Clinical chemistry score versus high-sensitivity cardiac troponin I and T tests alone to identify patients at low or high risk for myocardial infarction or death at presentation to the emergency department

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ABSTRACT

BACKGROUND: Testing for high-sensitivity cardiac troponin (hs-cTn) may assist triage and clinical decision-making in patients presenting to the emergency department with symptoms of acute coronary syndrome; however, this could result in the misclassification of risk because of analytical variation or laboratory error. We sought to evaluate a new laboratory-based risk-stratification tool that incorporates tests for hs-cTn, glucose level and estimated glomerular filtration rate to identify patients at risk of myocardial infarction or death when presenting to the emergency department.

METHODS: We constructed the clinical chemistry score (CCS) (range 0–5 points) and validated it as a predictor of 30-day myocardial infarction (MI) or death using data from 4 cohort studies involving patients who presented to the emergency

department with symptoms suggestive of acute coronary syndrome. We calculated diagnostic parameters for the CCS score separately using high-sensitivity cardiac troponin I (hs-cTnI) and high-sensitivity cardiac troponin T (hs-cTnT).

RESULTS: For the combined cohorts (*n* = 4245), 17.1% of participants had an MI or died within 30 days. A CCS score of 0 points best identified low-risk participants: the hs-cTnI CCS had a sensitivity of 100% (95% confidence interval [CI] 99.5%–100%), with 8.9% (95% CI 8.1%–9.8%) of the population classified as being at low risk of MI or death within 30 days; the hs-cTnT CCS had a sensitivity of 99.9% (95% CI 99.2%–100%), with 10.5% (95% CI 9.6%–11.4%) of the population classified as being at low risk. The CCS had better sensitivity than hs-cTn alone (hs-cTnI < 5 ng/L: 96.6%, 95% CI 95.0%–97.8%; hs-cTnT < 6 ng/L: 98.2%,

95% CI 97.0%–99.0%). A CCS score of 5 points best identified patients at high risk (hs-cTnI CCS: specificity 96.6%, 95% CI 96.0%–97.2%; 11.2% [95% CI 10.3%–12.2%] of the population classified as being at high risk; hs-cTnT CCS: specificity 94.0%, 95% CI 93.1%–94.7%; 13.1% [95% CI 12.1%–14.1%] of the population classified as being at high risk) compared with using the overall 99th percentiles for the hs-cTn assays (specificity of hs-cTnI 93.2%, 95% CI 92.3%–94.0; specificity hs-cTnT 73.8%, 95% CI 72.3–75.2).

INTERPRETATION: The CCS score at the chosen cut-offs was more sensitive and specific than hs-cTn alone for risk stratification of patients presenting to the emergency department with suspected acute coronary syndrome. **Study registration**: ClinicalTrials.gov, nos. NCT01994577; NCT02355457

The use of a single high-sensitivity cardiac troponin (hs-cTn) test concentration on presentation to the emergency department has been proposed for triage and early decision-making in patients with suspected acute coronary syndrome.[1–3] However, a single low concentration result for hs-cTn for identifying patients at low risk in the emergency department may misclassify patients, because an analytical variation of ± 3 ng/L for the hs-cTn assays at the low analytical range is

acceptable; yet, this variation will reclassify patients using the published algorithms.[4–6] In practice, different lots of reagents for both hs-cTnI and hs-cTnT have already been observed to yield variation that exceeds 3 ng/L.[7,8] In addition, there are several interferences that affect hs-cTn measurements.[9,10] Together, this necessitates improved laboratory health services to aid physicians in evaluating patients with possible acute coronary syndrome.

We have previously assessed the utility and cost-effectiveness of combining assessment of the glucose level with hs-cTn concentrations for diagnosing myocardial infarction (MI) in the emergency department.[11,12] While this dual-marker approach was cost-effective compared with hs-cTn alone, it was found to be suboptimal for short-term risk stratification. For risk stratification based on laboratory services to be accepted into practice, it must be easy to implement and involve only validated laboratory tests that are widely and routinely measured in patients presenting with symptoms of acute coronary syndrome and also safe.

In an effort to have a robust laboratory service to aid physicians and reassure patients in the emergency department setting, we have developed a laboratory medicine test score using common clinical chemistry tests (i.e., a clinical chemistry score [CCS]) for MI or death at 30 d). This score encompasses the measurement of hs-cTn concentration, glucose level and estimated glomerular filtration rate (eGFR), with eGFR also providing important prognostic information in this setting.[13] Specifically, for ST-segment elevation MI (STEMI), high glucose concentrations at admission to the emergency department identify patients who are more hemodynamically unstable, have a larger infarct size and have a high 30-day mortality.[14] Moreover, eGFR calculated by the CKD-EPI creatinine equation has been shown to be an independent predictor of major adverse cardiac outcomes in patients with acute coronary syndrome.[15] We previously assessed the utility of hematologic variables in addition to the clinical chemistry tests.[16] However, as our goal was to develop a simple algorithm that could be validated externally across different continents, we decided to limit the algorithm to these 3 clinical chemistry tests that are available in most populations of patients with chest pain in the emergency department. A recent publication using machine learning for predicting 30-day mortality after STEMI ranked creatinine and glucose among the top 3 variables (and top 2 laboratory tests) using classifier-based machine-learning algorithms,[17] which further supports the inclusion of eGFR, glucose and hs-cTn in assessing patients with possible non–ST-elevation acute coronary syndrome.

In the present study, we tested and assessed the CCS in patients without STEMI who presented to the emergency department, across different populations from North America, Europe and Australasia, to determine if score thresholds resulted in sufficient sensitivity and negative predictive value (NPV) to safely identify patients at low risk. We assessed whether the CCS could achieve a sensitivity greater than 99.0% for MI or death at 30 days as this is an estimate that most physicians in the emergency department consider as safe for discharge.[18] We also evaluated whether the score had sufficient positive predictive value (PPV) and specificity to identify patients at high risk who may benefit from early management.

