JACC: CASE REPORTS VOL. 30, NO. 14, 2025

ISCHEMIC HEART DISEASE

CLINICAL CASE

Defining Chronic Myocyte Injury With hs-cTnT

The Importance of Serial Measurements and the Value of hs-cTnI

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ABSTRACT

BACKGROUND There is increasing awareness of the differing characteristics of troponin subunits.

CASE SUMMARY We present a case where an elevation of high-sensitivity troponin T (hs-cTnT) (>6× 99th percentile) beyond the single-sample rule-in threshold led to an erroneous diagnosis of acute coronary syndrome (ACS). After exhaustive biochemical tests proving chronic myocardial injury, we also determined that 4 different high sensitivity assays for troponin I revealed values well below their respective 99th percentiles. This uniquely highlights the difference in troponin subunit characteristics in chronic myocyte injury and dispels any notion that the difference relates to assay characteristics.

DISCUSSION Chronic elevations of hs-cTnT can be sufficiently large to surpass single rule-in thresholds in some ACS pathways, but this case stresses the importance of the delta value regardless of the degree of elevation of the presentation sample. In cases of diagnostic doubt for ACS, clinicians should consider measuring hs-cTnI as an alternative troponin. (JACC Case Rep. 2025;30:103631) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

High-sensitivity cardiac troponin (hs-cTn), either T or I subunit, are recommended as the preferred biomarkers for diagnosis of myocardial infarction (MI). A single-sample elevation of high-sensitivity cardiac troponin T (hs-cTnT) several times the 99th percentile is used to classify rule-in for MI in most accelerated diagnostic protocols.[1] In the right context, this is often regarded as a good predictor for MI. However, the Fourth Universal Definition of MI[2] indicates that any nondynamic elevation in hs-cTn be considered as potential chronic myocardial injury (CMI), regardless of the degree of elevation beyond the 99th percentile. Both hs-cTnT and high-sensitivity cardiac troponin I (hs-cTnI) assays are thought to give elevated results in CMI,[3,4] but the relationship of each subtype of troponin to

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 30, 2024; revised manuscript received January 7, 2025, accepted January 30, 2025.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2025.103631

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CKD = chronic kidney disease

CMI = chronic myocardial infarction

hs-cTn = high-sensitivity cardiac troponin

MI = myocardial infarction

the severity of chronic kidney disease or other causes of chronic myocyte injury has not been well studied. We present a case of CMI, arrived at after exhaustive exclusion of other possible diagnoses, in which initial hs-cTnT was significantly elevated (>6× 99th percentile), resulting in an erroneous diagnosis of non-ST-segment elevation myocardial infarction, whereas hs-cTnI on multiple alternative platforms (2 criterion-standard central laboratory and 2 high-sensitivity point of care troponin I) were all below their respective 99th percentiles. Our case illustrates the need to assess dynamic shifts in troponin values and the benefit of analyzing troponin I to clarify the diagnosis.

HISTORY OF PRESENTATION

An 84-year man with a history of coronary artery bypass surgery presented to the accident and emergency department (AED) with sudden-onset left-side chest pain that was dull and nonpleuritic. His electrocardiogram was unremarkable, with no overt electrical evidence for ischemia. A subsequent echocardiogram revealed preserved left ventricular function with no regional wall motion abnormalities.

PAST MEDICAL HISTORY

The patient had several comorbidities, including hypertension, type 2 diabetes, dyslipidemia, chronic kidney disease (CKD) stage 3 with an estimated glomerular filtration rate of 47 mL/min/1.73 m^2 (stable for the patient). He also suffered from severe peripheral vascular disease with limited mobility owing to severe claudication.

TABLE 1 Summary of High-Sensitivity Cardiac Troponin T and I Results at Baseline and 1 Hour at Index Presentation

Troponin Assay	LOD	10% CV	99th Percentile	Result at baseline	Result at 1 h
Roche Elecsys TnT	3	4	14	109	107
Abbott Alinity TnI	1.6	4.7	26.2	10.1	9.1
Quidel Triage MeterPro Device TnI—Whole Blood[a]	1.7	6	20.5	4.6	5.1
Quidel Triage MeterPro Device TnI—Plasma[a]	1.2	6	20.5	5.2	5.1
Siemens Attellica (central lab) hs-cTnI	1.6		53	10	10
Siemens Atellica VTLi TnI[a]	1.6	4	22.9	6.3	

Values are ng/L. The serum creatinine was 126 mmol/L with an estimated glomerular filtration rate of 46 mL/min per m^2. [a]Point-of-care assay.

