Critical Appraisal Worksheet – Diagnosis
Eastern Virginia Medical School EM Journal Club

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Citation:
Jaeger, Cedric et al, One-hour rule-in and rule-out of acute myocardial infarction using high-sensitivity cardiac American Heart Journal, Volume 171, Issue 1, 92 - 102

Study Objectives: "The aim of the current study was to address 4 questions"

1. To prospectively derive and validate a novel (Siemens Vista assay) 0/1-hour algorithm using high-sensitivity cardiac troponin I (hs-cTnI) to possibly extend the former finding to hs-cTnI. for the early "rule-out" and "rule-in" of acute myocardial infarction.
2. "What are the specific cutoff values for hs-cTnI that allow safe rule-out and accurate rule-in within 1 hour
3. "How many patients can be reliably assigned rule-out and rule-in within 1 hour?
4. "How does the hs-cTnI 0-/1-hour algorithm compare versus the current standard of care combining the 12-lead ECG with hs-cTn?

Inclusion Criteria:
"Consecutive patients older than 18 years presenting to the ED with symptoms **suggestive of AMI** including acute chest discomfort (pain, pressure, burning, stabbing, or angina pectoris) with an onset or peak within the last 12 hours were recruited, after written informed consent was obtained"
Exclusion Criteria:

1. Under the age of 18
2. Terminal kidney failure requiring dialysis
3. STEMI
4. Final adjudication not possible (2^{nd} Trop collected incorrectly or patient refused)
5. No second Trop possible (Patient in cath lab, etc)

Methodology:

This was a prospective, multi-centered study that took place in 9 hospitals in Switzerland, Spain and Italy. Consecutive patients that presented and met inclusion criteria were recruited. 1500 patients were then divided into two groups. The first 750 were used to help create an algorithm using hs-cTnI to rule-in/rule-out AMI and to determine cut-off values for the test.. The second group was used to validate the algorithm created by the first group. All patients received high sensitivity troponin measurements at presentation, at 1 hour, at 2 hours, and at 3 hours.

All patients also underwent clinical assessment for AMI, including ECG, cardiac monitor, pulse ox, blood tests, history, and physical exam. Two independent cardiologists, blinded to high sensitivity results, then used the clinical assessment as well as any other clinical information 90 days after presentation to determine if the patients had an AMI. The 90-day clinical information included included cardiac stress test, coronary angiography, etc. An AMI was defined as "evidence of myocardial necrosis with a clinical setting consistent with myocardial ischemia."

The cut off for **rule out** AMI was designed using the derivation cohort to have a sensitivity of 95% for baseline values and 90% for absolute change over 1 hour. This was determined to be a hs-cTnI level less than 5ng/L with a change of less than 2ng/L. Interestingly four males were missed in this group.

The cute off for **rule in** AMI was determined using a CART (Classification and Regression Tree Analysis) not well elaborated on in the paper. This was determined to a high sensitivity Trop level >107ng/L and a change of greater than or equal to 17 ng/L.

Patients between these cutoffs were determined to be in the observational zone.

Then the cut off calculated for the three groups were used in a validation cohort. The validations cohort was again compared to the cardiologist's ruling on whether or not an AMI occurred.

Classical interpretation of high sensitivity Trop is 9 and 3 and has a sensitivity and NPV of 92.3, 98.2

Mortality in 30 day follow up was 0.4% in rule out, 0.6% in obs and 2.5% in rule in

