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All-cause mortality by age and gender based on coronary artery calcium scores

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Abbreviations

CAC Coronary artery calcium

CVD Cardiovascular disease

INTRODUCTION

Cardiovascular disease (CVD) has the highest morbidity and mortality rate of any disease process ¹. However, effective preventive therapies are available that can reduce CVD events. The population-based risk prediction models calculated using traditional clinical risk scoring upon which the current CVD prevention guidelines are based can overestimate or underestimate an individual's risk ^{2,3}.

Numerous studies have demonstrated the prognostic utility of coronary artery calcium (CAC) for risk stratification among asymptomatic patients ⁴⁻⁸. An increasing CAC is associated with a higher mortality and CVD risk regardless of age ⁹, gender ¹⁰, or ethnicity ¹¹ during an intermediate follow-up period. Its CVD risk prediction is superior to that of traditional CVD risk factors, novel biomarkers and other measures of sub-clinical atherosclerosis ^{7, 12-15}. However, the results of these studies were reported with a follow-up time of only 5 to 7 years and the longer term mortality associated with CAC has not been well defined. Moreover, CVD risk has been shown to increase with age and to be higher in men than in women. However, the association between CAC and long-term risk of CVD and mortality has not been explored. Therefore, we examined the relationship between CAC and all-cause mortality, used as a proxy for CVD risk, in a cohort with a median follow-up of at least 10 years.

METHODS

Study population

We studied 13,092 consecutive asymptomatic individuals without known coronary artery disease with a mean age of 58 ± 11 years (67% men) clinically referred for a CAC scan between July 1997 to December 2011 at our institution (Los Angeles Biomedical Institute at Harbor UCLA Medical Center). We stratified the population in groups by age [younger (<45 years for male, <55 years for female), intermediate (45-74 years for male and 55-74 years for female) or older (≥ 75 years for both male and female)] and gender, as has been previously proposed ¹³.

All subjects completed a questionnaire for ethnicity (Caucasian, Hispanic/Latino, African-American, Asian or other), and CVD risk factors including hypertension, hypercholesterolemia, diabetes mellitus, current cigarette smoking, and any family history of CVD determined as whether any member of their immediate family (parents or siblings) had a history of fatal or nonfatal myocardial infarction and/or coronary revascularization, as previously described ¹⁶. Exclusion criteria included age <20 years, any chest pain, prior known CVD (prior coronary revascularization or myocardial infarction), or follow-up of ≤ 365 days. This study was approved by the Institutional Review Board of Los Angeles Biomedical Institute at Harbor UCLA Medical Center. Informed consent was obtained from all patients.

Non-contrast CT Image Acquisition Protocol

All subjects underwent EBCT with an Imatron C-150XL Ultrafast computed tomography scanner (GE-Imatron, South San Francisco, California) or multi-detector 64-slices coronary CT (Lightspeed VCT, General Electric Healthcare Technologies, Milwaukee, WI). Each scan extended from 1 cm below the carina to the bottom of the

heart to include the entire coronary tree. Scan parameters included as follows: prospective electrocardiogram-triggering (typically 60–80% of the R–R interval for EBCT, 65-80% for multi-detector CT), 35 cm field-of-view, 512×512 matrix size, and peak tube voltage of 120 kVp. Slice thickness was 3 mm. CAC measurements were performed on a dedicated workstation (AW Volume Share™, GE Medical Systems, Milwaukee, WI), and CAC was quantified using the Agatston score ¹⁷.

Statistical analysis

Continuous variables are expressed as the mean \pm SD. The unpaired Student t test or the Wilcoxon rank-sum test was used to conduct the group comparisons by age (younger vs. older subjects) and/or gender, or ethnicity groups. Categorical variables were compared using the Pearson chi-square test.

All-cause death was defined as the end-point of this current study and verified using linkage with the Social Security Death Index ¹⁸ through December 2012. A full Social Security Death Index search was completely performed using the patient name and date of birth in all of patients.

CAC was categorized into 4 groups: 0, 1-99, 100-399 and \geq 400 Agatston units. The prevalence of CAC was assessed by age and gender groups. The mortality risk was analyzed across all CAC categories by age and gender groups. Kaplan-Meier models investigating the association between CAC and mortality were calculated. We also calculated multivariable Cox Proportional hazards models adjusted for age, hypertension, hyperlipidemia, diabetes, current smoking and family history, and ethnicity among CAC groups in each age and gender group. The mortality event rates per 1,000

person-years were assessed among age and gender group based on CAC categories.

We also compared the mortality event rates per 1,000 person-years between patients with CAC=0 and the general adult population in the U.S from the data based on the Center for Disease Control and Prevention ¹⁹ across various age groups for men and women.

