

Supplementary Information

Supplementary Table 1. Significance testing of C-index values between all model pairs. Relevant to Figure 1A.

Model A	Model B	C-index (95% CI), Model A	C-index (95% CI), Model B	p-value (paired)
Age	CHIP+Lab+Age	0.72 (0.69–0.75)	0.78 (0.74–0.82)	0.002
Age	IMF+Age	0.72 (0.69–0.75)	0.79 (0.75–0.84)	<0.001
Age	IMF+CHIP+Age	0.72 (0.69–0.75)	0.79 (0.76–0.83)	<0.001
Age	IMF+CHIP+Lab+Age	0.72 (0.69–0.75)	0.82 (0.78–0.86)	<0.001
Age	IMF+Lab+Age	0.72 (0.69–0.75)	0.82 (0.78–0.86)	<0.001
Age	Lab+Age	0.72 (0.69–0.75)	0.78 (0.73–0.82)	0.001
Age	SMART2	0.72 (0.69–0.75)	0.74 (0.69–0.78)	0.397
CHIP+Lab+Age	IMF+Age	0.78 (0.74–0.82)	0.79 (0.75–0.84)	0.341
CHIP+Lab+Age	IMF+CHIP+Age	0.78 (0.74–0.82)	0.79 (0.76–0.83)	0.296
CHIP+Lab+Age	IMF+CHIP+Lab+Age	0.78 (0.74–0.82)	0.82 (0.78–0.86)	0.010
CHIP+Lab+Age	IMF+Lab+Age	0.78 (0.74–0.82)	0.82 (0.78–0.86)	0.012
CHIP+Lab+Age	Lab+Age	0.78 (0.74–0.82)	0.78 (0.73–0.82)	0.918
CHIP+Lab+Age	SMART2	0.78 (0.74–0.82)	0.74 (0.69–0.78)	0.060
IMF+Age	IMF+CHIP+Age	0.79 (0.75–0.84)	0.79 (0.76–0.83)	0.993
IMF+Age	IMF+CHIP+Lab+Age	0.79 (0.75–0.84)	0.82 (0.78–0.86)	<0.001
IMF+Age	IMF+Lab+Age	0.79 (0.75–0.84)	0.82 (0.78–0.86)	<0.001
IMF+Age	Lab+Age	0.79 (0.75–0.84)	0.78 (0.73–0.82)	0.288
IMF+Age	SMART2	0.79 (0.75–0.84)	0.74 (0.69–0.78)	0.006
IMF+CHIP+Age	IMF+CHIP+Lab+Age	0.79 (0.76–0.83)	0.82 (0.78–0.86)	0.005
IMF+CHIP+Age	IMF+Lab+Age	0.79 (0.76–0.83)	0.82 (0.78–0.86)	0.006
IMF+CHIP+Age	Lab+Age	0.79 (0.76–0.83)	0.78 (0.73–0.82)	0.306
IMF+CHIP+Age	SMART2	0.79 (0.76–0.83)	0.74 (0.69–0.78)	0.002
IMF+CHIP+Lab+Age	IMF+Lab+Age	0.82 (0.78–0.86)	0.82 (0.78–0.86)	0.617
IMF+CHIP+Lab+Age	Lab+Age	0.82 (0.78–0.86)	0.78 (0.73–0.82)	0.003
IMF+CHIP+Lab+Age	SMART2	0.82 (0.78–0.86)	0.74 (0.69–0.78)	<0.001
IMF+Lab+Age	Lab+Age	0.82 (0.78–0.86)	0.78 (0.73–0.82)	0.003
IMF+Lab+Age	SMART2	0.82 (0.78–0.86)	0.74 (0.69–0.78)	<0.001
Lab+Age	SMART2	0.78 (0.73–0.82)	0.74 (0.69–0.78)	0.078

Supplementary Table 2. Cox regression coefficients and hazard ratios (HRs) for all indexed models. HRs correspond to a 1-SD increase in standardized predictors. IMF features are represented by principal components. Coefficients are reported for transparency and are not intended for direct individual-level risk calculation without validation. Relevant to Figure 1A.

Model	Predictor	HR (95% CI)	β Coefficient (log HR)
Age	Age	1.906 (1.606–2.261)	0.645
CHIP+Lab+Age	Age	1.632 (1.361–1.957)	0.490
	CHIP	1.202 (0.885–1.632)	0.184
	Creatine kinase	1.028 (0.938–1.125)	0.027
	CRP	1.182 (1.064–1.312)	0.167
	Total cholesterol	0.946 (0.751–1.192)	-0.055
	GFR (MDRD)	0.835 (0.699–0.998)	-0.180
	HDL-C	0.956 (0.808–1.132)	-0.045
	Hemoglobin	0.909 (0.755–1.095)	-0.095
	Hematocrit	0.899 (0.746–1.083)	-0.107
	Creatinine	1.132 (1.029–1.245)	0.124
	LDL-C	1.026 (0.824–1.277)	0.026
	Leukocytes	1.151 (1.038–1.276)	0.141
	MCV	1.008 (0.875–1.161)	0.008
	RDW	1.355 (1.185–1.548)	0.304
	Thrombocytes	0.884 (0.759–1.030)	-0.123
	Triglycerides	0.958 (0.801–1.147)	-0.043
	Troponin T	1.019 (0.901–1.152)	0.019
IMF+Age	Age	1.745 (1.458–2.089)	0.557
	PC1	1.148 (1.003–1.313)	0.138
	PC2	0.970 (0.840–1.119)	-0.031
	PC3	1.496 (1.323–1.693)	0.403
	PC4	1.092 (0.954–1.250)	0.088
	PC5	1.074 (0.935–1.234)	0.072
	PC6	0.991 (0.863–1.138)	-0.009
	PC7	1.013 (0.897–1.144)	0.013
	PC8	0.912 (0.776–1.071)	-0.092
	PC9	0.994 (0.870–1.137)	-0.006
	PC10	0.976 (0.854–1.117)	-0.024
	PC11	0.873 (0.751–1.015)	-0.136
	PC12	0.947 (0.821–1.093)	-0.055
	PC13	0.792 (0.686–0.915)	-0.233
	PC14	1.062 (0.916–1.232)	0.060
	PC15	1.029 (0.893–1.185)	0.028
	PC16	0.911 (0.790–1.049)	-0.094
	PC17	1.079 (0.940–1.238)	0.076
	PC18	1.002 (0.886–1.134)	0.002
	PC19	0.983 (0.857–1.126)	-0.018
	PC20	1.027 (0.901–1.171)	0.027
	PC21	1.040 (0.909–1.189)	0.039
	PC22	1.225 (1.066–1.408)	0.203
	PC23	0.988 (0.862–1.133)	-0.012
	PC24	1.221 (1.060–1.406)	0.200
IMF+CHIP+Age	Age	1.718 (1.434–2.057)	0.541
	CHIP	1.285 (0.950–1.739)	0.251
	PC1	1.153 (1.007–1.320)	0.143
	PC2	0.970 (0.840–1.120)	-0.031

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Supplementary Table 2. Cox regression coefficients and hazard ratios (HRs) for all indexed models.

