Radiology: Cardiothoracic Imaging

ORIGINAL RESEARCH

Prediction of Major Adverse Coronary Events Using the Coronary Risk Score in Women

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Purpose: To establish a COronary Risk Score in WOmen (CORSWO) to predict major adverse coronary events (MACE).

Materials and Methods: This retrospective analysis included 2226 female individuals (mean age, 66.7 years ± 11.6 [SD]) from a cohort of 25 943 consecutive patients referred for clinical gated SPECT myocardial perfusion imaging (gSPECT MPI). During the follow-up (mean, 4 years ± 2.7) after gSPECT MPI, occurrence of MACE (unstable angina requiring hospitalization, nonfatal myocardial infarction, coronary revascularization, cardiac death) was assessed. The patients were divided into training (n = 1460) and validation (n = 766) groups. To obtain the predictor model, multiple Cox regression analyses were performed.

Results: In the training group, 148 female individuals had MACE (2.6% per year). The best model (area under the receiver operating characteristic curve [AUC]: 0.80 [95% CI: 0.74, 0.83]; Brier score: 0.08) to predict MACE in female individuals included the following variables: age older than 69 years (hazard ratio [HR]: 1.58, P = .01), diabetes mellitus (HR: 1.47, P = .03), pharmacologic test (HR: 1.63, P = .01), ST-segment depression (≥1 mm) (HR: 2.02, P < .001), myocardial ischemia greater than 5% (HR: 2.21, P < .001), perfusion defect at rest greater than 9% (HR: 1.96, P = .009), perfusion defect at stress greater than 6% (HR: 1.63, P = .03), and end-systolic volume index greater than 15 mL (HR: 2.04, P < .001). During validation, the model achieved moderate performance (AUC: 0.78 [95% CI: 0.70, 0.83]). CORSWO obtained from these variables allowed for stratification of female individuals into four risk levels: low (score: 0–3, HR: 1), moderate (score: 4–6, HR: 1.58), high (score: 7–11, HR: 4.13), and very high (score: >11, HR: 13.87). The high and very high risk levels (HR: 5.29) predicted MACE in female individuals, with excellent performance (AUC: 0.78 [95% CI: 0.72, 0.80]).

Conclusion: With clinical, stress test, and gSPECT MPI variables, CORSWO effectively stratified female individuals according to coronary risk and was able to detect those with high and very high risk.

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Coronary artery disease (CAD) continues to be the leading cause of death among female individuals in the United States (1), Latin America (2), Europe (3), Asia (4), and the Pacific countries (5). Despite multiple methods evaluated for coronary risk stratification in female individuals, including an exercise treadmill test (6), isotopic techniques (7–9), cardiac MRI (10), coronary CT angiography (11–13), and stress echocardiography (14), the assessment of CAD is still a challenge.

The presentation of CAD in female individuals is 7–10 years later when compared with male individuals and involves atypical symptoms (15,16). Female individuals are more likely to present with acute myocardial infarction (MI) without chest pain and have a higher mortality rate, especially among the younger age groups (17,18). In contrast, MI with epicardial coronary stenosis is the most important manifestation of CAD in male individuals. However, female individuals can present with myocardial ischemia with no obstructive CAD, caused by microvascular dysfunction, vasospastic disorders, or any other mechanisms, such as spontaneous coronary artery dissection (19).

Female individuals have often been underrepresented in cardiovascular studies, and few studies in cardiovascular medicine have addressed the issue of coronary risk focused on clinical and imaging outcomes in female individuals alone (8–14). Furthermore, among female individuals, there is an increase in the impact of traditional atherosclerotic cardiovascular disease risk factors, including diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, and physical inactivity (1). Recently, an American Heart Association presidential advisory was published explaining the critical need for research toward achieving substantial progress in the health and well-being of all female individuals (19). Thus, from a clinical point of view, coronary risk stratification by means of clinical variables and noninvasive, imaging-based techniques is important and necessary. Hence, this study aims to establish a COronary Risk Score in WOmen (CORSWO) to predict major adverse coronary events (MACE) in a large population-based series of female individuals.

Materials and Methods

Study Sample

This study complies with the Declaration of Helsinki and was reviewed and approved by the ethics committee of Vall d'He-

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Abbreviations

AIC = Akaike information criterion, AUC = area under the receiver operating characteristic curve, BIC = Bayesian information criterion, CAD = coronary artery disease, CORSWO = COronary Risk Score in WOmen, EDV = end-diastolic volume, ESV = end-systolic volume, gSPECT MPI = gated SPECT myocardial perfusion imaging, HR = hazard ratio, LASSO = least absolute shrinkage and selection operator, MACE = major adverse coronary events, MI = myocardial infarction, SDS = summed difference score, SRS = summed risk score, SSS = summed stress score

Summary

The COronary Risk Score in WOmen (ie, CORSWO) accurately stratified the risk for major adverse coronary events into four levels (low, moderate, high, and very high).

Key Points

- The coronary risk stratification tool COronary Risk Score in Women (CORSWO) includes multiple clinical, exercise, and imaging variables to predict major adverse coronary events in female individuals.
- This new risk score allows for the simple calculation of individual risk over a mean follow-up of 4 years, with an excellent capacity prediction (area under the receiver operating characteristic curve: 0.80).
- CORSWO allows the stratification of female individuals into four risk levels: low (hazard ratio [HR]: 1), moderate (HR: 1.6), high (HR: 4.2), and very high (HR: 3.9).

Keywords

SPECT, Cardiac, Coronary Arteries, Women, Risk Stratification, Cardiac Event, CORSWO, MACE, Gated SPECT

bron Hospital (registered as PR(AG)168.2012). This observational cohort study was conducted in a university reference hospital. Of 25 943 consecutive patients who underwent gated SPECT myocardial perfusion imaging (gSPECT MPI) between 2000 and 2018, 2226 female individuals were included in the study (Fig 1). Written informed consent was obtained from all patients prior to gSPECT MPI. Patients who underwent stress testing only were excluded to allow for evaluation of the alterations in myocardial perfusion at rest (summed rest score [SRS]) and the difference (summed difference score [SDS]) between stress (summed stress score [SSS]) and rest (SRS), as the best parameter that expresses myocardial ischemia is the SDS.

This study was a retrospective analysis of data extracted from a prospectively collected database. Every female individual included was between 40 and 93 years of age. All female individuals (n = 2226) had been referred to our Nuclear Cardiology Unit for risk stratification or evaluation of their disease, and they were randomly split into training (n = 1460) and validation (n = 766) groups.

gSPECT MPI

All 2226 patients underwent stress-rest gSPECT MPI: 1410 patients underwent subjective maximal exercise MPI; 407 patients underwent submaximal exercise plus pharmacologic test because of their inability to achieve five metabolic equivalents or 80% of predicted peak heart rate for their age; and 409 patients underwent only pharmacologic MPI on account of their inability to exercise due to very low functional capacity.

