL-C: 0.857 total cholesterol - 0.915 high-density lipoprotein cholesterol - 0.115 triglycerides.
- Compared to other formulas, estimation by the proposed formula has the highest correlation with directly measured LDL-C.

Abstract

Background: Elevated low-density lipoprotein cholesterol (LDL-C) is a significant risk factor for cardiovascular diseases. LDL-C can be directly measured using various methods, but this requires expensive equipment. Currently, clinical laboratories estimate LDL-C based on Friedewald's formula (FF). We aimed to develop a modified formula based on directly measured LDL-C (D-LDL-C) values in a large population in Southern Iran and compare the results with various other estimation formulas.

Methods: The participants of this cross-sectional study were adults aged >18 years living in Southern Iran. Blood samples from 15,200 individuals were collected, and the measured lipid parameters were randomly divided into training (n=10,184) and validation (n=5,016) datasets. A new formula was developed using a linear regression model, and its accuracy was validated. Pearson's correlation and Cohen's kappa were used to determin the relationship between D-LDL-C and calculated LDL-C (C-LDL-C).

Results: The developed formula for the estimation of LDL-C was 0.857 total cholesterol (TC)-0.915 high-density lipoprotein cholesterol (HDL-C)-0.115 triglycerides (TG). Based on our proposed formula, for TG<150 and TG≥150 mg/dL, there was a significant correlation between mean values of D-LDL-C and C-LDL-C (r=0.985 and r=0.974, respectively). Compared to other formulas, C-LDL-C obtained from the proposed formula had the highest correlation with D-LDL-C. The agreement between D-LDL-C and C-LDL-C for TC<200, 200-239, and ≥240 mg/dL was 80.8%, 63.2%, and 67.4%, respectively, indicating a higher level of agreement than other formulas.

Conclusion: The new formula appears to be more accurate than FF when applied to the population of Southern Iran.

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Keywords ● Cardiovascular diseases ● Cholesterol ● HDL ● Lipoproteins ● LDL ● Iran

Introduction

Dyslipidemia is defined as a 90% increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), apolipoprotein B (Apo B), and lipoprotein-a (LP-a) levels or a 10% decrease in high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 levels compared to the levels in a

healthy population. More attention must be paid to hypercholesterolemia and high LDL-C levels, as they are the main modifiable risk factors for cardiovascular diseases (CVDs);[1, 2] the foremost cause of morbidity and mortality. According to Iranian population-based studies, approximately 50% of the general population suffers from hypercholesterolemia.[3, 4] LDL-C accounts for 70% of TC, and is an independent risk factor for CVD.[5-8] The guidelines for hypercholesterolemia stipulate different LDL-C cutoffs based on a 10-year CVD risk prediction.[9]

β-quantification using ultracentrifugation is the standard procedure for measuring LDL-C, however, ultracentrifuges are expensive devices and not widely used.[10] Further, direct methods for measuring LDL-C (D-LDL-C) concentrations, as recommended by the National Cholesterol Education Program (NCEP), are also not readily available in developing countries. Friedewald's formula (FF) was introduced in 1972 and is frequently used in clinical settings to estimate LDL-C. Calculated LDL-C (C-LDL-C) using FF (F-LDL-C) is estimated by the formula TC-HDL-C-TG/5.[11, 12] However, FF has several limitations despite a good correlation with D-LDL-C. The main limitations are that (i) blood samples must be collected in a fasting state, (ii) FF is not applicable when the serum TG is <100 or >400 mg/dL,[13] and (iii) FF cannot be used in patients with dysbetalipoproteinemia (type III) or hyperlipoproteinemia (type I).[14] In addition, this method is not recommended in individuals with certain conditions such as diabetes mellitus type 2, nephrotic syndrome, and chronic alcoholism since their TG:TC ratio in very low-density lipoprotein cholesterol (VLDL-C) is not constant.[15]

Given the above justifications, the present study aimed to develop a modified formula based on FF using D-LDL-C and compare the results with various other estimation formulas in a large population in southern Iran.

