International Journal of General Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

A Novel LDLC Equation is Superior to the NIH LDLC Equation and the Friedewald Equation

Guo-Ming Zhang[1,2,*], Jing Liu[1,2,*], Xu-Xiao Guo[3], Fu-Meng Yang[4]

[1]Department of Laboratory Medicine, Shuyang Hospital, Shuyang, People's Republic of China; [2]Department of Laboratory Medicine, the Affiliated Shuyang Hospital of Xuzhou Medical University, Shuyang, People's Republic of China; [3]Department of Laboratory Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong, People's Republic of China; [4]Department of Laboratory Medicine, the Second People's Hospital of Lianyungang, Lianyungang, People's Republic of China

*The authors contributed equally to this work

Correspondence: Guo-Ming Zhang, Department of Laboratory Medicine, Shuyang Hospital, No. 9, Yingbin Road, Shuyang, People's Republic of China, Email gm@xzhmu.edu.cn; zly52120@163.com

International Journal of General Medicine downloaded from https://www.dovepress.com/
For personal use only.

Background: LDLC equations have varying levels of underestimation for the calculated LDLC. Therefore, underestimating LDLC should be avoided as much as possible. We need to establish LDLC equations that underestimate LDLC as little as possible.

Methods: We established the equations with a healthy cohort from Shuyang Hospital and validated the equations with an unselected patient cohort from The Second People's Hospital of Lianyungang. We established the novel LDLC equations by using the regression equation. The relationship between two markers was analysed using Pearson's approach. The 95% limits of measuring agreement within ±2 SD for the LDLC equations was performed using Bland–Altman analysis. ROC curve analysis was used to predict LDLC levels and the accuracy of the LDLC equation for determining the direct LDLC levels at LDLC cut-offs was assessed.

Results: We obtained two novel LDLC equations (LDL_nonHDLC equation=−0.899+1.195*nonHDLC-0.00347*nonHDLC^2 and LDL_TC(total cholesterol) equation=−2.775+1.29*TC −0.00990* TC ^{2}). The correlation coefficient between the novel LDLC equation and the direct LDLC measurements is not lower than that between the LDL_NIH equation and the direct LDLC measurements. The AUCs of our novel LDLC equations were greater than those of the LDL_NIH equation and the LDL_F equation at the LDLC cut-offs for clinical decision-making. The measuring agreement in the methods of the LDL_nonHDL equation is superior to that of the LDL_NIH equation.

Conclusion: LDLC calculated by the novel LDL_nonHDL equation exhibited superiority over the LDL_NIH equation. Combining the LDL_NIH equation and our novel LDLC equation may improve accuracy and avoid undertreatment of high LDLC levels.

Keywords: low-density lipoprotein cholesterol, NIH LDL-C equation, friedewald equation, novel LDLC equation

Introduction

A lipid panel that includes triglycerides (TGs), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol (HDLC), and low-density lipoprotein (LDL) cholesterol (LDLC)[1] is used worldwide for routine testing to determine your cholesterol status. Routinely, the LDLC level is estimated by calculation using a formula (eg, the NIH LDLC (LDL_NIH) equation[2] and the Friedewald (LDL_F) equation).[3] However, direct measurement of LDLC is not a routine cholesterol test.[4] Research indicates[5] that the direct measurement of LDLC is important for information about CVD risk. However, its advantages are modest when comparing it to LDLC levels calculated using a formula. Because the LDLC calculated formula is a reliable and cost-effective method for routine cholesterol tests,[6] the LDLC calculated formula still needs to be optimized and improved. We read with interest an article titled "Validating the LDL_NIH equation in a specialized lipid cohort: Does it add up?" by Victoria Higgins et al that was published in Clinical Biochemistry.[7] The authors focused on which calculation equation is better for LDLC and concluded that the LDL_NIH equation was superior to the LDL_F equation based on ultracentrifugation LDLC. Is this true? It can be seen from the cohort of equations we established that the LDLC calculated by the LDL_NIH and LDL_F equations is lower than that measured by the direct method (Table 1).

Received: 25 November 2023
Accepted: 9 February 2024
Published: 14 February 2024

© 2024 Zhang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

Table 1 The Characteristics of Establishment of the LDLC Equation Group

Index	Establishment of the LDLC Equation Group	
	TG≤1.7 mmol/L	TG>1.7 mmol/L
n	16,143	7083
Age	51(35–65)	54(40–65)
TG	1.05(0.80–1.33)	2.30(1.95–2.97)
TC	4.58(4.00–5.22)	5.13(4.52–5.82)
nonHDLC	3.24(2.67–3.80)	3.96(3.42–4.57)
LDLC	2.97(2.51–3.46)	3.42(2.95–3.94)
LDL_F	2.74(2.23–3.28)	2.77(2.19–3.36)
LDL_NIH	2.82(2.27–3.40)	3.09(2.50–3.71)

Hence, we established an LDLC equation for estimating LDLC levels using cohorts of healthy individuals base on the direct measurement of LDLC and compared the novel LDLC equations, the LDL_NIH equation, and the LDL_F equation for use in other unselected patient cohorts.

