A Systematic Review and Meta-analysis of Diagnostic Performance of High Sensitivity Troponin in Acute Myocardial Infarction

Ayman Al-Saleh[1]; Ashraf Alazzoni[1]; Saleh Al Shalash[2]; Chenglin Ye[3-4]; Lawrence Mbuagbaw[3-5]; Lehana Thabane[3,6-7]; Sanjit S. Jolly[1,7]

[1]Department of Cardiology, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada. [2]Department of Internal medicine, McMaster University.[3]Department of Clinical Epidemiology and Biostatistics, McMaster University. [4]Biostatistics Unit, St Joseph's Healthcare, Canada. [5]Centre for Development of Best Practices in Health, Yaounde Central Hospital, Yaounde, Cameroon. [6]Departments of Anesthesia/Pediatrics, McMaster University. [7]Population Health Research Institute, Hamilton Health Sciences.

Abstract

Background:

High sensitivity Troponin (hs-Tn) is being adopted quickly into clinical practice, but there have been concerns about its reduced specificity. Our aim is to assess the diagnostic abilities of hs-Tn to diagnose acute myocardial infarction (AMI) in a systematic review.

Methods:

We performed a systematic search of PubMed, Embase and Cochrane up to April 2013 to identify studies that assessed the use of hs-Tn in patients presenting to hospital with chest pain and then assessed the new assay abilities to diagnose AMI. Bivariate random-effects modeling were used to obtain summary estimates of sensitivity and specificity.

Results:

A systematic search yielded 9 studies that assessed the use of hs-Tn T (9186 patients). At presentation to ER, in diagnosing AMI, the summary sensitivity was estimated to be 0.94 (95% CI: 0.89, 0.97) and 0.72 (95% CI: 0.63, 0.79) for hs-Tn T and conventional cardiac troponin (cTn) test, respectively. At presentation to ER, the summary specificity was estimated to be 0.73 (95% CI: 0.64, 0.81) and 0.95 (95% CI: 0.93, 0.97) for hs-Tn T and cTn test, respectively. The difference of the summary sensitivity or specificity between both hs-Tn T and cTn test was statistically significant ($p < 0.01$). At 3-6 hours from presentation, AUC were similar between hs-Tn T vs cTn.

Conclusions:

At presentation to ER, high sensitivity troponin has improved sensitivity but reduced specificity when compared to standard troponin. With repeated measurements over 6 hours, AUC are similar between hs-Tn T and cTn and so the major advantage of hs-Tn T is early diagnosis.

Introduction:

In the last few years, high sensitivity Troponin (hs-Tn) assays have been developed and have greatly improved the analytical performance of conventional cardiac troponin (cTn) T and I.[1-3] These assays permit the measurement of cardiac troponin concentrations that are approximately 10 times lower than those measurable with conventional assays,[4] approaching a detection level close to the physiologic concentrations of these biomarkers.[5] Therefore, high sensitivity Troponin assays are being investigated with regards to their ability to accurately diagnose myocardial infarction (MI), possibly earlier (within 3 hours of admission). Also, the ability to use the rate of change of troponin (Delta troponin) for diagnosis of MI is being investigated. Many institutions throughout Europe and North America have transitioned from the contemporary cTn T assays to the hs-Tn T with no technical issues specially that both assays run on the same analyzer.[6] Despite that, the Food and Drug Administration (FDA) has yet to approve the use of the high sensitivity troponin assays. This is partially due to the need for more information regarding analytical and clinical information for diagnostic accuracy and risk stratification.[7]

One of the main challenges is the potential for over diagnosis of acute coronary syndromes due to increased sensitivity of test. The aim of this systematic review and meta-analysis is to assess the utility of high sensitivity Troponin as a diagnostic tool using the rapidly evolving evidence. The early and accurate detection of myocardial injury leads to potentially earlier diagnosis and treatment with effective antiplatelet and antithrombotic therapies. Utilizing hs-Tn leads to an expedited exclusion of myocardial injury in patients presenting to emergency department (ED) with chest pain. On the other hand, an assay that is very sensitive but with low specificity may lead to unnecessary investigations. We aim to conduct a systematic review and a

meta-analysis of the literature to compare the sensitivity, specificity, summary Receiver operating characteristic (SROC) curves and test for heterogeneity hs-Tn to contemporary cTn T or I.