Materials and Methods

The present cross-sectional study evaluated the blood sample of individuals aged >18 years who had visited a clinical laboratory for routine check-ups between May and July 2019 in Bandar Abbas, Iran. The exclusion criteria were individuals with a history of diabetes mellitus, renal failure, and alcohol use in addition to a non-fasting blood test, serum triglycerides ≥400 mg/dL, and/or using medications such as lipid-lowering drugs and corticosteroids. The study was approved by the Ethics Committee of Hormozgan University of Medical Sciences, Bandar Abbas, Iran (code: IR.HUMS.REC.1398.004) and conforms with the Helsinki Declaration. Written informed consent was obtained from all the participants.

In total, 15,200 individuals were enrolled in the study. Blood samples were collected after 10-12 h of overnight fasting. The serum was separated at room temperature by centrifugation at 3,000 rpm for 10 min. All lipid parameters were determined using a commercially available kit (Pars Azmoon, Tehran, Iran) and a Cobas Integra 400 plus auto-analyzer (Roche AG, Basel, Switzerland). TG and TC assays were performed using the enzymatic GPO-PAP (kit lot number: 97002) and CHOD-PAP (kit lot number: 97003) colorimetric methods, respectively. Serum HDL-C (kit lot number: 97011) and LDL-C (kit lot number: 97001) were measured using standard kits and homogeneous assays. Non-HDL-C was estimated by subtracting HDL-C from TC. Internal quality control for each parameter was performed daily using a control serum (Pars Azmoon, Tehran, Iran) at two levels (normal: level I, pathologic: level II), and the results were interpreted according to Westgard rules. Subsequently, the mean and coefficient of variation (CV) for all lipid parameters were determined (table 1).

For both TG<150 and TG≥150 mg/dL, the C-LDL-C values were estimated using our developed formula (LDL-C=0.857TC - 0.915HDL-C - 0.115TG) and compared with the estimates from formulas developed by Friedewald,[16] Ahmadi,[13] de Cordova,[17] Vujovic,[18] Hattori,[19] Anandaraja,[7] Puavilai,[20] Martin,[21] and Sampson[22] (table 2).

Statistical Analysis

The interquartile range (IQR) was used

Table 1: The mean and inter-assay coefficient of variation for serum control levels I and II from Pars Azmoon

Lipid parameters	Reference mean of control serum		Laboratory mean of control serum		Coefficient of variation (%)	
	Level I	Level II	Level I	Level II	Level I	Level II
Triglyceride (mg/dL)	97.0	222.0	95.0	223.0	1.9	2.8
Total cholesterol (mg/dL)	144.0	190.0	145.2	194.0	1.9	2.9
HDL-C (mg/dL)	42.5	-	46.0	-	1.0	-
LDL-C (mg/dL)	73.8	123.0	70.4	126.0	1.0	2.3

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol

Table 2: A list of various proposed formulas for the estimation of LDL-C

Suggested	Formula
Friedewald[16]	LDL-C=TC - HDL-C - TG/5
Ahmadi[13]	LDL-C=TC/1.19 + TG/1.9 - HDL-C/1.1-38
de Cordova[17]	LDL-C=3/4 (TC - HDL-C)
Vujovic[18]	LDL-C=TC - TG/6.85 - HDL-C
Hattori[19]	LDL-C=0.94TC - 0.94HDL-C - 0.19TG
Anandaraja[7]	LDL-C=0.9TC - 0.9TG/5 - 28
Puavilai[20]	LDL-C=TC - HDL-C - TG/6
Martin[21]	LDL-C=TC - HDL-C - TG/adjustable factor
Sampson[22]	LDL-C=TC/0.948 - HDL-C/0.971 - TG/8.56 + TG×non-HDL-C/2140 - TG^2/16100 - 9.44
Current study	LDL-C=0.857TC - 0.915HDL-C - 0.115TG

TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol

Table 3: General characteristics and lipid profile of the study population

Variables		Training dataset (n=10,184)	Validation dataset (n=5,016)	P value
Age (years)		45.67±5.58	44.52±4.98	0.761
Sex (%)	Male	48	49	0.820
	Female	52	51	0.815
TC (mg/dL)		178.81±42.35	178.34±42.11	0.513
TG (mg/dL)		122.71±65.76	122.92±65.84	0.851
HDL-C (mg/dL)		46.00±11.56	46.01±11.74	0.948
Non-HDL-C (mg/dL)		132.81±39.93	132.32±39.35	0.475
D-LDL-C (mg/dL)		97.01±32.37	96.54±31.63	0.399

