ASLI QoL 2025
Annual Serial Landmark International Conference on QoL 2025
Indexed in Clarivate Analytics WoS

E-B Environment - Behaviour Proceedings Journal

AQoL2025Cherating

e-IPH e-International Publishing House Ltd., United Kingdom

https://www.amerabra.org/
09th Asia-Pacific International Conference on Quality of Life
Holiday Villa Beach Resort & Spa, Cherating, Malaysia, 17-18 Oct 2025

Comparison and Agreement of LDL-C Formulas in Cardiovascular Risk Stratification among Malaysians

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Abstract
Several formulas have been developed to estimate the LDL-C values, such as the Friedewald, Martin-Hopkins, Sampson, and Anandaraja equations. However, their performance has not been extensively evaluated. Therefore, this study aimed to evaluate the agreement of these LDL-C formulas and analyze the clinical LDL-C group reclassification. The results showed that Friedewald consistently underestimates LDL-C compared to the others, but reclassification using Martin or Sampson may not align with Friedewald-based risk categorization. Anandaraja showed the highest misclassification. These discrepancies may affect treatment decisions. Future studies should validate performance in high-risk subgroups and consider formula-specific cut-offs to improve cardiovascular risk assessment.

Keywords: LDL-C Formula; Friedwald; Martin-Hopkins; Sampson

DOI: https://doi.org/10.21834/e-bpj.v10i34.7352

1.0 Introduction

According to the Department of Statistics Malaysia (2020), ischemic heart disease accounted for around 15% of all medically certified deaths in 2019, making cardiovascular disease (CVD) the undisputed leading cause of death in Malaysia. Accurate cardiovascular risk stratification is essential for informing preventive and therapeutic strategies. Low-density lipoprotein cholesterol (LDL-C) is a critical causal factor in the progression of atherosclerotic cardiovascular disease (ASCVD), and its assessment is fundamental to lipid management guidelines. Direct LDL-C testing techniques, such as β-quantification by homogeneous assay and ultracentrifugation, are not commonly utilized in standard clinical practice because of their complexity, cost, and poor performance at increased triglyceride (TG) levels. Instead, clinical laboratories commonly adopt estimation formulas based on total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels (Rahim *et al*., 2024).

DOI: https://doi.org/10.21834/e-bpj.v10i34.7352

Although the Friedewald formula is still the most popular, it is less accurate when hypertriglyceridemia or low LDL-C concentrations are present. To increase accuracy across different lipid profiles and populations, more recent formulas have been developed, such as the Martin-Hopkins, Sampson, and Anandaraja formulas (Anandaraja *et al*., 2005; Martin *et al*., 2013; Sampson *et al*, 2020). Inaccurate LDL-C calculation values used in clinical practice to determine cardiovascular risk stratification may lead to underdiagnosis, delayed intervention, and prolonged exposure to cardiovascular risk. This conduct may eventually lead to the quiet onset of atherosclerosis (Ference *et al*., 2020). The increased incidence of obesity, diabetes, and hypertriglyceridemia highlights the need for further research on the validity and agreement of LDL-C estimation formulae (Nazli *et al*., 2024).

Thus, this study aims to address the limited data on their applicability in Malaysian cohorts by comparing the performance and agreement of four LDL-C estimation equations, including Friedewald, Martin-Hopkins, Sampson, and Anandaraja, in cardiovascular risk stratification among the Malaysian population. The study seeks to highlight the importance of selecting the most reliable estimation method for standard clinical practice and contributes to optimizing cardiovascular risk management.

2.0 Literature Review

In recent years, an increase in interest in the Martin-Hopkins, Sampson, and Anandaraja equations has been seen due to their higher accuracy under specific lipid profiles than Friedewald. Sajja *et al*. (2021) reported across the United States that the Martin-Hopkins equation outperforms the Friedewald and Sampson equations in terms of accuracy at triglyceride levels between 400 and 799 mg/dL, with less underestimation of LDL-C values. Its application in clinical practice is recommended by the American Heart Association (AHA) and the American College of Cardiology (ACC) as Class IIa, especially for individuals with elevated TG levels or low LDL-C (Grundy *et al*., 2019).

