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ORIGINAL RESEARCH ARTICLE

Single High-Sensitivity Point-of-Care Whole-Blood Cardiac Troponin I Measurement to Rule Out Acute Myocardial Infarction at Low Risk

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BACKGROUND: High-sensitivity cardiac troponin (hs-cTn) laboratory assays are used to rule out myocardial infarction (MI) on presentation, but prolonged result turnaround times can delay patient management. Our primary aim was to identify patients at low risk of index MI using a rapid point-of-care (POC) whole-blood hs-cTnI assay at presentation with potential early patient discharge.

METHODS: Consecutive patients presenting to the emergency department from 2 prospective observational studies with suspected acute coronary syndrome were enrolled. A POC hs-cTnI assay (Atellica VTLi) threshold using whole blood at presentation, which resulted in a negative predictive value of ≥99.5% and sensitivity of >99% for index MI, was derived (SEIGE [Safe Emergency Department Discharge Rate]) and validated with plasma (SAMIE [Suspected Acute Myocardial Infarction in Emergency]). Event adjudications were established with hs-cTnI assay results from routine clinical care. The primary outcome was MI at 30 days.

RESULTS: A total of 1086 patients (8.1% with MI) were enrolled in a US derivation cohort (SEIGE) and 1486 (5.5% MI) in an Australian validation cohort (SAMIE). A derivation whole-blood POC hs-cTnI concentration of <4 ng/L provided a sensitivity of 98.9% (95% CI, 93.8%–100%) and negative predictive value of 99.5% (95% CI, 97.2%–100%) for ruling out MI. In the validation cohort, the sensitivity was 98.8% (95% CI, 93.3%–100%), and negative predictive value was 99.8% (95% CI, 99.1%–100%); 17.8% and 41.8%, respectively, were defined as low risk for discharge. The 30-day adverse cardiac events were 0.1% (n=1) for SEIGE and 0.8% (n=5) for SAMIE.

CONCLUSIONS: A POC whole-blood hs-cTnI assay permits accessible, rapid, and safe exclusion of MI and may expedite discharge from the emergency department.

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Key Words: emergency service, hospital ■ myocardial infarction ■ troponin

Chest pain accounts for ≈6.5 million visits annually to emergency departments (EDs) in the United States, placing a significant burden on health care.[1,2] Implementation of high-sensitivity (hs) cardiac troponin (cTn) assays[3–6] has allowed the use of strategies to rapidly rule out acute myocardial infarction (MI) within 1 to 3 hours and to facilitate early discharge of low-risk patients.[7–16] The ability to rapidly rule out MI depends on turnaround time of hs-cTn results from the central laboratory, often delayed because of specimen transport and handling.

Point-of-care (POC) assays reduce turnaround times by 40 minutes (Figure S1), described as optimizing

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Clinical Perspective

What Is New?

- The Atellica VTLi point-of-care high-sensitivity cardiac troponin I assay provides excellent analytical precision with the use of whole blood and plasma.
- Derived and validated in large geographically distinct cohorts, a threshold of <4 ng/L with the Siemens Atellica VTLi high-sensitivity cardiac troponin I assay has the ability to define for early discharge a large proportion of patients presenting to the emergency department with symptoms suggestive of ischemia as low risk for myocardial infarction using a single baseline measurement.

What Are the Clinical Implications?

- A single measurement with the Atellica VTLi point-of-care high-sensitivity cardiac troponin I assay supports rapid identification of patients at low risk for acute myocardial infarction, with results available in 8 minutes, and supports timely disposition.
- A single measurement with the Atellica VTLi point-of-care high-sensitivity cardiac troponin I assay supports an early rule-out myocardial infarction strategy with the use of a derived and validated <4−ng/L threshold for whole blood, and was successful in rapidly identifying patients at low risk for myocardial infarction, cardiac and all-cause death, and unplanned revascularization at 30 days.

Nonstandard Abbreviations and Acronyms

cTn	cardiac troponin
ED	emergency department
hs	high-sensitivity
LoD	limit of detection
MI	myocardial infarction
NPV	negative predictive value
POC	point of care
T1MI	type 1 myocardial infarction
T2MI	type 2 myocardial infarction
URL	upper reference limit

patient throughput in EDs,[17] and provide opportunities to manage or redirect low-risk patients away from the ED[18] and assist in general practice. Early studies used frozen plasma biobanks to assess hs-cTnI POC assays.[19–21] No study has evaluated an hs-cTn POC assay with fresh whole blood to safely rule out MI in the ED.

Our primary aim was to derive and validate an optimal hs-cTnI threshold concentration using a whole-blood POC hs-cTnI assay on a single sample at presentation in the ED to identify patients at low risk of index MI for potential early discharge.

METHODS

Study Design and Patients

Study protocols were approved by each institutional review committee, and subjects gave informed consent: SEIGE (Safe Emergency Department Discharge Rate; HHRI 20-4828) and SAMIE (Suspected AMI in Emergency; LNR/2020/QRBW/65773). Patient management remained at the discretion of the treating clinician. Neither study altered standard of care, and POC results were not available for clinical management. The data that support the findings of this study are available from the corresponding author on reasonable request.

The US-based derivation cohort prospectively enrolled consecutive unselected patients from October 13, 2020, through January 20, 2021, to Hennepin Healthcare/HCMC (Minneapolis, MN; SEIGE, NCT04772157). Patients were included if they had initial predefined serial cTnI measurements (0, 2, 4, and 6 hours) at minimum at baseline and 2 hours; were undergoing investigation to rule in/out MI; and had at least one 12-lead ECG. Exclusion criteria were patients <21 years of age; having ST-segment−elevation MI, pregnancy, or trauma; declining to participate; or transferring from outside hospital. We included only first presentation for patients with multiple presentations. Follow-up information was obtained 30 days after presentation to the ED using review of medical records and social security records. Thirty-two patients (2.9%) were lost to follow-up.

The validation study, SAMIE (ACTRN12621000053820), included consecutive eligible patients presenting from 7:30 AM to 4 PM Monday through Friday in 5 Australian hospitals between November 17, 2020, and September 9, 2021. Eligible patients were ≥18 years of age, and the treating physician investigated for acute MI. Exclusion criteria included initial electrocardiographic changes consistent with an ST-segment−elevation MI, transfer from another hospital, previous enrollment within 30 days, pregnancy, inability or unwillingness to provide informed consent, or recruitment was considered inappropriate (eg, palliative patient). Samples were collected at presentation (0 hours) and 2 to 3 hours later. Additional plasma samples were sent to the local laboratory, stored at 4°C, and sent to the Royal Brisbane and Women's Hospital laboratory, where they were divided into aliquots and stored at −80°C for future POC hs-cTnI analysis. Follow-up information was obtained 30 days after presentation to the ED. Thirty-seven patients (2.5%) were unavailable for follow-up through medical record review or phone call.

