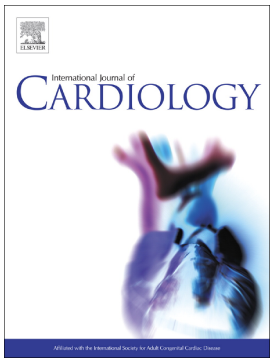

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Running Title: Biomarker algorithm and ACS

Comparison of two biomarker only algorithms for early risk stratification in patients with suspected acute coronary syndrome

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Key words: high-sensitivity cardiac troponin; glucose; eGRF; acute coronary syndrome; emergency department; myocardial infarction; cardiovascular death

Abstract

Background: We developed a biomarker algorithm encompassing the clinical chemistry score (CCS; which includes the combination of a random glucose concentration, an estimated glomerular filtration rate and high-sensitivity cardiac troponin; hs-cTn) with the Ortho Clinical Diagnostics hs-cTnI assay (CCS-serial) and compared it to the cutoffs derived from Ortho Clinical Diagnostics 0/1 hour (h) algorithm for 7-day myocardial infarction (MI) or cardiovascular (CV)-death.

Methods: The study cohort was an emergency department (ED) population (n=906) with symptoms suggestive of acute coronary syndrome (ACS) who had two Ortho hs-cTnI results approximately 3 hours apart. Diagnostic parameters (sensitivity / specificity / negative predictive value; NPV / positive predictive value; PPV) were derived for the CCS-serial and the 0/1h algorithm for 7-day MI/CV-death. A safety analysis was performed for patients in the rule-out arms of the algorithms for 30-day MI/death.

Results: The CCS-serial algorithm yielded 100% sensitivity / NPV (32% low-risk) and 95.7% specificity / 65% PPV (11% high-risk). The 0/1h algorithm-cutoffs yielded sensitivity / NPV / specificity / PPV of 97.8% / 99.4%/ 91.3%/ 50% , which classified 38% of patients as low-risk and 16% of patients as high-risk. Four patients (1.2%) in the 0/1h algorithm-cutoff rule-out arm had a 30-day MI/death outcome as compared to zero patients in the CCS-serial rule-out arm (p=0.06).

Conclusion: Both the CCS-serial and 0/1h algorithm cutoffs yield high NPVs with a similar proportion of patients identified as low-risk. These data may be useful for sites who are unable to collect samples at 0/1h in the emergency department.

ClinicalTrials.gov identifier: NCT01994577

INTRODUCTION

The analytical attributes of high-sensitivity cardiac troponin (hs-cTn) assays enable earlier decision making in the emergency department (ED) for patients presenting with possible acute coronary syndrome (ACS).[1-4] It is also evident that different cutoffs and concentration changes (i.e., deltas) will be needed for each of the hs-cTn assays to maximize clinical performance for the respective assays.[1,3,5] The amount of evidence for the specific hs-cTn cutoffs and algorithms for myocardial infarction (MI) varies for the different hs-cTn assays; with many more publications on the earliest regulatory approved hs-cTn assays (e.g., Roche Diagnostics and Abbott Diagnostics) compared to more recent hs-cTn assays.[1,3,6] With respect to the Ortho Clinical Diagnostics' hs-cTnI assay (VITROS® Immunodiagnostic Products hs Troponin I, Ortho Clinical Diagnostics, Pencoed, UK) only the 0/1 hour (h) algorithm has been published in a European cohort.[6]

We have previously published on the utility of the clinical chemistry score (CCS; which includes glucose and creatinine for the estimated glomerular filtration rate; eGFR) in the ACS setting with others also demonstrating the utility of glucose and eGFR for predicting in-hospital mortality in patients with MI.[7,8] As limited clinical data is available for the Ortho hs-cTnI assay, our objective was to develop an biomarker algorithm encompassing serial hs-cTnI results with the CCS for early risk stratification for MIor cardiovascular (CV)-death in patients presenting with suspected ACS to the ED.

