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High sensitivity troponin - Six hours is the magic number

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ABSTRACT

Background: High sensitivity troponin assays have become widespread for emergency department evaluation of acute chest pain. We assessed if a high sensitivity troponin under the 99th percentile upper reference limit drawn at 6 h or greater from symptom onset could safely rule out acute coronary syndrome in patients who did not meet the rapid rule-out strategy.

Methods: We conducted a multicenter retrospective study examining emergency department patients with chest pain who did not meet rapid-rule out criteria and were admitted for further evaluation. Among these admitted patients, we assessed the rate of clinically relevant adverse cardiac events (death, cardiac or respiratory arrest, STEMI, or life-threatening arrhythmia) and NSTEMI in patients with high sensitivity troponin less than the 99th percentile value obtained after at least 6 h of chest pain.

Results: Out of 1187 patients admitted, we found 30 clinically relevant adverse cardiac events, all of which occurred in patients admitted for another compelling reason or ischemic ECG. 36 patients had an NSTEMI, of which 33 were identified with high sensitivity troponin greater than 99th percentile upper reference limit within 6 h of chest pain onset. This left 0 clinically relevant adverse cardiac events and 3 NSTEMI among the 429 patients with high sensitivity troponin less than the 99th percentile at 6 h and nonischemic ECG and no other compelling reason for admission.

Conclusion: This study assessed patients with chest pain with high sensitivity troponin values between 3 ng/L and the 99th percentile upper reference limit after 6 h of chest pain and found that they have a low rate of clinically relevant adverse cardiac events and NSTEMI.

1. Introduction

Chest pain is the second most common reason that patients present to the emergency department in the United States, accounting for approximately 6.5 million visits annually. Establishing the clinical threshold above which discharges become unsafe and admissions become beneficial is of utmost importance for safely evaluating patients presenting with chest pain. While several tools have demonstrated an ability to identify a low risk cohort appropriate for discharge, their subjective inputs have inherent inconsistencies with interrater variability. Recent studies using two negative 4th generation troponin measurements demonstrated a low overall rate of adverse outcomes during admission regardless of cardiac risk factors [1].

The high-sensitivity troponin assay is the latest generation of cardiac enzyme testing, allowing for detection of myocardial infarction. The implementation of a "rapid rule-out" algorithm which incorporates high-sensitivity troponin has decreased emergency department length-of-stay and hospital admissions [2]. This decrease was not associated with any increase in myocardial infarctions, cardiac deaths, all-cause deaths, or unplanned coronary revascularizations for 1 year after discharge. With the increased sensitivity, there are a significant number of patients who will have detectable, but not abnormal high-sensitivity troponin levels, in an "intermediate high-sensitivity troponin zone" of unclear clinical significance [3]. Mueller et al. found that in patients evaluated in the emergency department with chest pain, the high-sensitivity troponin assay was only capable of safely ruling out a minority of patients [4]. Patients who had intermediate high-sensitivity troponin levels were placed in an "observational zone." In this subset of chest pain patients, the appropriate management strategy is unclear and leaves the decision to admit or discharge to the treating clinician. The HI-STEACS algorithm used a gender-specific 99th

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percentile upper reference limit for high-sensitivity troponin at 3 h from emergency department presentation and was dichotomous, however reported a sensitivity rate of 98%. A recent study by Anand et al. evaluated high sensitivity troponin drawn 6–12 h after emergency department presentation however, this would result in longer emergency department lengths of stay [5].

The aim of this multicenter study was to determine if patients with high-sensitivity troponin levels above 3 ng/l and below the gender specific 99th percentile upper reference limit at 6 h from symptom onset require further observation or inpatient admission for management.

2. Methods

2.1. Study design

This was a multicenter retrospective study consisting of four hospital emergency departments with a total volume of approximately 270,000 visits per year. The sites included urban, suburban, tertiary care, and community emergency departments. Data were collected from June 4, 2020 to February 28, 2021. During this period, each of the emergency departments used a rapid rule-out algorithm to determine need for admission, and this data analysis was intended to inform a change to a revised algorithm. The algorithm was designed to evaluate acute coronary syndrome in patients with chest pain using high sensitivity troponin and used patient's reported duration of chest pain from symptom onset, with the definition of chest pain dependent on clinician judgement. This study was conducted under our institution's universal open Institutional Review Board program.

