

Supplemental Material

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Unsupervised learning to characterize patients with known coronary artery disease undergoing myocardial perfusion imaging

Brief title: Cluster analysis in known coronary disease

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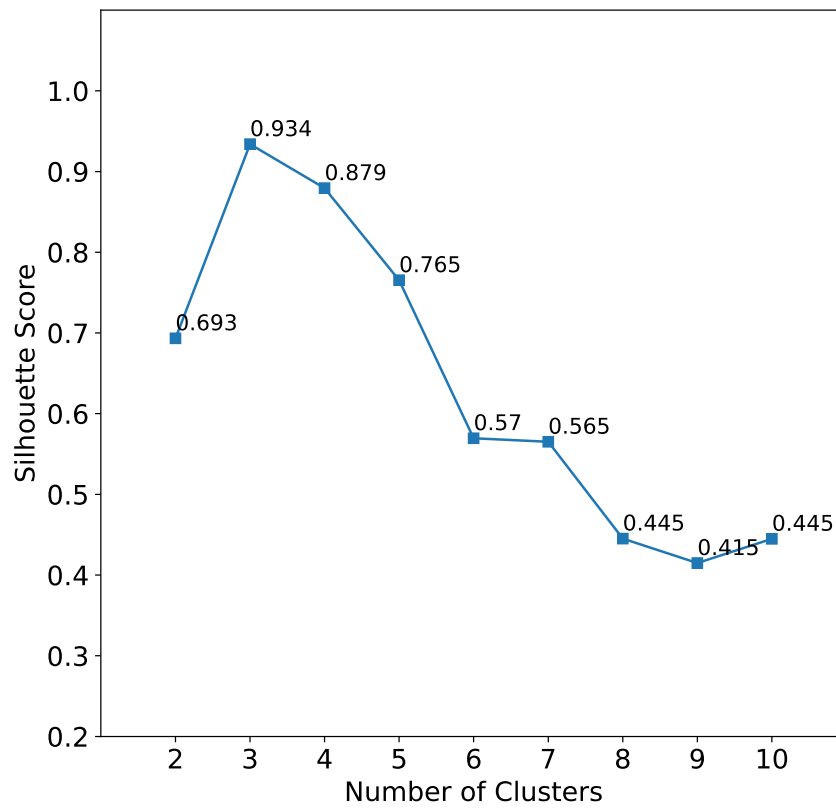
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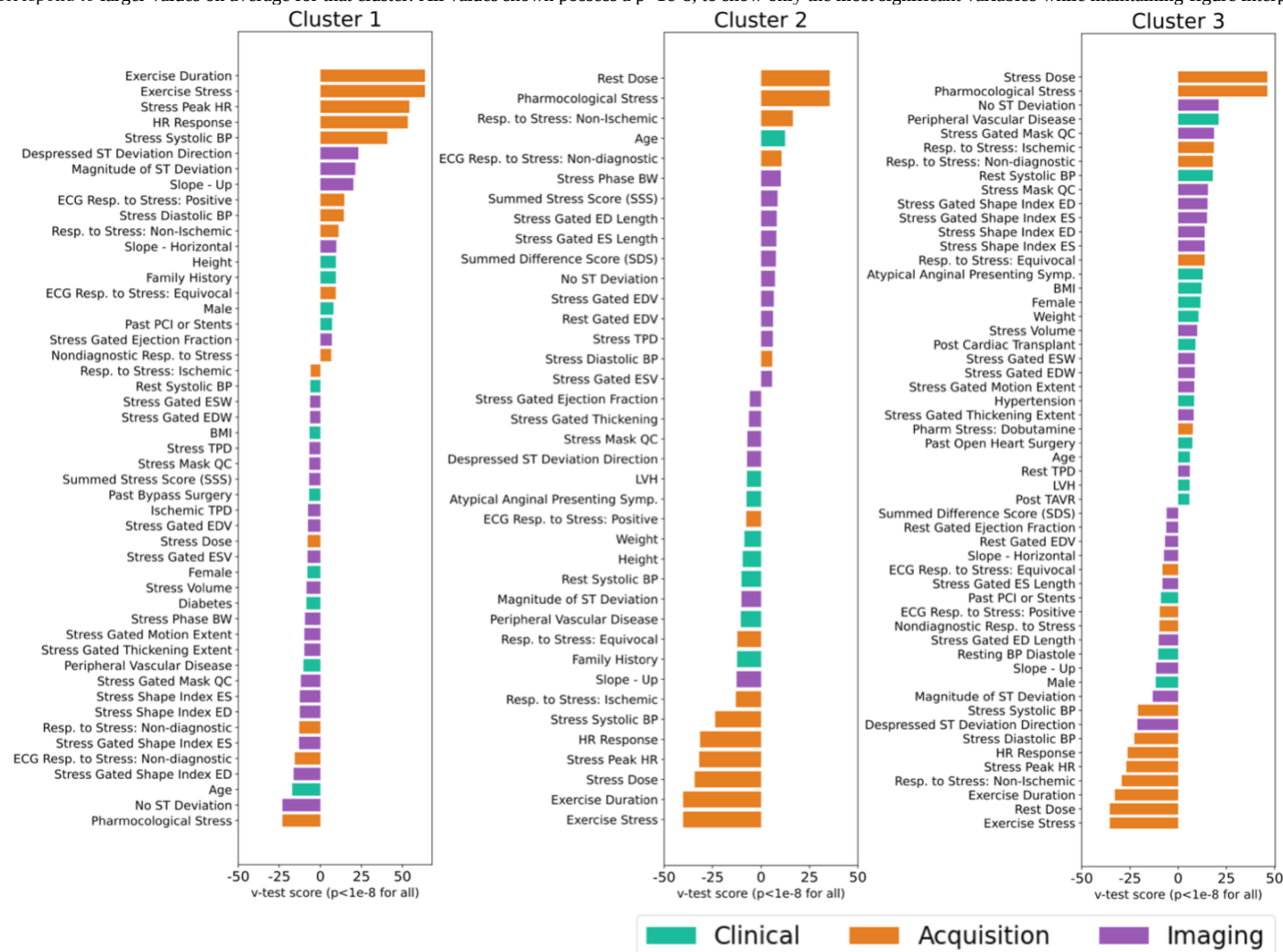
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Supplementary Figure 1: Silhouette scores for varying number of clusters in the internal cohort. The optimal number of clusters, with the highest Silhouette score, was three clusters.



