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Original Article

Sex-specific associations of myocardial perfusion imaging with outcomes in patients with suspected chronic coronary syndrome

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ABSTRACT

Background: Myocardial perfusion scintigraphy (MPS) is an established diagnostic technique for inducible ischemia in patients with suspected chronic coronary syndrome (CCS). Some MPS findings, most notably an ischemia extent>10% of the left ventricle (LV), hold prognostic significance and support maximization of anti-ischemic treatment. We aimed to assess sex-specific associations of MPS findings with cardiovascular (CV) events in a population at high risk of CCS.

Methods: In a prospective cohort study, 1,229 consecutive patients (age 70 ± 9.5 years, 73.5% males) without known CCS were referred to stress-rest MPS. All patients were followed for a median of 4.6 years for CV events.

Results: Men and women had comparable risk profiles and incidence rates of CV events (6.6% vs. 4.6% respectively, P = 0.186). A summed stress score (SSS) > 7 was associated with the primary endpoint, including CV death and/or nonfatal myocardial infarction (MI) (adjusted hazard ratio [HR], 3.13; 95% confidence interval [CI], 1.79-5.46; P = 0.001), all-cause mortality (HR, 3.01; 95% CI, 1.31-6.93; P = 0.01), and incidence of late revascularization (HR, 1.84; 95% CI, 1.22-2.78; P = 0.004) in men but not women. A summed difference score (SDS) > 6 was related to a higher rate of the primary endpoint only in men (adjusted HR, 1.97; 95% CI, 1.18-3.30; P = 0.009).

Conclusions: Among patients undergoing a diagnostic workup for suspected CCS, stress perfusion and reversible ischemia abnormalities may independently predict worse survival and more CV events in men. However, the obtained results indicated the need for sex-specific cutoffs to refine risk stratification and assist in clinical decisions on anti-ischemic therapy beyond coronary artery anatomy.

1. Introduction

In patients with chronic coronary syndrome (CCS), optimal medical therapy (OMT) relieves symptoms, improves the quality of life, and decreases the risk of death or major adverse cardiac events (MACE).[1,2] Large trials assessing the prognostic role of coronary revascularization on top of OMT did not find an incremental survival benefit in patients with moderate to severe extent of ischemia.[3,4] Nonetheless, the quantification of ischemia burden and risk stratification in CCS is crucial to guide therapeutic decisions, including optimization of anti-ischemic medications, and to identify patients who would benefit the most from intensive secondary prevention strategies. Contemporary prognostic tools often fail to

Abbreviations: ACS, acute coronary syndrome; AMICO, Analysis of Myocardial Ischemia by Cadmium-zinc-telluride: accuracy and Outcome; CAD, coronary artery disease; CCS, chronic coronary syndromes; CV, cardiovascular; ECG, electrocardiogram; LV, left ventricle; MACE, major adverse cardiac events; MI, myocardial infarction; MPS, myocardial perfusion scintigraphy; OMT, optimal medical therapy; SCORE2, Systemic Coronary Risk Estimation 2; SCORE2-OP, Systemic Coronary Risk Estimation 2-Older Persons; SDS, summed difference score; SPECT, single-photon emission computed tomography; SRS, summed rest score; SSS, summed stress score.

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capture residual cardiovascular (CV) risk or perform poorly in patients with CCS.[5] This translates into missed opportunities for effective secondary prevention or unnecessary high-risk procedures with short- and long-term complications.[6,7] Limitations of CV risk stratification appear more prominent in women[8] who are persistently underrepresented in relevant clinical trials.[4,9,10]

Single-photon emission computed tomography (SPECT) is an established noninvasive technique that combines high diagnostic yield for coronary artery disease (CAD) and ischemia assessment[11] while conferring incremental prognostic value in the prediction of CV events.[12,13] Specific thresholds of SPECT-detected perfusion abnormalities, particularly summed stress score (SSS) > 12, have been shown to confer additive prognostic value on top of conventional risk factors and might contribute to the refinement of risk stratification in patients with CCS.[12,14-17] However, whether ischemia burden has similar prognostic implications in men and women with CCS is not fully elucidated. Accumulating evidence suggests that sex-related differences in pathophysiological mechanisms of CV disease along with epidemiological patterns may affect the progression of atherosclerosis and mortality rates in CAD.[18] Still, there is a paucity of sex-specific survival data in CCS according to the baseline burden of inducible ischemia. To that end, we sought to investigate sex-specific associations of SPECT indices with the occurrence of CV outcomes in a large cohort of patients without known CAD.