Materials and Methods

Study Cohort and Data Extraction

We obtained a large cohort of data from routine check-ups of healthy individuals from the Shuyang Hospital laboratory information system for retrospective analysis by retrieving the results of serum TC, HDLC, LDLC, and TG tests that were performed over several months (from Jan 2019 to December 2019) to establish an equation group based on health standards from the literature.[8] Another larger cohort of unselected patient data from Jan 2022 to August 2022 was used for the validation group from The Second People's Hospital of Lianyungang. LDL_F=TC-HDLC-TG/2.2, in mmol/L.[3] LDL_NIH=TC/0.948-HDLC/0.971-TG/3.74-TG*nonHDLC/24.16+TG*TG/79.36–0.244, in mmol/L.[7] TG*nonHDLC/24.16+TG*TG/79.36–0.244, in mmol/L. This study was approved by the Ethics Committee of Medicine, Shuyang Hospital. The study accordented with the Declaration of Helsinki.

Laboratory Methods and Instruments

Serum TG (GPO-POD method), TC (Enzymatic method), HDLC (direct clearance method), and LDLC (direct clearance method) levels were measured with an AU5800 Modular System (Beckman Coulter, Inc., America). Calibration and verification (TG, TC, HDLC, and LDLC) of the instrument were performed annually, which also included reportable range, precision, and trueness (Table 2). A regular external quality assessment scheme and regular internal quality control procedures were performed throughout the study period. The ethics committee of Shuyang Hospital approved this study.

Table 2 Instrument Performance Parameters (TG, TC, HDL-C, and LDL-C) of AU5821 Chemistry Analyzer

Analytes	Trueness	Precision	Reportable Range
TC	NCCL EQA |bias|≤4.5%	Repetitive precision: CV ≤2.25% Intermediate precision: CV ≤3.00%	Linearity range: 0.5–18.0 mmol/L; Clinical reportable range: 0.5–36.0 mmol/L.
HDL-C	NCCL EQA |bias|≤15.0%	Repetitive precision: CV ≤7.50% Intermediate precision: CV ≤10.00%	Linearity range: 0.05–4.65 mmol/L; Clinical reportable range: 0.05–9.30 mmol/L.
LDL-C	NCCL EQA |bias|≤15.0%	Repetitive precision: CV ≤7.50% Intermediate precision: CV ≤10.00%	Linearity range: 0.26–10.30; Clinical reportable range: 0.26–20.60 mmol/L.
TG	NCCL EQA |bias|≤7.0%	Repetitive precision: CV ≤3.50% Intermediate precision: CV ≤4.67%	Linearity range: 0.1–11.3 mmol/L; Clinical reportable range: 0.1–45.2 mmol/L.

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

Statistical Analysis

NonHDLC was calculated as TC minus HDLC.[9] The relationship between two markers was analysed using Spearman's approach. Establishment of the novel LDLC equations was performed by using the regression equation ($y=a + b*x + c*x^2$) based on the direct measurement of LDLC levels as the reference method. Agreement of the LDLC equations was determined by using Bland–Altman plot. ROC curve analysis was used to predict LDLC and the accuracy of the LDLC equation for direct LDLC levels at LDLC cut-offs (1.55 mmol/L, 1.80 mmol/L, 2.60 mmol/L, 3.36 mmol/L, 4.12 mmol/L, and 4.90 mmol/L).[9] We performed statistical analyses by using MedCalc Version 18.1.1 (MedCalc Software, Ostend, Belgium) and Excel Version 2019 (Armonk, NY, USA). A p value below 0.01 was considered statistically significant.

Results

Establishing the LDL_nonHDLC Equation and LDL_TC Equation

The lipid profiles, including the TG, TC, HDLC, and LDLC levels, of 23,226 consecutive healthy individuals were measured at the laboratory of Shuyang Hospital between Jan 1, 2019, and Dec 31, 2019. Among these 23,226 patients, 16,143 individuals had a TG level below 1.71 mmol/L (Table 1 and Figure 1), We established two novel LDLC equations ($LDL\_nonHDLC = -0.899+1.195*nonHDLC-0.00347*nonHDLC^2$ and $LDL\_TC = -2.775+1.29*TC-0.00990*TC^2$) (Figure 2) for predicting TC and nonHDLC levels for various abnormal direct LDLC levels (>1.55 mmol/L, >1.80 mmol/L, >2.60 mmol/L, >3.36 mmol/L, >4.12 mmol/L, and >4.90 mmol/L) by using ROC curve analysis from 19,643 individuals. We obtained 6 points of different TC and nonHDLC with different LDLC levels.