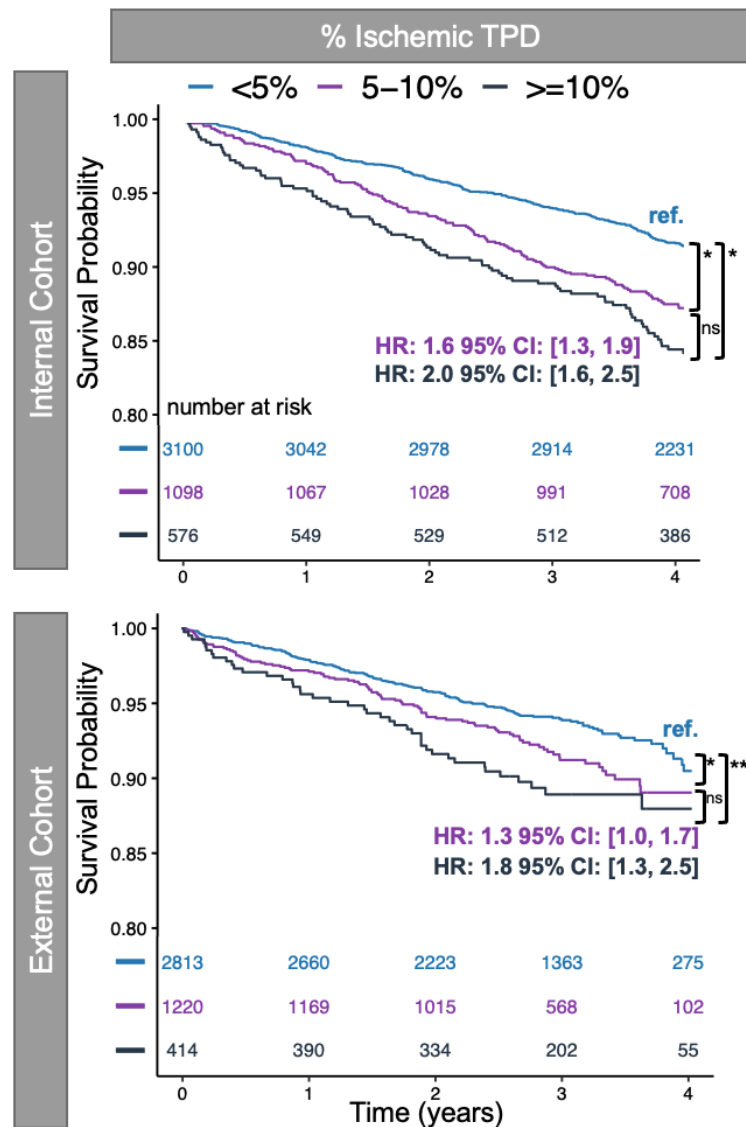
Supplementary Figure 2: Under- and over-representation of clinical (green), acquisition (orange) and image analysis (purple) features in Cluster 1, Cluster 2, and Cluster 3 in the internal cohort. All variables from the REFINE SPECT registry are analyzed here for their broad clinical interpretation, while only a subset of these were used to develop the model. Continuous variables are represented by a single entry, while categorical variables are encoded for each individual category. A positive v-test score indicates over-representation, and a negative v-test score indicates under-representation. Positive v-test scores for continuous variables (such as 'age') correspond to larger values on average for that cluster. All values shown possess a $p < 1e-8$, to show only the most significant variables while maintaining figure interpretability.