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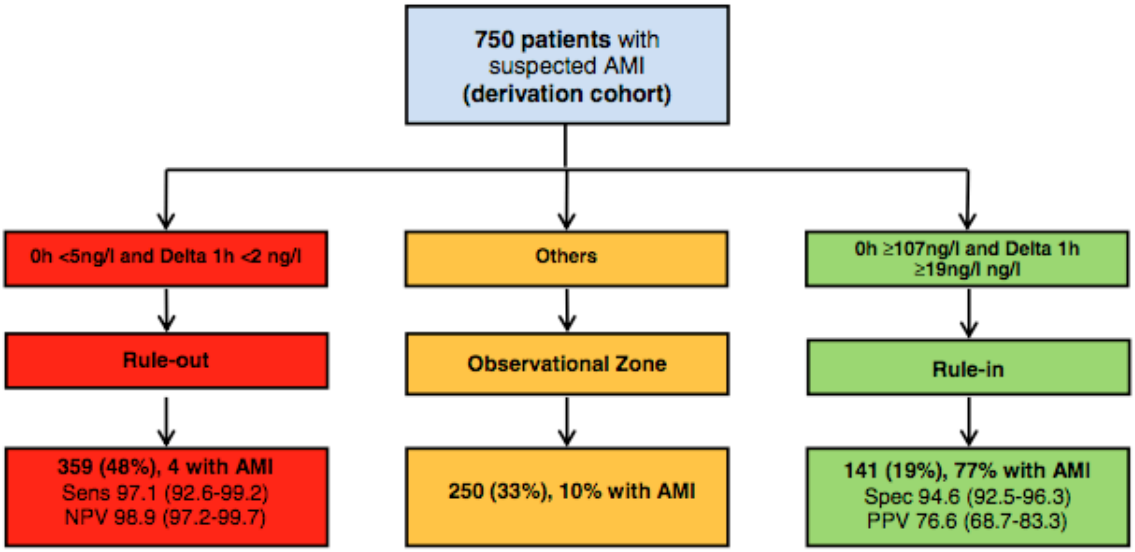