CV = coefficient of variation; LOD = limit of detectiion.

TAKE-HOME MESSAGES

- There are major differences between troponin subunit levels in chronic myocyte injury, with the propensity of markedly elevated troponin T levels but troponin I within normal limits
- Elevations of high-sensitivity troponin T, in chronic myocyte injury, can surpass single-sample rule-in thresholds for ACS, emphasizing the need for repeated samples regardless of the value of the presentation sample. Future assays, in development, may allow targeting of troponin epitopes in smaller fragments of troponin T, which are particularly frequent in renal failure, thus allowing differentiation from acute myocardial infarction.

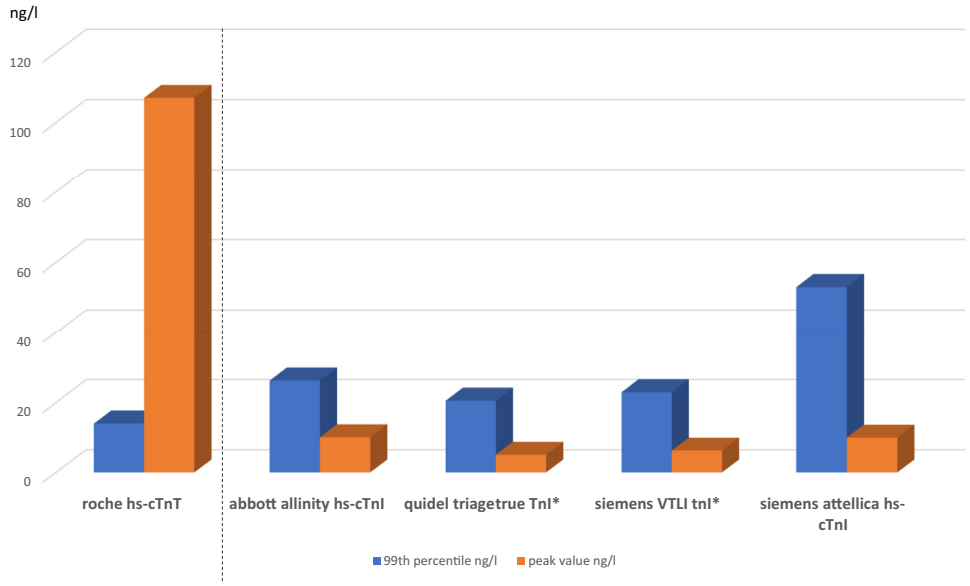
DIFFERENTIAL DIAGNOSIS

He was diagnosed as suffering a non-ST-segment elevation myocardial infarct based on hs-cTnT of 109 ng/L at presentation (Roche Diagnostics; 99th percentile: 14 ng/L). He was prescribed dual antiplatelet therapy (aspirin and clopidogrel) as well as low-molecular-weight heparin (fondaparinaux). Because he was enrolled in a randomized controlled trial (MACROS 2[5]), he consented to a range of other investigations, including 2 central laboratory hs-cTnI assays and 2 point-of-care hs-cTnI assays. His second hs-cTnT value was 107 ng/L 1 hour later (randomized to European Society of Cardiology 0-1 hour pathway). Whole blood was analyzed on the Siemens VTLI hs-cTnI point-of-care system,[6,7] and both whole blood and plasma on the Quidel Triage True hs-cTnI analyzer.[8] Frozen serum samples were subsequently also tested after thawing on central laboratory Siemens Attellica and Abbot Allinity assay. **Table 1** and **Figure 1** present the results with the corresponding limit of detection, 10% coefficient of variation, and 99th percentile for each assay.

INVESTIGATIONS

Interference investigations informed by the Fourth Universal Definition of MI[2] were conducted in house and by Roche. Similar hs-cTnT and hs-cTnI results were obtained on baseline samples in heterophilic blocking tubes (Scantibodies Laboratory) and after polyethylene glycol precipitation, suggesting that neither heterophilic antibodies nor macrotroponin was contributing to the analytical discrepancies.

