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Low-level troponin elevations following a reduced troponin I cutoff: Increased resource utilization without improved outcomes☆

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ABSTRACT

Objective: The study sought to evaluate changes in mortality and resource utilization in patients with low level troponin elevations following a reduction in the cutoff for normal troponin I (TnI) from 0.5 ng/mL to the 99th percentile (0.06 ng/mL).
Methods: This was an interrupted time series comparing emergency department (ED) patients with possible acute coronary syndrome (ACS) and TnI values 0.06–0.5 ng/mL before and after an institutional decrease in the TnI cutoff. The primary outcome was overall mortality at 90 days. Secondary outcomes included rates of re-hospitalization, subsequent ACS, and coronary intervention within 90 days, as well as rates of anticoagulation, cardiology consultation, cardiac testing, and coronary intervention during the index visit. Outcomes for the pre-cutoff change group (control) and post-cutoff change group (post) were compared using tests of proportions and odds ratios.
Results: The study included a total of 1058 subjects with 529 in each cohort. No significant differences in 90 day outcomes were observed between groups, including mortality (13.2% post vs 14.1% control, OR 0.93 [95% CI: 0.65–1.34], $p = 0.705$). During the index visit, the post-group demonstrated higher rates of cardiology consultation (55.4% vs 41.2%, OR 1.77 [1.39–2.26], $p < 0.0001$) and cardiac stress testing (16.4% vs 10.6%, OR 1.66 [1.16–2.38], $p = 0.006$), but no significant differences in coronary intervention or short-term mortality were observed.
Conclusion: A reduction in the TnI cutoff to the 99th percentile did not change mortality or rates of coronary intervention in ED patients with low level troponin elevations, but significantly increased the use of cardiology resources.

1. Introduction

1.1. Background

Acute coronary syndrome (ACS) is a critical entity in emergency and acute care that carries significant morbidity and mortality. ACS constitutes >780,000 cases annually in the US, almost 75% of which are further classified as non-ST elevation myocardial infarctions (NSTEMI). Elevated cardiac troponin levels define the diagnosis of MI, but there is considerable heterogeneity among the various troponin assays commercially available [1,2]. As early as 2000, consensus statements and clinical practice guidelines began recommending a standardized upper reference limit (URL) for normal cardiac troponin defined as the 99th percentile of a normal reference population for a given assay [2,3].

Adoption of the recommended 99th percentile URL creates a category of low level or "gray zone" troponin elevations with values falling above the 99th percentile URL, but below the previously used cutoff value. Compared to patients with definitive troponin elevations above the predefined cutoff URL, ACS patients with low level troponin elevations receive fewer therapeutic interventions, experience more recurrent MIs, and exhibit greater mortality [4,5]. Evidence suggests a lower diagnostic threshold for troponin improves outcomes in these patients. Mills et al. demonstrated a decrease in troponin cutoff from 0.2 ng/mL to 0.05 ng/mL significantly reduced the risk of death and recurrent MI in patients with suspected ACS, particularly in those with a peak troponin level in the study's "gray zone" range (0.05–0.19 ng/mL) [6].

In accordance with guideline recommendations the diagnostic threshold for the troponin I (TnI) assay in use at our institution was lowered from 0.5 ng/mL to 0.05 ng/mL, generating a "gray zone" TnI level of 0.06–0.5 ng/mL. Based on previously published research, we hypothesized that patients with TnI levels 0.06–0.5 ng/mL would receive increased cardiovascular testing/intervention and demonstrate decreased mortality compared to patients with similar troponin levels prior to the reduction in TnI cutoff.

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1.2. Goals of this investigation

The purpose of this study was to assess 90 day outcomes and in-hospital rates of cardiology consultation, diagnostic testing, and cardiovascular intervention in emergency department (ED) patients presenting with symptoms concerning for possible acute coronary syndrome (ACS) and "gray zone" TnI values (0.06–0.5 ng/mL) following an institutional decrease in the diagnostic threshold for a normal TnI.

2. Materials and methods

2.1. Study design and setting

The study was a retrospective interrupted time series comparing two cohorts of consecutive adult patients presenting to the ED with potential ACS and a TnI value in the "gray zone" range (0.06–0.5 ng/mL) before and after a change in the diagnostic threshold for TnI. On November 11, 2011, the URL for the ADVIA Centaur CP TnI-Ultra assay (Siemens Medical Solutions USA, Inc., Malvern, PA) was decreased from 0.5 ng/mL to the prior 99th percentile (0.06 ng/mL) across the institution [7]. Patients were identified from 3 discrete time intervals: (1) The 6-month period before the change in normal TnI threshold (May 2011 to October 2011), (2) the 3-month period following the change in TnI threshold (November 2011 to February 2012) and (3) a subsequent 3-month period starting one year after the change in TnI threshold (November 2012 to January 2013). The control cohort comprised patients presenting prior to November 11, 2011 (Interval 1) and the post-cohort consisted of patients presenting on or after November 11, 2011 (Intervals 2 and 3). We chose an interrupted time series design to assess both the immediate and sustained effects of the TnI cutoff change on resource utilization and outcomes.