BMI, body mass index; BW, bandwidth; ECG, electrocardiogram; ED, end diastolic; EDW, end diastolic width; ES, end systolic; ESW, end systolic width; EDV, end diastolic volume; ESV, end systolic volume; PCI, percutaneous coronary intervention; QC, quality control; TAVR, tricuspid aortic valve replacement, TPD, total perfusion defect.; LVH, left ventricular hypertrophy.

Supplementary Figure 3: Kaplan-Meier curves for all-cause mortality by unsupervised learning clusters demonstrate strong risk stratification compared to quantitative percent ischemia in internal and external cohorts.

** indicates $p < 0.001$; * indicates $p < 0.05$; ns indicates $p \geq 0.05$; TPD, total perfusion defect.



Supplementary Table 1: Parameters used for unsupervised cluster analysis.

Feature Group	Feature Names
Clinical parameters (n=23)	Age Gender Height Weight Body Mass Index Hypertension Diabetes Mellitus Dyslipidemia Family History of Coronary Artery Disease Smoking Anginal Presenting Symptoms Resting Heart Rate Resting Blood Pressure Systole Resting Blood Pressure Diastole Rest ECG Left Ventricular Hypertrophy Past Myocardial Infarction Peripheral Vascular Disease Previous PCI or Stents Previous TAVR Previous Coronary Artery Bypass Surgery Post Cardiac Transplant Past Other Open-Heart Surgery
Acquisition parameters (n=17)	Pharmacological or Exercise Stress Pharmacological Stress Agent Exercise Protocol Peak Stress Heart Rate Peak Stress Systolic Blood Pressure Peak Stress Diastolic Blood Pressure Exercise Duration Heart Rate Response ECG Response to Stress Clinical Response to stress Rest Dose Rest Isotope Stress Dose Imaging Protocols Magnitude of ST Deviation ST Deviation Direction Stress-Imaging Position
Quantitative imaging analysis parameters (n=24)	Stress Total Perfusion Deficit Stress Total Perfusion Deficit (combined 2 views) Stress End Diastolic Volume Stress End Diastolic Wall Volume Stress End Diastolic Length Stress Shape Index End Diastolic Stress End Systolic Volume Stress End Systolic Wall Volume Stress End Systolic Length Stress Shape Index End Systolic Stress Ejection Fraction Stress Thickening Abnormal Extent Stress Average Thickening Stress Motion Abnormal Extent Stress Average Motion Stress Volume Stress Phase Bandwidth Stress Perfusion Image Quality Control Flag Stress Gated Image Quality Control Flag Rest Total Perfusion Deficit Rest End Diastolic Volume Rest End Systolic Volume Rest Ejection Fraction Percent Ischemia

Supplementary Table 2: Demographic and imaging characteristics for all patients in the internal and external cohorts.