2. Methods

2.1. Patient population

The Analysis of Myocardial Ischemia by Cadmium-zinc-telluride: accuracy and Outcome (AMICO) study is an observational study conducted between January 2010 and June 2019 at the nuclear cardiology laboratory of the Fondazione Toscana Gabriele Monasterio in Pisa, Italy. In this analysis, we considered only patients without known CAD (n = 1,229). All patients were managed according to current recommendations.[19-23] We excluded patients with acute or recent (<3 months) myocardial infarction (MI), unstable angina, nonischemic cardiomyopathy, moderate-to-severe heart valve disease, end-stage renal disease, or active malignancy. All participants provided written informed consent. The study conformed to the Declaration of Helsinki and was approved by the institution's human research committee. Supplementary Fig. 1 depicts the flowchart of the study.

2.2. Myocardial perfusion scintigraphy

The MPS protocol was published previously.[19-22] Stress and rest images were semi-quantitatively scored according to the 17-segment left ventricle (LV) model and a five-point scale (0: normal; 1: equivocal; 2: moderate; 3: severe reduction in radioisotope uptake; and 4: absence of detectable tracer uptake). Accordingly, the SSS, summed rest score (SRS), and summed difference score (SDS) were calculated. Two experienced nuclear cardiologists performed the semi-quantitative analysis independently, and the consensus was reached when necessary (Fig. 1). The percent of LV myocardium with stress, fixed, or ischemic defects can be calculated as SSS, SRS, and SDS/68 (maximum potential score = 4 × 17%), respectively. The readers were blinded to clinical data and coronary anatomy. As per protocol, myocardial perfusion during stress was defined as moderately/severely abnormal by SSS>7 (involving >10% of LV myocardium) and SSS>12 (involving >15% of LV myocardium).[14,17,24,25] As cutoffs of reversible ischemia, SDS values > 4 and > 6 were considered depicting moderate and severe ischemia, respectively.[26]

2.3. Calculation of the SCORE2

In this observational prospective cohort study consisting of a European (Italian) population, we used the recommended 2021 European Society of Cardiology Guidelines Systemic Coronary Risk Estimation 2 (SCORE2) and the Systemic Coronary Risk Estimation 2-Older Persons (SCORE2-OP) for persons aged <70 and ≥ 70 years, respectively (country-specific calibrated version), to estimate the current 10-year fatal and nonfatal CV risk.[27]

2.4. Invasive coronary angiography and revascularization

Details about invasive coronary angiography and revascularization are provided in the Supplementary Material.

2.5. Follow-up

Follow-up data were retrieved in May 2020 from electronic health records and phone calls to patients or their relatives. For patients who died in a hospital or at home, the cause of death was elucidated from the medical records or the local physician who signed the death certificate. The attribution of CV death required the documentation of significant arrhythmias or cardiac arrest, or death attributable to heart failure or MI in the absence of any other precipitating factor. The primary endpoint was CV death and/or MI.[28] Late revascularization was defined when occurred over 90 days from enrollment, excluding cases of MI. Follow-up events were adjudicated by an independent trained investigator blinded to MPS data and coronary anatomy. Of these 1,229 patients, no patient was lost to follow-up.

2.6. Statistical analysis

We used a priori sex-stratified Cox proportional-hazards models to evaluate the association between baseline MPS indices – added one at a time to the model – and study endpoints. We used time-dependent receiver operating characteristic (ROC) curves to identify cutoffs in SSS and SDS discriminating patients in our study at high risk of experiencing the primary endpoint by maximizing the concordance probability function in a survival data framework.[29] To that end, we used the strategy proposed by Liu and Jin and selected the optimal cutoff point that maximized the product of sensitivity and specificity.[30] Statistical analysis was conducted with the Stata package, version 16.0 (StataCorp, College Station, Texas, USA). Detailed information about the statistical analyses can be found in the Supplementary Material.

3. Results

3.1. Population characteristics

Descriptive characteristics of the study population stratified by sex are summarized in Table 1. The mean age of the population was 69.7 years, and 73.5% of participants were men. Men and women did not differ with respect to the prevalence of traditional CV risk factors or CV treatment, excluding more frequent chronic kidney disease and lower utilization of aspirin in women (Table 1). Men had a higher pretest probability of CAD than women, but a similar frequency of positive electrocardiogram (ECG) stress test.

3.2. MPS findings

MPS protocol and cardiac functional parameters are summarized in Table 1. Median SSS and SRS were significantly higher in men than in women ($p < 0.01$), while no difference in SDS was noted. Male patients were characterized by higher LV volumes, a greater LV mass index, a lower ejection fraction, and a worse diastolic function (Table 1).

For the SSS cutoffs, specifically SSS>7 and SSS>12, men showed a higher burden of perfusion abnormalities, as well as SRS values (Table 1). Supplementary Fig. 2 depicts the prevalence of SPECT indices according to predefined cutoffs in males and females.

3.3. Outcomes and MPS indices in males and females

Across a median follow-up of 4.6 years (range 0.1-10.9), 37 deaths were recorded, of which 24 were adjudicated as CV, as well as 52 nonfatal MIs and 157 late revascularization procedures. The primary endpoint comprising CV death and/or nonfatal MI included 75 CV events.

