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15-Year Prognostic Utility of Coronary Artery Calcium Scoring for All-Cause Mortality in the Elderly

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Abstract

Introduction—Prior studies have demonstrated a decline in the predictive ability of conventional risk factors (RF) with advancing age, emphasizing the need for novel tools to improve risk stratification in the elderly. Coronary artery calcification (CAC) is a robust predictor of adverse cardiovascular events, but its long-term prognostic utility beyond RFs in elderly persons is unknown.

Methods—A consecutive series of 9,715 individuals underwent CAC scoring and were followed for a mean of 14.6±1.1 years. Multivariable Cox proportional hazards regression (HR) with 95% confidence intervals (95% CI) was employed to assess the independent relationship of CAC and RFs with all-cause death. The incremental value of CAC, stratified by age, was examined by using an area under the receiver operator characteristic curve (AUC) and category-free net reclassification improvement (NRI).

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CONFLICT OF INTEREST

None.

DISCLOSURES

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Results—Of the overall study sample, 728 (7.5%) adults (mean age 74.2±4.2 years; 55.6% female) were 70 years or older, of which 157 (21.6%) died. The presence of any CAC was associated with a >4-fold (95% CI = 2.84–6.59) adjusted risk of death for those over the age of 70, which was higher compared with younger study counterparts, or other measured RFs. For individuals 70 years or older, the discriminatory ability of CAC improved upon that of RFs alone (C statistics 0.764 vs. 0.675, $P < 0.001$). CAC also enabled improved reclassification (category-free NRI = 84%, $P < 0.001$) when added to RFs.

Conclusion—In a large-scale observational cohort registry, CAC improves prediction, discrimination, and reclassification of elderly individuals at risk for future death.

Keywords

Risk factors; elderly; coronary artery calcification; all-cause death; discrimination; reclassification

INTRODUCTION

In recent past, there has been an exponential rise in life expectancy with persons aged 65 years or older accounting for the fastest growing segment of the population [1, 2]. Epidemiological evidence has documented that the burden of adverse cardiovascular events increases markedly in old age [3–8]. Yet, in assessing the need for primary prevention measures, the efficacy of current risk algorithms for older adults is limited, in part, due to a diminished predictive utility of traditional cardiovascular risk factors (RF) in individuals of advanced age [9–11].

Coronary artery calcification (CAC) determined by computed tomography is a robust measurement of atherosclerotic plaque burden [12]. Numerous reports have shown CAC to be an effective predictor of cardiovascular and all-cause mortality [5, 13, 14], with limited short-term studies observing an incremental utility of CAC over RFs to improve cardiovascular risk prediction [15–17]. To date, the long-term value of CAC for risk assessment in the elderly has not been extensively examined.

In this prospective observational study lasting nearly 15 years, we examined the prognostic utility of CAC in the elderly. We hypothesized that CAC would be a robust independent predictor of death in older adults >70 years of age, and that the addition of CAC to RFs would improve discrimination and reclassification of deaths among the elderly.

METHODS

Study population

The study cohort comprised a consecutive series of 9,715 asymptomatic individuals initially screened by their general internists, and who were considered above-average risk for coronary artery disease (CAD) according to the presence of one or more of the following cardiac risk factors: older age, a history of high blood pressure, hypercholesterolemia, diabetes mellitus, and current smoking, as well as a family history of early coronary disease. Those with a history of CAD (i.e., including admission to hospital for chest pain, acute coronary syndrome, or myocardial infarction, as well as prior coronary angiography and

revascularization) at study entry were omitted. Individuals were referred by their primary care physicians for CAD evaluation and underwent CAC screening by EBCT at a single site (Nashville, Tennessee) between January 1996 and December 1999. All individuals provided written informed consent to undergo CAC screening and the study received further authorization from the appropriate Human Investigations Committee.