Validating That the LDL_nonHDLC Equation and LDL_TC Equation are Superior to the LDL_NIH Equation

The unselected outpatient cohort (Figure 3) included 21,168 subjects.

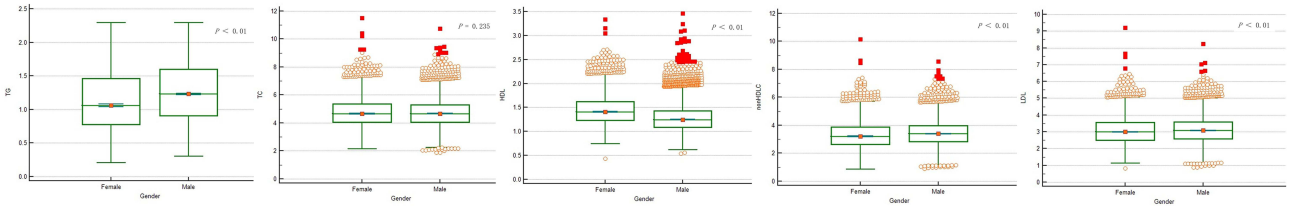

Figure 1 The characteristics of the participants included in the construction of the novel LDLC equations.
Abbreviations: TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides, in mmol/L.

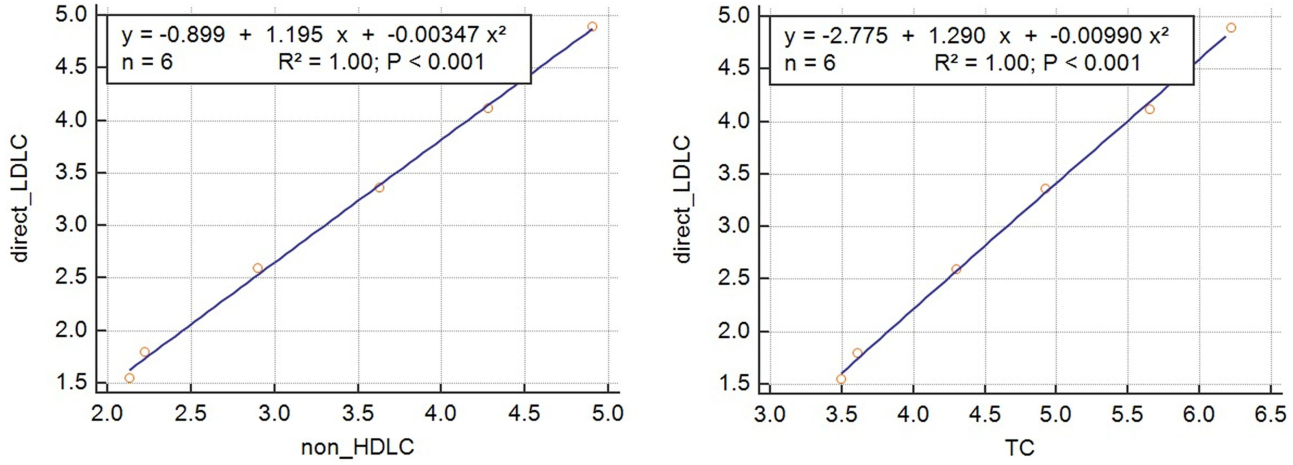

Figure 2 We obtained two novel LDLC equations.
Abbreviations: Direct_LDLC and LDL-C (direct clearance method) were tested with an AU5800 Modular System (Beckman Coulter, Inc., America). TC, total cholesterol; HDL, high-density lipoprotein cholesterol; NonHDLC=TC-HDL, in mmol/L.

