Title

Sensitivity and Specificity of Troponin-I in a County Hospital: Identifying when Troponin-I is Unreliable

Journal

Proceedings of the UCLA Department of Medicine, 19(1)

Authors

Arutyunov, Boris
Pearlman, Justin

Publication Date

2015-07-29

CLINICAL REVIEW

Sensitivity and Specificity of TroponinI in a County Hospital: Identifying when Troponin-I is Unreliable

Boris Arutyunov, M.D., and Justin Pearlman, M.D., Ph.D.

Abstract

Studies of Troponin have reported very high diagnostic value as reported by analysis of sensitivity and specificity via receiver operatory characteristic (ROC) area under the curve (AUC) close to 1 (no tradeoff between sensitivity and specificity). At a mid-sized academic community hospital where many patients have not had prior medical care in a decade, we found very different results: there is a sizeable subset of patients who have low AUC, indicating a significant drop in specificity at the usual "normal limit" threshold. Troponin I in our community hospital at lab recommended diagnostic threshold had a sensitivity of 57% and specificity of 71%. We found a high false positive rate in patients who have MAP $\geq$ 100, GFR $\leq$ 45, or Age $\leq$ 50. Area under the curve of the ROC plot for this group was 0.644 compared to patients who had none of these three findings and who had a total area under the curve of 0.858. These differences offer major savings in cost-effective strategic planning for management of patients with elevated troponin I.

Introduction

Cardiovascular disease is the leading cause of death in the United States. Myocardial infarction occurs in 1.5 million people per year in the United States.[1] In 2011, acute myocardial infarction cost $11.5 billion and 612,000 hospital days.[2] One of the most common laboratory tests ordered for chest pain is troponin I levels (TNI). TNI is a 209 amino acid protein, which is a structural protein in heart muscle. It binds to actin in thin myofilaments to hold the actin-tropomyosin complex in place. When myocardial damage occurs, TNI spills into the circulation and is measured by multiple assays that are available on the market. Reichlin et al[3] compared three assays of TNI and one assay of troponinT, plotted receiver operating characteristic plots and found high areas under the curve (AUC) for various TNI assays to be 0.96, 0.95, and 0.96.[3] Furthermore, troponinT had an area under the curve of 0.96. Corresponding to these high AUC values, Keller et al[4] showed that the sensitivity and specificity of TNI to be 90.7 and 90.2, respectively.[4] This group also showed the positive predictive value and negative predictive value to be 86.7 and 84.1, respectively. In our research, we examine the impact of confounding factors on the predictive accuracy of TNI in an indigent community. For example, patients with a MAP $\geq$ 100 tend to have ventricular hypertrophy and chronic TNI spillover into the blood. Patients with GFR $\leq$ 45 may have impaired clearance of TNI resulting in elevated lab result. Those patients who are $\leq$ 50 years of age are less likely to have cardiovascular disease, which promotes false positive elevated TNI level.

Methods

Between January 2013 and May 2014, 133 people had a dobutamine (DSE) or treadmill stress test and had TNI levels drawn around the time of the stress test. In that same time interval, predictive accuracy of DSE at our institution was established versus cardiac catheterization to have 95% accuracy for actionable coronary disease.[5] In the current study, we looked at all patients who had an elevated TNI level followed in 3 weeks or less by diagnostic stress testing. For this study, a stress test result was counted as POSITIVE for evidence of coronary disease if a patient had a new drop in ejection fraction to less than 55% or drop from prior >5%, stress induced ischemic ECG changes (ST shift >0.1 mV), or new segmental wall motion abnormalities. If a patient had chest pain maximal at peak but no ECG or imaging diagnostic changes, the stress test was counted as inconclusive. These criteria were applied to avoid underestimation of clinical true positives for TNI elevation related to myocardial injury. The population was divided into two subgroups. Group B included patients with at least one of the prior reasons a TNI elevation may be false positive: MAP $\geq$ 100, GFR $\leq$ 45, or Age $\leq$ 50. Group A was everyone with none of these three confounders. The null hypothesis was that differences were random; our alternate hypothesis (H1) was significant change in ROC AUC (e.g., a higher rate of falsely elevated TNI level in the presence of confounder factors).

Sensitivity and specificity were calculated directly using a 4 x 4 table. Receiver operating characteristic plot was calculated using an online program from Johns Hopkins University.[6] The method of Delong et al[7] for the calculation of the Standard Error of the Area Under the Curve (AUC) and the methods of Hanley & McNeil[7,8] for the calculation of the Standard Error of the Area Under the Curve (AUC) and of the difference between two AUCs were used to generate the p value to compare Group A and Group B.

