**­Title**: Secular trends in positive and negative predictive values of cardiac troponin I assays for myocardial infarction classification in 4 US communities: Findings from the Atherosclerosis Risk In Communities (ARIC) Community Surveillance study

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**Abstract (200 word limit)**

Population surveillance for myocardial infarction (MI) using discharge diagnosis codes may be enhanced using automated detection of abnormal cardiac troponin values, one criterion for diagnosis of MI, in the electronic medical record. The utility of these abnormal values may have changed because of increased cardiac troponin assay biochemical sensitivity. Assay sensitivity may affect the positive and negative predictive values (PPV and NPV) of abnormal troponins for detecting MI. Among four communities in the Atherosclerosis Risk In Communities (ARIC) study, we estimated the PPV and NPV of abnormal cardiac troponin I concentrations (> 2x the upper limit of normal) from 1996 – 2014. We assessed PPV and NPV using hospitalizations classified for MI by clinician review. PPV and NPV were calculated using Bayesian multilevel logistic regression with poststratification to account for the complex sampling design. Of the 27,180 hospitalizations included in our analysis, 65% had a normal troponin I and 25% had an abnormal troponin I. PPV decreased from 84% (95% credible interval: 76 – 91%) in 1996 to 70% (65 – 74%) in 2014. NPV increased from 87% (81 – 91%) in 1996 to 95% (93 – 97%) in 2014. Abnormal cardiac troponin I findings combined with discharge codes may cause misclassification error in up to 35% of records.

**Introduction**

Cardiac troponin (cTn) assessment in the context of acute cardiac symptoms is a major focus of the Fourth Universal Definition of acute myocardial infarction (MI).1 As with previous editions of the universal definition of acute MI, valid measures of cTn in clinical settings are relied upon heavily. Accurate cTn concentrations are also important for meaningful surveillance of MI in the community and greatly facilitate the ascertainment of temporal trends in MI event rates across demographic and geographic groups. Sensitive, modern assays for cTn have complicated MI surveillance efforts. It is unclear to what extent modern cTn assays have affected the utility of abnormal cTn values for detection of MI (e.g., positive predictive value [PPV] and negative predictive value [NPV]) and whether any chances in utility have varied among hospitals.

As the biochemical sensitivities of cTn assays have increased over time, two criteria have been proposed to consider a cTn assay as “high sensitivity”: (1) the coefficient of variation is <10% at its 99th percentile in a healthy population (i.e., its sample mean divided by its sample standard deviation, times 100); and (2) the percent of healthy individuals with a detectable cTn concentration below the 99th percentile is ≥ 50%.2 Many cTn assays used during the past two decades in clinical practice had a 20% coefficient of variation at the 99th percentile,3 but these assays did not broadly lead to event misclassification compared to more sensitive assays.4,5 Because high sensitivity assays can detect a broader range of cTn concentrations, more hospitalizations may be classified as a possible MI than with less sensitive assays, depending on evidence of cardiac ischemia. The PPV and NPV of cTn assays for MI may have changed over time.

The Atherosclerosis Risk In Communities (ARIC) study conducted community surveillance of hospitalized MI from 1987 to 2014 among four US communities (Jackson MS, Forsyth County NC, Washington County MD, and suburban Minneapolis MN). Among hospitalizations for potential MI identified by the ARIC study, we hypothesized that the PPV and NPV of abnormal cardiac troponin I (cTnI) findings (ARIC community surveillance criterion: > 2x upper limit of normal [ULN]) changed over time. Therefore, we estimated the yearly PPV and NPV of abnormal cTnI for MI from 1996 – 2014 across all hospitals within the four ARIC communities. We also estimated the PPV and NPV within each hospital for each year to determine whether the secular trends differed among hospitals with different laboratories.

**Methods**

Study population

From 1987 – 2014 ARIC Community Surveillance attempted to estimate the rates of coronary heart disease (CHD) hospitalizations within the four geographically defined communities through sampling events based on the following criteria: (1) the patient lived within the catchment area; (2) the patient was age 35 – 74 years (later increased to 84 years in 2005); and (3) the patient had an International Classification of Disease (ICD) discharge diagnosis code that broadly indicated possible CHD (see Table 1 in White et al. 19966). All eligible hospitalizations across 32 hospitals in the four catchment areas underwent single-stage stratified sampling with unequal probabilities of sampling across strata to select hospitalizations for medical record abstraction. Medical record abstraction collected information on chest pain symptoms, ECG, biomarkers, and the ULNs for biomarkers from the laboratory report. These elements were used to create an algorithmic classification, which was then checked and possibly modified by a clinician-reviewer. The target population for our analysis was all hospitalizations which met the ARIC criteria and had a cTnI measured during the hospitalization. These criteria not only explicitly excluded hospitalizations where no cTnI was assessed, but also implicitly excluded hospitalizations before 1996. We also explicitly excluded any observations that had an ULN of 0 ng/mL or a ULN of greater than 2 ng/mL for cTnI because these values were likely data inaccuracies.