Relative risk of mortality rate among men and women was assessed based on CAC with 0, 1-99, 100-399 and ≥ 400 . Area under the curves (AUC) by receiver operator characteristics (ROC) was used to predict all-cause mortality at 5 years and 15 years between traditional risk factors alone and risk factors plus the continuous CAC score among men and women.

In sub-analysis of 11790 patients, the different mortality risks by ethnicity (White, Hispanic/Latino, African-American or Asian) were also examined by multivariable Cox proportional hazards models adjusting for age, gender, CAD risk factors.

Scaled Schoenfeld residuals were used to verify the assumption of proportional hazards within the Cox models ²⁰. A hazard ratio (HR) and 95% confidence interval (CI) were calculated from the Cox models. P values < 0.05 were considered statistically significant. All statistical calculations were performed using SAS (Version 9.3, SAS Inc., Cary, NC) for Windows.

RESULTS

Baseline Characteristics

The median follow-up of this study was 11.0 (IQR: 8.9-12.5) years. Among the 13,092 patients, 8,713 (66.55%) were men and 4,379; (33.45%) were women. Women were older (58.7 ± 11.3 years vs. 57.7 ± 11.5 years, $p=0.0001$) and had a greater number of risk factors compared to men (1.77 ± 0.99 vs. 1.64 ± 1.01 , $p=0.0001$). By age and gender, there were 1,664 younger-women (38.0%), 1,213 younger-men (13.9%), 2,321 intermediate-women (53.0%), 6,813 intermediate-men (78.2%), 394 older-women (9.0%) and 687 older-men (7.9%). Baseline characteristics are shown in the Table1. Younger-women and men were less likely to have hypertension, diabetes and hyperlipidemia, resulting in a lower number of risk factors compared to other groups. Between gender, women were more likely to have a family history of CAD and a greater number of risk factors than men (Table1).

The prevalence and severity of coronary artery calcium

Figures 1a and b display the prevalence of CAC categories by age and gender. The prevalence of CAC=0 ranged from 73.6% in younger women to 10.6% in older men, and CAC ≥ 400 ranged from 1.3% in younger women to 51.8% in older men. Men were more likely to have higher CAC across various age groups compared to women.

Figures 2a and b also illustrate the prevalence of CAC categories by number of risk factors among men and women. Among both genders, patients with more risk factors had an increased CAC burden. This trend was more pronounced in women than in men, while approximately 30% of women ($n=1999$) and 60% of men ($n=2039$) without known risk factors had CAC>0. Compared to women, men had approximately 2-fold

higher prevalence of CAC at any level of number of risk factors, whereas a similar prevalence was observed between genders when patients had all of risk factors.

Mortality risk

522 (4.0%) of the 13,107 patients died and 15 (0.9%) were younger-women, 11 (0.9%) were younger-men, 84 (3.6%) were intermediate-women, 234 (3.4%) were intermediate-men, 55 (14.0%) were older-women and 123 (17.9%) were older-men. There was no significant difference in the risk of mortality between genders in the overall population as well as in the younger, intermediate or older age groups ($p < 0.05$ for all).

During a mean follow-up of up to 15 years the mortality rate was extremely low in patients with CAC=0 for men (1.6%) and women (1.8%) and increased progressively with each of CAC category (1-99, 100-399 and ≥ 400) for both men and women ($p < 0.001$ for all). Among men, there was a 2.1, 3.6 and 7.1 fold higher mortality risk by CAC category compared to those with CAC=0 (Figure 3a). The point estimates were higher in women at 3.1, 4.2 and 13.3 fold higher mortality risk for the respective CAC categories (Figure 3b). Relative risk (RR) in men at any level of CAC with 0 (RR 1.47, 95% CI 0.9-2.4, $p=0.13$), 1-99 (RR 1.51, 95% CI 0.99-2.30, $p=0.06$), 100-399 (RR 0.82, 95% CI 0.53-1.28, $p=0.39$) and ≥ 400 (RR 1.05, 95% CI 0.72-1.53, $p=0.79$) did not differ compared to women.

Among younger subjects, the mortality rates of those with CAC=0 were very low at 0.4 and 0.9 per 1,000 person-years of follow-up in younger men and women, 0.8 and

1.0 per 1,000 person-years follow-up for intermediate aged men and women, and 11.9 and 9.5 per 1,000 person-years follow-up for older men and women (Figure 4). Mortality increased progressively with each CAC category in younger and intermediated aged participants. The mortality risk was highest in participants with CAC \geq 400 for older participants in both genders. Similar findings were observed in the risk adjusted Cox proportional hazard models for all-cause mortality, stratified by CAC among age and gender groups (Table 2).

