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Validation of the Coronary Artery Calcium Data and Reporting System (CAC-DRS): Dual importance of CAC score and CAC distribution from the Coronary Artery Calcium (CAC) consortium

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ABSTRACT

Background: The Coronary Artery Calcium Data and Reporting System (CAC-DRS), which takes into account the Agatston score category (A) and the number of calcified vessels (N) has not yet been validated in terms of its prognostic significance.

Methods: We included 54,678 patients from the CAC Consortium, a large retrospective clinical cohort of asymptomatic individuals free of baseline cardiovascular disease (CVD). CAC-DRS groups were derived from routine, cardiac-gated CAC scans. Cox proportional hazards regression models, adjusted for traditional CVD risk factors, were used to assess the association between CAC-DRS groups and CHD, CVD, and all-cause mortality. CAC-DRS was then compared to CAC score groups and regional CAC distribution using area under the curve (AUC) analysis.

Results: The study population had a mean age of 54.2 ± 10.7 , 34.4% female, and mean ASCVD score $7.3\% \pm 9.0$. Over a mean follow-up of 12 ± 4 years, a total of 2,469 deaths (including 398 CHD deaths and 762 CVD deaths) were recorded. There was a graded risk for CHD, CVD and all-cause mortality with increasing CAC-DRS groups ranging from an all-cause mortality rate of 1.2 per 1,000 person-years for A0 to 15.4 per 1,000 person-years for A3/N4. In multivariable-adjusted models, those with CAC-DRS A3/N4 had significantly higher risk for CHD mortality (HR 5.9 (95% CI 3.6–9.9), CVD mortality (HR4.0 (95% CI 2.8–5.7), and all-cause mortality a (HR 2.5 (95% CI 2.1–3.0) compared to CAC-DRS A0. CAC-DRS had higher AUC than CAC score groups (0.762 vs 0.754, $P < 0.001$) and CAC distribution (0.762 vs 0.748, $P < 0.001$).

Conclusion: The CAC-DRS system, combining the Agatston score and the number of vessels with CAC provides better stratification of risk for CHD, CVD, and all-cause death than the Agatston score alone. These prognostic data strongly support new SCCT guidelines recommending the use CAC-DRS scoring.

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Abbreviations

ACC	American College of Cardiology
ACR	American College of Radiology
AHA	American Heart Association
ASCVD	Atherosclerotic Cardiovascular Disease
AUC	Area under the curve

CAC	Coronary Artery Calcium
CAC-DRS	Coronary Artery Calcium Data and Reporting System
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
MESA	Multi-Ethnic Study of Atherosclerosis
SCCT	Society of Cardiovascular Computed Tomography

1. Introduction

The 2017 expert consensus from the Society of Cardiovascular Computed Tomography (SCCT) recommends consideration of Coronary Artery Calcium (CAC) testing within the context of shared decision making for asymptomatic individuals aged 40–75 years without clinical ASCVD when the 10-year ASCVD risk using the Pooled Cohort Equations is between 5 and 20%, and selectively in patients with < 5% ASCVD risk, such as those with a strong family history of premature coronary artery disease.^{1,2} CAC is also endorsed by the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guidelines as an additional diagnostic tool for those borderline to intermediate risk individuals (5–20% 10-year ASCVD risk) for whom the decision to initiate statin therapy is uncertain.^{3,4} In these patients, CAC scoring leads to marked risk reclassification across different levels of ASCVD risk.³

In a separate document the, SCCT, in 2017, proposed a standardized method to communicate findings of CAC scanning on all non-contrast CT scans – the CAC Data and Reporting System (CAC-DRS).⁵ The CAC-DRS provides an option for visual estimation (V) of the extent of CAC⁶ assigning V0 = no CAC, V1 = mild CAC, V2 = moderate CAC, and V3 = severe CAC, directly analogous to Agatston CAC score groups of 0, 1–99, 100–299, > 300, respectively.⁵ The CAC-DRS also provides the option to add a classifier for the numbers of vessels with CAC (N), ranging from N1–4, indicating the cumulative involvement of the left main, left anterior descending, left circumflex, and right coronary artery.

To our knowledge no study has examined the prognostic implication of the CAC-DRS scoring. A barrier to adoption of CAC-DRS, particularly for non-gated chest CTs, could be the lack of validation with patient outcomes, and thus uncertain effects on future quality of care.