Methods

Study design and participants

Validation of the performance of the CCS test was a post hoc analysis performed in 4 emergency department populations in Hamilton, Ontario, Canada (Hamilton General Hospital and Juravinski Hospital, Hamilton Health Sciences, and St. Joseph's Healthcare Hamilton); Brisbane, Australia (Royal Brisbane and Women's Hospital); Christchurch, New Zealand (Christchurch Hospital); and Hamburg, Germany (University Hospital Hamburg-Eppendorf, University Heart Center Hamburg). Briefly, patients in the emergency department who were enrolled in all 4 studies had symptoms suggestive of acute coronary syndrome (patients with STEMI were excluded), with measurement of both glucose and creatinine levels at presentation as part of routine care (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180144/-/DC1; additional details of the study methods, Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180144/-/DC1).[19–23]

Health outcomes

The primary outcome was 30-day MI[24] or all-cause death. Secondary outcomes included index MI, 30-day revascularization rate (percutaneous coronary intervention or coronary artery bypass graft) and 30-day composite of unstable angina, MI or all-cause death (values for unstable angina were not available for the Hamburg cohort) (Appendix 2).

Assay methods and clinical chemistry score

Standard acceptable laboratory methods were used to measure glucose and creatinine levels (used to calculate eGFR). Both the Roche Elecsys Troponin T hs and Abbott ARCHITECT High Sensitive Troponin-I assays used in these studies met the most recent laboratory recommendations for total analytic error for hs-cTn assays[6] (Appendix 2).

The approach to developing the CCS was pragmatic, using equal weighting for eGFR and glucose, and using established and recognized cut-offs for normality for these tests. For hs-cTn, the weighting was based on the graded risk and on analytical performance characteristics of the assays. Briefly, the CCS included glucose, eGFR and hs-cTnT or hs-cTnI (i.e., CCS with hs-cTnT or CCS with hs-cTnI, respectively, as clinical laboratories will typically report only one hs-cTn test) (Box 1). The cut-offs used for each test were based on accepted normal levels and low-risk clinical cut points, with values of eGFR of 90 mL/min/1.73 m² or more, glucose of less than 5.6 mmol/L, hs-cTnI of less than 4 ng/L and of hs-cTnT less than 8 ng/L used to identify patients at low risk (i.e., abnormal value 1 point and normal 0 points).[13,25–27] For hs-cTn, 2 additional cut points were selected based on analytical variation, population and health outcome studies,[26–32] to have a final CCS range of 0–5 points (i.e., sum of the points for the results for glucose, eGFR and hs-cTn obtained from the patient's

Box 1: Clinical chemistry score

CCS with hs-cTnT

Glucose

- < 5.6 mmol/L = 0 points
- ≥ 5.6 mmol/L = 1 point

eGFR

- < 90 mL/min/1.73 m² = 1 point
- ≥ 90 mL/min/1.73 m² = 0 points

hs-cTnT

- hs-cTnT < 8 ng/L = 0 points
- hs-cTnI 8–18 ng/L = 1 point
- hs-cTnI 19–30 ng/L = 2 points
- hs-cTnI > 30 ng/L = 3 points

Sum of glucose, eGFR and hs-cTnT

CCS range: 0–5 points

CCS with hs-cTnI

Glucose

- < 5.6 mmol/L = 0 points
- ≥ 5.6 mmol/L = 1 point

eGFR

- < 90 mL/min/1.73 m² = 1 point
- ≥ 90 mL/min/1.73 m² = 0 points

hs-cTnT

- hs-cTnI < 4 ng/L = 0 points
- hs-cTnI 4–14 ng/L = 1 point
- hs-cTnI 15–30 ng/L = 2 points
- hs-cTnI > 30 ng/L = 3 points

Sum of glucose, eGFR and hs-cTnI

CCS range: 0–5 points

Note: CCS = clinical chemistry score, eGFR = estimated glomerular filtration rate, hs-cTn = high-sensitivity cardiac troponin.

blood work at presentation to the emergency department; Supplemental Table 1, Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.180144/-/DC1).

Statistical analyses

We first tested the CCS algorithm in the Hamilton cohort for risk stratification, with the expectation that a CCS closer to 0 points (all laboratory results were normal) would be suggestive of low risk (with scores that yielded about a 1% outcome rate evaluated further) and a CCS closer to 5 points would be suggestive of high risk (all laboratory results were abnormal with scores that yielded about a 50% outcome rate evaluated further). First, we used test parameters (sensitivity and specificity) to identify possible CCS cut-offs for 30-day MI and death via Kaplan–Meier survival analysis, and then the Cox proportional hazards model to provide hazard ratios (HRs; adjusted for age, sex, family history, hypertension, hypercholesterolemia, diabetes mellitus and smoking status)[19] to support the selected cut-offs. The selected CCS cutoffs were then applied to the other 3 population cohorts to assess sensitivity, specificity, PPV, NPV and likelihood ratios. In

this regard, we provided the CCS algorithm to each site to determine the test performance and descriptive statistics for their emergency department cohort.

We calculated the sensitivity, specificity, PPV, NPV and likelihood ratios with 95% confidence intervals (CIs) for each cohort as well as for the combined population (by adding the number of participants in each cohort) for the low- and high-risk CCS cutoffs. We performed receiver operating characteristic (ROC) curve analysis for the CCS algorithms for each emergency department population, including sex-specific analysis that assessed the CCS algorithms for the primary outcome, with comparison to hs-cTn concentration alone (low risk: hs-cTnI < 5 ng/L or hs-cTnT < 6 ng/L; high risk [overall 99th percentiles]: hs-cTnI > 26 ng/L or hs-cTnT > 14 ng/L)[3,30,33] in the overall emergency department population. We generated the ROC curves based on data without smoothing, and we calculated the area under the ROC curves (AUC) correspondingly. We performed the statistical analysis using SAS 9.4, MedCalc statistical software, Graphpad prism, R3.2.2 (R Project for Statistical Computing) and StatsDirect statistical software.

