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A laboratory score at presentation to rule-out serious cardiac outcomes or death in patients presenting with symptoms suggestive of acute coronary syndrome

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ABSTRACT

Background: We evaluated whether a low high-sensitivity cardiac troponin (hs-cTn) cutoff combined with glucose, red cell distribution width (RDW), and the estimated glomerular filtration rate (eGFR) can be used to rule-out a serious cardiac outcome or death in patients presenting with symptoms suggestive of acute coronary syndrome (ACS).

Methods: This was a prospective observational emergency department (ED) study enrolling consecutive patients presenting with symptoms suggestive of ACS (ClinicalTrials.gov: NCT01994577). The primary outcome was a 7-day composite of myocardial infarction, unstable angina, decompensated congestive heart failure, serious ventricular cardiac arrhythmia, or death. A laboratory score combining glucose, RDW, eGFR with hs-cTnT (Roche) or hs-cTnI (Abbott) was compared to hs-cTn alone using the limit of detection (LoD; hs-cTnT < 5 ng/l/ hs-cTnI < 2 ng/l) as the cutoff. A benchmark of > 99% sensitivity was used to assess the laboratory panel with hs-cTn versus the LoD alone to identify low-risk patients suitable for discharge.

Results: A total of 1095 patients (n = 267 composite-outcomes) had measurements of glucose, RDW, eGFR, hs-cTnT, and hs-cTnI at presentation. Applying the hs-cTn LoD alone as the cutoff missed 5 composite-outcomes (sensitivity = 98.1%), however the addition of the laboratory panel to the hs-cTn LoD increased the sensitivity to > 99% with approximately 10% of the population identified as low-risk. The percentage of low-risk patients was increased to 15% (1 composite-outcome missed) when employing a low measurable hs-cTnI cutoff with the laboratory panel (laboratory score < 2 points).

Conclusion: A laboratory score with hs-cTn may identify low-risk patients suitable for ED discharge at presentation.

1. Introduction

There is evidence and considerable interest to use a low cardiac troponin concentration, as measured by a high-sensitivity cardiac troponin (hs-cTn) assay, to rule-out acute myocardial infarction (MI) and other serious cardiac outcomes at presentation in the emergency department (ED) [1,2]. Notwithstanding the various data published in this area, there are still important gaps when using hs-cTn to rule-out an acute cardiac outcome. First, from a clinical perspective, there is variation on what an acceptable sensitivity threshold would be for detecting an acute cardiac outcome in the ED (i.e., 98% versus 99%) [1–3]. Second, from a laboratory perspective, it is uncertain whether the current analytical performance of hs-cTn assays at the low concentration end is sufficiently accurate and precise to yield reliable results over the long-term to prevent misclassification of patients due to different reagents and analyzer performance [4,5]. Third, a number of the studies proposing low hs-cTn concentration cutoffs utilized MI as the primary outcome and, as such, are subject to incorporation bias.

Several of the proposed pathways to use hs-cTn assays to rule-out an acute cardiac outcome have incorporated other clinical variables or

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history to improve performance over hs-cTn alone [1,2]. However, outside of copeptin testing, few studies have explored if currently available laboratory tests could be used in conjunction with hs-cTn to identify patients at low-risk for an acute cardiac outcome. In this regard, we have recently demonstrated that the combination of glucose and hs-cTn testing could rule-out MI or cardiovascular death in patients presenting to the ED with symptoms suggestive of acute coronary syndrome (ACS) [6]. Unfortunately, the performance of this dual test was suboptimal when the outcome was a diagnosis of ACS (MI or unstable angina; UA) or cardiovascular death [6].

Considering that glycemic status is only one of the important variables that predict cardiovascular outcomes, we hypothesized that the inclusion of additional laboratory parameters, such as the red cell distribution width (RDW) and the estimated glomerular filtration rate (eGFR), which are routinely measured and have a role in predicting cardiovascular outcomes, could further identify low-risk patients [7,8]. Accordingly, our aim of this study was to assess if the combination of routine laboratory tests (glucose, RDW, eGFR) with hs-cTn could be combined into a laboratory score to identify patients presenting with symptoms suggestive of ACS who are at low-risk of a composite-outcome consisting of MI, UA, decompensated congestive heart failure (HF), serious ventricular cardiac arrhythmia, or death within the first week of ED presentation.

2. Materials and methods

2.1. Study design and setting

This study was a post hoc analysis of a prospective multicenter cohort study conducted across a North American city (Optimum Troponin Cutoffs for ACS in the ED (ROMI-3); ClinicalTrials.gov Identifier: NCT01994577). The cohort used in this analysis is a subgroup from our previously described study for MI rule-in/rule-out [6]. Briefly, the study enrolled patients presenting to the ED from three tertiary care adult hospitals within Hamilton, Ontario (population ~500,000) from May 2013 to August 2013. Prior to study commencement, the study was approved by the local research ethics board and throughout the study patients consented to participate.

Consecutive patients, 18 years and older, who were not transferred from another hospital, and for whom the ED physician ordered cardiac troponin were screened for eligibility (24 h a day during the study; see Fig. 1). Patients were excluded if their symptoms were not due to ACS; or they had chest trauma, cardiac surgery or manipulation within 30 days of presentation; a MI (STEMI or NSTEMI) or pulmonary embolus confirmed within previous 30 days; known active malignancy or non-cardiac fatal illness; sepsis; ventricular fibrillation or sustained ventricular tachycardia; or STEMI at presentation. For this subgroup analysis, patients were also excluded if they did not have a result at presentation for glucose, RDW, eGFR, hs-cTnT (Roche Diagnostics) and hs-cTnI (Abbott Diagnostics).