MATERIALS and METHODS

Study Population

After research ethics approval, available ethylenediaminetetraacetic acid (EDTA) plasma samples (frozen below -70^{0}C at the Clinical Research Laboratory and Biobank, a facility in partnership with Hamilton Health Sciences and the Population Health Research Institute) were identified from the 2013 biobank of the prospective, multicenter observational ED study [Optimum Troponin Cutoffs for ACS in the ED (ROMI-3: Rule-out MI 3hours); ClinicalTrials.gov identifier: NCT01994577]. Details of the study have been previously published,[7,9,10] (see Supplemental Methods for further details) with inclusion criteria being adults presenting (not transferred from another hospital) to the ED with symptoms suggestive of ACS and an ED physician having ordered cTnI. Exclusion criteria included ST-elevation myocardial infarction (STEMI) or a serious ventricular cardiac dysrhythmia at presentation, as well as any patients who had any of the following issues within the previous 30-days: STEMI or non-STEMI (NSTEMI); traumatic chest pain including surgery or cardiac manipulation; a pulmonary embolus; known cancer; sepsis; or who were previously enrolled. Additionally, only patients that had research cardiac troponin I measured by the Ortho analyzer at zero hour (0h) and three hours (3h) were included (Supplemental Figure 1).

Laboratory Testing and Outcomes

The stored EDTA plasma samples were measured with the Ortho hs-cTnI assay on a VITROS 3600 analyzer, as long-term stability has been established with the assay validated for this sample type.[10,11] The manufacturer's stated limit of detection on this platform is 0.4ng/L with a limit of quantification of 1.2ng/L, with the manufacturer supporting an analytical range

from 1.5 to 30000ng/L. Testing during this study was in agreement with laboratory recommendations for hs-cTn testing.[4,10]

As previously described (see Supplemental Methods for further details), cardiovascular outcomes were independently adjudicated by at least two of the authors and disagreements not resolved by consensus were referred to a third blinded reviewer. All adjudicators were blinded to the research hs-cTn results.[7,9,10] MI was diagnosed consistent with the Third Universal Definition of MI when at least one cTnI concentration (from all clinically available cTnI results from a sensitive assay) was above the 99th-percentile with a significant rise/fall.[7,9,10]MIs after the index presentation (i.e., seven hours after presentation) until 7-days post presentation were also diagnosed using electrocardiogram findings indicative of new cardiac ischemia. CV-death was defined as death from a cardiovascular cause, including a revascularization procedure, cardiac arrest, MI, stroke or unknown cause. The primary outcome for this analysis was the composite of MI and/or CV-death at 7-days. For patients in the rule-out arms, a secondary safety analysis was performed to determine the number of patients in these groups who had a 30-day MI or death (incidence rate).

Algorithm development and Statistical analyses

We have previously detailed the development, external validation, and utility of the CCS with different hs-cTn assays and in different ED populations.[7] Briefly, the concentrations of glucose and hs-cTn with the eGFR are combined to generate a score ranging from 0 to 5. Concentrations of glucose ≥5.6mmol/L, eGFR <90mL/min/1.73m^2, or a hs-cTnI concentration between 4-14ng/L are assigned 1 point each (values <5.6mmol/L, ≥90mL/min/1.73m^2, and < 4ng/L are assigned 0 points, respectively), with hs-cTnI concentrations between 15-30ng/L

assigned 2 points and >30ng/L assigned 3 points. The lower the score of the CCS the lower the risk, with CCS=0 being previously reported to be able to rule-out MI and a CCS=5 to rule-in MI at presentation.[7] At 0h a CCS=0 (rule-out) or a CCS=5 (rule-in) was used. At 3h, those with the next lowest CCS (i.e., CCS=1) at presentation who had the 3h Ortho VITROS hs-cTnI concentration <3ng/L was also designated as rule-out. The cutoff of 3ng/L was pragmatically chosen as laboratories opting to use the lower limit of the analytical range (i.e., 1.5ng/L or <2ng/L when rounded), would still be able to measure and monitor the assay at 3ng/L and thus be able to institute quality assurance practices to mitigate erroneous reporting at this level.[4,12] For rule-in, an absolute change in concentrations of at least 9ng/L (i.e., delta ≥9ng/L) between 0h and 3h was used. Analytical testing of 12 different EDTA specimens on 11 different VITROS systems and analyzers and two different reagent lots from concentrations 11.1ng/L to 29.4ng/L identified that the 95th-percentile difference (max-min) in results across all samples and analyzers was 8ng/L (median difference was 5ng/L), so a change >8ng/L (or delta ≥9ng/L) was considered robust against analytical variation that can exist when multiple analyzers and reagents are used in practice for concentrations above 10ng/L.[13]