Patients presenting within <2 hours from symptom onset were considered early presenters.

cTn Assays

Derivation Cohort

Fresh EDTA plasma and lithium-heparinized whole blood were concurrently measured: plasma on the clinically used hs-cTnI Abbott ARCHITECT i2000$_{SR}$ analyzer[9,10] and whole blood on the hs-cTnI Siemens POC Atellica VTLi investigational assay.[22,23] The POC testing was performed by the same laboratory staff for both assays. The ARCHITECT hs-cTnI sex-specific 99th percentile upper reference limits (URLs) were 16 ng/L for female patients and 34 ng/L for male patients. The coefficient of variation at the limit of detection (LoD) of <2.0 ng/L was 20%.[9,10]

Validation Cohort

Lithium-heparin plasma samples were taken at the same time as standard care and sent to the central laboratory for storage at −80°C. These samples were later thawed and tested on the Siemens POC Atellica VTLi assay at Pathology Queensland by trained laboratory staff. In the event of processing error, the same sample underwent one repeat testing. The Beckman Coulter Access hs-cTnI assay used in clinical care[24] has 99th-percentile URLs of 10 ng/L for female patients and 20 ng/L for male patients, with a 20% coefficient of variation at 2.3 ng/L.

Investigational Assay

The Siemens POC Atellica VTLi assay had sex-specific 99th-percentile URLs of 27 ng/L for male patients and 18 ng/L for female patients, with coefficients of variation ranging from 7.1% to 9.5% between 12.2 and 14.0 ng/L; 20% coefficients of variation for plasma and whole blood were 2.1 and 3.7 ng/L, respectively, with an LoD of 1.24 ng/L.[22,23]

Event Adjudication

Patients with at least 1 hs-cTnI concentration >99th percentile were adjudicated by predetermined clinicians (emergency medicine and cardiology for SEIGE according to Abbott assay; cardiology for SAMIE according to Beckman assay) for MI or no MI after review of all available medical records, including 12-lead ECG, echocardiography, angiography, hs-cTnI concentrations, and clinical presentation. The diagnosis of MI was defined according to "The Fourth Universal Definition of MI"[25] and required symptoms suggestive of ischemia and a rise or fall in cTn with at least 1 concentration >99th percentile. In addition, MI criteria required: (1) the development of pathological Q waves in the 12-lead ECG; (2) electrocardiographic changes indicative of new ischemia; (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or (4) identification of an intracoronary thrombus by angiography or autopsy.[25] hs-cTnI assays used in clinical care (Abbott or Beckman) were used for patient adjudication. Patients adjudicated with MI were further classified as having type 1 MI (T1MI), defined as MI related to atherosclerotic plaque disruption, or type 2 MI (T2MI), defined as MI secondary to an ischemic imbalance between myocardial oxygen supply and demand not attributable to atherothrombosis and required to have objective evidence or documentation of supply/demand imbalance.[26–28] If no clear altered variable within the supply/demand balance was identified, T2MI was not supported. Myocardial injury was defined, according to "The Fourth Universal Definition of MI,"[25] as any hs-cTnI increased above the sex-specific 99th percentile URL for which an MI was ruled out.

Study Outcomes

The primary diagnostic outcome examined was overall MI (T1MI and T2MI), with a secondary outcome examining T1MI during the index hospitalization. The safety outcome was a composite of overall MI, all-cause death, and unplanned revascularization at 30 days, including events during the index hospitalization.

Statistical Analyses

Categorical variables are shown as percentages. Continuous variables are shown as mean±SD. Low risk was defined at <1.0% 30-day risk of death or major adverse cardiac events in patients with suspected acute coronary syndrome.[1,29] Results for hs-cTnI measurements are reported with rounded concentrations because international recommendations support the use of whole-number reporting in clinical practice.[3,4,25]

Selection criteria for derivation of the optimal rule-out threshold required a negative predictive value (NPV) of ≥99.5% and a sensitivity of >99% for index MI. Diagnostic performance statistics were sensitivity and NPV. The 95% CIs were ascertained from exact binomial proportions. Subgroup analyses were performed on early presenters. Derivation analyses were performed with R version 4.1.3; validation analyses were performed with Stata version 17.

RESULTS

In total, 2572 patients presenting to the ED with ischemic symptoms suggestive of acute coronary syndrome for whom cTn testing was obtained on clinical indication were enrolled: 1086 patients in US derivation cohort (SEIGE; Figure 1A), and 1486 patients in the Australian validation cohort (SAMIE; Figure 1B). Baseline characteristics showed that patients in the SAMIE cohort had a higher prevalence of personal and family history of coronary artery disease and a shorter median time from presentation to first blood draw compared with the SEIGE cohort (Table 1).

Derivation SEIGE Cohort

Acute MI occurred in 88 subjects (8.1%): 20 (1.8%) with T1MI and 68 (6.3%) with T2MI. Two hundred six patients (19.0%) were classified as having myocardial injury. Seventy-four patients (6.8%) had baseline hs-cTnI concentrations below the LoD; 813 (75.0%) had baseline hs-cTnI concentrations above the LoD and below the sex-specific URL; and 202 (19%) had baseline hs-cTnI concentrations above the sex-specific URL. Time from symptom onset to presentation was <2 hours (early presenters) in 210 subjects (19.3%).