Data are presented as mean±SD. An Independent *t* test was used to compare the mean of continuous variables between the training and validation datasets. The proportion of men and women between the training and validation datasets are compared separately. TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; D-LDL-C: Direct low-density lipoprotein cholesterol

as an outlier removal criterion. A dataset was determined by removing any D-LDL-C, TG, TC, and HDL-C values more than Q_3+3 IQR or less than Q_1-3 IQR (Q_1: 1st quartile, Q_3: 3rd quartile, IQR: Q_3-Q_1). The remaining dataset (n_{total}=15,200) was then randomly divided into two groups, namely the training dataset that included 67% of the total dataset ($n_{train\ set}$=10,184) and the remaining 33% as the validation dataset ($n_{test\ set}$=5,016). The normal distribution of data was examined using the Kolmogorov–Smirnov test. Continuous and categorical variables were expressed as mean±SD and number with percentage, respectively. Continuous variables between the training and validation datasets were compared using the independent *t* test. A linear regression model without an intercept was used to estimate LDL-C in the training dataset, in which TG, TC, and HDL-C were independent variables and D-LDL-C was a dependent variable. Further, another linear regression model without an intercept was applied to the training set, and the validation dataset was used to assess the performance of various formulas. The association between D-LDLC and C-LDL-C was determined using Pearson's correlation analysis. LDL-C was categorized into <100, 100-129, 130-159, 160-189, and ≥190 mg/dL, and Cohen's kappa was used to estimate the level of agreement between D-LDL-C and C-LDL-C. Kappa values of ≤0.2, 0.2–0.4, 0.4–0.6, 0.6–0.8, and >0.8 were considered poor, fair, moderate, good, and excellent levels of agreement, respectively.[23] Additionally, the Bland-Altman (B&A) plot was used to define the degree of agreement between D-LDL-C and C-LDL-C in the validation dataset.[23] P<0.05 was considered statistically significant.

Results

Male participants in the validation and training datasets were 48% and 49% of the total population, respectively. There was no statistically significant difference in age, sex, and serum lipid profile of the participants between the two datasets (table 3).

The validation dataset was divided into two groups based on the TG levels of the participants, namely TG<150 mg/dL (n=3,619) and TG≥150 mg/dL (n=1,397) (table 4). Different estimation formulas, including our proposed method, were used to calculate LDL-C values. Based on our formula, the results showed a significant correlation between the mean values of D-LDL-C and C-LDL-C for both TG<150 and TG≥150 mg/dL groups (r=0.985 and r=0.974, respectively). Notably, for TG<150 and TG≥150 mg/dL, the C-LDL-C values estimated with our formula, as well as the Martin, Sampson, and

Table 4: Estimation of low-density lipoprotein cholesterol with two triglyceride levels in the validation dataset based on various formulas

Formula	Mean±SD	Mean difference*(mg/dL)±SD	Correlation (r)	P value#
TG <150 mg/dL (n=3,619)				
Direct LDL	92.77±30.41			
Current study	92.84±29.19	0.008±0.065	0.985	<0.0001
Friedewald	105.63±33.71	0.145±0.082	0.981	<0.0001
Ghasemi	95.04±33.70	0.018±0.092	0.977	<0.0001
Ahmadi	110.13±38.76	0.197±0.254	0.872	<0.0001
de Cordova	92.75±26.62	0.017±0.088	0.981	<0.0001
Hattori	99.11±31.67	0.074±0.077	0.981	<0.0001
Anandaraja	110.00±33.95	0.204±0.182	0.922	<0.0001
Puavilai	108.63±33.93	0.180±0.081	0.983	<0.0001
Sampson	106.83±34.38	0.156±0.076	0.983	<0.0001
Martin	105.15±33.27	0.140±0.073	0.984	<0.0001
TG≥150 mg/dL (n=1,397)				
Direct LDL	107.81±33.98			
Current study	107.74±33.89	0.003±0.081	0.974	<0.0001
Friedewald	114.70±39.89	0.055±0.102	0.973	<0.0001
Ghasemi	106.64±39.85	0.027±0.112	0.973	<0.0001
Ahmadi	201.42±48.45	0.9736±0.553	0.661	<0.0001
de Cordova	117.54±30.39	0.117±0.136	0.956	<0.0001
Hattori	107.40±37.51	0.011±0.097	0.973	<0.0001
Anandaraja	112.52±40.03	0.034±0.131	0.957	<0.0001
Puavilai	121.70±39.79	0.128±0.093	0.974	<0.0001
Sampson	119.71±38.11	0.112±0.087	0.975	<0.0001
Martin	123.13±37.03	0.152±0.095	0.974	<0.0001