The Sampson or Martin-Hopkins equations have been recommended by the Polish Society of Laboratory Diagnostics (PSLD) and the Polish Lipid Association (PoLA) for routine use to estimate LDL-C values in place of the Friedewald equation (Solnica *et al*., 2024). Developed in India, the Anandaraja equation was proposed as a more straightforward substitute for Friedewald, utilizing fewer lipid factors (Anandaraja *et al*., 2005). Its use has remained restricted, as evidenced by limited validation attempts reported in Brazil, Greece, and Serbia. No significant recommendations body outside of India has recommended its normal usage (Gasko, 2006).

Collectively, these findings highlight a trend towards the gradual replacement of the Friedewald formula with more recent equations that provide greater accuracy across a range of lipid and TG profiles. Among these, the Sampson formula is being targeted for broader adoption for its improved accuracy across diverse lipid profiles, such as Poland and China (Li *et al*., 2022; Solnica *et al*., 2024), the Martin-Hopkins equation is acquiring the most international acceptance through routinely adopted in major clinical laboratories, including United States, Poland, and multi-country (Grant *et al*., 2024; Sajja *et al*., 2021; Solnica *et al*., 2024), while the Anandaraja equations are still mainly limited to research and regional use (Gasko, 2006).

3.0 Methodology

3.1 Study Design and Sampling

A total of 5,665 participants were included in this study, with data obtained from the Malaysian Health and Wellbeing Assessment (MyHEBAT) between 2011 and 2025. MyHEBAT is an ongoing cross-sectional study conducted through a national-level health screening program that covered urban and rural areas across 11 states in Malaysia (Firus Khan *et al*., 2022). The MyHEBAT data collection encompassed major ethnic groups in Malaysia, including the Malays, Chinese, Indians, and ethnic minorities of indigenous groups in Sabah, such as the Bajau, Kadazan, Bugis, Suluk, and Dusun. In Sarawak, the Iban and Bidayuh were also included.

Eligible participants were male and female Malaysians, irrespective of prior health status, in order to capture a broad distribution of LDL-C levels ranging from very low to high categories. The details of the inclusion and exclusion criteria, ethical approval, and variable definitions for the MyHEBAT study are described previously by Firus Khan *et al*. (2022). Written informed consent was collected from all participants prior to enrollment, while for participants under the age of 18 years, consent and study questionnaires were completed by their legal guardians. The biometric data to assess each participant's health status, including smoking status, alcohol consumption, body mass index (BMI), waist circumference, and blood pressure, were recorded through on-site measurement and from the clinics' database. The serum lipid profiles of each participant, including TC, TG, and HDL-C, were analyzed using an automatic analyzer (COBAS Integra® 400, Roche Holding AG; Basel, Switzerland) and recorded in the data. Samples with missing values or TG greater than 9.0 mmol/L were excluded due to calculation limitations.

3.2 LDL-C estimation calculations

Non-HDL-C was calculated by subtracting HDL from TC. LDL-C for each participant was estimated using four established formulas as presented below. All lipid values were standardized to mmol/L. LDL-C, HDL-C, and total cholesterol were converted from mg/dL to mmol/L using a factor of 0.0259, while triglycerides were converted using a factor of 0.0113 (David-Pardo *et al*., 2024).

Friedewald equation (Friedewald *et al*., 1972):

$$LDL-C\ (mmol/L) = TC - HDL-C - \frac{TG}{2.2}$$

(1)

Martin-Hopkins (Martin *et al*., 2013):

$$LDL-C\ (mg/dL) = TC - HDL-C - \left(\frac{TG}{adjustable\ \ factor}\right)$$

(2)

Sampson (Sampson *et al*., 2020):

$$LDL-C\ (mg/dL) = \frac{TC}{0.948} - \frac{HDL-C}{0.971} - \left[\left(\frac{TG}{8.56}\right) + \left(TG \times \frac{non-HDL-C}{2140}\right) - \left(\frac{TG \times TG}{16100}\right)\right] - 9.44$$

(3)

Anandaraja (Anandaraja *et al*., 2005):

$$LDL-C\ (mg/dL) = (0.9 \times TC) - \left(0.9 \times \frac{TG}{5}\right) - 28$$

(4)

The adjustable factor in the Martin-Hopkins formula was chosen from a 180-cell stratification table described by Martin *et al*. (2013). Each formula was applied to the same dataset of lipid values, and the Friedewald equation will serve as the reference formula for comparison. Calculated LDL-C values were expressed in both mg/dL and mmol/L to facilitate international comparability.