Search strategy:

A comprehensive systematic search strategy of MEDLINE (1946 to April 2013), EMBASE (1980 to April 2013), and Cochrane Central Register of Controlled Trials (CENTRAL) for studies that fulfilled the following criteria was done: (a) all trials that compared hs-Tn to contemporary cTn T or I assays; (b) patients presenting to the emergency room with chest pain and suspected to have acute myocardial infarction. Studies were excluded if they were case reports; evaluated hs-Tn in heart failure patients; were mainly designed to assess the prognostic impact of hs-Tn. Terms used in the database search are included in (Appendix). Studies were also excluded if they did not directly compare hs-Tn to conventional cTn. We restricted our search to English language and manually searched abstracts from the American heart association (AHA), American college of cardiology (ACC) and European society of cardiology (ESC) conferences for the past two years. The indexed search terms we used were: Highly sensitive troponin, High sensitivity troponin, High Sensitive troponin, hs-TnT, hs-cTnT, and hs-TnI. References listed on relevant articles were also reviewed for possible inclusion.

Study selection:

Titles and abstracts were screened for inclusion criteria independently by two authors (Ay.As. and As.Az). Agreement was estimated using the Kappa statistic. Full texts of the

selected articles were screened in duplicate for inclusion in the review. All disagreements were resolved by consensus.

Risk of Bias assessment:

Assessment of risk of bias was performed using the Cochrane risk of bias QUADAS tool for diagnostics accuracy studies (Figure 1).[8] The QUADAS risk of bias tool encompasses the following criteria which we followed: representative spectrum, acceptable reference standard, acceptable delay between tests, partial verification avoided, differential verification avoided, incorporation avoided, index test results blinded, reference standard results blinded, relevant clinical information, un-interpretable results reported, withdrawals explained.

Statistical analysis:

The reporting of the results follows the PRISMA criteria.[9] A flow-diagram is used to summarize the selection process for studies (Figure 2). Agreement was estimated using the Kappa statistic. Sensitivity and specificity estimates were calculated from the extracted contingency tables. Individual study estimates were plotted in receiver operating characteristics (ROC) curve. Heterogeneity was quantified utilizing the I^2 test, calculated using the random-effect approach. Heterogeneity was expressed as percentage of total variation across studies that was thought to be due to heterogeneity and could not be explained by the model. A higher percentage shows more heterogeneity.[10, 11] To obtain estimates of sensitivity and specificity, with corresponding 95% confidence intervals (CI), a bivariate random-effects model was used.[12] A summary ROC curve was drawn in the ROC space where the individual studies were plotted as well as the summary estimate. We also conducted a head-to-head comparison between

the new and standard tests on the summary estimates of sensitivity and specificity using the bivariate random-effects model. Modified paired z-test[13] was used to compare the mean logit sensitivity and logit specificity between the hs-Tn T and contemporary cTn T at presentation. The statistical software used for this analysis was R version 2.12.1.

Results:

The literature review yielded 652 article in MEDLINE and EMBASE, and 88 articles in the Cochrane database. After screening, applying the inclusion/exclusion criteria 50 articles were isolated. Further review of the 50 articles resulted in excluding 15 articles (not directly comparing hs-Tn to cTn), 3 articles (retrospective design), 20 articles (double/updated citation), (see Figure2).[14-22] The remaining 12 studies were included in our meta-analysis. The accepted studies were published between 2009-2012 (Table1 shows the 9 studies that assessed hs-Tn T specifically).

Biochemical Assays used:

Seven studies used the Elecsys system (by Roche Diagnostics) for measuring the hs-TnT. The remaining 2 studies used hs-TnT (by Roche Diagnostic) but did not report the analyzer system. In 4 studies, the comparison was made to 4th generation cTnT assay (by Roche Diagnostic); 3 studies used Roche diagnostic cTnT (did not report the assay). The Architect system cTnI (by Abbott Diagnostics) was used by 1 study. Another study used the Access analyser cTnI (by Beckman Coulter) or the Xpand HM analyzer (by Siemens Healthcare Diagnostics). The cut-off point ranged between 0.01-0.04 ng/ml (Table 2).

Sensitivity and Specificity of hs-Tn T:

At presentation:

Utilizing the data from all 9 studies that presented hs-Tn T and cTn measurements at presentation to emergency department (Figure 3), [14-22] the summary sensitivity for hs-Tn T was estimated to be 0.93 (95% CI: 0.89, 0.96).The I^2 was 32.53% (95% CI: 0, 0.68.88%). The summary specificity for hs-Tn T was estimated to be 0.74 (95% CI: 0.66, 0.81). The I^2 was 32.35% (95% CI: 0, 68.79%).