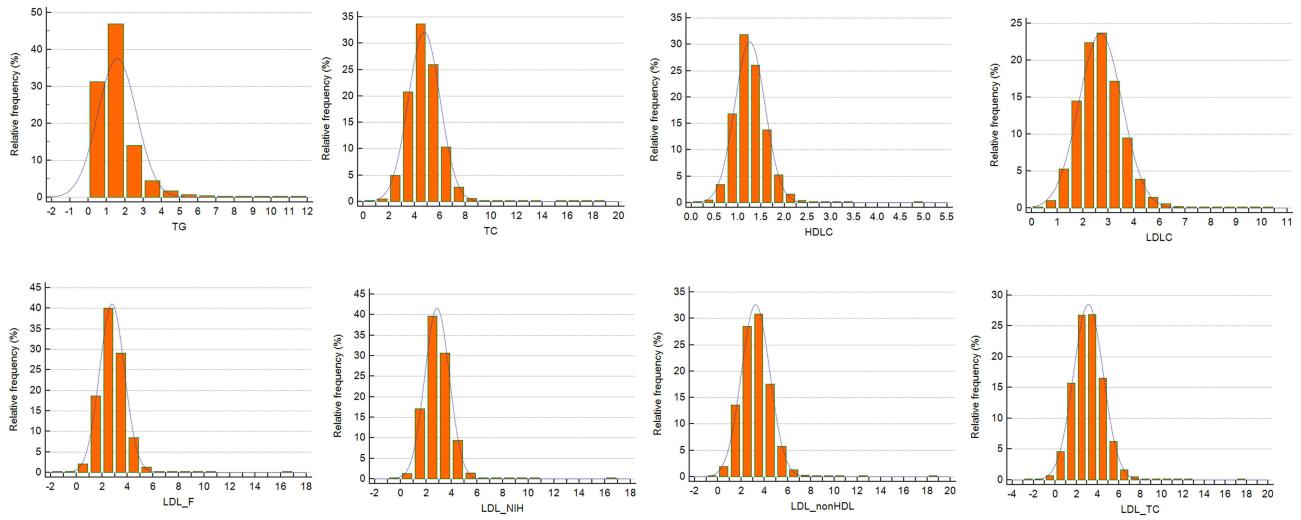

Figure 3 The histogram of the characteristics of the unselected patient cohort.
Abbreviations: TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; LDL_F, LDL-C calculated using the Friedewald equation; LDL_NIH, LDL-C calculated using the NIH equation; LDL_nonHDLC-equation=−0.899+1.195*nonHDLC-0.00347*nonHDLC^2 and LDL_TC-equation=−2.775+1.29*TC-0.00990*TC^2, in mmol/L.

