CLINICAL RESEARCH STUDY

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Cardiovascular and All-Cause Mortality Risk by Coronary Artery Calcium Scores and Percentiles Among Older Adult Males and Females

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ABSTRACT

BACKGROUND: Coronary calcium is a marker of coronary atherosclerosis and established predictor of cardiovascular risk in general populations; however, there are limited studies examining its prognostic value among older adults (≥75 years) and even less regarding its utility in older males compared with females. Accordingly, we sought to examine the prognostic significance of both absolute and percentile coronary calcium scores among older adults.

METHODS: The multicenter Coronary Artery Calcium Consortium consists of 66,636 asymptomatic patients without cardiovascular disease. Participants ages ≥75 were included in this study and stratified by sex. Multivariable Cox regression models were constructed to assess cardiovascular and all-cause mortality risk by Agatston coronary calcium scores and percentiles.

RESULTS: Among 2,474 asymptomatic patients (mean age 79 years, 10.4-year follow-up), prevalence of coronary artery calcium was 92%. For both sexes, but in females more so than males, higher coronary calcium score and percentiles were associated with increased cardiovascular and all-cause mortality risk. Those at the lowest coronary calcium categories (0-9 and <25 percentile) had significantly lower risk of cardiovascular and all-cause mortality relative to the rest of the population. Multivariable analyses of traditional cardiovascular risk factors and coronary artery calcium variables revealed that age and coronary calcium were the strongest independent predictors for adverse outcomes.

CONCLUSIONS: Both coronary artery calcium scores and percentiles are strongly predictive of cardiovascular and all-cause mortality among older adults, with greater risk-stratification among females than males. Both low coronary artery calcium scores 0-9 and <25th percentile define relatively low risk older adults.

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INTRODUCTION

The burden of cardiovascular disease increases markedly with age and is the predominant cause of death in older adults.[1] However, how to best stratify older adults for cardiovascular risk remains uncertain. Consistent data from population-based studies and large registries have demonstrated that coronary calcium scores provide added value over cardiac risk factors for risk assessment in general populations. By comparison, studies regarding the utility of coronary calcium scanning in older adults have been limited.[2-4] Thus, there is a need to further understand the prognostic value of coronary calcium in older adults, including its utility by sex. Additionally, whereas the interpretation of coronary calcium scores is aided by the concomitant comparison of these scores to age-, race-, and sex-based coronary calcium percentiles, the utility of these percentiles among older adults has heretofore not been assessed. Thus, the purpose of this study was 1) to investigate the prevalence and extent of coronary artery calcium among older (age ≥75) asymptomatic adults; 2) to identify sex differences in the relationship between coronary calcium score and cardiovascular risk in this age group; and 3) to evaluate whether coronary calcium percentiles for older adults developed in the community-based Multi-Ethnic Study of Atherosclerosis (MESA) study provide effective risk stratification in a clinical patient population.

CLINICAL SIGNIFICANCE

- Coronary artery calcium scores and percentiles are strong independent predictors of 10-year cardiovascular and all-cause mortality outcomes in older adults ages ≥75.
- In older adults, coronary artery calcium variables provided greater risk stratification for females than males.
- Patients at the lowest coronary artery calcium categories had a significantly lower risk of cardiovascular disease and all-cause mortality, suggesting a potential use for coronary artery calcium to identify low-risk older adults.

METHODS

Study Population

Patients in the study were from the Coronary Artery Calcium Consortium, a cohort of 66,636 clinically or self-referred patients who underwent coronary calcium scanning between 1991 and 2010 from four medical centers across the United States. Only asymptomatic patients without known history of coronary artery disease were included in the Consortium. For this study, we evaluated 2,474 participants who were ≥75 years at the time of coronary calcium scanning. For our analyses on coronary calcium percentiles, we further excluded 265 patients ages ≥85 because of the upper age limit of established coronary calcium percentiles.[5]

Clinical Variables

We obtained baseline clinical and demographic information using a medical questionnaire or interview at the time of coronary calcium scanning. Family history of premature coronary artery disease was defined as having a primary relative diagnosed with coronary artery disease prior to ages 55 or 65 for males and females, respectively. Smoking was based on self-reported smoking status. Hypertension and diabetes were defined as having a prior diagnosis or prescription of disease-specific medication. Dyslipidemia was identified as having a previous diagnosis for dyslipidemia, treatment with lipid-lowering drugs, a low density lipoprotein-cholesterol (LDL-C) level of greater than 160 mg/dL, a high density lipoprotein-cholesterol (HDL-C) level of less than 40 mg/dL for males or 50 mg/dL for females, or a total cholesterol of greater than 230 mg/dL. Multiple imputation was used for observations with missing risk factor data.[6]

Coronary Calcium Scanning

Noncontrast cardiac-gated computed tomography (CT) scans for coronary artery calcium were performed at each site using standard clinical protocols. Coronary calcium score was quantified using the Agatston method.[7] Coronary calcium percentiles were based on those derived from the MESA cohort.[5] Further details on procedures used at each participating site in the Coronary Artery Calcium Consortium have been previously documented.[6]

Patient Outcomes

Follow-up was obtained through June 2014. Patient records were linked with the National Death Index (NDI) to assess mortality. All-cause mortality was identified by either a match on social security number (SSN) and an additional parameter or a match on all patient identifiers if SSN was not available. Mortality causes were reported based on *International Classification of Diseases-9th Revision* (ICD-9) and *International Classification of Diseases-Tenth Revision* (ICD-10) codes. Cardiovascular mortality was defined as death from coronary heart disease, heart failure, stroke, or other cardiovascular causes. Informed consent was collected at each respective medical center during coronary calcium imaging and approval for coordinating center activities, including follow-up for mortality outcomes, was attained from the Johns Hopkins Hospital Institutional Review Board.