3.3 Statistical analysis

Data were analyzed using SPSS version 27 (IBM, NY, USA). Data are presented as mean ± standard deviation (SD). The significance of mean differences was compared using one-way analysis of variance (ANOVA) with Tukey's post hoc test. Prior to that, the data were assumed to follow a normal distribution based on the values of skewness and kurtosis falling within ±2, which is consistent with commonly accepted guidelines (Iacobucci *et al*., 2025). The *p*-value<0.05 was considered statistically significant. Meanwhile, the mean bias and 95% limit of agreement (LoA) of each equation were assessed from the Bland-Altman plot.

A reclassification analysis was performed by categorizing participants into standard clinical LDL-C groups according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines, which are <2.6 mmol/L (optimal), 2.6-3.3 mmol/L (near optimal), 3.4-4.0 mmol/L (borderline high), 4.1-4.8 mmol/L (high), and ≥4.9 mmol/L (very high). A cross-tabulation was constructed to quantify the improvement of the alternative equations over the Friedewald equation in correctly assigning individuals to LDL-C categories. A shift in the classification was defined as movement to a higher risk category (upward) or to a lower risk category (downward) relative to the Friedewald-derived category.

4.0 Findings

4.1 Demographic Data

Table 1. Distribution of individuals based on demographic data and lipid profiles from the MyHEBAT study. Data are presented as numbers (n) and percentages (%) for categorical data, and as means and standard deviations (SD) for continuous data.

Parameters	(n=5665)
Gender	
Male	2260 (39.9%)
Female	3396 (60.1%)
Age	15-75 (41.81±15.59)
Race	
Malay	4126 (72.8%)
Chinese	265 (4.7%)
Indian	153 (2.7%)

Orang Asli	23 (0.4%)
Bidayuh	284 (5.0%)
Iban	37 (0.7%)
Others	116 (2.0%)
Dusun	284(5.0%)
Bajau	304(5.4%)
Kadazan	21 (0.4%)
Suluk	13 (0.2%)
Banjar	1 (0.0%)
Bugis	9 (0.2%)
Non-Malaysian	8 (0.1%)
No Data	21 (0.4%)
Smoking	
Current Smoker	710 (12.5%)
Ex-Smoker	586 (10.3%)
Non-Smoker	4130 (72.9%)
No Data	239 (4.2%)
Alcohol	
No	4964 (87.6%)
Yes	196 (3.5%)
Weight, kg	65.6808±15.3
Height, cm	158.5±8.7
Waist Circumference, cm	86.1±13.3
Blood Pressure	
Diastolic Blood Pressure, mmHg	80.01±17.7
Systolic Blood Pressure, mmHg	120.86±22.3
Lipid Profile	
Total Cholesterol (TC), mmol/L	5.41±1.43
Triglyceride (TG), mmol/L	1.70±1.11
High-Density Lipoprotein Cholesterol (HDL-C), mmol/L	1.28±0.37
Current Low-Density Lipoprotein-Cholesterol (LDL-C) from Friedewald equation, mmol/L	3.26±1.134
Antihypertensive Medication	
No	4734 (83.60%)
Yes	646 (11.40%)
Lipid-Lowering Medication	
No	4692 (82.82%)
Yes	573 (10.11%)
Diabetes Mellitus Type 2	
Normal	4422 (78.10%)
Impaired Fasting Glucose	70 (1.20%)
Impaired Glucose Tolerance	237 (4.20%)
Diabetes Mellitus Type 2	584 (10.30%)
Anti-diabetic Medication	
No	5046 (89.10%)
Yes	304 (5.40%)
Coronary Artery Disease (CAD)	
No	5239 (92.50%)
Yes	287 (5.10%)

Based on Table 1, the population in this study is defined by a large proportion of females (60.1%) compared to males (39.9%). The mean age was 41.8 years ±15.6, indicating a relatively young population, with Malays as the predominant ethnic group, followed by Bajau, Bidayuh, Chinese, Indians, and other smaller proportions. The majority were non-smokers (72.9%), while 12.5% were current smokers and 10.3% ex-smokers. Alcohol consumption was relatively low (3.5%). An average waist circumference of 86 cm borders on central obesity thresholds, especially concerning women (≥80 cm) and men (≥90 cm). Blood pressure values were within normal limits on average, but the wide standard deviations suggest a subgroup with hypertension (120.86±22.3 systolic, 80.01±17.6 diastolic).