Sex-specific associations of MPS indices with the main outcomes of the study are shown in Table 2. Fig. 2 depicts the cumulative incidence of CV outcomes by sex depending on prespecified thresholds of MPS indices.

3.3.1. Primary endpoint

SSS>7 (adjusted HR, 3.13; 95% CI, 1.79-5.46; $P < 0.001$) and SDS>6 (adjusted HR, 1.97; 95% CI, 1.18-3.30; $P = 0.009$) were related to increased risk of the primary endpoint of CV death and/or nonfatal MI in men (log-rank test $P < 0.001$ and $P = 0.008$, respectively) (Fig. 3), whereas substantial overlapping of the Nelson-Aalen curves was found in women during the first 4 years of follow-up (log-rank test $P > 0.1$ for both MPS indices). Interestingly, the association of extensive stress perfusion abnormalities (i.e., SSS>12) with the composite cardiac outcome had a similar direction in both sexes (adjusted HR, 1.87; 95% CI, 1.04-3.37; $P = 0.038$ and adjusted HR, 4.76; 95% CI, 1.56-14.48; $P = 0.006$ for males and females, respectively) (Fig. 3). This finding was confirmed in the female sex even after bootstrapping (bias-corrected 95% CI, 1.28-17.64).

Extensive reversible ischemia (i.e., SDS>6) was related to inferior CV survival and/or nonfatal MI only in men (adjusted HR, 1.97; 95% CI, 1.18-3.30; $P = 0.009$ and adjusted HR, 2.02; 95% CI, 0.72-5.67; $P = 0.181$ for males and females, respectively) (Table 2 and Fig. 3).

Sex-differential results for MPS indices, in detail SSS>7, SSS>12, and SDS>6, did not substantially change after additional adjustments for the presence of CAD that led to early revascularization after MPS imaging except for SDS>4 in the female population (adjusted HR, 4.40; 95% CI, 0.97-19.89; $P = 0.054$) (Supplementary Table 1).

3.3.2. All-cause death

A higher incidence of all-cause death in men with SSS>7 was observed (log-rank test $P = 0.007$), while an inverse, nonsignificant pattern of lower mortality was seen in women with SSS>7 (log-rank test $P = 0.267$). Importantly, SSS>12 was also significantly associated with all-cause mortality in men but not in women (Table 2). These sex-specific associations remained significant even after additional adjustment for the event of early revascularization (Supplementary Table 1).

3.3.3. Late revascularization

Finally, SSS>7 identified only males at higher risk for late revascularization (adjusted HR 1.84; 95% CI, 1.22-2.78; $P = 0.004$ and adjusted HR, 1.00; 95% CI, 0.48-2.07; $P = 0.996$ for males and females, respectively) (Table 2). Likewise, after including early revascularization in the model, SSS>12 identified only females at raised risk for late revascularization (adjusted HR, 6.77; 95% CI, 1.23-37.36; $P = 0.028$ and adjusted HR, 1.34; 95% CI, 0.78-2.30; $P = 0.284$ for females and males, respectively), whereas SSS>7 and SDS>4 identified males but not females with an increased risk for a subsequent event of late revascularization (Supplementary Table 1).

3.4. MPS indices and cardiovascular risk scores in males and females

Associations between MPS indices and the SCORE2 are provided in Supplementary Table 2.

3.5. Subgroup analyses

A secondary analysis was conducted to assess the performance of MPS indices for the prediction of CV events in patients treated exclusively with optimal medical treatment ($n = 855$). Notably, results did not materially change in these patients compared with the whole population of the study (Supplementary Table 3). SSS>7 and SDS>6 were associated with an increased risk of the primary endpoint in men but not in women, whereas, similarly to the overall population, SDS>6 was related to inferior CV survival and/or nonfatal MI in both sexes. Interestingly, SSS>7 and SSS>12 were again the only cutoffs associated with increased all-cause mortality in male but not female patients on only medical treatment. Associations between MPS indices and CV outcomes in patients with only OMT are provided in detail in Supplementary Table 3.

Sex-specific associations of MPS thresholds with the primary outcome were also found in obese and nonobese patients as well as participants with a negative ECG stress test and a left ventricular ejection fraction≥50%. These associations were congruent with the findings from the analysis of the overall population and are provided in Supplementary Table 4.

