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Age- and gender-adjusted percentiles for number of calcified plaques in coronary artery calcium scanning

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A B S T R A C T

Background: Age- and gender-adjusted percentiles of coronary artery calcium (CAC) score are commonly reported to compare a patient's coronary atherosclerosis burden to that of others of the same age and gender. The number of calcified plaques (numCP) detected on CAC scanning, a measure of plaque diffusivity, is associated with increased cardiovascular risk and, in the intermediate CAC range, adds to the CAC score in predicting mortality. This study aims to develop adjusted percentiles for numCP to provide a better context for understanding CAC scan findings.
Methods and results: Using nonparametric modeling techniques, the distribution of numCP was analyzed in 70,320 consecutive, asymptomatic patients without prior clinically-diagnosed cardiovascular disease who were part of the Coronary Artery Calcium Consortium and supplemented by additional patients referred for clinical CAC scanning in a single center between 1998 and 2016. Nomograms for age-adjusted numCP percentiles for each gender were generated using quantile regression. The prevalence and average number of calcified coronary plaque were found to be higher in men than women. Distribution of numCP in women was found to closely mirror that of men approximately a decade younger. NumCP increased consistently across age groups in both men and women for each quantile category.
Conclusions: A nomogram for age and gender-adjusted percentiles for the numCP on CAC scans has been developed in a large population of asymptomatic patients studied across multiple centers. This numCP nomogram may provide an additional tool for refining physician recommendations regarding treatment and expressing to patients how their CAC findings relate to others of similar age and gender. The numCP percentiles may also provide a meaningful way to evaluate and report the rate of progression of CAC on serial studies.

1. Introduction

Coronary artery calcium (CAC) scanning provides an effective means for detecting and quantifying the burden of subclinical atherosclerosis. The predominant variable used to assess CAC is the Agatston score, a global summary measure of total coronary arterial calcification.[1] As a marker of the extent of coronary atherosclerosis, the CAC score is a strong predictor for adverse cardiovascular events and has been shown to consistently add to the predictive power provided by global risk scores.[2]

In recent years, there has been increased interest in using additional parameters from CAC scans beyond the traditional Agatston score, such as assessment of the diffuseness or distribution of CAC lesions (e.g., which vessels and number of coronary vessels involved)[3–5] and the density of coronary plaques.[6] Higher number of coronary plaques (numCP), a measure of the diffuseness of coronary atherosclerosis, has previously been found to be associated with elevated rates of mortality.[7] Further, for patients in the intermediate CAC score range, numCP has been shown to add to the CAC score in the prediction of mortality risk.[8] However, the age and gender-specific distribution of numCP has not yet been evaluated. Beyond raw number of calcified plaques, numCP percentiles may be a potentially useful tool for understanding the context of numCP findings in individual patients. Hence, there is a need to express dispersiveness of CAC relative to peer-adjusted data. The purpose of this study was to assess the distribution of numCP in a large multi-center clinical population and develop a

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nomogram to convert numCP into a percentile score adjusted by patient age and gender.

2. Methods

2.1. Study population

Our study included patients from the Coronary Artery Calcium (CAC) Consortium, a multi-center database of asymptomatic patients from four medical centers across the United States,[9] and a large cohort of additional patients who underwent CAC scanning at Cedars-Sinai Medical Center (CSMC) (Los Angeles, CA) between August 1998 and December 2016. Patients were either clinically or self-referred for CAC scanning. Patients who had prior cardiovascular disease were excluded, including those who had previously undergone heart surgery, angioplasty, or catheterization; or experienced prior heart attack, angina, stroke, heart failure; or had atrial fibrillation at the time of the CAC imaging procedure. Patients with missing variables including age, gender, and numCP were also excluded. This study was approved by the Cedars-Sinai Medical Center and Johns Hopkins Hospital Institutional Review Boards.