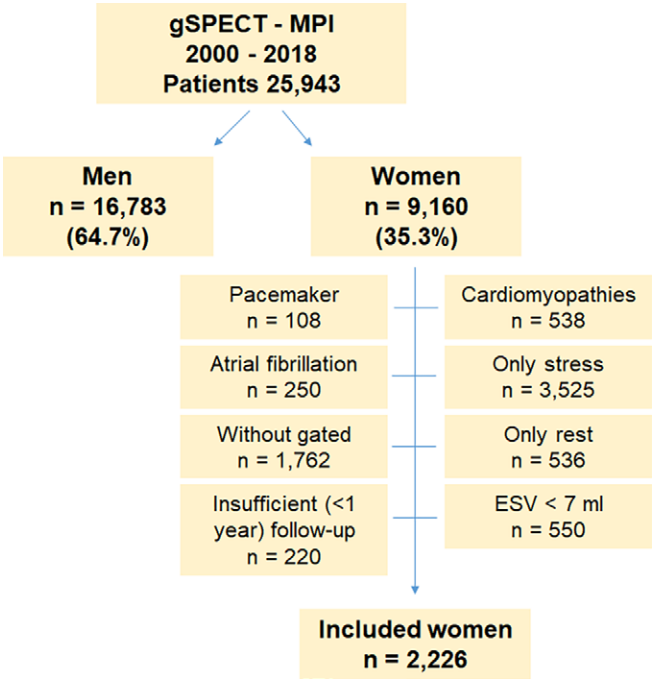


Figure 1: Flow diagram shows female individuals included in the study. ESV = end-systolic volume, gSPECT MPI = gated SPECT myocardial perfusion imaging.

The methods employed for gSPECT were the same methods employed in previous publications (20). CT attenuation correction was performed when the nuclear cardiologist considered it necessary.

A scintigraphic perfusion score ranging from 0 to 4 was assigned to each of the 17 segments in both stress (SSS) and rest (SRS) (0 = normal perfusion, 1 = mild hypoperfusion, 2 = moderate hypoperfusion, 3 = severe hypoperfusion, and 4 = no uptake). The SDS was calculated from the sum of the segmental difference scores between stress and rest scans. SSS, SRS, and SDS were converted to percent total myocardium (SSS%, SRS%, SDS%) by means of the following formula: summed scores/68 (maximum score = 4 · 17) × 100. The calculation of the left ventricular ejection fraction, end-diastolic volume (EDV) index, and end-systolic volume (ESV) index were performed automatically at rest gSPECT MPI by means of QGS software package (Cedars-Sinai Medical Center).

Clinical Outcomes

The minimum follow-up time was 1 year (maximum, 10 years), and the mean follow-up was 4 years ± 2.7 [SD] (median, 3.5 years [IQR: 1.4–6 years]). All patients were followed up in the hospital, and the follow-up information was obtained by clinical history. No patients were lost to follow-up. All patients were followed up for the occurrence of MACE (unstable angina, nonfatal MI, coronary revascularization, and cardiac death). The primary end point was the first occurrence of a composite of unstable angina, nonfatal MI, coronary revascularization, and cardiac death.

Statistical Analysis

All continuous data are expressed as means ± SDs, and all noncontinuous variables are expressed as percentages. Continuous variables were compared using the Student t test for unpaired

samples. Differences between proportions were compared using the χ^2 test. Fisher exact test was used when fewer than five patients were expected in any subgroup. Cutoff values for continuous variables were obtained by receiver operating characteristic curve analysis.

The population was divided into a training group (65.6%, *n* = 1460) and a validation group (34%, *n* = 766). In the training group, the variables for multivariable analysis were selected when they presented a *P* value less than or equal to .05 in the univariable analysis or when considered of clinical relevance.

This manuscript was analyzed with two different statistical analysis methods: least absolute shrinkage and selection operator (LASSO) regression analysis with 10-fold cross-validation (Fig S1B) and multivariate Cox regression analysis. Both methods obtained the same prediction capacity with equal areas under the receiver operating characteristic curve (AUC). The final model with LASSO regression analysis obtained 13 variables (Akaike information criterion [AIC]: 1862.3, Bayesian information criterion [BIC]: 1903.1, AUC: 0.79, and the final model with Cox regression analysis with eight variables (AIC: 1860.6, BIC: 1902.8, AUC: 0.79). Therefore, because molding with Cox regression was more parsimonious, the Cox regression method was chosen. Hence, the predictive model for MACE was constructed using multiple Cox regression analysis. Multivariable analysis was performed using both forward stepwise and backward variable selection techniques. The threshold for variable entry into models was *P* less than .05 and for variable removal was *P* greater than .10. Four models were analyzed (first model with clinical variables, second model with stress test variables, third model with rest-gated SPECT variables, and final model with the predictive variables obtained in previous models). We calculated the hazard ratio (HR) with 95% CIs for each variable and the Harrell C concordance statistic for all models. For each model, we calculated the probability of MACE for every patient in the training group, and with the coefficient of every variable obtained in that group, the probability of MACE in the validation group was calculated.

The Brier score was calculated in the training and validation groups. This score measures the total difference between the event and the forecast probability of that event as an average squared difference. As a benchmark, a perfect forecaster would have a Brier score of 0 and a perfect misforecaster would have a Brier score of 1.

Then, in the training group, a z-score was calculated by Cox regression analysis for every prognostic variable. Four risk levels of z-score were obtained according to MACE per patient per year: low risk (less than one MACE per year), moderate risk (one to two MACE per year), high risk (three to five MACE per year), and very high risk (more than five MACE per year). The warranty period for every risk level was calculated according to the methods used in previous studies (20). It was defined as the period during which patients remained at low risk (<1% events per year) (20).

The z-scores were also applied to the validation group, and the MACE per patient per year ratio of the four risk levels was compared between testing and validation groups. No missing data existed for the variables included in the prognostic score.

To compare the survival curves of the different risk levels, Cox regression analysis was used. HRs, 95% CIs, and statistical significance for each group in the model were determined. The proportional hazards assumption was tested in all Cox regression analyses. There was no evidence that the proportional hazards assumption was violated when the *P* value was less than .05 and when the plotted curves were parallel.

All statistical tests were two-sided. A *P* value less than .05 was considered to be indicative of statistical significance. Data were analyzed by STATA 18 (StataCorp).

Results

Study Sample Characteristics

During the follow-up (mean, 4 years ± 2.7), overall rates for mortality and MACE in the entire cohort (*n* = 2226; mean age, 66.7 years ± 11.6) were 6.7% (*n* = 218, 2.4% per year) and 6.6% (*n* = 220, 2.5% per year), respectively. Unstable angina occurred in 2.6% of patients (*n* = 57, 0.67% per year), nonfatal MI in 1.7% (*n* = 38, 0.44% per year), coronary revascularization in 2.9% (*n* = 64, 0.75% per year), and cardiac death in 4.3% (*n* = 95, 1.11% per year). Of the 64 patients who underwent coronary revascularization, 33 (51.56%) underwent early coronary revascularization (≤3 months after gSPECT MPI) and 31 (48.44%) underwent late coronary revascularization. The comparison of the baseline variables studied between the training and validation groups is represented in Table S1; nonsignificant results were observed.