The developed algorithm, CCS-serial was compared to the published 0/1h algorithm-cutoffs for the Ortho hs-cTnI assay which ruled-out patients if 0h <1ng/L or 0h < 2ng/L and an absolute delta <1ng/L and ruled-in if 0h ≥40ng/L or an absolute delta ≥4ng/L.[6] The ESC 0/3h algorithm could not be calculated as at the 3h sampling/time-point variables needed to rule-out were not obtained in this study (e.g., GRACE score, pain status, and differential diagnoses), with omission of these variables worsening the performance of the ESC 0/3h algorithm.[14]

Continuous variables are presented as median (interquartile range) and categorical variables as count (percentages). Diagnostic parameters including sensitivity, specificity,

negative predictive value (NPV) and positive predictive value (PPV) were also calculated. Analyses were performed in MedCalc Statistical Software version 19.1.6 (MedCalc Software Ltd, Ostend, Belgium; with $p<0.05$ considered significant).

RESULTS

From the study cohort of 906 participants, 53% of the population was female. At 7-days there were 90 MI/CV-deaths (47% of the outcomes occurred in females), with the median concentration of hs-cTnI at 0h in patients with outcomes being near 30ng/L (median=29ng/L) (Table 1). There were 52 index MIs, 34 subsequent MIs and 6 CV-deaths (2 patients had index MI and CV-deaths).

Applying the Ortho VITROS hs-cTnI cutoffs from the 0/1h algorithm to the 906 patients with serial samples, 38% (n=344) of the population would be designated as rule-out, with 2 of the 90 MI/CV-deaths yielding a sensitivity of 97.8% (95%CI:92.2-99.7) and NPV of 99.4% (95%CI:97.9-99.9%) (Figure 1). For rule-in, 16% (n=142) from the total population would be designated in this group, with a specificity of 91.3% (95%CI:89.2-93.1) and PPV of 50.0% (95%CI:43.9-56.1). Applying the CCS-serial algorithm, 32% (n=293) of the population would be designated as rule-out, with no outcomes missed (100% sensitivity and NPV). For rule-in, 11% (n=100) from the total population would be designated in this group with a specificity of 95.7% (95%CI:94.1-97.0) and PPV of 65.0% (95%CI:56.7-72.5). Four patients (1.2%) in the 0/1h algorithm-cutoff rule-out arm had a 30-day MI/death outcome as compared to zero patients in the CCS-serial rule-out arm ($p=0.06$). Applying the Abbott 0/1h and Roche 0/1h algorithm-cutoffs in these four patients would have missed two and one 30-day outcomes, respectively (Figure 1).

DISCUSSION

For the past several years, earlier testing algorithms or pathways have been developed and used for hs-cTn assays.[1,3,6,7,14-20] However, not all algorithms or pathways have achieved the required NPV or sensitivity for safe rule-out of acute coronary events.[7,20] The new CCS-serial algorithm did not miss any outcomes, while identifying one third of the population as low-risk, possibly suitable for discharge. The 0/1h cutoffs applied with the Ortho hs-cTnI assay in this setting missed four 30-day outcomes with a similar proportion of patients designated as rule-out with equally high NPV to the CCS-serial. For rule-in, the 0/1h cutoffs with a delta of 4 ng/L appear to be less suitable with a PPV of 50% .