2.2. Data collection

Data were extracted from the electronic medical record, and the data abstractors reviewed the data for quality and consistency across the clinical sites. Patient data were stored in an encrypted hospital server and deidentified.

2.3. Patient selection

Emergency department (ED) patients were included for review if they were admitted for a primary diagnosis of chest pain and had an initial high sensitivity troponin that was greater than 3 ng/l and less than or equal to the gender specific 99th percentile upper reference limit for the Siemen's Atellica analyzer (53 ng/l for men and 34 ng/l for women). Patients who met these criteria had their medical records electronically reviewed for clinically relevant adverse cardiac events during their inpatient admission using a search function of their final discharge diagnoses. Charts with a positive finding of clinically relevant adverse cardiac events were manually reviewed to confirm the diagnosis was made during the inpatient admission and not a historical or miscoded diagnosis.

To estimate the number of patients admitted with nonischemic ECG and no other compelling reason for admission such as unstable vital signs or other admissible diagnoses, we performed a manual chart review of 10% of randomly selected charts of admitted patients to extrapolate the number of patients admitted primarily for chest pain or for other reasons aside from chest pain. We calculated the proportion of patients admitted primarily for chest pain or for another compelling reason using this random sample of charts. This proportion was used to estimate the total number of patients that were admitted which were primarily admitted for chest pain versus for other compelling reason.

Two reviewers independently reviewed charts to determine if a clinically relevant adverse cardiac event had occurred and whether patients were admitted for a primary chief complaint of chest pain. If their decision was discrepant, a third reviewer adjudicated the decision.

2.4. Primary and secondary outcomes

The primary outcome we reviewed was clinically relevant adverse cardiac events during inpatient admission, defined as (1) death, (2) cardiac or respiratory arrest, (3) ST elevation myocardial infarction (STEMI), or (4) life threatening arrhythmia.

Cardiac arrest was defined as any documented loss of pulse. STEMI was defined by documentation of STEMI by the treating clinicians and the patient required emergency percutaneous coronary intervention. Life threatening arrhythmia was defined as any of the following arrhythmias requiring treatment: accelerated idioventricular, accelerated junctional, idioventricular, junctional rhythm, junctional ectopic tachycardia, junctional tachycardia, Torsades de pointes, ventricular escape, ventricular fibrillation, ventricular tachycardia, second degree AV block type II, third degree AV block, asystole.

Secondary outcomes included non-ST elevation myocardial infarction (NSTEMI) and patients who had non-invasive coronary testing during admission.

NSTEMI was defined using the 4th Universal Definition of type-1 NSTEMI, a detection of a rise and/or fall of troponin values with at least one value above the 99th percentile upper reference limit and at least one of the following:

- Symptoms of acute myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

Troponin elevations that did not meet the above criteria were considered non-acute coronary syndrome troponin elevations or myocardial injury due to oxygen demand and supply imbalance unrelated to acute coronary atherothrombosis.

2.5. Data analysis

We used simple descriptive statistics for the primary and secondary outcomes, with 95% confidence intervals for all proportions. We did not perform a formal power analysis, as our intent was to examine as many patients as possible within our time frame, to ensure the narrowest confidence intervals surrounding our point estimates.

3. Results

We identified 1187 patients who were admitted to the hospital for chest pain whose initial high sensitivity troponin was above the limit of detection (3 ng/l) but below the gender specific 99th percentile upper reference limit (34 ng/l for women and 53 ng/l for men). Of these, 758 patients (64%) also had another compelling reason for the admission (ischemic ECG, unstable vitals or additional diagnoses). Out of the total 1187 patients admitted, manual review of the charts showed 30 clinically relevant adverse cardiac events (2.5%). All clinically relevant adverse cardiac events occurred in patients who had another compelling reason for their admission. No clinically relevant adverse cardiac events occurred in the 429 patients who were admitted solely for acute chest pain with initial troponin under the 99th percentile upper reference limit at 6 h from symptom onset.