Model	Predictor	HR (95% CI)	β Coefficient (log HR)
	PC3	1.479 (1.306–1.674)	0.391
	PC4	1.082 (0.945–1.240)	0.079
	PC5	1.083 (0.942–1.245)	0.080
	PC6	0.992 (0.863–1.139)	-0.008
	PC7	1.011 (0.895–1.141)	0.011
	PC8	0.915 (0.779–1.074)	-0.089
	PC9	0.990 (0.865–1.132)	-0.010
	PC10	0.969 (0.847–1.109)	-0.031
	PC11	0.872 (0.749–1.016)	-0.136
	PC12	0.951 (0.823–1.098)	-0.050
	PC13	0.788 (0.681–0.912)	-0.238
	PC14	1.064 (0.917–1.234)	0.062
	PC15	1.026 (0.891–1.183)	0.026
	PC16	0.908 (0.788–1.046)	-0.096
	PC17	1.075 (0.937–1.234)	0.072
	PC18	1.001 (0.885–1.132)	0.001
	PC19	0.983 (0.858–1.126)	-0.017
	PC20	1.019 (0.893–1.163)	0.019
	PC21	1.044 (0.911–1.197)	0.043
	PC22	1.221 (1.063–1.404)	0.200
	PC23	0.985 (0.859–1.130)	-0.015
	PC24	1.215 (1.053–1.401)	0.195
IMF+CHIP+Lab+Age	Age	1.599 (1.325–1.930)	0.470
	CHIP	1.117 (0.815–1.531)	0.111
	Creatine kinase	1.022 (0.940–1.111)	0.022
	CRP	1.163 (1.040–1.301)	0.151
	Total cholesterol	0.942 (0.743–1.193)	-0.060
	GFR (MDRD)	0.893 (0.738–1.081)	-0.113
	HDL-C	0.972 (0.808–1.171)	-0.028
	Hemoglobin	0.921 (0.758–1.119)	-0.082
	Hematocrit	0.914 (0.752–1.109)	-0.090
	Creatinine	1.127 (1.017–1.249)	0.119
	LDL-C	0.988 (0.788–1.239)	-0.012
	Leukocytes	1.163 (1.042–1.298)	0.151
	MCV	1.040 (0.898–1.206)	0.040
	RDW	1.296 (1.126–1.493)	0.260
	Thrombocytes	0.883 (0.754–1.035)	-0.124
	Triglycerides	1.030 (0.844–1.257)	0.030
	Troponin T	0.986 (0.867–1.121)	-0.014
	PC1	1.149 (0.999–1.321)	0.139
	PC2	0.981 (0.834–1.153)	-0.019
	PC3	1.270 (1.102–1.464)	0.239
	PC4	1.042 (0.899–1.207)	0.041
	PC5	1.048 (0.907–1.211)	0.046
	PC6	1.001 (0.869–1.152)	0.001
	PC7	0.906 (0.788–1.041)	-0.099
	PC8	0.891 (0.741–1.073)	-0.115
	PC9	0.993 (0.862–1.143)	-0.007
	PC10	0.979 (0.849–1.128)	-0.022

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Supplementary Table 2. Cox regression coefficients and hazard ratios (HRs) for all indexed models.

Model	Predictor	HR (95% CI)	β Coefficient (log HR)
	PC11	0.852 (0.730–0.994)	-0.160
	PC12	0.970 (0.836–1.124)	-0.031
	PC13	0.827 (0.714–0.959)	-0.189
	PC14	1.009 (0.863–1.179)	0.009
	PC15	1.013 (0.874–1.174)	0.013
	PC16	0.884 (0.765–1.022)	-0.123
	PC17	1.027 (0.890–1.184)	0.026
	PC18	0.959 (0.846–1.086)	-0.042
	PC19	1.014 (0.881–1.167)	0.014
	PC20	1.009 (0.882–1.154)	0.009
	PC21	1.017 (0.884–1.171)	0.017
	PC22	1.185 (1.028–1.367)	0.170
	PC23	0.998 (0.869–1.146)	-0.002
	PC24	1.216 (1.050–1.408)	0.196
	IMF+Lab+Age		
	Age	1.605 (1.330–1.936)	0.473
	Creatine kinase	1.023 (0.940–1.112)	0.022
	CRP	1.163 (1.040–1.301)	0.151
	Total cholesterol	0.940 (0.742–1.191)	-0.062
	GFR (MDRD)	0.891 (0.737–1.078)	-0.115
	HDL-C	0.972 (0.807–1.171)	-0.028
	Hemoglobin	0.920 (0.757–1.118)	-0.083
	Hematocrit	0.912 (0.751–1.107)	-0.092
	Creatinine	1.122 (1.013–1.243)	0.115
	LDL-C	0.987 (0.787–1.237)	-0.013
	Leukocytes	1.165 (1.044–1.300)	0.153
	MCV	1.039 (0.897–1.204)	0.039
	RDW	1.308 (1.138–1.503)	0.268
	Thrombocytes	0.882 (0.752–1.033)	-0.126
	Triglycerides	1.028 (0.842–1.254)	0.027
	Troponin T	0.989 (0.869–1.124)	-0.011
	PC1	1.148 (0.999–1.320)	0.138
	PC2	0.979 (0.833–1.151)	-0.021
	PC3	1.275 (1.106–1.469)	0.243
	PC4	1.043 (0.900–1.208)	0.042
	PC5	1.045 (0.904–1.207)	0.044
	PC6	1.001 (0.869–1.152)	0.001
	PC7	0.905 (0.788–1.040)	-0.100
	PC8	0.890 (0.739–1.071)	-0.117
	PC9	0.995 (0.864–1.146)	-0.005
	PC10	0.983 (0.854–1.132)	-0.017
	PC11	0.852 (0.731–0.994)	-0.160
	PC12	0.968 (0.835–1.122)	-0.032
	PC13	0.829 (0.717–0.960)	-0.187
	PC14	1.008 (0.862–1.177)	0.008
	PC15	1.014 (0.875–1.175)	0.014
	PC16	0.885 (0.766–1.023)	-0.122
	PC17	1.025 (0.889–1.182)	0.025
	PC18	0.959 (0.846–1.087)	-0.042
	PC19	1.015 (0.882–1.169)	0.015

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Supplementary Table 2. Cox regression coefficients and hazard ratios (HRs) for all indexed models.

