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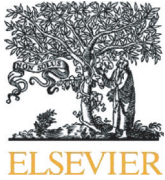
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Ideal high sensitivity troponin baseline cutoff for patients with renal dysfunction[☆]

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ABSTRACT

Objective: High-sensitivity cardiac troponin assays (hs-cTn) aid in diagnosis of myocardial infarction (MI). These assays have lower specificity for non-ST Elevation MI (NSTEMI) in patients with renal disease. Our objective was to determine an optimized cutoff for patients with renal disease.

Methods: We conducted an a priori secondary analysis of a prospective FDA study in adults with suspected MI presenting to 29 academic urban EDs between 4/2015 and 4/2016. Blood was drawn 0, 1, 2–3, and 6–9 h after ED arrival. We recorded cTn and estimated glomerular filtrate rate (eGFR) by Chronic Kidney Disease Epidemiology Collaboration equation. The primary endpoint was NSTEMI (Third Universal Definition of MI), adjudicated by physicians blinded to hs-cTn results. We generated an adjusted hscTn rule-in cutoff to increase specificity.

Results: 2505 subjects were enrolled; 234 were excluded. Patients were mostly male (55.7%) and white (57.2%), median age was 56 years 472 patients [20.8%] had an eGFR <60 mL/min/1.73 m². In patients with eGFR <15 mL/min/1.73 m², a baseline rule-in cutoff of 120 ng/L led to a specificity of 85.0% and Positive Predictive Value (PPV) of 62.5% with 774 patients requiring further observation. Increasing the cutoff to 600 ng/L increased specificity and PPV overall and in every eGFR subgroup (specificity and PPV 93.3% and 78.9%, respectively for eGFR <15 mL/min/1.73m²), while increasing the number (79) of patients requiring observation.

Conclusions: An eGFR-adjusted baseline rule-in threshold for the Siemens Atellica hs-cTnI improves specificity with identical sensitivity. Further study in a prospective cohort with higher rates of renal disease is warranted.

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1. Introduction

Each year, 6–8 million patients present to emergency departments (EDs) with symptoms of potential myocardial infarction (MI). Cardiac biomarkers such as cardiac troponin (cTn) have been the mainstay of initial ED assessment and triage. High-sensitivity troponin (hs-cTn) assays have been implemented worldwide, although only recently in the United States. Given the high sensitivity and precision of these assays, some studies have demonstrated that they allow rapid disposition of many ED patients within 1–2 h [1–9].

Reliance on cTn tests is complicated by the fact that numerous conditions other than MI can cause troponin elevations. One such condition is renal dysfunction, which is particularly problematic because it shares similar risk factors with MI [10–13]. Although hs-cTn assays retain high sensitivity and negative predictive value in patients with renal dysfunction, specificity is lower [12,14–16]. Use of absolute or relative deltas on serial cTn testing increases specificity but at the cost of sensitivity [17,18]. Although numerous studies have demonstrated that generally higher cTn levels still identify patients at higher risk for non-ST elevation MI (NSTEMI) in renal disease [16,19], in the individual patient it can be difficult to identify whether an initially elevated troponin value is acute or chronic.

Thus, there remains considerable uncertainty about the best use of hs-cTn assays in diagnosing NSTEMI in patients with renal dysfunction, and diagnostic algorithms for these patients are needed. Adjusting diagnostic cutoff criteria for patient sex [20] and age [21] has been proposed for hs-cTn to improve accuracy, and examples of patient-specific cutoff adjustment exist from other diseases as well [22–24]. The purpose of this study was to identify ideal cutoff values for the diagnosis of NSTEMI in patients across the spectrum of renal disease to determine whether different cutoffs based on renal function would improve accuracy.

2. Methods

2.1. Study design and setting

This is an a priori planned secondary analysis of prospectively collected data from a study of a hs-cTnI assay (Siemens, Munich, Germany). Results of the primary study have been previously reported [25,26] but are briefly described here. Patients were enrolled at 29 ED sites across the United States. All 29 sites obtained local Institutional Review Board approval before initiation of the study.