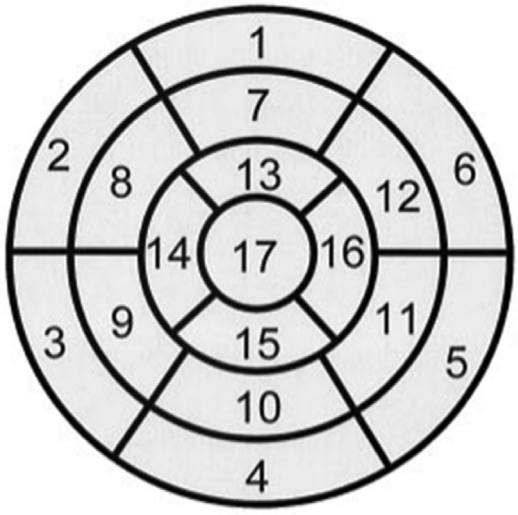

Figure 1. Display, on a polar map, of the 17 myocardial segments for tomographic imaging of the heart. The segments are numbered in counterclockwise order. The basal segments are numbered 1–6, the middle segments are numbered 7–12, and the paraapical segments are numbered 13–16. The figure also assigns the segments to particular coronary artery groups. Segments 1, 2, 7, 8, 13, 14, and 17 correspond to the territory of left anterior descending artery. Segments 3, 4, 9, 10, and 15 correspond to the territory of right coronary artery. Segments 5, 6, 11, 12, and 16 correspond to the left circumflex artery.

Table 1
Descriptive characteristics of our study's population according to sex

Variable	N	All	Men (N = 903)	Women (N = 326)	p
Age (years)	1229	69.7 (9.47)	69.4 (9.45)	70.6 (9.48)	0.041
Body mass index (kg/m^2)	1229	28.4 (4.56)	28.5 (4.25)	28.2 (5.33)	0.41
Typical angina	1229	577 (46.95)	411 (45.51)	166 (50.92)	0.094
Family history of CAD	1229	581 (47.27)	413 (45.74)	168 (51.53)	0.072
Smoking	1229	340 (27.66)	254 (28.13)	86 (26.38)	0.545
Diabetes mellitus	1229	478 (38.89)	342 (37.87)	136 (41.72)	0.222
Hypertension	1229	702 (57.12)	510 (56.48)	192 (58.90)	0.45
Hypercholesterolemia	1229	626 (50.94)	460 (50.94)	166 (50.92)	0.995
GFR (mL/min/1.73 m^2)	**1174**	**74.7 (55.6–94.6)**	**81.3 (64.1–99)**	**54.6 (44.2–70.4)**	**<0.001**
Aspirin	**1229**	**828 (67.37)**	**624 (69.10)**	**204 (62.58)**	**0.031**
Statins	1229	553 (45.00)	410 (45.40)	143 (43.87)	0.632
ACE inhibitors	1229	555 (45.16)	402 (44.52)	153 (46.93)	0.453
Angiotensin II receptor blockers	1229	229 (18.63)	166 (18.38)	63 (19.33)	0.708
Nitrates	1229	93 (7.57)	72 (7.97)	21 (6.44)	0.37
Diuretics	1229	481 (39.14)	363 (40.20)	118 (36.20)	0.204
Pretest probability of CAD >15%	**811**	**767 (94.57)**	**575 (97.62)**	**192 (86.49)**	**<0.001**
MPS parameters					
Positive ECG stress test	1150	150 (13.04)	107 (12.80)	43 (13.69)	0.767
Number of vessels disease with stenosis >70%	1229				
0 vessels		**460 (37.4)**	**314 (34.77)**	**146 (44.79)**	**0.001**
1 vessel		503 (40.93)	376 (41.64)	127 (38.96)	0.399
2 vessels		**198 (16.11)**	**161 (17.83)**	**37 (11.35)**	**0.006**
3 vessels		68 (5.53)	52 (5.76)	16 (4.91)	0.565
Baseline RPP	**1189**	**9400 (8100–11200)**	**9300 (8000–11000)**	**9900 (8400–11800)**	**<0.001**
Stress RPP	**1185**	**18600 (1300–23900)**	**19250 (13700–24400)**	**17100 (12400–22500)**	**<0.001**
Ejection fraction (%)	**1229**	**60 (55–65)**	**60 (54–63)**	**62(60–65)**	**<0.001**
Left ventricular mass index (g/m^2)	**797**	**71.9 (64.1–81)**	**73.5 (65.3–82.7)**	**68.4 (62–75.8)**	**<0.001**
Ejection fraction at rest (%)	**1228**	**61 (54–68)**	**60 (52–65)**	**68 (61–75)**	**<0.001**
Perfusion indices					
Baseline PFR (ml/s)	**848**	**2.32 (1.92–2.78)**	**2.23 (1.82–2.67)**	**2.5 (2.09–2.92)**	**<0.001**
Stress PFR (ml/s)	**348**	**2.35 (1.8–2.88)**	**2.3 (1.77–2.8)**	**2.55 (2–2.98)**	**0.016**
SSS	**1229**	**6 (4–10)**	**6 (4–11)**	**5 (3–9)**	**<0.001**
SRS	**1229**	**1 (0–4)**	**1 (0–4)**	**1 (0–3)**	**<0.001**
SDS	1229	4 (2-7)	4 (3-7)	4 (2-7)	0.175
SSS>7	**1229**	**518 (42.15)**	**397 (43.96)**	**121 (37.12)**	**0.032**
SSS>12	**1229**	**178 (14.48)**	**146 (16.17)**	**32 (9.82)**	**0.005**
SDS>1	**1229**	**1050 (85.44)**	**784 (86.82)**	**266 (81.60)**	**0.022**
SDS>4	1229	587 (47.76)	437 (48.39)	150 (46.01)	0.46
SDS>6	1229	328 (26.69)	235 (26.02)	93 (28.53)	0.381
Early revascularization	1229	374 (30.43)	276 (30.56)	98 (30.06)	0.866
Outcomes					
Follow-up (days)	1229	1700 (958-2184)	1635 (960-2177)	1655 (952-2205)	0.934
Late revascularization	1229	157 (12.77)	113 (12.51)	44 (13.50)	0.442
All-Cause Death	1229	37 (3.01)	27 (2.99)	10 (3.07)	0.944
Cardiac Death	1229	24 (1.95)	18 (1.99)	6 (1.84)	0.864
Nonfatal MI	1229	52 (4.23)	43 (4.76)	9 (2.76)	0.124
Cardiac death and/or nonfatal MI	1229	75 (6.10)	60 (6.64)	15 (4.60)	0.186
Cardiac death and/or nonfatal MI and/or late revascularization	1229	226 (18.39)	168 (18.60)	58 (17.79)	0.745

