ORIGINAL ARTICLE

Additional value of the coronary artery calcium score in patients for whom myocardial perfusion imaging is challenging

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KEY WORDS
artefacts, coronary artery calcium score, myocardial ischemia, myocardial perfusion imaging, single-photon emission computed tomography

ABSTRACT

BACKGROUND Determination of prognosis based on ischemia detection, using single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI), can be challenging in patients with multiple affected coronary arteries.

AIMS The aim of the study was to examine the outcomes of SPECT-MPI combined with the coronary artery calcium score (CACS) to identify predictors of adverse cardiac events (ACEs) in patients for whom ischemia detection may be difficult using SPECT-MPI.

METHODS The study group included 195 patients with a history of chronic kidney disease, suspected ischemic cardiomyopathy, or left bundle branch block. All patients underwent SPECT-MPI and CACS evaluation. During the follow-up, ACEs were recorded. Perfusion and functional parameters as well as the CACS were analyzed to find the predictors of ACEs.

RESULTS The ACEs were recorded in 58 individuals (29.7%) and were significantly associated with ischemia (P <0.001), abnormal functional parameters (P = 0.04), and higher CACSs (P <0.001). The optimal cutoff value of the CACS to predict an ACE was 530. Cox proportional hazards models revealed that age, mild and severe ischemia, functional abnormalities, and a CACS of 530 or higher were significant predictors of ACEs. In the subgroup of individuals without ischemia, a CACS of 530 or higher was significantly associated with poor outcome, while we recorded only 3 ACEs in these patients when the CACS was lower than 530.

CONCLUSIONS The addition of the CACS to SPECT-MPI improves the identification of patients at higher risk for ACEs, even in individuals for whom SPECT-MPI is challenging.

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INTRODUCTION Single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is a well-established noninvasive method for risk stratification of coronary artery disease (CAD). However, noninvasive tests, such as myocardial perfusion imaging (MPI), are intended for diagnosing patients with an intermediate risk of CAD.[1] Determining a prognosis based on ischemia detection by SPECT-MPI can be challenging for patients with multiple affected coronary arteries. These patients with multivessel CAD (MVD) are at higher risk of adverse cardiac events (ACEs) and may benefit from revascularization therapy; thus, their identification is important.[2] However, in such patients, imaging the perfusion defects may underestimate the real extent of ischemia.[3,4] Individuals with chronic kidney disease (CKD) or ischemic cardiomyopathy (ICM) can have MVD, with developed "balanced ischemia."[5,6] In addition, some conditions, such as left bundle branch block (LBBB), are related to artefacts that can affect MPI results.[7]

In patients with CKD, the risk of CAD increases with a reduction in estimated glomerular

WHAT'S NEW

Single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) is a well-established diagnostic method; however, its sensitivity is lower in some clinical states due to imaging perfusion defects. We showed that additional data from the coronary artery calcium score (CACS) assessment, representing morphological lesions in atherosclerosis, brings incremental value to SPECT-MPI for risk stratification of difficult patients. The CACS value can identify patients with a negative SPECT-MPI result but significantly higher cardiovascular risk.

filtration rate.[8-11] This arises from the clustering of traditional coronary risk factors and also uremic-related risk factors.[8,12] The Kidney Diseases Outcomes and Quality Initiative guidelines highlight the importance of cardiac risk screening in all patients with end-stage renal disease at the start of dialysis.[13] Additionally, CAD screening in renal transplant candidates helps assess the perioperative cardiovascular risk and can stratify the possible risk in the first years after transplantation.[14] Patients with ICM also have a high rate of MVD, reported to be 78.3% by Candell-Riera et al.[6]

The SPECT-MPI procedure can be accompanied by the assessment of morphological lesions in CAD, such as atherosclerosis. The widely available coronary artery calcium score (CACS) is measured by electrocardiographically-gated multidetector computed tomography (MDCT). The CACS has been described as an independent predictor of CAD, with advantages over cardiovascular risk scores. It can impact the interpretation of MPI owing to a correlation between the extent of coronary artery calcium and the coronary artery wall plaque burden.[15-21] In the current study, we examined the outcomes of SPECT-MPI combined with the CACS measurement to identify predictors of ACEs in a defined group of patients for whom ischemia detection was expected to be difficult with SPECT-MPI.

