**Impact of analytical error in lipid levels and LDL-c calculation on cardiovascular risk classification**

**ABSTRACT**

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| **Introduction** High levels of low-density lipoprotein cholesterol(LDL-c) are associated with a high risk of cardiovascular disease (CVD). The LDL-c value is the basis for a classification of the subject into low risk, moderate risk, and very high risk of developing CVD. Nevertheless, analytical error could be reflected in the various calculation parameters. The aim of this study was to determine the influence of analytical error and the method of LDL- c calculation on patient classification.**Material and methods**This was a retrospective study with data collection on lipid panels carried out in the laboratories of three hospitals in Gabon, between January 2023 and December 2023. Each data set included concentrations of total cholesterol (TC), HDL-c, LDL-c, and triglycerides (TG) measured simultaneously for each patient. Not included were all patients with TG >4 mmol/L. The LDL-c concentration was determined using the direct method and Friedewald equation. The total analytical error (TAE) used are for TC ≤ 9%, TG ≤ 15%, LDL-c ≤ 12%, and HDL-c ≤ 13%.**Results** A total of 2060 patients made up the study population. Before application of the TAE, the proportion of LDL-c concentration with the direct method against the Friedewald equation was comparable (p=0.14). After application of the positive TAE, the proportion of LDL-c concentration was statistically higher with the indirect method compared to direct method [596 (28.93%) versus 355 (17.23%); p<0.0001]. Thus, applying the positive TAE to the calculation formula and to the direct LDL-c, the Friedewald equation had more patients at very high risk and at high risk compared to the direct method (p<0.0001). However, the negative TAE on the indirect method classified few patients at very high risk and at high risk. We found that, the positive TAE reduced patients at low and intermediate risk and reclassified them at very high and at high risk of developing CVD (p<0.0001).**Conclusion**The analytical error and LDL-c calculation method significantly influence patient classification. It revealed that high-risk patients were more likely to be classified as CVD-related. The use of indirect methods led to higher high- and very high-risk patients. The TAE also altered patient classification, shifting some from lower to higher risk. This suggests that TAE should be considered for better patient management. |

Keywords: Total analytical error; lipids; cholesterol; cardiovascular risk

1. **INTRODUCTION**

Cardiovascular disease (CVD) refers to all pathologies affecting the cardio-circulatory system, such as the heart and blood vessels. They mainly comprise ischemic or coronary heart disease, cerebrovascular disease, and peripheral arterial disease. Other groups include congenital and rheumatic heart disease, deep vein thrombosis, and pulmonary embolism [1]. According to the Global Burden of Diseases (GBD) study in 2019, CVD is the leading cause of morbidity and mortality worldwide [2]. Indeed, cases are rising sharply worldwide. Between 1990 and 2019, the number of people living with CVD has risen from 271 million to 523 million respectively [2-3]. Furthermore, mortality rates from CVD are dominated by atheromatous diseases, in particular ischemic heart disease and stroke. Ischemic heart disease is responsible for around half of all CVD deaths (49.2%), while stroke accounts for a quarter (25.1%), around half of which is of ischemic etiology [2]. In Gabon, 13.3% of these diseases were estimated in 2012 [4]. Atheromatous CVD are chronic pathologies, secondary to cholesterol sticking on artery walls. Long-term exposure to high concentrations of cholesterol leads to its retention and accumulation on the inner walls of the blood vessels. Risk factors contributing to the development of CVD are classify into non-modifiable risks factors such as age, gender, ethnicity, family history, and modifiable risks factors including physical inactivity, diabetes, obesity, smoking, hypertension, and hypercholesterolemia [5-6]. However, a reduction in the morbidity and mortality of these diseases could be predicted by modifying sedentary lifestyle, smoking, diet, a reduction in hypercholesterolemia, as well as adequate drug management [5-9]. In addition, several studies have reported that high levels of low-density lipoprotein cholesterol(LDL-c) are associated with a high risk of CVD [5; 9-10]. According to the GBD study, elevated LDL-c is one of the main modifiable metabolic risk factors and one of the markers most closely associated with atheromatous CVD. In 2021, 3.81 million CVD -related deaths were attributed to elevated LDL-c levels [11]. LDL-c measurement is therefore essential in the prevention and treatment of these diseases. Since cholesterol plays a considerable role in the pathogenesis of CVD, an accurate estimate of LDL-c is crucial for better patient management. Moreover, LDL levels can be obtained in two ways: either by the more costly direct assay, or by the indirect method, which is a less costly computational method. The indirect method most widely used by laboratories is the Friedewald equation [12]. This calculated value, which is comparable to the direct method and enables an assessment of cardiovascular risk, is the basis for a classification of the subject into low risk, moderate risk, and very high risk of developing CVD. This classification is a guideline for appropriate management by the physician [13]*.* According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) of 2021, statins are the most recommended drug treatment for hypercholesterolemia, due to their lipid-lowering efficacy and safety [13-14]. They are introduced into patient management based on LDL-c classification and cardiovascular risk assessment. However, the various calculation parameters may reflect analytical error. Current analytical performance, as determined in 1990 and 1995 by NCEP, allows total errors of 9%, 13%, and 15% for total cholesterol, HDL-c and triglycerides, respectively [15]. Applying these errors to values obtained in the laboratory would lead to a change in the LDL-c value, reclassification of patients, and, consequently, a change in the treatment procedure. Consequently, the analytical error and the LDL-c calculation method can have a direct impact on the treating physician's decision. It is therefore essential to avoid classification errors that could lead to poor care management. In regard to this, the aim of this study was to determine the influence of analytical error and the method of LDL- c calculation on patient classification.