		All patients	Internal Cohort	External Cohort	P
N		9,221	4,774	4,447	-
Age (years)		68 (60, 75)	67 (60, 75)	68 (60, 76)	<0.001
Male		7,049 (76%)	3,704 (78%)	3,345 (75%)	0.008
BMI (kg/m ²)		27.7 (24.9, 31.0)	27.7 (25.1, 31.1)	27.5 (24.8, 30.9)	0.010
Hypertension		7,404 (80%)	3,658 (77%)	3,746 (84%)	<0.001
Diabetes Mellitus		3,266 (35%)	1,736 (36%)	1,530 (34%)	0.052
Dyslipidemia		6,952 (76%)	4,067 (85%)	2,885 (65%)	<0.001
Family History of CAD		3,098 (34%)	1,169 (24%)	1,929 (43%)	<0.001
Smoking		2,543 (28%)	594 (12%)	1,949 (44%)	<0.001
Previous MI		4,646 (50%)	2,166 (45%)	2,480 (56%)	<0.001
Previous Cardiac Surgery or Intervention	PCI	6,106 (66%)	3,409 (71%)	2,697 (61%)	<0.001
	CABG	2,720 (29%)	1,427 (30%)	1,293 (29%)	0.4
	TAVR	24 (0.3%)	21 (0.4%)	3 (<0.1%)	<0.001
	Other	62 (0.7%)	29 (0.6%)	33 (0.7%)	0.5
Presenting Symptoms	Asymptomatic	4,734 (54%)	2,595 (54%)	2,139 (54%)	<0.001
	Atypical Angina	2,123 (24%)	993 (21%)	1,130 (29%)	
	Non-Anginal	1,328 (15%)	839 (18%)	489 (12%)	
	Typical	553 (6.3%)	347 (7.3%)	206 (5.2%)	
Resting ECG Abnormal		5,296 (62%)	3,526 (74%)	1,770 (47%)	<0.001
Stress Type	Exercise	3,761 (41%)	1,987 (42%)	1,774 (40%)	<0.001
	Pharmacological	5,431 (58.9%)	2,787 (58.4%)	2,644 (28.7%)	
Clinical Response to Stress	Non-ischemic	6,625 (79%)	3,196 (76%)	3,429 (82%)	<0.001
	Equivocal	339 (4.0%)	187 (4.4%)	152 (3.7%)	
	Ischemic or Abnormal	1,420 (15.4%)	842 (17.6%)	578 (13.0%)	
ECG Response to Stress	Negative	5,490 (60%)	2,552 (54%)	2,938 (67%)	<0.001
	Borderline or Equivocal	453 (4.9%)	335 (7.0%)	118 (2.7%)	
	Positive	1,061 (12%)	513 (11%)	548 (12%)	
Heart Rate (BPM)	Rest	68 (60, 77)	68 (60, 77)	67 (60, 76)	0.056
	Stress Peak	107 (84, 137)	110 (88, 137)	102 (81, 136)	<0.001

Systolic Blood Pressure (mmHg)	Rest	130 (120, 146)	130 (120, 140)	134 (120, 150)	<0.001
	Stress Peak	146 (126, 170)	150 (130, 170)	144 (122, 170)	<0.001
Diastolic Blood Pressure (mmHg)	Rest	80 (71, 80)	80 (74, 80)	80 (70, 85)	0.048
	Stress Peak	80 (70, 80)	80 (70, 80)	78 (70, 84)	0.055
Location	Inpatient	938 (11%)	444 (9.3%)	494 (13%)	<0.001
	Outpatient	7,361 (87%)	4,285 (90%)	3,076 (83%)	
	Emergency	193 (2.3%)	43 (0.9%)	150 (4.0%)	

Number (%), median (Interquartile range), bold indicates $p < 0.05$.

BMI, body mass index; BPM, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; LVH, left ventricle hypertrophy; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; MI, myocardial infarction; TAVR, transcatheter aortic valve replacement.

Supplementary Table 3: Hyperparameter search parameters.

Parameter Name	Description	Range
Dimension Reduction Parameters		
n_components	dimensionality of ultimate embedding space	3
reducer	model for dimension reduction	UMAP
n_neighbors	controls size of local structure	5, 50, 100*
min_dist	minimum distance between embedded points	0.1, 0.15*, 0.25, 0.99
norm_embedding	Whether to normalize axes of embedding	True*, False
metric	evaluation criteria for distance between points	Euclidean, Minkowski, Canberra, Braycurtis*
Clustering Parameters		
cluster_option	method for clustering embedded points	hierarchical, kmeans*, gaussian mixture model
k	sweep range: number of clusters for any cluster_option	2,3*-10

* identifies the optimal parameter used for unsupervised cluster analysis.

