Cardiac Troponins and SARS-CoV-2:

Subclinical Myocardial Injury as he Long Shadow of the Pandemic

Vincenzo Castiglione, MD[1,2], Aldo Clerico, MD[1,2], Michele Emdin, MD, PhD[1,2], FESC, FHSA

1. Health Science Interdisciplinary Center, Scuola Superiore Sant'Anna, Pisa, Italy

2. Cardiology Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy

Key words: troponin; SARS-CoV-2; COVID-19.

Conflicts of interest: none

Word count: 1293

Address for correspondence

Michele Emdin, MD, PhD, FESC, FHFA

Scuola Superiore Sant'Anna, Pisa, Italy

Fondazione Toscana Gabriele Monasterio, Pisa, Italy

Via Giuseppe Moruzzi 1, 56124

Email: m.emdin@santannapisa.it, emdin@ftgm.it

Cardiac troponins have transformed cardiovascular medicine: once confined to the emergency department as a rule-in/out tool for the diagnosis of acute myocardial infarction, high-sensitivity

assays have shown that troponin concentrations well below the conventional 99th percentile diagnostic threshold carry strong, graded, and independent prognostic information for cardiovascular morbidity and mortality in the general population.[1] Nevertheless, the notion that subclinical myocardial injury exists on a continuum rather than as a binary phenomenon has only slowly permeated clinical practice, where troponin measurement remains largely restricted to the acute coronary syndrome diagnostic work-up.

The study by Omland and colleagues from the Trøndelag Health Study (HUNT)[2] provides a compelling argument for broadening that perspective, while raising fundamental questions about the long-term cardiovascular legacy of the coronavirus disease 2019 (COVID-19) pandemic.

Acute troponin elevations in hospitalised COVID-19 patients were among the earliest and most consistently reported cardiovascular hallmarks of the pandemic. Across multiple cohorts and healthcare systems, circulating troponin concentrations correlated with disease severity, need for mechanical ventilation, and in-hospital mortality, in proportion to both the infectious burden and underlying comorbid cardiovascular disease.[3,4] These observations established myocardial injury as a defining feature of severe COVID-19.[5] What remained unknown was whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection across the full epidemiological spectrum, and not merely among hospitalised patients, leaves a lasting imprint on subclinical myocardial injury at the population level. Answering this question requires something that most pandemic-era studies lacked entirely, i.e. biomarker measurements obtained before the infection occurrence.

The HUNT study[2] capitalised on a rare epidemiological opportunity. Indeed, high-sensitivity cardiac troponin I (hs-cTnI) had been measured in 37,823 community-dwelling Norwegian individuals between 2017 and 2019, immediately before the pandemic, as part of the fourth wave

of the HUNT study. Between 2021 and 2023, 19,550 of these participants underwent repeat hs-cTnI measurement alongside SARS-CoV-2 serological testing, enabling true longitudinal analysis of biomarker trajectories in relation to documented interim infection. Infection status was ascertained through 3 independent sources: self-report, linkage to Norwegian Surveillance System for Communicable Diseases (which received reports from all SARS-CoV-2 positive polymerase chain reaction tests during the pandemic), and SARS-CoV-2 nucleocapsid IgG serology. The latter immunological approach deserves emphasis, since vaccination elicits antibodies against the spike protein but not the nucleocapsid, so nucleocapsid IgG seropositivity serves as a specific marker of natural infection independently of vaccination status,[6] an important distinction in a cohort where 98.9% of participants reported having received immunisation for SARS-CoV-2 during the pandemic.

The central finding is that interim SARS-CoV-2 infection was independently associated with higher post-pandemic hs-cTnI concentrations and a greater probability of increasing hs-cTnI from pre- to post-pandemic measurements, after adjustment for a comprehensive covariate set including, critically, the pre-pandemic hs-cTnI value itself. Among participants with serological evidence of recent infection, mean post-pandemic hs-cTnI was 2.01 ng/L compared with 1.85 ng/L in seronegative individuals, corresponding to a fully adjusted difference of approximately 4.4%. Persons with self-reported or laboratory-confirmed infection had 17% higher odds of a greater than 50% increase in hs-cTnI over the pandemic interval. Consistent with the established prognostic weight of troponin trajectories in longitudinal cohort studies,[7] those who experienced rising hs-cTnI concentrations faced a significantly higher risk of all-cause mortality during subsequent follow-up. These findings do not suggest overt myocardial injury at the individual level. Rather, they demonstrate a population-level shift in the distribution of subclinical myocardial injury that,

scaled across the hundreds of millions of individuals infected globally, may carry a non-trivial future cardiovascular burden.