Clinical examination procedures

All study participants were queried for the following baseline cardiovascular RFs which were recorded as categorical variables: 1) cigarette smoking was present if a subject was an active smoker at the time of examination; 2) dyslipidemia was considered to be present for any individual reporting a history of high total cholesterol, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, high triglycerides, or current use of lipid-lowering therapy; 3) diabetes was defined as a self-reported history of elevated fasting blood glucose measurement >126 mg/dl, or use of anti-diabetic medication; 4) hypertension was defined as a self-reported history of high blood pressure ≥ 140 mmHg systolic or 90 mmHg diastolic, or use of antihypertensive medication; and 5) family history of early CAD was determined by asking individuals whether any member of their immediate family (i.e., parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization in a male relative <55 years or a female relative <65 years.

EBCT image acquisition

Subjects underwent electron beam computed tomography (EBCT) on either a C-100 or C-150 Ultrafast CT scanner (Imatron, South San Francisco, California). With a tomographic slice thickness of 3 mm, approximately 40 sections were obtained beginning at the level of the carina and proceeding caudally to the level of the diaphragm. Images were obtained with a 100 ms/slice scanning time, with image acquisition electrocardiographically triggered at 60% to 80% of the R-R interval. A calcified lesion was defined as >3 contiguous pixels with a peak attenuation of at least 130 Hounsfield units. The estimated radiation dose was approximately 2 mSv. Each lesion was then scored using the method developed by Agatston et al. [18] (Agatston units) and CAC scores were subset as 0, 1–399, 400–999, and $\geq 1,000$.

Study follow-up

Participants were followed for a mean of 14.6 ± 1.1 years for a primary endpoint of death from any cause. Trained individuals masked to baseline historical data and EBCT findings conducted ascertainment of mortality status, as verified by the National Death Index.

Statistical methods

Demographic characteristics are reported for the overall study sample as well as according to deciles of age (from <50 – 70 years). Categorical variables are presented as counts with proportions and continuous variables as mean $\pm$ SD or median (IQR) for normally and non-normally distributed variables, respectively. The Pearson chi-square test was employed for comparison of categorical variables. Differences in continuous variables according to age groups were examined by analysis of variance (ANOVA). The incidence rate of death was estimated for each category of CAC stratified by age deciles by dividing the number of

failures by person-years contributed. Multivariable Cox proportional hazard regression models reporting hazard ratios (HR) with 95% confidence intervals (95% CI) were performed to examine and compare the risk of death from all-causes among individuals. Two separate models were generated according to any CAC present as well as for categories of CAC. The latter models adjusted for several RFs including gender, cigarette smoking, diabetes, hypertension, dyslipidemia, and family history of early CAD. Further, as the calcification process might differ as a function of gender and age, we explored the potential interaction between categories of CAC, gender, and age for the relationship with all-cause death. Overall, the interaction term was non-significant ($P_{\text{interaction}} = 0.68$). Hence, the overall findings were retained in subsequent analyses. The ability of CAC to discriminate over and above RFs was evaluated using the area under the receiver operator characteristic curve (AUC) [19]. Reclassification was determined using category-free net reclassification improvement (NRI) indices [20]. Statistical analyses were performed using STATA version 12.0 (StataCorp LP, College Station, TX, USA). A two-tailed probability of less than 0.05 percent was considered statistically significant.

RESULTS

Study population

Baseline characteristics of the study sample are reported in Table 1. In total, 9,715 adults were followed for a mean duration of 14.6 ± 1.1 years. Of these, 728 (7.5%) participants were ≥ 70 years of age at the time of screening, of which 157 (21.6%) experienced the study endpoint. Those ≥ 70 years of age were more likely to be female, and had a lower prevalence of dyslipidemia, family history of early CAD, and smoking as compared with the younger aged counterparts. Hypertension as well as diabetes mellitus tended to be more prevalent with advancing age (Table 1).

Survival according to age and CAC score

The proportion of individuals assigned a higher CAC score according to categories of CAC appeared to increase with advancing age (Table 1). Figures 1 and 2 display incidence rates and cumulative events for all-cause death, respectively. Rates of death did not differ appreciably between age groups for CAC score of 0. However, incidence rates and cumulative events for all-cause death increased further with advancing age and CAC scores, with the most pronounced rates and events observed among those ≥ 70 years of age with a CAC score $\geq 1,000$ (Figures 1 and 2).