Statistical Methods

For non-normally distributed continuous baseline variables, nonparametric Wilcoxon-Mann-Whitney tests were used for the comparison of medians between males and females. Other continuous variables were compared using Welch's *t*-tests. Categorical variables were compared by sex using Pearson's χ^2 tests.

Stratified by sex, Kaplan Meier survival curves were constructed for cardiovascular and all-cause mortality by coronary calcium score (0-99, 100-299, 300-999, ≥1000) or percentile category (0%-24%, 25%-49%, 50%-74%, 75%-100%) and compared using the log-rank test. Hazard ratios (HRs) for cardiovascular and all-cause mortality by coronary calcium were estimated using multivariable Cox proportional hazards models with either coronary artery calcium 0-9 or 0%-24% as the reference group. Wald tests were used for the comparison of risk by coronary calcium category. Cox proportional hazards models were also used to generate adjusted HRs for cardiovascular disease risk factors. Continuous coronary calcium score was modeled as log (coronary calcium+1). As a secondary analysis, adjusted HRs between low coronary calcium (0-9 or 0%-24%) compared with all other patients were estimated using Cox proportional hazards models. Two-sided *P* values of less than 0.05 were required for statistical significance and 95% confidence intervals were reported. All computations were performed using R, version 3.5.0.[8]

RESULTS

Study Population and Outcomes

Of the 2,474 patients age ≥75 in the Coronary Artery Calcium Consortium, the average age was 79 ± 4 years with 44% females (Table 1). The male and female patients had similar ages and frequency of smoking, diabetes, and obesity. Females had a higher prevalence of hypertension, hyperlipidemia, and family history of coronary artery disease. Males had more coronary calcification, particularly of coronary calcium scores ≥1000: 32.6% vs 12.1% in females. Conversely, females had a higher frequency of coronary calcium zero scores: 12.9% vs 4.7% and minimal coronary calcification (<10): 19.8% vs 7.5%. However, a similar proportion of females and males had coronary artery calcium below 25% percentile: 19.6% of females and 18.7% of males.

During median follow-up of 10.4 years, 722 (29.2%) died, of which 293 (11.8%) experienced mortality from cardiovascular causes. Rates of all-cause and cardiovascular mortality were comparable between females and males (Table 1).

Survival by Coronary Calcium Scores

Figure 1 shows the Kaplan Meier curves for cardiovascular and all-cause mortality by coronary calcium score category for each sex. With increasing coronary calcium scores, a general stepwise increase in cardiovascular and all-cause mortality was observed in both sexes ($P < 0.001$). This stepwise increase in cardiovascular and all-cause mortality by coronary artery calcium was greater in females than males.

Among all patients, adjusted HRs for cardiovascular and all-cause mortality increased by coronary calcium category (Table 2A). For females, adjusted HRs for both cardiovascular and all-cause mortality were significantly elevated in the 100-299, 300-999, and ≥1000 coronary calcium score ranges relative to the baseline category of 0-9. For males, the adjusted HRs were significantly higher for only coronary calcium scores ≥1000 compared to the baseline category of 0-9. Secondary analyses revealed that adjusted risk of both all-cause and cardiovascular mortality were significantly lower in the lowest coronary calcium category (0-9) compared to coronary calcium ≥10 (Supplementary Figure, available online).

Survival by Coronary Calcium Percentiles

Figure 2 shows the Kaplan Meier survival curves for cardiovascular and all-cause mortality among the male and female patients by coronary calcium percentile. In the 20% of females in the lowest coronary calcium percentile category (0%-24%), cardiovascular mortality over follow-up was 5%, which was comparable to event rates in the lowest coronary calcium score category (0-9). For the 19% of males in the lowest coronary calcium percentile category, cardiovascular mortality was 8%, similar to the event rate in the 8% of males in the lowest coronary calcium score category. There was a stepwise increase in cardiovascular and all-cause mortality with increasing coronary calcium percentiles for both genders ($P < 0.01$). As noted for coronary calcium scores, the stratification of survival curves by patients' coronary calcium percentiles was greater for females compared with males.

Across all patients, the adjusted HRs for cardiovascular and all-cause mortality increased by coronary calcium percentile category (Table 2B). In females, adjusted HRs were significantly elevated in the 50%-74%, 75%-89%, and 90%-100% coronary calcium percentile categories for all-cause mortality compared with the 0%-24% percentile group. In males, the adjusted HRs were significantly higher in the 75%-89% and 90%-100% percentile categories for all-cause mortality compared with the 0%-24% percentile group. In secondary analyses, adjusted risk of all-cause and cardiovascular mortality were both significantly lower in the lowest coronary calcium percentile group (0%-24%) compared to coronary calcium ≥25% (Supplementary Figure, available online).