2.2. Clinical data collection

Clinical data collection methods for the CAC Consortium are delineated in a prior manuscript.[9] The CSMC patients completed a medical questionnaire at the time of their imaging visit. Pertinent variables included demographic information, cardiac risk factors, and use of medications. Serum lipids and fasting glucose levels were also measured at the time of the CAC scan. Cardiac risk factors queried included age, gender, diabetes, smoking, hypertension, dyslipidemia, family history of premature CAD, and body mass index (BMI). Family history of premature CAD was defined as having a primary relative diagnosed for CAD or cardiac event less than 55 years of age and smoking status was determined as having smoked within one year prior to scanning. Hypertension was defined as having been previously diagnosed with hypertension, receiving treatment of antihypertensive medication, or having a systolic blood pressure of greater than 140 mmHg. Diabetes mellitus was identified as a prior clinical diagnosis of diabetes, use of diabetes medication, or a fasting blood glucose of greater than 126 mg/dL (7.0 mmol/L). Dyslipidemia was defined as having a pre-existing diagnosis for dyslipidemia, taking lipid-lowering agents, a LDL-C level of greater than 130 mg/dL (3.36 mmol/L), a HDL-C level of less than 40 mg/dL (1.0 mmol/L) for men or 50 mg/dL (1.3 mmol/L) for women, or a total cholesterol of greater than or equal to 230 mg/dL (6.0 mmol/L).

2.3. Coronary artery calcium scanning

CAC scanning was performed at each of the study sites according to standard procedures using either an electron-beam computed tomography scanner or a multi-detector scanner. Additional information on detailed methods for computed tomography (CT) scanning in each of the study sites were previously described.[9] ECG-gated non-contrast CT was performed during diastole between 50% and 80% of the R-to-R cycle depending on heart rate, obtaining 30 to 40 images at 3-mm intervals from the carina caudally to the diaphragm. A CT threshold of 130 HU and three pixels was used to identify presence of calcified coronary artery lesions. Number of calcified plaques was quantified for each of the coronary arteries and totaled for each patient. Total CAC scores were determined through the Agatston method.[1] The scanning methods for the CSMC individuals outside of the CAC Consortium were the same as those within the Consortium.

2.4. Statistical analysis

The distribution of numCP was significantly skewed, with 49.1% of patients having zero coronary plaques; however, after log transformation, the positive portion of the numCP distribution did not demonstrate significant skew and was approximately normally distributed on the log scale. Due to the deviation from normality of numCP, similar to the distribution commonly observed in coronary artery calcium scores,[10] non-parametric statistical analyses were used. Proportions of individuals with one or more calcified coronary plaques by age for each gender were estimated using a local regression model (smoothing span = 0.7) to estimate the prevalence of coronary calcified plaques.[11]

For each gender, the distribution of numCP was used to derive age-adjusted percentiles for number of observed calcified plaques. Crude age- and gender-adjusted percentiles for number of CAC plaques were determined empirically by stratifying the final study group based on age and gender and then ranking the values for number of coronary plaques within their respective categories. These empirical percentiles were calculated based on rank within age range and gender subgroup then constructed into a nomogram for easy visualization[12,13] (Table 2). In addition to presenting the empirical percentiles which directly reflect the distribution of the population, a model was fitted to increase the precision of the calculated percentiles using age as a continuous variable. Gender-stratified percentiles were generated nonparametrically using a quantile regression model with locally weighted smoothing (span = 0.7) and depicted as a graphical nomogram.

Welch's *t*-test was used for the comparison of means for continuous variables that could reasonably meet the normality condition. For comparing the distribution of other continuous variables, including numCP and CAC score, a nonparametric Wilcoxon-Mann-Whitney test was used for comparison of medians. The z-test for independent proportions and Pearson's chi-square test were used for comparison of categorical variables studied. A two-sided p-value of less than 0.05 was required for statistical significance. All calculations were computed using R, version 3.4.4.[14]

3. Results

3.1. Study population

Table 1 shows the demographic and clinical characteristics of the final study population. After excluding 93 patients with missing age and/or gender, a total of 70,320 patients (45,615 from the CAC Consortium who had available numCP assessment and 24,705 additional patients from CSMC) were used to derive the nomogram. 34% of the patients were women (age of 56.4 ± 10.2) and 66% were men (age 53.1 ± 10.4). A greater proportion of men had hypertension, hyperlipidemia, obesity, and tobacco use compared to women. Additionally, coronary artery calcium (CAC) scores were higher in men than women ($p < 0.001$). Men also were found to have a higher median CAC score than women (Table 1). Similarly, numCP was significantly higher in men than women ($p < 0.001$).