Training Group

Baseline characteristics in the training group according to all-cause mortality and MACE are shown in Table 1A. The overall mortality and MACE rates in the training group (*n* = 1460) were 10.3% (*n* = 150, 2.5% per year) and 10.1% (*n* = 148, 2.6% per year), respectively. Four multivariable models were analyzed for the prediction of MACE.

In the first model with clinical variables (age > 69 years, obesity, hypertension, hypercholesterolemia, smoking, diabetes, previous MI, previous coronary revascularization, left bundle branch block, angina, dypsnea, treatment with β-blocker and/or nitrate), the independent predictors of MACE were as follows: diabetes (HR: 1.95 [95% CI: 1.36, 2.82], *P* < .001), nitrate use (HR: 1.72 [95% CI: 1.20, 2.47], *P* = .003), age older than 69 years (HR: 1.71 [95% CI: 1.18, 2.48], *P* = .004), and previous MI (HR: 1.62 [95% CI: 1.11, 2.39], *P* = .01) (Fig 2).

In the second model with stress test variables (exercise test, exercise test plus pharmacologic test, pharmacologic test, stress angina, and ST depression ≥ 1 mm), the independent predictive variables were: pharmacologic test (HR: 2.41 [95% CI: 1.67, 3.47], *P* < .001) and ST depression of 1 mm or greater (HR: 2.34 [95% CI: 1.59, 3.45], *P* < .001) (Fig 2).

In the third model with gSPECT MPI variables (SRS% > 9.6, SSS% > 6.6, SDS% > 5.2, EDV index > 38 mL, ESV index > 15 mL, and left ventricular ejection fraction < 50%), the independent predictive variables were: SRS% greater than 9.6 (HR: 2.14 [95% CI: 1.31, 3.51], *P* = .003), SSS% greater than 6.6 (HR: 1.96 [95% CI: 1.21, 3.17], *P* = .006), SDS% greater than 5.2 (HR: 2.65 [95% CI: 1.72, 4.08], *P* < .001), EDV index greater than 38 mL (HR: 0.52 [95% CI: 0.29, 0.91], *P* = .02), and ESV index greater than 15 mL (HR: 3.3 [95% CI: 1.81, 5.98], *P* < .001) (Fig 2).

Table 1: Baseline Clinical, Stress Test, and Gated SPECT Characteristics of Training and Validation Groups according to All-Cause Mortality and MACE

A. Training Group

Variables	Overall (n = 1460)	Alive (n = 1310)	All-Cause Mortality (n = 150)	P Value	Without MACE (n = 1312)	With MACE (n = 148)	P Value
Demographics							
Age (y)	66.7 ± 11.9	66.1 ± 11.8	72.7 ± 11.1	<.001	66.3 ± 11.9	70.8 ± 10.9	<.001
Age > 69 years	733 (50)	621 (47)	112 (75)	<.001	639 (49)	94 (64)	.001
Body surface (m^2)	1.8 ± 0.17	1.8 ± 0.18	1.8 ± 0.17	.99	1.8 ± 0.2	1.7 ± 1.6	.99
BMI	27.8 ± 4.6	27.8 ± 4.7	27.5 ± 3.9	.11	27.8 ± 4.4	27.8 ± 5.9	.96
Obesity (BMI ≥ 30)	340 (23)	309 (23)	31 (21)	.42	305 (23)	35 (24)	.91
Medical history							
Hypertension	964 (66)	855 (65.3)	109 (73)	.070	855 (65)	109 (74)	.04
Hypercholesterolemia	748 (51)	680 (52)	68 (45)	.13	663 (51)	85 (57)	.11
Smoking	188 (13)	177 (14)	11 (7)	.03	171 (13)	17 (12)	.59
Diabetes mellitus	329 (23)	257 (20)	72 (48)	<.001	265 (20)	64 (43)	<.001
CRF ≥ 1	1224 (84)	1094 (84)	130 (87)	.32	1090 (83)	134 (91)	.02
Previous MI	303 (21)	261 (20)	42 (28)	.02	251 (19)	52 (35)	<.001
Previous CR	184 (13)	164 (13)	20 (13)	.78	158 (12)	26 (18)	.05
Electrocardiogram finding							
Sinus rhythm	1460 (100)	1310 (100)	150 (100)	…	1312 (100)	148 (100)	…
Left bundle branch block	109 (7.5)	84 (6)	25 (17)	<.001	89 (6.8)	20 (14)	.007
Symptoms at gated SPECT							
Angina	255 (18)	218 (17)	37 (25)	.01	211 (16)	44 (30)	<.001
Medical treatment at gated SPECT							
β-Blocker	500 (34)	438 (33)	62 (41)	.05	425 (32)	75 (51)	<.001
Nitrate	422 (29)	373 (29)	49 (33)	.28	355 (27)	67 (45)	<.001
Calcium channel blocker	246 (17)	217 (17)	29 (20)	.39	216 (17)	30 (20)	.24
Stress test							
Exercise test	923 (63)	845 (65)	78 (52)	.003	846 (65)	77 (52)	.003
Exercise test plus pharmacologic test	275 (19)	262 (20)	13 (8.7)	<.001	249 (19)	26 (18)	.68
Pharmacologic test	262 (18)	203 (16)	59 (39)	<.001	217 (17)	45 (30)	<.001
Stress angina	179 (12)	169 (13)	10 (6.7)	.03	155 (12)	24 (16)	.12
↓ST ≥ 1 mm	213 (15)	194 (15)	19 (13)	.48	176 (13)	37 (25)	<.001
SPECT							
SRS	1.4 ± 3.6	1.2 ± 3.2	3.5 ± 5.8	<.001	1.1 ± 3.1	3.9 ± 6	<.001
SRS% > 9.6	90 (6.2)	64 (4.9)	26 (17)	<.001	115 (8.4)	33 (37)	<.001
SSS	2.4 ± 4.5	2.1 ± 4	5.4 ± 6.7	<.001	1.9 ± 3.7	6.7 ± 7.4	<.001
SSS% > 6.6	150 (10)	84 (7.1)	66 (24)	<.001	70 (5.9)	78 (28)	<.001
SDS	1 ± 2.3	0.9 ± 2.1	2 ± 3.4	<.001	0.8 ± 1.7	2.8 ± 4.5	<.001
SDS% > 5.2	150 (10)	120 (9.1)	30 (17%)	<.001	120 (9.1)	30 (21)	<.001
Gated SPECT							
EDV (mL)	81.3 ± 44.9	79.6 ± 3.8	95.8 ± 51	<.001	79.8 ± 42.7	94.7 ± 59.1	<.001
EDV index (mL/m^2)	45.5 ± 28.9	44.4 ± 25.1	54.5 ± 30.3	<.001	44.5 ± 24.7	53.7 ± 33.6	<.001
EDV index > 38 mL (mL/m^2)	705 (48)	612 (47)	93 (62)	<.001	616 (47)	89 (60)	.002
ESV (mL)	37.2 ± 38.5	35.4 ± 37.4	52.4 ± 44.4	<.001	35.6 ± 36.4	51.5 ± 52	<.001
ESV index (mL/m^2)	20.8 ± 21.9	19.8 ± 21.1	29.9 ± 26.3	<.001	19.9 ± 20.7	29.3 ± 29.3	<.001