Limitations

This was a retrospective analysis so there are uncertainties regarding analyte stability, analytical precision, multiple lots of reagents and different analyzers. We have demonstrated suitable long-term stability and precision of cTnI as measured by the Ortho hs-cTnI assay[10,11] and have used different VITROS systems and analyzers and lots to derive the absolute delta criteria. However, additional testing across many different sample types, analyzers and geographic locations (i.e., multicenter) would strengthen the findings. Finally, despite the criteria used for hs-cTnI in the CCS-serial algorithm being analytically derived, additional studies at 0/1h and 0/2h are needed to demonstrate that the CCS-serial algorithm works equally well for samples collected before 3h as evident for the 0/1h algorithm and other algorthms.[1,3,]

CONCLUSION

We have developed a CCS-serial algorithm in a North American ED population with similar ability to rule-out an acute event as compared to the 0/1h algorithm using Ortho Clinical Diagnostics hs-cTnI assay. External validation of the CCS-algorithm using earlier serial measurements before 3 hours is required.

Word Count: 1596

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Figure 1. The CCS-serial algorithm and the 0/1h algorithm clinical performance for 7-day MI/CV-death. Details regarding patients with 30-day MI/death outcomes in the rule-out arms are provided.

Table 1. Characteristics of cohort (n=906) based on MI/CV-death at 7-days

Characteristics	MI/CV-death at 7- Days (n=90)	No MI/CV-death at 7-days (n=816)
Age, median (IQR)	78 (64-84)	67 (55-79)
Sex, female, n (%)	42 (47%)	435 (53%)
Presenting Symptoms, n (%)		
Chest Pain	52 (58%)	482(59%)
Arm pain (either arm)	15 (17%)	133 (16%)
Jaw pain	7 (8%)	22 (3%)
Neck pain	5 (6%)	47 (6%)
Back pain	10 (11%)	114 (14%)
Abdominal Pain	12 (13%)	86 (11%)
SOB	57 (63%)	420 (51%)
Dizzy or light headedness	23 (26%)	230 (28%)
Nausea and/or vomiting	27 (30%)	239 (29%)
Diaphoresis	28 (31%)	174 (21%)
Palpitations	6 (7%)	87 (11%)
Laboratory tests in ED, median (IQR)		
Random Glucose mmol/L	8.1 (6.3-11.4)	6.0 (5.4-7.5)
Creatinine umol/L	88 (74-123)	76 (67-97)
eGFR mL/min/1.73m^2	63 (42-82)	79 (59-93)
Ortho hs-cTnI ng/L at 0 h	29 (10-107)	1 (1-5)
Time between samples, hours	3.1 (3.0-3.2)	3.0 (3.0-3.1)
Ortho hs-cTnI ng/L at 3 h	78 (25-305)	2 (1-5)
Clinical Chemistry Score	4 (3-5)	2 (1-2)
Absolute difference in hs-cTnI [ng/L] between the 2 samples	28 (6-115)	0 (0-1)