Figure 2A provides sensitivities and NPVs for index acute MI across a range of hs-cTnI thresholds. Diagnostic and safety outcomes were predicated on the derivation hs-cTnI threshold of <4 ng/L based on a single presentation (0 hours) measurement. The derivation of <4 ng/L threshold derived from the whole-blood POC hs-cTnI assay is also shown in Figure 2A. In 194 patients (17.8%) with hs-cTnI concentrations <4 ng/L at presentation, the sensitivity and NPV for MI (T1MI and T2MI) were 98.9% (95% CI, 94.0%−100%) and 99.5% (95% CI, 97.2%−100%), respectively (Table 2). One patient with T2MI (1.1%) was missed. The sensitivity and NPV for T1MI only (n=20) were 100% (95% CI, 83.2%−100%) and 100% (95% CI, 98.1%−100%), respectively (Table 2). The sensitivity and NPV for 30-day adverse events (acute MI, all-cause death, revascularization, including events during index admission)
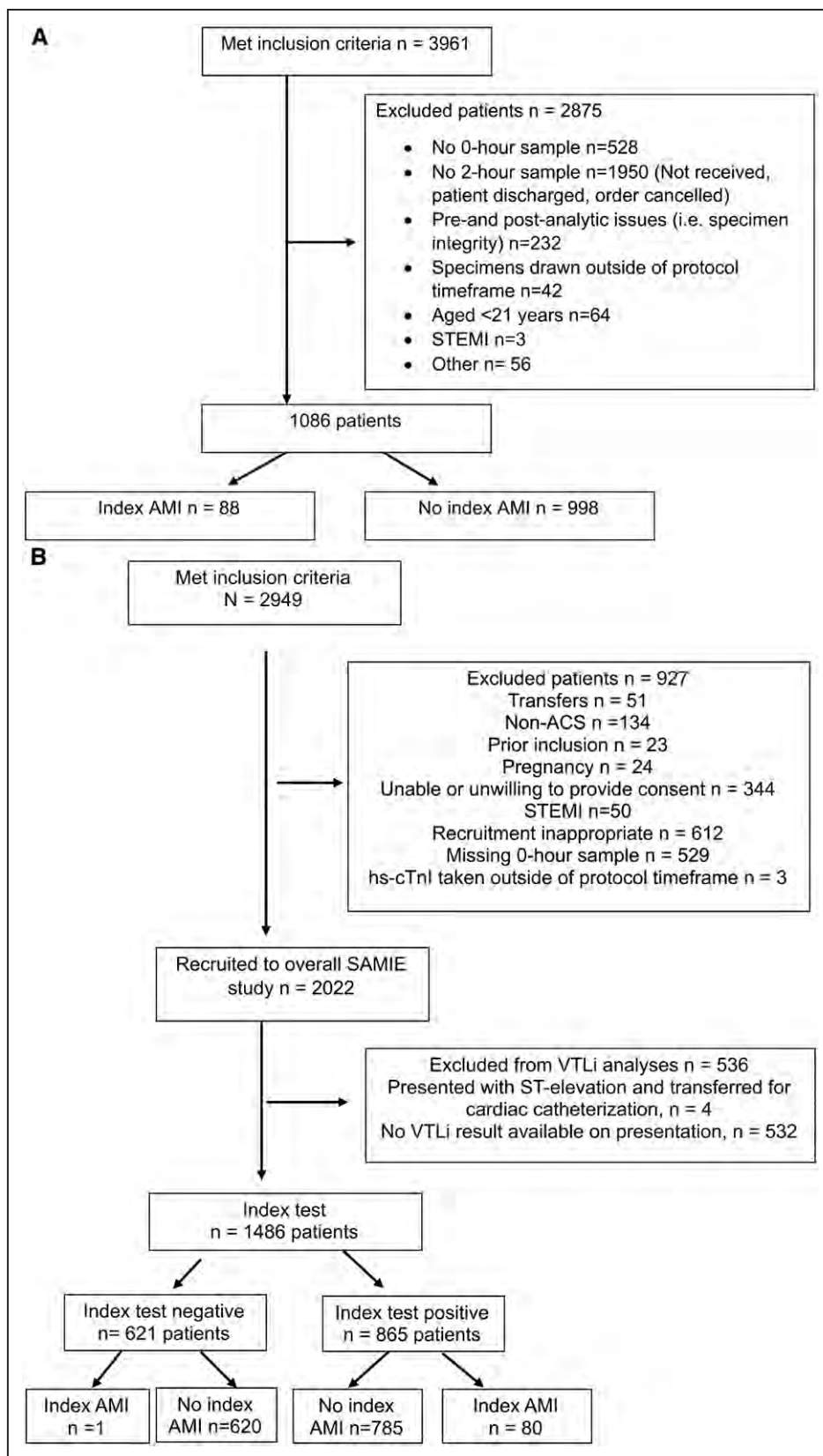
A

Met inclusion criteria n = 3961

Excluded patients n = 2875

- No 0-hour sample n=528
- No 2-hour sample n=1950 (Not received, patient discharged, order cancelled)
- Pre-and post-analytic issues (i.e. specimen integrity) n=232
- Specimens drawn outside of protocol timeframe n=42
- Aged <21 years n=64
- STEMI n=3
- Other n= 56

1086 patients

Index AMI n = 88   No index AMI n = 998

B

Met inclusion criteria
N = 2949

Excluded patients n = 927
Transfers n = 51
Non-ACS n =134
Prior inclusion n = 23
Pregnancy n = 24
Unable or unwilling to provide consent n = 344
STEMI n=50
Recruitment inappropriate n = 612
Missing 0-hour sample n = 529
hs-cTnI taken outside of protocol timeframe n = 3

Recruited to overall SAMIE
study n = 2022

Excluded from VTLi analyses n = 536
Presented with ST-elevation and transferred for
cardiac catheterization, n = 4
No VTLi result available on presentation, n = 532

Index test
n = 1486 patients

Index test negative   Index test positive
n= 621 patients   n = 865 patients

Index AMI   No index   No index   Index AMI
n =1   AMI n=620   AMI n=785   n = 80

Figure 1. Patient enrollment flowcharts for final inclusions in study cohorts: SEIGE (A) and SAMIE (B).
ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; SAMIE, Suspected Acute Myocardial Infarction in Emergency; SEIGE, Safe Emergency Department Discharge Rate; and STEMI, ST-segment–elevation myocardial infarction.

Table 1. Baseline Patient Characteristics for the SEIGE and SAMIE Cohorts

	SIEGE cohort		SAMIE cohort	
	No index AMI (n=998)	Index AMI (n=88)	No index AMI (n=1405)	Index AMI (n=81)
Age, y	59.0 (15.5)	59.5 (16.6)	56.1 (15.3)	66.1 (12.8)
Male sex, n (%)	615 (61.6)	53 (60.2)	770 (54.8)	56 (69.1)
Chest pain on presentation, n (%)	334 (33.5)	27 (30.7)	1316 (93.7)	78 (96.3)
Cardiac history, n (%)				
Previous MI	127 (12.7)	18 (20.5)	253 (18.0)	33 (40.7)
Previous CABG	26 (2.6)	7 (8.0)	81 (5.8)	10 (12.3)
Previous angioplasty	48 (4.8)	12 (13.6)	231 (16.4)	23 (28.4)
Previous CAD	222 (22.2)	28 (31.8)	326 (23.2)	37 (45.7)
Risk factors, n (%)				
Hypertension	655 (65.6)	61 (69.3)	657 (46.8)	53 (65.4)
Diabetes	379 (38.0)	36 (40.9)	235 (16.7)	27 (33.3)
Dyslipidemia	476 (47.7)	55 (62.5)	625 (44.5)	51 (63.0)
Family history of CAD	232 (23.2)	21 (23.9)	622 (44.3)	28 (34.6)
Smoking	361 (36.2)	31 (35.2)	293 (20.9)	14 (17.3)
Process data, n (%)				
Time to presentation >2 h	805 (80.7)	71 (80.7)	1056 (75.6)	59 (72.8)
Time to first troponin, median (IQR), min	54 (32–85)	39 (22–67)	39 (26–60)	34 (24–45)