The lipid profile in Table 1 demonstrated a common dyslipidemia pattern associated with increased cardiovascular risk in Asian populations, as shown by the borderline-high LDL-C and TC with means (3.26±1.13 and 5.41±1.43) mmol/L, respectively, coupled with low HDL-C (mean 1.28±0.37). Diabetes prevalence (10.3%) was consistent with national data, with additional cases of impaired fasting glucose and impaired glucose tolerance suggesting a significant pre-diabetic population at risk of progression (Ministry of Health Malaysia [NDR], 2023). However, the uptake of diabetes treatment (5.4%), antihypertensive medication (11.4%), and lipid-lowering drugs (10.1%) was lower than the proportion diagnosed in Malaysia (Institute for Public Health, 2023). Coronary artery disease (CAD) was reported in 5.1% of participants, which is lower than expected given their risk profile. This finding may be due to underdiagnosis, a younger mean age, or selection bias in the study sample.

4.2 Agreement analysis between LDL-C estimation methods

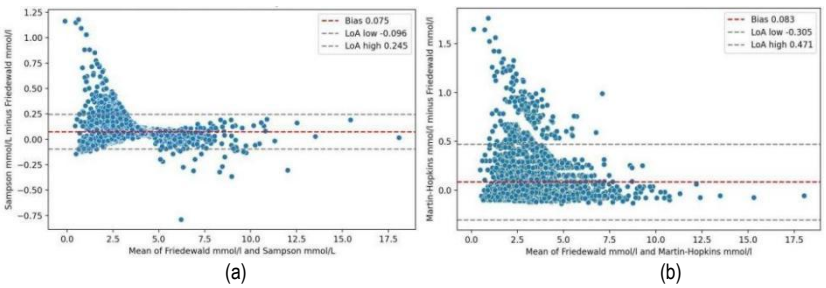
Table 2. One-way ANOVA table for mean differences in the LDL-C estimation values among the formulas.

LDL-C Values	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	30.678	3	10.226	6.399	.000
Within Groups	36204.428	22656	1.598		
Total	36235.106	22659			

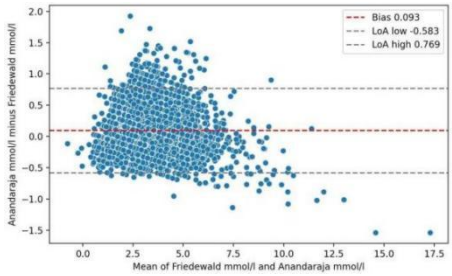
Table 3. The mean differences (mmol/L) and *p*-values between the four equations of the LDL-C estimation method.

Reference equations	Type of equations	Mean Differences (mmol/L)	Std. Error	*P*-value
Friedewald	Martin	-.08341*	0.02375	0.003
	Sampson	-.07440*	0.02375	0.009
	Anandaraja	-.09301*	0.02375	0.001
Martin	Friedewald	.08341*	0.02375	0.003
	Sampson	0.009	0.02375	0.981
	Anandaraja	-0.0096	0.02375	0.978
Sampson	Friedewald	.07440*	0.02375	0.009
	Martin	-0.009	0.02375	0.981
	Anandaraja	-0.0186	0.02375	0.862
Anandaraja	Friedewald	.09301*	0.02375	0.001
	Martin	0.0096	0.02375	0.978
	Sampson	0.0186	0.02375	0.862

Table 2 showed a statistically significant difference in the LDL-C estimation values between the formulas (p=0.000). As referred to in Table 3, the multiple comparisons showed that LDL-C values estimated using the Friedewald equation were significantly lower compared to Anandaraja (Mean Diff = -0.093, p=0.001), followed by Martin-Hopkins (-0.083, p=0.003) and Sampson (-0.074, p=0.009) equations. No significant differences were observed between Martin and Sampson (0.009, p=0.981), or Martin and Anandaraja (-0.0096, p=0.978). Similarly, no significant difference was found between Sampson and Anandaraja (-0.0186, p=0.862). The mean bias for all three equations indicates that these equations consistently yield slightly higher LDL-C values than Friedewald.