Continuous variables are presented as mean (SD) or median ($25^{th} - 75^{th}$ percentile); nominals are shown as counts and valid percentages.
Pretest probability of CAD was defined according to the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain.[47].
P-values are derived from the two independent-samples *t*-test or the Mann–Whitney test for continuous variables and the chi-squared test for nominal variables. Bold values indicate statistical significance, which was set at the level of p-value <0.05.
Abbreviations: CAD, coronary artery disease; GFR, glomerular filtration rate; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; ECG, electrocardiogram; RPP, rate pressure product; PFR, peak filling rate; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; MI, myocardial infarction.

3.6. Study-specific cutoffs for the primary outcome

By using time-dependent ROC curves, we found that the optimal cutoff points for SSS to predict CV death and nonfatal MI in our study were 6 in males and 9 in females (Supplementary Fig. 3). Further details are given in the Supplementary Material.

4. Discussion

To our knowledge, this is the first study indicating sex-differential associations of MPS indices with CV outcomes in a population at high risk for CCS. Our results also stress the priority role of ischemia in sex-specific risk stratification beyond coronary artery anatomy. The sex-stratified analysis in this large cohort of patients without known CAD showed that validated thresholds of MPS-detected stress perfusion and reversible ischemia abnormalities were associated with the occurrence of adverse CV events mainly in male subjects. A moderate degree of stress perfusion abnormalities as reflected in SSS>7 independently predicted all-cause death, CV mortality, and nonfatal MI or late revascularization selectively in men but not in women. Similarly, extensive inducible ischemia (SDS>6) identified male but not female participants at increased risk of CV mortality and/or nonfatal MI. Interestingly, these findings did not materially change and retained their statistical significance in a secondary analysis of patients treated exclusively with OMT, while they were also consistent in subgroup analyses based on obesity status, baseline LV systolic function, and the result of the ECG stress test. Of note, MPS indices also conferred

Table 2
Uni- and multi-adjusted sex-stratified associations of SPECT indices with the main outcomes of the study

	Univariable				*Multivariable			
	Males		Females		Males		Females	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
(Males N = 60, Females N = 15)								
Cardiovascular death and/or nonfatal MI								
SSS>7	**2.99 (1.72, 5.20)**	**<0.001**	1.94 (0.70, 5.37)	0.200	**3.13 (1.79, 5.46)**	**<0.001**	1.86 (0.67, 5.18)	0.235
SSS>12	1.77 (0.99, 3.18)	0.055	**6.02 (2.14, 16.93)**	**0.001**	**1.87 (1.04, 3.37)**	**0.038**	**4.76 (1.56, 14.48)**	**0.006**
SDS>4	**3.20 (1.79, 5.75)**	**<0.001**	**4.75 (1.34, 16.85)**	**0.016**	**3.16 (1.76, 5.68)**	**<0.001**	**4.61 (1.28, 16.59)**	**0.019**
SDS>6	**1.98 (1.18, 3.30)**	**0.009**	2.14 (0.78, 5.91)	0.141	**1.97 (1.18, 3.30)**	**0.009**	2.02 (0.72, 5.67)	0.181
(Males N = 27, Females N = 10)								
All-cause death								
SSS>7	**2.97 (1.3, 6.8)**	**0.01**	0.43 (0.09, 2.01)	0.281	**3.01 (1.31, 6.93)**	**0.01**	0.38 (0.08, 1.82)	0.225
SSS>12	**3.64 (1.69, 7.85)**	**0.001**	2.30 (0.49, 10.85)	0.292	**3.70 (1.7, 8.04)**	**0.001**	1.95 (0.39, 9.68)	0.414
SDS>4	0.95 (0.45, 2.02)	0.902	0.79 (0.22, 2.78)	0.708	0.96 (0.45, 2.05)	0.922	0.66 (0.18, 2.39)	0.522
SDS>6	1.58 (0.72, 3.45)	0.251	0.27 (0.03, 2.14)	0.215	1.57 (0.72, 3.43)	0.258	0.24 (0.03, 1.94)	0.182
(Males N = 113, Females N = 44)								
Late revascularization								
SSS>7	**1.79 (1.2, 2.68)**	**0.004**	1.07 (0.56, 2.03)	0.844	**1.84 (1.22, 2.78)**	**0.004**	1.00 (0.48, 2.07)	0.996
SSS>12	1.4 (0.83, 2.37)	0.210	0.77 (0.23, 2.64)	0.681	1.28 (0.74, 2.21)	0.383	1.33 (0.29, 6.21)	0.716
SDS>4	1.34 (0.83, 2.17)	0.233	1.36 (0.59, 3.09)	0.470	1.48 (0.91, 2.42)	0.118	1.24 (0.47, 3.26)	0.664
SDS>6	1.31 (0.88, 1.93)	0.179	1.08 (0.57, 2.03)	0.815	1.41 (0.93, 2.13)	0.102	1.05 (0.52, 2.13)	0.895