Independent Predictors of Cardiovascular and All-Cause Mortality

Table 3 shows the adjusted HRs for mortality by traditional cardiovascular risk factors and coronary calcium score (Table 3A) ranked by z-score magnitude. Considering all patients, age was the strongest predictor of cardiovascular and all-cause mortality, followed by coronary calcium score. Other significant predictors were diabetes and hypertension. Among females and males separately, age and coronary calcium scores remained the strongest independent predictors of mortality, and diabetes also remained a

Table 1 Study Population Characteristics

	Overall (n = 2474)	Females (n = 1097)	Males (n = 1377)	*P**
Age (mean (SD))	79.1 (3.7)	79.2 (3.8)	79.1 (3.7)	0.411
Race[†]				0.007
White (%)	1492 (89.4)	657 (87.5)	835 (91.0)	
Asian (%)	70 (4.2)	29 (3.9)	41 (4.5)	
Black (%)	50 (3.0)	34 (4.5)	16 (1.7)	
Hispanic (%)	33 (2.0)	19 (2.5)	14 (1.5)	
Other (%)	24 (1.4)	12 (1.6)	12 (1.3)	
Risk Factors				
Diabetes (%)	344 (13.9)	144 (13.1)	200 (14.5)	0.347
Current Smoker (%)	122 (4.9)	52 (4.7)	70 (5.1)	0.765
Hypertension (%)	1442 (58.3)	689 (62.8)	753 (54.7)	< 0.001
Hyperlipidemia (%)	1604 (64.8)	741 (67.5)	863 (62.7)	0.013
CAD Family History (%)	987 (39.9)	514 (46.9)	473 (34.4)	< 0.001
BMI, kg/m^2 (median [IQR])[†]	25.1 [22.9, 28.1]	24.6 [21.6, 27.8]	25.7 [23.7, 28.1]	< 0.001
BMI Category[†]				< 0.001
<25 kg/m^2 (%)	569 (46.7)	326 (54.9)	243 (38.9)	
25-29.9 kg/m^2 (%)	454 (37.2)	170 (28.6)	284 (45.4)	
≥30 kg/m^2 (%)	196 (16.1)	98 (16.5)	98 (15.7)	
Coronary Artery Calcium				
CAC Prevalence (%)	2269 (91.7)	956 (87.1)	1313 (95.4)	< 0.001
CAC Score (median [IQR])	312 [65, 927]	151 [26, 512]	520 [136, 1281]	< 0.001
CAC Category (%)				< 0.001
0	206 (8.3)	141 (12.9)	65 (4.7)	
1-9	115 (4.6)	76 (6.9)	39 (2.8)	
10-99	432 (17.5)	241 (22.0)	191 (13.9)	
100-299	468 (18.9)	243 (22.2)	225 (16.3)	
300-999	671 (27.1)	263 (24.0)	408 (29.6)	
≥1000	582 (23.5)	133 (12.1)	449 (32.6)	
CAC Percentile (%)[‡]				< 0.001
0%-24%	421 (19.1)	192 (19.6)	229 (18.7)	
25%-49%	447 (20.2)	196 (20.0)	251 (20.5)	
50%-74%	630 (28.5)	258 (26.3)	372 (30.3)	
75%-89%	454 (20.6)	190 (19.3)	264 (21.5)	
90%-100%	257 (11.6)	146 (14.9)	111 (9.0)	
Follow-up, years (median [IQR])	10.4 [4.5, 13.2]	10.2 [4.4, 13.1]	10.6 [4.6, 13.2]	0.175
Patient Outcomes				
Cardiovascular Death (%)	293 (11.8)	117 (10.7)	176 (12.8)	0.120
All-Cause Mortality (%)	722 (29.2)	296 (27.0)	426 (30.9)	0.035
Cardiovascular Death Rate (per 100 person-years)	1.28	1.17	1.36	0.210
Mortality Rate (per 100 person-years)	3.15	2.96	3.29	0.165

BMI = body mass index; CAC = coronary artery calcium; CAD = coronary artery disease; IQR = interquartile range; SD = standard deviation.
**P* values represent comparisons by sex.
†Missing observations of race and BMI resulted in sample sizes of 1669 and 1219, respectively.
‡Conducted on subset of patients between ages 75 and 84, resulting in n = 2209, with 1277 males and 982 females.

significant predictor in both groups. The same set of significant predictors was noted when percentiles were employed instead of coronary calcium scores (Table 3B).

DISCUSSION

In this study, we examined the association between both coronary calcium scores and percentiles with subsequent all-cause and cardiovascular mortality risk over 10.4-year follow-up in a multicenter cohort of patients ages ≥75. In both females and males, we observed higher cardiovascular and all-cause mortality risk with increasing coronary calcium score, with greater risk stratification for females than males. In females, after adjusting for cardiovascular disease risk factors, higher coronary artery calcium was associated with a progressively increased risk of mortality for coronary calcium categories ≥100. In males, after risk adjustment, HRs for cardiovascular death and all-cause mortality were elevated only at coronary calcium ≥1000; however, nearly a third of males fell into this high-risk category. Similar results were found for coronary calcium percentiles. Both low