FIGURE 1 Chronic Myocyte Injury: High-Sensitivity Troponin T and I (hs-cTnT, hs-cTnI) Results at Index Presentation



*represent point of care assays measuring whole blood results troponin I.

Serum immunoglobulins were measured and found to be within normal ranges (IgG: 11.7 g/L [normal range: 6.0-16.0 g/L]; IgA: 3.8 g/L [0.80-4.00 g/L]; IgM: 1.51 g/L [0.50-2.00 g/L]). Creatine kinase MB isoenzyme (3 μg/L; reference interval: ≤6 μg/L) and myoglobin (57 ng/L) were within the reference intervals. Size-exclusion chromatography was performed to assess for high-molecular-weight interfering factors from 0.2 to 970 kD; no increased reactivity with the hs-cTnT assay (TnT hs v2.1 sales lot kit) was found in fractions where proteins with molecular weight of IgM (~970 kD) or IgG (~150 kD) are expected, excluding IgG/IgM interfering factors. On cardiology review, his antiplatelet therapy was withdrawn because chronic myocardial injury, explained by the patient's multiple pathologies, was deemed more likely than MI.

MANAGEMENT

He had several subsequent presentations to ho-spital over the ensuing year. Table 2 demonstrates serial TnT measurement, and hsTnI when sampled, during subsequent presentations with paired renal function analysis, showing chronic elevation with only a modest decline in renal function. hs-TnI results were consistently well below the 99th percentile.

OUTCOME AND FOLLOW-UP

The patient did not go undergo further investigations, such as magnetic resonance imaging. The case was managed by clinicians who thought that a conservative strategy for presumed MI was appropriate for an octogenarian with multiple comorbidities. Once investigations were complete the acute coronary syndrome treatment was withdrawn.

DISCUSSION

This case illustrates the striking differences that can occur between hs-cTnT and several hs-cTnI assays in chronic myocyte injury, with other potential causes for hs-cTnT elevation having been excluded. It also highlights the need for serial samples and adherence to dynamic change in hsTn's even when the baseline troponin is several times greater than the 99th percentile (>7× in this case). Rule-in single-presentation-sample hs-cTn's with accelerated diagnostic protocols should ideally be corroborated with the diagnosis refined by serial samples, or occasionally by alternate hsTn's, when the clinical picture is inconsistent with myocardial ischemia or infarction.

The majority of research relating to troponin kinetics and CKD is in end-stage renal disease (ESRD)

TABLE 2 Serial Measurement of High-Sensitivity Troponin T and I (Various Assays) and Renal Function During Index and Subsequent Presentations

Date	Roche Elecsys hs-TnT, ng/L (≤14[a])	Abott Allinity hs-cTnI, ng/L (<26.2[a])	Quidel POCT hsTnI, ng/L (<20.5[a])	Siemens POCT hs-TnI, ng/L (<22.9[a])	eGFR, mL/min/1.73 m^2	Creatinine, μmol/L
May 29, 2023, baseline	109	10.1	4.6 (WB), 5.2 (plasma)	6.3	46	128
May 29, 2023, +1 h	107	9.1	5.2 (WB), 5.1 (plasma)	Invalid sample		
February 15, 2024	84				31	171
May 16, 2024	120		3.1 (blood)		32	166

[a]Assay 99th percentile value.
eGFR = estimated glomerular filtration rate; hs-Tn = high-sensitivity troponin; POCT = point-of-care testing; WB = whole blood.

with hemodialysis; therefore, differential binding of cTnT and cTnI to polysulphone dialyzer membranes is not applicable in this case.[9] The prevalence of elevated TnT and TnI in CKD has also been reported and can differ substantially.[10,11] However, it is unlikely that CKD alone is the sole causative factor to explain the difference in assay values. The patient had multiple risk factors contributing to troponin release, including hypertension, peripheral vascular disease, and known coronary artery disease. Chronic wall tension and raised end-diastolic pressures are known to result in chronically raised hs-cTnT.[12] It is also known that ESRD patients have smaller proteoforms of troponin compared with troponin release in acute MI: approximately 15-18 kD. TnT and TnI have different sizes: 37 kD and 24 kD, respectively.[13] Wu et al found fragmentation products in rats to be of differing sizes depending on their original isoform: TnT had larger fragmentation products at 33, 27, and 25 kD, whereas TnI degraded to 15 and 16 kD.[14] Bearing this in mind, one theory is that TnI fragments are smaller than TnT products in chronic injury and CKD. The epitopes for detection differ between cTnT and cTnI. Epitope sizes for cTnI display a wider spread compared with cTnT, and so there is a higher degree of chance that cTnI fragments go undetected. cTnT, however, given the more uniform, centrally located epitopes, are more likely to pick up the majority of epitopes, even if there is fragmentation.[15]