Abbreviations: SPECT, single-photon emission computed tomography; HR, hazard ratio; CI, confidence intervals; SSS, summed stress score; SDS, summed difference score; MI, myocardial infarction; NP, not performed.
* Adjusted for a prespecified set of confounders, including age, smoking, hypertension, hyperlipidemia, and diabetes mellitus. Bold values indicate statistical significance, which was set at the level of p-value <0.05.

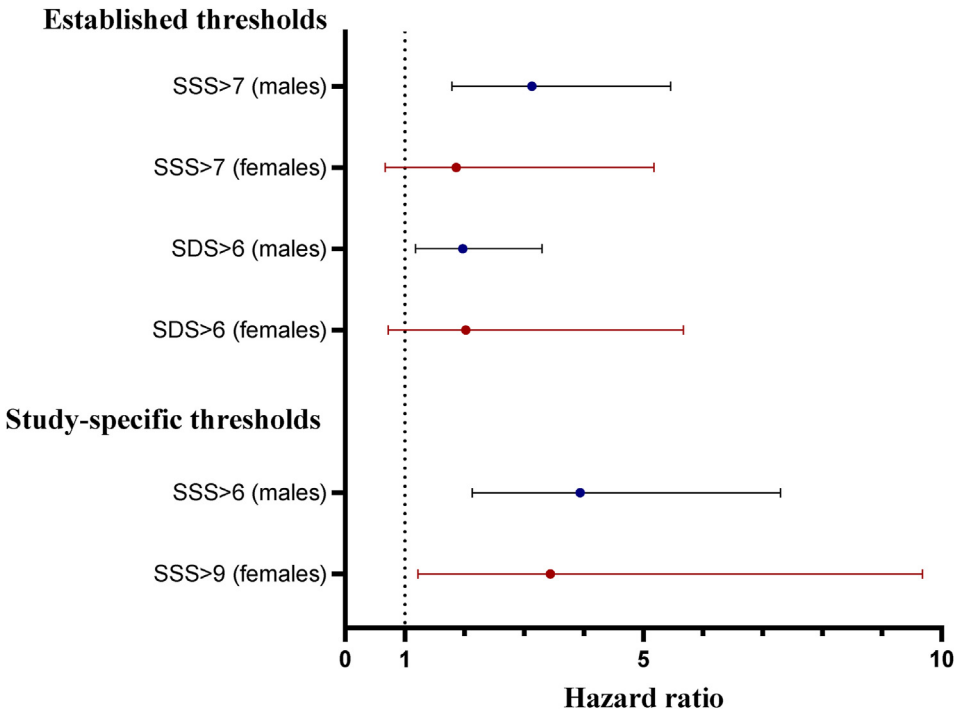

Figure 2. Association of established and study-specific thresholds of SPECT indices with the primary endpoint of CV death and/or nonfatal MI. Hazard ratios adjusted for a prespecified set of confounders, including age, smoking, hypertension, hyperlipidemia, and diabetes mellitus. Abbreviations: SSS, summed stress score; SDS, summed difference score; CV, cardiovascular; MI, myocardial infarction.

sex-specific additive prognostic value beyond the SCORE2 for the primary endpoint.

