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Research paper

Estimation of cardiovascular risk on routine chest CT: Ordinal coronary artery calcium scoring as an accurate predictor of Agatston score ranges

Lea Azour [a, b, *], Michael A. Kadoch [c], Thomas J. Ward [d], Corey D. Eber [a], Adam H. Jacobi [a, b]

[a] Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
[b] The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States
[c] Department of Radiology, University of California Davis, Sacramento, CA 95817, United States
[d] Radiology Specialists of Florida, Maitland, FL 32751, United States

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ABSTRACT

Background: Coronary artery calcium (CAC) is often identified on routine chest computed tomography (CT). The purpose of our study was to evaluate whether ordinal scoring of CAC on non-gated, routine chest CT is an accurate predictor of Agatston score ranges in a community-based population, and in particular to determine the accuracy of an ordinal score of zero on routine chest CT.
Methods: Two thoracic radiologists reviewed consecutive same-day ECG-gated and routine non-gated chest CT scans of 222 individuals. CAC was quantified using the Agatston scoring on the ECG-gated scans, and using an ordinal method on routine scans, with a score from 0 to 12. The pattern and distribution of CAC was assessed. The correlation between routine exam ordinal scores and Agatston scores in ECG-gated exams, as well as the accuracy of assigning a zero calcium score on routine chest CT was determined.
Results: CAC was most prevalent in the left anterior descending coronary artery in both single and multi-vessel coronary artery disease. There was a strong correlation between the non-gated ordinal and ECG-gated Agatston scores ($r = 0.811$, $p < 0.01$). Excellent inter-reader agreement ($k = 0.95$) was shown for the presence (total ordinal score ≥ 1) or absence (total ordinal score $= 0$) of CAC on routine chest CT. The negative predictive value for a total ordinal score of zero on routine CT was 91.6% (95% CI, 85.1–95.9). Total ordinal scores of 0, 1–3, 4–5, and ≥ 6 corresponded to average Agatston scores of 0.52 (0.3–0.8), 98.7 (78.2–117.1), 350.6 (264.9–436.3) and 1925.4 (1526.9–2323.9).
Conclusion: Visual assessment of CAC on non-gated routine chest CT accurately predicts Agatston score ranges, including the zero score, in ECG-gated CT. Inclusion of this information in radiology reports may be useful to convey important information on cardiovascular risk, particularly premature atherosclerosis in younger patients.

1. Introduction

Coronary heart disease is the leading cause of mortality in the US.[1] Traditionally, heart disease has been assessed qualitatively with risk factor models incorporating demographics and/or biomarkers, such as the Framingham Risk Score,[2] the European Society of Cardiology Score,[3] and the AHA/ACC Pooled Cohort Equations.[4]

In contrast to the binary nature of risk factors, imaging allows for the noninvasive quantification of atherosclerosis, specifically the quantification of coronary artery calcium through ECG-gated CT.[5] The most frequently used method for calcium quantification on CT, the Agatston score, relies on software to multiply the volume of coronary artery calcium deposits by a coefficient that corresponds to their peak density.[5]

Coronary artery calcium (CAC) scoring has been shown to be more predictive of cardiovascular events than traditional risk

Abbreviations: CAC, coronary artery calcium; CT, computed tomography; LM, left main; LCx, left circumflex; LAD, left anterior descending; RCA, right coronary artery; MIP, maximum intensity projection.

* Corresponding author. Department of Radiology, Icahn School of Medicine at Mount Sinai, PO Box 1234, 1 Gustave L. Levy Place, New York, NY 10029, United States.
E-mail address: lea.azour@mountsinai.org (L. Azour).