1. **MATERIALS AND METHODS**
	1. **Study site and population**

This was a retrospective study with data collection on the lipid panel carried out in the laboratories of three hospitals of Gabon, two in Libreville, the *Centre Hospitalier Universitaire Mère- Enfant Fondation Jeanne Ebori (*CHUME-FJE*)* and the *Hôpital d'Instruction des Armées OMAR BONGO ONDIMBA (*HIAOBO*)*, and one in Akanda, the *Hôpital d'Instruction des Armées d'Akanda (*HIAA*)*. Test results from patients who underwent lipid testing between January 2023 and December 2023 at the 3 sites CHUME-FJE, HIAOBO and HIAA were collected. Each data set included concentrations of total cholesterol (TC), HDL-c, LDL-c, and triglycerides (TG) measured simultaneously for each patient.

**2.2 Inclusion and exclusion criteria**

We included all patients with records in biochemistry registries running from January 1 to December 31, 2023; patients with an age range between 06 and 90 years; and patients of both sexes who performed triglycerides (TG), total cholesterol (TC), HDL-c, and LDL-c determinations. Not included were all patients with TG >4 mmol/L. A total of 2060 patients made up the study population (Figure 1).

Number of files consulted

(n=53429)

Lipid panel and number of each test measured

* Total cholesterol (TC): n=4015
* Triglycerides (TG): n=2690
* High density lipoprotein cholesterol (HDL-c): n=3385
* Low density lipoprotein cholesterol (LDL-c): n=3782

Number of patients who did simultaneous lipid panel (TC, TG, HDL-c and LDL-c)

(n=2094)

Excluded

(n=34)

Included

(n=2060)

All analysed

**Figure 1:** Flowchart of patient’s selection

**2.3 Calculation of LDL-c concentration before and after application of the total analytical error**

The LDL-c concentration was determined using the direct method and Friedewald equation (Table 1). The total analytical error (TAE) of the different lipid parameters that were used in this study are for TC ≤ 9%, TG ≤ 15%, LDL-c ≤ 12%, and HDL-c ≤ 13%. Then a widening factor is then applied to the result, which was k=2 (Table 1).

**Table 1: LDL-c concentration methods after total analytical error (TAE) application**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | **Equations** | **Equation of total analytical error (TAE)**  | **TAE value** |
| Direct measurement | $$LDLc= Direct data values$$ | $$TAE of LDL₋c$$ | ±0.12 |
| Friedewald [16] | $$LDL₋c=TC-HDL₋c-\frac{TG}{5}$$ | $$LDLc=\sqrt{\left[TAE.TC-TAE.HDL^{-}c-\frac{TAE.TG}{5}\right]}.K$$ | ±0.53 |

**2.4 Statistical analysis**

Data were entered into Microsoft Excel 2010 and analyzed using Excel 2010, Kutools TM for Excel, Epi-info 7.2.6.0, and MedCalc statistical software version 22.023. Positive and negative TAE were determined, as well as means of quantitative and qualitative variables. A p-value of less than 0.05 was statistically significant.

1. RESULTS

**Distribution of LDL-c concentration among patients according to LDL-c by method before and after application of the total analytical error (TAE)**

More than 80% of patients had normal LDL-c (Table 2). Nevertheless, before application of the TAE, 14.76% of patients had a high concentration of LDL-c with the direct method versus 16.45% with the Friedewald equation (p=0.14). After application of the positive TAE, the proportion of LDL-c concentration was statistically high with the indirect method [596 (28.93%) versus 355 (17.23%); p<0.0001] Table 2. With the application of negative TAE, the direct method was found to have more patients with high proportion of patients with elevated LDL-c concentration [268 (13.01%) versus 183 (8.89%); p<0.0001] Table 2.