After identifying the study sample we further identified hospitalizations where the worst cTnI measurement over the first four days of the hospitalization was “abnormal” or “not abnormal.” ARIC community surveillance has traditionally defined an abnormal cTnI concentration to be one that is more than 2 times the reported ULN for the assay used within each hospital. We used the same definition for the current study. Hospitalizations where the worst cTnI was abnormal were used to estimate PPV. Hospitalizations where the worst cTnI was not abnormal were used to estimate NPV.

Outcome definition

Cases were defined as hospitalizations classified as a definite or probable MI by trained ARIC study clinician reviewers. Controls were defined as hospitalizations classified as a suspect MI or not an MI. The outcome when estimating PPV was being a case; when estimating NPV the outcome was being a control.

Data analysis

Descriptive statistics of events included age, sex, race, ULN of cTnI assay, the highest cTnI measurement, year of the event, and the ARIC algorithmic classification of the biomarker. We also provided estimates of the median ULN of troponin I for each year, along with 95% confidence intervals. Design-based survey procedures that accounted for the stratified sampling with unequal probabilities among stratum were used for descriptive statistics, supporting inference to all target hospitalizations in the four ARIC communities each year, rather than only the hospitalizations that were sampled for medical record abstraction.

To estimate PPV of troponin I assays within each year, we used a Bayesian multilevel logistic regression framework among hospitalizations where the worst cTnI value was abnormal. An analogous strategy was used to estimate NPV among controls. We allowed the overall PPV and NPV, as well as the PPV and NPV in each year, to vary by hospital using multilevel modeling. We accounted for the sampling design of ARIC in this framework by using multilevel regression with poststratification.7 In brief, this method adjusted for all of the relevant sampling strata, as well as any variables that affected nonresponse, then used weighted averages of posterior PPVs and NPVs across the strata to produce estimates for the population of hospitalizations. Sampling strata were modeled as varying intercepts. This strategy had two main advantages: (1) the ability to use generalized linear mixed models with complex survey data, which were used to explore variation in trends over time by hospital; and (2) better accuracy in prediction in groups with small sample sizes (e.g., small hospitals). These models were fit using the rstanarm package,8 which is a front-end in the R9 software environment to the Stan probabilistic programming language.10 We used a normal(1, 2) prior for the intercept and scaled normal(0, 1 / sdx) for year, where sdx was the standard deviation of the dummy variable for a particular year. The prior distribution for the covariance of random effects for sampling stratum () and hospital () used a combination of an LKJ(1) prior11 and Dirichlet prior. Additional details can be found at <http://mc-stan.org/rstanarm/articles/glmer.html>. These priors were smaller in standard deviation / more weakly informative that the rstanarm defaults to aid convergence of this complex model. The prior for the intercept was based on a rough 75% prevalence of MIs.

**Results**

Among the 93,986 hospitalizations investigated by ARIC community surveillance from 1987 - 2014, 27,199 met our inclusion criteria. Sixteen observations were excluded due to having a ULN equal to 0 ng/mL and 3 were excluded due to a ULN greater than 2 ng/mL. Therefore, the analysis sample contained 27,180 participants (99.9% of target sample). Table 1 shows the summary statistics for these hospitalizations, as well as for the subsets classified as cases (11,367) and controls (15,813). Design-based summary statistics are available in Table 1. Cases were more likely to be male, have a lower upper limit normal for the assay used, and have orders of magnitude larger maximum troponin values during their hospitalizations. The probability of a normal troponin I value was 0.16 for cases and 0.80 for controls. The probability of an abnormal troponin I value was 0.77 for cases and 0.09 for controls. For all hospitalizations that met our inclusion and exclusion criteria, approximately twice as many hospitalizations had a normal troponin value versus an abnormal troponin value.