It has been demonstrated that that both elevated TnT and TnI carry prognostic value, with TnI more predictive of cardiovascular death in particular. Steiro et al found that TnT assays diagnosed approximately 4 times more patients with CMI compared with TnI assays, although the reason for the marked discrepancy remains biologically unclear on a molecular level.[3]

Hammarsten et al[16] describe the effects of proteolysis on the release of cTn. Because of the structure of the troponin complex, TnT is the only fragment that has affinity to the sarcomere and so remains bound while TnI and TnC are degraded and released more quickly when subjected to stress or necrosis. They also describe the release of exospheres, small blebs released because of myocardial stress but not overt cardiac necrosis. These blebs contain damaged mitochondria and sarcomere fragments, and this process increases in frequency depending on the level of cardiac stress, with there also being a dependency on cardiac macrophages. It may be that in chronic blebbing, and importantly not in acute necrosis due to myocardial infarction, chronic release of sarcomere-bound TnT constantly occurs, along with free TnI. Free TnI is cleared, whereas sarcomere-bound TnT undergoes a delayed degradation process, resulting in a chronically elevated level of TnT but not TnI.

It should be noted that another explanation is underlying skeletal disease with possible reexpression of hs-cTnT.[17] The present patient had a normal reatine kinase MB value, and no symptoms of musculoskeletal disease were recorded. Schmid et al[18] demonstrated a significant discrepancy between cTnT and cTnI in skeletal disease, suggesting cross-reactivity of skeletal and cardiac TnT. However, according to Roche package inserts for current-generation assays, there is minimal cross-reaction with skeletal muscle troponin.

CONCLUSIONS

Chronic elevations of hs-cTnT can be sufficiently large to surpass single rule-in thresholds in some ACS pathways, but the present case stresses the importance of the delta value, regardless of the degree of elevation of the presentation sample. In cases of diagnostic doubt for ACS, clinicians should measure troponin I. Future assays, in development, may allow targeting of troponin epitopes in smaller fragments of troponin T, which are particularly frequent in renal failure, thus allowing differentiation from acute MI.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Khand has been a speaker or expert member for and has received fees from Bayer, Daiichi Sankyo, AstraZeneca, Menarini, St Jude, and Abbot Vascular; has received research funds from Bayer Medical, Menarini, and Dragons Den awards (Liverpool University Hospitals); holds research contracts with Abbott Diagnostics; is the director for Northwest Educational Cardiac Group, a not-for-profit medical educational group, and has received sponsorship for educational courses from Bayer, AstraZeneca, Genzyme (Sanofi), Daiichi Sankyo, Circle Cardiovascular, Menarini, and Circle; and works with the Northwest Coast Innovation Agency in England as a clinical champion for high-sensitivity troponins with funds awarded (both personal payment for work and transformation funding) for dissemination of accelerated diagnostic pathways. Dr Collinson is an Associate Editor of *The Journal of Applied Laboratory Medicine*, has received honoraria for lectures from Siemens Healthineers, is on the advisory boards of Psyros Diagnostics and Radiometer, has previously advised Siemens Healthineers and LumiraDx, and is a consultant for the IFCC Committee on Clinical Applications of Cardiac Bio-Markers (unpaid). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Collinson P, Dakshi A, Khand A. Rapid diagnostic strategies using high sensitivity troponin assays: what is the evidence and how should they be implemented? *Ann Clin Biochem*. 2023;60(1). https://doi.org/10.1177/00045632221100347

2. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Russ J Cardiol*. 2019;24(3):107–138. https://doi.org/10.15829/1560-4071-2019-3-107-138