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; MI, myocardial infarction; SAMIE, Suspected Acute Myocardial Infarction in Emergency; and SEIGE, Safe Emergency Department Discharge Rate.

were 99.3% (95% CI, 96.0%–100%) and 99.5% (95% CI, 97.2%–100%; Table 2), respectively. Table S2 provides the diagnostic accuracy for early rule-out with the ARCHITECT hs-cTnI assay used in clinical practice for comparison. One T2MI event (0.1% of all subjects) was missed (Table S1). For ruling out T1MI alone, baseline hs-cTnI concentrations <4 ng/L showed a sensitivity of 100% (95% CI, 83.2%–100%) and an NPV of 100% (95% CI, 98.1%–100%) for 30-day T1MI. For index MI and myocardial injury, the sensitivity was 98.3% (95% CI, 96.1%–99.4%), and NPV was 97.4% (95% CI, 94.1%–99.2%; Table 2).

Results for 210 early presenters are provided in Table 3. hs-cTnI concentrations <4 ng/L resulted in a sensitivity of 94.1% (95% CI, 71.3%–99.9%) and an NPV of 98.3% (95% CI, 91.1%–100%) for MI. For 30-day safety outcomes, hs-cTnI concentrations <4 ng/L had a sensitivity of 95.7% (95% CI, 78.1%–99.9%) and an NPV of 98.3% (95% CI, 91.1%–100%), with 1 T2MI event missed.

The diagnostic accuracy for subgroups, including patients with renal impairment, the elderly, or those with coronary artery disease, is provided in Table S3. Figure 3A shows receiver-operating characteristic curves for the Atellica POC VTLi assay and the ARCHITECT hs-cTnI used in clinical practice during the study period. The receiver-operating characteristic area for the ARCHITECT assay (0.85) was not significantly different from that for the POC assay area (0.85).

Validation SAMIE Cohort

For the validation cohort, MI was identified in 81 patients (5.5%), including 57 (3.8%) with T1MI and 24 (1.6%) with T2MI. Ninety patients (6.1%) were classified as having myocardial injury. Sixteen patients (1.1%) had hs-cTnI concentrations below the LoD; 1380 (92.9%) had hs-cTnI concentrations above or equal to the LoD and the sex-specific URL; and 90 (6.1%) had hs-cTnI concentrations above the sex-specific URL. There were 363 early presenters (24.4%).

A total of 621 patients (41.8%) had hs-cTnI concentrations <4 ng/L at presentation. The sensitivity was 98.8% (95% CI, 93.3%–100%), and the NPV was 99.8% (95% CI, 99.1%–100%) for MI (Table 2). One T2MI was missed. The sensitivity and NPV for T1MI (n=57) were 100% (95% CI, 93.7%–100%) and 100% (95% CI, 99.4%–100%), respectively (Table 2). The sensitivity and NPV for 30-day adverse events were 94.5% (95% CI, 87.6%–98.2) and 99.2% (95% CI, 98.1%–99.7; Table 2), respectively. For 30-day T1MI (n=61), the sensitivity was 96.7% (95% CI, 88.7%–99.6%) and the NPV was 99.7% (95% CI, 98.8%–100%). For index MI and myocardial injury (n=171), the sensitivity was 96.5% (95% CI, 92.5%–98.7%) and the NPV was 99.0% (95% CI, 97.9%–99.6%; Table 2). Table S2 provides the diagnostic accuracy for early rule-out with the Access hs-cTnI assay used in clinical practice for comparison. Figure 2B provides sensitivities and NPVs for index acute MI across a range of hs-cTnI thresholds. Five events (0.8%) were
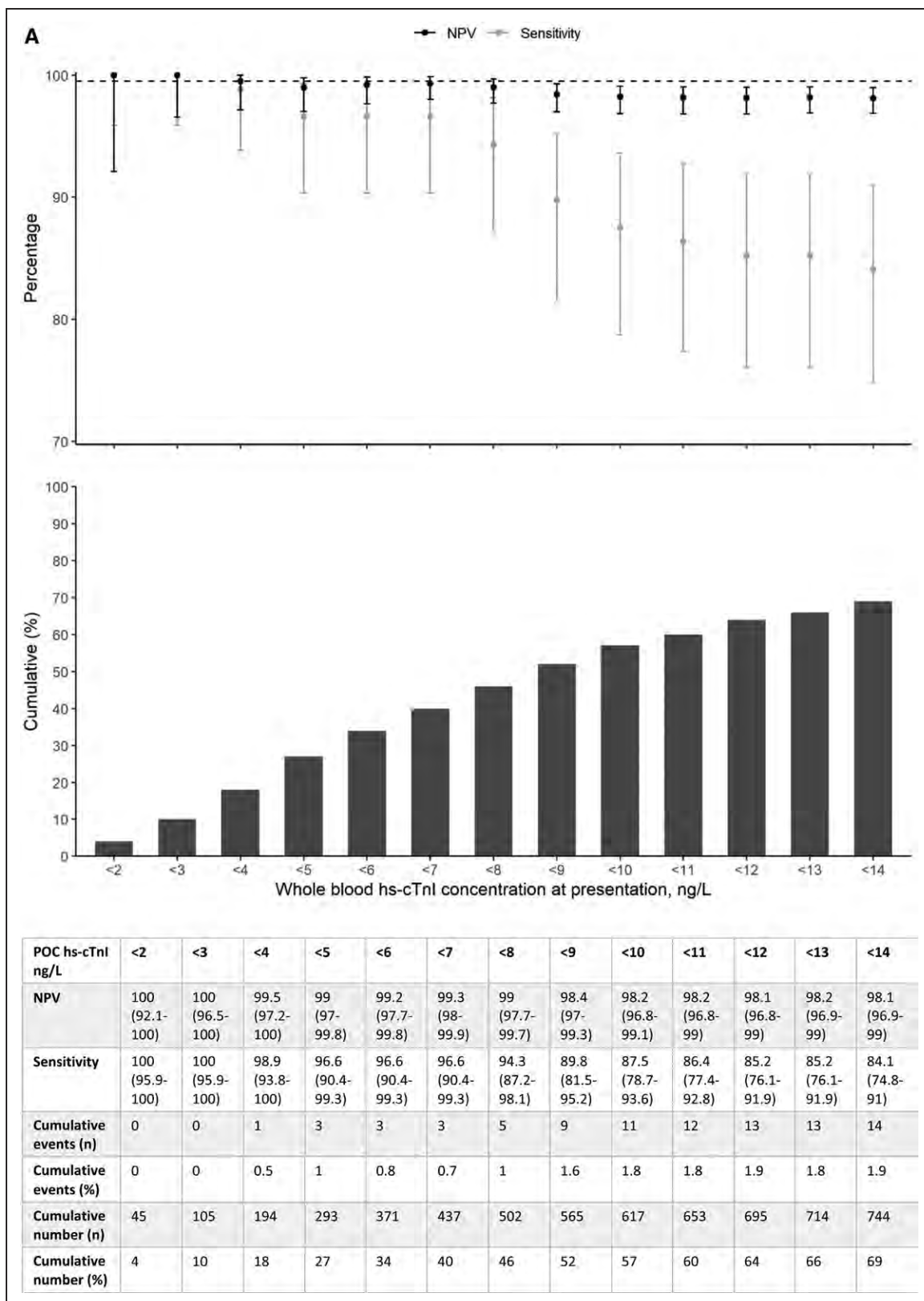
POC hs-cTnI ng/L	<2	<3	<4	<5	<6	<7	<8	<9	<10	<11	<12	<13	<14
NPV	100 (92.1-100)	100 (96.5-100)	99.5 (97.2-100)	99 (97-99.8)	99.2 (97.7-99.8)	99.3 (98-99.9)	99 (97.7-99.7)	98.4 (97-99.3)	98.2 (96.8-99.1)	98.2 (96.8-99)	98.1 (96.8-99)	98.2 (96.9-99)	98.1 (96.9-99)
Sensitivity	100 (95.9-100)	100 (95.9-100)	98.9 (93.8-100)	96.6 (90.4-99.3)	96.6 (90.4-99.3)	96.6 (90.4-99.3)	94.3 (87.2-98.1)	89.8 (81.5-95.2)	87.5 (78.7-93.6)	86.4 (77.4-92.8)	85.2 (76.1-91.9)	85.2 (76.1-91.9)	84.1 (74.8-91)
Cumulative events (n)	0	0	1	3	3	3	5	9	11	12	13	13	14
Cumulative events (%)	0	0	0.5	1	0.8	0.7	1	1.6	1.8	1.8	1.9	1.8	1.9
Cumulative number (n)	45	105	194	293	371	437	502	565	617	653	695	714	744
Cumulative number (%)	4	10	18	27	34	40	46	52	57	60	64	66	69