Therefore, in this study, we aimed to assess the prognostic value of CAC-DRS using data from the CAC Consortium, the largest cohort of CAC scoring assembled.⁷ Specifically, we sought to compare the utility of the CAC-DRS score for predicting CHD mortality, CVD mortality and of all-cause mortality beyond traditional risk factors, and to compare CAC-DRS to traditional CAC score groups and regional CAC distribution data.

2. Methods**2.1. Study design and study population**

The CAC Consortium is a large multi-center cohort of 66,636 patients designed to study the association of CAC score with long-term cause-specific mortality. Details on the study population and design of CAC Consortium have been described elsewhere.^{7–9} In brief, the CAC Consortium enrolled asymptomatic patients aged 18 years or more, without any coronary heart disease (CHD) at the time of the CAC scan, who were referred for risk stratification. Four participating sites were included in the CAC Consortium: Cedars-Sinai Medical Center, Los Angeles, CA (n = 13,972); PrevaHealth Wellness Diagnostic Center, Columbus, OH (n = 7,042); Harbor-UCLA Medical Center, Torrance, CA (n = 25,563); and Minneapolis Heart Institute (MHI), Minneapolis, MN (n = 20,059).

Baseline data were collected from 1991 to 2010 and patients were followed through June 2014. Comparison of the CAC Consortium with

NHANES 2001–2002, the Multi-Ethnic Study of Atherosclerosis (MESA), and Framingham Offspring suggest similar baseline characteristics and pharmacotherapy rates.⁷ All participants signed informed consents at the time of CAC scanning at the participating centers. IRB approval for death ascertainment in coordinating centers was obtained at the Johns Hopkins Hospital.

2.2. Measurement of Coronary Artery Calcium (CAC)

Non-contrast ECG-gated CT scans for CAC calculation were performed at each site using a shared standard procedure for each CT scanner technology. All centers originally reported CAC using the Agatston method.¹⁰ Most centers (93%) performed CT scans using electron beam tomography (EBT) while two centers (7%) with more recent CAC data used multi-detector CT (MDCT). Prior studies have demonstrated no clinically meaningful differences between CAC scores derived from EBT versus MDCT scanners.¹¹ Information on number of vessels with CAC, a qualitative measure of regional CAC distribution,¹² was available in 54,678 participants (from Harbor-UCLA, Cedars, MHI).

2.3. Definition of CAC-DRS: Coronary Artery Calcium Data and Reporting System

CAC-DRS could be defined in 54,768 patients from the CAC Consortium with full data on Agatston CAC scores and number of vessels with CAC. The simple CAC-DRS integration of severity and dispersion of CAC was proposed based on studies from the multi-Ethnic Study of Atherosclerosis (MESA), which showed that number of vessels with CAC have prognostic significance beyond absolute CAC score, particularly in the CAC range of 1–300.^{12,13} For this study, the CAC-DRS categories were defined using A_X/N_Y scoring (using Agatston score data and number of vessels with CAC). Therefore, CAC-DRS scores ranged from A0 to A3/N4. *Definition of CVD Risk Factors.*

2.4. Definition of CVD Risk Factors

Patients' information, including demographic, clinical, and laboratory data, were obtained as part of routine clinical visit at each site. Smoking status was defined based on current cigarette smoking status (Yes/No). Hypertension was defined as having a previous diagnosis of hypertension or using anti-hypertensive medications. Dyslipidemia was defined as the previous diagnosis of primary hyperlipidemia (LDL-C > 160 mg/dL), previous diagnosis of dyslipidemia (elevated triglycerides and/or low high-density lipoprotein cholesterol [HDL-C]) or treatment with lipid-lowering medications. If concomitant laboratory lipid results were present, dyslipidemia was additionally defined as LDL-C > 160 mg/dL, HDL-C < 40 mg/dL in men and < 50 mg/dL in women, or fasting triglycerides > 150 mg/dL. Diabetes was defined as a previous diagnosis of diabetes or using blood sugar lowering medications. Family history of CHD was predominantly determined by the presence of a first degree relative with a history of CHD. Among 28% of the cohort, partially missing covariates were imputed using multiple imputations.⁷ In the event of missing data, we used simple rule-based imputation to estimate the relevant measures using the remainder of the dataset and analogous subgroups in MESA. Ten-year atherosclerotic CVD (ASCVD) risk was calculated in all patients using the Pooled