Ethics approval

This study was approved by the Hamilton Integrated Research Ethics Board, the Royal Brisbane and Women's Hospital Human Research Ethics Committee, the New Zealand Health and Disability Ethics Committee, and the local ethics board of Hamburg (Ethics committee of the Ärztekammer Hamburg, Germany). We followed the Standards for the Reporting of Diagnostic Accuracy Studies guideline.

Results

We included 4245 participants in this study, with 727 (17.1%) having the primary outcome (30-d MI or all-cause death). The prevalence of the primary outcome was different between the cohorts (p < 0.001), with the Brisbane cohort (n = 795) having the lowest prevalence at 6%, followed by the Hamilton cohort (n = 1092) at 16%, the Hamburg cohort (n = 1412) at 20%, and the Christchurch cohort at 24% (Table 1). A higher percentage of males were enrolled at the Brisbane, Christchurch and Hamburg sites (≥ 60% of the 3 cohorts) compared with the Hamilton site (< 50% males). Nearly 30% of participants in the Hamilton cohort had diabetes compared with less than 20% in the 3 other cohorts.

In the Canadian test population (Hamilton), the lower the CCS, the lower the rates of MI or death over 30 days (i.e., the primary outcome, Supplemental Figure 2, Appendix 1). In the Hamilton cohort, a CCS value less than 1 yielded 100% sensitivity, less than 2 yielded a sensitivity of 99% and less than 3 a sensitivity of 93% for the primary outcome using either hs-cTnI or hs-cTnT (Supplemental Figure 3, Appendix 1). A CCS of 4 points or more yielded a specificity of 85% with hs-cTnI and 76% with hs-cTnT, whereas a CCS of 5 points yielded a specificity of 96% with hs-cTnI and 90% with hs-cTnT. Participants with a CCS of 5 points, reflecting abnormal results for all laboratory tests, represented a high-risk group, with an adjusted HR for patients with a CCS of 5 points versus those with a CCS of less than 5 points of 4.63

Table 1: Participant characteristics

Characteristic	No. (%) of participants* in the Hamilton cohort n = 1092	No. (%) of participants* in the Brisbane cohort n = 795	No. (%) of participants* in the Christchurch cohort n = 946	No. (%) of participants* in the Hamburg cohort n = 1412
Age, mean ± SD; yr	66.5 ± 16.6	55.2 ± 15.2	64.5 ± 12.8	62.7 ± 15.6
Male sex	515 (47.2)	476 (59.9)	569 (60.1)	899 (63.7)
Family history of coronary artery disease	596 (54.6)	367 (46.2)	538 (56.9)	257 (18.2)
Hypertension	767 (70.2)	397 (49.9)	566 (59.8)	N/A
Hypercholesterolemia	646 (59.2)	381 (47.9)	542 (57.3)	N/A
Diabetes mellitus	319 (29.2)	104 (13.1)	165 (17.4)	193 (13.7)
Current smoking	278 (25.5)	217 (27.3)	135 (14.3)	338 (23.9)
History of MI	388 (35.5)	137 (17.2)	277 (29.3)	228 (16.1)
History of congestive heart failure	211 (19.3)	39 (4.9)	80 (8.5)	211 (14.9)
History of angina	288 (26.4)	184 (23.1)	421 (44.5)	N/A
Detectable hs-cTnI concentration	941 (86.2)	708 (88.7)	888 (93.9)	1185 (83.9)
Detectable hs-cTnT concentration	922 (84.4)	573 (72.1)	680 (71.9)	899 (63.7)
30-d MI or death†	177 (16.2)	47 (5.9)	225 (23.8)	276 (19.5)

Note: hs-cTnI = high-sensitivity cardiac troponin I, hs-cTnT = high-sensitivity cardiac troponin T, MI = myocardial infarction, N/A = not available, SD = standard deviation.
*Unless specified otherwise.
†Within 30 days after presentation to the emergency department.

(95% CI 3.31–6.47) with CCS hs-cTnT and 7.46 (95% CI 5.38–10.36) with CCS hs-cTnI.

The analytical performances of the hs-cTn assays in the 4 cohorts were in agreement with laboratory recommendations for hs-cTn assays (i.e., > 50% above the limit of detection);[6] the range of detectable hs-cTnI concentrations was 84%–94% and that for hs-cTnT concentrations was 64%–84% (Table 1). And across all 4 cohorts, the higher the CCS, the older the participant's age, the higher the hs-cTn level, the higher the glucose level and the lower the eGFR (Table 2). The prevalence of the primary outcome varied between the cohorts and hs-cTn assays, with about 50%–90% of participants with a CCS of 5 points having the outcome. However, among all participants in the 4 cohorts with normal laboratory results and a CCS of 0, there was only 1 participant (male) who had testing with both hs-cTn assays and who had the primary outcome. The AUCs for CCS were higher in the Brisbane (hs-cTnI CCS AUC 0.95, 95% CI 0.93–0.97; hs-cTnT CCS AUC 0.91, 95% CI 0.87–0.94) and Christchurch (hs-cTnI CCS AUC 0.94, 95% CI 0.92–0.95; hs-cTnT CCS AUC 0.90, 95% CI 0.87–0.92) cohorts compared with the Hamilton (hs-cTnI CCS AUC 0.87, 95% CI 0.85–0.89; hs-cTnT CCS AUC 0.83, 95% CI 0.81–0.85) and Hamburg (hs-cTnI CCS AUC 0.86, 95% CI 0.85–0.89; hs-cTnT CCS AUC 0.84, 95% CI 0.81–0.86) cohorts (Supplemental Figure 3, Appendix 1).

In the Hamilton cohort, the sensitivity for a CCS of 0 points was 100% (95% CI 97.9%–100%) with hs-cTnI (Table 3) and with hs-cTnT (Table 4). A CCS of 1 point yielded a sensitivity close to 99% with both hs-cTn assays. The specificity of a CCS of 5 points was higher for hs-cTnI CCS (95.6%, 95% CI 94.1%–96.9%) than for hs-cTnT CCS (90.4%, 95% CI 88.3%–92.2%).