Table 1 *(continues)*

Table 1 *(continued)*: Baseline Clinical, Stress Test, and Gated SPECT Characteristics of Training and Validation Groups according to All-Cause Mortality and MACE

Variables	Overall (*n* = 1460)	Alive (*n* = 1310)	All-Cause Mortality (*n* = 150)	*P* Value	Without MACE (*n* = 1312)	With MACE (*n* = 148)	*P* Value
ESV index > 15 mL (mL/m^2)	643 (44)	550 (42)	93 (62)	<.001	547 (42)	96 (65)	<.001
LVEF (%)	60.8 ± 16.1	61.9 ± 15.5	51.3 ± 17.8	<.001	61.8 ± 15.7	52.4 ± 16.7	<.001
LVEF < 50%	690 (47)	592 (45)	98 (65)	<.001	591 (45)	99 (67)	<.001
B. Validation Group							
Variables	Overall (*n* = 766)	Alive (*n* = 698)	All-Cause Mortality (*n* = 68)	*P* Value	Without MACE (*n* = 694)	With MACE (*n* = 72)	*P* Value
Demographics							
Age (y)	66.9 ± 11.2	66.1 ± 11.2	74.1 ± 7.9	<.001	66.3 ± 11.3	71.8 ± 7.9	<.001
Age > 69 years	380 (50)	324 (46)	56 (82)	<.001	330 (48)	50 (69)	.001
Body surface (m^2)	1.8 ± 0.2	1.8 ± 0.17	1.8 ± 0.2	.48	1.8 ± 0.17	1.8 ± 0.15	.33
BMI	27.5 ± 4.2	27.6 ± 4.3	26.6 ± 3.5	.07	27.5 ± 4.3	26.8 ± 3.5	.19
Obesity (BMI ≥ 30)	154 (20)	145 (21)	9 (13)	.14	142 (21)	12 (17)	.44
Medical history							
Hypertension	465 (61)	416 (60)	49 (72)	.05	416 (60)	49 (68)	.18
Hypercholesterolemia	401 (52)	368 (53)	33 (49)	.51	367 (53)	34 (47)	.36
Smoking	122 (16)	114 (16)	8 (12)	.33	112 (16)	10 (13.9)	.62
Diabetes mellitus	175 (23)	140 (20)	35 (52)	<.001	139 (20)	36 (50)	<.001
CRF ≥ 1	642 (84)	581 (83)	61 (90)	.167	576 (83)	66 (92)	.06
Previous MI	169 (22)	142 (20)	27 (40)	<.001	133 (19)	36 (50)	<.001
Previous CR	99 (13)	91 (13)	8 (12)	.77	90 (13)	9 (13)	.91
Electrocardiogram finding							
Sinus rhythm	766 (100)	698 (100)	68 (100)	…	694 (100)	72 (100)	…
Left bundle branch block	48 (6)	37 (5)	11 (16)	<.001	38 (6)	10 (14)	.005
Symptoms at gated SPECT							
Angina	101 (13)	88 (13)	13 (19)	.13	82 (12)	19 (26)	.001
Medical treatment at gated SPECT							
β-Blocker	282 (37)	250 (36)	32 (47)	.07	245 (35)	37 (51)	.007
Nitrate	232 (30)	202 (29)	30 (44)	.009	193 (28)	39 (54)	<.001
Calcium channel blocker	126 (17)	114 (16)	12 (18)	.78	112 (16)	14 (19)	.47
Stress test							
Exercise test	487 (64)	452 (65)	35 (4.3)	.03	445 (64)	42 (58)	.33
Exercise test plus pharmacologic test	132 (17)	123 (17.6)	9 (13.2)	.361	123 (17.7)	9 (12.5)	.264
Pharmacologic test	147 (19)	123 (17.6)	24 (35.3)	<.001	126 (18.2)	21 (29.2)	.02
Stress angina	95 (12)	93 (13.3)	2 (2.9)	.013	91 (13.1)	4 (5.6)	.06
↓ST ≥ 1 mm	99 (13)	90 (12.9)	9 (13.2)	.936	84 (12.1)	15 (20.8)	.04
SPECT							
SRS	1.4 ± 3.1	1.2 ± 3	3.1 ± 3	<.001	1.2 ± 2.9	3.4 ± 3	<.001
SRS% > 9.6	45 (5.9)	36 (5.2)	9 (13)	.007	34 (4.9)	11 (15)	<.001
SSS	2.2 ± 3	1.9 ± 3.1	5.2 ± 4	<.001	1.8 ± 3	5.3 ± 4	<.001
SSS% > 6.6	136 (18)	105 (15)	31 (46)	<.001	101 (15)	35 (49)	<.001
SDS	0.8 ± 1	0.7 ± 1.2	2.1 ± 2	<.001	0.7 ± 1.5	2 ± 2	<.001
SDS% > 5.2	52 (6.8)	38 (5.4)	14 (21)	<.001	40 (5.8)	12 (17)	<.001

Table 1 *(continues)*

Table 1 *(continued)*: Baseline Clinical, Stress Test, and Gated SPECT Characteristics of Training and Validation Groups according to All-Cause Mortality and MACE

Variables	Overall (*n* = 766)	Alive (*n* = 698)	All-Cause Mortality (*n* = 68)	*P* Value	Without MACE (*n* = 694)	With MACE (*n* = 148)	*P* Value
Gated SPECT							
EDV (mL)	80.1 ± 42.9	77.9 ± 41	102.3 ± 51	<.001	78.7 ± 42.6	92.9 ± 44	.008
EDV index (mL/m²)	44.6 ± 24.3	43.3 ± 23.5	57.2 ± 28.6	<.001	43.8 ± 24	52.1 ± 25.2	.006
EDV index > 38 mL (mL/m²)	358 (47)	311 (45)	47 (69)	<.001	313 (45)	45 (63)	.005
ESV (mL)	36.9 ± 20	35 ± 30	57 ± 40	<.001	35.6 ± 30	49.1 ± 36	.003
ESV index (mL/m²)	20.5 ± 20	19.5 ± 16	32 ± 24	<.001	19.7 ± 10	27.6 ± 20	.002
ESV index > 15 mL (mL/m²)	342 (45)	294 (42)	48 (71)	<.001	297 (43)	45 (63)	.001
LVEF (%)	60.5 ± 16.3	61.6 ± 15	49 ± 15.8	<.001	61.4 ± 16	51.2 ± 15.9	<.001
LVEF < 50%	190 (25)	155 (22)	35 (52)	<.001	155 (22)	35 (49)	<.001

Note.—Continuous variables are reported as means ± SDs, and categorical variables are reported as numbers, with percentages in parentheses. Cutoff values for quantitative variables were obtained by receiver operating characteristic curve analysis. BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), CR = coronary revascularization, CRF = coronary risk factors, EDV = end-diastolic volume, ESV = end-systolic volume, LVEF = left ventricular ejection fraction, MACE = major adverse coronary events, MI = myocardial infarction, SDS = summed difference score, SDS% = ischemic myocardium percentage, SRS = summed rest score, SRS% = necrotic myocardium percentage, SSS = summed stress score, SSS% = percentage of myocardium with altered stress perfusion.