Patients with CAC of zero had a lower rate of mortality at all ages compared to general U.S. population. The difference in mortality increased exponentially with age (Figure 5 a and b).

In sub-analysis of 11790 patients whose ethnicity are White (n=9435), Hispanic/Latino (n=913), African-American (n=436) or Asian (n=1006), the mean of CACS were 174.0, 125.2, 144.2 and 144.6, respectively ($p < 0.001$). During a mean follow-up of 10.2 ± 3.2 years, 465 individuals (3.9%) died. Hispanic/Latinos and African-American patients experienced higher mortality risk compared to White or Asian patients (3.6% vs. 4.7% vs. 9.2% vs. 3.9%, $p < 0.001$). Compared to patients with CAC score of zero, the mortality rates were significantly higher in patients with increasing CAC scores among all ethnicity groups (Table 3).

The additive value of CAC to traditional risk factors to predict all-cause mortality

In men, at 5 years, CAC showed an incremental prognostic value over traditional risk factors alone (AUC: 0.702 vs. 0.655, $p = 0.002$) (Figure 6a). This incremental value

was greater at 15 years (AUC: 0.723 vs. 0.656, $p < 0.0001$) (Figure 6b). In women, there was a trend towards incremental value of CAC over risk factors in predicting mortality risk at 5 years (AUC: 0.650 vs. 0.612, $p = 0.065$) (Figure 6c). In women at 15 years, CAC significantly improved this prediction over risk factors alone (AUC: 0.690 vs. 0.624, $p < 0.0001$) (Figure 6d).

DISCUSSION

This is the first study demonstrating the long-term prognostic utility of CAC in asymptomatic patients by age and gender. This long-term observational study builds on previous studies that demonstrated the added prognostic information provided by CAC among asymptomatic patients during intermediate follow-up ^{4, 16, 21}. In patients who are less than 75 years old, the ability of CAC to stratify risk at 10 years is similar to what it has previously been described at 5 years ⁹.

An interesting novel finding of this study is the observation that the long-term risk stratification by CAC is attenuated in the older patients. In patients older than 75 years, the ability of CAC to stratify risk was still present, but was lower than in the other groups and lower than was previously described in intermediate follow-up ⁹. This finding may be explained by competing risks associated with an increased overall mortality rate in older patients. In contrast to the younger and intermediate age patients with CAC=0, the annualized mortality rate in the patients 75-84 years of age was still relatively low but higher (0.7-1.1%/year) and was even higher in the ≥ 85 year old patients (3.7%/year). This increase in mortality rates for the older patients with low CAC may be due to the

increased in non-cardiac death in these age groups. Of importance, however, in these older patients with CAC=0 or low CAC (1-99), the mortality risk at 10 years is much lower than that of the general population.

A CAC=0 has been shown to confer an extremely low mortality risk over an intermediate duration follow-up, regardless of traditional risk factors^{16, 22}. Our prior study reported demonstrated findings similar to those of this manuscript in 25,253 patients over a duration mean follow-up of 6.8 years⁴. Other study similarly reported an excellent survival rate of CAC=0 with >99% in 44,052 patients at a mean follow-up of 5.6 years²³. The results of our study expand on these intermediate term findings by demonstrating the consistent associations between CAC=0 and very low long-term all-cause mortality, except in the older group. In the current study, annualized mortality risk among patients <75 years old with CAC=0 (30% in men and 56% in women of this age group) was only <0.35%/year, which is comparable to the results of a prior study in this age group showing <0.2%/year of mortality risk⁹. In patients ≥75 years of age with CAC=0 (10.6% of men and 17.8% of women of this age group), our study demonstrated that annualized mortality rate is higher than in the younger and intermediate age groups; however, it is still relatively low. Importantly, this risk is 70% lower than that of the general U.S adult population in this age group.

The most recent U.S. prevention guidelines recommend using the 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk score to determine the appropriateness of statin therapy among asymptomatic individuals²⁴. This guideline considers patients with a ≥7.5% ASCVD risk to be at high risk and suggests initiating statin therapy. However, Kavousi et al. have recently reported that nearly all men ≥55

years of age and women ≥ 65 years of age would have a $\geq 7.5\%$ predicted 10-year risk and be recommended for treatment intervention with a statin regardless of their risk factor burden, since an estimated 10-year ASCVD risk is heavily weighted based on age². By showing that a substantial proportion of the patients in this age group have a CAC=0 and that this is associated with low long term risk, the findings of this study support the concept that selection of the intensity of therapy might be better based on observed sub-clinical atherosclerosis in individual patients rather than on population-based risk.