Only 8 studies[14-19, 21, 22] reported sensitivity and specificity for both hs-Tn T and cTn. For that we were able to conduct a head-to-head comparison between hs-Tn T and cTn. The summary sensitivity was estimated to be 0.94 (95% CI: 0.89, 0.97) and 0.72 (95% CI: 0.63, 0.79) for hs-Tn T and cTn, respectively. The summary specificity was estimated to be 0.73 (95% CI: 0.64, 0.81) and 0.95 (95% CI: 0.93, 0.97) for hs-Tn T and cTn, respectively (Table 3). The difference of the summary sensitivity or specificity between both hs-Tn T and cTn was statistically significant ($p < 0.01$).

Equivalently, the SROC curve shows that the 95% confidence region (CR) of the pair of summary measures estimated from the hs-Tn T test did not overlap with the one estimated from the cTn (Figure4). Thus, the results suggest that the hs-Tn T test has a significantly higher sensitivity while the cTn standard test has a significantly higher specificity.

Serial Troponin Measurement:

On analysis of the data from studies that presented serial troponin measurements from the time of patient presentation to emergency room, we found the following (Table 4): two studies presented AUC levels of hs-Tn T at three hours and six hours from presentation. Reichlin et al (2009) reported similar AUC for hs Tn T and cTn at 3 and 6 hours (AUC level for hs-Tn T 0.98 (95% CI: 0.97, 0.99) at three hours, 0.98 (95% CI: 0.96, 0.99) at six hours, vs. cTn 0.97 (95% CI: 0.94, 1.00) and 0.98 (95% CI: 0.96, 0.99). Reiter et al (2011) reported AUC for hs Tn T and cTn at 3 and 6 hours (AUC level for hs-Tn T 0.97 (95% CI: 0.94, 0.99) at three hours, 0.96 (95% CI: 0.92, 0.99) at six hours, vs. cTn 0.97 (95% CI: 0.93, 0.99) and 0.97 (95% CI: 0.92, 0.99). In summary, given repeated measures over a period of 6 hours from presentation, AUC for hs-Tn T and c Tn are similar.

Sensitivity and Specificity of hs-Tn I:

Different assays and cut-offs have been utilized for studies using hs-Tn I (Table 5). Reichlin et al (2009) used an ADVIA Centaur immunoassay system (cut-off 0.04 µg/L) to measure hs-Tn I and [21] found the sensitivity of hs-Tn I to be 89% and a specificity of 92% compared with 72% and 97% respectively for cTn. Using Abbott-Architect Assay (cut-off 0.028 µg/L) yielded a sensitivity of 86% and a specificity of 92% while using a Roche Troponin I assay (cut-off 0.160 µg/L) yielded a sensitivity of 84% and a specificity of 94%. On the other hand, Bhardwaj et al (2011) used an Erenna hsTnI assay (cut-off 6.28 pg/ml).[23] They found the sensitivity of hs-Tn I to be 57% and a specificity of 86% compared with 22% and 97% respectively for cTn. Given the heterogenous findings of different hs-Tn I assays it is not possible to combine the results. It appears that the Abbott Architect and Advia Centaur hs-Tn I assays have lower sensivity but improved specificity when compared to hs Tn T assay.

Discussion:

The results of our meta-analysis of hs Tn shows that the use of hs-Tn at presentation to emergency room to diagnose myocardial infarction resulted in a significantly higher sensitivity compared to conventional cTn, however, with reduced specificity. However, with repeated measures over 6 hours AUC values were similar between hs-Tn T and cTn. Thus, the major advantage of hs-Tn is early diagnosis and treatment of non ST elevation myocardial infarction.

The early diagnosis of NSTEMI will allow earlier initiation of anticoagulant and antiplatelet therapy and potentially more efficient care. Triaging of patients presenting with chest pain may be improved with hs-Tn. On the other hand, reduced specificity may result in prolonged hospital stays, increased use of invasive tests such as angiography in patients with normal coronary arteries.

A randomized trial comparing cTn vs. hs-Tn in patients presenting with chest pain would be able to examine the rate of unneeded angiography but also potential benefit of early initiation of therapies. However, no such randomized trials have been performed so in the mean time we must rely on large scale registries to look before and after effect of adopting hs-Tn.