METHODS

Study population The study group included 195 consecutive patients referred for cardiac gated SPECT-MPI imaging, who fulfilled the following inclusion criteria: a history of CKD, end-stage renal disease (n = 145), or suspected ICM (n = 35), or the presence of LBBB (n = 17). These subgroups were combined, and the sensitivity of SPECT-MPI was expected to be lower for the whole group. The mean (SD) age of patients was 62.2 (10.9) years (range, 35–100 years), and 139 of patients (71.3%) were male. Diabetes was present in 94 patients (48.2%). The whole study group underwent gated SPECT-MPI and CACS measurement. Informed consent was obtained from all individual participants included in the study.

Stress and rest testing Patients were examined according to a 1-day stress–rest or a 2-day rest–stress protocol. The selection of the protocol primarily depended on the distance of the patient's residence from the laboratory. Patients with a history of myocardial infarction or revascularization (n = 12) were examined at least 2 months after the event. The stress test consisted of exercise on a bicycle ergometer. The exercise was conducted until reaching 85% of the age-predicted maximal heart rate, or the onset of angina pectoris, dyspnea, fatigue, dizziness, frequent (more than 10 per minute) multifocal or paired ventricular extrasystoles, ST-segment depression (>0.2 mV), or until blood pressure decreased 10 Torr below the previous stage value.

If the patient did not fulfil the criteria for adequate exercise stress test or was unable to exercise at all, they received a 4-minute dipyridamole infusion at a standard dose of 0.56 mg/kg of body weight or regadenoson injection at a dose of 0.4 mg combined with a low level of exercise. Patients with LBBB were stressed by dipyridamole alone to avoid tachycardia and reduce the possibility of septal artefacts.[7] Pharmacological stress was indicated in 53 cases (27.2%). If the stress study was completely normal in terms of left ventricular (LV) perfusion and function, the rest of the study was waived (13 cases, 6.7%). The radiopharmaceuticals used were ^{99m}Tc-labelled sestamibi or tetrofosmin. The administered activity of the radiotracer for the reference patient (adult, 70 kg) was 300 MBq for the stress study. The dose for the rest study was 750 MBq for the 1-day protocol or 300 MBq for each rest and stress study in the 2-day protocol. The administered activities of the radiopharmaceuticals were adjusted according to body weight.

Gated single-photon emission computed tomography acquisition and processing The SPECT was acquired using a GE Discovery NM 630 or NM/CT 670 tomographic camera (GE Medical Systems Israel, Functional Imaging, Tirat Carmel, Israel), equipped with low-energy high-resolution collimators in an L-mode (90°) configuration. Images were gated at 8 frames per cardiac cycle. In the case of an inferior wall defect, additional prone position imaging was performed to identify a possible attenuation artefact.[7] The acquired studies were processed and automatically evaluated using a 4-DM software application (INVIA, Ann Arbor, Michigan, United States) to calculate the following values: summed difference score (SDS), SDS converted to percentage of ischemic myocardium (%SDS),[22] stress and resting LV volumes, and LV ejection fraction (LVEF).

The severity of the detected ischemia was stratified into 2 groups: 1) mild ischemia with a %SDS of less than 10%, and 2) severe ischemia