3.2. Development of initial calcified plaque

For each gender, the proportion of individuals demonstrating a calcified coronary plaque increased directly as a function of increasing age (Fig. 1). For both men and women, the relationship between age and prevalence of calcified coronary plaques closely followed a logistic, S-shaped pattern. The estimated 50% prevalence age for having any calcified plaque was 61 for women and 50 for men, respectively. A difference of nine years was observed between the estimated age of 75% prevalence of calcified plaque in women and men (age 73 and 64, respectively). From the inflection point of a logistic equation fitted to the observed prevalence of calcified plaque by age, coronary calcified plaques were found to start developing at the highest rate at age 53 for

Table 1
Baseline characteristics of study population.

	Total N = 70,320	Women N = 23,942	Men N = 46,378	P-Values
Age (mean [SD])	54.24 (10.46)	56.37 (10.19)	53.13 (10.42)	< 0.001
≤ 40 (%)	6061 (8.6)	1265 (5.3)	4796 (10.3)	< 0.001
41–45 (%)	7817 (11.1)	1918 (8.0)	5899 (12.7)	< 0.001
46–50 (%)	10,866 (15.5)	3174 (13.3)	7692 (16.6)	< 0.001
51–55 (%)	12,660 (18.0)	4465 (18.6)	8195 (17.7)	0.001
56–60 (%)	11,010 (15.7)	4349 (18.2)	6661 (14.4)	< 0.001
61–65 (%)	7604 (10.8)	3100 (12.9)	4504 (9.7)	< 0.001
66–70 (%)	4877 (6.9)	2138 (8.9)	2739 (5.9)	< 0.001
71–75 (%)	2723 (3.9)	1177 (4.9)	1546 (3.3)	< 0.001
> 75 (%)	2046 (2.9)	903 (3.8)	1143 (2.5)	< 0.001
Risk Factors				
Current Smoker (%)	6528 (9.4)	2023 (8.6)	4505 (9.8)	< 0.001
Diabetes (%)	3341 (4.8)	1067 (4.5)	2274 (4.9)	0.009
Hypertension (%)	21,791 (31.4)	7645 (32.3)	14,146 (30.9)	< 0.001
Dyslipidemia (%)	42,210 (60.8)	14,624 (61.8)	27,586 (60.2)	< 0.001
Family History of CAD (%)	31,268 (46.1)	12,138 (52.5)	19,130 (42.8)	< 0.001
BMI, kg/m^2 (mean [SD])	27.22 (5.19)	26.07 (5.80)	27.85 (4.71)	< 0.001
Underweight (%)[b]	524 (1.1)	395 (2.3)	129 (0.4)	< 0.001
Overweight (%)[b]	19,853 (41.6)	4725 (27.7)	15,128 (49.3)	< 0.001
Obese (%)[b]	11,125 (23.3)	3547 (20.8)	7578 (24.7)	< 0.001
Number of Coronary Plaques (median [IQR])[a]	0 [0, 4]	0 [0, 2]	1 [0, 6]	< 0.001
Coronary Artery Calcium Score (median [IQR])[a]	1 [0, 76]	0 [0, 21]	7 [0, 119]	< 0.001

All values indicate mean ± standard deviation unless otherwise specified.
CAD = coronary artery disease; BMI = body mass index; ACE = angiotensin-converting enzyme; IQR = interquartile range.
[a] Wilcoxon test was used for statistical comparison between gender.
[b] BMI categories were defined as BMI < 18.5 kg/m^2 (underweight), 20.0 ≤ BMI < 30.0 kg/m^2 (overweight), BMI ≥30.0 kg/m^2 (obese).

men and 62 for women.