Cohort Equations (PCE)¹⁴ Detailed explanation for calculation of 10-year ASCVD has been published elsewhere⁷

2.5. Outcome Ascertainment

Primary outcomes of this study were all-cause and cause-specific mortality including CHD and CVD death. In the CAC Consortium, mortality was assessed via linkage of patient records from the Social Security Administration (SSA) Death Master File (DMF) using a previously validated algorithm. Death certificates were obtained from the National Death Index (NDI), and the underlying cause of death was categorized into common causes of death using International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) codes. Prior studies have shown comparable death rates in the CAC Consortium with those in the US Census and MESA. Internal validation for known death rates identified via the electronic medical record revealed > 90% specificity and 72–90% sensitivity⁷

CVD death was defined in the CAC Consortium as death from cardiovascular disease causes including coronary heart disease, stroke, heart failure and other circulatory diseases.

2.6. Statistical Analysis

Baseline sociodemographic and clinical characteristics were reported for the overall population. Absolute numbers and percentages were calculated for categorical variables, mean with standard deviation and medians with interquartile range were presented for normal and skewed data, respectively. The distribution of CAC-DRS scores across the population was described using histograms.

Mortality rates were calculated by dividing the all-cause or cause-specific number of deaths by the total number of patient-years of follow-up and reported per 1,000 patient-years, and these were tabulated and displayed graphically across increasing CAC-DRS scores. We used Cox regression (for all-cause mortality) proportional hazard and Fine-and-Gray competing-risk regression (for CVD and CHD) models to examine the association between CAC-DRS scoring categories and mortality outcomes. Unadjusted and multivariable adjusted model 1 (age, sex, and race) and model 2 (model 1 + hypertension, hyperlipidemia, active smoking, family history of CHD, and diabetes mellitus) were used.

Using receiver-operating characteristic curves, we then compared the discriminatory performance of models with CAC-DRS to models using traditional CAC score groups or number of vessels with CAC. Traditional CAC groups were defined as CAC = 0 (reference group), CAC = 1–99, CAC = 100–299, and CAC ≥ 300. Number of vessels with CAC ranged from 0 to 4 for the major epicardial coronary arteries.

Finally, we repeated all analyses in a subset of patients at borderline to intermediate risk (5–20% 10-year ASCVD risk). All analyses were performed by Stata version 13 SE (Stata Inc., TX, USA), with a two-tailed *P*-value of less than 0.05 considered statistically significant.

3. Results

3.1. Baseline demographics

In the final analytic sample of 54,678 patients, mean age was 54.2 ± 10.7 with 34.4% women. Full baseline characteristics of the study population are shown in Table 1. Patients were predominantly white (89%), 31% of participants had hypertension, 7% had diabetes, 58% had hyperlipidemia, 10% were current cigarette smokers, and 49% reported a family history of CHD. The mean 10-year ASCVD risk score was 7.3 ± 9.0 with 56% of the cohort having a low ASCVD risk score (< 5%) and nearly a third (36%) having an ASCVD risk score 5–20% (intermediate risk group).

3.2. Distribution of CAC-DRS in the CAC consortium

Table 2 and Fig. 1 represent distribution of CAC-DRS. Approximately half of patients ($N = 26,531$) were A0 (48.5%), followed by A1/N1 (16.2%), A1/N2 (8.9%) and A3/N3 (6.3%). There was insufficient data for further analysis on A3/N1 (0.13%) and A1/N4 (0.42%), as these groups proved to be very rare phenotypes. Suppl. table 1 and Suppl. figure 1 represent distribution of CAC-DRS among participants in the intermediate risk group.