(a) (b)



(c)

Fig. 1. Bland-Altman plots with mean bias and limits of agreement for comparison between Friedewald and LDL-C estimation methods (a) Friedewald vs Sampson equation; (b) Friedewald vs Martin-Hopkins equation; (c) Friedewald vs Anandaraja equation

The narrowest 95% limit of agreement is shown by Sampson relative to Friedewald in Fig. 1(a), ranging from -0.096 to +0.245 mmol/L, which indicates that most differences fell within this interval, and most points cluster tightly around zero difference. The plot showed the scatter widens at lower mean LDL-C values (<2 mmol/L), which suggests greater variability and poor agreement between methods in the lower range. Based on Fig. 1 (b), the 95% limits of agreement for Martin-Hopkins relative to Friedewald were -0.305 to +0.471 mmol/L, which is slightly wider than those observed for Sampson but still clinically acceptable in many cases. Similar to the Sampson comparison, greater variability was observed for Martin-Hopkins at lower LDL-C levels, but agreement improves as values increase. The 95% limit of agreement for Anandaraja relative to Friedewald in Fig. 1(c) was -0.583 to 0.769 mmol/L and showed the widest limit of agreement among the three equations. The Anandaraja equation showed more variability across the whole range, which was particularly noticeable at low and mid values. The finding suggests weaker agreement compared to Sampson and Martin-Hopkins.

4.2 Reclassification of LDL-C estimation values

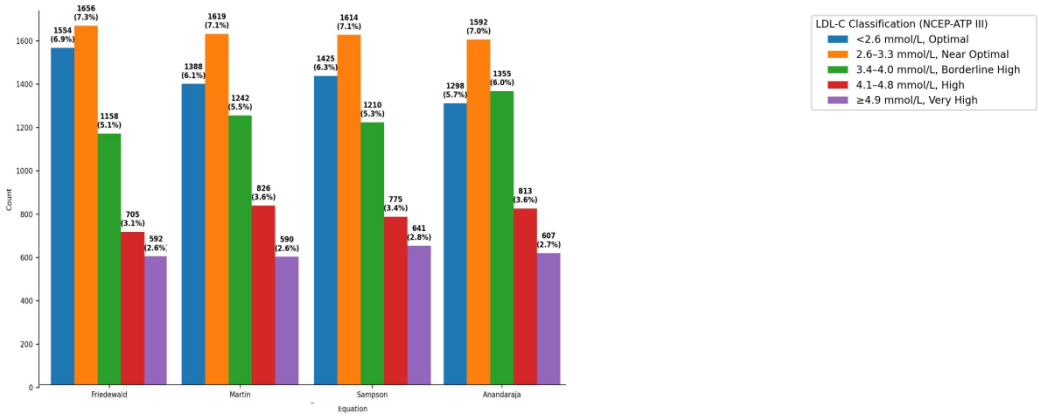


Fig. 2. Grouped bar chart showing the number of patients classified into LDL-C categories using four different estimation equations based on National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines.

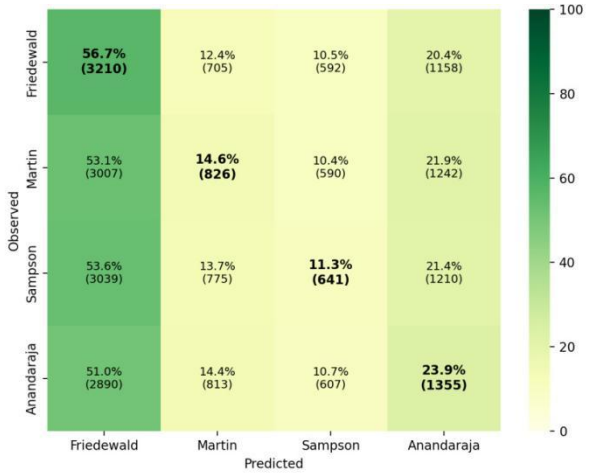


Fig. 3. The heatmap of observed and predicted classification across four LDL-C estimation methods.