On analysis of secondary outcomes, 36 patients developed NSTEMI (3%), 33 patients had coronary CT scan, 270 patients had either ECG, echo or nuclear stress testing and 461 patients had echocardiograms during their admission.

Of the 36 patients who developed NSTEMI during their admission, 7 were admitted for another compelling reason while 29 were admitted primarily for chest pain. Of those 29 patients, 26 had high sensitivity troponin elevated above the 99th percentile upper reference limit within 6 h of symptom onset. 3 patients had inpatient NSTEMI who had high sensitivity troponin elevated after 6 h. Of these 3 patients, one had a cardiac catheterization which showed stenosis of the mid left anterior descending artery, ramus intermedius artery, and mid right coronary artery. That patient subsequently received percutaneous coronary intervention of the ramus intermedius artery and was recommended for outpatient elective coronary artery bypass graft. The other two patients also underwent cardiac catheterization which both showed 3 vessel disease with no percutaneous coronary intervention performed and were recommended for elective coronary artery bypass graft as well. Most importantly, none of the patients who developed inpatient NSTEMI had clinically relevant adverse cardiac events during their hospitalization, including the 3 that had delayed high sensitivity troponin elevation (Fig. 1).

4. Limitations

This study had several notable limitations including the retrospective study design as well as the inclusion of patients admitted with a primary diagnosis of chest pain. Although it is the practice in our emergency departments to use chest pain as the reason for admission when the primary concern is acute coronary syndrome, it is possible that there were other patients admitted with other diagnoses not included in this analysis. Additionally, since we only looked at admitted patients with chest pain, there is a chance that discharged patients also experienced clinically relevant adverse cardiac events or NSTEMI events, but we are not aware of any such cases to date.

5. Discussion

High sensitivity troponin allows for detection of myocardial injury at much lower concentration and thus helps expedite the evaluation of patients presenting to the emergency department with possible acute coronary syndrome. There are robust data to show that a single undetectable high sensitivity troponin (below the limit of detection) along with a nonischemic ECG can rule out acute myocardial infarction with high sensitivity [6]. Similarly, elevated high sensitivity troponin above a certain threshold can rule in acute myocardial infarction with high specificity [7–9]. Although the disposition is clear for those meeting rule-out and rule-in criteria, little is known about patients who are in between these thresholds, often leading to diagnostic uncertainty for this patient population.

As a result, this multicenter retrospective study was performed to evaluate the subset of patients with high sensitivity troponin above the limit of detection but below the 99th percentile gender specific upper reference limit. We found that the overall rate of inpatient clinically relevant adverse cardiac events was low at 2.5% with the most frequent event being STEMI. All clinically relevant adverse cardiac events were either identified on arrival to the emergency department and were the reasons for admission or they occurred in patients who had another compelling reason for admission other than chest pain. No clinically relevant adverse cardiac events occurred in patients admitted solely for chest pain who had high sensitivity troponin under the 99th percentile gender specific upper reference limit at 6 h from symptom onset.

Additionally, we observed that the overall rate of NSTEMI was 3%, which is higher than the typical 2% acceptable rate of missed diagnosis cited in ACEP's clinical policy [10]. However, of the 36 patients who had inpatient NSTEMI, 31 of them had serial high sensitivity troponin elevated above the 99th percentile within 6 h of symptoms onset. Of the 430 patients admitted solely for chest pain without another compelling reason for admission, only 3 patients had NSTEMI occurring after 6 h from symptom onset, a rate of 0.7%, well below the 2% acceptable miss rate.