A secondary observation of Omland et al.'s study is that higher pre-pandemic hs-cTnI concentrations were paradoxically associated with a lower subsequent risk of contracting SARS-CoV-2. The authors attribute this to differential exposure risk, protective behaviours, and more intensive medical surveillance among older and more comorbid individuals. This interpretation is biologically plausible and epidemiologically coherent but remains presumptive since the observational design of the study does not permit causal attribution.

Several methodological considerations must inform the interpretation of these findings. First, the most prominent is the use of different analytical platforms at baseline (Abbott Architect) and follow-up (Abbott Alinity). The authors present Bland-Altman analysis demonstrating acceptable mean agreement between assays; however, the 95% limits of agreement span approximately ±57 ng/L, a range that substantially exceeds the biological differences under investigation (0.1 to 0.2 ng/L). Systematic inter-platform drift at this scale cannot be excluded with confidence, and this uncertainty cannot be fully corrected by statistical adjustment alone. Second, the reduction from 37,823 baseline participants to 19,550 with complete follow-up data raises the possibility of participation bias. Those without repeat measurements were more frequently younger men with lower educational attainment, a demographic arguably at higher infection risk and lower healthcare engagement, potentially causing underestimation of the true pandemic-related troponin effect. Third, antibody waning introduces a further source of misclassification. Nucleocapsid IgG titres decline over months to years,[6] meaning that infections occurring in the earliest pandemic waves may have been misclassified as seronegative by the time of the 2021 to 2023 follow-up visits. This

non-differential exposure misclassification would bias results toward the null, suggesting that the reported associations may underestimate the true effect of infection on troponin trajectories.

Notwithstanding these limitations, the study by Omland et al. has the merit of underscoring that troponin measurement has a role well beyond the acute coronary syndrome setting. High-sensitivity troponin assays have demonstrated powerful prognostic utility in population cohorts,[1] in patients with stable coronary disease,[8] and in risk stratification of individuals at intermediate cardiovascular risk, yet routine troponin measurement in primary and secondary prevention remains uncommon in clinical practice. The HUNT data, by demonstrating that pandemic-related troponin shifts track longitudinal mortality risk even within the normal reference range, reinforce the case for expanding the clinical application of this biomarker beyond its current diagnostic niche. Additionally, the study invites a broader reconceptualization of infectious cardiotropism that extends well beyond COVID-19. Comparable troponin associations have been described for influenza[9] and respiratory syncytial virus,[10] suggesting that SARS-CoV-2 does not represent a unique cardiovascular threat but rather the most extensively studied member of a class of respiratory pathogens capable of inducing subclinical myocardial injury on a large scale. Whether the cumulative burden of recurrent seasonal respiratory infections contributes meaningfully to the age-related rise in population troponin concentrations and to the background incidence of heart failure and cardiovascular death in older adults is a hypothesis with substantial public health implications that deserves prospective investigation.

Two further questions are pressing. First, if the COVID-19 pandemic has systematically upshifted the population distribution of high-sensitivity hs-cTnI, then reference ranges calibrated on pre-pandemic cohorts may require revision, with potential implications for diagnostic thresholds in acute coronary syndromes and for the cardiovascular risk algorithms embedded in

prevention guidelines. Second, the present study used high-sensitivity hs-cTnI, widely regarded as more cardiac-specific than troponin T given the absence of significant hs-cTnI expression in healthy skeletal muscle. Yet high-sensitivity troponin T assays remain more widely deployed in routine clinical practice across Europe and globally. Whether analogous population-level troponin shifts are detectable using hs-cTnT, and how the differential cardiac specificity of the two isoforms affects observed associations in the context of systemic inflammation and multiorgan involvement, characteristic features of COVID-19, remains to be established.

In conclusion, the "long shadow" of SARS-CoV-2 on cardiovascular health may extend further than the acute phase of infection. The Trøndelag Health Study provides large-scale evidence that SARS-CoV-2 infection is associated with a population-level upward shift in hs-cTnI, consistent with acceleration or new development of chronic subclinical myocardial injury. The individual clinical implications of this shift are modest in absolute terms, but, at a population scale, in a world permanently altered by pandemic exposure, they may not be. Additionally, integrating troponin measurement into broader cardiovascular surveillance and recognising that respiratory viruses may leave an indelible mark on myocardial health should occupy a central place in the post-pandemic research agenda.

Acknowledgements: none

Funding: none

Data availability: n/a

CENTRAL FIGURE.

The long shadow of SARS-CoV-2 on subclinical myocardial injury in the general population.