3.3. Number of coronary plaques percentiles by age and gender

Table 2 displays a nomogram of the numCP percentiles by five-year age group and gender. The number of plaques associated with each percentile category was found to increase monotonically with age in both genders with a similar delay in the development of numCP in women versus men, as was observed for the development of the initial plaque.

Fig. 2 shows the predicted percentile of number of plaques for patients based on age and stratified by gender. In both men and women, numCP increased steadily with age across percentile category. The number of calcified plaques associated with higher percentiles demonstrated a sharper rate of increase with age relative to the lower percentiles, resulting in a fan-shaped distribution of quantiles expanding outwards with increased age. Comparing the numCP development rate between the genders, numCP distribution in women at any

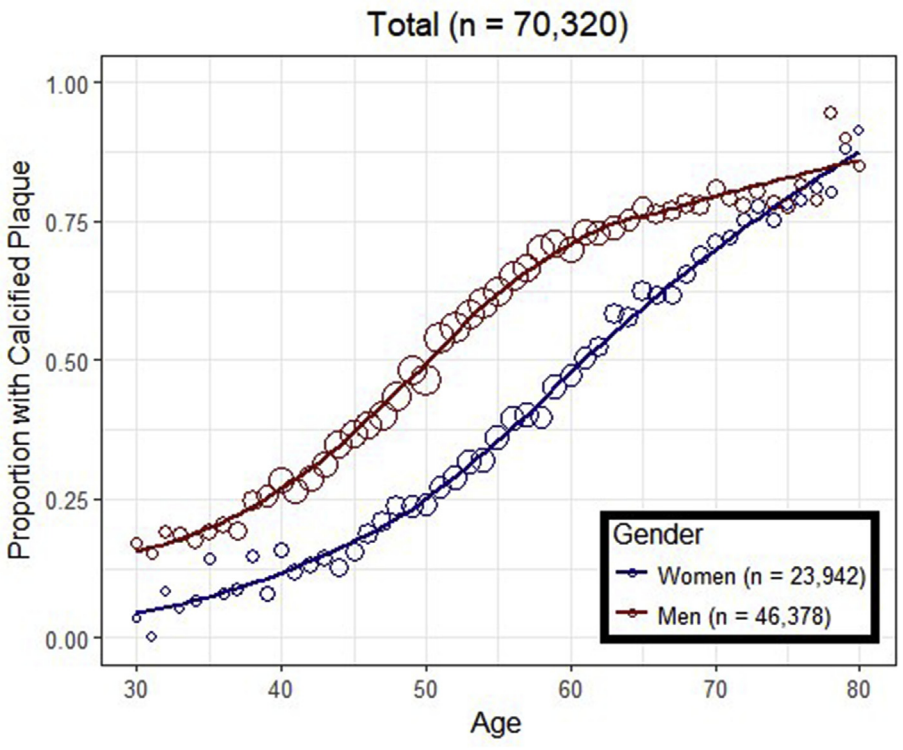

Fig. 1. Proportion of individuals with calcified coronary plaques by age and gender. Circles represent observed prevalence of calcified coronary plaque by age with size relative to sample numbers (smaller points reflect smaller sample size and larger points reflect larger samples). The solid line is a smoothed local polynomial regression derived from the observed proportions.

Table 2
Number of coronary artery plaques nomogram by age and gender for 70,320 consecutive patients.

Age Group		≤ 40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	> 75
Women, n		1346	2067	3466	4801	4606	3285	2291	1258	822
	10th	0	0	0	0	0	0	0	0	0
	25th	0	0	0	0	0	0	0	1	2
Percentile	50th	0	0	0	0	0	1	2	4	7
	75th	0	0	0	1	2	4	6	10	14
	90th	1	1	2	4	5	9	12	17	24
Men, n		5156	6396	8353	8818	7139	4864	2963	1684	1005
	10th	0	0	0	0	0	0	0	0	0
	25th	0	0	0	0	0	0	1	2	4
Percentile	50th	0	0	0	1	2	4	7	9	13
	75th	0	1	2	5	8	11	15	18	24
	90th	2	4	7	11	16	20	23	28	33