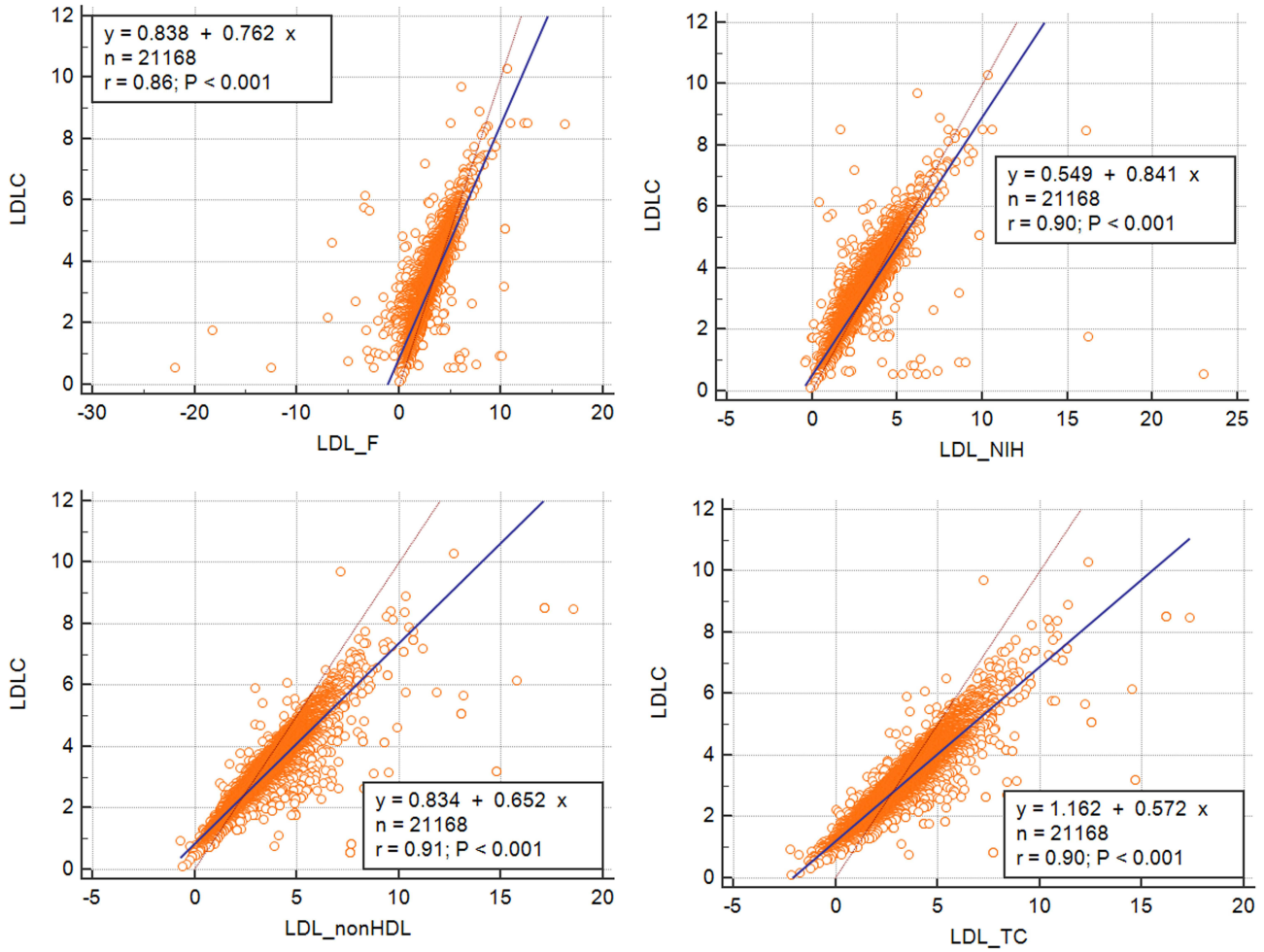

Figure 4 Scatter plots for the direct low-density lipoprotein cholesterol (LDLC) and LDLC equations. Their relationship was analysed using Spearman's approach.
Abbreviations: LDL (direct clearance method) was tested with an AU5800 Modular System (Beckman Coulter, Inc., America); LDL_F, LDL-C calculated using the Friedewald equation; LDL_NIH, LDL-C calculated using the NIH equation; LDL_nonHDLC-equation=−0.899+1.195*nonHDLC-0.00347*nonHDLC^2 and LDL_TC-equation =−2.775+1.29*TC-0.00990*TC^2, in mmol/L.

LDL_F, LDL_NIH, LDL_nonHDLC, and LDL_TC levels were significantly positively correlated with direct LDLC levels (Figure 4).

Figure 5 shows the ROC curves of LDL_F, LDL_NIH, LDL_nonHDLC, and LDL_TC for predicting the 6 different direct LDLC levels. As listed in Figure 5, these novel LDLC equations (LDL_nonHDLC and LDL_TC equations) are superior to the LDL_NIH equation and the Friedewald equation.

The Bland–Altman plot (Figure 6) showed that the number of overestimated LDLC and underestimated LDLC of LDL_F and LDL_NIH was greater than that of LDL_nonHDL and LDL_TC. Overestimation with LDL_F and LDL_NIH occurred at low LDLC levels, and several paired data points fell below 5 mmol/L.

Discussion

Here, we describe the performance of the Friedewald equation, the LDL_NIH equation, and two novel LDL equations in the clinical setting using direct-LDL (direct clearance method) as a reference method. This study has three novel aspects: 1) it is the first publication to use ROC for establishing LDL-equations using direct-LDL as a reference method, 2) the overestimation for LDLC is better than the underestimation from three different perspectives of analysis