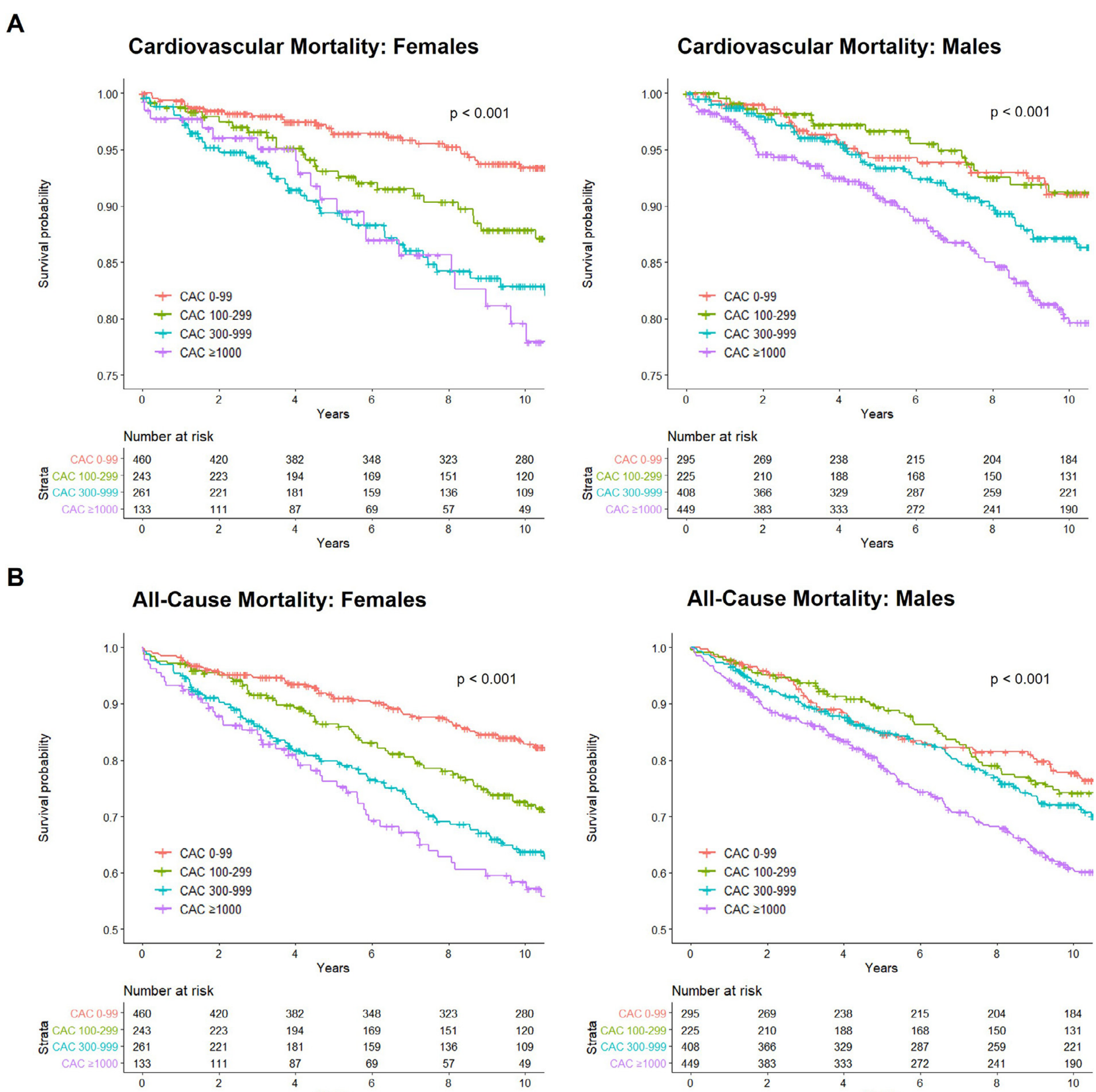

Figure 1 Kaplan Meier survival from **(A)** cardiovascular mortality and **(B)** all-cause mortality according to coronary artery calcium score group.

coronary calcium scores (0-9) and percentiles (<25%) were significantly associated with significantly lower risk of cardiovascular and all-cause mortality. Across traditional cardiovascular risk factors, age and coronary artery calcium were the strongest predictors of cardiovascular and all-cause mortality.

Comparison Between Coronary Calcium Scores and Percentiles Regarding Clinical Outcomes

The conventional use of coronary calcium scanning in clinical practice includes both patients' Agatston coronary calcium score and their percentiles. However, assessment of clinical outcomes using coronary calcium percentiles has not previously been evaluated among older adults. Coronary calcium percentiles are derived from the MESA study, a *population-based* cohort without clinical suspicion for cardiovascular disease. Thus, the utility of using the MESA algorithm in older adults who are *patients*, as opposed to the general population, is particularly unknown. Of note, there can be a wide discrepancy between moderate Agatston scores and demographic-adjusted coronary calcium percentiles. For example, a coronary calcium score of 100 in a 49-year old white male places him in the 90th percentile, but the same score at age 82 places him into just the 20th percentile.[5] As such, patient-

Table 2 Adjusted Cardiovascular and All-Cause Mortality Risk over 10.4-Year Follow-Up by Coronary Artery Calcium

(A) By coronary artery calcium score

			Cardiovascular Mortality		All-Cause Mortality	
	CAC Category	N	Events (%)	HR* [95% CI]	Events (%)	HR* [95% CI]
All Patients (n =2474)	0-9	321	21 (6.5)	1 [ref.]	67 (20.9)	1 [ref.]
	10-99	432	35 (8.1)	1.46 [0.85, 2.52]	90 (20.8)	1.13 [0.82, 1.55]
	100-299	468	45 (9.6)	1.66 [0.99, 2.79]	124 (26.5)	1.41 [1.04, 1.90]
	300-999	671	90 (13.4)	2.45 [1.52, 3.95]	214 (31.9)	1.78 [1.35, 2.34]
	≥1000	582	102 (17.5)	3.22 [2.01, 5.17]	227 (39.0)	2.22 [1.69, 2.93]
Females (n = 1097)	0-9	217	13 (6.0)	1 [ref.]	38 (17.5)	1 [ref.]
	10-99	241	16 (6.6)	1.28 [0.61, 2.67]	45 (18.7)	1.18 [0.76, 1.82]
	100-299	243	26 (10.7)	2.02 [1.03, 3.95]	66 (27.2)	1.78 [1.19, 2.66]
	300-999	263	38 (14.4)	3.08 [1.63, 5.83]	91 (34.6)	2.51 [1.71, 3.67]
	≥1000	133	24 (18.0)	3.51 [1.77, 6.95]	56 (42.1)	3.00 [1.97, 4.56]
Males (n = 1377)	0-9	104	8 (7.7)	1 [ref.]	29 (27.9)	1 [ref.]
	10-99	191	19 (9.9)	1.62 [0.70, 3.72]	45 (23.6)	1.02 [0.64, 1.64]
	100-299	225	19 (8.4)	1.27 [0.55, 2.91]	58 (25.8)	1.04 [0.66, 1.63]
	300-999	408	52 (12.7)	1.96 [0.92, 4.14]	123 (30.1)	1.26 [0.84, 1.89]
	≥1000	449	78 (17.4)	2.81 [1.35, 5.87]	171 (38.1)	1.69 [1.13, 2.52]