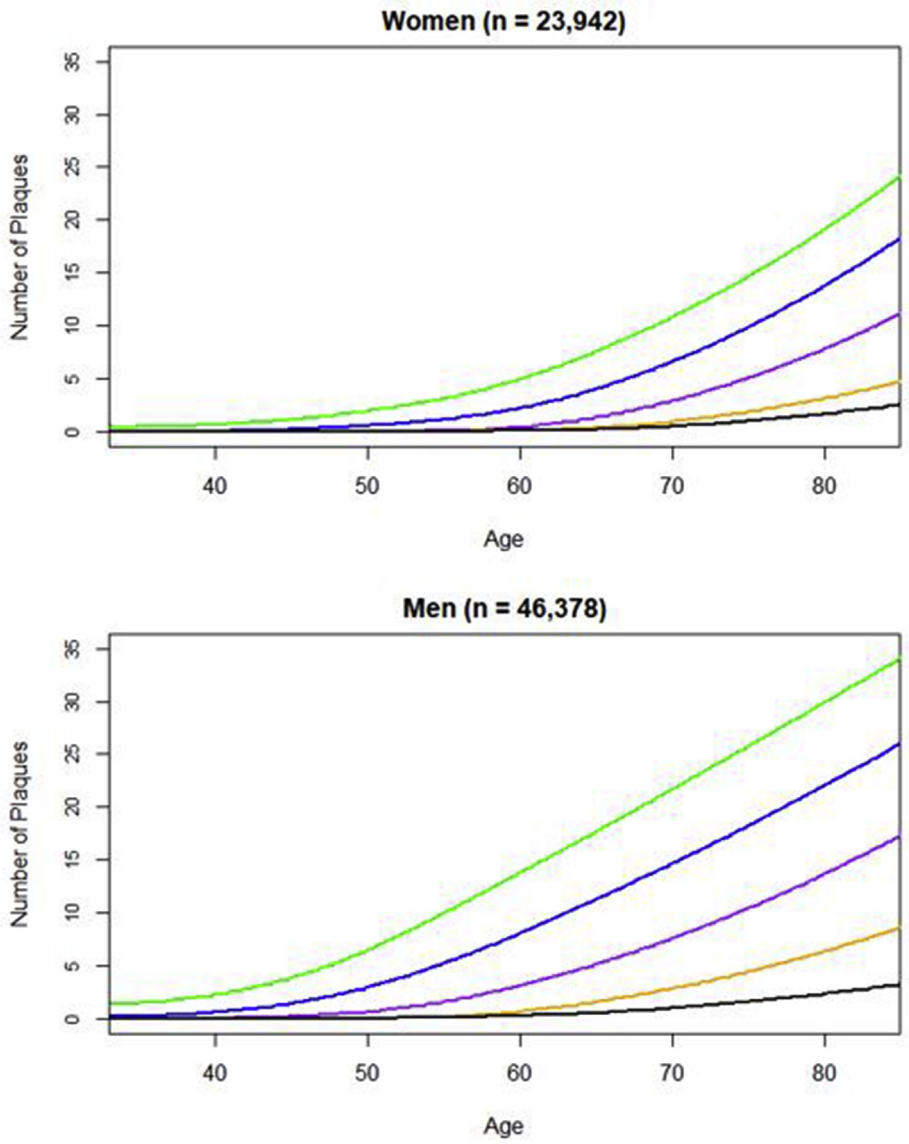

Fig. 2. Estimated percentiles of number of plaques for 23,942 women and 46,378 men. Solid lines represent the quantile local regression models for number of plaques in each percentile category relative to age grouped by gender.

given age was similar to that of men who were approximately a decade younger. After adjusting for a ten-year temporal difference in plaque development, the rates of developing numCP with age across all quantiles between the two genders were almost visually identical.

