Letter to the Editor

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Response to the editorial by Karl Lackner

https://doi.org/10.1515/cclm-2025-0334
Received March 18, 2025; accepted July 16, 2025;
published online July 30, 2025

Keywords: analytical performance specifications; cardiac troponin; reference change value; clinical decision limit; data simulation

To the Editor,

A recent edition of the journal of Clinical Chemistry and Laboratory Medicine (CCLM) features an editorial by Karl J. Lackner about the assay performance in high sensitivity cardiac troponin (hs-cTn) assays [1]. The editorial highlights recent publications on the safety of single sample cTn-based rule-out algorithms for myocardial infarction (MI). The editorial comments on the negligible effect of random analytical variation on the negative predictive value (NPV), which remains above 99 % even in the case of a coefficient of variation (CV) of 10 %. Although the data used justify this conclusion, this is only valid within the scope of direct rule-out of MI. Since hs-cTn is not solely used to rule-out patients at admission, but can also be used evaluate the change in hs-cTn concentration over one or 2 h to rule-out patients, this application comes with its own unique performance specifications (APS). We would like to illustrate why we think that such use of hs-cTn requires separate attention and possibly different APS.

Our concern rises as the few studies that specifically address the safety of the 0/1-2 h protocols have evaluated the impact of analytical variation expressed as a relative CV [2–5]. However, the delta values mentioned in the ESC guideline are absolute values and can be used at different initial concentrations of hs-cTn, indicating that the performance specifications should be established and evaluated as absolute units [6]. It is known that cardiac troponin results do not have a linear imprecision, but at the lower concentration there is an absolute imprecision expressed as standard deviation (SD) [3]. Therefore, even if compliance at the relative level is acceptable, this does not indicate compliance and safety for patients that are evaluated using absolute delta thresholds.

To our knowledge, the only paper that evaluated the impact of passing or failing absolute analytical performance (APS) on the rate of rule-in and rule-out misclassification is the study by van Schrojenstein Lantman et al. [3]. The rate of misclassification was established by simulating 10.000 estimates of a real-world patient dataset (n=3,289) using precision profiles of laboratories that passed or failed 0/1 h APS. For patients with a t=0 hs-cTnT below 12 or 14 ng/L (for resp. 0/1 h and 0/2 h), a delta of 0 ng/L resulted in false observation in 1.7 % of cases for laboratories that passed 0/1 h APS, vs. 24.2 % when laboratories failed. Aggravatingly, the risk of misclassification of these patients to rule-in increased from 0 to 3.4 % when laboratories failed to comply.

Although we agree that the 0/1 h algorithms can be robust and an excellent example of value-based laboratory medicine, our work shows that the needed analytical performance cannot be taken for granted and needs local verification, corrective actions when needed, and mitigating policies when corrective actions fail. In the case of delta troponin changes, APS should be inferred by making sure the clinical decision delta is larger than the Reference Change Value (RCV). Specifically in the case of cardiac troponin, when following the European Society of Cardiology (ESC) guideline, a two-sided 99 % sensitivity formula should be used. This results in in equation (1), where RCV is the reference change value, SD_i is the within-person biological variation in absolute units and SD_a is the analytical variation in absolute units.

$$RCV = \sqrt{2} \times 2.33 \times \sqrt{SD_i^2 + SD_a^2} \quad (1)$$

To determine the maximum allowable imprecision ($SD_{a,allowable}$), Eq. (1) can be rewritten where the delta (Δ) change is filled in for the RCV, and the SD_i is set to 0.7 ng/L (Eq. (2)) or 0 ng/L (Eq. (3)), depending on the interpretation of the laboratory whether natural biological variation is present in healthy persons.

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Table 1: Overview of used delta decision-limits for rule-out of a non-ST-elevated myocardial infarction (NSTEMI) using 0/1 h or 0/2 h time points [6].