(B) By coronary artery calcium percentile

			Cardiovascular Mortality		All-Cause Mortality	
	CAC Percentile	N	Events (%)	HR [95% CI]*	Events (%)	HR [95% CI]*
All Patients (n = 2209)	0%-24%	421	28 (6.7)	1 [ref.]	86 (20.4)	1 [ref.]
	25%-49%	447	36 (8.1)	1.22 [0.74, 2.00]	99 (22.1)	1.09 [0.82, 1.46]
	50%-74%	630	71 (11.3)	1.81 [1.17, 2.82]	171 (27.1)	1.44 [1.11, 1.86]
	75%-89%	454	57 (12.6)	2.04 [1.29, 3.22]	141 (31.1)	1.67 [1.27, 2.19]
	90%-100%	257	51 (19.8)	3.54 [2.21, 5.67]	112 (43.6)	2.63 [1.97, 3.50]
Females (n = 982)	0%-24%	192	10 (5.2)	1 [ref.]	32 (16.7)	1 [ref.]
	25%-49%	196	14 (7.1)	1.47 [0.65, 3.34]	35 (17.9)	1.13 [0.70, 1.83]
	50%-74%	258	23 (8.9)	1.86 [0.88, 3.92]	64 (24.8)	1.62 [1.06, 2.48]
	75%-89%	190	23 (12.1)	2.50 [1.18, 5.29]	57 (30.0)	1.97 [1.27, 3.06]
	90%-100%	146	27 (18.5)	4.37 [2.08, 9.14]	65 (44.5)	3.34 [2.17, 5.13]
Males (n = 1227)	0%-24%	229	18 (7.9)	1 [ref.]	54 (23.6)	1 [ref.]
	25%-49%	251	22 (8.8)	1.05 [0.56, 1.97]	64 (25.5)	1.04 [0.73, 1.50]
	50%-74%	372	48 (12.9)	1.69 [0.98, 2.91]	107 (28.8)	1.30 [0.94, 1.81]
	75%-89%	264	34 (12.9)	1.69 [0.95, 3.03]	84 (31.8)	1.45 [1.02, 2.05]
	90%-100%	111	24 (21.6)	2.99 [1.59, 5.63]	47 (42.3)	2.14 [1.43, 3.20]

ACM = all-cause mortality; CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio.
*HRs adjusted by age, diabetes, smoking status, hypertension, hyperlipidemia, and family history.

specific coronary calcium percentile potentially adds to coronary calcium scores for preventive treatment considerations by taking into account factors such as age in older patients.

Applying the MESA algorithm for coronary calcium percentiles, we observed a stepwise increase in the risk for both cardiovascular and all-cause mortality with increasing percentiles, a pattern that persisted after stratifying patients by sex. These results parallel those noted for Agatston coronary calcium scores: coronary calcium percentiles tended to better risk stratify females than males, with each increase in percentile category leading to a greater increase in relative risk of mortality in females.

Comparison of Clinical Predictors of Mortality

We also assessed the comparative risk assessment value of coronary calcium scores compared with other traditional cardiovascular disease risk factors. Among these, four were significant predictors for cardiovascular and all-cause mortality: age, coronary calcium, diabetes, and hypertension, with age and coronary calcium score as the strongest predictors. In females, these same four factors remained significant predictors of mortality risk. However, among males, hypertension was not a significant risk predictor. These results are consistent with observations from the Framingham study that found higher risk of adverse cardiovascular outcomes among older females compared with males who