The sensitivity of a CCS of 0 points in the Brisbane, Christchurch and Hamburg cohorts with hs-cTnI was 100% (Table 3). In each of these cohorts, the point-estimate specificity was greater than 95% with an hs-cTnI CCS of 5 points. For a hs-cTnT CCS of 0 points, the point-estimate sensitivity was greater than 99.5%; the point-estimate specificity of a CCS of 5 points with the hs-cTnT assay was greater than 93.9% across the 3 non–North American cohorts (Table 4). A CCS of 1 point did not consistently achieve sensitivities greater than 99%, with the hs-cTnT CCS of 1 yielding sensitivities of 98% or less in the 3 non–North American cohorts.

Combining all 4 cohort populations (n = 4245 participants), a CCS of 0 points yielded a sensitivity of 100% (95% CI 99.5%–100%) with no false negatives with hs-cTnI, and a sensitivity of 99.9% (95% CI 99.2%–100%) with 1 false negative with hs-cTnT (Table 5). Because the sensitivity estimates are greater than 99.0%, 378 participants (8.9% of the population) would be classified as low risk using hs-cTnI with CCS and 444 participants (10.5% of the population) using hs-cTnT with CCS. Applying a cut-off value for hs-cTnI of less than 5 ng/L alone, the sensitivity was 96.6% (95% CI 95.0%–97.8%) with 25 false negatives, and for hs-cTnT of less than 6 ng/L alone, the sensitivity was 98.2% (95% CI 97.0%–99.0%) with 13 false negatives. The specificity of a CCS of 5 points was 96.6% (95% CI 96.0%–97.2%) with a PPV of 75.1% (95% CI 71.3%–78.5%) for hs-cTnI, and a specificity of 94.0% (95% CI 93.1%–94.7%) with a PPV of 61.7% (95% CI 58.1%–65.2%) for hs-cTnT. Applying the overall 99th percentile as the cut-off, the specificity was lower for hs-cTnI (> 26 ng/L) at 93.2% (95% CI 92.3–94.0) and for hs-cTnT (> 14 ng/L) at 73.8% (95% CI 72.3–75.2) compared with the respective CCSs of 5.

Assessing the performance of the CCS with regard to sex, in women, the specificity for the primary outcome was higher with a CCS of 5 (hs-cTnI CCS specificity 96.4%, 95% CI 95.3–97.3; hs-cTnT CCS specificity 94.4%, 95% CI 93.1–95.5) compared with using the overall 99th percentile hs-cTn cut-offs (hs-cTnI specificity 93.6%, 95% CI 92.3–94.8; hs-cTnT specificity 76.1%, 95% CI 73.9–78.2). Higher specificity with a CCS of 5 was evident in men as well (Supplemental Table 2, Appendix 3). Overall, there were no obvious differences between men and women in the performance of the CCS for the primary outcome.

For the secondary outcomes, the CCS algorithms also outperformed testing for hs-cTn alone for the index MI diagnosis (i.e., higher sensitivity and higher specificity; Supplemental

Table 2 (part 1 of 2): Participant characteristics and partitioning per the clinical chemistry score (range 0 to 5 points) at presentation to the emergency department for all cohorts, by tests for cardiac troponin I or T*

Characteristic	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5
Hamilton cohort						
hs-cTnI test						
No. of participants	91	208	264	264	146	119
Age, median (IQR); yr	44 (33–53)	55 (46–63)	69 (58–80)	76 (64–83)	78 (64–86)	78 (70–86)
No. (%) of male participants	43 (47.3)	109 (52.4)	117 (44.3)	115 (43.6)	70 (4847.9)	61 (51.3)
hs-cTnI, median (IQR); ng/L	1 (< 1–2)	2 (1–3)	3 (2–6)	8 (5–12)	26 (19–48)	67 (40–169)
Glucose, median (IQR); mmol/L	5.1 (4.9–5.3)	5.8 (5.2–6.6)	6.1 (5.5–7.2)	6.7 (5.8–8.7)	6.4 (5.6–8.2)	8.2 (6.7–11.4)
eGFR, median (IQR); mL/min/1.73 m²	101 (96–112)	94 (86–103)	77 (61–86)	68 (46–80)	58 (34–77)	47 (30–66)
No. (%) of participants with MI or who died within 30 d	0 (0)	2 (1.0)	10 (3.8)	35 (13.3)	51 (34.9)	79 (66.4)
hs-cTnT test						
No. of participants	88	193	229	228	182	172
Age, median (IQR); yr	44 (34–54)	54 (45–62)	64 (56–76)	75 (63–83)	80 (68–86)	79 (70–86)
No. (%) of male participants	41 (46.6)	101 (52.3)	101 (44.1)	114 (50.0)	83 (45.6)	95 (55.2)
hs-cTnT, median (IQR); ng/L	4 (< 3–5)	5 (< 3–7)	8 (5–12)	13 (10–16)	28 (23–49)	56 (39–96)
Glucose, median (IQR); mmol/L	5.1 (4.9–5.3)	5.7 (5.1–6.6)	6.1 (5.5–7.8)	6.8 (5.8–8.4)	5.9 (5.4–7.7)	7.7 (5.6–10.3)
eGFR, median (IQR); mL/min/1.73 m²	101 (96–110)	94 (87–103)	81 (69–89)	69 (53–81)	60 (40–77)	44 (27–65)
No. (%) of participants with MI or who died within 30 d	0 (0)	2 (1.0)	10 (4.4)	29 (12.7)	52 (28.6)	84 (48.8)
Brisbane cohort						
hs-cTnI test						
No. of participants	147	260	175	127	45	41
Age, median (IQR); yr	46 (38–52)	50 (41–59)	57 (47–66)	64 (54–77)	72 (55–82)	76 (65–83)
No. (%) of male participants	77 (52.4)	158 (60.8)	111 (63.4)	81 (63.8)	25 (55.6)	24 (58.5)
hs-cTnI, median (IQR); ng/L	2 (2–2)	2 (2–3)	4 (3–5)	6 (4–12)	30 (18–83)	130 (52–273)
Glucose, median (IQR); mmol/L	5.2 (4.9–5.3)	5.7 (5.2–6.4)	6.1 (5.6–7.2)	6.4 (5.7–8.0)	6.3 (5.6–8.3)	8.0 (6.6–9.2)
eGFR, median (IQR); mL/min/1.73 m²	104 (97–112)	99 (91–107)	84 (72–95)	74 (57–86)	70 (42–70)	60 (42–74)
No. (%) of participants with MI or who died within 30 d	0 (0)	0 (0)	1 (0.6)	9 (7.1)	13 (28.9)	26 (63.4)
hs-cTnT test						
No. of participants	162	250	176	108	53	46
Age, median (IQR); yr	46 (38–52)	49 (40–57)	58 (49–66)	65 (57–74)	76 (61–80)	79 (67–84)
No. (%) of male participants	84 (51.9)	161 (64.4)	106 (60.2)	69 (63.9)	28 (52.8)	28 (60.9)
hs-cTnT, median (IQR); ng/L	4 (3–5)	5 (4–7)	8 (6–11)	12 (9–17)	28 (22–40)	69 (45–134)
Glucose, median (IQR); mmol/L	5.1 (4.9–5.3)	5.8 (5.3–6.4)	6.1 (5.4–7.1)	6.6 (5.9–8.0)	6.7 (5.6–9.0)	7.6 (6.5–8.5)
eGFR, median (IQR); mL/min/1.73 m²	104 (97–112)	100 (92–108)	84 (73–92)	73 (61–84)	64 (43–78)	55 (36–72)
No. (%) of participants with MI or who died within 30 d	0 (0)	1 (0.4)	5 (2.8)	9 (8.3)	9 (17.0)	25 (54.4)