2.2. Selection of participants

Adult patients of age ≥ 22 years presenting to the ED with chest pain or other symptoms suggestive of MI prompting a clinician to order a cTn test were eligible for inclusion in the study. Further inclusion criteria were giving informed consent to participate and being able to provide at least a baseline blood sample. We otherwise did not exclude qualifying patients. Patients were identified through screening ED tracking boards and through clinician referral. For this analysis, we further excluded those with ST segment elevation MI (but not Left Bundle Branch Block), missing creatinine values, race designation, and those who had prior myocardial infarction within 14 days of data collection. All participants provided informed consent before participating.

2.3. Interventions

Patients were recruited from April 2015 to April 2016. Trained research personnel enrolled participants after obtaining informed consent. Data collected included demographic information, medical history, weight and height, MI symptoms, vital signs, cardiac therapies, and ED diagnoses. In addition, research personnel recorded the results of electrocardiography (ECG), chest radiography, cardiac imaging, stress testing, and bloodwork, including locally-performed contemporary cTn assays and creatinine. All data were entered into an electronic case report form.

2.4. Measurements

Blood samples were obtained from a peripheral intravenous line or phlebotomy at 0, 1 (45 to 75 min post-baseline), 2–3, and 6–9 h after baseline. Blood was centrifuged, and plasma was extracted and frozen. All samples were stored at -80 degrees F at local sites until batch shipping for processing at a central lab.

Troponin I levels were measured using the Siemens Atellica IM Analyzer at one of 3 core laboratories. This high-sensitivity assay reports a 10% coefficient of variation (CV) at 6 ng/L, a measuring range of 2.5–25,000 ng/L, a limit of detection (LoD) of 1.6 ng/L and limit of quantitation (LoQ, defined as the 20%CV) of 2.5 ng/L. The 99th percentile upper reference limit (URL) for plasma was determined to be 34 ng/L for females, 53 ng/L for males and 45 ng/L for all [27].

Phone and medical record follow-ups were conducted by research personnel on all enrolled patients at 30 days, 90 days, 6 months, and 1 year for major cardiac events (MACE) and all-cause mortality (ACM).

2.5. Outcomes

The primary study outcome was NSTEMI, as determined by an adjudication committee. The adjudication committee consisted of five board-certified cardiologists and ED physicians with at least two members of each specialty assigned to each patient. The adjudication committee used the Third Universal Definition of MI consensus guidelines [28], which define MI as a rise or fall in cTn with at least one value above the 99th percentile upper reference limit and symptoms of ischemia, ECG changes, findings of MI at coronary angiography and/or imaging evidence of ischemia. Adjudicators had access to all study data including locally performed cTn assay results as well as local cTn assay package inserts and local cut-off values (during enrollment no FDA-approved hs-cTn assays were available). No relative or absolute thresholds were pre-specified for a significant rise and/or fall of cTn levels. Adjudicators were blinded to the results of the investigational hs-cTnI assay as well as local diagnosis.

2.6. Data analysis

All data analysis was performed in SAS software version 9.4 (SAS Institute Inc., Cary, NC). Demographic, baseline, and procedure characteristics were summarized using mean with standard deviation, median with interquartile range (IQR), and ranges (min and max), or frequency with percentage (where appropriate). Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Eq. [29].

We evaluated sensitivity and specificity in the context of a 0/2 h algorithm using different cut-offs for ruling in and ruling out NSTEMI, similar to previously reported approaches [5,7] (Fig. 1). Patients are divided into one of 3 groups based on initial and subsequent blood draws: rule-out, rule-in, and observe. Patients rule in if their initial hs-cTnI ≥ 120 ng/L or their 2 h delta is ≥ 20 ng/L; they rule out if their initial hs-cTnI < 3 ng/L or their initial hs-cTnI < 8 ng/L AND 2 h delta is < 7 ng/L. All other patients are placed in the observe category. Sensitivity was calculated by dividing the NSTEMI patients classified as “rule-in” and “observe” by the total number of NSTEMI patients, whereas specificity was calculated by dividing non-NSTEMI patients classified as “rule-out” and “observe” by the total number of non-NSTEMI patients.