Limitations:

hs-Tn I has multiple analyzers and different cut-off points that precludes attempts to meta-analyze the data due to significant heterogeneity. Another limitation was that all studies assessed the diagnostic accuracy of hs-Tn T at different time intervals from symptom onset

which limits the ability to assess the diagnostic accuracy of hs-Tn T at different time intervals except at presentation where the data was available from all trials.

Conclusion:

For patients presenting to the emergency department, hs-Tn compared to cTn has improved sensitivity but reduced specificity which may be useful in triaging patients. Over a period of 6 hours, AUC of both hs-Tn T and cTn are similar. Future studies are needed to determine potential benefits of earlier treatment and health economic consequences of use of hs Tn.

References

1. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of the centaur TnI-ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. Clin Chem. 2008 Apr;54(4):723-8.

2. Casals G, Filella X, Auge JM, Bedini JL. Impact of ultrasensitive cardiac troponin I dynamic changes in the new universal definition of myocardial infarction. Am J Clin Pathol. 2008 Dec;130(6):964-8.

3. Kavsak PA, MacRae AR, Yerna MJ, Jaffe AS. Analytic and clinical utility of a next-generation, highly sensitive cardiac troponin I assay for early detection of myocardial injury. Clin Chem. 2009 Mar;55(3):573-7.

4. Tate JR. Troponin revisited 2008: Assay performance. Clin Chem Lab Med. 2008;46(11):1489-500.

5. Missov ED, De Marco T. Clinical insights on the use of highly sensitive cardiac troponin assays. Clin Chim Acta. 1999 Jun 30;284(2):175-85.

6. Twerenbold R, Reichlin T, Reiter M, Muller C. High-sensitive cardiac troponin: Friend or foe? Swiss Med Wkly. 2011 May 10;141:w13202.

7. Apple FS. High-sensitivity cardiac troponin for screening large populations of healthy people: Is there risk? Clin Chem. 2011 Apr;57(4):537-9.

8. Reitsma JB, Rutjes AWS, Whiting P, Vlassov VV, Leeflang MMG, Deeks JJ. Cochrane handbook for systematic reviews of diagnostic test AccuracyVersion 1.0.0..Chapter9: Assessing methodological quality. in: Deeks JJ, bossuyt PM, gatsonis C (editors). . 2009.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ. 2009 Jul 21;339:b2535.

10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539-58.

11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 6;327(7414):557-60.

12. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005 Oct;58(10):982-90.

13. Kiewiet JJ, Leeuwenburgh MM, Bipat S, Bossuyt PM, Stoker J, Boermeester MA. A systematic review and meta-analysis of diagnostic performance of imaging in acute cholecystitis. Radiology. 2012 Sep;264(3):708-20.

14. Aldous SJ, Florkowski CM, Crozier IG, Elliott J, George P, Lainchbury JG, et al. Comparison of high sensitivity and contemporary troponin assays for the early detection of acute myocardial infarction in the emergency department. Ann Clin Biochem. 2011 May;48(Pt 3):241-8.

15. Body R, Carley S, McDowell G, Jaffe AS, France M, Cruickshank K, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol. 2011 Sep 20;58(13):1332-9.

16. Melki D, Lind S, Agewall S, Jernberg T. Diagnostic value of high sensitive troponin T in chest pain patients with no persistent ST-elevations. Scand Cardiovasc J. 2011 Aug;45(4):198-204.

17. Freund Y, Chenevier-Gobeaux C, Bonnet P, Claessens YE, Allo JC, Doumenc B, et al. High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. Crit Care. 2011 Jun 10;15(3):R147.

18. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, et al. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. Eur Heart J. 2011 Jun;32(11):1379-89.

19. Christ M, Popp S, Pohlmann H, Poravas M, Umarov D, Bach R, et al. Implementation of high sensitivity cardiac troponin T measurement in the emergency department. Am J Med. 2010 Dec;123(12):1134-42.

20. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ. 2012 Mar 20;184(5):E260-8.

21. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009 Aug 27;361(9):858-67.

22. Weber M, Bazzino O, Navarro Estrada JL, de Miguel R, Salzberg S, Fuselli JJ, et al. Improved diagnostic and prognostic performance of a new high-sensitive troponin T assay in patients with acute coronary syndrome. Am Heart J. 2011 Jul;162(1):81-8.

23. Bhardwaj A, Truong QA, Peacock WF, Yeo KT, Storrow A, Thomas S, et al. A multicenter comparison of established and emerging cardiac biomarkers for the diagnostic evaluation of chest pain in the emergency department. Am Heart J. 2011 Aug;162(2):276,282.e1.