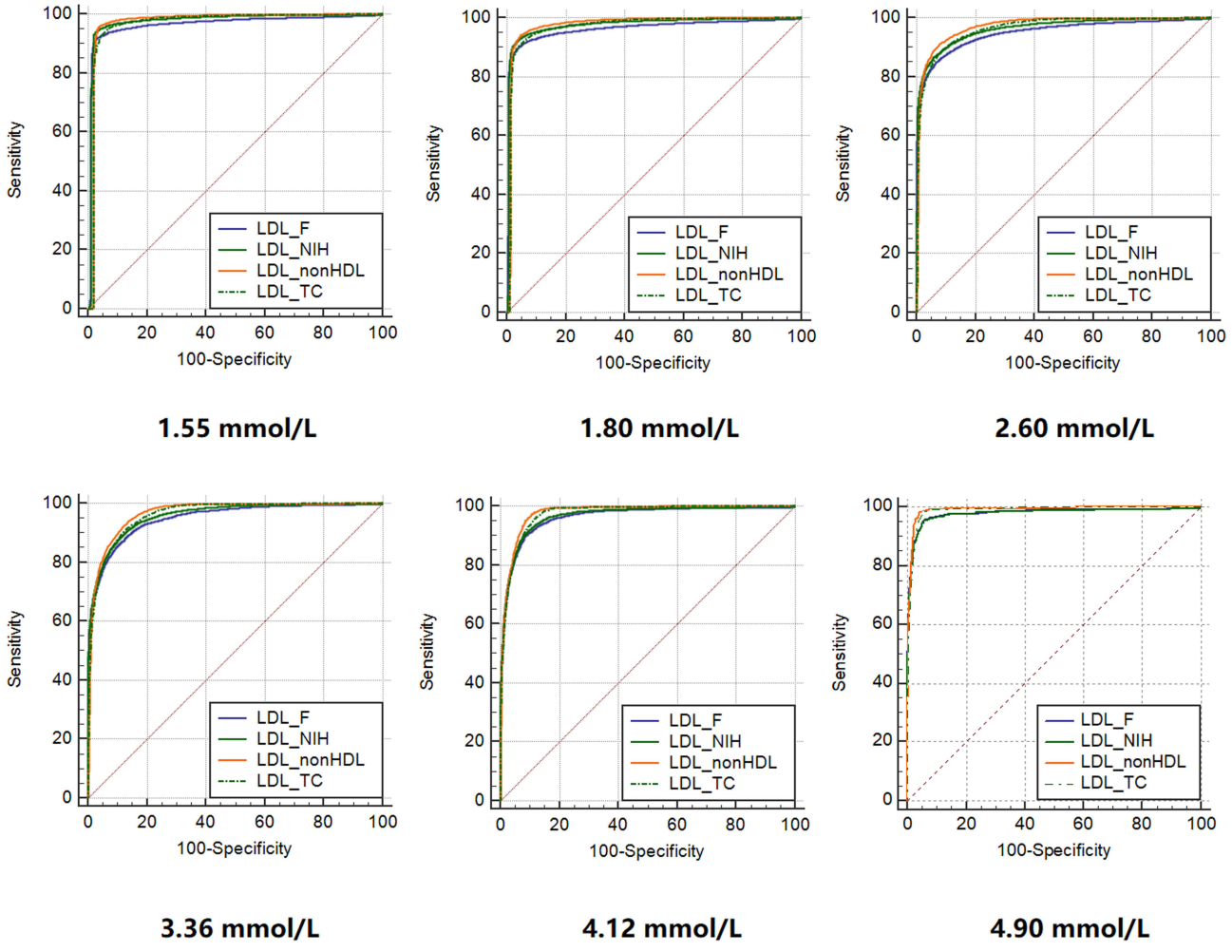

Figure 5 Receiver operating characteristic curves of the LDLC equations for predicting direct low-density lipoprotein cholesterol (direct LDLC levels are >1.55 mmol/L, >1.80 mmol/L, >2.60 mmol/L, >3.36 mmol/L, >4.12 mmol/L, and >4.90 mmol/L).

Abbreviations: LDL (direct clearance method) was tested with an AU5800 Modular System (Beckman Coulter, Inc., America); LDL_F, LDL-C calculated using the Friedewald equation; LDL_NIH, LDL-C calculated using the NIH equation; LDL_nonHDLC-equation=−0.899+1.195*nonHDLC-0.00347*nonHDLC^2 and LDL_TC-equation =−2.775+1.29*TC-0.00990*TC^2, in mmol/L.