The median ULN for hospitalizations abruptly increased or dropped four times from 1996 to 2014, indicating sudden and broad changes to values of troponin that were considered abnormal (Figure 1).The PPV of an abnormal cTnI concentration was highest in the late 1990s and declined over the next 15 years by 15 percentage points (95% credible interval, 5 – 22 percentage points; Figure 2) from 1996 to 2014. The PPV was 84% (76 – 91%) in 1996 and 70% (65 – 74%) in 2014. The NPV of a normal cTnI concentration increased slightly from 87% (81 – 91%) in 1996 to 95% (93 – 97%) in 2014 (Figure 2). The increase in NPV was 8 percentage points (3 – 14 percentage points). The PPVs and NPVs of a cTnI concentration varied across hospitals, both in absolute values and in secular trends from 1996 – 2014 (Figures 3 and 4).PPV decreased in most hospitals, but in others the PPV stayed relatively constant or increased. The pattern for NPV appeared more consistent than for PPV, with almost all hospitals increasing slightly.

**Discussion**

In this analysis of ARIC community surveillance data from 1996 to 2014, we investigated whether PPV and NPV of cTnI for MI changed over time, since the biochemical sensitivities of cTnI assays were increasing during that time. Abruptchanges in the ULN for troponin I assays can be caused by introduction of new, more sensitive assays to the market, administrative changes made by hospital laboratories, or by new recommendations from scientific groups (e.g., the universal definitions of MI1,12,13). We also investigated whether the secular changes in abnormal cTnI PPV and NPV varied among the hospitals included in the ARIC communities. Using multilevel logistic regression with poststratification to account for the stratified sampling with unequal probabilities of ARIC community surveillance, we estimated yearly PPV and NPV. The estimated PPV of an abnormal cTnI value fell slowly between 1996 and 2014. The estimated NPV rose slowly from 1996 to 2014 among hospitals in the four ARIC communities.

The median ULN for hospitalizations abruptly increased or decreased four times from 1996 to 2014, indicating sudden and broad changes to values of cTnI that were considered abnormal. Abruptchanges in the ULN for cTnI assays could have been caused by introduction of new, more sensitive assays to the market, administrative changes made by hospital laboratories, or by new recommendations from Scientific groups, such as updates to the universal definition of MI.12–14 The timing of the abrupt changes in the ULN for cTnI assays coincided with changes to the universal definition of MI. The median ULN in the year 2000 was nearly identical to that of 1999, but then had a drop in median ULN in 2001 around the publication of the first Universal Definition of MI. The median ULN abruptly increased in 2003, the same year that recommendations for epidemiologists conducting retrospective surveillance on coronary heart disease was published,14,15 but the increase could have been spurious. Then, a sudden decrease in median ULN occurred in 2006, the same year that the second Universal Definition of MI was created by the task force, before being ultimately published in 2007.13 We see a final drop in median ULN in 2012, coinciding with the publication of the third Universal Definition of MI. Although we cannot prove whether the new definitions of MI caused these changes in median ULN among hospitals in the 4 ARIC communities, the repeated patterns provide reasonable evidence that the changes in ULN and releases of the universal definitions of MI were linked.

Other studies have noted that changing reference limits for cTn assays can affect what cTn concentration would be considered abnormal. And the reference limits themselves can carry uncertainty, which has more than one source. First, the ULN may be estimated with too few participants, with varying statistical estimators, or with unclear definitions of the healthy reference population.3 Second, the 99th percentile of cTn measurements varies among healthy reference populations. By including participants with mild subclinical disease16 in the reference population, the 99th percentile can increase substantially. One analysis of an assay from Singulex demonstrated the 99th percentile of cTnI in healthy men (16.6 ng/mL) was almost twice that in healthy women (9.36 ng/mL).17 Third, more biochemically sensitive cTn assays can: (1) result in more measured values in the lower tail of the distribution17; and (2) shrink the magnitude of overestimation at the upper tail of the distribution, resulting in a narrower observed distribution and subsequent reduction of the estimated 99th percentile.4 If the true 99th percentile for a given patient is different than the one used for surveillance, then surveillance efforts could systematically under- or over-estimate the rate of MI in different subpopulations. Using abnormal cTnI concentrations to perform surveillance of MI can result in systematic case misclassification because the thresholds (ULN or 99th percentile13) are noisy measures of what is “abnormal.”

These findings have implications for current research in automated MI surveillance, particularly for studies using electronic medical records. In our study sample of 35 - 74-year-old patients hospitalized with a broad variety of discharge codes indicating cardiovascular disease, there was an approximately 30% chance of a false positive classification of MI and a 5% chance of a false negative classification of MI based solely on whether the cTnI was above or below the 2x the ULN cutoff. Because of constant improvement in the biochemical sensitivities of cTn assays, these error rates may have changed since 2014. Surveillance studies using the electronic medical record may not restrict the population of interest to only those with possible evidence of cardiovascular disease, making the overall prevalence of true MIs in a given surveillance database lower than what we observed in ARIC, leading to a decrease in the PPV of an abnormal cTnI compared to ARIC. Alternatively, if a surveillance study used a population with a more narrow set of codes indicative of MI than ARIC, PPV may be increased compared to ARIC. Identifying abnormal cTnI concentrations in the electronic health record may be easier compared to identifying ECG evidence of an MI or specifics about type and duration of symptoms, but in isolation the information may have limited benefit to performing automated MI surveillance in US hospitals.