3.3. CHD, CVD and all-cause mortality rates by CAC-DRS

In the overall populations, there were 2,469 deaths (including 398 CHD deaths and 762 CVD deaths) and in the intermediate risk population there were 1,067 deaths (including 141 CHD deaths and 288 CVD deaths) over a median follow-up duration of 11.7 years (Table 3 and Suppl. table 2). Table 3 and Figs. 2–4 shows the cumulative incidence and incidence rates of CHD, CVD and all-cause mortality by CAC-DRS group. Patients had a graded increase in incidence of CHD, CVD and all-cause mortality with increasing categories of CAC-DRS. Additionally, there was increase in incidence rates (per 1000 person-years) of CHD death, CVD death and all cause death with increasing CAC-DRS group in the intermediate risk group (Suppl. table 2 and suppl. fig. 2.1, 2.2, 2.3)

3.4. Predictive value of CAC-DRS for CHD, CVD and all-cause mortality

Table 4 demonstrate the relative mortality hazards across CAC-DRS groups, with CAC-DRS A0 considered as the reference group. In minimally adjusted (age, sex, and race adjusted) models, we noted greater hazards of cause-specific and all-cause death with increasing levels of CAC-DRS. In the fully adjusted Cox proportional hazard models (model 2: model 1 + hypertension, hyperlipidemia, smoker, family history of CHD and the presence of diabetes mellitus), those with CAC-DRS A3/N4 had a 5.9 (95% CI 3.6–9.9) higher risk of CHD mortality, 4.0 (95% CI 2.8–5.7) times higher risk of CVD-specific mortality, and a 2.5 (95% CI 2.1–3.0) times higher risk of all-cause mortality compared to

Table 1
Baseline demographic characteristics of the study population.

All (N = 54,678)	
Demographics	
Mean age	54.2 ± 10.7
Female	18,816, 34.4%
White	37,580, 89.2%
Black	955, 2.3%
Hispanic	1307, 3.1%
Risk factors	
Hypertension	16,767, 30.7%
Diabetes	3580, 6.6%
Hyperlipidemia	31,509, 57.6%
Current Smoking	5286, 9.7%
Family History of CHD	26,492, 48.5%
Risk measures	
Mean CAC Score	155.0 ± 477
Median CAC Score	1 (0, 78.9)
Mean number of vessels	1.12 ± 1.31
Median number vessels	1 (0, 2)
Mean number of vessels with CAC	2.2 ± 1.07
Median number vessels with CAC	2 (1, 3)
ASCVD Risk	
ASCVD Risk Categories	7.3 ± 9.0
< 5%	30,637, 56.0%
5–20%	19,837, 36.3%
≥ 20%	4204, 7.7%
CAC score groups	
0	26,531, 48.5%
1–100	15,679, 28.7%
100–300	5569, 10.2%
> = 300	6899, 12.6%

Table 2
Distribution of CAC-DRS scores.

CAC DRS	N = 54,678, %
A0	48.5%
A1/N1	16.2%
A1/N2	8.9%
A1/N3	3.2%
A1/N4	0.42%
A2/N1	1.3%
A2/N2	3.6%
A2/N3	4.1%
A2/N4	1.2%
A3/N1	0.13%
A3/N2	1.5%
A3/N3	6.3%
A3/N4	4.8%

Fig. 1. Distribution of CAC-DRS scores.

individuals with CAC-DRS A0. Results were consistent for intermediate risk participants (Suppl. table 3), showing in the fully adjusted model that those with CAC-DRS A3/N4 had an 8.0 (95% CI 3.7–17.4.9) higher risk of CHD mortality, 4.1 (95% CI 2.5–6.7) times higher risk of CVD-specific mortality, and a 2.6 (95% CI 2.0–3.3) times higher risk of all-cause mortality compared to individuals with CAC-DRS A0.

3.5. CAC-DRS vs. CAC score groups and regional distribution for prediction of CHD, CVD and all-cause death

Table 5 shows comparative AUC analysis for CAC-DRS, CAC score groups, and number of vessels with CAC for prediction of CHD death,

Table 3

Cumulative incidence and incidence rates (per 1000 person-years) of CHD death, CVD death and All-cause death by CAC-DRS categorical groups.