Model	Predictor	HR (95% CI)	β Coefficient (log HR)
	PC20	1.011 (0.884–1.157)	0.011
	PC21	1.015 (0.883–1.167)	0.015
	PC22	1.188 (1.030–1.370)	0.172
	PC23	1.001 (0.873–1.149)	0.001
	PC24	1.219 (1.054–1.409)	0.198
Lab+Age	Age	1.646 (1.372–1.974)	0.498
	Creatine kinase	1.027 (0.936–1.127)	0.027
	CRP	1.182 (1.065–1.312)	0.167
	Total cholesterol	0.943 (0.749–1.188)	-0.059
	GFR (MDRD)	0.834 (0.698–0.996)	-0.182
	HDL-C	0.954 (0.806–1.129)	-0.047
	Hemoglobin	0.905 (0.751–1.090)	-0.100
	Hematocrit	0.896 (0.743–1.080)	-0.110
	Creatinine	1.125 (1.023–1.236)	0.117
	LDL-C	1.025 (0.824–1.276)	0.025
	Leukocytes	1.153 (1.040–1.279)	0.143
	MCV	1.007 (0.874–1.160)	0.007
	RDW	1.375 (1.206–1.568)	0.318
	Thrombocytes	0.881 (0.756–1.027)	-0.127
	Triglycerides	0.955 (0.797–1.143)	-0.047
	Troponin T	1.023 (0.904–1.157)	0.023
SMART2	SMART2	1.778 (1.583–1.997)	0.576

SMART2 model	IMF+Age model			Row total, n
	Less than 25%	25 to 30%	Greater than 30%	
Less than 25%	516; 10.0% (5.0%-19.5%)	143; 26.1% (12.6%-49.2%)	76; 41.9% (24.3%-65.3%)	735
25 to 30%	142; 9.2% (4.3%-19.0%)	150; 19.5% (10.5%-34.5%)	122; 65.7% (44.5%-85.6%)	414
Greater than 30%	33; 17.1% (3.5%-62.4%)	54; 19.2% (10.3%-34.1%)	105; 63.9% (46.5%-80.9%)	192
Column total, n	691	347	303	1,341

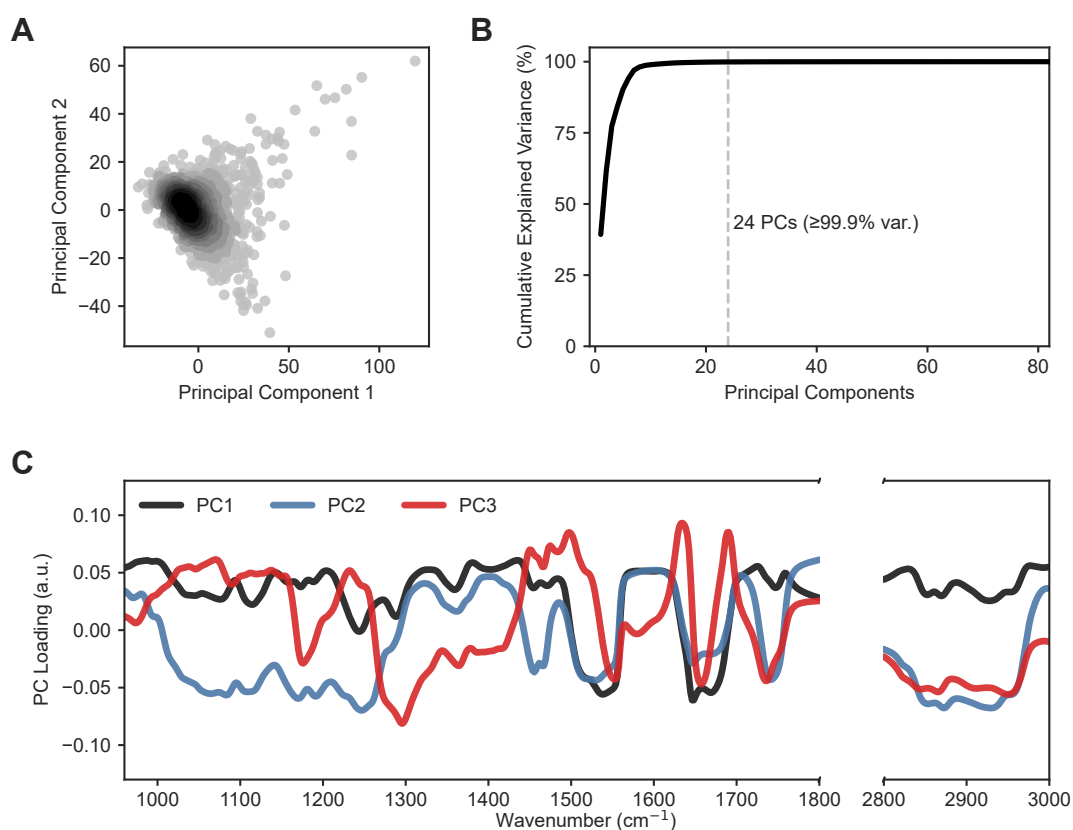
Supplementary Table 3. Reclassification between the SMART2 model and IMF+Age model at 10 years using the category-based net reclassification improvement (NRI) method. Each cell reports the number of participants (n) and the observed 10-year event probability estimated with the Kaplan-Meier method, followed by 95% confidence intervals. Categories are based on predicted absolute 10-year risk: Less than 25%, 25 to 30%, and Greater than 30%. Rows show categories assigned by the SMART2 model; columns show categories assigned by the IMF+Age model.