Using adjudicated NSTEMI outcomes as the criterion standard, we systematically adjusted baseline rule-in thresholds for patients with eGFR < 60 mL/min/1.73 m² to maximize specificity without reducing sensitivity. Separate calculations were performed for patients with eGFR > 60 , 31–60, 16–30 and < 15 mL/min/1.73 m². Patients were classified according to their 2 to 3 h delta values as per the previous algorithm. We did not change the rule in, rule out, or observation criteria for delta values.

3. Results

3.1. Characteristics of study subjects

There were 2505 patients who were enrolled, and after applying the exclusion criteria, 234 subjects were excluded, leaving 2271 patients for analysis (Fig. 2).

hs-cTnI Assay Result	Clinical Assessment	
	AMI (Positive)	Non-MI (Negative)
Ruled In	A	B
Observe	C	D
Ruled Out	E	F
Sensitivity	$(A+C/A+C+E) * 100\%$	
Specificity	$(D+F/B+D+F) * 100\%$	
Positive Predictive Value (PPV)	$(A/A+B) * 100\%$	
Negative Predictive Value (NPV)	$(F/E+F) * 100\%$	

Fig. 1. Algorithm for determining rule-in and rule-out status, and calculating diagnostic test characteristics.

Patients were mostly male (1264, [55.7%]) and white (1299, [57.2%]) with a median age of 56 years (interquartile range [IQR]: 48.0, 65.0). A sizeable number of patients had a past MI (443, [19.5%]) and 472, [20.8%]) had an eGFR <60 mL/min/1.73 m² but only 75 (3.3%) were on dialysis. Fig. 3 shows the hs-cTnI values for all patients with renal disease. The median (IQR) time from symptom onset to presentation was 5.7 (IQR 2.0, 26.5) hours. Table 1 show characteristics of the patients.

Without adjustment (rule-in cutoff = 120 ng/L), specificity and PPV was 95.9% (95%CI 95.0–96.8%) and 76.2 (95%CI 71.7–80.7%) respectively in all patients, but only 85.0% (95%CI 76.0–94.0%) and 62.5% (95%CI 43.1–81.9%) in patients with GFR < 15 mL/min/1.73 m² (Table 2).

Increasing the cutoff to 600 ng/L increased specificity to 97.8% overall and 93.3% in patients with GFR < 15 mL/min/1.73 m². We could not identify a cutoff that improved this specificity. Increasing the baseline Rule-in cutoff in all patients to 600 ng/L would observe 79 patients more for all observations (41 NSTEMI and 38 negative patients), but have 38 less false positive NSTEMI predictions. It would also raise the NSTEMI rate within the observation group from 6.4% to 10.6%. Applying the increased baseline cutoff only to patients whose eGFR is <60 mL/min/1.73 m² would observe only 37 more patients, reduce false positives by 20 patients, and raise the NSTEMI rate in the observation group to 8.2%. Likewise, applying the increased baseline cutoff only to patients whose eGFR is <30 mL/min/1.73 m² would observe only 19

more patients, reduce false positives by 8 patients, and raise the NSTEMI rate in the observation group to 7.6% (Supplementary Table 1). The full diagnostic test characteristics of the adjusted baseline Rule-in cutoff of 600 ng/L are shown in Table 3. Specificity and PPV are increased in the total population and in every subgroup of GFR using a baseline Rule-in cutoff of 600 ng/L compared to 120 ng/L.

4. Discussion

MI remains a difficult disease to diagnose due to the variant clinical symptoms. The task is even more difficult in patients with comorbid renal disease because renal disease can be associated with an elevated troponin level even in the absence of MI. Thus, hs-cTn assays have a lower specificity for NSTEMI in patients with renal disease. Patients with renal disease could suffer even further renal injury if they are falsely diagnosed with NSTEMI, since cardiac angiography requires iodinated contrast that is processed by the kidney. Thus, it can be difficult to make risk stratification and treatment decisions in a patient presenting with NSTEMI symptoms, renal disease, and an elevated troponin level.