Table 1. Characteristics of included trials

Study (year)	Number of participants	Gender, Males %	Funding	Design	Center(s)	Troponin measurement timing	Outcome N, %	Follow-up
Reichlin 2009	718	66%	Swiss Heart Foundation, University Hospital, Basel, Abbott, Roche, Siemens	Prospective	(Multi-center) Switzerland, Italy, and Spain	At presentation and 6-9 hours post 1st measurement	MI 123, 17%	60 days
Christ 2010	2340	64%	Roche Diagnostics	Retrospective	Single-center Germany	At presentation +/- 6 hours post 1st measurement	MI 20, 15%	2 weeks
Aldous S 2011	332	60%	National Heart Foundation of New Zealand, Christchurch Hospital, Roche diagnostics	Prospective	Single-center New Zealand	At presentation and 6-24 hours after presentation	MI 110, 33%	Not Reported
Body 2011	703	61%	Manchester NHS Foundation Trust, Roche Diagnostics	Prospective	Single-center U.K.	At presentation and (at least) 12 hours after symptoms onset	MI 130, 18%	6 months
Freund 2011	317	65%	Université Pierre et Marie Curie-Paris 6 (UPMC), Roche Diagnostics	Prospective	3 centers France	At presentation and 3-9 hours (if clinically indicated)	MI 45, 14%	30 days
Melki 2011	233	67%	Stockholm County Council and Karolinska Institute, Swedish Heart and Lung Foundation, the National Board of Health and Welfare and Roche Diagnostics	Prospective	Single-center Sweden	At presentation then 9-12 hours	MI 114, 48%	Discharge from hospital
Reiter 2011*	1098	67%	Swiss Heart Foundation, University Hospital, Basel, Abbott, Roche, Siemens	Prospective	(Multi-center) Switzerland, Italy, and Spain	At presentation and 6-9 hours post 1st measurement	MI 159, 14%	90 days
Weber 2011	2506	66%	Kerckhoff-Stiftung Foundation, Sanofi Aventis, Roche Diagnostics	Retrospective analysis of data from 2 ACS registries	Multi-center Germany Argentina	At presentation	MI 1082, 43%	6 months
Aldous 2012	939	59%	National Heart Foundation of New Zealand, Health Research Council of New Zealand, Roche Diagnostics	Prospective	Multi-center 9 countries in the Asia-Pacific region	At presentation and after 2 hours from 1st measurement	MI 205, 21%	1 year

*(Elderly population: Age≥70 years). Abbreviations: MI, myocardial infarction.

Table 2. Diagnostic performance of hs-TnT and cTn at presentation.

Study	hs-TnT (14 ng/L)					Conventional Troponin				
	Assay	Sensitivity	Specificity	NPV	PPV	Cut point and assay	Sensitivity	Specificity	NPV	PPV
Reichlin 2009	Elecsys 2010 system (Roche Diagnostics)	95	80	99	50	cTnT (0.035 ng/ml) Roche cTnT 4th generation	72	97	94	85
Christ 2010	Elecsys 2010 system (Roche Diagnostics)	95	61.7	98.6	29.7	cTnT (0.04 ng/ml) fourth generation assay (Roche Diagnostic)	65	90.6	93.8	54.2
Aldous S 2011	Elecsys system (Roche Diagnostics)	83.6	83.8	91.2	71.9	cTnT (0.03 ng/ml) Elecsys 2010 system (Roche Diagnostics)	42.7	97.3	77.4	88.7
Body 2011	Roche hs-cTnT	85.4	82.4	96.1	52.4	cTnT (0.01 ng/ml) 4th generation assay	75.2	94.6	94.4	75.8
Freund 2011	Elecsys 2010 analyzer (Roche Diagnostics)	93	82	99	47	cTnI (0.06 ng/ml) Access analyser (Beckman Coulter or cTnI (0.14 ng/ml) Xpand HM analyzer (Siemens Healthcare Diagnostics)	71	97	95	78
Melki 2011	Roche Diagnostics	97	74	97	78	cTnT (0.04 ng/ml) fourth generation assay (Roche Diagnostic)	79	94	82	93
Reiter 2011	Elecsys 2010 system (Roche Diagnostics)	98	49	99	38	cTnT (0.035 ng/ml) Roche cTnT	76	96	93	86
Weber 2011	Elecsys system, Roche Diagnostics	96	61	80	91	cTnT (0.03 ng/ml) Elecsys system (Roche Diagnostics)	82	90	54	97
Aldous 2012	Elecsys system, Roche Diagnostics	88.3	81.7	96.2	57.5	cTnI (0.028 ng/ml) Architect system (Abbott Diagnostics)	n/a	n/a	n/a	n/a

Abbreviations: hs-Tn, high sensitivity troponin; cTn, conventional cardiac troponin.