	Low			Moderate			High		
	ALL	CHIP+	CHIP–	ALL	CHIP+	CHIP–	ALL	CHIP+	CHIP–
N	690	229	461	376	160	216	275	155	120
Age (years)	67.0 ± 7.7	66.9 ± 7.8	67.0 ± 7.6	77.3 ± 4.9	76.9 ± 5.3	77.7 ± 4.5	82.0 ± 4.5	82.2 ± 4.3	81.8 ± 4.8
Gender = M	540 (78.3%)	172 (75.1%)	368 (79.8%)	282 (75.0%)	123 (76.9%)	159 (73.6%)	198 (72.0%)	115 (74.2%)	83 (69.2%)
BMI (kg/m ²)	27.8 ± 4.8	27.8 ± 4.9	27.8 ± 4.7	27.3 ± 4.5	27.5 ± 4.4	27.1 ± 4.5	26.8 ± 4.2	26.8 ± 4.0	26.6 ± 4.5
Diabetes	151 (21.9%)	52 (22.7%)	99 (21.5%)	105 (27.9%)	47 (29.4%)	58 (26.9%)	79 (28.7%)	50 (32.3%)	29 (24.2%)
Hypertension	584 (84.6%)	192 (83.8%)	392 (85.0%)	329 (87.5%)	137 (85.6%)	192 (88.9%)	249 (90.5%)	141 (91.0%)	108 (90.0%)
Hyperlipidemia	622 (90.1%)	202 (88.2%)	420 (91.1%)	331 (88.0%)	142 (88.8%)	189 (87.5%)	241 (87.6%)	138 (89.0%)	103 (85.8%)
COPD	28 (4.1%)	11 (4.8%)	17 (3.7%)	20 (5.4%)	12 (7.6%)	8 (3.7%)	18 (6.6%)	12 (7.8%)	6 (5.0%)
Nicotine intake	306 (44.3%)	106 (46.3%)	200 (43.4%)	132 (35.1%)	65 (40.6%)	67 (31.0%)	82 (29.8%)	49 (31.6%)	33 (27.5%)
History of MI	177 (25.7%)	51 (22.3%)	126 (27.3%)	92 (24.5%)	45 (28.1%)	47 (21.8%)	66 (24.0%)	36 (23.2%)	30 (25.0%)
Family history of CAD	234 (33.9%)	85 (37.1%)	149 (32.3%)	86 (22.9%)	41 (25.6%)	45 (20.8%)	42 (15.3%)	27 (17.4%)	15 (12.5%)
Vessels affectede>1	465 (67.4%)	148 (64.6%)	317 (68.8%)	278 (73.9%)	120 (75.0%)	158 (73.1%)	217 (78.9%)	122 (78.7%)	95 (79.2%)
Left ventricular function<50%	194 (28.1%)	75 (32.8%)	119 (25.8%)	125 (33.2%)	61 (38.1%)	64 (29.6%)	111 (40.4%)	55 (35.5%)	56 (46.7%)
Atrial fibrillation	25 (3.7%)	6 (2.6%)	19 (4.2%)	33 (8.9%)	13 (8.2%)	20 (9.3%)	41 (15.0%)	22 (14.3%)	19 (15.8%)
RDW (fl)	42.9 ± 3.1	43.4 ± 3.3	42.7 ± 3.1	45.0 ± 3.8	45.5 ± 4.5	44.7 ± 3.1	48.5 ± 5.2	49.1 ± 5.9	47.7 ± 4.2
Creatinine (mg/dl)	1.00 ± 0.21	0.99 ± 0.23	1.00 ± 0.20	1.10 ± 0.26	1.09 ± 0.26	1.11 ± 0.26	1.33 ± 0.65	1.27 ± 0.38	1.40 ± 0.88
hsCRP (mg/l)	4.2 ± 12.9	5.9 ± 19.2	3.3 ± 8.0	4.9 ± 16.5	4.0 ± 7.5	5.5 ± 20.8	7.3 ± 14.6	7.5 ± 16.0	7.0 ± 12.7
Total cholesterol (mg/dl)	168.9 ± 48.5	163.5 ± 50.4	171.6 ± 47.4	159.0 ± 41.9	155.5 ± 40.0	161.5 ± 43.2	154.1 ± 42.3	148.9 ± 36.5	160.7 ± 48.2
Hematocrit (l/l)	0.41 ± 0.05	0.41 ± 0.05	0.41 ± 0.05	0.40 ± 0.06	0.41 ± 0.07	0.40 ± 0.06	0.38 ± 0.05	0.37 ± 0.05	0.38 ± 0.05
Hemoglobin (g/dl)	14.1 ± 1.5	14.0 ± 1.6	14.1 ± 1.4	13.6 ± 1.7	13.6 ± 1.7	13.5 ± 1.7	12.6 ± 1.7	12.5 ± 1.8	12.8 ± 1.6
GFR (MDRD) (ml/min)	80.6 ± 18.4	79.8 ± 18.1	81.0 ± 18.5	68.9 ± 16.8	70.4 ± 17.3	67.8 ± 16.3	56.6 ± 18.6	56.9 ± 17.3	56.2 ± 20.2
Leukocytes (10 ⁹ /l)	7.2 ± 2.1	7.3 ± 2.4	7.2 ± 1.9	7.6 ± 2.4	7.8 ± 2.4	7.5 ± 2.4	8.1 ± 3.5	8.2 ± 4.1	7.9 ± 2.5
LDL-C (mg/dl)	98.0 ± 41.8	94.3 ± 42.2	99.9 ± 41.6	90.3 ± 38.3	87.9 ± 36.0	92.1 ± 39.9	85.5 ± 36.9	81.3 ± 32.4	91.0 ± 41.5
Thrombocytes (10 ⁹ /l)	218.1 ± 57.4	218.6 ± 56.6	217.9 ± 57.9	205.2 ± 60.1	207.0 ± 64.4	203.8 ± 56.8	210.6 ± 66.3	207.6 ± 65.3	214.3 ± 67.6
Creatine kinase (U/l)	129.4 ± 92.4	129.5 ± 85.0	129.4 ± 96.0	130.5 ± 110.7	128.5 ± 88.2	132.0 ± 124.9	134.8 ± 301.8	146.3 ± 381.1	119.9 ± 146.5
Troponin T (ng/l)	86.2 ± 327.5	89.2 ± 267.8	84.7 ± 353.8	122.3 ± 418.0	158.3 ± 525.0	95.6 ± 314.9	133.6 ± 689.3	146.1 ± 798.6	117.4 ± 517.8
Triglycerides (mg/dl)	140.7 ± 90.5	135.0 ± 79.6	143.5 ± 95.4	120.9 ± 69.9	122.3 ± 80.8	119.9 ± 60.7	113.2 ± 58.1	109.0 ± 54.7	118.6 ± 61.9
HDL-C (mg/dl)	52.5 ± 15.8	52.4 ± 15.9	52.6 ± 15.7	54.9 ± 16.1	53.9 ± 16.0	55.5 ± 16.1	54.0 ± 15.9	53.3 ± 15.5	54.9 ± 16.4
MCV (fl)	88.9 ± 4.2	89.6 ± 4.4	88.6 ± 4.1	89.8 ± 4.9	89.8 ± 5.0	89.8 ± 4.9	91.9 ± 5.7	91.8 ± 5.9	92.0 ± 5.4
ASXL1	30 (4.3%)	30 (13.1%)	0 (0.0%)	21 (5.6%)	20 (12.5%)	1 (0.5%)	24 (8.7%)	23 (14.8%)	1 (0.8%)
CALR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CBL	3 (0.4%)	3 (1.3%)	0 (0.0%)	4 (1.1%)	4 (2.5%)	0 (0.0%)	4 (1.5%)	4 (2.6%)	0 (0.0%)
DNMT3A	159 (23.0%)	125 (54.6%)	34 (7.4%)	99 (26.3%)	84 (52.5%)	15 (6.9%)	91 (33.1%)	80 (51.6%)	11 (9.2%)
JAK2	9 (1.3%)	8 (3.5%)	1 (0.2%)	4 (1.1%)	4 (2.5%)	0 (0.0%)	6 (2.2%)	6 (3.9%)	0 (0.0%)
MPL	2 (0.3%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.7%)	2 (1.3%)	0 (0.0%)
PPM1D	20 (2.9%)	14 (6.1%)	6 (1.3%)	14 (3.7%)	11 (6.9%)	3 (1.4%)	15 (5.5%)	15 (9.7%)	0 (0.0%)
SF3B1	6 (0.9%)	6 (2.6%)	0 (0.0%)	8 (2.1%)	6 (3.8%)	2 (0.9%)	13 (4.7%)	13 (8.4%)	0 (0.0%)
SRSF2	3 (0.4%)	3 (1.3%)	0 (0.0%)	8 (2.1%)	7 (4.4%)	1 (0.5%)	15 (5.5%)	14 (9.0%)	1 (0.8%)
TET2	83 (12.0%)	66 (28.8%)	17 (3.7%)	79 (21.0%)	68 (42.5%)	11 (5.1%)	70 (25.5%)	60 (38.7%)	10 (8.3%)
TP53	13 (1.9%)	12 (5.2%)	1 (0.2%)	20 (5.3%)	19 (11.9%)	1 (0.5%)	15 (5.5%)	13 (8.4%)	2 (1.7%)
U2AF1	2 (0.3%)	2 (0.9%)	0 (0.0%)	5 (1.3%)	4 (2.5%)	1 (0.5%)	8 (2.9%)	8 (5.2%)	0 (0.0%)
ZRSR2	3 (0.4%)	3 (1.3%)	0 (0.0%)	4 (1.1%)	4 (2.5%)	0 (0.0%)	6 (2.2%)	6 (3.9%)	0 (0.0%)
Death recorded	24 (3.5%)	10 (4.4%)	14 (3.0%)	44 (11.7%)	17 (10.6%)	27 (12.5%)	75 (27.3%)	47 (30.3%)	28 (23.3%)
Risk score (IMF+Age model)	0.51 ± 0.29	0.53 ± 0.29	0.50 ± 0.29	1.67 ± 0.36	1.66 ± 0.37	1.69 ± 0.36	4.05 ± 1.33	4.09 ± 1.34	4.01 ± 1.31