Results

Of the 133 people who had dobutamine echo or a treadmill stress test, 10 subjects had an inconclusive result (e.g., progressive chest pain but no evidence of induced wall motion abnormality). These 10 cases were excluded from the study. Of the 123 remaining cases, 4 were true positive, 82 were true negative, 34 were false positive, and 3 were false negative. Using the lab standard threshold for TNI elevation at 0.05 ng/mL, these corresponded to sensitivity of TNI of 57% and specificity of 71%. Using the methods described above to plot the ROC curve of the overall results, the total area under the curve was calculated to be .681 (Figure 1).

These 123 patients were further subdivided into Group A and Group B. Group B was patients with a MAP $\geq$ 100, or GFR $\leq$ 45, or Age $\leq$ 50. Group A was everyone else. This gave a total of 86 patients in Group B and 37 patients in Group A. Of the 86 patients in Group B, 3 were true positive, 3 were false negative, 25 were false positive, and 55 were true negative. Of the 37 patients in Group A, 1 was true positive, 0 were false negative, 9 were false positive, and 27 were true negative. After plotting the ROC curves for Group A and Group B, the area under the curve (AUC) for Group A and Group B were calculated. Group A area under the curve (AUC) was .644 and Group B area under the curve (AUC) was .858 (Figure 2). Using the diagonal as a standard operating point threshold, when the Group A sensitivity is 60%, the false positive rate is 0.40 (specificity 60%). When Group B sensitivity is 85%, the false positive rate is 0.25 (specificity 75%). When using the lab cutoff for these same groups, Group A had a sensitivity of 100% and specificity of 75%, while Group B had a sensitivity of 50% and specificity of 69%.

Discussion

Our study showed that TNI has the sensitivity of 57% and specificity of 71% in detecting myocardial injury or inducible ischemia. This is in contrast to multiple studies claiming that TNI has the sensitivity and specificity approaching 99%. These differences are substantial and have major consequences on cost. If TNI were 99% accurate, we might be obliged to send every patient to an outside facility for interventional catheterization at a cost exceeding $10,000 per incident. Knowledge of confounding factors that lower TNI accuracy to a coin flip changes management strategy. TNI can be elevated due to normal cardiac enzymes spillover, renal failure, or non-coronary cardiac stress. Furthermore, it is expected that a certain subgroup of the population will have an elevated TNI without it necessarily representing any clinically significant myocardial injury. As we demonstrated, patients in Group B, which included patients with a MAP $\geq$ 100, or GFR $\leq$ 45, or Age $\leq$ 50, is a group that has a high rate of elevated TNI with no subsequent evidence of myocardial injury or coronary disease. Recently, the American College of Cardiology has acknowledged limitations of TNI by recommending that positives be interpreted in conjunction with independent evidence for coronary ischemia.[9]

Limitations

There are several limitations in the study that affect policy considerations. First, in this study we used a dobutamine or a treadmill stress test as a surrogate for clinically significant coronary disease. A minority also had catheterization proven "clean coronaries" while a majority declined catheterization. Cardiac catheterization in all cases would be more definitive. The high predictive accuracy for lack of coronary disease with the definition of negative findings as used in this study indicates that was not a major issue. Second, a larger number of cases with a greater number of false negatives would improve the power of the study. Third, the study was done in a county hospital, which serves a specific subgroup of the population with particular socioeconomic and cultural backgrounds. Fourth, we did not distinguish between the absolute values of the TNI.

Conclusions

TNI (TNI) is not reliable in all settings. In particular, patients with hypertension (mean arterial pressure > 100 mmHg), renal impairment (glomerular filtration rate <60%), or youth (age <50) have distinctly lower predictive accuracy of TNI elevations. Particular care to confirm evidence for coronary ischemia should factor into decisions to perform catheterization in such patients.

Figures and Table.

Figure 1. This ROC plot represents the cumulative data for all the patients.

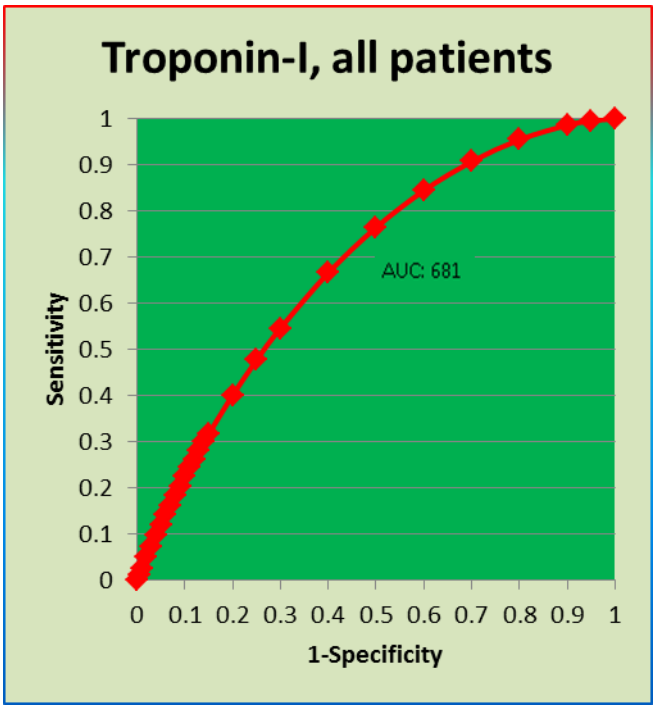

Figure 2. The red curve is Group B (MAP ≥ 100, GFR ≤ 45, or Age ≤ 50). The blue curve is Group A (none of the confounding factors).