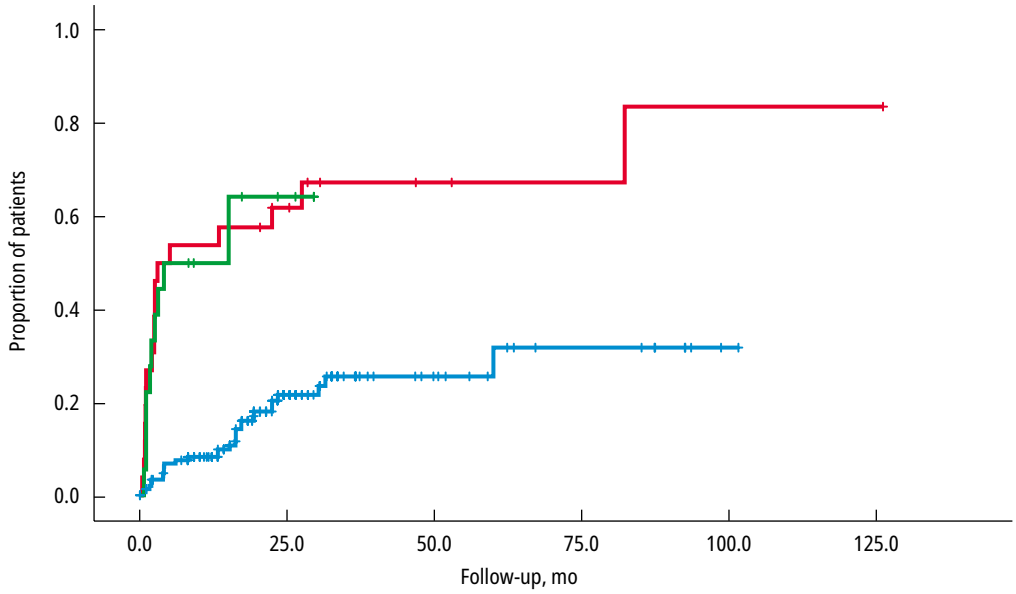

FIGURE 1 Kaplan–Meier survival curves: blue line, patients without ischemia; red line, patients with mild ischemia; and green line, patients with severe ischemia. Patients with mild or severe ischemia had significantly poorer outcomes (P <0.001, P <0.001); however, there was no difference in the cardiac event distribution between patients with mild and severe ischemia (P = 0.84).

with a %SDS of 10% or higher. Positive parameters from the gating study were defined as an LVEF of less than 40%, end-systolic volume of more than 70 ml, and worsening (≥5%) of LVEF after stress.

Coronary artery calcium scoring All 195 patients were evaluated to determine the CACS, following the SPECT-MPI examination. A positron emission tomography–computed tomography (PET-CT) scanner (Biograph mCT 40, Siemens, Germany) or GE Discovery NM/CT 670 tomographic camera was used with the standard vendor's software based on the Agatston method (cutoff >130 Hounsfield units).

Follow-up During the follow-up, the ACEs were recorded, including angina requiring hospitalization and coronary revascularization, nonfatal myocardial infarction, or cardiac death. Patients were categorized into 2 groups: with and without an ACE.

Statistical analysis Continuous variables were expressed as the mean (SD) or median with interquartile range (IQR), and categorical variables, as the count and percentage. Categorical variables were compared using the Fisher exact test, while continuous variables, using the t test or nonparametric tests (Mann–Whitney test, median test), where appropriate. Odds ratios were calculated with 95% CIs. The receiver operating characteristic (ROC) analysis was performed to select the optimal CACS value and identify patients at higher risk of ACEs. The optimal cutoff was determined by the value with the highest sensitivity and specificity. Univariate Cox proportional hazards models were used to determine whether the evaluated variables predicted ACEs. Multivariable Cox proportional hazards models were used to calculate an adjusted hazard ratio (HR) and 95% CI for selected predictors. For the purpose of regression analyses, the base 2 logarithm of the CACS was used, as described in previous studies.[23] To analyze patients with zero scores, all values were summed with 1 before transformation, using the following formula: $\log_2(\text{CACS}+1)$. One unit in the transformed variable indicates doubling the CACS. The Kaplan–Meier analysis with survival curve plots was used to determine the effect of the CACS and ischemia severity on the survival time to ACEs. The data were evaluated using a log-rank test. The level of significance was set for all tests at a P value of less than 0.05 (2-tailed). Statistical analysis was done using IBM SPSS Statistics for Macintosh (Version 25.0, IBM Corp, Armonk, New York, United States).