Although high sensitivity troponin has greatly increased the sensitivity in evaluating acute coronary syndrome in patients presenting to the emergency department with chest pain, this increased sensitivity comes at the cost of specificity. Lower thresholds for high sensitivity troponin lead to over-diagnosis and over-testing without a clear improvement in patient-centered outcomes. Our study demonstrates that the incidence of inpatient clinically relevant adverse cardiac events and NSTEMI were still low even in patients with high sensitivity troponin above the limit of detection but below the 99th percentile upper reference limit, when symptoms have been present for greater than 6 h. Hospital admission for these patients is not only costly, but can cause harm due to unnecessary testing and treatment. The more appropriate disposition for these patients may be discharge with appropriate outpatient follow up.

The use of a single high sensitivity troponin after 6 h of symptoms may facilitate expedient dispositions in the emergency department, as many patients in this study had been evaluated by the clinician greater than 6 h after symptom on set. However, even in cases that require serial troponins, the ability to safely discharge patients presenting with chest pain with high sensitivity troponins below the 99th percentile would likely reduce inpatient hospital admissions and short-term observation visits.

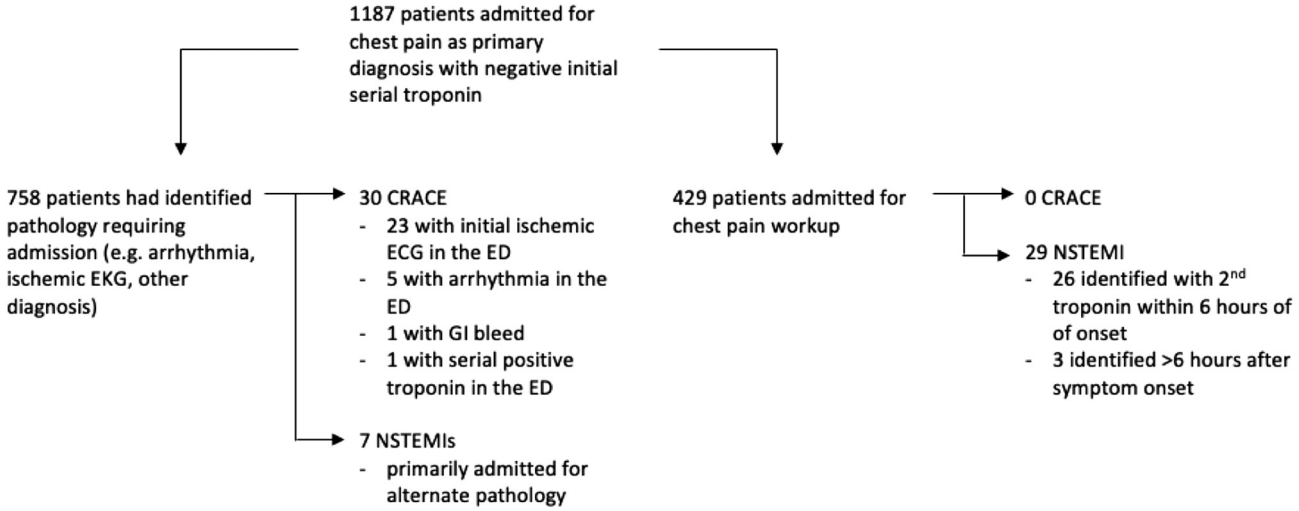

Fig. 1. Patient charts reviewed for clinically relevant adverse cardiovascular events.

6. Conclusion

Patients who have high sensitivity troponin values between 3 ng/l and the 99th percentile after 6 h of chest pain have a low rate of clinically relevant adverse cardiac events and NSTEMI. Future prospective studies to evaluate the risks and benefits of outpatient management are warranted.

Author contributions

RGB and RS were the co-primary investigators and proposed the study.

MVN, OB, HT, MC, and HH did data collection and analysis.

MVN, OB, and HT wrote the manuscript.

MVN submitted the manuscript.

All authors reviewed the manuscript and made edits before submission.

CRediT authorship contribution statement

Rahul G. Bhat: Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Michael V. Nguyen:** Writing – review & editing, Writing – original draft, Formal analysis. **Omoyemen Blue:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Huyen-Trang Thai:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Maria Cacciapuoti:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Hayley Harvey:** Formal analysis, Data curation. **Rory Spiegel:** Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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