Figure 2. Percentages, cumulative events, and diagnostic sensitivities and NPVs for index acute MIs across a range of whole-blood Atellica VTLi POC hs-cTnI concentrations for derivation of optimal rule-out threshold in SEIGE (A) and plasma Atellica VTLi POC hs-cTnI concentrations for validation of optimal rule-out threshold in SAMIE (B).
Data were not shown after 14 ng/L in SEIGE (Safe Emergency Department Discharge Rate) and 10 ng/L in SAMIE (Suspected Acute Myocardial Infarction in Emergency) because they were diagnostically declining below clinical acceptability. hs-cTnI indicates high-sensitivity cardiac troponin I; MI, myocardial infarction; NPV, negative predictive value; and POC, point of care. (*Continued*)
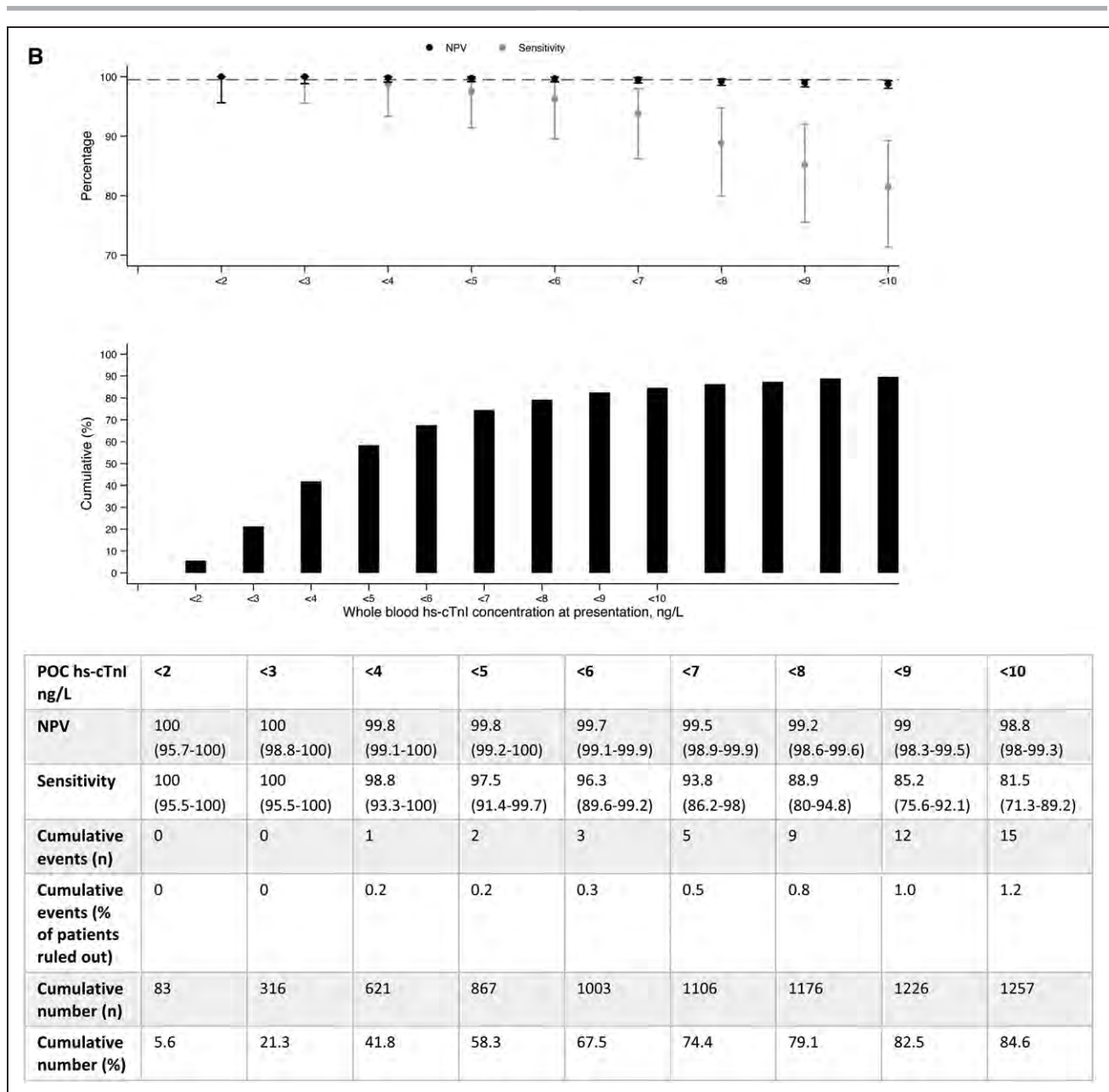
POC hs-cTnI ng/L	<2	<3	<4	<5	<6	<7	<8	<9	<10
NPV	100 (95.7-100)	100 (98.8-100)	99.8 (99.1-100)	99.8 (99.2-100)	99.7 (99.1-99.9)	99.5 (98.9-99.9)	99.2 (98.6-99.6)	99 (98.3-99.5)	98.8 (98-99.3)
Sensitivity	100 (95.5-100)	100 (95.5-100)	98.8 (93.3-100)	97.5 (91.4-99.7)	96.3 (89.6-99.2)	93.8 (86.2-98)	88.9 (80-94.8)	85.2 (75.6-92.1)	81.5 (71.3-89.2)
Cumulative events (n)	0	0	1	2	3	5	9	12	15
Cumulative events (% of patients ruled out)	0	0	0.2	0.2	0.3	0.5	0.8	1.0	1.2
Cumulative number (n)	83	316	621	867	1003	1106	1176	1226	1257
Cumulative number (%)	5.6	21.3	41.8	58.3	67.5	74.4	79.1	82.5	84.6