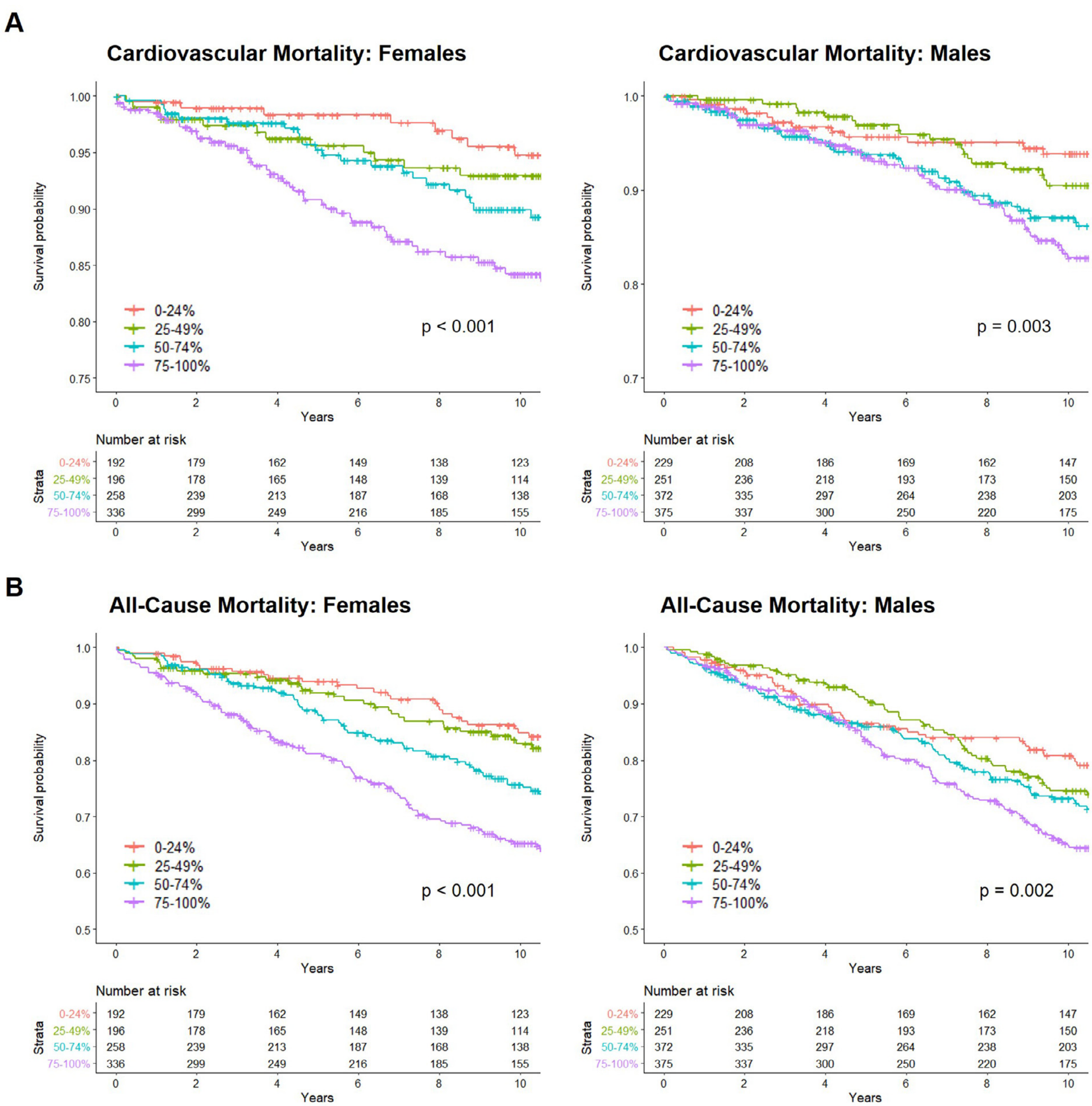

Figure 2 Kaplan Meier survival curves from **(A)** cardiovascular mortality and **(B)** all-cause mortality by coronary artery calcium percentile group, n = 2209.

had had mild to moderate hypertension.[9] In a parallel analysis using coronary calcium percentiles, coronary calcium percentile was also consistently one of the strongest predictors for mortality in both males and females.

Comparison to Prior Studies in Older Patients

Whereas the strong prognostic utility of coronary calcium scanning in middle-aged populations has been well demonstrated, studies regarding coronary calcium in older adults are sparse. Among six prior outcome studies, two involved small samples,[10,11] two others examined the relationship between coronary calcium scores and all-cause mortality,[3,12] and two others examined the relationship between coronary calcium scores and cardiovascular events.[2,4] In common within each study, an incremental increase in clinical risk was generally observed with increasing coronary calcium score. However, little has been reported regarding sex differences in the association between coronary calcium score and outcomes in older adults. Of the six studies listed, three investigated sex-related differences and two found

Table 3 Association Between Cardiovascular Risk Factors and Mortality.

(A) By continuous coronary artery calcium score

	Cardiovascular Mortality				All-Cause Mortality			
	Risk Factors	HR* [95% CI]	z-score	P	Risk Factors	HR* [95% CI]	z-score	P
All Patients	Age	1.11 (1.08, 1.14)	7.42	< 0.001	Age	1.09 (1.07, 1.11)	9.94	< 0.001
(n = 2474)	Log CAC Score	1.24 (1.16, 1.33)	6.23	< 0.001	Log CAC Score	1.16 (1.12, 1.21)	7.35	< 0.001
	Diabetes	1.63 (1.22, 2.17)	3.33	0.001	Diabetes	1.60 (1.33, 1.93)	4.95	< 0.001
	Hypertension	1.42 (1.11, 1.82)	2.82	0.005	Hypertension	1.21 (1.04, 1.41)	2.45	0.014
	Current Smoker	0.81 (0.46, 1.41)	-0.75	0.453	Family History of CAD	0.86 (0.74, 1.00)	-1.93	0.053
	Male Sex	0.91 (0.71, 1.17)	-0.73	0.465	Male Sex	0.92 (0.78, 1.07)	-1.10	0.273
	Family History of CAD	0.95 (0.75, 1.20)	-0.46	0.648	Current Smoker	1.12 (0.82, 1.52)	0.70	0.482
	Hyperlipidemia	1.00 (0.78, 1.27)	-0.04	0.970	Hyperlipidemia	0.95 (0.82, 1.11)	-0.65	0.519
(n = 1097)	Age	1.13 (1.08, 1.17)	5.81	<0.001	Log CAC Score	1.21 (1.14, 1.28)	6.44	< 0.001
	Log CAC Score	1.26 (1.14, 1.39)	4.73	<0.001	Age	1.09 (1.06, 1.12)	6.29	< 0.001
	Hypertension	1.90 (1.24, 2.92)	2.95	0.003	Diabetes	1.88 (1.41, 2.52)	4.24	< 0.001
	Diabetes	1.87 (1.18, 2.96)	2.68	0.007	Family History of CAD	0.74 (0.59, 0.94)	-2.50	0.012
	Family History of CAD	0.72 (0.50, 1.05)	-1.69	0.091	Hypertension	1.28 (1.00, 1.63)	1.94	0.053
	Current Smoker	0.56 (0.22, 1.39)	-1.26	0.209	Current Smoker	0.81 (0.49, 1.35)	-0.80	0.422
	Hyperlipidemia	1.01 (0.68, 1.50)	0.05	0.961	Hyperlipidemia	0.95 (0.74, 1.21)	-0.41	0.681
(n = 1377)	Log CAC Score	1.21 (1.11, 1.33)	4.03	< 0.001	Age	1.09 (1.06, 1.11)	6.90	< 0.001
	Age	1.09 (1.05, 1.13)	4.51	< 0.001	Log CAC Score	1.12 (1.06, 1.18)	4.06	< 0.001
	Diabetes	1.53 (1.06, 2.22)	2.26	0.024	Diabetes	1.48 (1.16, 1.89)	3.16	0.002
	Hypertension	1.22 (0.90, 1.65)	1.26	0.208	Hypertension	1.18 (0.97, 1.43)	1.63	0.102
	Family History of CAD	1.12 (0.83, 1.52)	0.73	0.462	Current Smoker	1.36 (0.92, 2.02)	1.54	0.123
	Hyperlipidemia	1.03 (0.76, 1.40)	0.17	0.863	Family History of CAD	0.95 (0.78, 1.17)	-0.46	0.647
	Current Smoker	0.99 (0.48, 2.02)	-0.03	0.973	Hyperlipidemia	0.97 (0.80, 1.18)	-0.33	0.744