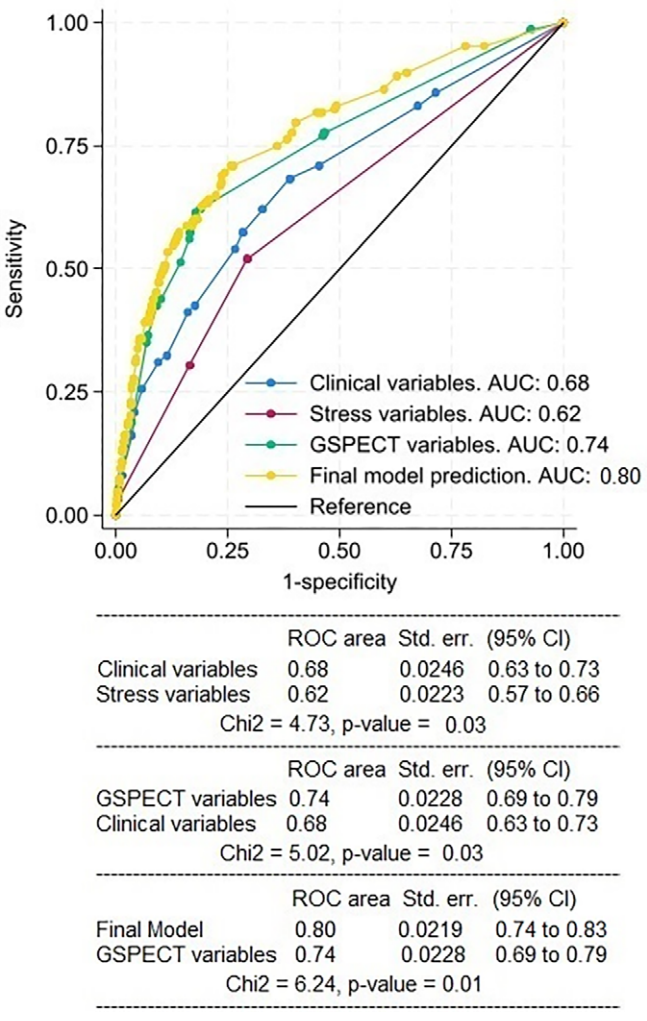


Figure 2: Receiver operating characteristic (ROC) curves for internal validation of the predictor clinical model, stress model, gated SPECT (GSPECT) model, and final model to predict major adverse cardiovascular events. The clinical model was more predictive than the stress model, and the final model had a moderate area under the ROC curve (AUC). Std. err. = standard error.

The final predictive model for MACE included all the independent predictive variables obtained in previous models (diabetes, nitrate use, age > 69 years, previous MI, pharmacologic test, ST depression ≥ 1 mm, SRS% > 9.6, SSS% > 6.6, SDS% > 5.2, EDV index > 38 mL, ESV index > 15 mL). Figure 2 and Table 2 show the final predictive model (AIC: 1860.6 and BIC: 1902.9). Figure 3 shows the Brier score analysis for the final model.

The z-score (from 0 to 24) was calculated for every predictive variable (Table 2). According to MACE per patient per year, different levels of z-score risk were calculated (Table 3). Figure 4 shows the relationship between predicted (CORSWO: low risk, moderate risk, high risk, and very high risk) and observed MACE. A comparison by means of Cox regression analysis between patients with different risk levels and MACE was made (Fig 5A).

Validation Group

Baseline characteristics in the training group according to all-cause mortality and MACE are shown in Table 1B. The overall rates of mortality and MACE in the validation group (*n* = 766) were 8.9% (*n* = 68, 2.2% per year) and 9.4% (*n* = 72, 2.4% per year), respectively. To validate CORSWO for MACE, we used the predictive variables obtained in the training group (Table 2). We obtained the prognosis index using the following regression equation: (age > 69 years × 0.457) + (diabetes × 0.384) + (pharmacologic test × 0.487) + (↓ST mm ≥ 1 × 0.704) + (SRS > 9.6 × 0.675) + (SDS > 5.2 × 0.793) + (SSS > 6.6 × 0.487) + (ESV index > 15 mL × 0.714). Then, the

Table 2: Predictive Model Obtained to Create CORSWO

MACE Predictor in Female Individuals	Hazard Ratio	z-Score	*P* Value
Age > 69 years	1.58 (1.12, 2.24)	3	.01
Diabetes	1.47 (1.03, 2.70)	2	.03
Pharmacologic stress	1.63 (1.11, 2.39)	2	.01
↓ST ≥ 1 mm	2.02 (1.36, 2.99)	4	<.001
Myocardial necrosis > 9.6%	1.96 (1.19, 3.24)	3	.009
Myocardial perfusion stress > 6.6%	1.63 (1.2, 2.69)	2	.03
Myocardial ischemia > 5.2%	2.21 (1.42, 3.43)	4	<.001
ESV index > 15 mL	2.04 (1.38, 3.02)	4	<.001
Total z-score		24	

Note.—Data in parentheses are 95% CIs. CORSWO = COronary Risk Score in WOmen, ESV = end-systolic volume, MACE = major adverse coronary events.