4. Discussion

The development of myocardial infarction is usually a consequence of coronary thrombosis secondary to plaque rupture and the likelihood of plaque rupture leading to myocardial infarction has been related to

the number of coronary plaques.[15] The CAC score is a global measure of atherosclerotic burden, but it does not distinguish between coronary calcium which is just focally or widely distributed. Assessment of the numCP has been shown to be a significant predictor of mortality and, for patients in the intermediate CAC range, to have incremental value over the CAC score in prediction of risk of death.[7,8] In this study, we developed age and gender-based percentile scores for coronary plaque measurements from a large, multi-center cohort of asymptomatic patients referred for CAC testing. These percentiles provide health care providers and patients a metric by which the clinical implications of numCP can be easily understood.

In our analysis, we explored the prevalence and general distribution of numCP by age and gender. Similar to prior findings, CAC prevalence was found to increase monotonically with age among both men and women.[10] The increase in numCP also was seen to occur approximately ten years earlier among men than women. Additionally, for both genders, percentiles for numCP demonstrated an outward fanning distribution with increasing age, suggesting that the use of age-adjusted numCP percentiles for risk stratification may have greater importance in older patients, while the presence of coronary plaque and the CAC score alone may be sufficient for assessing cardiovascular risk in younger individuals.

Our proposed use of coronary plaque percentiles parallels the traditional method used to evaluate CAC scores. Coronary artery calcium is commonly expressed as both an absolute CAC score and a percentile CAC score, providing a context of how a given absolute CAC score reflects the relative risk of a patient compared to age and gender-adjusted standards.[10] Combining the CAC score and percentile based on age and gender provides an index of the aggressiveness of the disease in an individual patient that can be used to influence physician risk management recommendations and patient compliance with heart-healthy behaviors. Further, regarding treatment, the Society of Cardiovascular Computed Tomography (SCCT) and the Society of Thoracic Radiology (STR) guidelines recommend that patients with CAC scores 1–100 whose CAC percentiles are greater than 75th percentile for age and gender be treated with high intensity statin therapy,[16] more intensively than those with lower percentiles. As presented in this study, numCP percentiles may be used in a similar fashion, adding information that might complement CAC percentiles in guiding the intensity of therapy.

CAC scans are also often repeated in attempt to understand the rate of progression of CAD; however, the CAC score virtually always goes up over time. The rate of increase in the CAC score may reflect a healing process and may progress at a greater rate in patients placed on statin therapy.[17,18] Thus, it is difficult to interpret the clinical implications of changes in CAC score. While the relationship between serial assessment of plaque number and risk has yet to be reported, increases in plaque numbers may be reflective of new plaque development and may prove to be of greater value than the CAC score in assessing the rates of CAD progression on serial CAC scanning. In individual patients undergoing repeat CAC scanning, changes in the numCP percentiles may provide a useful means for conveying the implications of changes in numCP to health care providers and patients.

4.1. Limitations

As the patients in this study were either clinically or self-referred for CAC, the results may be dissimilar to subjects culled from community cohorts and referral bias may be a concern when generalizing results to the overall population; however, as patients in this cohort had clinical reasons for undergoing a CAC scan relative to the general population, the population used to develop the percentiles is likely to reflect the type of patients seen in clinical practice. Additionally, in this study, both multi-detector CT (MDCT) and electron beam tomography (EBT) scanners were used for CAC scanning. Although CAC scores have been shown to be highly correlated between the MDCT and EBT systems,[19] the correlation and variability of numCP measured between these two systems have not been previously assessed. Third, racial differences in CAC distribution have previously been observed[10]; however, due to limitations in sample sizes after stratifying by race, differences in numCP distribution and percentile values between racial groups were not assessed in this study.

5. Conclusions

A nomogram for age and gender-adjusted percentiles for the numCP on CAC scans has been developed in a large population of asymptomatic patients studied in multiple centers. Since the numCP may add to CAC score in assessing patient prognosis, the numCP nomogram could provide an additional tool for refining physician recommendations regarding treatment and expressing to patients how their CAC findings relate to others of similar age and gender. The numCP percentiles may also provide a meaningful way for evaluating and reporting the rate of progression of CAC on serial studies.

Conflicts of interest

The authors declare no conflicts of interest in this submission.

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