RESULTS The mean (IQR) follow-up was 19.3 (21.0) months. During this period, ACEs were recorded in 58 patients (29.7%) (14 cardiac deaths, 44 myocardial infarctions or revascularizations). The ACE group had an overall higher rate of ischemia detection on SPECT than the non-ACE group (50.0% vs 10.9%, P <0.001), and a higher percentage of ischemic myocardium (median, 5.9 vs 0.0, P <0.001). We also observed a difference in the proportions of stratified ischemia severity between both groups (P <0.001). In the Kaplan–Meier analysis, patients with mild or severe ischemia had poorer outcomes (P <0.001 for both), but there was no difference in the ACE distribution between patients with mild and severe ischemia (P = 0.84, FIGURE 1). Patients with ACEs more often had functional abnormalities (58.6% vs 41.6%, P = 0.04), had higher CACSs (1166 vs 152, P <0.001), and were older (median, 66.3 vs 60.1 years, P = 0.01)

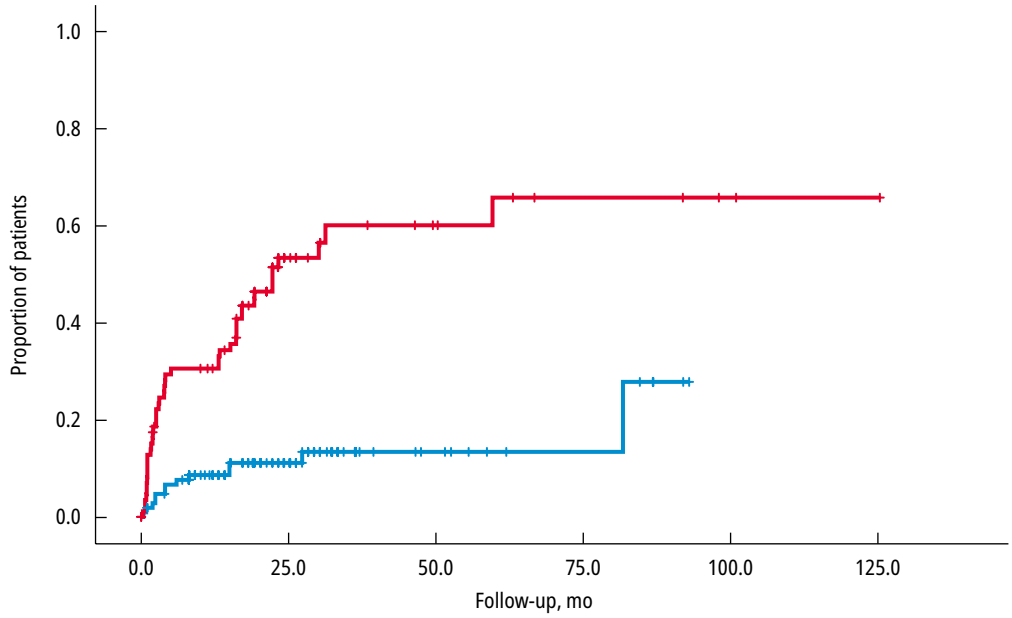

FIGURE 2 Kaplan–Meier survival curves: blue line, patients with a coronary artery calcium score (CACS) <530; red line, patients with a CACS ≥530. Patients with higher CACSs had significantly poorer outcomes (P <0.001).

compared with patients without ACEs. However, there were no differences in sex distribution and history of diabetes between ACE and non-ACE groups (P = 0.12 and 0.06, respectively). No difference was found between stress and resting LVEF values (mean [SD], 50.7 [12.7] vs 53.8 [13.5], P = 0.14 and 50.2 [14.0] vs 51.5 [12.9], P = 0.54).

The ROC analysis revealed that the optimal cutoff value for the CACS to predict ACEs was 530 (area under the curve, 0.79), with a sensitivity of 77.6% and a specificity of 68.6%. The CACS was also assessed as a dichotomous variable (<530 and ≥530, FIGURE 2). The characteristics of the study group are summarized in Supplementary material (*Table S1 and S2*). The univariate Cox proportional hazards models revealed that mild ischemia (HR, 4.99; 95% CI, 2.77–9.01; P <0.001), severe ischemia (HR, 5.31; 95% CI, 2.63–10.72; P <0.001), abnormal functional parameters (HR, 1.99; 95% CI, 1.17–3.33; P = 0.01), age (HR, 1.03; 95% CI, 1.01–1.06; P = 0.01), the CACS as a transformed continuous variable [$\log_2$(CACS+1)] (HR, 1.41; 95% CI, 1.24–1.61; P <0.001), and the CACS of 530 or higher as a categorical variable (HR, 5.16; 95% CI, 2.78–9.58; P <0.001) were associated with ACEs (Supplementary material, *Table S3*). There were 23 patients with a CACS of 0, and none of them had an ACE recorded during follow-up.