3. Steiro OT, Aakre KM, Tjora HL, et al. Association between symptoms and risk of non-ST segment elevation myocardial infarction according to age and sex in patients admitted to the emergency department with suspected acute coronary syndrome: a single-centre retrospective cohort study. *BMJ Open*. 2022;12(5):e054185. https://doi.org/10.1136/bmjopen-2021-054185

4. Brunner FJ, Kröger F, Blaum C, et al. Association of high-sensitivity troponin T and I with the severity of stable coronary artery disease in patients with chronic kidney disease. *Atherosclerosis*. 2020;313:81–87. https://doi.org/10.1016/j.atherosclerosis.2020.09.024

5. Khand A, Hatherley JDA, et al. Safety and feasibility of triage and rapid discharge of patients with chest pain from emergency room: a pragmatic, randomised noninferiority control trial of the European Society of Cardiology (ESC) 0-1 hour pathway vs conventional 0-3 hour accelerated. *Am Heart J*. 2024;278:235–247. https://doi.org/10.1016/j.ahj.2024.08.005

6. Christenson RH, Frenk LDS, De Graaf HJ, et al. Point-of-care: roadmap for analytical characterization and validation of a high-sensitivity cardiac troponin I assay in plasma and whole blood matrices. *J Appl Lab Med*. 2022;7(4):418. https://doi.org/10.1093/jalm/jfac028

7. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem*. 2012;58(1):54–61. https://doi.org/10.1373/clinchem.2011.165795

8. Dakshi A, Hatherley JCP, et al. Evaluation of the analytical and clinical performance of a high-sensitivity troponin I point-of-care assay in the Mersey Acute Coronary Syndrome Rule Out Study (MACROS-2). *Clin Chem Lab Med*. 2025;63(2):422–432. https://doi.org/10.1515/cclm-2024-0138

9. Gaze DC, Collinson PO. Cardiac troponin I but not cardiac troponin T adheres to polysulfone dialyser membranes in an in vitro haemodialysis model: Explanation for lower serum cTnI concentrations following dialysis. *Open Heart*. 2014;1:e000108. https://doi.org/10.1136/openhrt-2014-000108

10. Vestergaard KR, Jespersen CB, Arnadottir A, et al. Prevalence and significance of troponin elevations in patients without acute coronary disease. *Int J Cardiol*. 2016;222. https://doi.org/10.1016/j.ijcard.2016.07.166

11. Árnadóttir Á, Falk Klein C, Iversen K. Head-to-head comparison of cardiac troponin T and troponin I in patients without acute coronary syndrome: a systematic review. *Biomarkers*. 2017;22(8):701–708. https://doi.org/10.1080/1354750X.2017.1335779

12. Roe MT, Armstrong PW, Fox KAA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367(14):1297–1309. https://doi.org/10.1056/nejmoa1205512

13. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res*. 2017;113(14):1708–1718. https://doi.org/10.1093/cvr/cvx183

14. Wu AHB. Release of cardiac troponin from healthy and damaged myocardium. *Front Lab Med*. 2017;1(3):144–150. https://doi.org/10.1016/j.flm.2017.09.003

15. Airaksinen KEJ, Aalto R, Hellman T, Vasankari T, Lahtinen A, Wittfooth S. Novel troponin fragmentation assay to discriminate between troponin elevations in acute myocardial infarction and end-stage renal disease. *Circulation*. 2022;146(18):1408–1410. https://doi.org/10.1161/circulationaha.122.060845

16. Hammarsten O, Wernbom M, Mills NL, et al. How is cardiac troponin released from cardiomyocytes? *Eur Hear J Acute Cardiovasc Care*. 2022;11(9):718–720. https://doi.org/10.1093/ehjacc/zuac091

17. du Fay de Lavallaz J, Prepoudis A, Wendebourg MJ, et al. Skeletal muscle disorders: a noncardiac source of cardiac troponin T. *Circulation*. 2022;145(24):1764–1779. https://doi.org/10.1161/circulationaha.121.058489

18. Schmid J, Liesinger L, Birner-Gruenberger R, et al. Elevated cardiac troponin T in patients with skeletal myopathies. *J Am Coll Cardiol*. 2018;71(14):1540–1549. https://doi.org/10.1016/j.jacc.2018.01.070

KEY WORDS chronic myocyte injury, high-sensitivity troponin subtypes, suspected acute coronary syndromes