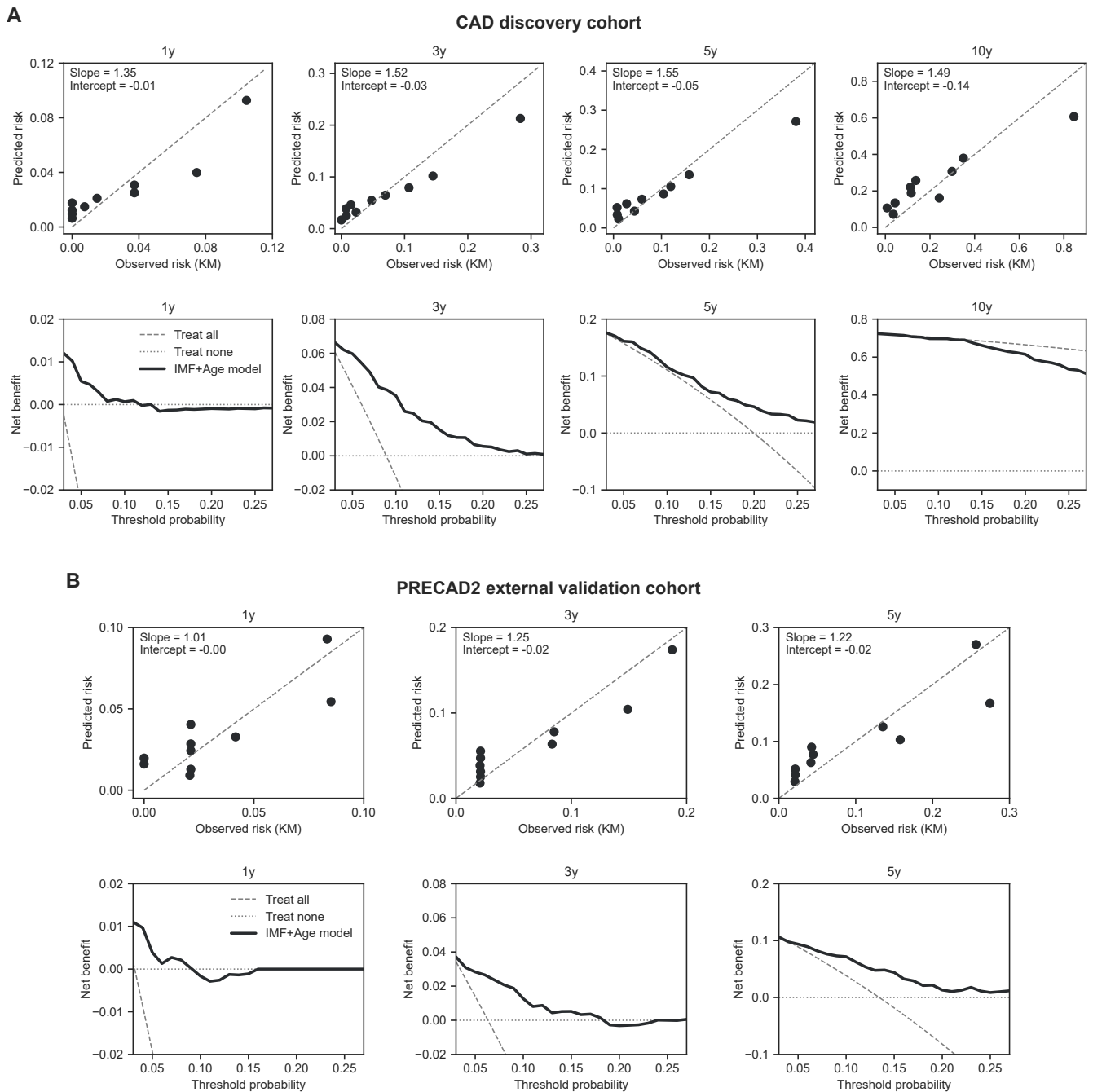
Supplementary Table 4. Baseline characteristics by IMF+Age-derived risk strata (Low, Moderate, High) in the CAD cohort, each further stratified by CHIP status (ALL, CHIP+, CHIP–). Clonal haematopoiesis mutations in the control arm are by definition <2% VAF. Continuous variables are presented as mean ± standard deviation; binary variables as count (percentage).

Classification	Group	N	Age (years)	Gender = M	BMI (kg/m ²)
ASXL1 classification	ASXL1+	75	74.7 ± 8.1	67 (89.3%)	27.6 ± 4.0
	ASXL1−	75	74.7 ± 8.1	67 (89.3%)	26.9 ± 4.4
TET2 classification	TET2+	232	75.9 ± 7.7	167 (72.3%)	27.2 ± 4.5
	TET2−	232	76.0 ± 7.7	167 (72.3%)	26.8 ± 4.4
DNMT3A classification	DNMT3A+	349	73.8 ± 9.1	258 (73.9%)	27.4 ± 4.7
	DNMT3A−	349	73.8 ± 9.0	258 (73.9%)	27.4 ± 4.5
CHIP (VAF ≥ 2%) classification	CHIP+	544	74.2 ± 9.1	410 (75.4%)	27.5 ± 4.5
	CHIP−	544	73.9 ± 8.7	410 (75.4%)	27.3 ± 4.6
CHIP (VAF ≥ 5%) classification	CHIP+	307	74.9 ± 9.2	235 (76.5%)	27.4 ± 4.4
	CHIP−	307	74.7 ± 9.0	235 (76.5%)	27.3 ± 4.7
CHIP (VAF ≥ 10%) classification	CHIP+	167	76.0 ± 9.4	133 (79.6%)	27.1 ± 3.8
	CHIP−	167	75.8 ± 9.2	133 (79.6%)	27.1 ± 4.9
CHIP (VAF ≥ 15%) classification	CHIP+	104	75.7 ± 9.9	90 (86.5%)	27.3 ± 3.7
	CHIP−	104	75.6 ± 9.8	90 (86.5%)	27.8 ± 5.3

