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■ Letter

Requirement for Appropriate Methodology to Evaluate the Clinical Relevance of the Difference in Low-Density Lipoprotein Cholesterol Concentrations Obtained by Different Methods

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To the Editor

We read with great interest the original article titled, "Measuring low density lipoprotein cholesterol: comparison of direct measurement by HiSens Reagents and Friedewald Estimation" by Lee et al.[1] The authors compared two methods of low-density lipoprotein cholesterol (LDLC) measurement—direct estimation and indirect calculation (Friedewald formula)[2]—and further explored variables that might potentially influence the difference in LDLC levels obtained by these methods. However, we believe that certain concerns about their methodology warrant further discussion.

The authors compared the two methods using the following approaches: two sample paired t-test, Pearson's correlation, and percentage of concordance in the National Cholesterol Education Program's Adult Treatment Panel III categories.[1] These approaches, though appealing, are flawed and inappropriate for reasons long recognized.[3,4] Inferences based on whether the means of observations obtained by the two methods were 'significantly different' or not (using t-test) provide little information about the accuracy of the methods (which the authors wished to investigate).[3] Moreover, they do not provide any indication on whether the differences are clinically relevant. Likewise, correlation gives a measure of the relation between two sets of variables, not the agreement or lack of it between them.[4] It would not be surprising if two methods designed to measure the same parameter were strongly correlated. The strong correlation (r=0.917, P<0.001) reported by the authors is in tune with this fact. However, this approach does not address whether the two methods are in agreement or not. Besides, correlation depends on the distribution of the data. A high correlation between two methods can itself be an indication of a widely distributed sample.[5] Correlation assesses the overall association across many observations—not the individual agreement—and, as such, does not guide clinical decisions.[6] However, simple percent concordance across categories does not take into account the possible bias that may occur due to agreement by chance.

A desirable approach in lieu of the methods used by the authors would have been to use Bland-Altman plots,[3,5,7] which could help not only in evaluating the bias between the mean differences from the two methods but also in identifying the

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limit of agreement between the two methods. This limit of agreement could then be assessed for its acceptability (which should be ideally defined *a priori* based on clinical goals and biological considerations).[5] Other popular alternatives are Passing and Bablok regression[8] and Deming regression.[9] For assessing categorical concordance, Cohen's kappa co-efficient (which takes into account agreement by chance) would have been suitable.[7]

The second concern is about the performance characteristics and quality control of the biochemical assays. Direct LDLC measured by HiSens reagent was validated using a dedicated reagent (BCDR). However, the authors are silent as to whether quality control measures were implemented for the other biochemical tests (*viz*. glucose, creatinine, triglycerides, high-density lipoprotein cholesterol, and total cholesterol).

In conclusion, the authors investigate the important issue of the difference in LDLC concentrations obtained by the direct and Friedewald methods and its clinical relevance. However, the use of appropriate methodology and clarity on the above-mentioned aspects could have helped in drawing more acceptable inferences and meaningful conclusions in this regard.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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