*Mean difference (mg/dL) based on (C-LDL-C - D-LDL-C)/D-LDL-C; #Significance at 0.0001; TG: Triglyceride; D-LDL-C: Direct low-density lipoprotein cholesterol

Puavilai formulas had the highest correlation with the D-LDL-C values, followed by FF (r=0.981), de Cordova (r=0.981), Hattori (r=0.981), Ghasemi (r=0.977), Anandaraja (r=0.922), and Ahmadi (r=0.872) formulas, showing a high degree of correlation with D-LDL-C for participants with TG<150 mg/dL. Among the participants with TG≥150 mg/dL, our formula (r=0.974) and those of Sampson (r=0.975), Puavilai (r=0.974), and Martin (r=0.974) showed the highest degree of correlation with D-LDL-C (table 4). Conversely, de Cordova and Ahmadi's formulas showed the least correlation (r=0.956 and r=0.661, respectively).

Figure 1 illustrates the correlation between D-LDL-C and C-LDL-C in the validation dataset for both TG<150 and TG≥150 mg/dL groups using our proposed formula. Figure 2 presents the B&A plot to illustrate the degree of agreement between D-LDL-C and C-LDL-C in the validation dataset.

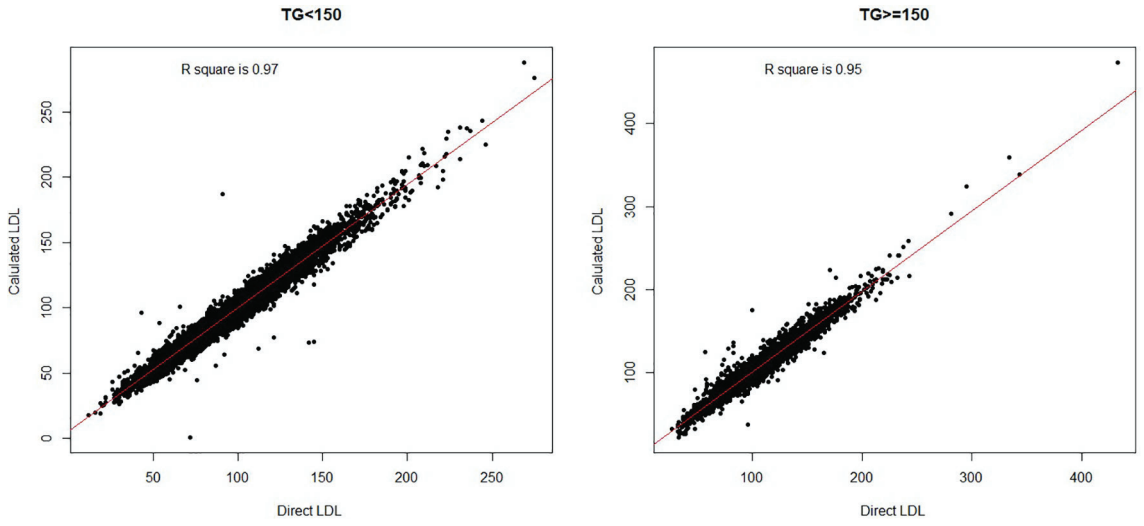

Figure 1: This figure shows the correlation between directly measured and calculated low-density lipoprotein (LDL) in patients with triglyceride (TG) <150 mg/dL (left) and TG≥150 mg/dL (right).