Table 2 (part 2 of 2): Participant characteristics and partitioning per the clinical chemistry score (range 0 to 5 points) at presentation to the emergency department for all cohorts, by tests for cardiac troponin I or T*

Characteristic	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5
Christchurch cohort						
hs-cTnI test						
No. of participants	32	154	266	220	132	142
Age, median (IQR); yr	50 (42–55)	56 (50–63)	62 (53–70)	70 (60–79)	71 (60–78)	71 (62–80)
No. (%) of male participants	25 (78.1)	88 (57.1)	137 (51.5)	134 (60.9)	87 (65.9)	98 (69.0)
hs-cTnI median ng/L (IQR)	2 (2–3)	2 (2–3)	3 (2–5)	7 (5–11)	28 (20–134)	231 (75–1099)
Glucose median mmol/L (IQR)	5.1 (5–5.4)	5.3 (5.1–5.7)	5.9 (5.3–6.7)	6.5 (5.8–7.6)	6.2 (5.5–7.6)	7.1 (6.0–9.1)
eGFR median mL/min/1.73m^2 (IQR)	98 (93–105)	85 (76–95)	74 (64–81)	67 (56–80)	64 (49–79)	63 (48–74)
No. (%) of participants with MI or who died within 30 d	0 (0)	1 (0.6)	2 (0.8)	27 (12.3)	68 (51.5)	127 (89.4)
hs-cTnT test						
No. of participants	43	191	269	168	129	146
Age, median (IQR); yr	50 (45–58)	57 (50–63)	61 (54–69)	73 (64–79)	73 (61–80)	73 (64–80)
No. (%) of male participants	29 (67.4)	114 (59.7)	135 (50.2)	104 (61.9)	85 (65.9)	102 (69.9)
hs-cTnT, median (IQR); ng/L	3 (3–4)	4 (3–6)	5 (3–8)	13 (10–16)	30 (22–49)	85 (47–223)
Glucose, median (IQR); mmol/L	5.1 (4.9–5.3)	5.3 (5.1–5.7)	6.1 (5.6–7.1)	6.6 (5.9–7.8)	6.0 (5.4–7.4)	7.0 (6.0–8.9)
eGFR, median (IQR); mL/min/1.73 m^2	97 (93–104)	83 (75–93)	75 (67–82)	64 (56–73)	65 (48–81)	60 (44–71)
No. (%) of participants with MI or who died within 30 d	0 (0)	6 (3.1)	8 (3.0)	24 (14.3)	75 (58.1)	112 (76.7)
Hamburg cohort						
hs-cTnI test						
No. of participants	108	225	347	404	153	175
Age, median (IQR); yr	43 (33–52)	52 (43–62)	62 (50–73)	71 (61–77)	72 (60–79)	73 (64–79)
No. (%) of male participants	60 (55.6)	142 (63.1)	211 (60.8)	277 (68.6)	104 (68.0)	105 (60.0)
hs-cTnI, median (IQR); ng/L	2 (2–3)	2 (2–4)	4 (2–8)	8 (5–12)	27 (19–114)	172 (59–749)
Glucose, median (IQR); mmol/L	5.1 (4.8–5.3)	5.4 (5.0–5.8)	5.8 (5.3–6.7)	6.5 (5.9–7.9)	6.1 (5.6–7.4)	7.1 (6.1–9.6)
eGFR, median (IQR); mL/min/1.73 m^2	103 (97–112)	94 (86–105)	80 (66–91)	67 (53–82)	60 (45–80)	58 (39–72)
No. (%) of participants with MI or who died within 30 d	0 (0)	2 (0.9)	20 (5.8)	60 (14.9)	68 (44.4)	126 (72.0)
hs-cTnT test						
No. of participants	151	254	338	311	168	190
Age, median (IQR); yr	43 (34–54)	52 (45–61)	62 (51–72)	73 (64–78)	73 (62–79)	75 (66–82)
No. (%) of male participants	86 (57.0)	160 (63.0)	207 (61.2)	209 (67.2)	120 (71.4)	117 (61.6)
hs-cTnT, median (IQR); ng/L	4 (< 3–5)	5 (< 3–6)	7 (5–10)	13 (10–17)	28 (23–56)	74 (41–188)
Glucose, median (IQR); mmol/L	5.1 (4.8–5.3)	5.6 (5.2–6.0)	6.0 (5.5–6.9)	6.5 (5.8–8.0)	6.2 (5.6–7.7)	7.2 (6.2–9.7)
eGFR, median (IQR); mL/min/1.73 m^2	103 (96–112)	94 (82–102)	78 (65–87)	67 (53–80)	57 (43–77)	51 (35–69)
No. (%) of participants with MI or who died within 30 d	1 (0.7)	10 (3.9)	25 (7.4)	49 (15.8)	70 (41.7)	121 (63.7)

Note: eGFR = estimated glomerular filtration rate, hs-cTnI = high-sensitivity cardiac troponin I, hs-cTnT = high-sensitivity cardiac troponin T, IQR = interquartile range, MI = myocardial infarction.
*Values rounded to nearest whole number except for glucose.

