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Coronary Artery Disease, Acute Coronary Syndromes, Acute Cardiac Care –
Acute Coronary Syndromes, Diagnostic Methods, Biomarkers

A pooled multi-national validation study of a machine learning, high-sensitivity troponin-based multi-proteomic model to predict the presence of obstructive coronary artery disease

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Background: Undetected obstructive coronary artery disease (oCAD) is a global health problem associated with significant morbidity and mortality. A need exists for an accurate and easily accessible diagnostic test for oCAD. Using machine learning, a multi-biomarker blood diagnostic test for oCAD based on high-sensitivity cardiac troponin-I (hs-cTnI) has been developed.
Purpose: To validate the performance of a previously developed, algorithmically weighted, multiple protein diagnostic panel to diagnose oCAD in a pooled multi-national cohort and to compare the diagnostic panel's performance to predict oCAD to hs-cTnI alone.
Methods: Three clinical factors (sex, age, and previous coronary percutaneous intervention) and three biomarkers (hs-cTnI, Adiponectin, and Kidney Injury Molecule-1) were combined. hs-cTnI blood samples were assayed on the Siemens Atellica and Abbott Diagnostics ARCHITECT immunoassay platforms. Adiponectin and Kidney Injury Molecule-1 were measured with a multiplex assay on blood samples via the Luminex 100/200 xMAP platform. Individual data from a total of 924 patients with a mixture of acute and lesser acute presentations from three centers were pooled (Table 1). oCAD was defined as >50% coronary obstruction in at least one coronary artery (for the University Hospital Hamburg-Eppendorf cohort) or >70% coronary obstruction in at least one coronary artery (for the other two cohorts). The multiple biomarker diagnostic panel's performance to predict oCAD was also compared to hs-cTnI alone.
Results: The multiple protein panel had an area under the receiver-operating characteristic curve of 0.80 (95% CI, 0.77, 0.83, p<0.001) for the presence of oCAD (Figure 1). At optimal cutoff, the score had 74% sensitivity, 72% specificity, and a positive predictive value of 81% for oCAD. The multiple biomarker panel had a diagnostic odds ratio of 7.48 (95% CI 5.55, 10.09, p<0.001). In comparison, in patients without an acute MI, hs-cTnI alone had an area under the receiver-operating characteristic curve of 0.63 (95% CI, 0.60, 0.67, p<0.001)) for oCAD (Figure 1).
Conclusions: In this multinational pooled cohort, a previously described novel machine learning, multiple biomarker panel provided high accuracy to diagnose patients for oCAD.