In this study, we sought to determine whether adjusting the baseline rule-in cutoff for hs-cTnI in patients with renal disease could retain high sensitivity and improve specificity for NSTEMI. We found that adjusting the baseline rule in cutoff to a high level (600 ng/L) retained high sensitivity while also increasing specificity. Doing so would require observing 79 more patients and would raise the NSTEMI rate within the observation group from 6.4% to 10.6%. This seems an acceptable tradeoff, since experts propose an acceptable inpatient admission rate for ED observation units to be as high as 20% [30].

Prior studies have established that hs-cTn has high sensitivity but decreased specificity for NSTEMI in patients with renal disease. Gunsolas et al. [31] found that specificity ranged from 93%–95% in patients with normal renal function to 57%–61% in patients with severely impaired renal function and 40%–41% for those on dialysis (n = 78). Miller-Hodges et al. [14] studied 4726 patients, 904 (19%) of whom had renal impairment. They found that using the assay's 99th percentile as the rule-in cutoff resulted in a positive predictive value and specificity of 50.0% and 70.9%, respectively, for NSTEMI in patients with renal impairment. Both groups [14,31] found that increasing troponin concentrations were associated with increased rates of cardiac mortality.

Both of these groups also tested the use of serial sampling in patients with renal disease. Combining the 99th percentile with a 20% delta change in serial sampling increased specificity in those with renal impairment from 68.8% to 78.1% but reduced sensitivity from 97.8% to 78.4%. This 20% relative delta threshold appears to have been selected based on recommendations from the IFCC Task Force on Clinical Applications of Cardiac Biomarkers [32]. Vasudevan et al. proposed the use of

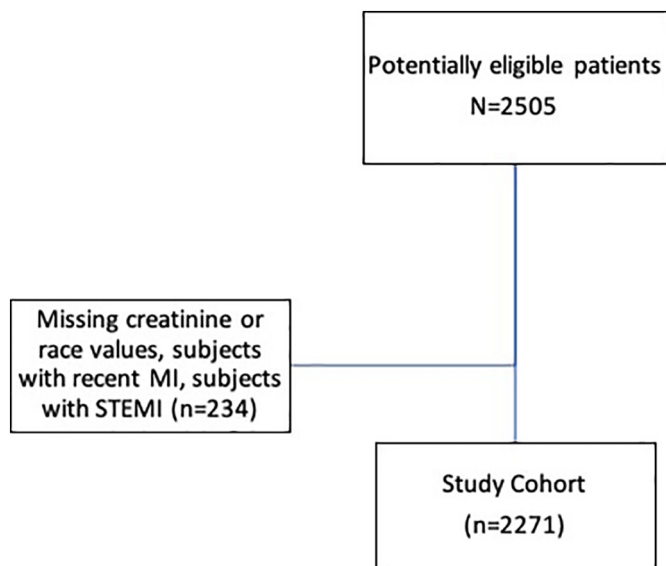


Fig. 2. Patient flow of included patients.