**Table 2: Stratification of LDL-c according to methods used before and after total analytical error (TAE) application**

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| --- | --- | --- | --- |
| **Methods** | **Stratification of LDL-c before (TAE)** | **Stratification of LDL-c after positive (TAE)**  | **Stratification of LDL-c after negative (TAE)**  |
| **High n (%)** | **Normal n (%)**  | **High n (%)** | **Normal n (%)** | **High n (%)** | **Normal n (%)** |
| **LDL-c direct**  | 304 (14.76) | 1756 (85.24) | 355 (17.23) | 1705 (82.77) | 268 (13.01) | 1792 (86.99) |
| **Friedewald**  | 339 (16.45) | 1721 (83.55) | 596 (28.93) | 1464 (71.07) | 183 (8.89) | 1877 (91.11) |
| **p-value** | 0.14 | <0.0001 | <0.0001 |

**Risk assessment according to methods used before and after application of the TAE**

In the total population, before application of the TAE, the direct LDL-c assay yielded direct LDL-c in 5.05% of patients at very high risk and 9.71% at high risk of developing atheromatous CVD. However, using indirect LDL-c calculation methods, the Friedewald equation yielded 6.11% and 10.34% of patients, respectively, at very high and high risk of developing CVD (**Table 3**).

After applying the positive TAE to the calculation formula and to direct LDL-c, the Friedewald equation had more patients at very high risk and at high risk compared to the direct method (p<0.0001) Table 3.

However, the negative TAE on the indirect method classified fewer patients at very high risk and at high risk of developing CVD compared to the direct LDL-c (Table 3). More patients (n=+223 (10.82%) at low risk were found after application of negative TAE on the Friedewald equation compared to direct LDL-c (p<0.0001) Table 3.

**Table 3:** Risk assessment according to LDL-c methods and TAE

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| **Parameters** |  | **Methods** |
| **Risk** | LDL-c direct (1) | Friedewald (2) | **(2-1)** |
| **Before TAE application n (%)** | **Very high** | 104 (5.05) | 126 (6.11) | 22 (1.06) |
| **High** | 200 (9.71) | 213 (10.34) | 13 (0.63) |
| **Intermediate** | 1514 (73.50) | 1466 (71.17) | -48 (2.33) |
| **Low** | 242 (11.75) | 255 (12.38) | 13 (0.63) |
| **After positive TAE application n (%)** | **Very high** | 123 (5.97) | 257 (12.48) | 134 (6.51) |
| **High** | 232 (11.26) | 339 (16.45) | 107 (5.19) |
| **Intermediate** | 1507 (73.16) | 1378 (66.90) | -129 (6.26) |
| **Low** | 198 (9.61) | 86 (4.17) | -112 (5.44) |
| **After negative TAE application n (%)** | **Very high** | 86 (4.17) | 62 (3.01) | -24 (1.16) |
| **High** | 182 (8.83) | 121 (5.88) | -61 (2.95) |
| **Intermediate** | 1482 (71.94) | 1344 (65.24) | -138 (6.70) |
| **Low** | 310 (15.05) | 533 (25.87) | 223 (10.82) |

*NB:* ***2-1****: [Friedewald – direct LDL-c];* Before TAE application p-value>0.05; After positive TAE application p-value <0.0001; After negative TAE application p-value <0.0001 except for Very high risk (p-value =0.05)

**Difference in patient distribution before and after application of the total analytical error (TAE)**

After application of the positive TAE, the direct method showed a difference of 0.92% of patients (n= +19) for very high risk and 1.55% of patients (n= +32) for high risk, which means that the positive TAE reduced patients at low and intermediate risk from n=-51 which was reclassified as very high and at high risk of developing CVD (Table 4). The negative TAE, reclassified patients at very high and at high risk with the direct method to the intermediate and low risk of developing CVD (Table 4). Accordingto the Friedewald equation reclassification of patients into very high and high risk after positive TAE was found (Table 4).