Table3. Summary sensitivity and specificity for hs-TnT and cTn at presentation

	hs-Tn T		**cTn**		
	Summary estimate	95% CI	Summary estimate	95% CI	p value*
Sensitivity	0.94	(0.89, 0.97)	0.72	(0.63, 0.79)	<0.01
Specificity	0.73	(0.64, 0.81)	0.95	(0.93, 0.97)	<0.01

*p value was calculated from a modified paired Z-test for testing the equality of summary estimate between the TNT test and the standard test.

Abbreviations: hs-Tn, high sensitivity troponin; cTn, conventional cardiac troponin; CI, confidence interval.

Table 4. Diagnostic performance of hs-TnT and cTn at serial times from presentation.

Study (year)	Diagnostic performance using serial hs-TnT measurements	
Reichlin 2009	**At 3 hours from presentation**	**At 6hours from presentation**
	AUC 0.98; 95CI (0.97-0.99)	AUC 0.98; 95% CI(0.96-0.99)
Reiter 2011*	**At 3 hours from presentation**	**At 6 hours from presentation**
	AUC0.97; 95% CI(0.94-0.99)	AUC 0.96; 95%CI (0.92-0.99)
Christ 2010	NA	NA
Aldous S 2011	NA	**At 6-24 hours from presentation**
		AUC 0.94; 95% CI(0.91-0.97)
Body 2011	NA (reported at 3hours from symptom onset)	NA (reported at six hours from symptom onset)
Freund 2011	NA	NA
Weber 2011	NA	NA
Melki 2011	**At 2 hours from presentation**	NA
	Sensitivity99%, Specificity71%, PPV77, NPV99.	
Aldous 2012	**At 2 hours from presentation**	NA
	Sensitivity92.2%, Specificity79.7%, PPV=55.9, NPV=97.3.	

*(Elderly population: Age≥70 years).

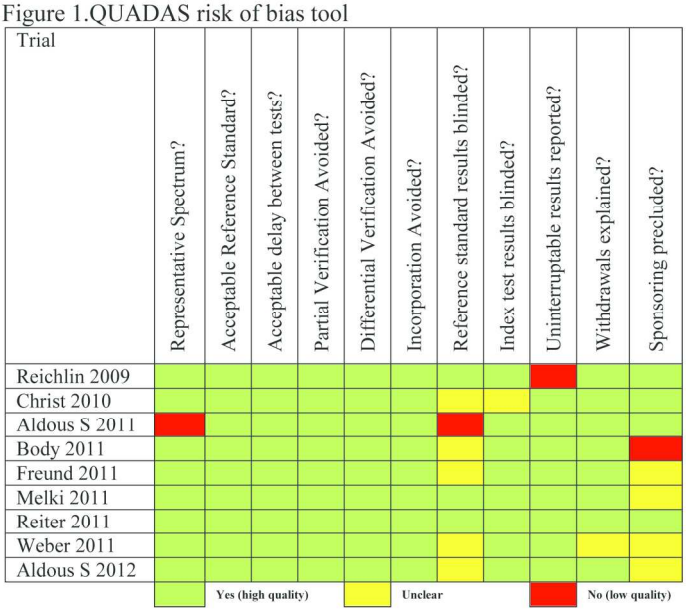
Abbreviations: hs-Tn, high sensitivity troponin; cTn, conventional cardiac troponin; NA, not available; AUC, area under the curve; CI, confidence interval; PPV, positive predicative value; NPV, negative predictive value.

Table 5. Diagnostic performance of hs-TnI and cTn at presentation.

Study	hs-TnI					Conventional Troponin				
	Assay	Sensitivity	Specificity	NPV	PPV	Cut point and assay	Sensitivity	Specificity	NPV	PPV
Reichlin 2009	hs-TnI (0.04 µg/L) ADVIACentaur immunoassay system (Siemens)	89	92	98	68	cTnT (0.035 ng/ml) Roche cTnT 4th generation	72	97	94	85
Bhardwaj 2011	hs-TnI (6.28 pg/ml) Erenna hsTnI (Singulex)	57	86	89	50	cTnT (0.03 ng/ml) Either Roche Elecsys 2010 or E170 platforms (Roche Diagnostics)	22	97	84	65
Keller 2009	hs-TnI (0.04 µg/L) Troponin I Ultra, Siemens Healthcare Diagnostics	90.7	90.2	96.4	76.7	cTnT (0.03 ng/ml) Roche Troponin T	63.7	97.2	88.3	88.8

Abbreviations: hs-Tn, high sensitivity troponin; cTn, conventional cardiac troponin.