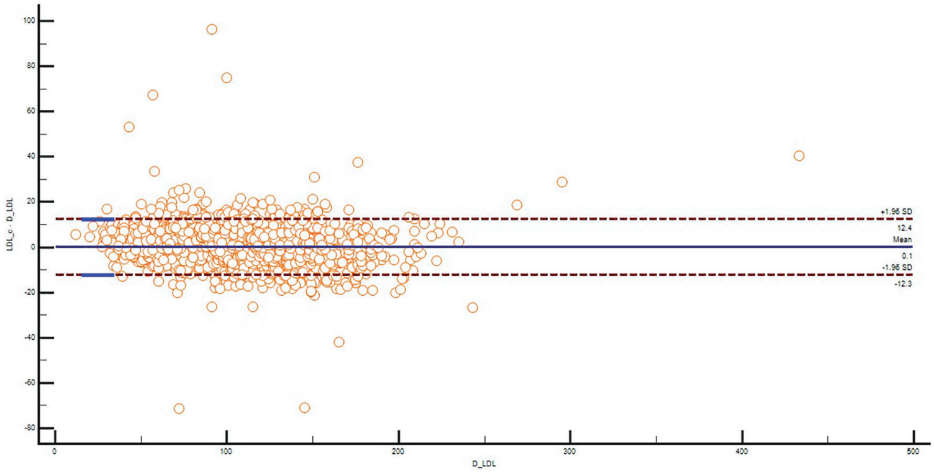

Figure 2: Bland-Altman (B&A) plot of differences between direct low-density lipoprotein cholesterol (D-LDL-C) and calculated LDL-C (C-LDL-C) in the validation dataset shows a perfect agreement (line Y=0). The average bias (the average of the difference) is equal to 0.1, which is close to zero. P (H0: Mean=0)=0.538 indicates an agreement between the two methods.

In this plot, the X-axis represents the value of D-LDL-C and the Y-axis represents the difference between D-LDL-C and C-LDL-C. It is suggested that 95% of the data points should lie within ±2 SD of the mean difference line. Additionally, highly scattered points on the B&A plot above and below the zero line, as observed in this study, indicate that there is no consistent bias in favor of one method over another.

Table 5 shows the percentage of agreement between D-LDL-C and C-LDL-C based on different TC, TG, and non-HDL-C categories in the validation dataset. Based on our formula, the percentage of agreement between D-LDL-C and C-LDL-C for TC <200, 200-239, and ≥240 mg/dL was 80.8%, 63.2%, and 67.4%, respectively; indicating a higher level of agreement compared to other formulas. This was followed by the result from Ghasemi's formula, with a better agreement percentage for TC<240 mg/dL, and de Cordova's for TC≥240 mg/dL. The percentage of agreement between D-LDL-C and C-LDL-C using our formula for TG<150 and ≥150 mg/dL was 84.5% and 78.8%, receptively. The best agreement was obtained with de Cordova's formula for TG<150 mg/dL (80.4%) and Hattori's for TG≥150 mg/dL (76.9%). Furthermore, the percentage of agreement between D-LDL-C and C-LDL-C determined by our formula for non-HDL-C<130, 130-159, 160-189, 190-219, and ≥220 mg/dL was 23.7%, 62.8%, 58.5%, 53.0%, and 63.6%, respectively. In the case of non-HDL-C<130 mg/dL, the best result was estimated with Hattori's formula (33.4%). Whereas in other ranges, our formula showed the highest percentage of agreement. Compared to other formulas, estimation using Hattori's formula showed a better agreement for non-HDL-C<130, 190-219, and ≥220 mg/dL, and Ghasemi's for non-HDL-C 130-159 and 160-189 mg/dL.

Table 6 shows the correlation coefficients between D-LDL-C and C-LDL-C in the validation dataset. Interestingly, for TG<150 mg/dL, our formula (0.980), Martin's (0.982), and Sampson's resulted in a better correlation coefficient than others; whereas, for TG≥150 mg/dL, our formula (0.978) and Puavilai's (0.978) performed better than others.

Table 5: Percentage of agreement between direct and calculated low-density lipoprotein cholesterol in terms of various total cholesterol, triglyceride, and non-high-density lipoprotein cholesterol levels in the validation dataset using Cohen's Kappa