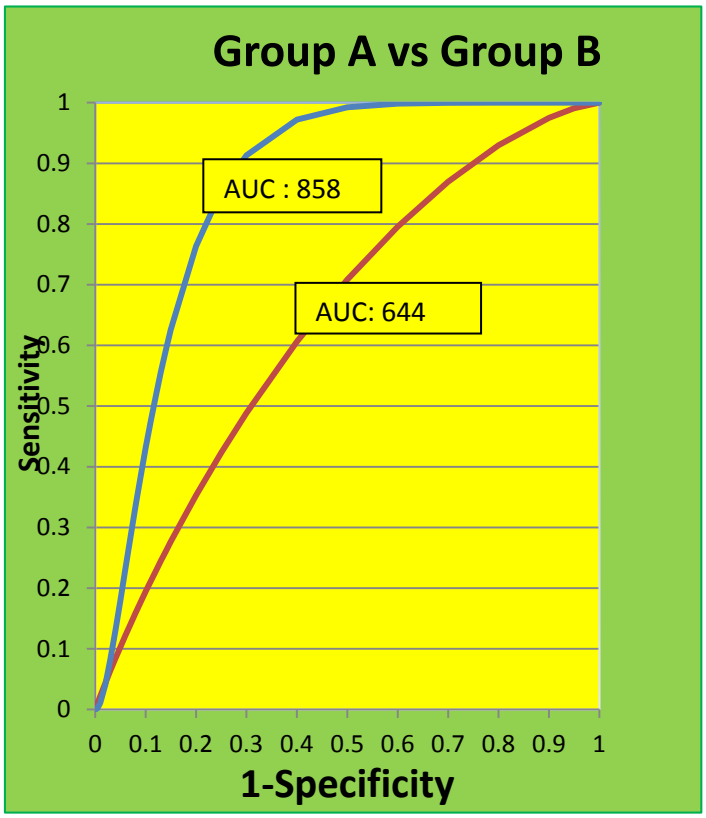

Table 1.

LAB "cutoff"	Sensitivity	Specificity
Group A	100%	75%
Group B	50%	69%
Group A (None of the confounding factors) Group B (MAP ≥ 100, GFR ≤ 45, or Age ≤ 50)		

REFERENCES

1. **Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee**. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006 Feb 14;113(6):e85-151. Epub 2006 Jan 11. Erratum in: Circulation. 2006 Apr 11;113(14):e696. Circulation. 2006 Dec 5;114(23):e630. PubMed PMID: 16407573.
2. **Torio CM, Andrews RM**. National Inpatient Hospital Costs: The Most Expensive Conditions by Payer, 2011: Statistical Brief #160. 2013 Aug. *Healthcare Cost and Utilization Project (HCUP) Statistical* Briefs [Internet]. Rockville (MD): Agency for Health Care Policy and Research (US); 2006 Feb-. Available from http://www.ncbi.nlm.nih.gov/books/NBK169005/PubMed PMID: 24199255.
3. **Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C**. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009 Aug 27;361(9):858-67. doi: 10.1056/NEJMoa0900428. PubMed PMID: 19710484.
4. **Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Fröhlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Münzel TF, Blankenberg S**. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med*. 2009 Aug 27;361(9):868-77. doi:10.1056/NEJMoa0903515. PubMed PMID: 19710485.
5. **Chandrasekaran V, Pearlman JD, Michael A, Numair O, Javad N, Lamartine N**. Impact of Introducing Dobutamine Stress Echocardiography (DSE) for Chest Pain Evaluation in an Indigent Care Community Hospital. Presented at UCLA Solomon Scholars 2014.
6. **Eng J**. ROC analysis: web-based calculator for ROC curves. Baltimore: Johns Hopkins University [updated 2014 March 19]. Available from: http://www.jrocfit.org.
7. **DeLong ER, DeLong DM, Clarke-Pearson DL**. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988 Sep;44(3):837-45. PubMed PMID: 3203132.
8. **Hanley JA, McNeil BJ**. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982 Apr;143(1):29-36. PubMed PMID: 7063747.
9. **Newby LK, Jesse RL, Babb JD, Christenson RH, De Fer TM, Diamond GA, Fesmire FM, Geraci SA, Gersh BJ, Larsen GC, Kaul S, McKay CR, Philippides GJ, Weintraub WS**. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2012 Dec 11;60(23):2427-63. doi: 10.1016/j.jacc.2012.08.969. Epub 2012 Nov 12. PubMed PMID: 23154053.

Submitted May 10, 2015