The presence of an elevated cTn is indicative of myocardial injury; however, by itself, a cTn elevation does not necessarily equate to an MI. According to the 4th Universal Definition of MI,1 an MI is defined when there is evidence of myocardial injury with at least one cTn above the 99th percentile with detection of rise or fall pattern and at least one of the following: symptoms of ischemia (typically chest pain), new ischemic ECG changes or new pathological Q waves, imaging evidence of ischemic myocardium, or evidence of coronary thrombus. An elevated cTn alone does not determine whether an MI has occurred or not, but the changing sensitivities in the cTn assays can influence whether this important criterion is met.

Limitations and strengths

A limitation of this study was the classification of MI in a manner that ignores current understanding of various subtypes of MI,18 for which cTnI assays could have variable PPVs and NPVs. The time period of this analysis (1996 – 2014) spanned 3 universal definitions of MI. To maintain the integrity of secular comparisons within ARIC community surveillance, the criteria used by ARIC clinician reviewers to classify an MI has remained consistent. Because the changes in median ULN coincided with changes in the universal definition of MI, the trends in PPV and NPV may reflect not only changes in assay biochemical sensitivity, but also changing guidelines for defining an MI. Finally, the increase in non-ST segment elevation MIs (NSTEMIs) relative to ST segment elevation MIs (STEMIs) may have affected the distribution of abnormal or not abnormal cTnI levels, regardless of whether an MI occurred. NSTEMIs often result in less myocardial injury and lower cTnI levels. Therefore, we cannot rule out that the PPV and NPV patterns are caused by secular changes in MI case mixture. It is difficult to say whether these limitations would have caused over- or under-estimation of the PPVs and NPVs.

In our view, the strengths of our approach for estimating the validity of cTnI assays outweigh the limitations*.* Our study used data from a multi-decade community surveillance effort in four distinct geographic locations, with medical record abstraction performed by trained medical abstractors that underwent annual re-evaluation and training. This approach likely led to less measurement error in the analysis dataset than other less resource-intensive approaches, such as using the electronic medical record. Another key strength of our study was the statistical approach of multilevel regression with poststratification, compared to traditional design-based methods for survey samples. Using multilevel regression with poststratification allowed us to provide less variable estimated trends of sensitivity and specificity in hospitals with small sample sizes, since information was “borrowed” from the larger hospitals in the multilevel model. Estimating hospital-specific trends using a multilevel model would have been difficult in the traditional design-based approach, since this approach is actively under development in the statistical community.19–21

In conclusion, we demonstrated that the PPV of cTnI assays for population-level MI surveillance fell from 1996 to 2014 among hospitals in four US communities.We postulate that further increases in biochemical sensitivity of cTnI assays since 2014 may have reduced their utility in MI surveillance even further, due to likely further decreases in PPV.Some have called for a renewed investment in national surveillance systems for cardiovascular disease.22,23 The desire to use modern data sources such as electronic medical records in national surveillance systems is warranted, but relying on discharge codes and cTn alone could cause approximately 35% misclassification error in communities similar to the ARIC study. This error rate is concerning because some surveillance systems may elect to avoid automated use of additional criteria such as chest pain and ECG evidence due to the need of more advanced methods for these criteria (i.e., natural language processing and image recognition). If surveillance systems do avoid these components, then manual case review by clinicians may remain necessary in epidemiologic surveillance systems to prevent overestimating the US burden of MI.

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**Tables**

**Table 1. Summary statistics of hospitalizations from 1996 – 2014 in the four ARIC communities.** Statistics are weighted for the complex sampling. Numbers are median (q1, q3) unless otherwise indicated; \*proportion (frequency)