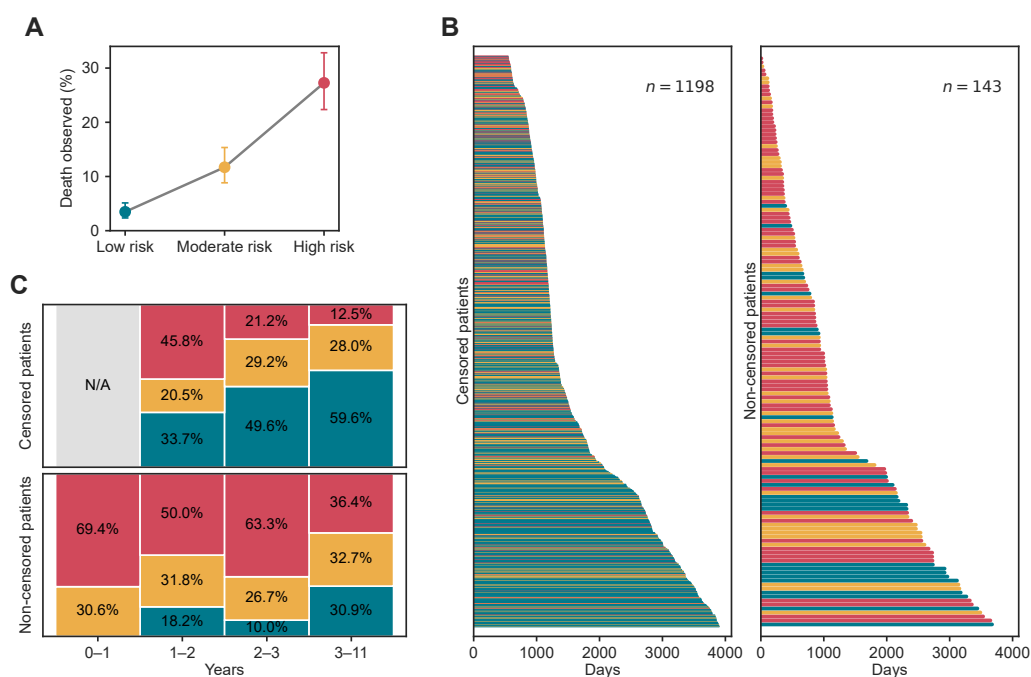
Supplementary Table 5. Characteristics of age-, gender-, and BMI-matched cohorts across different classification tasks. Relevant to Figure 2D.



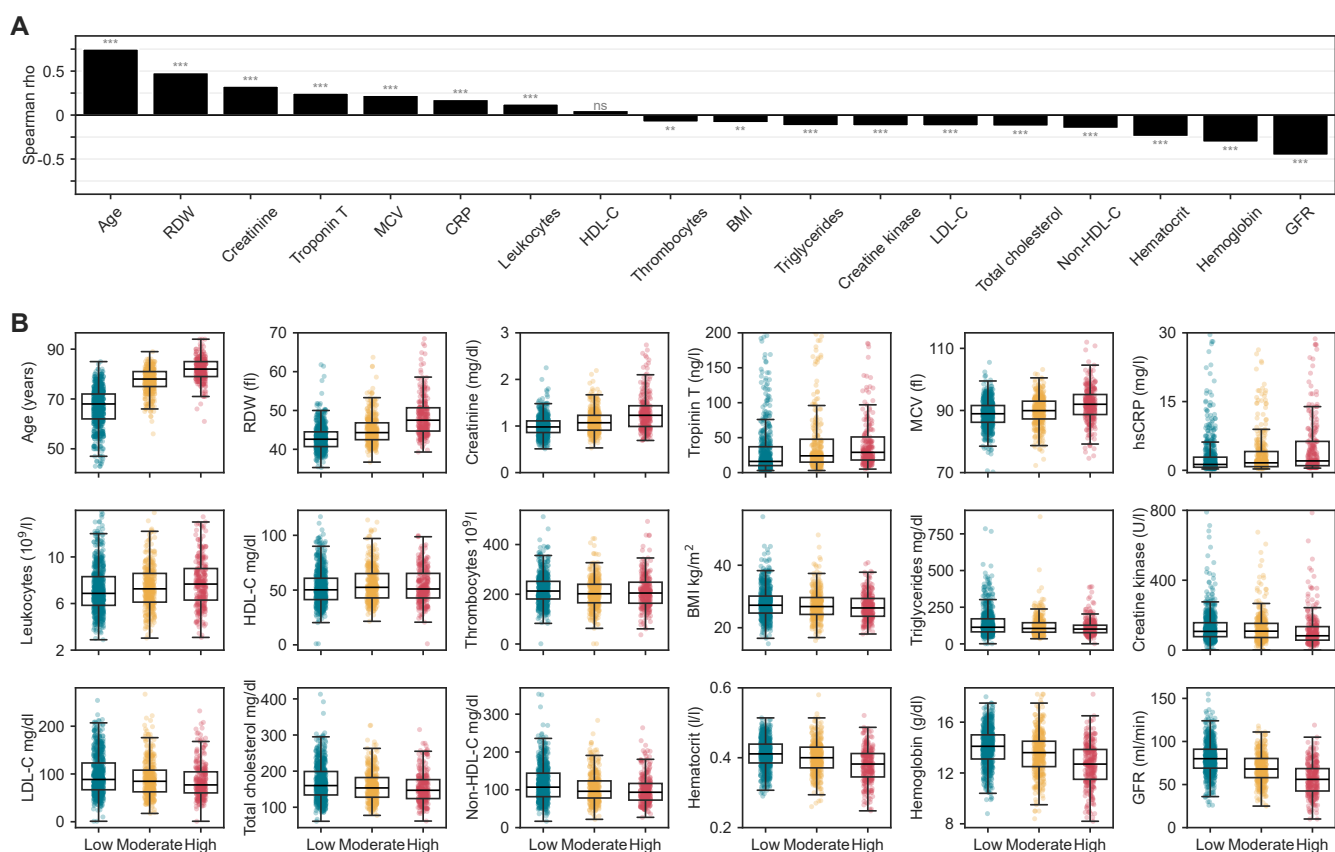
Supplementary Figure 1. Principal component analysis of plasma infrared molecular fingerprints (IMFs) in the CAD discovery cohort. **(A)** Scatter plot of the first two principal components (PC1 and PC2) derived from the IMFs, with kernel density shading indicating sample concentration. **(B)** Cumulative explained variance as a function of the number of principal components retained. A threshold of 99.9% cumulative variance was reached at 24 components (dashed line). **(C)** Spectral loading profiles of the first three principal components (PC1, PC2, PC3) across wavenumber feature space.