Age, sex, history of diabetes, severity of ischemia, and the presence of functional abnormalities on gated SPECT were considered in the Cox proportional hazards model. Age (HR, 1.04; 95% CI, 1.01–1.06; P = 0.002), mild ischemia (HR, 4.32; 95% CI, 2.34–8.00; P <0.001), severe ischemia (HR, 6.00; 95% CI, 2.92–12.34; P <0.001), and a functional abnormality (HR, 2.00; 95% CI, 1.15–3.48; P = 0.014) were predictors of ACEs (Supplementary material, *Table S4a*). After adding the CACS as a stratified variable into the model, age (HR, 1.03; 95% CI, 1.00–1.05; P = 0.021), mild ischemia (HR, 3.58; 95% CI, 1.91–6.77; P <0.001), severe ischemia (HR, 6.85; 95% CI, 3.31–14.18; P <0.001), a functional abnormality (HR, 1.89; 95% CI, 1.07–3.36; P = 0.030), and a CACS of 530 or higher (HR, 4.60; 95% CI, 2.42–8.73; P <0.001) were all predictors of ACEs, while sex and a history of diabetes were not (Supplementary material, *Table S4b*).

There were slight differences after evaluating the CACS as a continuous variable. Mild and severe ischemia, abnormal functional parameters, and CACS [$\log_2$(CACS+1)] were significant predictors of ACEs, while age, history of diabetes, and sex were not (Supplementary material, *Table S4c*).

In the subset of patients without ischemia on MPI (151 patients), 29 ACEs were recorded (19.2%). An additional stratification by a CACS of 530 or higher was performed, and the Kaplan–Meier analysis showed a significant association between the higher CACS and the occurrence of ACEs during follow-up (P <0.001). We observed only 3 ACEs (10.3%) within this subset of patients when the CACS was lower than 530. There were no differences in abnormal functional parameters in this subset (P = 0.75) (FIGURES 3 and 4; Supplementary material, *Table S5*).

DISCUSSION The relative nature of perfusion data processing on SPECT-MPI requires at least one unaffected coronary artery for accurate interpretation.[3,24] In our study, we examined patients with a high pretest probability of CAD. It can be difficult to assess perfusion with SPECT-MPI in these patients because of multiple affected coronary arteries. We combined information from the perfusion study with data from the gated SPECT to evaluate functional changes of the left ventricle, and used the CACS to depict