| **Variable** | **Cases *(n = 11367+)*** | **Controls *(n = 15813+)*** | **Overall *(n = 27180+)*** |
| --- | --- | --- | --- |
| Age | 60.01 (52.02, 67.28) | 61.80 (53.45, 68.55) | 61.36 (53.08, 68.29) |
| Sex\*     Female | 0.36 (7706.34) | 0.44 (30825.78) | 0.42 (38532.12) |
| Male | 0.64 (13744.60) | 0.56 (40029.82) | 0.58 (53774.43) |
| Race\*     Black | 0.31 (6592.94) | 0.29 (20849.39) | 0.30 (27442.33) |
| White | 0.69 (14857.99) | 0.71 (50006.22) | 0.70 (64864.21) |
| Upper limit normal (ng/mL) | 0.49 (0.09, 1.29) | 0.68 (0.30, 1.39) | 0.62 (0.29, 1.39) |
| Worst troponin I (ng/mL) | 3.39 (0.40, 18.69) | 0.10 (0.02, 0.25) | 0.10 (0.04, 0.60) |
| Year\*     1996 | 0.00 (104.27) | 0.00 (290.64) | 0.00 (394.92) |
| 1997 | 0.06 (1197.11) | 0.05 (3420.24) | 0.05 (4617.35) |
| 1998 | 0.05 (998.37) | 0.04 (3130.01) | 0.04 (4128.38) |
| 1999 | 0.06 (1321.05) | 0.05 (3476.72) | 0.05 (4797.77) |
| 2000 | 0.06 (1381.54) | 0.06 (4464.85) | 0.06 (5846.39) |
| 2001 | 0.07 (1485.50) | 0.06 (4469.48) | 0.06 (5954.98) |
| 2002 | 0.05 (1058.91) | 0.07 (4767.19) | 0.06 (5826.11) |
| 2003 | 0.05 (1051.93) | 0.07 (4786.97) | 0.06 (5838.90) |
| 2004 | 0.04 (956.08) | 0.06 (4147.95) | 0.06 (5104.03) |
| 2005 | 0.05 (1130.29) | 0.06 (3981.65) | 0.06 (5111.94) |
| 2006 | 0.05 (1171.94) | 0.06 (4373.79) | 0.06 (5545.72) |
| 2007 | 0.05 (1071.32) | 0.06 (4104.14) | 0.06 (5175.46) |
| 2008 | 0.06 (1247.06) | 0.06 (4573.41) | 0.06 (5820.47) |
| 2009 | 0.06 (1223.89) | 0.06 (4168.74) | 0.06 (5392.63) |
| 2010 | 0.05 (1093.54) | 0.06 (4297.00) | 0.06 (5390.54) |
| 2011 | 0.07 (1414.10) | 0.06 (4284.75) | 0.06 (5698.85) |
| 2012 | 0.07 (1443.10) | 0.05 (3664.06) | 0.06 (5107.16) |
| 2013 | 0.05 (1080.73) | 0.03 (2438.80) | 0.04 (3519.52) |
| 2014 | 0.05 (1020.22) | 0.03 (2015.22) | 0.03 (3035.44) |
| Worst troponin I classification\*     Normal (<ULN) | 0.16 (3399.32) | 0.80 (56799.59) | 0.65 (60198.91) |
| Equivocal (1 – 2x ULN) | 0.07 (1455.58) | 0.10 (7266.90) | 0.09 (8722.48) |
| Abnormal (>2x ULN) | 0.77 (16497.78) | 0.09 (6345.82) | 0.25 (22843.60) |
| Incomplete | 0.00 (98.25) | 0.01 (443.30) | 0.01 (541.55) |

+Counts are unweighted

   Minimum number of hospitalizations at an individual hospital: (1)

   Maximum number of hospitalizations at an individual hospital: (6054)

**Figures**

Chart, scatter chart, box and whisker chart

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**Figure 1. Median upper limit normal of troponin assay and 95% confidence intervals among 27,180 hospitalizations from 1996 - 2014 in the four ARIC communities.** Medians and confidence intervals are weighted to account for the complex sampling strategy of ARIC community surveillance.

**Chart, scatter chart

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**Figure 2. Estimated positive and negative predictive values of cTnI assays with 95% credible intervals from 1996 - 2014 in the 32 hospitals contributing to ARIC surveillance.** Multilevel regression with poststratification was used to account for the complex sampling strategy of ARIC community surveillance. Point estimates are posterior means.

Diagram

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**Figure 3. Estimated positive predictive value of cTnI assays by hospital with 95% credible intervals from 1996 - 2014 in the four ARIC communities.** Multilevel regression with poststratification was used to account for the complex sampling strategy of ARIC community surveillance. Point estimates are posterior means.

Diagram

Description automatically generated

**Figure 4. Estimated negative predictive value of troponin assays by hospital with 95% credible intervals from 1996 - 2014 in the four ARIC communities.** Multilevel regression with poststratification was used to account for the complex sampling strategy of ARIC community surveillance. Point estimates are posterior means.