Supplementary Table 4: Demographic and imaging characteristics for all patients and clusters in the external cohort.

		All patients	Cluster 1	Cluster 2	Cluster 3	P
N		4,447	1,799	2,213	435	-
Age (years)		68 (60, 76)	65 (57, 71)	71 (63, 77)	72 (64, 79)	<0.001
Male		3,345 (75%)	1,480 (82%)	1,586 (72%)	279 (64%)	<0.001
BMI (kg/m ²)		28 (25, 31)	28 (25, 31)	27 (25, 31)	29 (26, 33)	<0.001
Hypertension		3,746 (84%)	1,433 (80%)	1,930 (87%)	383 (88%)	<0.001
Diabetes Mellitus		1,530 (34%)	521 (29%)	811 (37%)	198 (46%)	<0.001
Dyslipidemia		2,885 (65%)	1,083 (60%)	1,536 (70%)	266 (61%)	<0.001
Family History of CAD		1,929 (43%)	901 (50%)	934 (42%)	94 (22%)	<0.001
Smoking		1,950 (44%)	721 (40%)	1,096 (50%)	132 (30%)	<0.001
Previous MI		2,480 (56%)	961 (53%)	1,312 (59%)	207 (48%)	<0.001
Previous Cardiac Surgery or Intervention	PCI	2,697 (61%)	1,145 (64%)	1,299 (59%)	253 (58%)	0.004
	CABG	252 (6.7%)	115 (8.1%)	112 (5.8%)	25 (5.9%)	0.029
	TAVR	3 (<0.1%)	0 (0%)	3 (0.1%)	0 (0%)	0.2
	Other	33 (0.7%)	4 (0.2%)	25 (1.1%)	4 (0.9%)	0.004
Presenting Symptoms	Asymptomatic	2,139 (54%)	855 (53%)	1,179 (59%)	105 (29%)	<0.001
	Atypical Angina	1,130 (29%)	458 (28%)	453 (23%)	219 (62%)	
	Non-Anginal	489 (12%)	214 (13%)	244 (12%)	31 (8.7%)	
	Typical	206 (5.2%)	84 (5.2%)	121 (6.1%)	1 (0.3%)	
Resting ECG Abnormal		1,770 (47%)	774 (47%)	913 (46%)	83 (59%)	0.017
Stress Type	Exercise	1,774 (40%)	1,749 (97%)	16 (0.7%)	9 (2.1%)	<0.001
	Pharmacological	2,644 (59%)	49 (2.7%)	2,169 (99%)	426 (98%)	
Clinical Response to Stress	Non-ischemic	3,429 (82%)	1,359 (78%)	1,884 (87%)	186 (72%)	<0.001
	Equivocal	152 (3.7%)	70 (4.0%)	47 (2.2%)	35 (13%)	
	Ischemic or Abnormal	578 (13%)	309 (18%)	230 (10.7%)	39 (15%)	
ECG Response to Stress	Negative	2,938 (67%)	974 (54%)	1,789 (82%)	175 (40%)	<0.001
	Borderline or Equivocal	118 (2.7%)	80 (4.4%)	16 (0.7%)	22 (5.1%)	
	Positive	548 (12%)	449 (25%)	75 (3.4%)	24 (5.5%)	
Heart Rate (BPM)	Rest	67 (60, 76)	69 (60, 79)	65 (58, 75)	69 (61, 77)	<0.001
	Stress Peak	102 (81, 136)	139 (129, 150)	83 (73, 96)	88 (77, 101)	

Systolic Blood Pressure (mmHg)	Rest	134 (120, 150)	130 (120, 144)	135 (122, 150)	140 (125, 154)	<0.001
	Stress Peak	144 (122, 170)	170 (150, 184)	128 (114, 144)	137 (117, 159)	
Diastolic Blood Pressure (mmHg)	Rest	80 (70, 85)	80 (70, 84)	80 (70, 85)	76 (69, 83)	<0.001
	Stress Peak	78 (70, 84)	82 (78, 90)	72 (65, 80)	72 (62, 80)	
Location	Inpatient	494 (13%)	117 (7.9%)	330 (17%)	47 (15%)	<0.001
	Outpatient	3,076 (83%)	1,323 (90%)	1,536 (79%)	217 (71%)	
	Emergency	150 (4.0%)	33 (2.2%)	74 (3.8)	43 (14%)	
Dose (MBq)	Rest	142 (7, 160)	149 (0, 155)	150 (18, 166)	18 (8, 19)	<0.001
	Stress	185 (25, 450)	185 (28, 450)	185 (29, 492)	9 (8, 23)	<0.001

Number (%), median (Interquartile range), bold indicates $p < 0.05$.