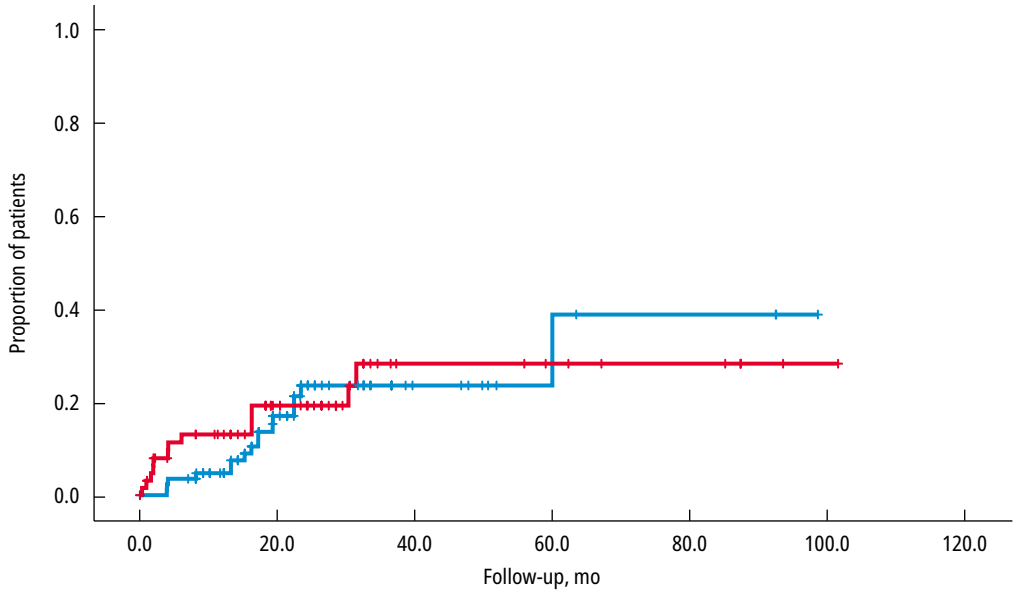

FIGURE 3 Kaplan–Meier survival curves, subgroup of patients without detected ischemia on single-photon emission computed tomography (SPECT) myocardial perfusion imaging: blue line, patients without functional abnormality; red line, patients with functional abnormality on gated SPECT. No difference was found (P = 0.75).

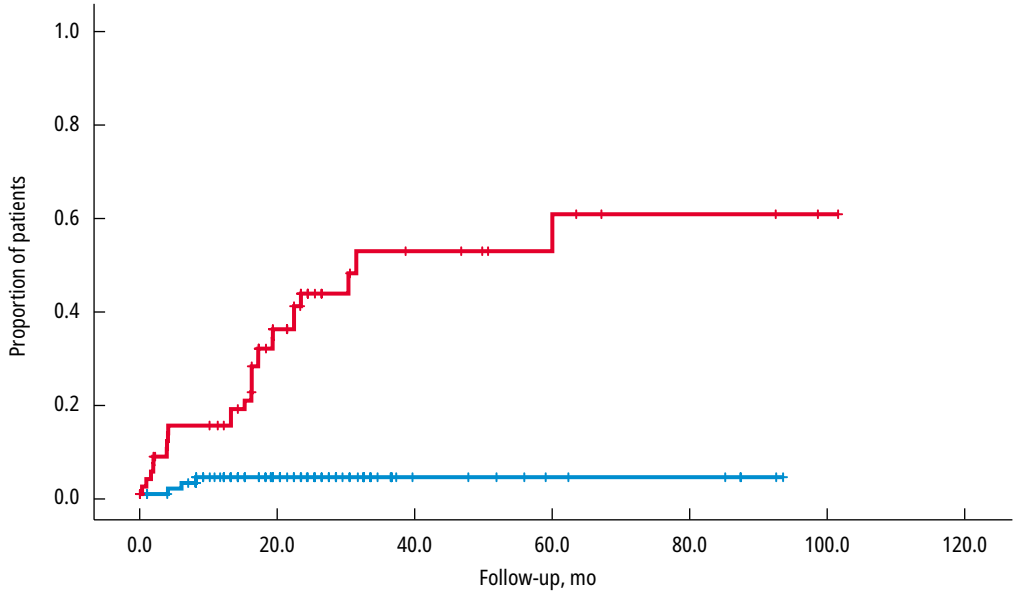

FIGURE 4 Kaplan–Meier survival curves, subgroup of patients without detected ischemia on single-photon emission computed tomography myocardial perfusion imaging: blue line, patients with a coronary artery calcium score (CACS) <530; red line, patients with a CACS ≥530. Patients with higher CACSs had significantly poorer outcomes (P <0.001).

morphological lesions related to atherosclerosis. Our results showed that the detection of an ischemic myocardium on SPECT-MPI can help identify patients with a higher cardiovascular risk. We did not find significant differences between the outcome of patients with mild and severe ischemia detected by SPECT-MPI. This is consistent with the assumption that perfusion defects are underestimated during the procedure in patients with MVD.[3,4] However, a different therapeutic approach based on previous results from diagnostic tests could influence the prognosis.

Patients with ACEs show significantly higher CACS values. Based on the ROC analysis, we defined the optimal cutoff value for the prediction of an ACE as 530. The European guidelines on cardiovascular disease prevention in clinical practice note that a higher cardiovascular risk is associated with a CACS over 300.[25] Our higher value may be due to the study population. Coronary artery calcification is affected by age, sex, and race. Some studies stratified the coronary calcium values in population percentiles, where a higher risk is associated with a CACS exceeding the 75th percentile for a particular age interval.[26,27] We did not use this principle because we wanted to identify a single parameter for daily practice.

