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Issues Related to High-Sensitivity Troponin Assays — Reply —

We appreciate the comments from Tada et al regarding our recent publication in *Circulation Reports*,[1] which evaluated the diagnostic performance of the 0-hour/1-hour (0/1-h) algorithm with both high-sensitivity cardiac troponin (hs-cTn) T and I, as recommended in the 2015 European Society of Cardiology (ESC) guideline, and showed that the algorithm could effectively rule-in or rule-out patients with acute myocardial infarction (AMI).

First, Tada et al mentioned that hs-cTnI assays have different cut-off values and diagnostic performance, and that the diagnostic performance of the 0/1-h algorithms is assay specific, and they are concerned our meta-analysis of 6 studies using different hs-cTnI assays is probably incorrect and that the results of studies using different assays should be reported separately. In this regard, a meta-analysis according to the assay method may be warranted, but we have determined that there are not enough studies at this stage to allow for such a meta-analysis. We used the same meta-analysis approach as in previous research papers.[2–4]

Conversely, another opinion suggested that a systematic review and meta-analysis should be conducted integrating hs-cTnI and T data, but this was not done for the following reasons: the greater potential for heterogeneity in the meta-analysis; none of the previous published reports as such combined the 2 troponin assays; and the anticipation that clinicians would not be able to translate the integrated results into actual patient care, even if they could be presented.

In the first place, detection of an elevated hs-cTn value above the 99th percentile upper reference limit (URL) is defined as myocardial injury,[5] and the 99th percentile should be determined in a healthy population. The 99th percentile URL (i.e., the cut-off value) is derived from hs-cTn measurements in an apparently healthy cohort and is dependent on participant selection, statistical analyses, and analytical and biological variability.[6] It has been shown to be influenced by age, sex, and the presence of comorbidities;[7] for example, it is higher with increasing age, higher in males than in females, and appears to vary by race.[8] In statistical analyses, robust statistical methods are also considered inappropriate, and non-parametric methods are preferred.[7] However, at least, the criteria to select healthy reference subjects and statistical analyses have not yet been standardized across assay methods, and those are issues for future investigation. In the future, a guidance will be provided to define the establishment of a uniform or standards for these hs-cTn assays, which would standardize the 99th percentile URL and increase the accuracy of the assay.

In our study, a systematic review and meta-analysis, albeit somewhat imprecise, we confirmed that the ESC 0/1-h algorithm with both hs-cTnI and hs-cTnT has valid diagnostic performance for the diagnosis and exclusion of AMI in patients with chest pain without ST-segment elevation.[1] At this present time, we reiterate the need to understand the diagnostic performance of the assay methods employed at each institution and to use them clinically.

Second, Tada et al pointed out an error for the fifth-generation troponin T assay. We are grateful for this and are considering issuing an Erratum.

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Disclosures

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References

1. Nomura O, Hashiba K, Kikuchi M, Kojima S, Hanada H, Mano T, et al. Performance of the 0-hour/1-hour algorithm for diagnosing myocardial infarction in patients with chest pain in the emergency department: A systematic review and meta-analysis. *Circ Rep* 2022; **4:** 241–247.
2. Lee CC, Huang SS, Yeo YH, Hou YT, Park JY, Inoue K, et al. High-sensitivity-cardiac troponin for accelerated diagnosis of acute myocardial infarction: A systematic review and meta-analysis. *Am J Emerg Med* 2020; **38:** 1402–1407.
3. Burgos LM, Trivi M, Costabel JP. Performance of the European Society of Cardiology 0/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin: Systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care* 2021; **10:** 279–286.
4. Chiang CH, Chiang CH, Lee GH, Gi WT, Wu YK, Huang SS, et al. Safety and efficacy of the European Society of Cardiology 0/1-hour algorithm for diagnosis of myocardial infarction: Systematic review and meta-analysis. *Heart* 2020; **106:** 985–991.
5. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *Circulation* 2018; **138:** e618–e651.
6. Aakre KM, Saenger AK, Body R, Collinson P, Hammarsten O, Jaffe AS, et al. Analytical considerations in deriving 99th percentile upper reference limits for high-sensitivity cardiac troponin assays: Educational recommendations from the IFCC Committee on Clinical Application of Cardiac Bio-Markers. *Clin Chem* 2022; **68:** 1022–1030.
7. Apple FS, Wu AHB, Sandoval Y, Sexter A, Love SA, Myers G, et al. Sex-specific 99th percentile upper reference limits for high sensitivity cardiac troponin assays derived using a universal sample bank. *Clin Chem* 2020; **66:** 434–444.
8. Gore MO, de Lemosd JA. Clinical relevance of the 99th percentile upper reference limit for high-sensitivity cardiac troponin assays. *Clin Chem* 2020; **66:** 403–405.

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