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Letters to the Editor

External Quality Assessment Testing Near the Limit of Detection for High-Sensitivity Cardiac Troponin Assays

To the Editor:

The latest laboratory recommendations on high-sensitivity cardiac troponin (hs-cTn)[1] endorse imprecision ≤10% at the 99th percentile with a total analytic error of <3.5 ng/L for concentrations ≤10 ng/L *(1)*. However, for physicians using the European Society of Cardiology guideline's alternative 0/1-h early rule-in and rule-out algorithm, which uses the limit of detection (LoD) for an immediate rule-out, laboratories may need to limit total error to <1 ng/L to prevent patient misclassification *(1)*. This metric may be difficult for laboratories to achieve and maintain over the long term when instrument performance and reagent lot-to-lot variation can easily exceed this error limit *(2)*.

There is an increasing appreciation that proficiency testing materials are required at <10 ng/L if physicians are making clinical decisions on hs-cTn results in this low range *(1, 2)*. In this regard, the United Kingdom–National External Quality Assessment Service (UK-NEQAS) is producing material at this low concentration range, with a lyophilized sample in the concentration range of 3 to 20 ng/L being produced and used for the hs-cTn assays *(3)*. This material (which needs to be reconstituted with 500 μL of distilled water) for the UK-NEQAS cardiac markers survey is manufactured using pooled female human plasma or serum base matrix with different levels obtained by the addition of the troponin complex *(3)*. The initial published report from 33 instruments on 1 such low external quality assessment (EQA) material (which is not commutable) yielded an overall mean of 3.45 ng/L and SD of 0.44 with an overall CV of 12.8% *(4)*. Rounding may increase the variation at low concentrations. The previously reported variation of Abbott's hs-cTnI assay near the LoD (n = 4 sites across 5 instruments) in EDTA plasma at 1.2 ng/L (CV = 33%; SD = 0.4 ng/L) increased when whole numbers were used in the calculations (CV = 42%; SD = 0.5 ng/L) *(5)*.

The Institute for Quality Management in Healthcare (IQMH) provides internationally recognized proficiency testing programs through its Centre for Proficiency Testing and is accredited by the American Association for Laboratory Accreditation. In January 2018, IQMH provided 3 vials for assessment of Abbott's hs-cTnI assay, with the assigned hs-cTnI values being the mean across the Abbott peer group with the allowable performance limits of ±25.0% from the mean. The EQA material (pooled human sera) arrives ready to use, with testing for hs-cTnI to be performed within 24 h and the results reported in whole numbers. Across 32 instruments, vial 1 had a mean = 35 ng/L, SD = 3.1 ng/L, and CV = 8.9% (n = 32); vial 2, mean = 15 ng/L, SD = 1.3 ng/L, and CV = 8.7% (n = 32); and vial 3, mean = 2 ng/L, SD = 0.8 ng/L, and CV = 40% (n = 18, with 14 sites reporting "<"). Across the 4 hospital sites within Hamilton that use Abbott's hs-cTnI assay (site A, ARCHITECT ci16200; site B, ARCHITECT ci8200; site C, ARCHITECT ci4100; site D, ARCHITECT ci8200), the range of concentrations for vial 1 was 32 to 38 ng/L (allowable limits, 26–44 ng/L); for vial 2, 13 to 15 ng/L (allowable limits, 11–19 ng/L); and for vial 3, 1 to 3 ng/L (allowable limits not assessed because of lack of consensus; see Fig. 1 for vial 3 comparison).

The findings from this IQMH survey are noteworthy, as the CV is <10% for concentrations near the reported male 99th percentile of 34 ng/L and the female 99th percentile of 16 ng/L *(4)*. However, for vial 3 (not spiked), there was variation in reporting at the low end with 1 site reporting <1 ng/L, 6 sites reporting 1 ng/L, 11 sites reporting <2 ng/L, 8 sites reporting 2 ng/L, 3 sites reporting 3 ng/L, 1 site reporting 4 ng/L, and 2 sites reporting <10 ng/L on this EQA material. This variation in reporting for vial 3 was also evident for hs-cTnT in this survey with 1 site reporting <3 ng/L, 3 sites reporting 3 ng/L, 3 sites reporting 4 ng/L, 1 site reporting <5 ng/L, and 1 reporting <13 ng/L. These data indicate that there is variation in hs-cTn measurements near the LoD and differences in the lower limit of reporting across laboratories, with 3 sites having a lower reportable limit of ≥10 ng/L and, thus, not able to use the European Society of Cardiology's alternative rule-out algorithms. Specifically, for hs-cTnI (n = 30 sites), 60% reported a concentration <2 ng/L with 40% reporting a concentration ≥2 ng/L on vial 3. Of the 18 sites with results that generated an average of 2 ng/L for this material, 33% of the results were <2 ng/L. These data support the recent AACC Academy/IFCC Task Force second practice recommendation: "During initiation of hs-cTn testing, clinical laboratories should validate the LoB [limit of blank], LoD outside the US, or LoQ [limit of quantitation] as applicable per FDA [Food and Drug Administration] regulations in the US. These analytical parameters should be validated minimally on an annual basis or more frequently as deemed necessary" *(1)*, as this may help achieve greater comparability near the LoD. Moreover, the lack of consensus between sites on the lower reportable limit concentration calls

[1] Nonstandard abbreviations: hs-cTn, high-sensitivity cardiac troponin; LoD, limit of detection; UK-NEQAS, United Kingdom–National External Quality Assessment Service; EQA, external quality assessment; IQMH, Institute for Quality Management in Healthcare.