2.2. Laboratory tests

During the initial assessment in the ED, the clinical staff drew blood for clinical care as well as extra tubes for the ROMI-3 study. For the hs-cTn results (hs-cTnI on the Abbott Architect i2000SR analyzer and hs-cTnT on the Roche E-modular Elecsys analyzer) testing was performed on fresh (non-frozen) EDTA plasma samples with the results blinded to the clinical team. Briefly, hs-cTnI testing was performed at the tertiary care adult hospital sites with performance being monitored with both manufacturer QC material [6] and patient pool material (Hamilton General Hospital on 2 Architect ci16200 analyzers: Analyzer 1 low cTnI pool QC = 36.0 ng/l; CV = 9.9%; Analyzer 2 low cTnI pool = 37.2 ng/l; CV = 6.1%; Juravinski Hospital on 1 Architect ci8200 analyzer: low cTnI pool QC = 36.5 ng/l; CV = 6.3%; St. Joseph's Healthcare Hamilton Carlton Campus on 1 Architect ci8200 analyzer: low cTnI pool QC = 35.2 ng/l; CV = 5.3%). For hs-cTnT testing, blood was sent to a central site for testing with the assay performance being monitored by manufacturer QC material [6] and 2 patient pools (St. Joseph's Healthcare Hamilton King Campus on 1 Roche E-modular Elecsys analyzer: low cTnT pool QC = 13.5 ng/l; CV = 6.2% and high cTnT pool QC = 71.9 ng/l; CV = 1.8%). Patient results were reported as a whole number for both hs-cTnI and hs-cTnT as per the IFCC recommendations for hs-cTn assays [9]. Glucose (hexokinase method) and creatinine (kinetic alkaline picrate method) were measured in lithium heparin samples on the Abbott Architect c4000, ci8200 and ci16200 analyzers at the tertiary care adult hospital sites; also on fresh (non-frozen) samples with the results available to the clinical team. Representative data on the performance of these common core clinical chemistry tests during the study timeframe are as follows: Bio-Rad multiqual QC level 1: glucose = 3.35 mmol/l; CV = 1.2%; creatinine = 49.3 umol/l; CV = 1.8% and QC level 3: glucose = 21.0 mmol/l; CV = 1.0%; creatinine = 625.1 umol/l; CV = 1.0%; from the Juravinski Hospital Architect ci8200. The eGFR used in this analysis was calculated with the CKD-EPI equation [10] and was not reported to the clinical team. Finally, the RDW is one of the variables reported from the complete blood count EDTA tube, which was also measured on fresh (non-frozen) samples at the tertiary care adult hospital sites with the results available to the clinical team. The Beckman Coulter LH750 analyzers reported the RDW-CV [(standard deviation of red cell volume ÷ mean cell volume) × 100] with representative data on performance during the study timeframe as follows based on the manufacturer's QC material: normal QC = 15.82%; CV = 1.2% and abnormal II QC = 17.08%; CV = 1.3% (May); normal QC = 15.72%; CV = 1.3% and abnormal II QC = 16.63%; CV = 1.4% (June); normal QC = 15.54%; CV = 1.9% and abnormal II QC = 17.06%; CV = 1.3% (July); normal QC = 15.44%; CV = 1.3% and abnormal II QC = 16.59%; CV = 1.4% (August); from the Juravinski Hospital LH750. All data was collected by research staff with the hs-cTnI and hs-cTnT results blinded to those collecting clinical and outcome data.

2.3. Laboratory score

For the development of the laboratory score, cutoffs for each of the laboratory tests were selected from previous studies demonstrating utility in the assessment of future cardiac outcomes [7,8,11,12]. Briefly, for RDW the cutoff > 13.3% was used to assign a score of 1, with ≤ 13.3% a score of 0, as from 36 different laboratory tests evaluated, RDW showed the greatest association with cardiac outcomes in symptomatic chronic HF patients with 13.3% being the lowest cutoff that identified higher risk patients [7]. An eGFR value < 90 ml/min/1.73 m^2 was assigned a score of 1, with ≥ 90 ml/min/1.73 m^2 assigned a score of 0, as a previous study in patients presenting to the ED with chest pain identified this cutoff as the lowest-risk cutoff and encouraged use of reduced eGFR in risk stratification tools [8]. A glucose > 5.5 mmol/l was assigned a score of 1, with ≤ 5.5 mmol/l a score of 0, as per our previous analyses focused on rule-out of an acute cardiac outcome [11]. Also, in line with our previous work utilizing a low measurable hs-cTn concentration to rule-out an outcome we assigned a score of 0 for hs-cTnI < 4 ng/l, 1 for hs-TnI 4–14 ng/l and 2 for hs-cTnI ≥ 15 ng/l, and a score of 0 for hs-cTnT < 8 ng/l, 1 for hs-cTnT 8–18 ng/l and 2 for hs-cTnI ≥ 19 ng/l [11]. The 10 ng/l range was used to define the range of hs-cTn that could be assigned a score of 1 as data supports differences 10 ng/l or more can be used to rule-in MI, while higher concentrations are less likely due to analytical variation of the assay so a score of 2 was assigned [12]. The laboratory score was generated by summing the points from glucose, RDW, eGFR and hs-cTn (separate score for each hs-cTn) with the minimum score being 0 and the maximum 5. A second laboratory score was generated by using the limit of detection (LoD) for each hs-cTn assay to stratify hs-cTn (i.e., hs-cTnI: < 2 ng/l:0-point/2–12 ng/l:1-point/≥13 ng/l:2-points and hs-cTnT: < 5 ng/l:0-point/5–15 ng/l:1-point/≥15 ng/l:2-points) with the same cutoffs for glu-