The CACS has a high negative predictive value, as found by Valenti et al[28] in a prospective follow-up study of 9715 individuals. A score of 0 conferred 15 years without mortality in individuals at low to intermediate risk and better survival of individuals at high risk than those with a low to intermediate risk but a CACS higher than 0.[28] In our study, no patient in the ACE group had a CACS of 0. However, an absence of calcification (CACS of 0) does not exclude CAD.

Acute coronary artery thrombosis can be caused by plaque erosion (in about 30%), which is associated with low calcification.[29,30] Plaque erosion is more frequent in certain groups of patients, especially the young, smokers, and women.[30,31]

In the ACE group, we found significant ischemia (mild or severe) based on the perfusion data in only 50% of patients, which is lower than the broadly reported sensitivity of SPECT-MPI (approximately 70%–90%).[1] Adding the functional assessment should improve the detection[4,22,32]; however, in the subgroup of patients without ischemic defects, the functional parameters did not help identify individuals with poor outcomes. Significant differences were identified with the CACS. When we used a calculated CACS cutoff of 530, higher values were significantly associated with ACEs, while only 3 patients without ischemia on SPECT-MPI and a CACS of less than 530 experienced an ACE.

Multivariate regression models showed that ischemia (both mild and severe), abnormal functional parameters, and the CACS expressed as $\log_2$(CACS+1) were all significant predictors of an ACE, as was a CACS of 530 or higher and age in the dichotomous model. The HR for the ischemic myocardium values when the CACS was 530 or higher was 4.6, while it was 1.5 for the model considering doubling of the CACS. The HR from the univariate analysis for the $\log_2$(CACS+1) was similar to that reported by Church et al[33] in a population of 10 746 patients and Han et al[34] in a study of 34 386 individuals. We did not find a difference in the proportions of patients with diabetes between the groups with and without ACEs, and the Cox regression models did not associate this with ACEs. Although diabetes is a traditional risk factor and there is evidence for risk heterogeneity in populations with diabetes, guidelines did not sufficiently acknowledge diabetes as a coronary risk factor, and additional stratification in diabetic patients is recommended.[25,35]

Detection of small calcified lesions requires sufficient spatial and time resolution, which can be accomplished with modern MDCT systems. Yet, some minor foci will not be identified by noninvasive imaging techniques. Some studies, based on detection of calcifications by intravascular ultrasound or optical coherence tomography, depict variable patterns of plaque calcifications. These can have a spotty or dense character, but a spotty pattern is more frequent in high-risk plaques. Differentiating these patterns by MDCT is not possible,[30] but PET-CT with ^{18}F-sodium fluoride appears to be a promising method for identification of microcalcifications and high-risk plaques.[36] Inflammation processes are involved in all phases of atherosclerosis, and the activity of inflammation correlates with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake.[37,38] Higher accumulation of ^{18}F-FDG could be a marker of potential plaque instability.[39] All these methods can help identify patients with higher cardiovascular risk, but their utilization on a daily basis is limited.

On the other hand, there are hybrid SPECT-CT systems available in nuclear medicine departments, where the CACS can be acquired during a single visit as an adjunct to SPECT-MPI. The MDCT is associated with an additional radiation burden to the patient. However, some researchers described only a very low radiation load when utilizing a modern dual-source computed tomography system for CACS, with the effective dose reduced to 0.3 mSv. In general, the protocol should not exceed an effective dose of 1.0 mSv.[40,41] The Society of Cardiovascular Computed Tomography, in a consensus statement, recommended measuring the CACS in addition to SPECT-MPI or MPI-PET in patients without prior anatomic evaluation for CAD.[41]

In conclusion, CACS evaluation as an adjunct to SPECT-MPI is useful for identifying patients at higher risk of ACEs, even in individuals for whom evaluation by SPECT-MPI is difficult due to the magnitude of atherosclerotic burden or artefacts. A score of 0 on the CACS predicts a favorable outcome.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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