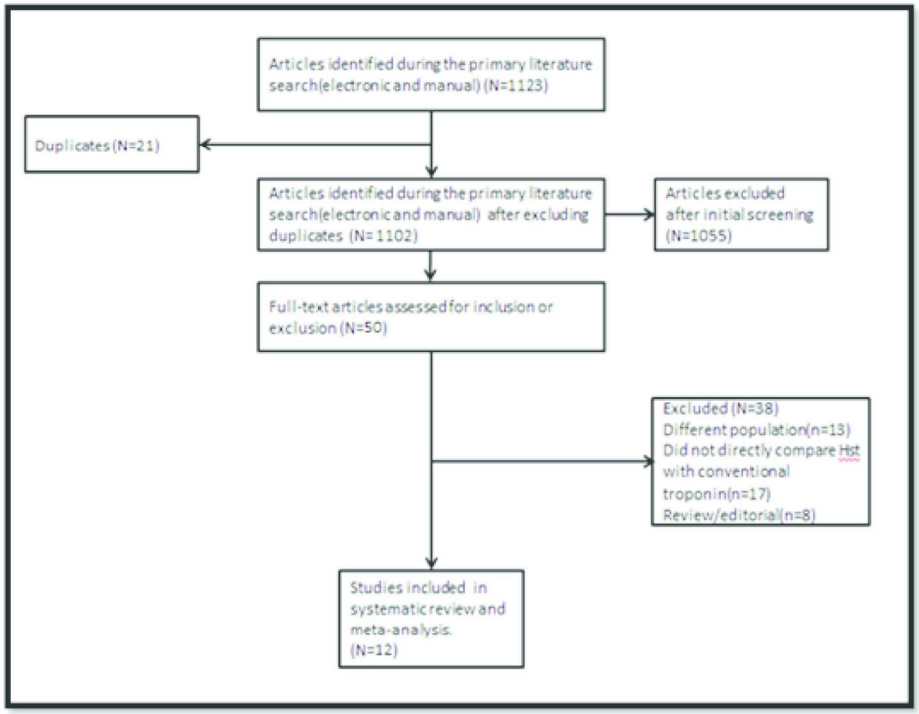
Figure 1.QUADAS risk of bias tool



Weighted Kappa: 0.70; 95% CI 0.54 to 0.87; p<0.001 (substantial agreement according to Koch and Landis) [9,10]

174x129mm (300 x 300 DPI)

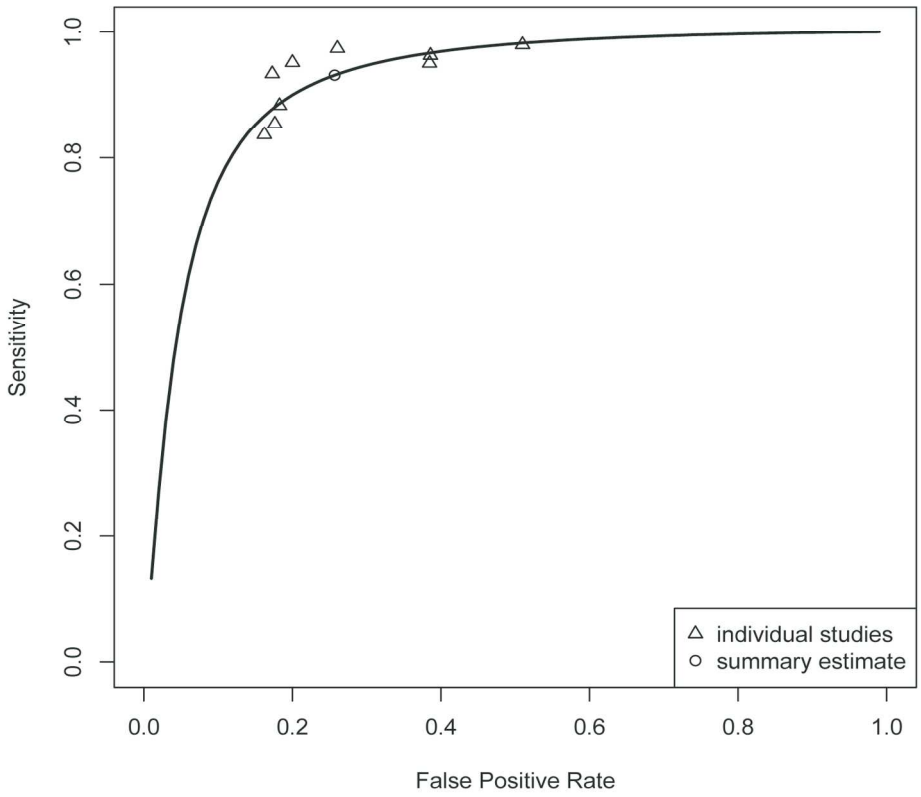
Figure 2.PRISMA 2009 flow diagram of studies included in systematic review.