(B) By continous coronary artery calcium percentile

	Cardiovascular Mortality				All-Cause Mortality			
	Risk Factors	HR* [95% CI]	z-score	P	Risk Factors	HR* [95% CI]	z-score	P
All Patients	Age	1.16 [1.10, 1.22]	5.72	< 0.001	Age	1.12 [1.08, 1.15]	6.83	< 0.001
(n = 2209)	CAC Percentile	3.64 [2.22, 5.96]	5.13	< 0.001	CAC Percentile	2.67 [1.98, 3.61]	6.43	< 0.001
	Diabetes	1.75 [1.28, 2.39]	3.49	< 0.001	Diabetes	1.68 [1.37, 2.06]	5.01	< 0.001
	Hypertension	1.44 [1.10, 1.88]	2.67	0.008	Hypertension	1.22 [1.03, 1.43]	2.32	0.021
	Sex	1.23 [0.95, 1.60]	1.57	0.117	Family History of CAD	0.87 [0.73, 1.03]	-1.67	0.095
	Hyperlipidemia	1.13 [0.86, 1.48]	0.90	0.366	Current Smoker	1.26 [0.92, 1.73]	1.41	0.158
	Family History of CAD	0.99 [0.77, 1.29]	-0.05	0.958	Sex	1.11 [0.94, 1.30]	1.23	0.218
	Current Smoker	1.01 [0.57, 1.76]	0.02	0.983	Hyperlipidemia	1.02 [0.86, 1.21]	0.24	0.814
(n = 982)	Age	1.23 [1.14, 1.33]	5.29	< 0.001	CAC Percentile	3.66 [2.32, 5.77]	5.59	< 0.001
	CAC Percentile	4.30 [2.02, 9.15]	3.78	< 0.001	Age	1.13 [1.08, 1.19]	5.13	< 0.001
	Hypertension	2.14 [1.34, 3.42]	3.19	0.001	Diabetes	1.85 [1.35, 2.55]	3.78	< 0.001
	Diabetes	1.77 [1.06, 2.95]	2.19	0.028	Hypertension	1.40 [1.08, 1.83]	2.50	0.012
	Family History of CAD	0.79 [0.52, 1.18]	-1.16	0.248	Family History of CAD	0.78 [0.61, 1.01]	-1.88	0.060
	Hyperlipidemia	1.28 [0.81, 2.01]	1.06	0.289	Hyperlipidemia	1.13 [0.86, 1.49]	0.88	0.380
	Current Smoker	0.90 [0.36, 2.23]	-0.23	0.820	Current Smoker	1.12 [0.67, 1.86]	0.42	0.671
(n = 1227)	CAC Percentile	3.02 [1.56, 5.83]	3.29	< 0.001	Age	1.10 [1.06, 1.15]	4.47	< 0.001
	Age	1.11 [1.03, 1.18]	2.95	0.003	Diabetes	1.62 [1.24, 2.10]	3.56	< 0.001
	Diabetes	1.76 [1.18, 2.63]	2.78	0.005	CAC Percentile	2.02 [1.35, 3.03]	3.40	< 0.001
	Family History of CAD	1.17 [0.84, 1.64]	0.92	0.357	Current Smoker	1.34 [0.89, 2.02]	1.41	0.160
	Hypertension	1.15 [0.82, 1.60]	0.79	0.428	Hypertension	1.11 [0.90, 1.37]	0.94	0.345
	Hyperlipidemia	1.09 [0.78, 1.54]	0.52	0.602	Family History of CAD	0.94 [0.75, 1.17]	-0.58	0.559
	Current Smoker	1.08 [0.53, 2.20]	0.20	0.839	Hyperlipidemia	0.96 [0.78, 1.19]	-0.38	0.707

CAC = coronary artery calcium; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio.
*HRs adjusted for listed risk factors and ranked by magnitude of z-score.

a similar stepwise increase in all-cause mortality with increasing coronary calcium in both older males and females.[3,12] Notably, no prior studies have examined the prognostic value of coronary calcium percentiles in older adults or sex-related differences regarding coronary calcium percentiles and outcomes.