Variables		Current study	Friede-wald	Ghasemi	Ahmadi	de Cordova	Hattori	Anand-araja	Puavilai	Sampson	Martin
TC (mg/dL)	<200	80.8%	55.2%	76.0%	16.6%	71.0%	73.1%	43.2%	43.4%	49.2%	51.3%
	200-239	63.2%	22.0%	53.8%	4.9%	50.5%	51.2%	14.7%	4.5%	10.8%	12.3%
	240≤	67.4%	19.8%	47.1%	4.0%	54.5%	52.1%	18.6%	4.7%	12.6%	12.7%
TG (mg/dL)	<150	84.5%	50.9%	76.9%	31.7%	80.4%	73.6%	39.4%	41.2%	46.3%	52.7%
	≥150	78.8%	65.3%	75.3%	4.9%	62.8%	76.9%	64.2%	44.8%	52.4%	42.5%
Non-HDL-C (mg/dL)	<130	23.7%	20.3%	31.7%	2.5%	0.0%	33.4%	10.7%	15.5%	18.7%	20.2%
	130-159	62.8%	25.5%	56.1%	5.6%	26.9%	52.7%	22.9%	4.8%	8.4%	2.1%
	160-189	58.5%	22.5%	51.2%	3.9%	41.8%	49.4%	26.4%	1.1%	8.8%	5.2%
	190-219	53.0%	11.9%	36.2%	1.6%	21.0%	40.9%	19.0%	3.7%	3.1%	1.4%
	220≤	63.6%	22.3%	41.5%	0.0%	41.8%	54.9%	37.8%	8.3%	20.6%	17.2%

TC: Total cholesterol; TG: Triglyceride; Non-HDL-C: Non-high-density lipoprotein cholesterol

Table 6: The results of Pearson's correlation coefficient between direct and calculated low-density lipoprotein cholesterol in the validation dataset for various formulas

	Current study	Friedewald	Ghasemi	Ahmadi	de Cordova	Hattori	Anandaraja	Puavilai	Sampson	Martin
TG<150	0.980	0.978	0.966	0.923	0.979	0.977	0.912	0.979	0.981	0.982
TG≥150	0.978	0.976	0.975	0.653	0.956	0.975	0.945	0.978	0.975	0.972

All P values were <0.001, Pearson's correlation were used for statistical analysis. TG: Triglyceride

Discussion

In the present study, lipid parameters from 10,184 individuals were used to develop a modified version of FF for the estimation of LDL-C. The results showed a strong correlation and high percentage of agreement between the calculated and direct measurement of LDL-C. Based on the B&A plot, there was a clear correlation between D-LDL-C and C-LDL-C in the validation dataset. Further, the low bias found in the plot was favorable. Altogether, our proposed formula estimated similar results to D-LDL-C.

Serum LDL-C levels play an important role in the management of CVDs. Moreover, LDL-C concentration is used as a basis to develop treatment strategies for lipid disorders. Therefore, an accurate estimate of LDL-C is essential to appropriately manage the risk of CVDs.[24] Over the past decades, next to the widely used FF, several attempts have been made to develop formulas for a more accurate calculation of LDL-C. Since its initial introduction, FF has largely been used for serum LDL-C calculation. This method requires the measurement of three serum or plasma variables, namely TC, TG, and HDL-C. However, it is known that TG:TC ratio varies greatly in VLDL-C,[25] and that the other lipoprotein remnants and lipoproteins make up the triglyceride pool. Therefore, this ratio may not be applicable to all individuals. Originally, FF was based on theoretical considerations only and validated in 448 patients, showing a good correlation with direct measurements (r=0.98). According to Warnick and colleagues,[26] at TG levels >200 mg/dL, about 90% of C-LDL-C values within 10% of the values measured by β-quantification are acceptable. However, in the case of TG 200-400 mg/dL, only 72% of the calculated values are acceptable. Similarly, we found a good correlation (r=0.981) between C-LDL-C derived from FF and D-LDL-C. We also found a good correlation between the results of our proposed formula and those of other formulas.

In general, any LDL-C formula should be easy to apply. Formulas based on TG levels may be accurate, but they are not suitable for routine use. In this regard, Piani and colleagues evaluated 12 formulas for LDL-C estimation and showed that some are superior to others. However, they categorized the study population into two TG and five D-LDL-C groups.[27] Similarly, Karkhaneh and colleagues assessed eight LDL-C estimation formulas across multiple TC and HDL-C categories.[28]

Hattori and colleagues proposed a new estimation formula (LDL-C=0.94TC - 0.94HDL-C - 0.19TG).[19] Moreover, Vujovic and colleagues developed a modified estimation formula (LDL-C=TC - HDL-C - TG/6.85) in a Serbian population, which showed to be more accurate than the formulas of Friedewald and Anandaraja.[18] Based on FF, Puavilai and colleagues developed another modified formula (LDL-C=TC - HDL-C - 1/6TG) for fasting TG 200-499 mg/dL. However, they recommended that this modified formula should be re-examined, specifically with sera obtained from dyslipidemic patients.[20] In an additional study in Brazil, de Cordova and colleagues used an extensive database of directly measured lipid values from 10,664 individuals. They developed a new estimation formula (LDL-C=3/4[TC - HDL-C]) that accurately estimated LDL-C with a higher correlation with D-LDL-C (r=0.93) than with F-LDL-C (r=0.87).[17] However, they did not include medication intake by the study population.