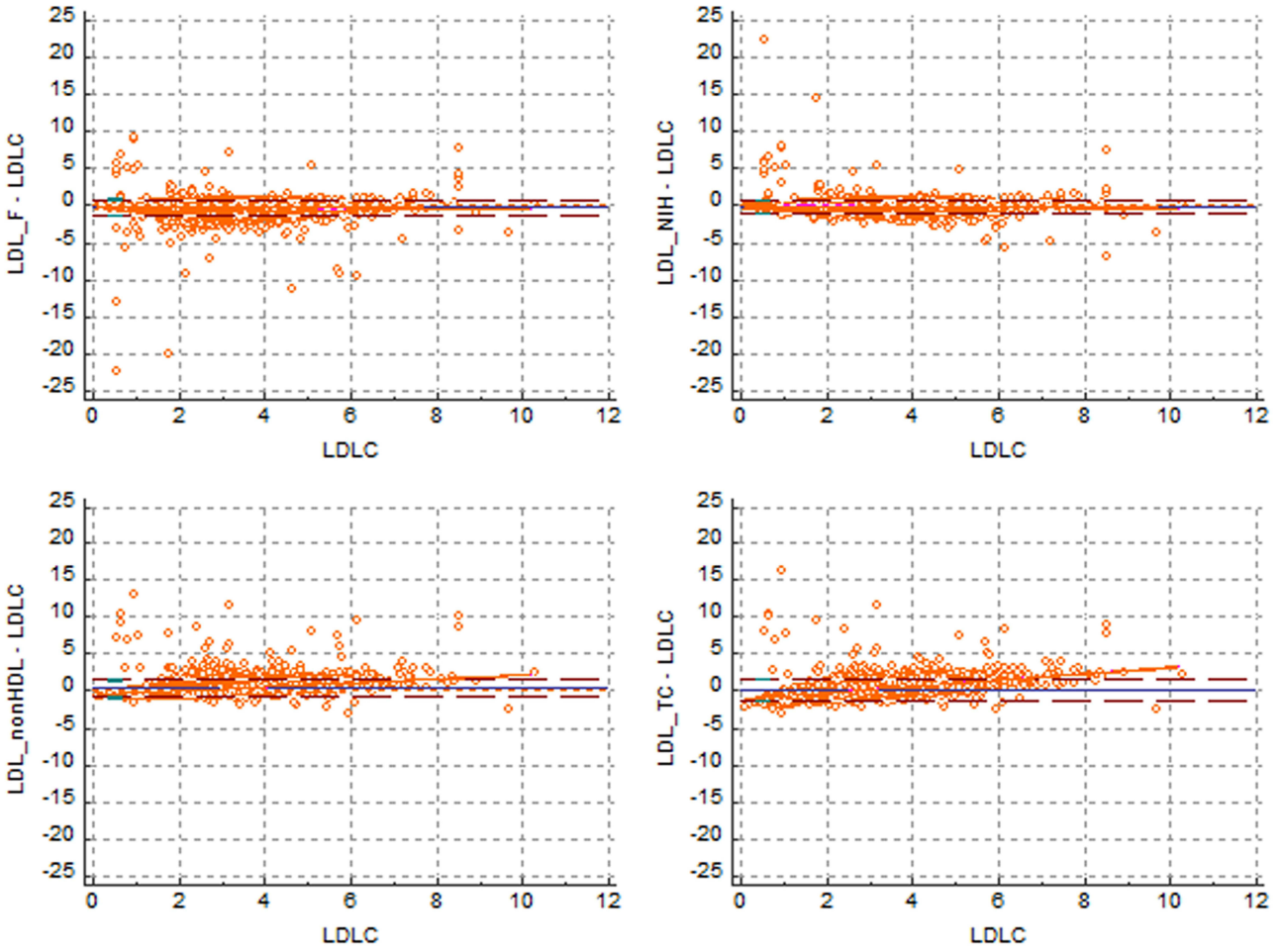

Figure 6 Bland–Altman plot of LDLC from four LDLC equations.
Abbreviations: LDL (direct clearance method) was tested with an AU5800 Modular System (Beckman Coulter, Inc., America); LDL_F, LDL-C calculated using the Friedewald equation; LDL_NIH, LDL-C calculated using the NIH equation; LDL_nonHDLC-equation=−0.899+1.195*nonHDLC-0.00347*nonHDLC^2 and LDL_TC-equation =−2.775+1.29*TC-0.00990*TC^2, in mmol.

for clinical significance, and 3) we established the equations with a healthy cohort and validated the equations with an unselected patient cohort.

In this study, we analysed direct LDLC measurements and LDLC equations and their correlations in a large, unselected outpatient cohort. We found that the novel LDLC equations were positively correlated with direct LDLC measurements, and the correlation coefficient between the novel LDLC equation and direct LDLC measurements was greater than the correlation coefficient between the NIH LDLC equation and the Friedewald equation and the direct LDLC measurements. The ROC of these four LDLC-equations at the cutoffs of clinical decision limits of 1.55 mmol/L, 1.80 mmol/L, 2.60 mmol/L, 3.36 mmol/L, 4.12 mmol/L, and 4.90 mmol/L indicated that the AUC of our novel LDLC-equations were greater than the AUCs of the NIH LDLC-equation and the Friedewald equation. Our results are consistent with Victoria Higgins's findings.[7]

However, all LDLC equations overestimate and underestimate LDLC.[10] Underestimating results in a false negative, a misdiagnosis, and this is undesirable.[10,11] Overestimation results in a false-positive and can be corrected by using more specific methodologies. Therefore, underestimation should be avoided as much as possible. As the Bland–Altman plot in Figure 5 shows, among the 21,168 paired LDL_F and LDL_NIH equation LDLC levels, several results underestimated the direct-LDLC levels by more than 5 mol/L, and LDL_nonHDL and LDL_TC did not. Combining the NIH LDLC equation and our novel LDLC equation may improve accuracy while avoiding underestimation to avoid undertreatment of high LDLC

levels.[11] In clinical practice, the method with a relatively overestimated LDLC equation should be selected as the first method, and the direct LDLC method should be used after it exceeds the standard.