Limitations

Our study has several limitations. Coronary calcium scan results were reported to patients and their referring physicians, which likely led to changes in medical management, as demonstrated in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) Trial.[13] However, this limitation is common to most observation-based longitudinal studies involving coronary calcium scanning and posttest changes in medication intensity would likely attenuate the risk differences across coronary calcium score categories. Because study participants were clinically or self-referred for coronary calcium scanning, the generalizability of these findings to general populations may be limited; however, these results may be more useful to clinicians since they are more reflective of patients in standard clinical practice.[14] In addition, this analysis did not take into consideration noncardiovascular comorbid conditions that may affect clinical risk and be particularly pertinent to older patient populations. Another limitation was the lack of analysis of other coronary calcium scan variables beyond the Agatston score such as number of calcified plaques,[15] plaque location,[16,17] coronary calcium volume,[18] plaque density,[18] and epicardial adipose tissue,[19,20] which have been shown to be predictive of cardiovascular events.

Clinical Implications

Because of improvements in public health and medical therapies, the number of older adults is increasing on a worldwide basis. Since cardiovascular disease poses the greatest mortality risk among older adults, developing strategies for optimally risk stratifying this population is a pressing clinical issue.[1] Coronary calcium scanning has potential appeal for such risk stratification given its ubiquity and proven ability to risk stratify middle-aged adults. Our findings confirm that coronary calcium scanning retains its prognostic value in older adults, both for cardiovascular and all-cause mortality and across both sexes. Thus, consideration should be given for developing practice guidelines on coronary calcium in adults ≥75 years that are presently lacking, for example (due to a upper age limit) in the 2018 ACC/AHA guidelines on cholesterol management.[21]

Our study also provides support for applying coronary calcium percentiles for risk assessment. However, future study is needed to clarify how these percentiles may be best applied for clinical decision-making. Within the 2018 ACC/AHA guidelines for cholesterol management, statin treatment is based on both coronary calcium score and percentile (≥100 or ≥75th percentile).[21] Potentially, coronary calcium percentiles could also aid therapeutic decision-making among older adults by helping refine the identification of a low-risk older population who may not require statin therapy. This possibility is supported by our finding that patients in the lowest coronary calcium percentile category were at significantly lower risk.

We further noted that among older adults, caution may need to be applied in making prognostic estimates and treatment recommendations based on coronary calcium findings alone. Within our data, for example, diabetes and hypertension were also significant risk predictors. Moreover, because we exclusively considered asymptomatic patients, we did not assess the added value of considering patients' clinical symptoms, nor did we consider some variables that may be particularly relevant for older adults, including the presence of comorbidities and physical activity or ability.[22] Concomitant consideration of such variables is likely to improve the application of coronary calcium scanning for risk assessment among older adults.

CONCLUSION

Both coronary calcium scores and percentiles are strongly predictive of cardiovascular mortality and all-cause mortality among older adults, with greater risk-stratification for females than males. Patients at the lowest coronary calcium score (0-9) and percentile category (0%-24%) had significantly lower risk of cardiovascular and all-cause mortality, suggesting a potential use for coronary calcium to help guide the use and intensity of preventive medical therapies in the older adult population.

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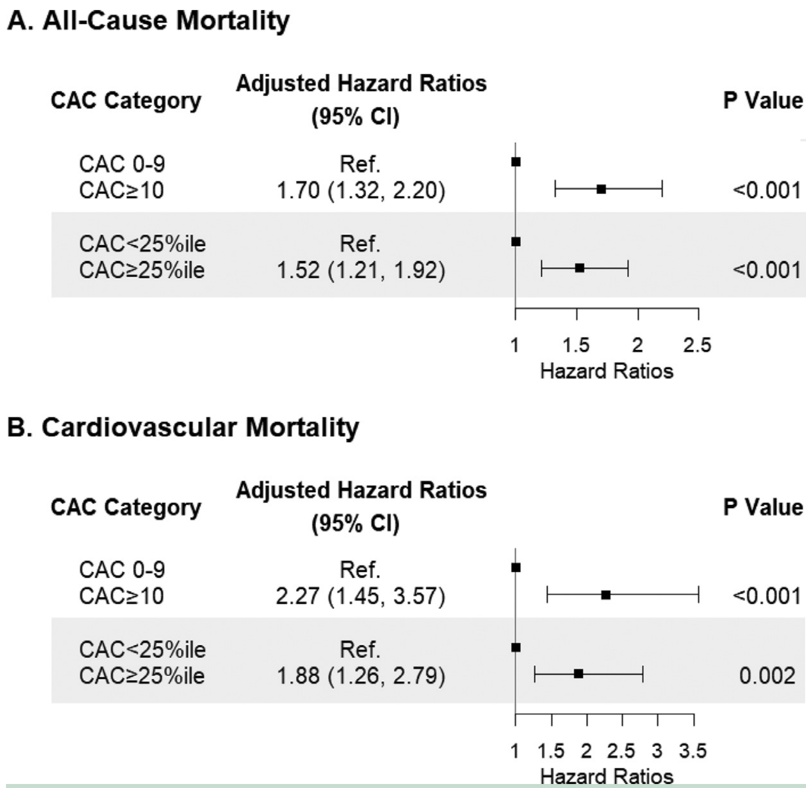
SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.07.024.



Supplementary Figure Adjusted risk ratios of (**A**) all-cause mortality and (**B**) cardiovascular mortality in low coronary artery calcium compared with all other asymptomatic patients.
CAC = coronary artery calcium; CI = confidence interval.
*Hazard ratios adjusted by sex, age, diabetes, smoking status, hypertension, hyperlipidemia, and family history.