Upper panel: schematic representation of the association between SARS-CoV-2 infection, subclinical myocardial injury as reflected by increasing cardiac troponin I concentrations from pre- to post-pandemic measurements, and subsequent cardiovascular risk and mortality. Lower panels: key findings from the Trøndelag Health Study (left) and unanswered questions arising from the present investigation (right). hs-cTnI, cardiac troponin I; hs-cTnT, cardiac troponin T; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

REFERENCES

1. Neumann JT, Twerenbold R, Weimann J, Ballantyne CM, Benjamin EJ, Costanzo S, et al. Prognostic Value of Cardiovascular Biomarkers in the Population. *JAMA* 2024;**331**:1898–1909.

2. Omland T, Hveem K, Varounis C, Lyngbakken M. Impact of SARS-CoV-2 infection on subclinical myocardial injury in the general population: The Trøndelag Health Study. *Eur J Prev Cardiol* 2026.

3. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;**5**:802–810.

4. Artico J, Shiwani H, Moon JC, Gorecka M, McCann GP, Roditi G, et al. Myocardial Involvement After Hospitalization for COVID-19 Complicated by Troponin Elevation: A Prospective, Multicenter, Observational Study. *Circulation* 2023;**147**:364–374.

5. Barison A, Aimo A, Castiglione V, Arzilli C, Lupón J, Codina P, et al. Cardiovascular disease and COVID-19: les liaisons dangereuses. *Eur J Prev Cardiol* 2020;**27**:1017–1025.

6. Mizoue T, Yamamoto S, Tanaka A, Oshiro Y, Inamura N, Konishi M, et al. Sensitivity of three antibody assays to SARS-CoV-2 nucleocapsid protein in relation to timing since diagnosis. *GHM Open* 2022;**2**:51–53.

7. McEvoy JW, Chen Y, Ndumele CE, Solomon SD, Nambi V, Ballantyne CM, et al. Six-Year Change in High-Sensitivity Cardiac Troponin T and Risk of Subsequent Coronary Heart Disease, Heart Failure, and Death. *JAMA Cardiol* 2016;**1**:519–528.

8. Omland T, Lemos JA de, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. *N Engl J Med* 2009;**361**:2538–2547.

9. McAlister FA, Guo Y, Roberts SB, Ismail M, Malecki SL, Ko DT, et al. Myocardial Involvement Is Just as Common in Patients Hospitalised for Influenza as in Those Hospitalised for Covid-19: Insights From the GEMINI Initiative. *Can J Cardiol* 2025;**41**:1342–1349.

10. McAlister FA, Guo Y, Roberts SB, Verma AA. Respiratory syncytial virus infections and myocardial injury: the GEMINI Initiative. *Eur Heart J* 2026:ehag048.

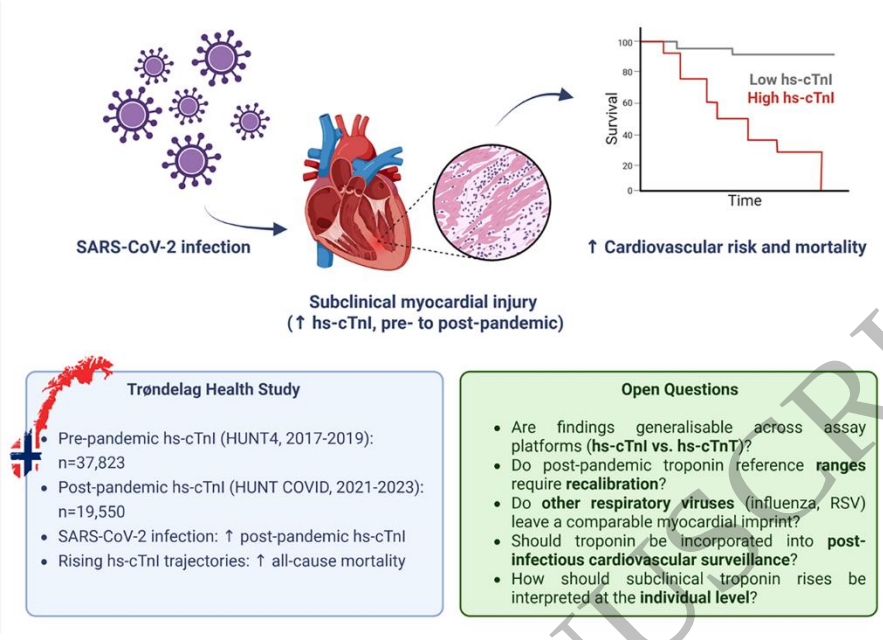

Figure 1
120x84 mm (x DPI)