	CHD death		CVD death		All-cause death	
	N, %	per 1000 pyrs	N, %	per 1000 pyrs	N, %	per 1000 pyrs
A0	46, 0.17%	0.14 (0.11, 0.19)	114, 0.43%	0.35 (0.29, 0.42)	562, 2.12%	1.7 (1.6, 1.9)
A1/N1	25, 0.28%	0.25 (0.17, 0.37)	70, 0.79%	0.70 (0.55, 0.88)	308, 3.5%	3.1 (2.8, 3.4)
A1/N2	27, 0.56%	0.48 (0.33, 0.70)	53, 1.1%	0.95 (0.72, 1.2)	198, 4.1%	3.5 (3.1, 4.1)
A1/N3	16, 0.92%	0.79 (0.48, 1.3)	30, 1.7%	1.5 (1.04, 2.1)	83, 4.8%	4.1 (3.3, 5.1)
A2/N1	4, 0.56%	0.51 (0.19, 1.4)	6, 0.84%	0.76 (0.34, 1.7)	42, 5.9%	5.3 (3.9, 7.2)
A2/N2	19, 0.97%	0.86 (0.55, 1.4)	43, 2.2%	2.0 (1.5, 2.6)	119, 6.1%	5.4 (4.5, 6.5)
A2/N3	34, 1.5%	1.4 (0.98, 1.9)	60, 2.7%	2.4 (1.9, 3.1)	168, 7.5%	6.8 (5.8, 7.9)
A2/N4	11, 1.7%	1.7 (0.92, 3.0)	23, 3.6%	3.5 (2.3, 5.2)	50, 7.9%	7.5 (5.7, 9.9)
A3/N2	20, 2.5%	2.3 (1.5, 3.6)	34, 4.3%	3.9 (2.8, 5.5)	104, 13.0%	12.0 (9.9, 14.6)
A3/N3	100, 2.9%	2.7 (2.2, 3.3)	170, 5.0%	4.6 (4.0, 5.4)	422, 12.3%	11.5 (10.5, 12.7)
A3/N4	93, 3.6%	3.6 (2.9, 4.4)	154, 5.9%	6.0 (5.1, 7.0)	397, 15.3%	15.4 (14.0, 17.0)

A1/N4 and A3/N1 and are not shown in Table 3 because these particular groups are very rare phenotypes and there is insufficient data.

CHD death

Fig. 2. Cumulative incidence and incidence rates (per 1000 person-years) of CHD death.

CVD death

Fig. 3. Cumulative incidence and incidence rates (per 1000 person-years) of CVD death.

Fig. 4. Cumulative incidence and incidence rates (per 1000 person-years) of All-cause death.

Table 4

Multivariable-adjusted hazard ratios for All-cause and cause-specific mortality by CAC-DRS score.