	CASABLANCA Validation Set (n = 275)			BACC (n = 241)			Inova (n = 408)			All Patients (n = 924)		
	With CAD (n=177)	Without CAD (n=98)	p-value	With CAD (n=199)	Without CAD (n=42)	p-value	With CAD (n=197)	Without CAD (n=211)	p-value	With CAD (n=573)	Without CAD (n=351)	p-value
Demographics												
Age	67.949 (11.555)	65.5 (11.86)	p = 0.1	64.976 (13.179)	61.119 (13.459)	p = 0.091	68.604 (9.924)	64.888 (12.516)	p < 0.001	67.487 (11.619)	64.608 (12.487)	p < 0.001
Sex Is Male	143 / 177 (80.8%)	54 / 98 (55.1%)	p < 0.001	187 / 245 (76.3%)	22 / 42 (52.4%)	p = 0.002	149 / 197 (75.6%)	125 / 211 (59.2%)	p < 0.001	439 / 573 (76.6%)	201 / 351 (57.3%)	p < 0.001
BMI	28.841 (5.205)	28.009 (5.752)	p = 0.236	27.35 (5.074)	27.377 (4.718)	p = 0.974	31.119 (24.039)	30.598 (7.979)	p = 0.773	29.145 (14.771)	29.502 (7.212)	p = 0.625
Current smoker	28 / 175 (16%)	11 / 97 (11.3%)	p = 0.367	82 / 245 (33.5%)	10 / 42 (23.8%)	p = 0.283	16 / 197 (8.1%)	15 / 211 (7.1%)	p = 0.713	104 / 571 (18.2%)	36 / 350 (10.3%)	p = 0.001
Medical History												
Hypertension	129 / 177 (72.9%)	69 / 98 (70.4%)	p = 0.676	188 / 243 (77.4%)	25 / 41 (61%)	p = 0.032	161 / 197 (81.7%)	145 / 211 (68.7%)	p = 0.003	451 / 571 (79%)	239 / 350 (68.3%)	p < 0.001
Hyperlipoproteinemia	127 / 177 (71.8%)	53 / 98 (54.1%)	p = 0.004	126 / 245 (51.4%)	14 / 42 (33.3%)	p = 0.044	154 / 197 (78.2%)	120 / 211 (56.9%)	p < 0.001	395 / 573 (68.9%)	187 / 351 (53.3%)	p < 0.001
CAD/CAGB/PCI	144 / 177 (81.4%)	31 / 98 (31.6%)	p < 0.001	111 / 245 (45.3%)	2 / 42 (4.8%)	p < 0.001	108 / 197 (54.8%)	60 / 211 (28.4%)	p < 0.001	356 / 573 (62.1%)	93 / 351 (26.5%)	p < 0.001
Prior MI	47 / 177 (26.6%)	15 / 98 (15.3%)	p = 0.035	60 / 245 (24.5%)	2 / 42 (4.8%)	p = 0.002	54 / 197 (27.4%)	16 / 211 (7.6%)	p < 0.001	158 / 573 (27.6%)	33 / 351 (9.4%)	p < 0.001
Congestive heart failure	34 / 177 (19.2%)	21 / 98 (21.4%)	p = 0.753	44 / 245 (18%)	9 / 42 (21.4%)	p = 0.667	37 / 197 (18.8%)	44 / 210 (21%)	p = 0.62	111 / 573 (19.4%)	74 / 350 (21.1%)	p = 0.553
Peripheral artery disease	38 / 177 (21.5%)	9 / 98 (9.2%)	p = 0.012	29 / 245 (11.8%)	0 / 42 (0%)	p = 0.012	26 / 197 (13.2%)	10 / 211 (4.7%)	p = 0.003	90 / 573 (15.7%)	19 / 351 (5.4%)	p < 0.001
Family history of CAD	81 / 177 (45.8%)	26 / 98 (26.5%)	p = 0.003	63 / 239 (26.4%)	9 / 40 (22.5%)	p = 0.699	76 / 195 (39%)	70 / 210 (33.3%)	p = 0.255	208 / 567 (36.7%)	105 / 348 (30.2%)	p = 0.075
Medication Use												
Antiplatelet	153 / 177 (86.4%)	58 / 98 (59.2%)	p < 0.001	113 / 229 (49.3%)	12 / 40 (30%)	p = 0.026	127 / 163 (77.9%)	134 / 169 (79.3%)	p = 0.79	451 / 572 (78.8%)	206 / 351 (58.7%)	p < 0.001
Hypertension	151 / 177 (85.3%)	84 / 98 (85.7%)	p = 1	151 / 229 (65.9%)	26 / 40 (65%)	p = 1	114 / 163 (69.9%)	128 / 169 (75.7%)	p = 0.267	446 / 571 (78.1%)	237 / 351 (67.5%)	p < 0.001
Hyperlipoproteinemia	142 / 177 (80.2%)	63 / 98 (64.3%)	p = 0.006	72 / 227 (31.7%)	7 / 38 (18.4%)	p = 0.125	114 / 163 (69.9%)	120 / 169 (71%)	p = 0.904	380 / 567 (67%)	195 / 350 (55.7%)	p < 0.001
Anti-diabetics	30 / 177 (16.9%)	14 / 98 (14.3%)	p = 0.61	46 / 233 (19.7%)	4 / 40 (10%)	p = 0.185	20 / 55 (36.4%)	22 / 48 (45.8%)	p = 0.422	102 / 454 (22.5%)	38 / 189 (20.1%)	p = 0.531
Protein Concentrations												
Adiponectin (ug/mL)	3.9 (2.3, 5.9)	4.3 (2.9, 7.45)	p = 0.03	4.6 (3, 7.6)	7.15 (4.4, 9.55)	p = 0.007	4.2 (3, 7.4)	4.5 (3, 7.5)	p = 0.711	4 (2.6, 6.6)	5 (3.2, 8.4)	p < 0.001
Kidney Injury Molecule-1 (ng/mL)	0.043 (0.015, 0.085)	0.031 (0.015, 0.054)	p = 0.009	0.024 (0.024, 0.073)	0.051 (0.024, 0.074)	p = 0.52	0.024 (0.024, 0.068)	0.024 (0.024, 0.05)	p = 0.059	0.034 (0.024, 0.079)	0.024 (0.024, 0.05)	p < 0.001
Tn-I (pg/mL)	10.3 (4, 110.6)	6.2 (3.1, 20.8)	p = 0.002	37.9 (9.6, 539.8)	26.35 (9.125, 114.5)	p = 0.376	6.9 (5.15, 11.75)	7.1 (5.3, 12.1)	p = 0.529	11.6 (5.6, 69.2)	7 (4.6, 13.85)	p < 0.001

Table 1. Pooled Variable Data

HART CADhs:
AUC = 0.802
Sn = 0.743
Sp = 0.721
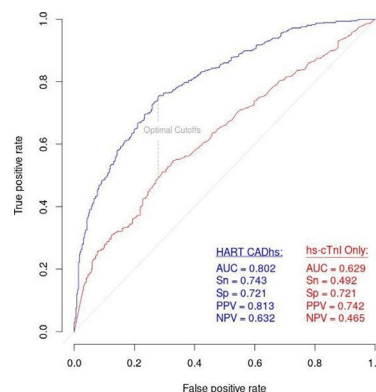PPV = 0.813
NPV = 0.632

hs-cTnI Only:
AUC = 0.629
Sn = 0.492
Sp = 0.721
PPV = 0.742
NPV = 0.465

Figure 1. ROC for HART CADhs and hs-cTnI