**EDITORIAL COMMENT**

# High-Sensitivity Troponin in Patients With Cancer

## Sensitive But Not Specific*

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Acute chest pain is 1 of the most common causes of presentation to the emergency department (ED), accounting for approximately 8 million ED visits each year.[1] Of these patients, as few as 10% will ultimately be diagnosed with acute myocardial infarction (MI), the most common life-threatening cause of acute chest pain, but many more undergo a prolonged ED observation or hospital admission to rule out MI.[2] Because of the lack of sensitivity and specificity of elements of the history, physical examination, and electrocardiogram alone for ruling in or ruling out the diagnosis of acute MI,[3] a number of clinical algorithms incorporating serial cardiac-specific troponin values have been developed for the rapid diagnosis of MI among patients presenting to the hospital with acute chest pain. MI diagnostic algorithms are judged by their ability to avoid false negatives (sensitivity) while still ruling out MI in as many patients as possible (efficiency).

The European Society of Cardiology (ESC) 0/1-hour MI rule-out protocol is a highly sensitive and efficient algorithm recommended by ESC and American College of Cardiology/American Heart Association guidelines.[1,4] The protocol measures serum high-sensitivity cardiac troponin (hs-cTn) at presentation and 1 hour thereafter, and the absolute hs-cTn value and the change from baseline to 1 hour are used to divide patients into 3 groups: MI ruled out, MI ruled in, and continued observation. "Rule-out" patients are appropriate for early discharge, and "rule-in" patients should receive strong consideration for MI diagnosis and treatment. In a meta-analysis of 20 studies that collectively enrolled 30,066 patients presenting to the ED with chest pain and no ST-segment elevation on electrocardiography, MI could be ruled out in 54% of patients using the ESC 0/1 hour protocol with a sensitivity of 99.1% and a negative predictive value of 99.8%.[5] Conversely, the ESC 0/1-hour MI rule-out protocol indicated that 17% of patients could be ruled in for MI with a specificity of 94% and a positive predictive value of 65.1%. This leaves 29% of patients in the continued observation category.

Although the ESC 0/1-hour MI rule-out protocol has demonstrated high sensitivity and efficiency in an all-comers population, questions have been raised regarding its performance in specific subgroups. Among patients with renal dysfunction, the protocol is less efficient, but similarly sensitive. In a multicenter study of 487 patients with renal dysfunction, just 18% of patients could be ruled out for MI by the ESC protocol, but the sensitivity and negative predictive value were 100%.[6] Conversely, among patients with coronary artery disease, the protocol is both less efficient and less sensitive. In another multicenter study, the protocol classified just 40% of patients with known coronary artery disease into the rule-out category, and the negative predictive value for 30-day death or MI was lower at 96.6% in this subgroup.[7]

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Like patients with known coronary artery disease or renal dysfunction, patients with active cancer or a history of cancer represent a large and growing population with a number of clinical and demographic features that may affect the sensitivity, specificity, and efficiency of the ESC 0/1-hour MI rule-out protocol. In this issue of *JACC: CardioOncology*, Bima et al[8] present an important study that provides definitive data on the performance of diagnostic tools for MI in patients with active cancer or a history of cancer. This study analyzed patients previously enrolled in the APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation) study, a multicenter, prospective diagnostic study of the performance of chest pain characteristics and serial hs-cTn values in patients presenting with chest pain to 12 EDs in 5 European countries. Of the 8,267 patients enrolled, 711 (8.6%) had cancer. The cancer cohort (Supplemental Table 5 of Bima et al[8]) included 195 (28.8%) patients with active cancer, 190 (28.0%) with advanced cancer, and 64 (9.4%) who were receiving ongoing treatment with cancer therapeutic drugs, 37 of whom were being treated with drugs potentially linked to acute coronary syndrome and 39 with potentially cardiotoxic drugs. MI was the final diagnosis in a significantly higher proportion of patients with cancer compared with those without cancer (26.8% vs 21.1%); both type 1 and type 2 MI diagnoses were more prevalent in patients with cancer than those without. The ESC 0/1-hour MI rule-out protocol was less efficient in patients with cancer than in those without; MI could be ruled out in 35.7% of patients with cancer vs 62.7% of patients without cancer. However, the sensitivity and negative predictive value were > 99% in patients with and without cancer. By contrast, patients with cancer were more likely to be classified in the observe zone than patients without cancer (39.0% vs 20.0%), and those classified as "rule-in" were less likely to have a final diagnosis of MI (positive predictive value = 77.2% vs 81.0%).

This study has a number of strengths that will position it as the definitive paper on the performance of diagnostic tools for MI in patients with cancer. First, the final diagnosis was centrally adjudicated by expert reviewers, increasing the study's rigor. Second, cancer status (present/absent and active/inactive) was prospectively assessed for all patients, and retrospective chart review was undertaken to collect more granular data on cancer treatments, including collecting records of cancer treatment for patients treated for cancer at a different hospital than the one they presented to with chest pain. Third, the authors provide a comprehensive report on the performance of multiple diagnostic tools for MI, including chest pain characteristics, electrocardiographic findings, and both subtypes of hs-cTn (I and T). Lastly, the authors validated their findings in a separate prospective, multicenter study of the performance of hs-cTn for the diagnosis of MI.

The most clinically relevant finding in this paper is that the ESC 0/1-hour MI rule-out protocol has similar sensitivity but lower specificity and efficiency in patients with cancer compared with those without cancer, and it is worth considering this finding in more detail. It is reassuring that patients with cancer and serial hs-cTn below the upper limit of normal were not more likely than those without cancer to have an ultimate diagnosis of MI (ie, that the protocol sensitivity was preserved and that a rule-out categorization was reliable regardless of the cancer status of a patient). However, it is important to highlight that the study found decreased specificity of the ESC 0/1-hour MI rule-out protocol in patients with cancer, meaning that more patients with cancer had elevated hs-cTn values ultimately attributed to a diagnosis other than MI.

There are a number of reasons that patients with active or previously treated cancer might have elevated hs-cTn values in the absence of MI. First, patients with cancer in APACE were older than those without cancer and had a higher prevalence of cardiovascular risk factors and pre-existing coronary artery disease. Given the lower efficiency of the ESC 0/1-hour MI rule-out protocol in patients with pre-existing coronary artery disease and renal dysfunction,[7] at least part of the lower efficiency of this protocol in patients with cancer may be explained by demographic differences and a higher prevalence of comorbidities that lead to nonspecific hs-cTn elevation. In addition, patients' cancer may directly contribute to non-MI myocardial injury by directly invading the myocardium or pericardium; predisposing to venous thromboembolism; or causing myocardial supply-demand mismatch because of anemia, tachyarrhythmia, or sepsis. Cancer therapies including chemotherapy, immunotherapy, and radiation therapy can also lead to non-MI myocardial injury through mechanisms such as coronary vasospasm, endothelial dysfunction, fibrosis, and immune myocarditis. Importantly, elevated cardiovascular biomarkers in patients with cancer are associated with worse all-cause mortality even in the absence of acute MI and may be a marker of subclinical myocardial damage related to cancer progression.[9]

Ultimately, the key lesson of this important paper is that serial values of hs-cTn below the upper limit of normal with a flat trend are adequate to rule out MI in patients with or without cancer, but elevations in hs-

cTn cannot be interpreted without clinical context. As in all patients, a holistic consideration of all elements of a patient's clinical history and presentation is critical to assessing the likelihood of acute MI in patients with cancer presenting with acute chest pain and elevated hs-cTn.

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