To date, few studies have examined sex-specific clinical trajectories in CCS.[31] Women reportedly showed increased mortality than men, but this disparity was more prominent in younger subjects[32] and was mainly driven by inferior survival after acute coronary syndromes (ACS)[31] and a lower rate of OMT in women than men.[33,34] Importantly, we did not find dedicated studies using MPS to investigate the sex-specific incidence of CV events conditional on the ischemic burden and CAD severity. Furthermore, in large studies aiming to assess the effect of revascularization strategies on CCS patients, female patients were underrepresented, and associations were not investigated separately in men and women, highlighting the current limitations in sex-specific CV risk stratification.[4,10]

MPS detects CAD with high diagnostic accuracy in both sexes.[35] Beyond CAD diagnosis, impaired myocardial perfusion in MPS imaging portends a significantly increased risk of long-term CV

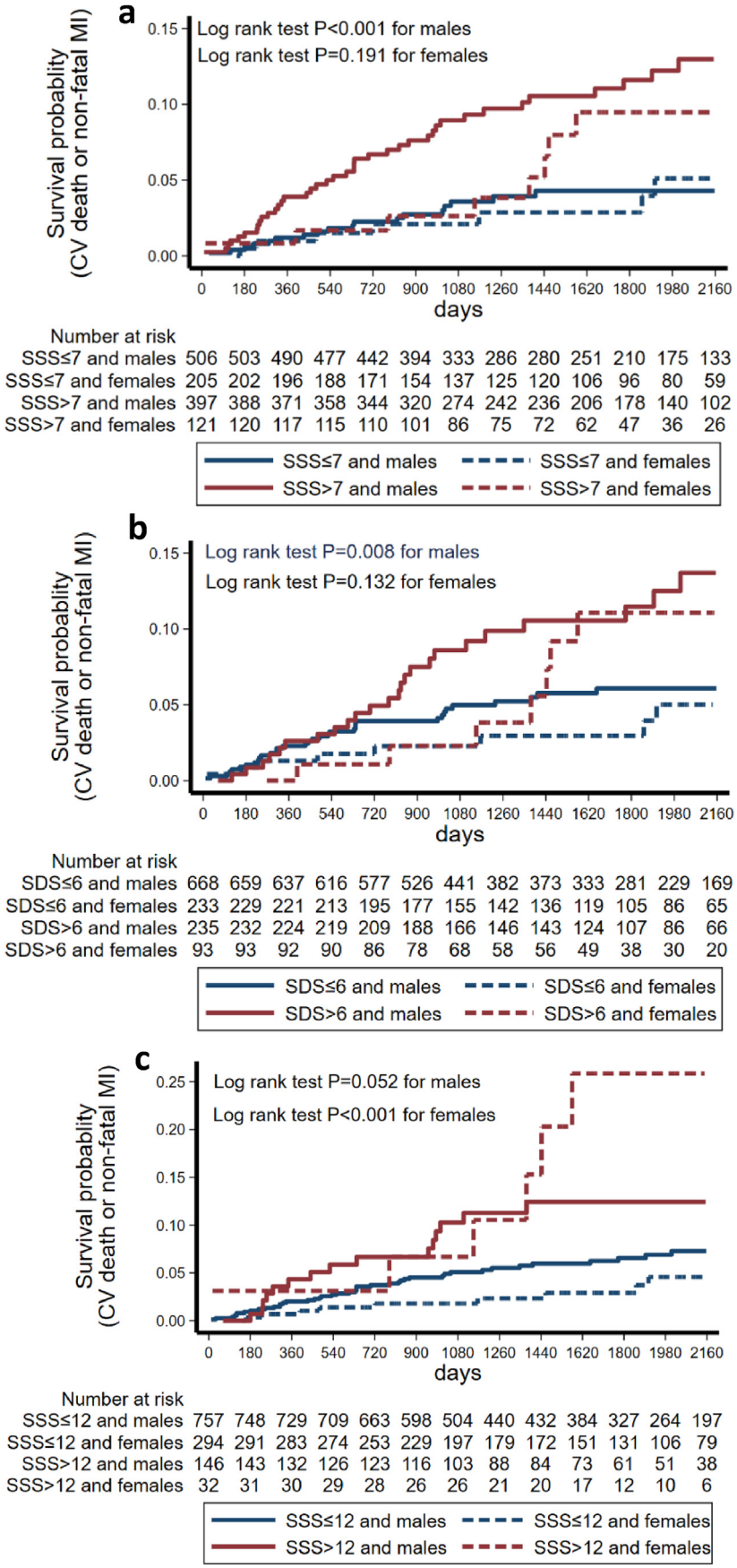

Figure 3. Nelson-Aalen curves for sex-stratified cumulative incidence of the primary endpoint depending on (a) SSS>7 or SSS≤7, (b) SDS>6 or SDS≤6, and (c) SSS>12 or SSS≤12. Abbreviations: CV, cardiovascular; SSS, summed stress score; SDS, summed difference score; MI, myocardial infarction.