	Unadjusted	Model 1	Model 2
CHD death			
A0	1.0	1.0	1.0
A1/N1	1.7 (1.1, 2.8)	1.2 (0.67, 2.1)	1.1 (0.64, 2.03)
A1/N2	3.4 (2.1, 5.4)	1.8 (1.0, 3.3)	1.7 (0.92, 3.0)
A1/N3	5.5 (3.1, 9.7)	3.9 (2.1, 7.2)	3.5 (1.9, 6.4)
A1/N4	5.3 (1.3, 22)	3.7 (0.90, 15.2)	3.3 (0.79, 13.5)
A2/N1	3.5 (1.2, 9.6)	2.3 (0.80, 6.7)	2.1 (0.73, 6.1)
A2/N2	5.9 (3.5, 10.1)	2.7 (1.4, 5.1)	2.4 (1.2, 4.6)
A2/N3	9.3 (6.0, 14.5)	4.2 (2.4, 7.3)	3.7 (2.1, 6.5)
A2/N4	11.1 (5.7, 21.3)	3.8 (1.7, 8.5)	3.2 (1.4, 7.3)
A3/N2	15.4 (9.1, 26.0)	5.2 (2.6, 10.5)	4.6 (2.3, 9.2)
A3/N3	18.1 (12.8, 25.7)	6.1 (3.7, 10.0)	5.1 (3.1, 8.4)
A3/N4	23.2 (16.3, 33.0)	7.4 (4.5, 12.2)	5.9 (3.6, 9.9)
CVD death			
A0	1.0	1.0	1.0
A1/N1	1.9 (1.4, 2.6)	1.5 (1.03, 2.1)	1.4 (0.99, 2.0)
A1/N2	2.6 (1.9, 3.6)	1.6 (1.1, 2.4)	1.5 (1.0, 2.2)
A1/N3	4.1 (2.8, 6.2)	2.6 (1.6, 4.0)	2.3 (1.5, 3.6)
A1/N4	2.1 (0.52, 8.6)	1.5 (0.38, 6.1)	1.4 (0.33, 5.5)
A2/N1	2.1 (0.91, 4.7)	1.3 (0.58, 3.1)	1.2 (0.53, 2.8)
A2/N2	5.4 (3.8, 7.6)	2.5 (1.7, 3.9)	2.3 (1.5, 3.5)
A2/N3	6.6 (4.8, 9.0)	3.0 (2.0, 4.4)	2.6 (1.8, 3.9)
A2/N4	9.3 (6.0, 14.6)	3.3 (1.9, 5.7)	2.9 (1.7, 5.0)
A3/N1	10.6 (3.4, 33.6)	3.5 (0.87, 14.4)	3.0 (0.71, 12.5)
A3/N2	10.5 (7.2, 15.4)	3.9 (2.4, 6.3)	3.4 (2.1, 6.0)
A3/N3	12.4 (9.8, 15.7)	4.2 (3.0, 5.8)	3.5 (2.5, 4.9)
A3/N4	15.6 (12.2, 19.8)	4.9 (3.5, 6.9)	4.0 (2.8, 5.7)
All-cause death			
A0	1.0	1.0	1.0
A1/N1	1.7 (1.5, 2.0)	1.4 (1.2, 1.6)	1.3 (1.1, 1.6)
A1/N2	2.0 (1.7, 2.4)	1.3 (1.04, 1.5)	1.2 (1.01, 1.5)
A1/N3	2.3 (1.8, 2.9)	1.4 (1.1, 1.8)	1.3 (1.03, 1.70)
A1/N4	1.5 (0.71, 3.2)	0.97 (0.43, 2.2)	0.90 (0.40, 2.0)
A2/N1	3.0 (2.2, 4.1)	1.5 (1.1, 2.2)	1.5 (1.0, 2.0)
A2/N2	3.1 (2.5, 3.7)	1.4 (1.1, 1.8)	1.4 (1.1, 1.7)
A2/N3	3.8 (3.2, 4.6)	1.9 (1.5, 2.3)	1.7 (1.4, 2.1)
A2/N4	4.2 (3.2, 5.7)	1.6 (1.1, 2.3)	1.5 (1.04, 2.1)
A3/N1	6.8 (3.5, 13.2)	1.8 (0.73, 4.3)	1.6 (0.67, 3.9)
A3/N2	6.8 (5.5, 8.4)	2.6 (2.0, 3.4)	2.4 (1.9, 3.15)
A3/N3	6.5 (5.7, 7.4)	2.4 (2.0, 2.8)	2.1 (1.8, 2.5)
A3/N4	8.7 (7.6, 9.9)	2.8 (2.4, 3.4)	2.5 (2.1, 3.0)

Table 5

Comparison of traditional risk factors to traditional risk factors + CAC-DRS scores for CHD-specific mortality, CVD-specific mortality and All-cause mortality.

AUC	CHD death	CVD death	All-cause death
CAC-DRS	0.795	0.762	0.700
Number of vessels	0.780	0.748	0.687
CAC Score Groups	0.785	0.754	0.696
p-value CAC-DRS vs. Number of vessels	< 0.001	< 0.001	< 0.001
p-value CAC-DRS vs. CAC Score Groups	< 0.001	< 0.001	< 0.001

CVD death and all cause death. The use of CAC-DRS yielded significant improvements in risk discriminatory value above CAC score groups alone (CHD mortality p-value: < 0.001, CVD mortality p-value: < 0.001, all-cause mortality p-value: < 0.001) or number of vessels alone (CHD mortality p-value: < 0.001, CVD mortality p-value: < 0.001, all-cause mortality p-value: < 0.001) or. Importantly, the significant improvement in discriminatory value was consistent across all outcomes, CVD, CHD and all-cause mortality. Results were consistent in analyses restricted to intermediate risk participants (Suppl. table 3 and Suppl. table 4).