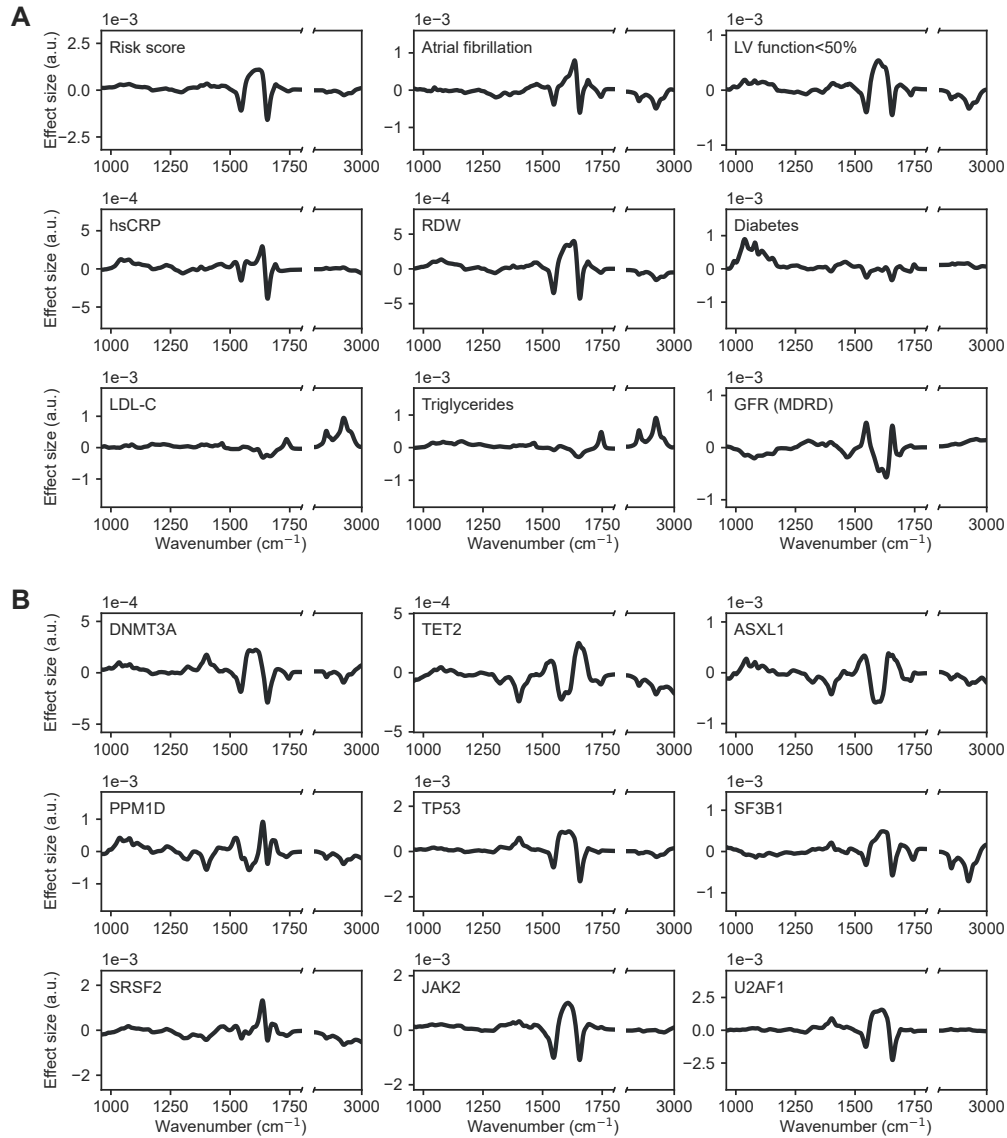
Supplementary Figure 2. Calibration and decision-curve analysis of the IMF+Age model across follow-up years. **(A)** Upper panels: Calibration plots at 1-, 3-, 5-, and 10-year follow-up, comparing predicted and observed mortality risk across 10 deciles of predicted probability. Dashed lines indicate perfect calibration. Lower panels: Decision-curve analysis at corresponding follow-up times, showing the net benefit of using the IMF+Age model to identify individuals above specified risk thresholds (5–25%) compared with “treat all” and “treat none” strategies. **(B)** Calibration and decision-curve plots in the external validation PRECAD2 cohort. The model trained on the discovery cohort was applied to the PRECAD2 cohort. 10-year follow-up is unavailable in the PRECAD2 cohort.



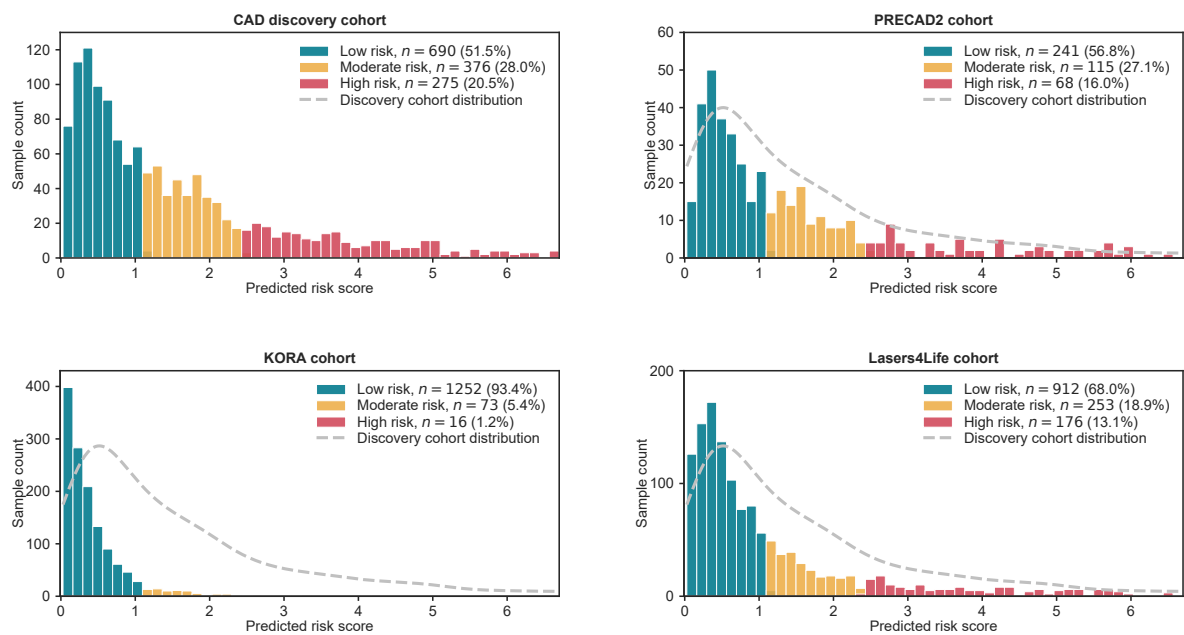
Supplementary Figure 3. Survival outcomes by model-derived risk strata in the CAD discovery cohort. **(A)** Percentage of observed deaths by risk group over the full follow-up period. Error bars represent the Wilson confidence intervals for each group. **(B)** Patient-level time-to-event durations. Each horizontal line represents a test-set individual, colored by the predicted risk group and ordered by follow-up duration. **(C)** Temporal composition of predicted risk strata among patients, aggregated into yearly intervals. Bars indicate the proportion of each risk group within each interval. Grey bar denotes the time interval with no samples, as individuals with no event and <1.5 follow-up years were excluded.