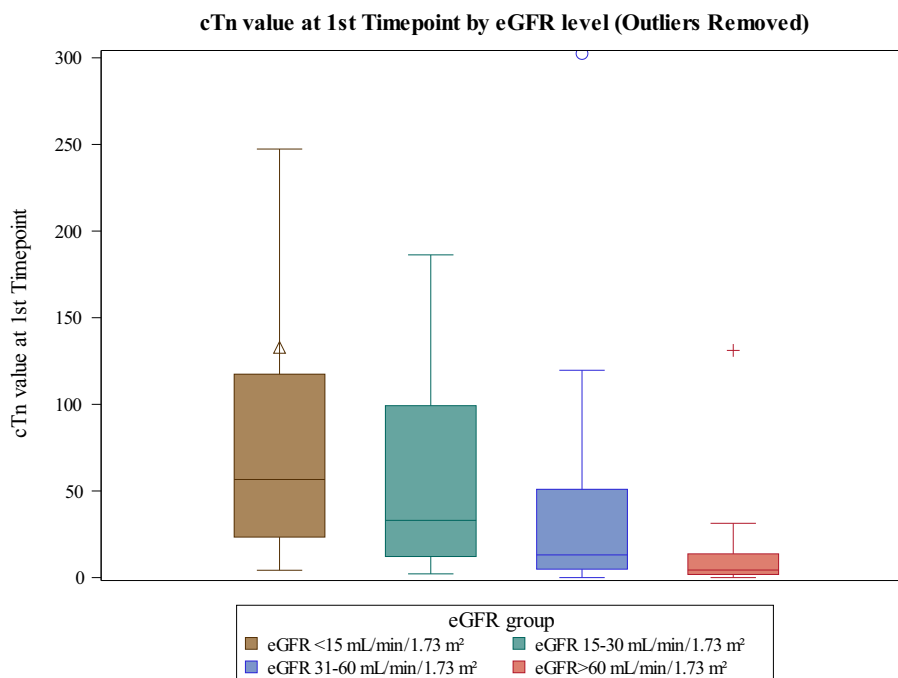


Fig. 3. Hs-cTnI values for all patients with renal disease.

a “scaled” troponin change to define an abnormal rise in a cohort of 430 patient (87 with renal dysfunction). In this paradigm, an abnormal rise is defined as a multiple of the assay-specific 99th percentile upper limit

Table 1
Patient demographics and characteristics.

Characteristic	All patients (N = 2271)
Age (years)	
Median (25th, 75th)	56.0 (48.0, 65.0)
Min, Max	23.0, 93.0
Sex	
Male	1264 (55.7%)
Female	1007 (44.3%)
Ethnicity	
Hispanic or Latino	157 (7.0%)
Race	
Asian	26 (1.1%)
Black or African American	924 (40.7%)
White/Caucasian	1299 (57.2%)
Other	22 (1.0%)
Hypertension	1571 (69.4%)
Diabetes	658 (29.1%)
History of tobacco use	
Current	614 (27.0%)
Former	701 (30.9%)
Hyperlipidemia	874 (40.1%)
Renal disease/insufficiency	287 (12.8%) (22 missing)
eGFR>60 mL/min/1.73 m ²	1799 (79.2%)
eGFR 31–60 mL/min/1.73 m ²	331 (14.6%)
eGFR 15–30 mL/min/1.73 m ²	65 (2.9%)
eGFR <15 mL/min/1.73 m ²	76 (3.3%)
On dialysis	75 (27.4%)
Past myocardial infarction	443 (57.1%)
Coronary artery disease	840 (37.5%)
Coronary Intervention (Percutaneous angioplasty, stent, or bypass graft surgery)	23 (1.0%)
Stroke/CVA	237 (10.9%)
Time since symptom onset (hours)	
Median (25th, 75th)	5.7 (2.0, 26.5)

Clinical features and characteristics of the study population. Min = Minimum. Max = Maximum. CVA = Cerebrovascular Accident. TIMI = Thrombolysis in Myocardial Infarction Risk Score.

of normal. They found that patients with an adjudicated diagnosis of NSTEMI demonstrated an increase that was at least 5 times the assay-specific 99th percentile upper limit compared to non-NSTEMI patients, regardless of renal function. This approach thus reflects a form of “relative” delta approach serial testing.

All of these groups examined serial sampling as a strategy to improve test performance. In our study, we did not attempt to adjust delta-cutoffs in light of these previous efforts. Instead, we found that simple adjustment of the baseline rule-in rate could increase specificity. The advantage of our approach is that a disposition can be obtained sooner in the ED course. Furthermore, obtaining blood samples in patients with renal disease can be challenging; our approach does not require serial sampling.