With respect to gender, among patients who were referred for a CAC scan, we observed that women were likely to have a greater prevalence of family history of CAD compared to men. Possible explanation of the finding may be that a family history of CAD has been considered as a high risk of CAC in women despite they were at a low risk of CAD²⁵. While there was a lower prevalence of CAC in women, CAC equally predicted mortality risk among men and women in the current study. A previous systematic meta-analysis of 17,850 men and 17,779 women with CAC scanning similarly demonstrated that there was no difference in stratifying risk between men and women²⁶. Our study also did not show any difference in predicting mortality risk at any level of CAC between genders ($p > 0.05$)²⁷.

Numerous previous studies have shown an independent prognostic value of CAC over clinical risk factors during an intermediate term follow-up^{5, 7, 11}. In our study, we similarly demonstrate that CAC has an incremental value in predicting long-term mortality over traditional risk factors alone among men and a trend toward incremental

value in women at the intermediate 5 year follow-up. This incremental value of CAC burden was more prominent in both genders at 15 years.

We recognize several limitations in the current study including that this is a single center study. Since CAC scanning was referred for clinical purposes in our cohort, the association between CAC and long-term mortality rate among population-based cohorts remains unclear. In addition, risk factors were self-reported by patients, which may underestimate their true prevalence. Although numerous previous studies demonstrated the prognostic value of CAC beyond other risk scoring such as Framingham Risk Score^{7,28}, we did not have fasting lipid values to calculate this or other commonly used scores. Further, we cannot determine how the single CAC measurement might compare to multiple assessments of risk factors over time in the prediction of mortality. Further studies examining the comparative ability of CAC and risk scores to predict long term CVD events appear warranted. The Multi-Ethnic Study of Atherosclerosis (MESA) has reported differences in CAC scores and their prognostic implications in various ethnicities¹¹. We did not examine the effect of ethnicity in this predominantly Caucasian patient population. There were no data regarding medication use after CAC scanning. Increased CAC has been associated with the increased prescription of statins and aspirin^{29,30}, but we did not have data about post-CAC scan medication use. However, if patients with non-zero CAC score were prescribed statin therapy, we would expect lower event rates in those groups, which would make our results more conservative. We did not assess the incremental prognostic utility of CCTA adding CAC in the present study. Recent data has suggested that CCTA may be superior to CAC in risk prediction in patients with CAC scores 100-400; however, superiority in unselected asymptomatic

patients has not been shown ³¹. In addition, current guidelines do not recommend use of CCTA to stratify future mortality or cardiovascular risk among asymptomatic patients ³² and current appropriate use criteria considers that CCTA is inappropriate in asymptomatic patients ³³. The outcome variable in this study was all-cause mortality. While CVD mortality is the most common cause of death in middle aged individuals, the risk of death from cancer and other causes increases with age and we were not able to examine cause of death. Further studies examining the relationship between CAC and cardiovascular events during a long-term follow-up are needed.

CONCLUSION

Increasing CAC was strongly associated with an increased long-term mortality risk in the young and middle age groups of both genders. In older patients, the long-term risk stratification of CAC was lower, due principally to competing risk of mortality. However, even in the older patients, those with absent or low CAC had a significantly lower risk of mortality compared to the general population.

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Figure legends

Figure1a. Prevalence of coronary artery calcium (CAC) among men stratified by age group

Figure 1b. Prevalence of coronary artery calcium (CAC) among women stratified by age group

Abbreviations: CAC- coronary artery calcium

Figure 2a. Prevalence of coronary artery calcium (CAC) among men stratified by the number risk factors

Figure 2b. Prevalence of coronary artery calcium (CAC) among women stratified by the number risk factors

Abbreviations as in Figure1.

Figure 3a. Kaplan-Meier analysis for all-cause mortality among men stratified by coronary artery calcium group.

Figure 3b. Kaplan-Meier analysis for all-cause mortality among women stratified by coronary artery calcium group.

Abbreviations as in Figure1.

Figure 4a. Annualized mortality risk per 1,000 person-years stratified by age group and coronary artery calcium (CAC) categories among men.

Figure 4b. Annualized mortality risk per 1,000 person-years stratified by age group and coronary artery calcium (CAC) categories among women.

Figure 5a. Annual mortality rates per 1,000 person-years among men with CAC=0 compared to those from general U.S. population in 2012.

Figure 5b. Annual mortality rates per 1,000 person-years among women with CAC=0 compared to those from general U.S. population in 2012.

Figure 6 a-d. Receiver operator characteristics curves for prediction of all-cause mortality by traditional risk factors alone and risk factors plus the CAC score among men and women at 5 years (a: men, c: women) and 15 years (b: men, d: women).

Abbreviations as in Figure1.