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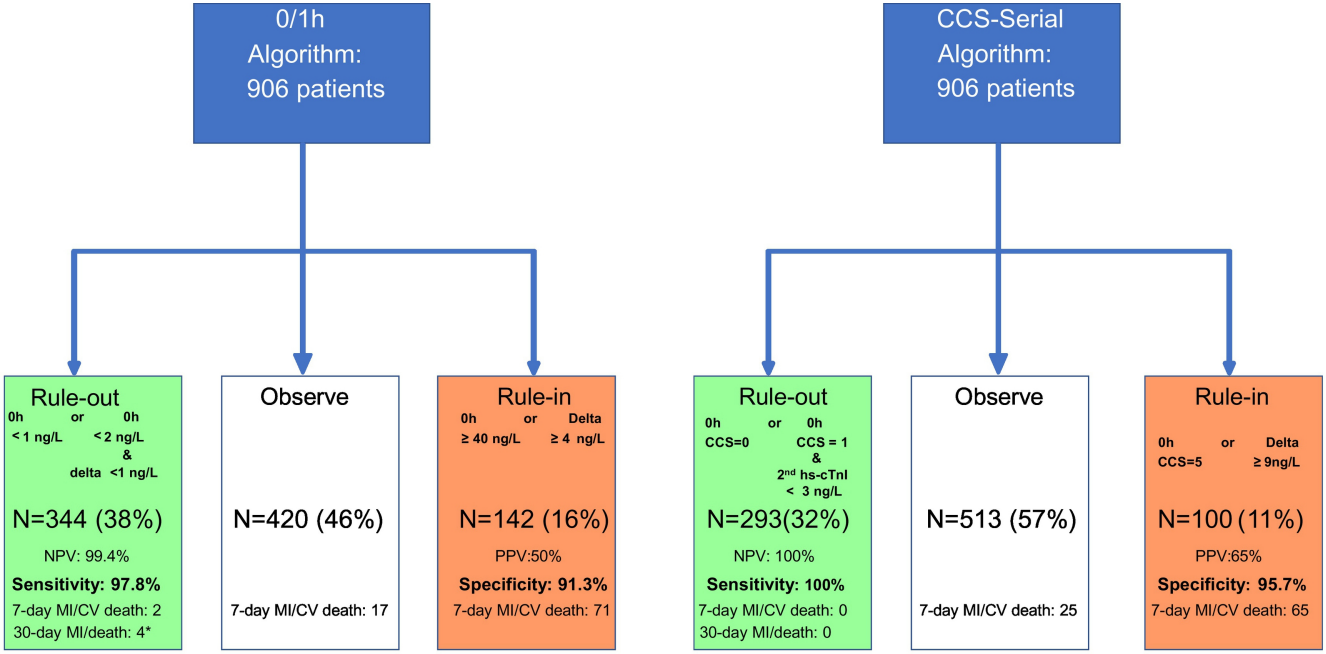
Conflict of interest/Disclosures: Dr. Kavsak has received grants/reagents/consultant/advisor/ honoraria from Abbott Laboratories, Abbott Point of Care, Beckman Coulter, Ortho Clinical Diagnostics, Randox Laboratories, Roche Diagnostics and Siemens Healthcare Diagnostics. McMaster University has filed patents with Drs. Kavsak and Worster listed as an inventor in the acute cardiovascular biomarker field, in particular, a patent has been filed on aspects related to the data presented in this study "A LABORATORY SCORE FOR RISK STRATIFICATION FOR PATIENTS WITH POSSIBLE CARDIAC INJURY". No other disclosures were reported.

Contributors: Peter Kavsak had access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Peter Kavsak and Andrew Worster were responsible for concept and design. Peter Kavsak, Jinhui Ma, Jonathan Sherbino, Shawn E Mondoux, Natasha Clayton, Stephen A. Hill, Matthew McQueen, Lauren Griffith, Shamir R. Mehta, PJ Devereaux, and Andrew Worster acquired, analyzed or interpreted the data. Peter Kavsak and Andrew Worster drafted this manuscript with the remaining authors providing important input and revisions.

Highlights

- Biomarker only algorithms used in patients with possible ACS
- 0/1h algorithm and clinical chemistry score algorithm provide high NPV
- Both algorithms can be used at 0 and 3 hour sampling timeframes



*Patients in the rule-out arm with Ortho's hs-cTnI assay that had an outcome (note the CCS for Abbott, Roche and Ortho assays ≥1)

Sex	AGE	Glucose [mmol/L]	eGFR mL/min/1.73m^2	Abbott hs-TnI [ng/L] 0h	Abbott CCS	Abbott hs-TnI [ng/L] 3h	Roche hs-cTnT [ng/L] 0h	Roche CCS	Roche hs-cTnT [ng/L] 3h	Ortho hs-cTnI [ng/L] 0h	Ortho CCS	Ortho hs-TnI [ng/L] 3h	Outcome
Male	48	6.0	101	6	2	332	5	1	53	<1	1	98	Index MI
Female	91	14.4	38	7	3	6	19	4	18	1	2	1	7-day MI
Male	63	11.0	55	4	3	4	14	3	13	1	2	1	30-day MI
Female	94	8.6	63	3	2	3	8	3	8	1	2	1	30-day Death

Figure 1