When LDLC cannot be calculated from the LDLC equations, a direct-LDLC test is used. We can calculate LDLC through a laboratory information system based on a lipid panel. Our lab automatically performs a direct-LDLC analysis when TGs are high, or a doctor may request direct-LDLC measurement if you have a history of high LDLC calculated from the LDLC-equation or high TG. When the calculated LDLC level is high or the TG level is high, a reflex direct-LDLC test is automatically performed by a full duplex system consisting of a laboratory information system and biochemical analyser.[12]

There is a limitation in this study. The reference method of LDLC is direct-LDL (direct clearance method).

The results of the present study indicate that our novel LDLC equations may be superior to the LDL_NIH equation. To the best of our knowledge, this study is the first to establish LDLC equations by using ROC curve analysis. The novel LDLC equation may be suitable for other labs. However, because of different detection systems and different subjects, the novel LDLC equation may be slightly differ across all clinics.

In summary, LDLC calculated by the novel LDLC equation exhibited superiority over the NIH equation in terms of their correlations with direct LDLC, and this was concordant with the direct LDLC levels at the LDLC cut-offs. The LDL_NIH equation and our novel equations can be utilized to calculate LDLC and replace the Friedewald equation. Combining the NIH LDLC equation and our novel LDLC equation may improve accuracy and avoid the underestimation of high LDLC levels. Our study demonstrated that the strategy in this study is worth promoting.

Data Sharing Statement

All data reported in this study are included in this published article. Further details can be available from the corresponding author upon request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committees of Shuyang Hospital (Reference No. SYYYLL 202352). The funding organization played no role in the study design, the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit the report for publication.

Funding

This study was supported by a research grant from Xuzhou Medical University (XZSYSKF2020034).

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. *JAMA*. 2013;310:2061–2068.
2. Sampson M, Ling C, Sun Q, et al. A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients With Normolipidemia and/or Hypertriglyceridemia. *JAMA Cardiol*. 2020;5:540–548.
3. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499–502. doi:10.1093/clinchem/18.6.499
4. Wolska A, Remaley AT. Measuring LDL-cholesterol: what is the best way to do it? *Curr Opin Cardiol*. 2020;35(4):405–411. doi:10.1097/HCO.0000000000000740
5. Ikezaki H, Fisher VA, Lim E, et al. Direct Versus Calculated LDL Cholesterol and C-Reactive Protein in Cardiovascular Disease Risk Assessment in the Framingham Offspring Study. *Clin Chem*. 2019;65(9):1102–1114. doi:10.1373/clinchem.2019.304600
6. Stein EA. Measuring LDL cholesterol: for old and new calculations, is there an optimal formula? *Clin Chem*. 2014;60(12):1466–1468. doi:10.1373/clinchem.2014.232793
7. Higgins V, Leiter LA, Delaney SR, et al. Validating the NIH LDL-C equation in a specialized lipid cohort: does it add up? *Clin Biochem*. 2022;99:60–68.
8. Zhang G-M, Zhang G-M, Hu S, et al. Is testing of aspartate aminotransferase necessary along with every alanine aminotransferase for health check in elderly individuals? *Clin Chim Acta*. 2020;507:224–227. doi:10.1016/j.cca.2020.05.003

9. Zhang GM, Bai SM, Zhang GM, et al. A Novel Method for Estimating Low-Density Lipoprotein (LDL) Levels: total Cholesterol and Non-High-Density Lipoprotein (HDL) Can Be Used to Predict Abnormal LDL Level in an Apparently Healthy Population. *Med Sci Monit*. 2018;24:1688–1692. doi:10.12659/MSM.909226
10. Sajja A, Park J, Sathiyakumar V, et al. Comparison of Methods to Estimate Low-Density Lipoprotein Cholesterol in Patients With High Triglyceride Levels. *JAMA Network Open*. 2021;4(10):e2128817. doi:10.1001/jamanetworkopen.2021.28817
11. Brownstein AJ, Martin SS. More accurate LDL-C calculation: externally validated, guideline endorsed. *Clin Chim Acta*. 2020;506:149–153. doi:10.1016/j.cca.2020.03.030
12. Xu Q, Higgins T, Cembrowski GS. Limiting the testing of AST: a diagnostically nonspecific enzyme. *Am J Clin Pathol*. 2015;144(3):423–426. doi:10.1309/AJCPO47VAWYRIDHG

International Journal of General Medicine Dovepress

Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-general-medicine-journal