5. Limitations

Overall, our study cohort had a low rate of renal disease with only 6% of patients having an eGFR <30 mL/min/1.73 m². These patients may not reflect the full spectrum of patients with renal disease. However, they were recruited from over 29 sites across the United States reflecting a geographically and demographically diverse area. Furthermore, classification of renal function was based on creatinine values drawn during an ED visit. These may reflect a mix of acute and chronic kidney dysfunction. Our current study used a hs-cTnI assay that was a different model than that used for the 2 to 3-h European rule out algorithm. However, the assay used was made by the same company and differences between models were minimal. We did not assess the impact of altering the serial delta cutoffs at 1 or 2 h; this will be the subject of future study. Furthermore, since this is an observational study, we cannot fully define the clinical impact of using an adjusted cutoff. Last, our proposed alteration to baseline cutoff has only been studied using a hs-cTnI assay. However, we believe this hypothesis-generating work can spur future prospective study, which can further delineate the impact on patient-oriented outcomes.

In conclusion, adjusting for renal disease, a higher baseline rule-in hs-cTnI cutoff results in higher specificity, while shifting an acceptable number of patients to observation status and without a concomitant

Table 2
Unadjusted Diagnostic Test Characteristics of Siemens hs-cTnI Assay Using 2–3 h Algorithm

0 h ≥ 120 ng/L	N	Sensitivity %, (95%CI)	Specificity %, (95%CI)	NPV %, (95%CI)	PPV %, (95%CI)
All patients	2271	98.1% (96.5, 99.8)	95.9% (95.0, 96.8)	99.7% (99.5, 100)	76.2% (71.7, 80.7)
GFR >60	1799	98.3% (96.4, 100)	97.2% (96.5, 98.1)	99.8% (99.6, 100)	80.0% (74.7, 85.3)
GFR 31–60	331	98.3% (95.0, 100)	92.6% (89.5, 95.7)	99.6% (98.8, 100)	74.4% (64.7, 84.0)
GFR 15–30	65	100.0% (100, 100)	82.4% (71.9, 92.8)	100.0% (100, 100)	60.9% (40.9, 80.8)
GFR <15	76	93.8% (81.9, 100)	85.0% (76.0, 94.0)	98.1% (94.3, 100)	62.5% (43.1, 81.9)

Unadjusted Diagnostic Test Characteristics of Siemens hs-cTnI Assay Using 2–3 h Algorithm. ng/L = nanograms per liter. GFR = estimated glomerular filtration rate, in mL/min/1.73 m². NPV = negative predictive value. PPV = positive predictive value. 95% CI = 95% Confidence intervals.

Table 3
Diagnostic Test Characteristics of Optimal Baseline Rule-in Cutoff (0 h ≥ 600 ng/L) for Index Visit Myocardial Infarction

0 h ≥ 600 ng/L	N	Sensitivity %, (95%CI)	Specificity %, (95%CI)	NPV %, (95%CI)	PPV %, (95%CI)
All patients	2271	98.1% (96.5, 99.8)	97.8% (97.2, 98.4)	99.7% (99.5, 100)	85.7% (81.7, 89.6)
GFR >60	1799	98.3% (96.4, 100)	98.4% (97.8, 99.0)	99.8% (99.6, 100)	87.1% (82.5, 91.7)
GFR 31–60	331	98.3% (95.0, 100)	97.1% (95.1, 99.1)	99.6% (98.8, 100)	87.9% (80.0, 95.8)
GFR 15–30	65	100.0% (100, 100)	88.2% (79.4, 97.1)	100.0% (100, 100)	70.0% (49.9, 90.1)
GFR <15	76	93.8% (81.9, 100)	93.3% (87.0, 99.6)	98.1% (94.3, 100)	78.9% (60.6, 97.3)

Diagnostic Test Characteristics of Optimal Baseline Rule-in Cutoff (0 h ≥ 600 ng/L) for Index Visit Myocardial Infarction. ng/L = nanograms per liter. GFR = estimated glomerular filtration rate, in mL/min/1.73 m². NPV = negative predictive value. PPV = positive predictive value.

decrease in sensitivity. Future studies should further validate this finding and assess impact on patient-oriented outcomes.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajem.2020.06.072>.

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Declaration of Competing Interest

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