Table 3, Appendix 3). With respect to interventions, there was nearly a doubling per score in the revascularization rate, with a hs-cTnI CCS of 0 yielding 0.79% (95% CI 0.16–2.32) compared with a hs-cTnI CCS of 5 with 26.2% (95% CI 21.8–31.2) revascu- larization rate ($p > 0.05$ between hs-cTnI CCS and hs-cTnT CCS; Table 6). The sensitivities of the CCS for 30-day unstable angina, MI and death (sensitivity for a hs-cTnI CCS of 0 points 99.3%, 95% CI 98.3–99.8; for a hs-cTnT CCS of 0 points 98.8%,

Table 3: Diagnostic accuracy of the clinical chemistry score with high-sensitivity cardiac troponin I for myocardial infarction or death at 30 days after presentation to the emergency department, by cohort

Score	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative predictive value, % (95% CI)	Positive predictive value, % (95% CI)	Negative likelihood ratio (95% CI)	Positive likelihood ratio (95% CI)
Hamilton cohort, *n* = 1092						
0	100 (97.9–100)	10.0 (8.1–12.1)	100 (95.1–100)	17.7 (17.4–18)	0 (0–0.21)	1.11 (1.08–1.13)
1	98.9 (96.0–99.8)	32.5 (29.4–35.6)	99.3 (97.4–99.8)	22.1 (21.3–22.9)	0.03 (0.01–0.12)	1.46 (1.40–1.54)
5	44.6 (37.1–52.3)	95.6 (94.1–96.9)	89.9 (88.6–91.1)	66.4 (58.3–73.6)	0.58 (0.50–0.65)	10.2 (7.2–14.4)
Brisbane cohort, *n* = 795						
0	100 (92.7–100)	19.7 (16.9–22.7)	100 (97.5–100)	7.6 (5.6–9.9)	0 (0–0.37)	1.25 (1.13–1.29)
1	100 (92.7–100)	54.6 (50–9–58.2)	100 (99.1–100)	12.6 (9.5–16.4)	0 (0–0.13)	2.20 (1.97–2.37)
5	53.1 (38.3–67.5)	98.0 (96.7–98.9)	96.9 (95.5–98.1)	63.4 (46.9–77.9)	0.48 (0.43–0.61)	26.4 (15.0–45.9)
Christchurch cohort, *n* = 946						
0	100 (97.6–100)	4.4 (3.1–6.2)	100 (84.2–100)	24.6 (21.9–27.5)	0 (0–0.38)	1.05 (1.02–1.06)
1	99.6 (97.5–100)	25.7 (22.5–29.0)	99.5 (97–100)	29.5 (26.3–32.9)	0.02 (0–0.10)	1.34 (1.28–1.40)
5	56.4 (49.7–63.0)	97.9 (96.6–98.8)	87.8 (85.3–90.0)	89.4 (83.2–94.0)	0.44 (0.38–0.51)	27.1 (16.4–45.2)
Hamburg cohort, *n* = 1412						
0	100 (98.6–100)	9.5 (7.9–11.4)	100 (96.6–100)	21.2 (19.0–23.5)	0 (0–0.14)	1.11 (1.08–1.13)
1	99.3 (97.4–99.8)	29.1 (26.6–31.8)	99.4 (97.8–99.8)	25.4 (22.9–28.1)	0.02 (0.01–0.09)	1.40 (1.35–1.46)
5	45.7 (39.9–51.5)	95.7 (94.3–96.7)	87.9 (85.9–89.6)	72.0 (64.9–78.1)	0.57 (0.51–0.63)	10.6 (7.8–14.3)

Note: CI = confidence interval.

Table 4: Diagnostic accuracy of the clinical chemistry score with high-sensitivity cardiac troponin T for myocardial infarction or death at 30 days after presentation to the emergency department, by cohort

Score	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Negative predictive value, % (95% CI)	Positive predictive value, % (95% CI)	Negative likelihood ratio (95% CI)	Positive likelihood ratio (95% CI)
Hamilton cohort, *n* = 1092						
0	100 (97.9–100)	9.6 (7.8–11.7)	100 (95.0–100)	17.6 (17.3–17.9)	0 (0–0.22)	1.11 (1.07–1.13)
1	98.9 (96.0–99.9)	30.5 (27.5–33.6)	99.3 (97.2–99.8)	21.6 (20.8–22.4)	0.04 (0.01–0.13)	1.42 (1.36–1.49)
5	47.5 (39.9–55.1)	90.4 (88.3–92.2)	89.9 (88.5–91.1)	48.8 (24.6–55.1)	0.58 (0.50–0.66)	4.9 (3.8–6.3)
Brisbane cohort, *n* = 795						
0	100 (92.7–100)	21.7 (18.8–24.8)	100 (97.7–100)	7.7 (5.8–10.1)	0 (0–0.34)	1.28 (1.16–1.32)
1	98 (89.1–99.9)	55.1 (51.4–58.7)	99.8 (98.7–100)	12.5 (9.4–16.3)	0.04 (0.01–0.19)	2.18 (1.96–2.38)
5	51 (36.3–65.6)	97.2 (95.7–98.2)	96.8 (95.3–97.9)	54.3 (39.0–69.1)	0.50 (0.37–0.64)	18.1 (10.9–29.6)
Christchurch cohort, *n* = 946						
0	100 (97.6–100)	6.0 (4.3–7.9)	100 (88.0–100)	24.9 (22.1–27.9)	0 (0–0.28)	1.06 (1.04–1.08)
1	97.3 (94.3–99.0)	31.6 (28.2–35.2)	97.4 (94.5–99.1)	30.8 (27.4–34.3)	0.08 (0.04–0.18)	1.42 (1.35–1.50)
5	49.8 (43.1–56.5)	95.3 (93.5–96.7)	85.9 (83.3–88.2)	76.7 (69.0–83.3)	0.53 (0.46–0.60)	10.6 (7.4–15.0)
Hamburg cohort, *n* = 1412						
0	99.6 (98.0–100)	13.2 (11.4–15.3)	99.3 (96.3–100)	21.8 (19.6–24.2)	0.03 (0–0.15)	1.15 (1.12–1.18)
1	96.0 (93.0–97.8)	34.7 (32.0–37.5)	97.3 (95.2–98.5)	26.3 (23.7–29.1)	0.11 (0.06–0.20)	1.47 (1.40–1.54)
5	43.8 (38.1–49.7)	93.9 (92.4–95.2)	87.3 (85.3–89.1)	63.7 (56.6–70.2)	0.60 (0.53–0.66)	7.2 (5.5–9.4)