In the overall, the largest group is in the near optimal, 2.6-3.3 mmol/L range, constituted of 6481 (28.6% of the total sample) while the smallest group is in the very high, ≥4.9 mmol/L range constituted of 2430 (10.7% of the total sample) as shown in Fig. 2. The optimal, <2.6 mmol/L group is consistently the second-largest, constituted of 5665 (25% of the total sample). Friedewald has slightly more cases classified in the lowest category (<2.6 mmol/L), constituting 1554 (6.9% of total), compared to Martin (1388, 6.1% of total), Sampson (1425, 6.3% of total), and Anandaraja (1298, 5.7% of total). Anandaraja tends to shift more cases into the 3.4-4.0 mmol/L range (1355, 6.0% of total), which is the highest among other methods. Martin yielded more results in the higher category (4.1-4.8 mmol/L), which constituted 826 (3.6% of the total), compared to Friedewald. Sampson assigns more cases into the ≥4.9 mmol/L group (641, 2.8% of total), which is the highest among other methods.

Using Friedewald as the reference, the correctly classified were 3210 (56.7%), with most misclassified as Anandaraja were 1158 (20.4%), as shown in Fig. 3. Meanwhile, the correctly classified were only 826 (14.6%), with most misclassified as Friedewald were 3007 (53.1%) when Martin was used as the reference. The lowest percentage of correct classification indicates that Martin does not align well with the observed data. For Sampson as the reference, the correctly classified cases were 641 (11.3%), and most misclassified as Friedewald were 3039 (53.6%), reflecting a similar pattern to Martin. When Anandaraja was the reference, the correctly classified cases were 1355 (23.9%), but a significant portion was misclassified as Friedewald (2890, 51.0%). Overall, Friedewald dominated predictions (53.6% of total misclassification), which may indicate bias or closer resemblance across methods, but shows a high degree of overlap with others.

5.0 Discussion

Traditional LDL-C estimation methods, such as the Friedewald equation, do not perform well in non-fasting samples, at low LDL-C values, or elevated TG (>400 mg/dL; >4.5 mmol/L) (Friedewald *et al*., 1972). Newer formulas, including Martin-Hopkins, introduced an adjustable factor for the TG-to-VLDL-C ratio to improve a broad range of lipid levels, especially at low LDL-C values (Martin *et al*., 2013). The Sampson equation was designed to resolve inaccuracies for individuals with TG levels (>800 mg/dL, 9.0 mmol/L), and the Anandaraja equations eliminate the need for HDL-C, relying solely on total cholesterol and TG concentrations (Anandaraja *et al*., 2005; Sampson *et al.,* 2020). These equations have demonstrated varying performances across populations related to lipid distribution, particularly TG and HDL-C levels. Dietary, demographic, and ethnic variables are factors that influence an individual's lipid profile (Sun *et al*., 2023). Therefore, this study provides demographic data within the Malaysian cohort to ensure that LDL-C estimation methods can produce clinically meaningful results in diverse settings.

The ethnic composition reflects local demographics and provides insight into cardiometabolic health across subpopulations (Firus Khan *et a*l., 2022). Notably, smoking prevalence was higher than predicted for women but lower for men, while alcohol consumption was minimal, consistent with cultural norms in Malaysia (Ling *et al*., 2022). Although average BMI appeared acceptable, the physical measurements, including the average waist circumference, weight, and height, indicate an elevated risk of metabolic syndrome. Despite favorable lifestyle variables, the group exhibited significant cardiometabolic risks (Nazli *et al,* 2014). Central obesity, dyslipidemia defined by increased LDL-C, low HDL-C, and a significant diabetic burden, were all present. While hypertension and CAD were comparatively prevalent, a large number of people had impaired glucose tolerance and abnormal lipid profiles, indicating a significant future risk for cardiovascular illness (Razman *et al*., 2022). The Malaysian National Diabetes Registry has also demonstrated that diabetic individuals continue to have high rates of dyslipidemia and hypertension (NDR, 2023). Importantly, treatment uptake for diabetes, hypertension, and dyslipidemia was lower than the proportion diagnosed, suggesting possible gaps in healthcare access, knowledge, or adherence.