4. Discussion

In light of recent recommendations for wider use of CAC in national guidelines^{3,4}, and calls for at least qualitative visual CAC scoring on all chest CTs¹, we sought to examine the prognostic significance of the new, simple CAC-DRS scoring system recently proposed by the SCCT. In the largest CAC cohort yet assembled, we confirmed that CAC-DRS has predictive value independent of cardiovascular risk factors, and is a better predictor of CHD mortality, CVD mortality and all-cause mortality than either traditional CAC score groups or number of vessels with CAC alone. Our study emphasizes on the value of both overall CAC score and its regional distribution in the coronary tree. Results were robust in dedicated analysis of the 5–20% 10-year ASCVD risk group where CAC is most likely to be utilized. Our results have implications for broader use of CAC-DRS in clinical practice, which would enable systematization of CAC score reports across gated and non-gated studies, and linkage to treatment recommendations. These findings strongly support the new SCCT CAC guidelines and may guide clinicians in earlier identification of at-risk patients across a variety of chest CT applications, leading to earlier preventive interventions.

Risk factor-based models for risk estimation continue to serve as the primary basis for decision making in primary prevention. However, limitations of such models are increasingly recognized, leading to uncertainty in clinical management in those patients who are at intermediate risk. Compared to risk factor models, CAC integrates the cumulative lifetime effects of both measured and non-measurable risk factors, accounting for individual vulnerability to these risk determinants, via the direct representation of accumulated damage within the coronary vascular bed.¹⁵ Accordingly, CAC can be considered a measure of arterial aging.¹⁶

A 2017 guideline from the SCCT considered the primary role for CAC scanning to be a facilitator of shared decision making in those with “intermediate” 5%–20% ASCVD risk.¹⁷ Similarly, the 2018 cholesterol guideline stated that coronary artery calcium (CAC) scoring can be utilized to withhold, postpone, or initiate statin therapy in individuals with uncertain risk. Subsequently, there is an increasing interest in CAC scoring, including identification of CAC on non-gated chest CTs. Therefore, our findings would serve as a reference for clinicians who routinely interpret CAC using the CAC-DRS scoring system.

The SCCT/STR guidelines gave a class I recommendation for at least qualitative visual CAC scoring on all chest CTs, and CAC-DRS appears to be an excellent method for conveying risk information in these patients. This recommendation follows an overwhelming body of evidence showing that reporting CAC in non-gated chest CTs have a strong prognostic implication. For example Chiles et al. reported that a simple visual assessment of CAC can be generated for risk assessment of CHD death and all-cause mortality, which is comparable to Agatston scoring and strongly associated with outcomes, on low-dose CT performed for lung cancer screening in older, heavy smokers.⁶ The primary advantage of CAC-DRS is thought to be in systematizing scores across gated and non-gated studies. With our data, we expect a greater push from SCCT to educate providers about this simple scoring system. Electronic medical records, including imaging databases, would allow for reinterpretation of existing gated and non-gated images with rapid assessment of their predictive value. In the future, CAC-DRS scoring could likely even be automated, with limited involvement of the interpreting clinician.

However, a limitation of our study is that we used Agatston scores to calculate DRS, and did not have access to the primary images for visual re-interpretation. Our study would have been greatly enhanced by performing the visual analysis as well since all radiology driven chest CT will use the visual analysis. Additional research is still needed to confirm the equivalence of A and V scoring, and to demonstrate the ability of interpreting to physicians to reliably categorize patients into equivalent groups using A and V scoring.

Our study is also subject to additional limitations. Additional limitations include that our study is an observational, retrospective cohort study of patients referred for clinical CAC scanning, and as such, our results may not be generalizable to the general population because of potential referral bias. Our population is predominantly white (89.2%), which limits its generalizability to other ethnic groups. Additionally, the predictive value of CAC-DRS in our study is likely to be underestimated as both patients and clinicians were informed about the results of the CAC scan, which may have led to altered treatment decisions and risk factor modification in those with the highest CAC-DRS scores.

However, our study also has a number of strengths - the CAC Consortium represents the largest database of CAC scans linked to long-term cause-specific mortality. The 54,678 patients in this analysis have a mean follow-up of 11.7 years.⁷ Additionally, there is cause-specific mortality data, which has been gathered using validated methods¹⁸, and can provide insights which were not previously possible.

5. Conclusions

In conclusion, our findings are the first to validate the new SCCT CAC-DRS scoring system for prediction of cause-specific and total mortality, and support the recommendation for consideration of CAC-DRS scoring for risk stratification on all chest CT, especially in the "intermediate" 5%–20% ASCVD risk group who might undergo non-contrast chest CT. Our study supports^{19–21} and validates the dual value of both CAC score and regional distribution and strongly supports the new SCCT guidelines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcct.2019.03.011>.

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