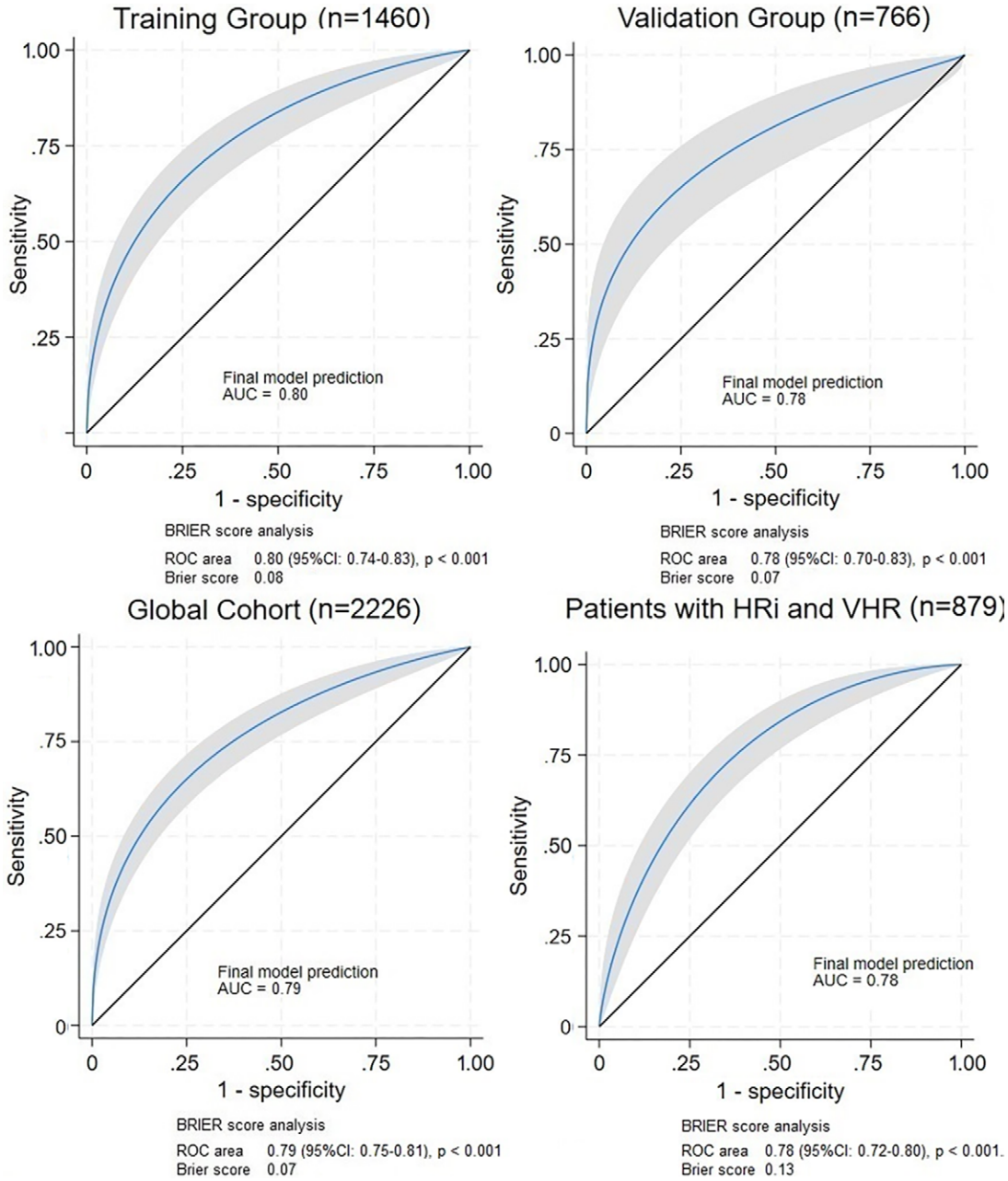


Figure 3: Receiver operating characteristic (ROC) curves analysis to evaluate the ability of the final model to predict major adverse cardiovascular events in the training group (*n* = 1460), validation group (*n* = 766), global cohort (*n* = 2226), and in patients with high risk (HRi) and very high risk (VHR) (*n* = 879) shows a moderate predictive value. AUC = area under the ROC curve.

Table 3: z-Scores in Training Group according to MACE per Patient per Year

Risk Level	z-Score	MACE% per year	Patient-Time	Warranty Period
Low risk	0 to 3	0.66 (0.39, 1.09)	2267.9	9 years
Moderate risk	4 to 6	1.57 (1.04, 2.36)	1463.6	5 years
High risk	7 to 11	3.70 (2.81, 4.89)	1349.9	1.5 years
Very high risk	>11	12.56 (9.71, 16.25)	461.8	4 months

Note.—Estimated person-time and incidence rates. Data in parentheses are 95% CIs. Warranty period is the period during which patients remained at low risk (<1% events/year). MACE = major adverse coronary event.

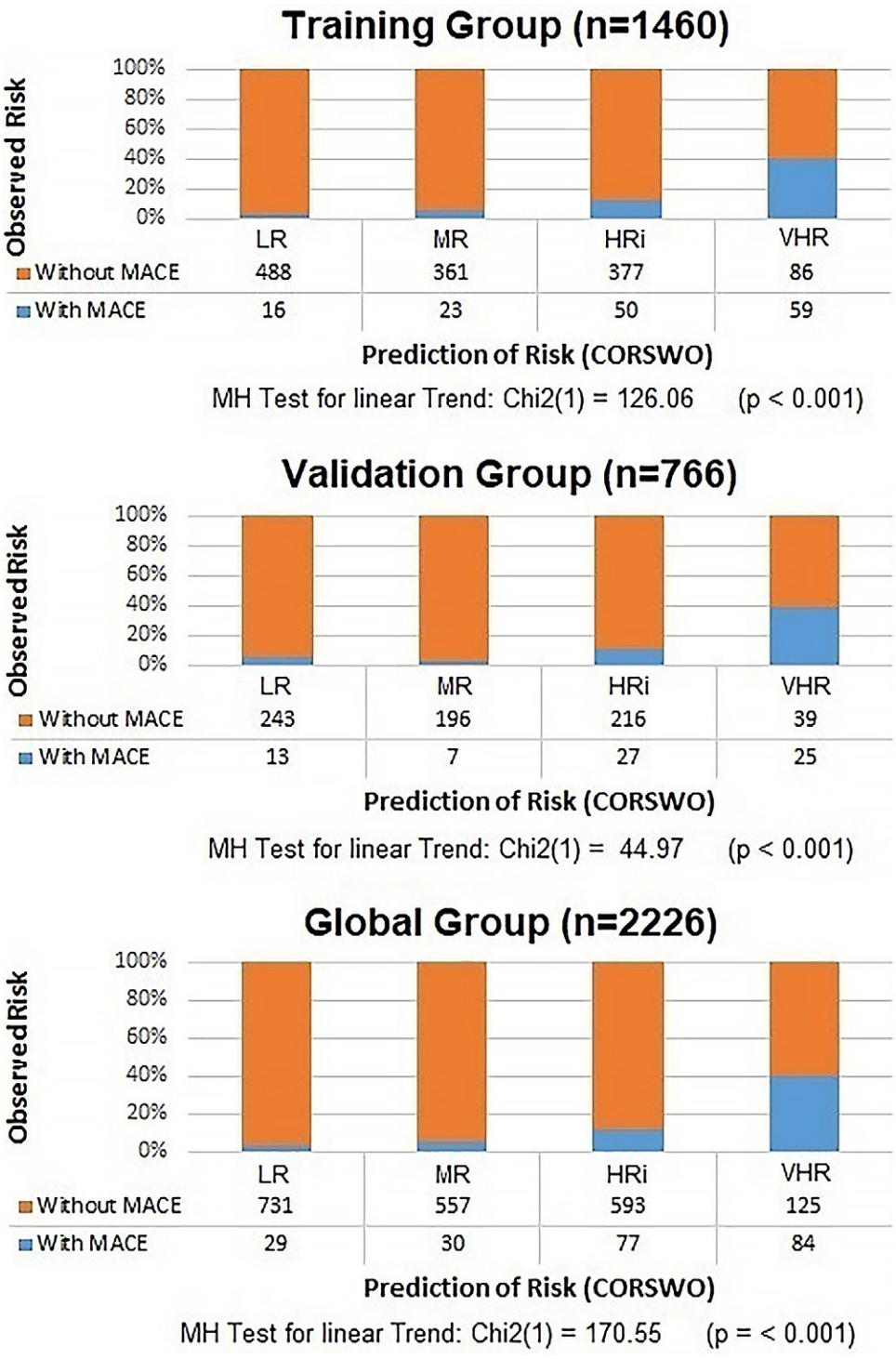


Figure 4: COronary Risk Score in WOmen (CORSWO) to predict MACE. When increasing the levels of CORSWO (risk prediction) calculated by using z-score, the prevalence of MACE (risk observed) also increases. MR, HRi, and VHR detect 89.18%, 83.32%, and 86.82% of MACE in the training, validation, and global cohorts, respectively. HRi = high risk, LR = low risk, MACE = major adverse coronary events, MH test = Mantel-Haenszel test, MR = moderate risk, VHR = very high risk.