Kappa = 0.80; 95% CI 0.59 to 1.00; p<0.001(Substantial agreement according to Koch and Landis)[25,26]

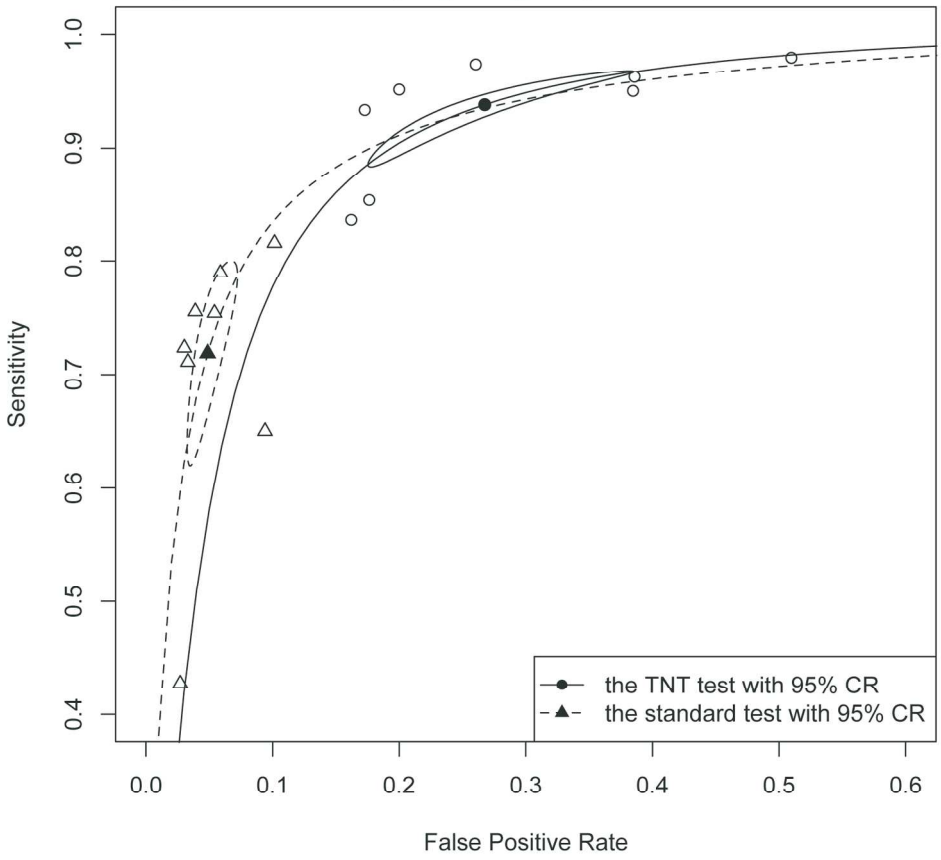
155x135mm (300 x 300 DPI)

Figure3. SROC curve summarizing the diagnostic performance of hs-TnT



146x128mm (300 x 300 DPI)

Figure 4. SROC curve comparing the diagnostic performance of hs-TnT and cTn



TNT refers to high sensitivity troponin while standard test refers to conventional cardiac troponin

160x148mm (300 x 300 DPI)

APPENDIX

Appendix: Medline Search Strategy

MEDLINE(R) <1948 to April 2013>

Search Strategy:

---

1 Highly sensitive troponin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (49)

2 High sensitivity troponin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (138)

3 High Sensitive troponin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (52)

4 hs-TnT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (34)

5 hs-cTnT.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (98)

6 hs-TnI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5)

7 1 or 2 or 3 or 4 or 5 or 6 (310)

8 limit 7 to english language (297)

****