Figure 2 Continued.

missed: 1 T2MI, 2 unplanned revascularizations, and 2 non–ST-segment–elevation MIs (Table S1).

In early presenters (Table 3), hs-cTnI concentrations <4 ng/L resulted in a sensitivity of 95.5% (95% CI, 77.2%–99.9%) and an NPV of 99.3% (95% CI, 96.1%–100%) for MI. For safety outcome at 30 days, hs-cTnI concentrations <4 ng/L had a sensitivity of 87.5% (95% CI, 67.6%–97.3%) and an NPV of 97.9% (95% CI, 93.9%–99.6%), with 5 events missed. The diagnostic accuracy for subgroups, including patients with renal impairment, the elderly, or those with coronary artery disease, is provided in Table S3.

Figure 3B includes receiver-operating characteristic curves for the Atellica POC assay and the Access

hs-cTnI assay that was in clinical use during the study period. The receiver-operating characteristic area for the Access assay was significantly higher (0.97) than the POC assay (0.94; P<0.01). However, at 4 ng/L, the Access and Atellica POC assays had similar sensitivity (P=0.32) and NPV (P=0.25).

DISCUSSION

Our findings are unique in several aspects. First, this is the first report of the safety and accuracy of a single whole-blood POC hs-cTnI test for rapid exclusion of MI in patients at presentation to the ED. Implementation of the whole-blood POC hs-cTnI assay is designed to

Table 2. Diagnostic Accuracy for Atellica VTLi POC hs-cTnI <4–ng/L Threshold for the SEIGE and SAMIE Cohorts

	TP	FN	FP	TN	Sensitivity, %	NPV, %	Specificity, %	PPV, %
Index AMI (T1MI and T2MI)								
SEIGE	87	1	805	193	98.9 (93.8–100)	99.5 (97.2–100)	19.3 (16.9–21.9)	9.8 (7.9–11.9)
SAMIE	80	1	785	620	98.8% (93.3–100)	99.8 (99.1–100)	44.1 (41.5–46.8)	9.2 (7.4–11.4)
Index T1MI								
SEIGE	20	0	872	194	100 (83.2–100)	100 (98.1–100)	18.2 (15.9–20.6)	2.2 (1.4–3.4)
SAMIE	57	0	808	621	100 (93.7–100)	100 (99.4–100)	43.5 (40.9–46.1)	6.6 (5.0–8.5)
30-d MACE (MI, unplanned revascularization or death during index or within 30 d)								
SEIGE	137	1	755	193	99.3 (96.0–100)	99.5 (97.2–100)	20.4 (17.8–23.1)	15.4 (13.1–17.9)
SAMIE	86	5	779	616	94.5 (87.6–98.2)	99.2 (98.1–99.7)	44.2 (41.5–46.8)	9.9 (8.0–12.1)
Index injury (T1MI, T2MI, acute myocardial injury, or chronic myocardial injury)								
SEIGE	289	5	603	189	98.3 (96.1–99.4)	97.4 (94.1–99.2)	23.9 (20.9–27.0)	32.4 (29.3–35.6)
SAMIE	165	6	700	615	96.5 (92.5–98.7)	99.0 (97.9–99.6)	48.8 (44.0–49.5)	19.1 (16.5–21.9)
30-d T1MI								
SEIGE*								
SAMIE	59	2	806	619	96.7 (88.7–99.6)	99.7 (98.8–100)	43.4 (40.8–46.1)	6.8 (5.2–8.7)

AMI indicates acute myocardial infarction; FN, false negative; FP, false positive; hs-cTnI, high-sensitivity cardiac troponin I; MACE, major adverse cardiac event; MI, myocardial infarction; NPV, negative predictive value; POC, point-of-care; PPV, positive predictive value; SAMIE, Suspected Acute Myocardial Infarction in Emergency; SEIGE, Safe Emergency Department Discharge Rate; TN, true negative; T1MI, type 1 myocardial infarction; TP, true positive; and T2MI, type 2 myocardial infarction.