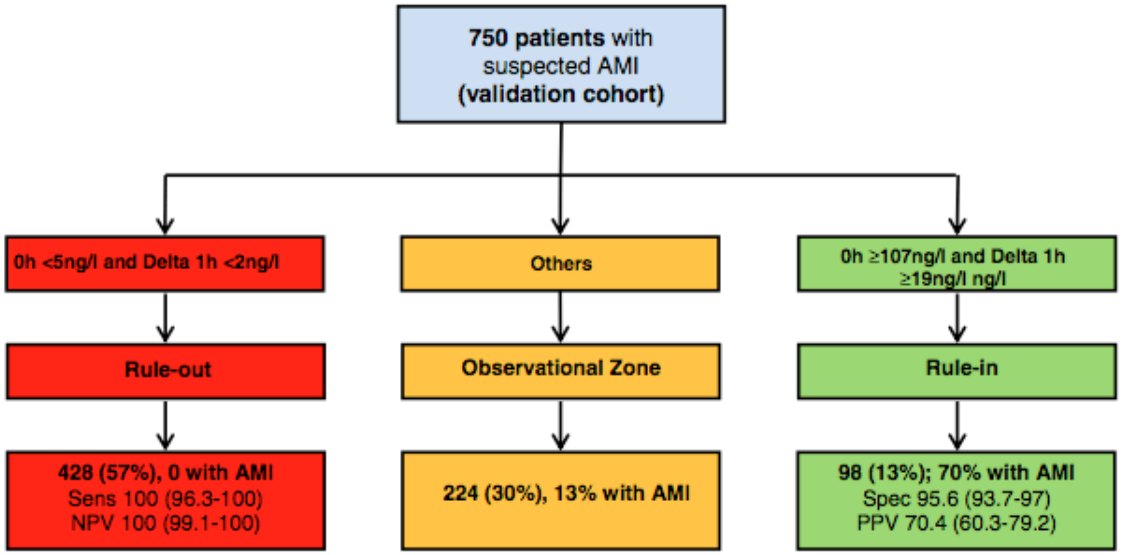

Are the Results Valid?*	
Questions	***Comments***
A. Did clinicians face diagnostic uncertainty?	Yes, Chest pain patients presenting to the ED a minority of which generally have AMI. In this case 16% ruled in. A diagnostic test to assist with early recognition and rule out could be of utility in ED diagnoses is needed to confirm myocardial necrosis to know if a patient is having acute myocardial infarction, not everyone should or can be sent to the cath lab.
B. Was there a blind comparison with an independent gold standard applied similarly to the treatment group and the control group? (Confirmation bias)	No. Their surrogate for a "gold standard"(catherization, stress studies) included independent assessment by two cardiologists who were blinded to the results of the hs-cTnT with more information about the patient but only some patients received a cardiac cath.
C. Did the results of the test being evaluated influence the decision to perform the reference standard? (Ascertainment Bias)	No, In the study the clinicians did not have access to the high sensitivity Trops, they were collected, centrifuged, frozen, and blinded.
What are the Results?*	
Questions	***Comments***
A. What reported likelihood ratios were associated with the range of possible test results?	LR's were not included however sensitivity, specificity PPV and NPV were reported. 48% of the derivation cohort were "ruled out," with a sensitivity of 97.1% (95% CI 92.6-99.2), negative predictive value of 98.9% (95% CI 97.2-99.7). **Four** males with acute MI were missed 19% of the derivation cohort were "ruled-in", with a specificity of 94.6% (95% CI 92.5-96.3) and positive predictive value of 76.6% (95% CI 68.7-83.3). 57% of patients in the validation cohort "ruled out" by the algorithm at one hour. The sensitivity and NPV in this cohort were 100% (95% CI 96.3-100) and 100% (95% CI 95-100). **No patients** with MI were missed 13% of patients in the validation cohort were considered "ruled-in" with a specificity of 95.6% (95% CI 93.7-97) and positive predictive value of 70.4% (95% CI 60.3-79.2). The negative predictive value was similar in women (100%, 95% CI 98.6-100) and men (99.2%, 95% CI 98-99.8).

How Can the Results Apply to Patient Care?*	
Questions	***Comments***
A. Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?	Yes, This could easily be implemented into our clinical practice.
B. Are the results applicable to patients in my clinical setting?	Somewhat, looking at the co-morbidities of patients that presented in this study, the patients at Norfolk General are sicker. This study was also done in hospitals in Switzerland, Spain, and Italy which has a very different population than Norfolk, Va. On the other hand, there was no pre-test probabilities (PTP's) applied to their patients and they state that their patients included those with "symptoms suggestive of AMI" I expect we admit many patients to CP OBS with low-PTP's and possibly lower risk than their patients.
C. Will the results change my management strategy?	Maybe, the high sensitivity and specificity for the rule-in and rule-out groups have the potential to get patients home or admitted quicker. It will do little to change the management of the observation group. Further prospective studies in broader populations could assist in determining applicability. Also, impact studies that help to define favorable or non-favorable consequences on ED workflow, and potentially, a higher false positive rate that may predispose patients to the harms of unnecessary testing
D. Will patients be better off as a result of the test?	Yes, this test has the potential for earlier discharge in "rule-out" patients. This will also allow for earlier detection of AMI in NSTEMI patients. Time is muscle. Will the percentage of patients in the observation group be vulnerable to harms from additional testing And over-diagnosis.

Limitations:

1. This study had a population of only 1500 with only 750 used for validation. A larger validation study should be performed to test this new algorithm. In addition, the percentage of women was small and results may not be as broadly applicable as the authors conclude.

2. 450/1500 patients were excluded, who known how their data may have changed the results. Also, we do not know how many patients were eligible but did not enroll which could lead to selection bias.
3. Two cardiologists in a room without set criteria determined what was an AMI and what wasn't and most patients did not get the gold standard of a cardiac cath but adjudication was primarily based upon hs-cTnT levels
4. This was an industry-sponsored study and may represent a conflict of interest by the authors.

Your Clinical Bottom Line:

1. A reasonably well performed observational study that, with more external validation and impact studies, has the potential to change how we practice. Good negative predictive values in both derivation and validation groups. Positive predictive value and specificity were lower. Impact studies may help to demonstrate real-time clinical impact on ED management, throughput and additional (possibly unnecessary) diagnostic testing ordered when compared to usual care.