Deriving Peace of Mind: In Search of a Fifth-Generation Troponin Testing Threshold to Safely Rule Out Acute Myocardial Infarction

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Editor's Note: *You are reading the 68th installment of* Annals of Emergency Medicine *Journal Club. As the Journal Club enters its second decade of publication, we are making a number of changes to the format. Dr. David Schriger, the originator of the* Annals of Emergency Medicine *Journal Club and its first editor, has retired from his Journal Club editorial role. The journal and his fellow editor are indebted to Dr. Schriger for his outstanding contributions and the success of this educational section. The Journal Club section welcomes Dr. Ryan Radecki and Dr. Rory Spiegel to the editorial staff. The Journal Club format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Nowak RM, Gandolfo CM, Jacobsen G, et al. Ultrarapid rule-out for acute myocardial infarction using the generation 5 cardiac troponin T assay: results from the REACTION-US study. *Ann Emerg Med.* 2018;72:654-664.

What Question Did This Investigation Aim to Answer?

In emergency department (ED) patients with symptoms of acute coronary syndrome, what were the negative predictive value and sensitivity for acute myocardial infarction of the fifth-generation cardiac troponin T test below the level of quantification (6 ng/L)? What is the optimal cardiac troponin T threshold at baseline and change in cardiac troponin T level at 30 minutes to safely exclude acute myocardial infarction?[1]

What Study Design Did the Authors Choose?

Design: Prospective, observational, cohort study.

Setting: A single ED in a US tertiary care center.

Population: Convenience sample of 569 ED patients older than 21 years with any symptoms suspicious for acute coronary syndrome.

Intervention: All patients had a fifth-generation cardiac troponin T test at baseline and after 30 minutes.

Analyses: The primary analysis was the negative predictive value and sensitivity of a baseline cardiac troponin T test less than the level of quantification (6 ng/L) for acute myocardial infarction. Secondary analyses determined the baseline and 30-minute cardiac troponin T threshold at which acute myocardial infarction was safely excluded in their sample.

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How Did the Authors Interpret the Results?

No patient with a baseline cardiac troponin T level less than 6 ng/L had an adjudicated acute myocardial infarction at the index visit, yielding a negative predictive value of 100% (95% confidence interval [CI] 97.8% to 100%) and sensitivity of 100% (95% CI 92.0% to 100.0%). With the cutoff of 6 ng/L, the positive predictive value was 10.9% (95% CI 8.0% to 14.3%) and specificity was 31.2% (95% CI 27.3% to 35.4%).

The authors found that a baseline cardiac troponin T level less than 8 ng/L and a 30-minute increase (ie, Δ) of less than 3 ng/L from the baseline measurement was 100% sensitive (95% CI 92.0% to 100.0%) for acute myocardial infarction, with a positive predictive value of 13.8% (95% CI 10.2% to 18.1%) and specificity of 44.6% (95% CI 40.2% to 49.2%).

Conclusion

In a single ED, a baseline cardiac troponin T level less than 6 ng/L was 100% sensitive for acute myocardial infarction. Alternatively, a baseline cardiac troponin T level less than 8 ng/L and a 30-minute increase of less than 3 ng/L was also 100% sensitive for acute myocardial infarction, improving specificity to 44.6%.

How Might This Study Affect Your Clinical Practice in the ED?

In this single-center trial, the authors derived thresholds for fifth-generation cardiac troponin T level, resulting in 100% sensitivity for acute myocardial infarction. This study provides potential cutoffs for future validation and implementation studies on the use of cardiac troponin T testing to rule out acute myocardial infarction in the ED.

DISCUSSION POINTS

1. *The authors propose a baseline and 30-minute threshold to rule out acute myocardial infarction. Did this study derive or validate these cutoffs? What is the difference between a derivation and validation study? What types of studies are ideally conducted before a testing strategy is implemented?*

Nowak et al did not prospectively define a baseline cardiac troponin T level cutoff of less than 8 ng/L or a change of less than 3 ng/L at 30 minutes. Rather, the authors designed this study to identify the specific troponin thresholds to meet their predefined sensitivity and negative predictive requirements for ruling out acute myocardial infarction.