Platform	0/1 h algorithm delta decision points						0/2 h algorithm delta decision points					
	No 1 hΔ	Low	APS (SD)	APS (CV_a)	APS (SD_i+SD_i)	APS (CV_a+CV_i)	No 2 hΔ	Low	APS (SD)	APS (CV_a)	APS (SD_i+SD_i)	APS (CV_a+CV_i)
Roche elecsys	<3	<12	0.9	8 %	0.6	5 %	<4	<14	1.2	9 %	1.0	7 %
Abbott Architect	<2	<5	0.6	12 %	NP	NP	<2	<6	0.6	10 %	NP	NP
Siemens Centaur	<3	<6	0.9	15 %	0.6	10 %	<7	<8	2.1	27 %	2.0	25 %
Access, Beckman Coulter	<4	<5	1.2	24 %	1.0	20 %	<5	<5	1.5	30 %	1.3	27 %
Clarity Singulex	<1	<2	0.3	15 %	NP	NP	TBD	TBD	TBD	TBD	TBD	TBD
Vitros Clinical diagnostics	<1	<2	0.3	15 %	NP	NP	TBD	TBD	TBD	TBD	TBD	TBD
Pathfast LSI medicine	<3	<4	0.9	23 %	0.6	15 %	TBD	TBD	TBD	TBD	TBD	TBD
Triagetrue, Quidel	<3	<5	0.9	18 %	0.6	12 %	TBD	TBD	TBD	TBD	TBD	TBD

A NSTEMI can be ruled out if the delta between t=0 and t=1/2 h is lower than "no hΔ" and both values are below "Low". The calculated absolute APS (absolute as SD, and relative at the level of "Low" as CV_a in %) are noted, also when including the within-person biological variation (SD_i) of 0.7 ng/L. When APS cannot be met the result is not possible (NP), whereas TBD indicates the decision limits are to be determined.

$$SD_{a,\,allowable} = \sqrt{\frac{\Delta^2}{2 \times 2.33^2} - SD_i^2} \quad (2)$$

$$SD_{a,\,allowable} = \frac{\Delta}{\sqrt{2} \times 2.33} \quad (3)$$

Table 1 shows delta values and required APS based on Eqs. (2) and (3). From these calculations, various aspects about required analytical performance become clear which cannot just be assumed to be met. Firstly, inclusion of biological variation of 0.7 ng/L leaves minimal room for analytical variation. Only delta values of 3 or greater have achievable APS when biological variation is considered. Secondly, relative to the threshold 'low' under which the 0/1 h or 0/2 h rule-out protocol applies, APS for some suppliers should be more tight tan the suggested 'rule of thumb of standard of 10 % (e.g. Roche), whereas for other 12–24 % CV_a is acceptable. This is attributable to the extremely low threshold under which these rule-out algorithms are valid (e.g. patients can be ruled out using the Vitros when the delta is <1 and patient values are <2). Inherently, the rounding to integer units prevents this rule-out from happening in the first place, and provides a mission impossible by definition. What these numbers do indicate is at which APS, both absolute and relative, one can safely assume that there is less than 1 % chance of falsely exceeding the delta due to analytical variation. Lastly, it becomes clear how much the APS for the 0/1 h and 0/2 h differ and that this discrepancy is vastly different among manufacturers. Considering the data presented before regarding Roche and the marginal relative increase in allowable performance (7.6–8.7 % at the level of 12 and 14 ng/L) and the substantial impact on incorrect rule-in of rule-out patients (which reduces from 3.4 % in the simulation of van Schrojenstein Lantman to 0.001 %), we can gauge that meeting APS is absolutely vital and that a ballpark '10 % CV_a is okay' does not cut the cake for delta-based rule-out.

Lastly, the editorial of Lackner highlighted that an elevated CV had a negligible effect for direct rule-out NPV, we cannot assume similar conclusions for delta-based decision limits. Namely, patients who are subjected to a delta-based decision limit already did not pass the direct rule-out, and thus *a-priori* risk is higher in this cohort. Whilst the diagnosis may be identical to direct rule-out, delta rule-out is done in a different population and requires different APS, and thus highlights the need for separate evaluation and monitoring of its analytical and clinical efficacy. This includes the application of hs-cTn results in clinical decision aids and (artificial intelligence (AI)) risk scores that incorporate hs-cTn and the time between sampling [4, 7]. Application of such tools in clinical practice requires tailoring of the APS while incorporating the impact of uncertainty on composite end results [8]. Ideally, this incorporates the inherent misclassification, rather than assuming perfect clinical specificity and sensitivity.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
Conflict of interest: The authors state no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

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