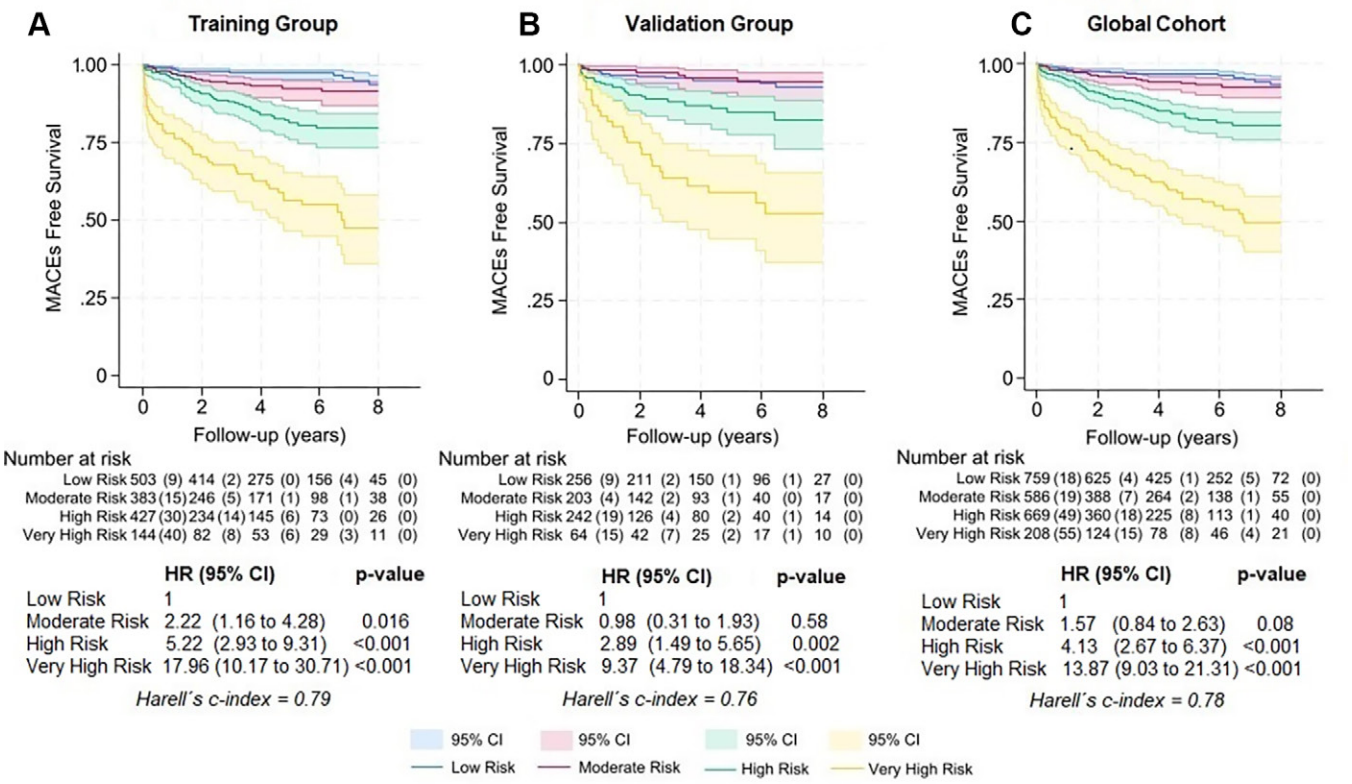


Figure 5: Kaplan-Meier curve analysis. During follow-up after gated SPECT myocardial perfusion imaging, for a one-unit increase in risk level, the MACE incidence rate ratio increases **(A)** 2.85 (95% CI: 2.42, 3.35; $P < .001$) in the training group, **(B)** 2.49 (95% CI: 1.96, 3.15; $P < .001$) in the validation group, and **(C)** 2.73 (95% CI: 2.39, 3.12; $P < .001$) in the global cohort. **(D)** Patients with high (HRi) and very high (VHR) risk levels ($n = 879$) are the groups with the worst prognosis. HR = hazard ratio, LR = low risk, MACE = major adverse coronary events, MR = moderate risk.

probability of MACE = 1/(1 + Exp [−(prognosis index)]) was calculated. Figure 3 shows the receiver operating characteristic curve and Brier score analysis.

The z-scores obtained in the training group (Table 2) were applied to every patient in the validation group to obtain different levels of risk according to the range of z-scores (Table 3). A comparison of MACE per patient per year between the risk levels of training and validation groups was made (Table 4). Furthermore, a comparison by means of Cox regression analysis between patients with different risk levels and MACE was made in the validation group (Fig 5B) and in the cohort ($n = 2226$) (Fig 5C). Higher CORSWO (risk prediction) levels were associated with higher prevalence of MACE (risk observed) (Fig 4). In female individuals with high risk and very high risk levels ($n = 879$, 39.5%), the final model had a good predictive performance (AUC: 0.78 [95% CI: 0.72, 0.80]) (Figs 3 and 5D).

Discussion

The present study demonstrates the feasibility of calculating risk of MACE in female individuals by means of CORSWO. This new risk score allows the calculation of risk for female individuals in a simple way over a mean follow-up of 4 years using eight variables: age older than 69 years, diabetes, pharmacologic stress, ST-segment depression of 1 mm or greater, myocardial necrosis greater than 9.6%, myocardial ischemia greater than 5.2%, myocardial perfusion stress greater than 6.6%, and ESV index greater than 15 mL.

In our cohort of female individuals, the most important clinical predictors of MACE were age older than 69 years and diabetes mellitus. Age is demonstrated as a prognostic variable for MACE in several studies, and female individuals are generally older when diagnosed with CAD and have a higher prevalence of comorbid conditions (21,22). It is important to note that 50% of female

Table 4: Differences between Risk Levels in Training and Validation Groups

	Training Group (n = 1460)		Validation Group (n = 766)		
Risk Level	MACE per Patient	MACE% per Year	MACE per Patient	MACE% per Year	P Value
Low risk	16/504 (3.2)	0.66 (0.39, 1.09)	13/256 (5)	0.97 (0.62, 1.84)	.20
Moderate risk	23/384 (6)	1.57 (1.04, 2.36)	7/203 (3.5)	1.2 (0.42, 1.84)	.18
High risk	50/427 (12)	3.70 (2.81, 4.89)	27/243 (11)	3.52 (2.39, 5.18)	.82
Very high risk	59/145 (41)	12.56 (9.71, 16.25)	25/64 (39)	10.41 (7.03, 15.40)	.57
Total	148/1460 (10)	2.6 (2.2, 3.1)	72/766 (9.4)	2.34 (1.88, 2.99)	.48

Note.—Data for MACE per patient are numerators and denominators, with percentages in parentheses. Data in parentheses for MACE% per year are 95% CIs. MACE = major adverse coronary event.

individuals older than 75 years are diagnosed with acute MI without chest pain (23). Additionally, a recent prospective study of 41 350 participants with diabetes without cardiovascular disease reported that a total of 6945 experienced cardiovascular events during follow-up (24). Female individuals with diabetes have a three- to sevenfold increased risk of developing CAD (25) and have a significantly higher mortality rate after MI than male individuals with diabetes (26).