events.[12,13] Threshold values are generally used in clinical practice to evaluate semi-quantitatively the extent of reversible ischemia evinced by stress/rest MPS. However, our results indicate that different sex- and study-specific cutoff points for MPS might be of clinical usefulness if validated in more cohorts. We demonstrated that higher thresholds of SSS are needed in women to predict adverse CV events than in men, while SDS had a less clear sex-specific prognostic pattern. This might partially be related to the lower prevalence of significant CAD in women in contrast to men, leaving a subgroup of very high-risk women (i.e., SSS>12) accounting for most CV events. A previous study in the same population showed that SSS outperformed SDS with respect to diagnostic accuracy for CAD.[36] It should be noted that SSS and SDS reflect different pathologies of the myocardium; SSS identifies scarred and ischemic myocardial tissue, whereas SDS captures reversible ischemia. In light of their discrimination value for patients at increased odds for CV events, SSS and SDS cutoffs have been endorsed by both European and US guidelines to facilitate therapeutic decisions in patients with CCS.[37,38] Common thresholds in SSS and SDS appear to be a practical but counterintuitive approach in the context of distinct risk profile as striking differences in the prevalence of males and females in relevant studies might blunt sex-specific prognostic associations in pooled analyses.[12,15,16] These concerns are further aggravated if the technical limitations of MPS examination, which are more prominent in women because of smaller LV chamber size,[39] soft tissue attenuation due to breast tissue, body habitus[40], and regional obesity[33], as well as smaller caliber coronary arteries,[41] are taken into consideration.

Sex-specific pathophysiological mechanisms and epidemiological trends may account for the poor prognostic performance of MPS indices in women compared with men with CCS.[18] Distinct coronary plaque characteristics and a higher prevalence of plaque erosion instead of rupture alongside a higher frequency of microvascular angina rather than epicardial stenosis have been observed in women.[18] As a result, ischemia detected in women might represent a diffuse perfusion imbalance rather than focal coronary pathology with decreased susceptibility to ACS. Moreover, women often present with atypical symptoms for ACS,[42] without culprit coronary lesions[43], and have lower odds of diagnostic electrocardiographic changes and elevated troponin levels than men,[18] hence a higher possibility of incorrect diagnosis. Increased mortality in men with CCS compared with age-matched women might also be attributed to a higher number of traditional CV risk factors such as smoking, hypertension, and dyslipidemia in the former and sustained protection from sex hormones in the latter.[44] In fact, it has been postulated that CV risk is equalized for men and postmenopausal women, but with a lag of several years.[45]

Our findings could raise clinical implications for current therapeutic strategies in patients with CCS. According to our results, men with moderate to severe ischemia in MPS have a higher risk of CV events and should be prioritized for aggressive secondary CV prevention and possibly coronary revascularization, while a more conservative approach may be selected for women with up to moderate perfusion defects. Women with extensive ischemic burden (i.e., SSS>12) should be considered at very-high CV risk accordingly to their male counterparts. Sex-specific degree of ischemia was conferring prognostic value for adverse CV events independently of severity of CAD in this study in predicting, and this concept may be supported by the latest trials.[4,10] Sex-specific cutoffs in SPECT imaging merit further investigation; large multicenter studies should reappraise ischemia thresholds for men and especially women to reflect more accurately sex-specific CV risk in patients with CCS. The paradigm shift from the ISCHEMIA trial will upgrade the role of evidence-based medical treatment, but it will also necessitate improved risk stratification in this population; in this context, MPS thresholds may identify patients treated only with OMT who would benefit the most from possible coronary revascularization.

4.1. Study limitations

Our cohort comprised mainly of male patients while female subjects represented a fraction of the population. Despite the small number of women resulting in lower events in this group, the incidence rate of the main outcomes was comparable between the sexes. We also used resampling techniques to confirm significant associations among women who presented less events. Second, the mean age of our population was approximately 70 years, and the advanced age of patients might partially account for the limited prognostic value of traditional CV risk factors and of ischemia's burden. Third, we have not accounted for changes in risk factors or therapy as well as for adherence to medical treatment across the follow-up. Fourth, subgroup analyses according to obesity or LV systolic function status were conducted at a univariable level because of a limited number of events in subcategories. Fifth, we did not formally test interaction terms of sex with SPECT indices but followed a predefined research design of stratified analysis in males and females. Sixth, although the survival curves of SSS showed a decline also in women, the statistical analysis did not show any significant results; this may be attributed to type II statistical error. Therefore, our findings mandate further confirmation by testing appropriate interaction terms of sex with cutoffs for perfusion abnormalities in adequately powered cohorts. Similarly, our findings on sex-specific associations of ischemia burden with CV outcomes were not externally validated in additional cohorts.

5. Conclusions

In conclusion, stress perfusion MPS indices displayed sex-specific associations with CV outcomes in a cohort of patients evaluated for suspected CCS, strongly predicting adverse events in men but not women. Given its high cost-effectiveness[46] and accuracy in the detection of CAD, MPS may offer additional prognostic information in patients with CCS and contribute to refined risk stratification according to sex and degree of reversible ischemia beyond anatomical information on CAD severity.

Declaration of interest

None.

Disclosures

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2022.12.008.

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