BMI, body mass index; BPM, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; LVH, left ventricle hypertrophy; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; MI, myocardial infarction; TAVR, transcatheter aortic valve replacement.

Supplementary Table 5: Quantitative imaging features for all clusters in the internal cohort.

	Cluster 1	Cluster 2	Cluster 3	P value Cluster 1 vs 3
N	2,005	1,580	1,189	-
Percent Ischemia (%)	2.8 [1.0, 5.7]	4.4 [2.3, 7.2]	2.8 [0.6, 6.8]	0.69
Stress Total Perfusion Deficit (%)	3.9 [1.4, 9.9]	6.4 [2.8, 14.2]	5.2 [2.0, 13.0]	<0.001
Rest Total Perfusion Deficit (%)	0.5 [0.0, 3.7]	1.2 [0.0, 6.9]	2.9 [0.7, 8.3]	<0.001
Stress End Diastolic Volume (ml)	85.9 [69.5, 107.0]	96.5 [75.9, 122.9]	87.5 [66.0, 119.3]	0.103
Stress End Diastolic Wall Volume (ml)	136.5 [121.1, 154.9]	138.8 [122.2, 161.0]	144.6 [123.4, 173.2]	<0.001
Stress End Diastolic Length (mm)	75.5 [69.9, 81.2]	77.1 [70.7, 83.2]	72.2 [64.6, 80.1]	<0.001
Stress Shape Index End Diastolic (%*0.01)	0.61 [0.57, 0.66]	0.64 [0.60, 0.69]	0.67 [0.61, 0.73]	<0.001
Stress End Systolic Volume (ml)	35.2 [25.1, 50.8]	41.9 [28.8, 61.9]	36.9 [23.8, 62.1]	0.020
Stress End Systolic Wall Volume (ml)	136.4 [121.1, 155.0]	138.8 [122.2, 161.0]	144.8 [123.3, 173.3]	<0.001
Stress End Systolic Length (mm)	68.6 [62.5, 74.9]	70.5 [63.6, 78.0]	66.0 [57.8, 74.4]	<0.001
Stress Shape Index End Systolic (%*0.01)	0.46 [0.42, 0.51]	0.48 [0.43, 0.54]	0.51 [0.45, 0.59]	<0.001
Stress Ejection Fraction (%)	58.6 [51.7, 64.4]	55.9 [47.2, 63.4]	57.1 [46.6, 65.4]	0.0016
Stress Thickening Abnormal Extent (%)	0.16 [0.0, 7.0]	2.6 [0.0, 14.4]	1.8 [0.0, 16.7]	<0.001
Stress Motion Abnormal Extent (%)	1.4 [0.0, 15.3]	4.1 [0.1, 27.8]	7.5 [0.4, 31.4]	<0.001
Stress Average Motion (mm)	6.7 [5.9, 7.5]	6.7 [5.6, 7.6]	6.4 [5.3, 7.5]	<0.001
Rest Ejection Fraction (%)	59.7 [52.3, 65.9]	59.5 [50.9, 67.1]	57.6 [45.7, 67.0]	<0.001
Rest End Diastolic Volume (ml)	90.8 [74.0, 111.6]	96.1 [76.3, 122.7]	78.0 [59.6, 108.6]	<0.001
Rest End Systolic Volume (ml)	36.1 [25.8, 51.6]	38.6 [25.9, 57.3]	33.0 [20.7, 56.5]	0.020
Transient Ischemic Dilation	0.95 [0.88, 1.0]	1.0 [0.94, 1.1]	1.0 [0.95, 1.1]	<0.001

Number (%), median (Interquartile range), bold indicates p<0.05.

Supplementary Table 6: Cardiovascular outcomes for all patients and clusters in the external cohort.