The mean differences analysis showed that the Friedewald equation consistently underestimates LDL-C compared to the Martin, Sampson, and Anandaraja equations. LDL-C calculated using the Sampson equation showed the closest values with the Friedewald equation, as indicated by the least significant difference in mean. This finding was further supported by Bland-Altman analysis, which demonstrated the lowest bias, which was close to zero, and the narrowest limits of agreement for the Sampson equation relative to Friedewald (Nuwaylati & Awan, 2024). The Sampson equation has shown less stability to estimate LDL-C values at lower range (<2 mmol/L) but more consistent at moderate-to-high LDL-C values (>3 mmol/L). These findings are consistent with existing literature, which states that the Friedewald equation has been noted to underestimate LDL-C, particularly in patients with higher triglyceride levels or at lower LDL-C ranges (David-Pardo *et al*., 2024). The Martin-Hopkins equation showed strong agreement, with slightly variability than the Sampson equation. However, the Anandaraja equation showed the weakest performance with the highest bias and wider limits of agreement. Its ease of calculation may be advantageous in resource-limited settings, but its reliability in clinical decision-making might raise concerns (Gupta *et al*., 2012). These findings suggest that the Sampson equation clearly outperforms the other two in this dataset and serves as a more precise alternative to Friedewald.

When assessing classification accuracy, the low overall correct prediction rate (26.6%) highlights the limited agreement between equations and does not classify patients into LDL-C categories consistently. Clinically, this could result in borderline differences around treatment threshold, particularly in deciding the statin therapy (David-Pardo *et al*., 2024). The Friedewald equation performed best in terms of concordance, reflecting its long-standing use as the conventional method, but it also showed substantial misclassification into other equations' categories. In contrast, Martin and Sampson, which were designed to improve accuracy in specific populations, showed poor agreement, diverging substantially from Friedewald, suggesting that their reclassification may not align well with Friedewald-based risk categories in this dataset (Aly *et al*., 2025). The Anandaraja equation may overestimate LDL-C relative to Friedewald, as reflected by fewer patients classified in the optimal category and more in the borderline-high categories. Although the Anandaraja equation shows moderate alignment, it still heavily overlaps with Friedewald (Gasko, 2006). Clinically, these discrepancies are significant. Depending on the chosen equation, misclassification between lower and higher LDL-C ranges could lead to undertreatment or overtreatment of

patients. Therefore, the correct application of alternative LDL-C equations is warranted, and further validation in the target population is essential.

6.0 Conclusion & Recommendations

The Friedewald formula tends to underestimate LDL-C, especially in individuals within the optimal-risk range, whereas the Sampson formula shows stronger agreement with higher misclassification than other formulas. In this study, the comparisons were based on the Friedewald formula rather than direct LDL-C measurements. Therefore, the agreement observed reflects relative consistency rather than absolute accuracy. Future studies should validate these formulas against direct LDL-C, assess their performance in high-risk subgroups, and consider formula-specific cut-offs to improve cardiovascular risk assessment. Clinicians may need to consider a correction factor when interpreting Friedewald-derived results, while the Sampson and Martin-Hopkins formulas can generally be used without adjustment in most cases. In addition, collaborative efforts among clinical laboratories, epidemiologists, and policymakers are needed to integrate these findings into national lipid management guidelines.

Acknowledgement

This work was supported by the Higher Institution Centre of Excellence (HICoE) research grant 600-RMC/MOHE HICoE CARE-I 5/3 (01/2025) awarded to the Cardiovascular Advancement and Research Excellence Institute (CARE Institute), Universiti Teknologi MARA. The authors would like to acknowledge Prof Dr Hapizah Md Nawawi, who was the former principal investigator of MyHEBAT.

Paper Contribution to Related Field of Study

This study contributed to the field of lipidology and cardiovascular health. The findings highlight risks of misclassification and support the need for formula-specific validation to improve cardiovascular risk assessment and treatment decision-making.

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