Anandaraja and colleagues examined the lipid profile of 2,008 individuals and demonstrated that the correlation between D-LDL-C and F-LDL-C improved after excluding patients with TG>350 mg/dL (r=0.92). In addition, they showed a strong correlation between D-LDL-C and LDL-C calculated by their new formula (r=0.97).[7] Based on a modified FF, the results of a study by Ghasemi and colleagues showed that TG coefficients were 2.7, 3.7, 4.6, and 5 for TG<100, 100-200, 200-300, and 300-400 mg/dL, respectively. However, by replacing TG/5 with TG/4 in FF, the mean difference was smaller than with the original formula (4.03 vs. 10.86 mg/dL), higher kappa coefficient (0.691 vs. 0.505), and better classification of patients (80.8 vs. 67.1%) was achieved. They also reported that after applying the modified formula to specific TG classifications, the difference between D-LDL-C and C-LDL-C reduced to 1.41 mg/dL. They concluded that the proposed formula

provides a more accurate estimate of LDL-C compared to F-LDL-C and a better classification of patients.[29]

Martin and colleagues claimed that their proposed estimation formula using an adjustable TG/VLDL-C ratio (LDL-C=TC - HDL-C - TG/adjustable factor) provided a more accurate risk classification. They reported the highest agreement in classifying LDL-C <70 mg/dL, especially in patients with high TG levels.[21] As a limitation of their study, the extent of treatment with lipid-lowering drugs was unknown, whereas participants taking these medications were excluded. In addition, they were unaware of the fasting status of their patients. TG/VLDL-C ratio may also vary in fasting samples,[30] and such variations are much higher in a heterogeneous population using both fasting and non-fasting samples.

Sampson and colleagues developed their own formula (LDL-C=TC/0.948 - HDL-C/0.971 - TG/8.56 + TG×non-HDL-C/2140 - TG^2/16100 - 9.44). They suggested that the new formula provided a more accurate estimate of LDL-C than other formulas (Friedewald and Martin). With their formula, the estimated LDL-C level was as accurate for patients with TG up to 800 mg/dL as the FF for TG<400 mg/dL, which was associated with a 35% reduction in misclassification, when patients with 400-800 mg/dL TG levels were classified to different LDL-C treatment groups.[22] However, unlike our study, they developed the formula based on the evaluation of a unique population with a high prevalence of hypertriglyceridemia.

Overall, our proposed estimation formula exhibited a strong correlation with FF, other previously developed and validated formulas, and the direct measurement method. Since our formula was derived from a large population in Southern Iran, our study has good generalizability and applicability to other populations. The extent of its clinical use can be confirmed by applying the formula to other populations and comparison with D-LDL-C values. Additionally, the new modified formula only requires TC, TG, and HDL-C values. Notably, the percentage of agreement between D-LDL-C and those estimated by all other formulas (based on TC, TG, non-HDL-C, and HDL-C) was much lower than ours. Therefore, our proposed formula will provide a more accurate estimate than FF. However, the formula is better suited for TG<150 mg/dL, since the agreement between C-LDL-C and D-LDL-C was higher for TG<150 than for TG≥150 mg/dL.

Conclusion

The accuracy and simplicity of our proposed formula make it an ideal candidate for use in clinical laboratories, especially where cost is the main concern. Further studies in different populations are required to fully validate the proposed formula and better establish its clinical use.

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Authors' Contribution

M.K: Study design. S.A.S: Project coordination, analysis of laboratory data. Sh.R and M.M: Statistical analysis, data interpretation. M.R, R.Sh, A.A, S.K: Conduct of the study. E.E: Project supervision. All authors have to various degrees contributed to the writing of the draft manuscript. They have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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