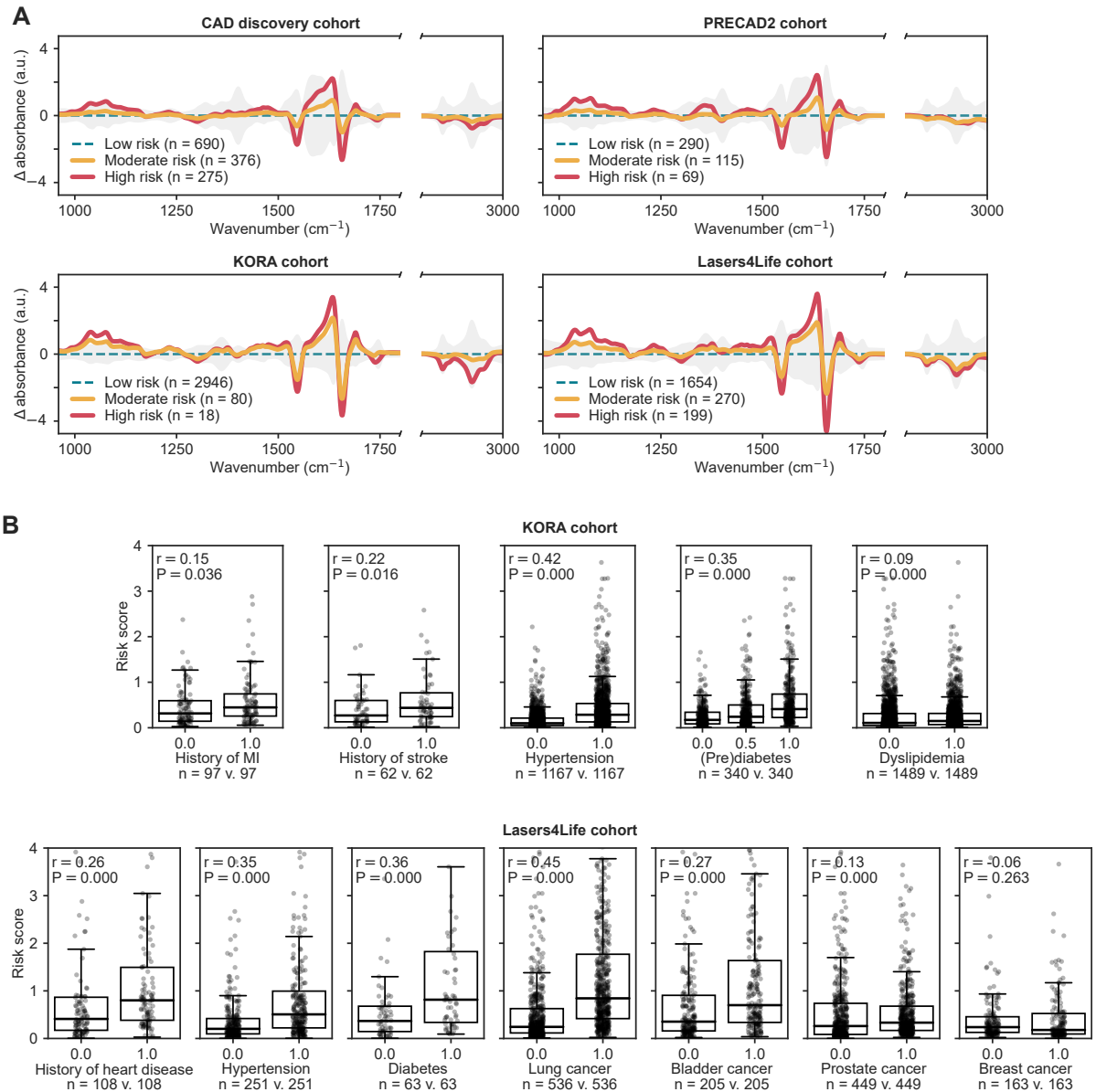
Supplementary Figure 4. Associations of age, BMI, and clinical laboratory parameters with IMF+Age-derived risk strata in the CAD cohort. **(A)** Spearman rank correlation between continuous clinical parameters and the model-derived risk strata in the CAD cohort. Bars represent correlation coefficients, with asterisks indicating significance (ns = not significant; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$). **(B)** Distribution of each parameter across low-, moderate-, and high-risk groups shown as boxplots with overlaid individual data points. Boxes indicate the interquartile range with median lines, and whiskers extend to 1.5x the interquartile range.



Supplementary Figure 5. Associations between infrared absorbance features and individual variables. Each patient characteristic was tested for its association with spectral absorbance values across all wavenumbers using univariate linear regression, after z-score standardization of the variables. The resulting regression coefficients (β_1) represent the change in absorbance per one standard deviation increase in the variable, forming an effect size spectrum across wavenumbers. **(A)** Spectral effect size profiles for the derived risk score and phenotypic outcomes. **(B)** Spectral effect size profiles for the top nine most prevalent CHIP mutations.



Supplementary Figure 6. Validation of risk model in age- and gender-matched sub-cohorts from independent studies. Risk strata were defined using the developed risk model (IMF+Age) in the discovery cohort (upper left) and applied to age- and gender-matched subsets of the PRECAD2 (upper right), KORA (lower left), and Lasers4Life (lower right) cohorts. Each CAD sample was pair-matched to one individual from each independent cohort. The dashed line shows the discovery cohort risk score distribution on an arbitrary y-axis for reference.



Supplementary Figure 7. External validation of the risk model across spectral and clinical features. **(A)** Differences in absorbance between group-averaged IMFs: moderate-risk minus low-risk (orange), and high-risk minus low-risk (red). Risk strata were defined using the developed risk model (IMF+Age; upper left panel) and applied to the external cohorts (remaining panels). Shaded region depicts the standard deviation across the spectral features of the low-risk stratum. **(B)** Distribution of diseases, phenotypes, and clinical characteristics in the KORA and Lasers4Life cohorts, with Spearman's rank correlation coefficients (r) and P values indicated. For all disease/condition groups, pair-matching was performed for age and gender. In the Lasers4Life cohort, individuals with any cancer diagnosis were excluded from all analyses except when assessing the targeted cancer.