Note: CI = confidence interval.

Table 5 (part 1 of 2): Performance of the clinical chemistry score for identifying patients at low and high risk for myocardial infarction or death within 30 days after presentation to the emergency department*

Score cut-off	No. of participants with MI or who died†	No. of participants with no MI or death
CCS with hs-cTnI test		
CCS > 0	727	3140
CCS = 0	0	378
Sensitivity, % (95% CI)	100 (99.5–100)	
NPV, % (95% CI)	100 (98.9–100)	
Negative likelihood ratio	0 (0–0.05)	
Patients at low risk, % (95% CI)	8.9 (8.1–9.8)	
CCS = 5	358	119
CCS < 5	369	3399
Specificity, % (95% CI)	96.6 (96.0–97.2)	
PPV, % (95% CI)	75.1 (71.3–78.5)	
Positive likelihood ratio	14.6 (12.0–17.6)	
Patients at high risk, % (95% CI)	11.2 (10.3–12.2)	
CCS with hs-cTnT test		
CCS > 0	726	3075
CCS = 0	1	443
Sensitivity, % (95% CI)	99.9 (99.2–100)	
NPV, % (95% CI)	99.8 (98.4–100)	
Negative likelihood ratio	0.01 (0–0.06)	
Patients at low risk, % (95% CI)	10.5 (9.6–11.4)	
CCS = 5	342	212
CCS < 5	385	3306
Specificity, % (95% CI)	94.0 (93.1–94.7)	
PPV, % (95% CI)	61.7 (58.1–65.2)	
Positive likelihood ratio	7.8 (6.7–9.1)	
Patients at high-risk, % (95% CI)	13.1 (12.1–14.1)	
hs-cTnI test only		
≥ 5 ng/L	702	1543
< 5 ng/L	25	1975
Sensitivity, % (95% CI)	96.6 (95.0–97.8)	
NPV, % (95% CI)	98.8 (98.2–99.2)	
Negative likelihood ratio	0.06 (0.04–0.09)	
> 26 ng/L	537	239
≤ 26 ng/L	190	3279
Specificity, % (95% CI)	93.2 (92.3–94.0)	
PPV, % (95% CI)	69.2 (65.8–72.4)	
Positive likelihood ratio	10.9 (9.6–12.4)	

Table 5 (part 2 of 2): Performance of the clinical chemistry score for identifying patients at low and high risk for myocardial infarction or death within 30 days after presentation to the emergency department*

Score cut-off	No. of participants with MI or who died†	No. of participants with no MI or death
hs-cTnT test only		
≥ 6 ng/L	714	2262
< 6 ng/L	13	1256
Sensitivity, % (95% CI)	98.2 (97.0–99.0)	
NPV, % (95% CI)	99.0 (98.3–99.5)	
Negative likelihood ratio	0.05 (0.03–0.09)	
> 14 ng/L	640	922
≤ 14 ng/L	87	2596
Specificity, % (95% CI)	73.8 (72.3–75.2)	
PPV, % (95% CI)	41.0 (38.5–43.5)	
Positive likelihood ratio	3.4 (3.2–3.6)	

Note: CCS = clinical chemistry score, CI = confidence interval, hs-cTnI = high-sensitivity cardiac troponin I, hs-cTnT = high-sensitivity cardiac troponin T, MI = myocardial infarction, NPV = negative predictive value, PPV = positive predictive value.
*Combined cohorts, n = 4245.
†Unless specified otherwise.

95% CI 97.6–99.5) were significantly higher than those for hs-cTn alone (sensitivity for hs-cTnI < 5 ng/L 87.7%, 95% CI 84.8–90.2; for hs-cTnT < 6 ng/L 93.0%, 95% CI 90.6–94.9). The specificity of a CCS of 5 was also significantly higher than using the overall 99th percentiles of hs-cTn (Supplemental Table 4, Appendix 3).

Interpretation

The CCS coupled with other existing accelerated diagnostic pathways[1,30,34] may further identify patients at low and high risk of MI or death on presentation to the emergency department.