*Data not available for SEIGE.

be done by both nonlaboratory and laboratory personnel after appropriate training. Figure S1 illustrates the time-saving benefits for using POC testing compared with central laboratory testing that should benefit health care providers globally for patients for whom safe and rapid discharge potentially prevents longer ED stays and admission. Improvement in ED efficiency by decreasing cardiac biomarker testing turnaround time to <40 minutes with the use of POC assays has been reported.[17] The whole-blood POC hs-cTnI assay identifies a substantial number of patients as being at very low risk of MI who may be rapidly and safely discharged from the ED on the basis of a single baseline measurement. POC testing also has potential benefits for centers that do not

have a central laboratory but only have immediate access to POC testing. This is a big issue for countries like Australia, for example, with very dispersed regional hospitals with populations spread >10-fold the area compared with some US states. Patients deemed low risk (<1% index MI) are reasonable to discharge; however, the 30-day risk of major adverse cardiac events is higher than defined by the "2021 AHA/ACC/ASE CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines."[1] Such patients may require additional investigation within 30 days. The UK National Institute for Health and Care Excellence

Table 3. Diagnostic Accuracy for Early Presenters for Atellica VTLi POC hs-cTnI <4 ng/L Threshold for Patients Presenting at <2 Hours After Symptom Onset

	TP	FN	FP	TN	Sensitivity, %	NPV, %
Index AMI (T1MI and T2MI)						
SIEGE	16	1	134	59	94.1 (71.3–99.9)	98.3 (91.1–100)
SAMIE	21	1	201	140	95.5 (77.2–99.9)	99.3 (96.1–100)
Index T1MI						
SIEGE	5	0	145	60	100 (47.8–100)	100 (94.0–100)
SAMIE	15	0	207	141	100 (78.2–100)	100 (97.4–100)
30-d MACE (MI, unplanned revascularization, or death)						
SIEGE	22	1	128	59	95.7 (78.1–99.9)	98.3 (91.1–100)
SAMIE	21	3	201	138	87.5 (67.6–97.3)	97.9 (93.9–99.6)

AMI indicates acute myocardial infarction; FN, false negative; FP, false positive; hs-cTnI, high-sensitivity cardiac troponin I; MACE, major adverse cardiac event; MI, myocardial infarction; NPV, negative predictive value; POC, point-of-care; SAMIE, Suspected Acute Myocardial Infarction in Emergency; SEIGE, Safe Emergency Department Discharge Rate; TN, true negative; T1MI, type 1 myocardial infarction; TP, true positive; and T2MI, type 2 myocardial infarction.
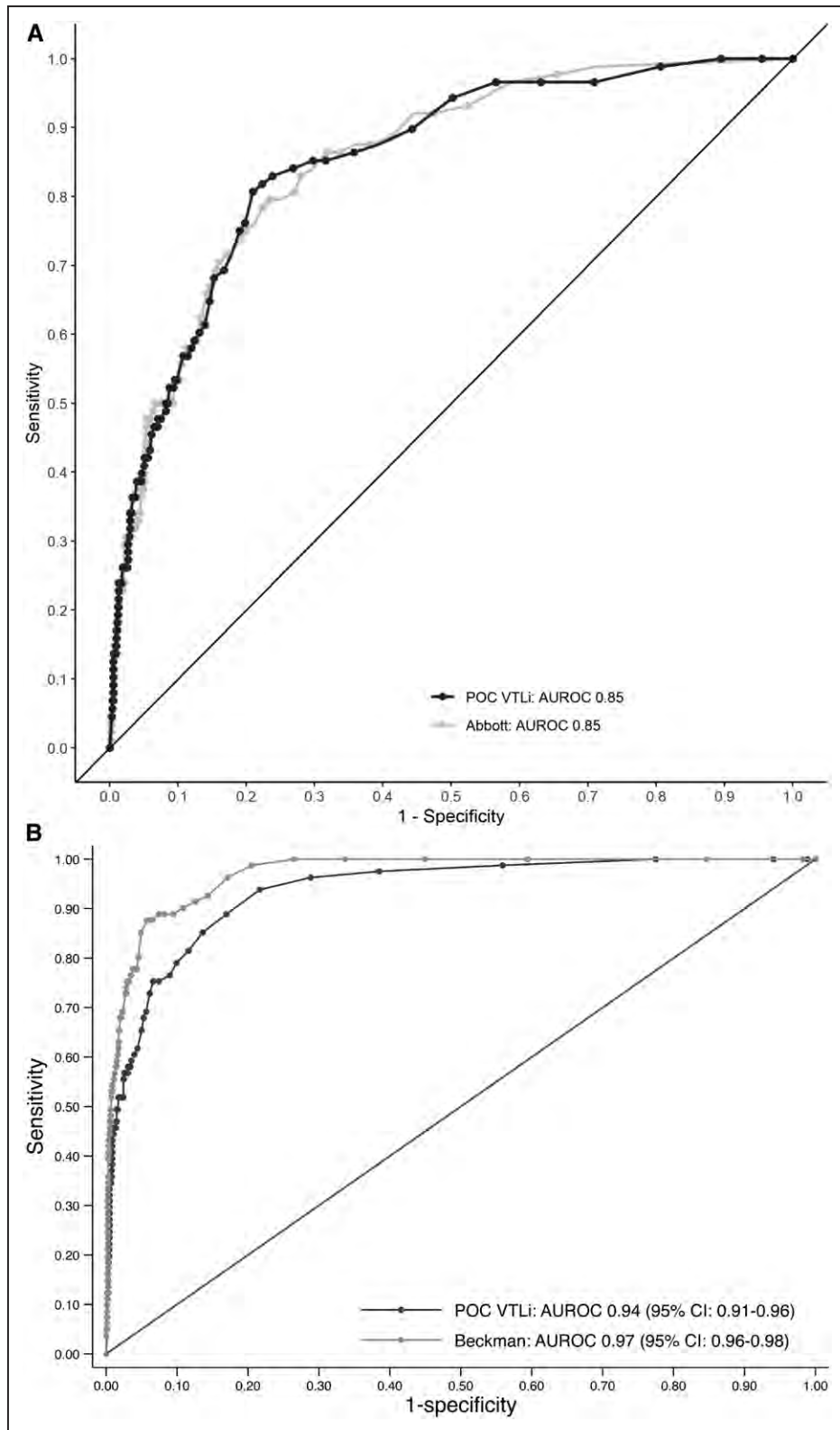
Figure 3. ROC curves for the POC VTLi assay compared with the clinically used hs-cTnI assays for derivation SEIGE cohort Abbott hs-cTnI assay(A) and validation SAMIE cohort Beckman hs-cTnI assay (B).
AUROC indicates area under the receiver-operating characteristic (ROC) curve; hs-cTnI, high-sensitivity cardiac troponin I; POC, point of care; SAMIE, Suspected Acute Myocardial Infarction in Emergency; and SEIGE, Safe Emergency Department Discharge Rate.

diagnostic guideline recently concluded that studies are lacking for hs-cTn POC assays.[29] Our current study begins to address this gap.