Age, CAC score and risk of mortality

Table 2 reports the adjusted risk of death for the presence of any CAC according to each age group. The presence of any CAC was associated with an increased risk of death across all age categories, with a >4 -fold (95% CI = 2.84–6.59) adjusted risk for those ≥ 70 years, which was higher when compared with the younger study counterparts or other measured RFs. Likewise, in Table 3, increases in the adjusted risk of death for all age groups corresponded with higher CAC strata. In particular, for individuals older than 70 years, the adjusted risk of death from all-causes was >6 -fold (95% CI = 3.67–10.49) and 9-fold (95% CI = 5.02–16.52) higher based on a CAC score of 400–999 and $\geq 1,000$, respectively (Table 3).

Discrimination and reclassification of mortality risk

Table 4 displays the discriminatory capacity of CAC to identify individuals who did versus did not experience death. Based on age groups, AUC values ranged from 0.660 – 0.687 according to a base model inclusive of traditional RFs. When CAC was added to the base model, discrimination improved further across all age groups, and was more pronounced in those ≥ 70 years of age (e.g., AUC = 0.764 vs. 0.675, change in AUC: 0.089, P for difference <0.001). Likewise, the addition of CAC to the base model improved category-free NRI across all age groups (P <0.001 for all), with the greatest improvement observed among individuals ≥ 70 years of age (e.g., category-free NRI [95% CI] = 84.0% [67.7–99.5], P <0.001). In particular, 46% of events and 38% of non-events were correctly reclassified when CAC was added to the base model for those ≥ 70 years of age (Table 4).

DISCUSSION

In this prospective, longitudinal 15-year study of asymptomatic individuals undergoing CAC screening, we identified CAC to be a strong and independent predictor of all-cause mortality. The addition of CAC to RFs resulted in a substantial improvement in discrimination and reclassification of risk. Notably, these findings were most prominent in adults ≥ 70 years of age, wherein almost half of individuals who experienced incident mortality and more than one third of individuals who did not experience incident mortality were correctly reclassified by CAC scores.

To date, cardiovascular risk prediction has relied primarily upon RFs for forecasting adverse outcomes in asymptomatic persons [21]. This method, while robust for population-based studies, misclassifies many who are considered low or high risk, but have high versus low CAC scores, respectively. Further, the prognostic utility of the majority of RFs have been primarily validated in persons below the age of 75 years [6, 22]. Based upon the results of the present study, reliance upon RFs alone for identifying asymptomatic elderly adults at greater risk of adverse outcomes appears less than maximally effective, and could potentially be explained by reduced predictive power and accuracy of some RFs with advancing age [9–11]. CAC reflects the lifetime integration of conventional RFs (as well as non-traditional RFs) to encourage the formation and progression of subclinical atherosclerosis, and thus may serve as a risk marker that summates risk in a manner superior to RF assessment alone [23].

Previous studies have considered the use of CAC to be an age-dependent phenomenon, but few have included elderly individuals for CAC screening [16]. In addition, investigations that have evaluated CAC as a function of age and clinical events have been generally short- or intermediate-term in their follow-up, with generally positive findings towards risk prediction by CAC [15–17, 24]. The results from the present study add to existing literature by not only confirming the strong risk prediction of CAC scores in the elderly, but also showing an improvement in discrimination and reclassification of fatal events on top of RFs with long-term follow-up.

Importantly, approximately 50% of persons above the age of 70 years presented with a CAC score of zero. For this subgroup of elderly individuals, the reported incidence rate of death

was substantially lower compared with similar older-aged counterparts who had a CAC score of 1–399, 400–999, or ≥1,000. In the absence of CAC, incident death rates for those ≥70 years of age were comparable with the younger age groups. Further still, persons ≥70 years of age with a CAC score of zero had an excellent 15-year survival rate, which was also comparable with the younger study counterparts. These findings are particularly supportive of the importance of distinction between vascular and chronological age [25, 26]. Based on the rate of events in this study, a person with a chronological age ≥70 years displayed an equivalent vascular age of a 50 year old in the absence of CAC, thereby lowering the risk of mortality events by as many as 20 years. In light of the low likelihood of adverse events, it seems worthwhile to explore the utility of a CAC score of zero in elderly persons, as it may prove useful for guiding downstream clinical decision making on drug therapy or other treatments for primary prevention in this age group.