In previous studies, it was observed that other clinical variables are related to cardiovascular mortality in female individuals, such as obesity and physical inactivity (1), metabolic syndrome (27), hypertension (21), tobacco use (21), cholesterol level (21), depression (28), anxiety-related psychiatric disorder (21,22), and menopause (29). In our study, 86% of female individuals were older than 55 years, with most likely in the menopausal stage. This typically occurs at age 51, and there is an increased risk for CAD in female individuals 10 years after the onset of menopause (9). This may be related to our cutoff age of 69 years as a predictor of MACE. Thus, there are multiple clinical variables related to cardiac complications during follow-up that need to be taken into account for proper risk stratification in female individuals.

The most predictive exercise and gSPECT MPI variables included in CORSWO are the following: ST depression of 1 mm or greater, pharmacologic stress, myocardial necrosis greater than 9.6%, myocardial perfusion stress greater than 6.6%, myocardial ischemia greater than 5.2%, and ESV index greater than 15 mL. It is well known that ST depression during stress test is a criterion for myocardial ischemia and has prognostic value in female individuals (30). Furthermore, in the Finnish Cardiovascular Study (ie, FINCAVAS), it was observed that ST-segment depression/heart rate hysteresis accurately detects CAD in female individuals (31). However, there may be false-positive findings in female individuals; therefore, it is more convenient to associate imaging techniques with stress tests. gSPECT MPI, with a reported sensitivity ranging from 85% to 90% and reported specificity ranging from 70% to 75% (7), provides a more sensitive and specific prediction of the presence of CAD than exercise electrocardiography. Hence, and as previously commented by Acampa et al (6), a noninvasive imaging-based test for ischemia, combining exercise electrocardiography with MPI, is preferred in female individuals at an intermediate pretest probability of disease whenever local expertise and availability could permit it. Regarding the different types of stress tests (exercise, exercise plus vasodilator drugs, and only vasodilator drugs), patients treated with vasodilator drugs have a worse prognosis (HR: 2.9) for cardiac death or nonfatal MI (20). In a series of 6069 patients with a mean follow-up of 10 years, those undergoing an adenosine test had higher rates of mortality than the patients who underwent an exercise test (32). Within the propensity-matched cohorts, the annualized MACE rate in the adenosine versus exercise patients also remained twofold higher (1.1% vs 0.2%, $P < .001$) (32). This result is comparable with another series that included 2922 patients with a mean follow-up of 5 years, demonstrating that patients who underwent dipyridamole MPI had a worse prognosis than patients who underwent an exercise test (20). Symptomatic or asymptomatic myocardial ischemia detected using different imaging techniques (10,11,14) is a variable known to have the highest prognostic value for CAD. The SSS is another predictive variable with high prognostic value. Previously, 2194 female individuals with intermediate to high CAD pretest risk were studied by means of gSPECT MPI, with a mean follow-up of 2.4 years (33). It was observed that gSPECT MPI provides risk stratification for cardiac events (nonfatal MI, cardiac death, unstable angina requiring hospitalization, and late coronary revascularization) beyond standard exercise stress testing for female individuals with suspected CAD (odds ratios for SSS > 3, SSS 4–8, and SSS > 8 were 2.5, 1.9, and 4.5, respectively) (33).

While SRS is generally an underestimated perfusion parameter, it has prognostic value because it is an indicator of myocardial scarring. When evaluating a prospective series of 7849 outpatients in the Myoview Prognosis Registry (34), it was observed that as the percentage of myocardium with resting defects increased, overall CAD event rates increased regardless of sex. For example, for patients with 10% or more of myocardium perfusion defects at rest, cardiovascular death or MI rates ranged from 7% to 44% ($P < .001$) (34). The ESV is also a recognized prognostic variable for CAD because it directly indicates systolic left ventricular function and remodeling.

There are few studies evaluating risk stratification exclusively in female individuals by using gSPECT MPI with more than 2000 patients and extensive follow-up. Most studies evaluate the diagnosis of CAD in female individuals, and others evaluate prognosis or coronary risk stratification in female individuals to assess independent prognostic variables but not global models that include clinical, stress test, and gSPECT MPI variables. Furthermore, most studies do not provide data regarding the global capacity of the predictor model, such as the AUC.

The CRAX2MACE model (35) was developed using data from 5842 patients who underwent gSPECT MPI, and the composite outcome was all-cause mortality, nonfatal MI, or late coronary revascularization. The variables included into the model were: age, sex, diabetes, pharmacologic stress, recent cardiac hospitalization, stress total perfusion deficit, ischemic total perfusion deficit, left ventricular ejection fraction, and transient ischemic dilatation. MACE risk stratification for the validation subgroup was similar in sex-stratified analyses (AUC: male individuals, 0.77; female individuals, 0.78). Recently, Kujala et al (12) investigated the prognostic value (all-cause death, MI, or unstable angina) of combined coronary CT angiography and myocardial perfusion (PET) imaging in 1948 patients. In female individuals, it was observed that the model with only clinical variables had an AUC of 0.70, the model with clinical and coronary calcium score variables had an AUC of 0.72, and the model with clinical (age, dyspnea), coronary calcium score, and myocardial perfusion blood flow variables had an AUC of 0.75.

In our study, the CORSWO model with different variables had an AUC value of 0.79, which is slightly higher compared with the two models described previously, despite the use of the calcium score and myocardial blood flow analysis in the PET study by Kujala et al (12). Therefore, while the CORSWO model requires multiple variables, our study demonstrates the feasibility of good coronary risk stratification in a contemporary cohort of female individuals.

This study had important limitations. First, this analysis was conducted in a single tertiary teaching hospital. Thus, while the study included a large number of female individuals followed up over a long period of time, extrapolation of the findings should be performed with caution. Additionally, the prognostic cutoff values of greater than 9.6% for myocardial necrosis, greater than 6.6% for myocardial perfusion stress, and greater than 5.2% for myocardial ischemia were obtained with gSPECT MPI, and future studies are needed to determine if these cutoff values are comparable with those of other imaging techniques.

In conclusion, risk stratification for cardiac events in female individuals is a constant challenge. This study provides new information about a risk score that offers a simple method to predict MACE in female individuals over a mean follow-up of 4 years. CORSWO is an effective tool to stratify the risk for MACE into four risk levels, including high and very high risk, with good accuracy, although requiring multiple imaging variables.

In the future, we will study whether the effect of left ventricular synchrony, remodeling, coronary CT, and the study of myocardial flow influence the risk stratification obtained by the CORSWO model. Moreover, in another phase of the study, we will compare the CORSWO model with the Framingham score, European Society of Cardiology Systematic COronary Risk Evaluation (ie, SCORE) model, and calcium score.

Author contributions: Guarantors of integrity of entire study, **G.R.F., S.A.B.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **G.R.F., S.A.B.**; clinical studies, **G.R.F., S.A.B.**; statistical analysis, **G.R.F., I.F.G.**; and manuscript editing, all authors

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