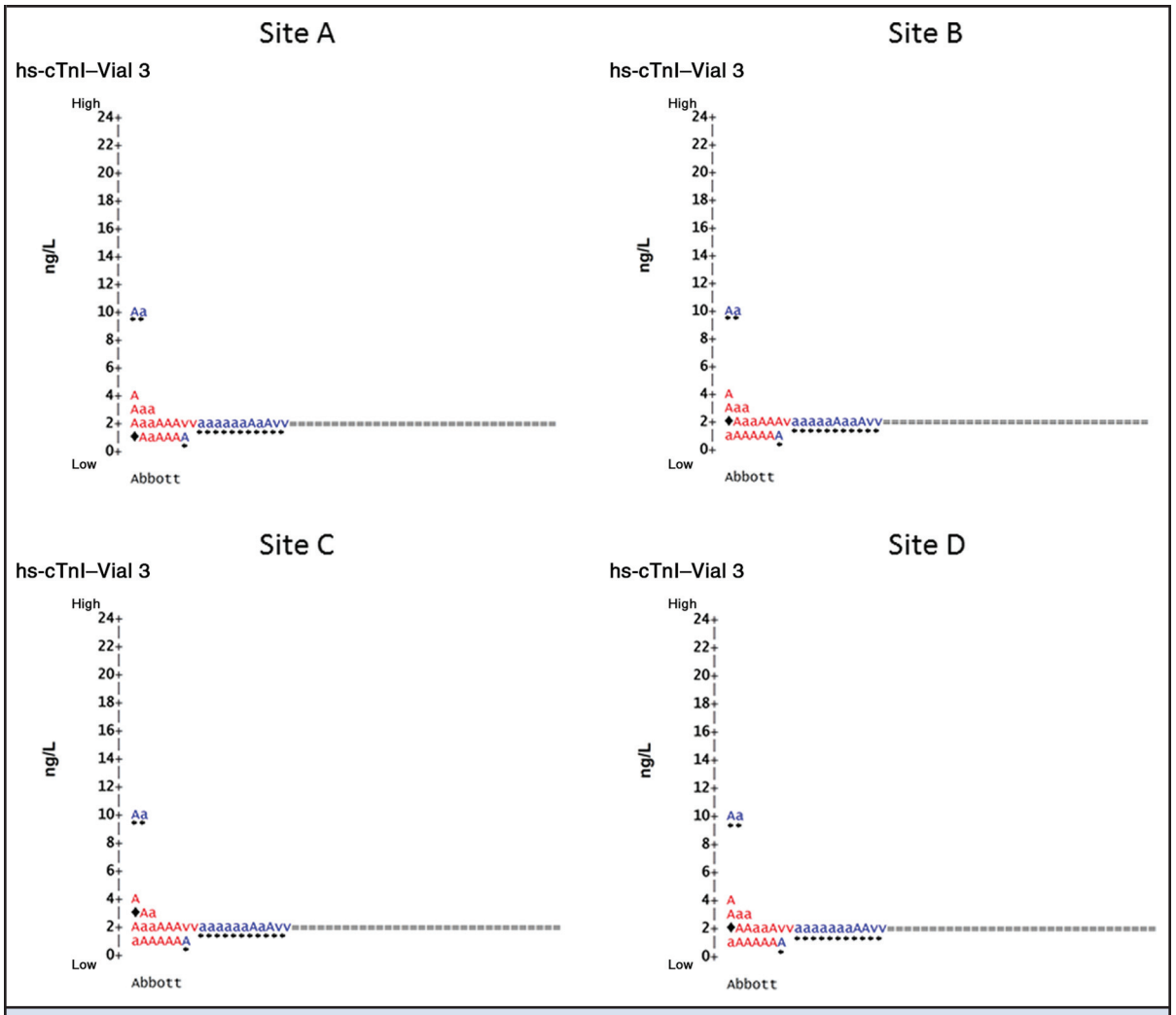

Fig. 1. Reported hs-cTnI concentrations from 4 hospital sites (sites A–D) within a city (Hamilton, ON, Canada) in an EQA survey at a concentration near the LoD.

The solid diamonds (◆) are the concentrations reported per the hospital site, with the (=) line being the mean/assigned value. Results with an * below the letter on the histograms are reported as less than (<) (n = 14) and are not included in the calculation of the all-methods mean (n = 18; mean = 2 ng/L). Per the legend from IQMH: A = Abbott Architect C4000, C8000, C16000; a = Abbott Architect Ci4100, Ci8200, Ci16200; v = Abbott CI 8200.

for efforts to standardize reporting at the lower limit.

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References

1. Wu AHB, Christenson RH, Greene DN, Jaffe AS, Kavsak PA, Ordonez-Llanos J, Apple FS. Clinical laboratory practice recommendations for the use of cardiac troponin in acute coronary syndrome: expert opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018;64:645–55.
2. Kavsak PA, Worster A, Oliver R, Clark L, Parry D, Randell E, et al. Variability between reagent lots for high-sensitivity cardiac troponin I may affect performance of early rule out strategies. Can J Cardiol 2018;34:209.e5–e6.
3. UK-NEQAS Cardiac Markers. http://www.ukneqas-cm.org.uk/wp-content/uploads/2018/06/SM18-Copy.pdf (Accessed June, 2018).
4. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015;386:2481–8.
5. Kavsak PA, Beattie J, Pickersgill R, Ford L, Caruso N, Clark L. A practical approach for the validation and clinical implementation of a high-sensitivity cardiac troponin I assay across a North American city. Pract Lab Med 2015;1:28–34.

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