**Table 4: Difference between classification frequencies before and after TAE**

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| --- | --- | --- | --- |
| **Parameters**  | **Risk** | **[B-A]** | **[D-C]** |
| **After positive TAE n (%)** | **Very high** | 19 (0.92) | 112 (5.45) |
| **High** | 32 (1.55) | 94 (4.56) |
| **Intermediate** | -7 (0.34) | -82 (3.97) |
| **Low** | -44 (2.14) | -99 (4.81) |
| **After negative TAE n (%)** | **Very high** | -18 (0.88) | -2 (0.10) |
| **High** | -18 (0.88) | -48 (2.32) |
| **Intermediate** | -32 (1.56) | -90 (4.37) |
| **Low** | 68 (3.30) | 210 (10.19) |

*NB:* ***A****= direct LDL-c without TAE;* ***B****= direct LDL-c with TAE;* ***C****=Friedewald without TAE;* ***D****= Friedewald with TAE; p-value* <0.0001

1. **DISCUSSION**

Accurate estimation of LDL-c is essential in determining a treatment strategy for lipid disorders. Several studies show the limitations and challenges of standard direct and indirect lipid assays [17]. Lipid parameters remain the main biomarkers recommended for risk stratification of atheromatous CVD [18-20]. Any improvement in the measurement and reliability of LDL-c is therefore crucial. The aim of the present study was therefore to assess the influence of analytical error and the method of LDL-c calculation on patient classification. This involved calculating LDL-c concentrations by applying the total analytical error to the result and stratifying CV risk. To this end, we used the Friedewald equation to determine LDL-c levels. The direct LDL-c levels were obtained retrospectively. Direct LDL-c was found to be elevated in 14.76% of the population, but with the indirect calculation method, this increased to 16.45%. This could reflect biases in the determination of lipid parameters. When positive TAE is applied to direct method, the number of patients with elevated LDL-c rises from 14.8% to 17.23%. This shows that 2.43% of this study population should have been classified in an elevated range. But the total admissible negative error reduces the frequency of high LDL- c from 14.76% to 13.01%. With the indirect method same line was observed where after application of the positive TAE, a high LDL-c level is more frequent. This TAE should be communicated to physicians for better treatment of the patient.

This showed that the application of this error changed the classification of patients at risk of being put on treatment from low to very high risk. On the basis of the risk classification before the application of the total analytical error, it emerged that with the direct method, 9.71% and 5.05% of patients were classified, respectively, as high and very high risk of developing CVD and had to be systematically put on lipid-lowering medication, and with Friedewald 10.34%, and 6.11% of patients were at high- and very high-risk. The difference between these two methods was 1.06% of patients (n=+22 for Friedewald). This difference represents the frequency of additional patients found using the indirect method. Given the involvement of LDL-c in the development of CVD, these additional patients will benefit from appropriate management. After application of positive TAE, patient frequency increased with two methods used. Whereas with negative TAE, the direct method led to an increase in the frequency of high- and very high-risk patients. This difference in frequency also represents the additional patients who may be candidates for lipid-lowering therapy. This suggests that using the indirect method and applying the total analytical error would lead to an increase in the frequency of high- and very high-risk patients. This in turn would have an impact on patient risk classification.

On the other hand, for both direct and indirect methods of analysis, we obtained +1.55% versus +0.92% and 4.56% versus 4.45%, respectively, of high- and very high-risk patients after application of the positive TAE. Overestimation of values has already been demonstrated in several studies for indirect methods [16, 21]. Indeed, the TAE applied to the direct method was ±0.12, whereas with the indirect method, it was ±0.53. This result was due to different lipid parameters of the indirect calculation formula where analytical error was applied. Consequently, the TAE of each parameter was added together. This meant that patients could switch from a lower to a higher risk after classification. The frequency of patients requiring treatment should increase. However, after application of the negative TAE difference, the frequency of patients at risk decreases.

Consequently, in view of these results, which reveal a difference between the direct and indirect methods, it follows that from the direct method to the indirect method before and after application of the total analytical error will underestimate risk classification. It would therefore be wise to use the indirect method, which appreciates the risk and leaves almost no patient untreated. For low-risk patients who are reclassified as being at intermediate risk of developing atheromatous CVD, the application of hygienic-dietary measures will be suggested and beneficial to health. However, patients at intermediate risk who have been reclassified as high risk will benefit from lipid-lowering drugs. Nevertheless, antihyperlipidemics drugs have side effects [22-24]. For this reason, physicians should be aware of TAE for a more appreciable interval in decision-making.

1. **LIMITATION OF THE STUDY**

This work had a number of limitations. The retrospective data obtained from the various sites did not include the patient's clinical data, such as clinical information and anthropometric data such as height, weight, and blood pressure. Those data would have provided a more detailed interpretation of the results.

1. **CONCLUSION**

The study found that analytical error and LDL-c calculation method significantly influence patient classification. It revealed that high-risk patients were more likely to be classified as CVD-related. The use of indirect methods led to higher high- and very high-risk patients. The total allowable error (TAE) also altered patient classification, shifting some from lower to higher risk. This suggests that TAE should be considered for better patient management.

**ETHICAL APPROVAL**

This work was carried out with the approval of the chief executive’s officers of the three hospitals. Anonymity and confidentiality of patients’ data were respected according to the Helsinki declaration.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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