The goal for electrocardiograms, testing for laboratory biomarkers and clinical algorithms when patients present to the emergency department with symptoms suggestive of acute coronary syndrome is both diagnostic and for risk stratification. For identifying low-risk patients who may be suitable for discharge, many different approaches have been proposed, with the simplest being a low or undetectable hs-cTn concentration.[2,3] Despite the ease of these approaches, using hs-cTn alone has not reliably achieved a sensitivity greater than 99.0% to safely rule out MI and discharge patients presenting to the emergency department in large populations.[2,3] At the other extreme, for rule in of MI and identifying patients at high risk who require hospital admission, besides the use of electrocardiograms, algorithms that have used hs-cTn tests alone use cut-offs that are several-fold higher than the published 99th percentiles.[35] The required specificity or PPV for algorithms to identify patients at high risk have not undergone the same methodological approach as the sensitivity estimate.[30]

Table 6: Rate of revascularization* per clinical chemistry score in participants at 30 days after presentation to the emergency department in the overall cohort population†

Intervention rate by score of the CCS	Rate of revascularization					
CCS with hs-cTnI test						
Score and no. of participants	CCS 0 $n = 378$	CCS 1 $n = 847$	CCS 2 $n = 1052$	CCS 3 $n = 1015$	CCS 4 $n = 476$	CCS 5 $n = 477$
No. of events	3	13	38	75	67	125
% (95% CI)	0.79 (0.16–2.32)	1.54 (0.82–2.63)	3.61 (2.56–4.96)	7.39 (5.81–9.26)	14.1 (10.9–17.9)	26.2 (21.8–31.2)
CCS with hs-cTnT test						
Score and no. of participants	CCS 0 $n = 444$	CCS 1 $n = 888$	CCS 2 $n = 1012$	CCS 3 $n = 815$	CCS 4 $n = 532$	CCS 5 $n = 554$
No. of events	6	19	43	65	73	115
% (95% CI)	1.35 (0.50–2.94)	2.14 (1.29–3.34)	4.25 (3.08–5.72)	7.98 (6.15–10.2)	13.7 (10.8–17.3)	20.8 (17.1–24.9)
p value between rates for hs-cTnI and hs-cTnT	0.5	0.7	0.9	0.9	0.9	0.1

Note: CCS = clinical chemistry score, CI = confidence interval, hs-cTnI = high-sensitivity cardiac troponin I, hs-cTnT = high-sensitivity cardiac troponin T.
*Percutaneous coronary intervention or coronary artery bypass graft.
†Combined cohorts, $n = 4245$.

Our proposed CCS includes measurements and cut-offs for accepted normality for glucose and eGFR, and includes measurable normal concentrations of hs-cTn, all of which permits clinical laboratories to monitor these cut-offs with quality control procedures to ensure reliable and accurate results. These are essential elements for the provision of optimal laboratory services. Algorithms that use the lower limit of reporting, such as the limit of detection, for hs-cTn assays are approaches that pose a safety risk for patients, because this metric is not monitored by clinical laboratories and is subject to analytical bias, with wide variation on repeat measurements on different instruments and different lots of reagents; all of which may lead to patient misclassification.[4,6–8,36] Just as important is that there is no standardization on reporting at the low end: in a 2018 quality survey, undetectable ranges were reported from clinical laboratories that ranged from less than 1 to less than 10 ng/L for the Abbott hs-cTnI assay and less than 3 to less than 13 ng/L for the Roche hs-cTnT assay.[37] In this regard, physicians using "undetectable concentrations" will misclassify patients depending on how the clinical laboratory reports their results, if they use results from hs-cTn testing alone.

We based the inclusion of different concentration ranges for different hs-cTn scores on published low-risk cutoffs, clinical outcomes, observed analytical variation and different 99th percentiles.[19,26–32] Importantly, these concentrations can be monitored by laboratories via different quality assurance procedures, which will mitigate misclassification of patients owing to unacceptable analytical variation.[5,38] The CCS was reproducible across different sample types (ethylenediaminetetraacetic acid plasma, lithium heparin plasma and serum), and under different storage and preanalytical conditions, which should be reassuring to physicians and clinical laboratories, because hs-cTn measurements alone can be affected by different blood collection tubes and preanalytical interferences.[6,39] Some of these preanalytical sources of variation easily exceed the analytical imprecision benchmark of 10% for hs-cTn assays, and despite attempts to sensitize the clinical community to the importance of this matter, it still represents a substantial gap in optimizing patient care.[6,39]

Adoption of the CCS algorithm would standardize reporting of hs-cTn test results, how the tests are interpreted in the normal range, and represent an option less susceptible to both analytical and preanalytical errors. This could result in the safest laboratory approach for physicians to use at presentation in the emergency department. Specifically, for physicians who do not want to miss an outcome or patients who want reassurance that they are at low risk after the first blood draw, a CCS of 0 would safely classify close to 10% of the population in the emergency department who present with symptoms of acute coronary syndrome as being at low risk for unstable angina, MI, revascularization procedures and death. Those with a CCS of 5 points would be at high risk, with the remaining patients needing additional serial testing of hs-cTn using the 0/1 hour, 0/2 hour or 0/3 hour blood sampling protocols.[30,34]

Limitations

First, only about 10% of patients would be considered to be at low risk; this is similar to other studies rendering results for hs-cTn tests as detectable versus nondetectable.[3] However, as hs-cTn assays become even more analytically sensitive and precise at lower concentrations, it will be expected that all individuals will have a detectable concentration of cardiac troponin, which would make this cut-off obsolete. Second, we elected to assess outcomes only to 30 days after presentation to the emergency department. A longer-term outcome assessment may be beneficial for some clinicians, but an acute outcome within 30 days of presentation to the emergency department might be sufficient for those physicians

involved in the setting of acute care. Third, despite our intention to use MI as a common outcome across the cohorts, we emphasize that each site employed different cardiac troponin assays and change criteria (i.e., rise or fall of cardiac troponin levels) for the adjudication of MI. Only a prospective study using the same cardiac troponin assay, the same rise/fall change criteria in cardiac troponin levels, and adjudication criteria would ensure that the patients were assessed in a similar manner across the different sites.

Conclusion

A CCS of 0 points, indicating that all laboratory test levels are normal, can achieve the clinically recommended sensitivity of greater than 99.0% for 30-day MI and death, and can identify about 10% of patients as at low risk and suitable for discharge in the acute care setting. A CCS of 5 points, indicating that all laboratory test levels are abnormal, can identify patients at high risk who are suitable for hospital admission and evaluation, with about 10% of patients identified as being at high risk. The similar performance of the CCS using either hs-cTnI or hs-cTnT in different geographical locations and emergency department populations calls for a clinical study to evaluate its clinical effectiveness prospectively.

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