	All patients	Cluster 1	Cluster 2	Cluster 3	P
N	4,447	1,799	2,213	435	
Early revascularization *	401 (11%)	172 (13%)	176 (9.3%)	53 (15%)	<0.001
Revascularization	551 (15%)	233 (16%)	222 (11%)	95 (25%)	<0.001
Myocardial infarction	201 (5.6%)	52 (3.9%)	105 (5.6%)	44 (12%)	<0.001
Unstable angina	118 (4.4%)	48 (4.3%)	64 (4.2%)	6 (40%)	<0.001
PCI	243 (6.4%)	76 (5.3%)	112 (5.8%)	55 (13%)	<0.001
CABG	252 (6.7%)	115 (8.1%)	112 (5.8%)	25 (5.9%)	0.029
MACE	1,063 (24%)	365 (20%)	549 (25%)	149 (34%)	<0.001
All-cause mortality	312 (7.0%)	52 (2.9%)	206 (9.3%)	54 (12%)	<0.001

Number (%), bold indicates p<0.05.

* 90 days.

CABG, coronary artery bypass graft; MACE, major adverse cardiovascular events. PCI, percutaneous coronary intervention.

Supplementary Table 7: Disaggregation of MACE survival by gender in the internal cohort.

Cohort subset	Cluster 1		Cluster 2		Cluster 3		Global Log-Rank Significance
	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	
All (n=4,774)	2,005	reference	1,580	1.5 [1.4-1.7]	1,189	1.7 [1.5-1.9]	2.3e-17
Males (n=3,704)	1,667	reference	1,264	1.5 [1.3-1.8]	773	1.7 [1.5-1.9]	1.4e-14
Females (n=1,070)	338	reference	316	1.6 [1.2-2.2]	416	1.9 [1.5-2.6]	1.3e-5

Supplementary Table 8: Disaggregation of all-cause mortality survival by gender in the internal cohort.

Cohort subset	Cluster 1		Cluster 2		Cluster 3		Global Log-Rank Significance
	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	
All (n=4,774)	2,005	reference	1,580	3.1 [2.4-3.9]	1,189	4.7 [3.7-5.9]	4.5e-47
Males (n=3,704)	1,667	reference	1,264	2.8 [2.2-3.7]	773	4.5 [3.5-5.8]	2.2e-34
Females (n=1,070)	338	reference	316	4.8 [2.5-9.4]	416	7.0 [3.7-13.0]	8.9e-14

Supplementary Table 9: Disaggregation of MACE survival by gender in the external cohort.

Cohort subset	Cluster 1		Cluster 2		Cluster 3		Global Log-Rank Significance
	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	
All (n=4,447)	1,799	reference	2,213	1.2 [1.1-1.4]	435	4.2 [3.4-5.1]	9.9e-37
Males (n=3,345)	1,480	reference	1,586	1.2 [1.0-1.4]	279	4.2 [3.3-5.3]	6.8e-25
Females (n=1,102)	319	reference	627	1.6 [1.1-2.2]	156	5.4 [3.6-7.9]	3.4e-15

Supplementary Table 10: Disaggregation of all-cause mortality survival by gender in the external cohort.

Cohort subset	Cluster 1		Cluster 2		Cluster 3		Global Log-Rank Significance
	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	
All (n=4,447)	1,799	reference	2,213	3.3 [2.5-4.5]	435	5.9 [4.0-8.6]	8.9e-24
Males (n=3,345)	1,480	reference	1,586	3.3 [2.3-4.7]	279	6.1 [3.9-9.6]	1.0e-17
Females (n=1,102)	319	reference	627	3.2 [1.7-6.1]	156	5.2 [2.5-10.8]	6.0e-06

Supplementary Table 11: MACE survival by site in the internal cohort.

Internal Cohort Site	Assuta		Brigham and Women's		Cedars-Sinai		Oregon		Global Log-Rank Significance
	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	
Patients (n=4,774)	2,773	reference	759	0.7 [0.6-0.9]	803	1.2 [1.0-1.3]	439	1.2 [1.0-1.4]	2.5e-7

Supplementary Table 12: All-cause mortality survival by site in the internal cohort.

Internal Cohort Site	Assuta		Brigham and Women's		Cedars-Sinai		Oregon		Global Log-Rank Significance
	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	N	Hazard Ratio	
Patients (n=4,774)	2,773	reference	759	0.7 [0.4-1.3]	803	1.7 [1.1-2.7]	439	2.0 [1.3-3.1]	1.5e-4