With the introduction of a new fifth-generation troponin assay, the optimal threshold to use when evaluating ED patients presenting with symptoms concerning for acute coronary syndrome is unclear. The authors prospectively enrolled patients presenting to the ED about whom the treating clinician was concerned for acute coronary syndrome. They identified patients who experienced the primary outcome of acute myocardial infarction and determined the optimal cardiac troponin T threshold for diagnosis. To validate these cutoffs, however, their performance must be further evaluated to ensure that their results are generalizable and externally valid. Some studies will use the same cohort for derivation and validation, which can be done with split-sample validation or bootstrap resampling. Unfortunately, both these validation methods tend to overestimate a test's diagnostic performance. External validation ultimately provides the most reliable estimate. Readers interested in additional discussion on validation may refer to the November 2009 and March 2012 Journal Clubs, available at: https://www.annemergmed.com/journalclub.[2,3]

Furthermore, after validation, an implementation study should be performed. Rather than focusing on diagnostic accuracy, this step examines how a testing strategy affects patient outcomes. For example, even a more profoundly sensitive diagnostic test for acute myocardial infarction could theoretically be deemed unimportant if downstream changes in management failed to improve patient outcomes. The current study by Nowak et al presents only the first step in this process.

2. *The authors used a convenience sample in this study. How does this differ from other sampling methods? What are the positive and negative aspects of using a convenience sample?*

In emergency medicine research, patient enrollment is typically conducted in one of two ways: consecutive sampling or convenience sampling. In a consecutive sample, every patient presenting to the ED and meeting study entry criteria would be approached for enrollment in the study. In a convenience sample, potential patients are identified only when the necessary study staff are available. A better term for a convenience sample may be *pragmatic sample* because it is often used when investigators do not have the resources and staffing necessary for consecutive enrollment. Readers interested in additional discussion on sampling may refer to previous Journal Clubs, available at https://www.annemergmed.com/journalclub.[4,5]

This study screened patients "when research coordinators were available." The study did not specify when coordinators were available, but typically this means patients are screened during the daytime and on weekdays.

The benefit of a convenience sample is effectively a tautology. If a consecutive sample were always necessary, clinical research would be possible only in the largest, best-funded academic research centers capable of having dedicated research staff available every hour of every day. This would limit the ability to perform research in community EDs and smaller academic centers, which could have the effect of diminishing exploratory and novel questions and small pilot studies.

The primary disadvantage of a convenience sample is potential introduction of bias. A study can be biased by a convenience sample if the patient features that are associated with making a patient "convenient" for enrollment also affect the outcome of interest. One potential way a study could be affected by a convenience sample is if patient acuity is a barrier to enrollment. For example, it is conceivably challenging to enroll patients with active chest pain or shortness of breath. This could bias a study toward inclusion of healthier patients, which is relevant to a study focusing on negative predictive value because this measure is affected by outcome prevalence. If the testing strategy derived by Nowak et al, for example, were applied in a population with a higher rate of acute myocardial infarction, it is statistically more likely for the primary outcome to occur in the population testing below their cutoff threshold. Additional groups potentially disproportionately enrolled in convenience samples include non-English speakers (if the research team does not have interpreter services available) and those who

arrive to the ED at night or on weekends (individuals who are not able to come during daytime hours because of work or family responsibilities). The exclusion of these groups may bias the results of the study and certainly limit the external validity (ie, generalizability) of the conclusions.[4,5] Although articles rarely mention the exact constraints on their convenience sample, it is worthwhile to consider the potential implications.

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IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Posttraumatic peripancreatic pseudocyst. Imaging demonstrated a loculated fluid collection along the anterior and superior aspect of the pancreatic body and tail, and a second cystic area along the posterior aspect of the pancreatic tail (Figures 1 to 3). Given the history of recent trauma, as well as elevated lipase levels, this was thought to be consistent with posttraumatic peripancreatic pseudocyst. The patient was treated successfully with a delayed endoscopic cystogastrostomy and endoscopic retrograde cholangiopancreatography with biductal sphincterotomy and pancreatic stent placement.

Pancreatic injury is uncommon and occurs in only 0.2% of blunt abdominal injuries.[1] Approximately 3% of pancreatic injuries result in pancreatic pseudocyst.[1,2] Presentation can be delayed an average of 59 days after injury,[3] and the rates of complications are higher in patients with delayed diagnosis.[2] Pancreatic trauma can be challenging to identify on CT immediately after an accident, and often secondary findings are required to recognize injury.[4]

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