This study is not without limitations. Participants' information was collected using self-reported categorical risk factors only, which may have underestimated the true prevalence of these factors. Nonetheless, this study reflects that of common practice in individuals undergoing imaging procedures. Further, all-cause death was used as the primary endpoint in this study and cause-specific mortality was not obtained. Though given the complexities of assigning reasons for death, the use of death by any cause mitigates any bias related to ascertainment or misclassification [27]. In keeping with general practice, study participants were referred for CAC screening by their physicians for further risk assessment. Thus, we cannot discount the possibility of a selection bias. Our cohort comprised of only approximately 41% women. As such, the current study sample reflects a selected cohort that is perhaps not entirely representative of the general population. Despite the large sample size, the number of subjects who were ≥70 years of age and who had a CAC score above 1,000 was relatively small. Thus, caution should be taken when interpreting these participants' findings. Last, information regarding other clinical factors such as medication use was unavailable, which as a consequence, could have further influenced the interpretation of our findings.

In this 15-year study of nearly 10,000 individuals, CAC screening affords improved prediction, discrimination, and reclassification towards the risk of mortality in elderly persons ≥70 years of age. Foremost, a CAC score of zero was observed in approximately 50% of elderly persons, and conferred an exceptionally favorable prognosis. The finding that CAC provides additional prognostic value in the elderly is of particular relevance given the aging U.S. population, as it creates a novel avenue for more accurate risk stratification in the elderly, and may help guide clinical decisions on medical therapy and lifestyle modification.

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Highlights

1. There has been a decline in the predictive ability of established risk factors (RF) with advancing age.
2. This decline underlines the need for novel tools to improve risk stratification in older adults.
3. Coronary artery calcification (CAC) was assessed for its long-term prognostic utility beyond a panel of traditional RFs in elderly persons.
4. For individuals 70 years or older, CAC was associated with a higher risk of adverse events, and improved discrimination and reclassification beyond conventional RFs.
5. Assessing CAC reflects a novel avenue for more accurate risk stratification in the elderly, and may help guide clinical decisions on medical therapy and lifestyle modification.

Figure 1.
Incident rate for all-cause death according to age groups and coronary artery calcium categories.

Figure 2.
Cumulative events by deciles of age within coronary artery calcium score categories.

Study demographics

Table 1

Characteristic	Overall (N=9,715)	Age <50 (N=3,666)	Age 50–59 (N=3,423)	Age 60–69 (N=1,898)	Age 70 (N=728)	P _{trend} *
Age, mean±SD	53.4±10.5	43.0±4.9	54.1±2.8	64.0±2.8	74.2±4.2	<0.001
Female sex, n (%)	3,950 (40.7)	1,232 (33.6)	1,380 (40.3)	933 (49.2)	405 (55.6)	<0.001
Hypertension, n (%)	4,220 (43.4)	1,460 (39.8)	1,538 (44.9)	886 (46.7)	336 (46.2)	<0.001
Dyslipidemia, n (%)	6,077 (62.6)	2,211 (60.3)	2,216 (64.7)	1,218 (64.2)	432 (59.3)	0.14
Diabetes, n (%)	810 (8.3)	276 (7.5)	278 (8.1)	173 (9.1)	83 (11.4)	<0.001
Smoker, n (%)	3,817 (39.3)	1,418 (38.7)	1,364 (39.9)	788 (41.5)	247 (33.9)	0.77
Family history of early CAD, n (%)	6,672 (68.7)	2,571 (70.1)	2,336 (68.2)	1,275 (67.2)	490 (67.3)	0.017
All-cause deaths, n (%)	936 (9.6)	219 (6.0)	291 (8.5)	269 (14.2)	157 (21.6)	<0.001
Incidence rate, per 1,000 person years	6.9 (6.5–7.4)	4.2 (3.7–4.8)	6.1 (5.5–6.9)	10.5 (9.3–11.8)	16.9 (14.4–19.7)	<0.001
Coronary artery calcium, median (IQR)	0 (0–71)	0 (0–31)	4 (0–81)	9 (0–142)	3.5 (0–133.5)	<0.001
Coronary artery calcium score, n (%)						<0.001
0	4,864 (50.1)	2,117 (57.7)	1,592 (46.5)	806 (42.4)	349 (47.9)	
1–399	4,011 (41.3)	1,357 (37.0)	1,537 (44.9)	838 (44.2)	279 (38.4)	
400–999	562 (5.7)	138 (3.8)	202 (5.9)	157 (8.3)	65 (8.9)	
1,000	278 (2.9)	54 (1.5)	92 (2.7)	97 (5.1)	35 (4.8)	

* P values for trend were obtained using ANOVA.