Second, we were successful in deriving a <4–ng/L POC hs-cTnI threshold that offered a high NPV (99.5%). We validated this threshold using plasma in the Australian SAMIE cohort without compromising the NPV. Both cohorts had a <1% miss rate for 30-day events. There was, however, a substantial difference in the number of patients who would potentially qualify for early discharge: 17.8% in SEIGE, and 41.8% in SAMIE. The 17.8% finding in SEIGE was similar to the 23% observed in a previous ClinicalTrials.gov study from our US group, UTROPIA (Use of Abbott High Sensitivity Troponin I Assay in Acute Coronary Syndromes; NCT02060760), using a central laboratory hs-cTnI ARCHITECT assay.[9,10] It should be noted that there is a difference in clinical practice used in the Hennepin study protocol compared with SAMIE. During SEIGE enrollment, the clinical protocol allowed discharge after a single hs-cTnI concentration <5 ng/L in the very lowest-risk group, derived in High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome)[12] and validated in UTROPIA.[10,12] As shown in Figure 1A, 1950 patients in this group did not have a 2-hour blood draw and were excluded from this study. Had they been included, there could have been a much higher number of patients with <4 ng/L on POC testing, resulting in ≈60% qualifying for early discharge. In comparison, no SAMIE patients were missing a 2-hour blood draw in the validation group because their ED clinical protocol required 0/2-hour testing for early rule out. This is an important and enlightening observation for future studies/trials to consider.

The US cohort represents a safety net level-1 trauma center, treating a heterogeneous group of patients with a high comorbidity burden. Consistently, ≈33% of patients monitored for cTnI in the ED have an increased cTn concentration >99th percentile, indicating myocardial injury.[9,10] The lower rate of MI diagnosis in patients presenting to the ED reported in the present and previous Australian studies likely also contributes to the high proportion of low-risk patients in SAMIE.[24,30] The differences in MI types are easy to understand. The US hospital is an inner-city medical center where many of the hs-cTnI measurements are obtained in patients with a large diversity of diseases, as is common in the United States. In Australia, the hospitals involved use hs-cTnI more selectively to evaluate patients with possible MI more exclusively, with chest pain more prevalent in the Australian cohort. Our present study also confirms the 2- to 3-fold increase of T2MI over T1MI in the US cohort, in contrast to the Australia cohort, which showed a 3.8-fold higher T1MI rate. However, the sensitivities achieved for MI diagnostics and safety for both cohorts were very good: SEIGE, 98.9% and 99.3%; and SAMIE, 98.8% and 94.5%, respectively. Our findings for the novel whole-blood POC hs-cTnI assay are comparable to central laboratory hs-cTnI[9] and hs-cTnT[11] observations.

Third, because of the variable rising kinetics of cTnI after acute MI in early presenters,[31] the lower sensitivities and NPVs for early rule-out were not as robust, and we suggest measuring a second sample to rule out MI in early presenters. This finding is no different from that observed with the use of central laboratory hs-cTnI and hs-cTnT assays.

The basic concept underlying POC testing is that results are provided in a more rapid manner directly to the clinician responsible for patient care. This allows more rapid inclusion of results in clinical decision-making pathways, aiming to improve the quality of patient care and outcomes. Overall, this should result in less crowded assessment areas, shorter lengths of stay in the ED, and potentially improved clinical outcomes. International Laboratory Medicine guidelines[3–5] require that POC hs-cTn assay evaluations be performed to the same standards as evaluation of the central laboratory hs-cTn assays. The novel POC hs-cTnI assay used in the present study has met these analytical requirements, with the current study being the first to show clinical documentation for its use in whole blood as an early rule-out biomarker, ready for implementation in clinical practice, replacing the relatively insensitive contemporary cTn POC assays.[3,32,33] The POC hs-cTnI assay also potentially benefits medical locations that only have immediate access to POC testing. This is a big issue for very dispersed regional hospitals with populations spread over very large geographic areas. Recent analytical data have demonstrated that whole-blood and lithium-heparin plasma results correlated well in serial specimens from patients presenting to the ED.[23] We also acknowledge the need for future studies to address any potential bias or difference between plasma and whole-blood measurements that may or may not be clinically meaningful at concentrations close to the rule-out threshold. The present study supports the use of this hs-cTnI POC assay to facilitate early safe discharge without admission or urgent cardiac testing[1] but not in early presenters. Our study has shown appropriate clinical validation of a whole-blood POC hs-cTnI demonstrating clinical equivalence with central laboratory–based hs cTn measurement when tested in the real-world environment.

Limitations

Our study is not without limitations. First, the POC hs-cTnI assay has not been evaluated in routine clinical practice in the United States because the US Food and Drug Administration has not yet cleared the assay. Therapeutic Goods of Australia approval was obtained after SAMIE study completion, and the assay has achieved the Therapeutic Goods of Australia and a CE mark approval. We expect the rest of the world (outside the United States) to begin a rollout of this analytically superior POC hs-cTnI assay

compared with the many contemporary assays currently used in practice. Second, we assessed the POC cTnI assay results only in early rule-out and risk, and other than the electrocardiographic diagnosis of ST-segment–elevation MI, we did not take into account the ECG or imaging in combination with cTn. We support that biomarker testing should not be implemented in isolation without clinical assessment. Third, different central laboratory hs-cTnI assays, ARCHITECT and Access, were used for adjudication. However, this adds to the strength of our observations and is representative of global practice variations. Fourth, there were differences in enrollment, with the US cohort enrolling around the clock and the Australian cohort enrolling only during daytime hours. Fifth, enrollment protocols differed between cohorts, with the SEIGE cohort discharging patients early on the basis of a single baseline hs-cTnI concentration who were deemed low risk (NPV >99.5%), per hospital protocol. Sixth, the POC testing in SEIGE was performed by laboratory staff, not nursing staff, as would be the practice in near-bedside testing in EDs.

Conclusions

A single-measurement rule-out MI strategy using a derived and validated <4–ng/L threshold for a whole-blood POC hs-cTnI assay was successful in rapidly identifying patients for safely ruling out acute MI and those at low risk for MI, cardiac and all-cause death, and unplanned revascularization at 30 days. Our findings provide great promise for improving patient care in both rural and inner-city medical settings with potential financial benefits.

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APPENDIX

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