The study was conducted at a university-affiliated, community teaching hospital with chest pain center accreditation and an annual ED census of approximately 81,000 patients. Patients with potential ACS were hospitalized under the internal medicine, family medicine or medical intensivist services. The cardiology consultation service was comprised exclusively of board-certified attending cardiologists. The decision to obtain cardiology consultation or cardiovascular testing was left to the discretion of the admitting physician. Options for non-invasive provocative cardiac testing for hospitalized patients at the institution include exercise and chemical stress tests with echocardiography and nuclear imaging, as indicated. Stress testing was typically ordered by the admitting service with or without consultant input, while invasive cardiac testing and interventions were initiated exclusively by a cardiologist. Coronary computed tomography angiography (CCTA) was not performed.

The study team consisted of two attending EM physicians, five EM residents, one clinical research manager and six undergraduate research assistants. Study design and execution were performed in accordance with previously published guidelines regarding retrospective and observational studies [8-10]. Institutional review board approval was obtained with waiver of consent.

2.2. Troponin I assay

Blood TnI concentrations were measured using the ADVIA Centaur CP TnI-Ultra assay (Siemens Medical Solutions USA, Inc., Malvern, PA) with analytic range 0.006–50 ng/mL and a 10% coefficient of variation of 0.03 ng/mL. Prior to November 11, 2011 the clinical decision point was 0.5 ng/mL. Starting November 11, 2011, the clinical decision point was decreased to 0.06 ng/mL based on a 99th percentile cutoff [7].

2.3. Selection of participants

An initial query of electronic laboratory records generated a master list of consecutive ED patients with a TnI of 0.06–0.5 ng/mL between May 2011 and February 2012 and between November 2012 and February 2013. Patients were eligible for inclusion if they were at least 18 years old and demonstrated a TnI value 0.06–0.5 ng/mL. Patients were excluded for active DNR, DNI or "comfort care only" status at the time of ED assessment, initial presentation consistent with ST-elevation myocardial infarction (STEMI), lack of an initial EKG or a chief complaint other than chest pain, dyspnea, generalized weakness, syncope/near syncope, or upper abdominal pain. These specific complaints were chosen to include atypical ACS presentations while excluding patients with conditions for which TnI is often obtained, but ACS is not a primary clinical concern, such as sepsis and altered mental status.

2.4. Measurements

Data were abstracted from the EMR utilizing a standardized closed-response data collection form. We conducted a comprehensive chart review of eligible patients, including a review of physician and nursing notes, laboratory values, diagnostic testing reports, operative notes, discharge summaries and subsequent follow up documentation. Basic patient demographics were collected, including age, gender, race, baseline creatinine (Cr), and TnI value. Relevant comorbidities were recorded, including chronic kidney disease (CKD), coronary artery disease (CAD), diabetes mellitus (DM), hyperlipidemia, hypertension (HTN), and history of current or prior smoking. Data for continuous variables (age, Cr, TnI) were collected via manual input and data for categorical variables (all others) were collected using a multiple choice, closed response format.

To assess outcomes at 90 days, charts were reviewed for subsequent visits to outpatient facilities, EDs, and hospitals within our institutional health system. As determination of outcomes at 90 days relied on documentation in the EMR, we anticipated that in some cases this information would be missing or otherwise unobtainable. In such instances, the corresponding 90 day outcomes were deemed "unknown". Missing mortality data triggered a manual search for the corresponding patient in the Social Security Death Index (SSDI). Mortality was ultimately deemed unknown if death was not reported in the SSDI within one year of the index visit.

All members of the research team participated in chart review and data collection after one-on-one instruction by the principal investigator (PI). Following abstraction of 10–20 charts, each abstractor met with the PI and reviewed the collected data to ensure accuracy, consistency and proper adherence to definitions. A random selection of charts underwent redundant abstraction by a second different study team member to assess for interobserver agreement. In cases of disagreement between abstractors, final data were determined via adjudication by the primary author (BB) and clinical research manager (BS).

2.5. Outcomes

The primary outcome of the study was mortality at 90 days. Secondary outcomes consisted of additional outcomes at 90 days, including rehospitalization following discharge from the index visit, as well as a diagnosis of MI/ACS, percutaneous intervention (PCI) or coronary bypass grafting (CABG) during subsequent hospital visits. MI/ACS was defined as a discharge diagnosis of ACS, acute MI, or unstable angina, as documented by the treating physician in the discharge summary.

Further secondary outcomes assessed resource utilization during the index visit, including full anticoagulation with cardiac-dose heparin, cardiology consultation, stress testing, cardiac catheterization, PCI, and CABG. Stress tests were considered positive in the presence of inducible ischemia, as documented by the interpreting cardiologist.

2.6. Sample size

Based on prior research, the reduced TnI threshold was expected to decrease mortality at 90 days by 70% in patients with a "gray zone" TnI value [6]. Pilot data at our institution suggested a baseline mortality of

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