Abbreviations: SD = standard deviation; CAD = coronary artery disease; IQR = interquartile range.

Table 2

Independent associations of risk factors with all-cause death by age categories

	Multivariable hazard ratios (95% confidence intervals) [#]			
	Age <50 years	Age 50–59 years	Age 60–69 years	Age 70 years
Coronary artery calcium >0	2.71 (2.03–3.62)	1.74 (1.34–2.25)	3.59 (2.60–4.96)	4.33 (2.84–6.59)
Age	1.00 (0.98–1.03)	1.01 (0.97–1.05)	1.04 (1.00–1.08)	1.03 (0.99–1.06)
Female Gender	0.95 (0.72–1.26)	0.78 (0.62–1.00)	1.15 (0.91–1.47)	0.80 (0.59–1.10)
Hypertension	1.46 (1.11–1.91)	1.78 (1.40–2.26)	1.80 (1.41–2.31)	2.47 (1.75–3.50)
Dyslipidemia	0.69 (0.52–0.90)	0.88 (0.69–1.12)	0.62 (0.49–0.80)	0.79 (0.57–1.08)
Diabetes	2.48 (1.72–3.55)	3.06 (2.31–4.05)	2.29 (1.68–3.11)	1.96 (1.33–2.89)
Family history of early CAD	0.87 (0.65–1.16)	0.83 (0.65–1.06)	0.70 (0.54–0.89)	0.54 (0.39–0.75)
Smoking	2.70 (2.06–3.56)	2.12 (1.68–2.68)	1.91 (1.50–2.43)	1.16 (0.83–1.62)

[#] All covariates were entered into the multivariable model.

Abbreviations: CAD = coronary artery disease.

Table 3

Risk of all-cause death according to coronary artery calcium score and age categories

Coronary artery calcium score	Multivariable hazard ratios (95% confidence intervals) [§]			
	Age <50 years	Age 50–59 years	Age 60–69 years	Age 70 years
0	1.00	1.00	1.00	1.00
1–399	2.44 (1.81–3.30)	1.55 (1.18–2.03)	3.01 (2.15–4.22)	3.54 (2.27–5.50)
400–999	3.53 (2.08–5.99)	2.56 (1.73–3.78)	5.71 (3.78–8.62)	6.20 (3.67–10.49)
>1,000	8.22 (4.63–14.57)	2.96 (1.81–4.84)	5.50 (3.47–8.73)	9.11 (5.02–16.52)

[§]Model adjusted for sex, hypertension, smoking, diabetes, dyslipidemia, and family history of coronary artery disease.

Table 4
Age-stratified discrimination and reclassification in risk of death with the use of coronary artery calcium

Age Category	AUC Base model	AUC Base model + CAC	P value	Category-Free NRI	95% CI	P value	% Events correctly reclassified	P value	% Non events correctly reclassified	P value
<50	0.673	0.722	<0.001	44%	30.3–57.4	<0.001	8%	0.25	36%	<0.001
50–59	0.687	0.709	0.02	38%	25.5–49.1	<0.001	20%	<0.001	18%	<0.001
60–69	0.660	0.742	<0.001	59%	46.5–70.7	<0.001	36%	<0.001	23%	<0.001
70	0.675	0.764	<0.001	84%	67.7–99.5	<0.001	46%	<0.001	38%	<0.001

Base model included: sex, smoking, hypertension, dyslipidemia, diabetes, and family history of early CAD. Abbreviations: AUC = area under the receiver operator characteristic curve; NRI = net reclassification improvement; CI = confidence interval.