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factors across various ethnicities,[6–11] with a net reclassification index as high as 66% in patients categorized as intermediate risk by the Framingham score.[12–14] Additional studies have demonstrated the prognostic value of CAC scoring for death, non-fatal myocardial infarction, and future revascularization.[8,15–20]

When applied to routine non-ECG gated chest CT, the modified Agatston score has proven concordant with the ECG-gated scan derived Agatston score in lung cancer screening patients,[21–23] as well as in community-based populations.[24] Evaluating CAC on routine non-contrast chest CTs is a cost- and radiation-free method of quantifying coronary calcium, and it is increasingly utilized in clinical practice, particularly in the low dose lung cancer screening population.[25,26] While lung cancer is the leading cause of cancer mortality in the United States, heart disease remains the foremost cause of mortality even within the National Lung Cancer Screening Trial (NLST) cohort,[27] adding clinical relevance to "incidental" coronary calcium. CAC measurement is considered a reasonable tool (class IIa and/or IIb) for cardiovascular risk assessment, particularly for intermediate-risk asymptomatic adults.[3,28,29] Patient knowledge of their calcium score has also been shown to correlate with improved adherence to medical therapy and more effective lifestyle modification.[30,31]

Qualitative visual assessment methods have been developed to quantify CAC.[32–35] One of the most widely used methods, ordinal scoring, relies on the visual assessment of the left main, left anterior descending, left circumflex, and right coronary arteries. Ordinal scoring has been shown to be independently predictive of cardiovascular death, with a quantitative relationship between the ordinal score and odds of cardiovascular death.[36–38]

In the United States in 2007, more than 600,000 dedicated CAC scoring exams were performed. In contrast, over 9 million routine chest CT exams were performed for a variety of indications, with the number only projected to rise.[39] Despite the routine visualization of coronary artery calcium on these exams, CAC is neither systematically nor routinely reported by radiologists.[40,41] In a study of 207 patients with CAC, radiologists reported the presence of CAC in only 44% of patients, with only 1% of the involved coronary vessels reported by name.[41]

As most CT chest exams are performed among community-living individuals, we sought to assess ordinal scoring on routine chest CT scans as an accurate predictor of Agatston score ranges. Additionally, since the community-based population includes individuals younger than those included in the lung cancer screening population, we suggest a radiology-reporting method for coronary calcium burden relative to age and gender matched peers.

2. Methods

2.1. Study design

This retrospective HIPPA-compliant study protocol was approved by the institutional review board. The requirement for informed consent was waived.

2.2. Subjects

Between 2008 and 2013, 3602 community-living individuals underwent ECG-gated cardiac CT examinations, 226 of whom who were self-or physician-referred for a "whole-body" CT scan in addition to the cardiac CT examination, with both exams performed consecutively on the same day. One patient with a previously implanted coronary artery stent was excluded from the study. Three individuals underwent same-day scanning twice during the study interval, with exclusion of the older scan set. This yielded 222 unique patients.

2.3. Agatston and routine chest CT protocol

All patients underwent two consecutive CT examinations in one session using a 64-slice GE Lightspeed VCT scanner (GE Healthcare, Milwaukee, USA).

For ECG-gated calcium scoring CT, the scanning protocol was as follows: prospective ECG-triggering set at 75% of the RR interval; scan range, carina to cardiac apex; peak voltage, 120 kVp; tube current modulation 210–500 mA; rotation time, 0.35 s; detector collimation, 64 $\times$ 0.5 mm; section thickness/increment, 2.5 mm/2.5 mm; reconstruction kernel, standard; field of view, 250 mm; matrix, 512 $\times$ 512.

For routine non-contrast chest CT, the protocol was as follows: scan range, thoracic inlet to adrenal glands; peak voltage, 120 kVp; tube current modulation 80–500 mA; rotation time, 0.4 s; pitch, 0.984; detector collimation, 64 $\times$ 0.5 mm; section thickness/increment, 2.5–5 mm/2.5–5 mm; reconstruction kernel, standard; field of view, 360 mm; matrix, 512 $\times$ 512. 199 (89.6%) non-gated scans were acquired at 5 mm slice thickness, with 23 (10.4%) acquired at 2.5 mm slice thickness.

2.4. CAC assessment by Agatston scoring

CAC scoring on the ECG-gated studies was performed utilizing commercially available calcium scoring software (PHILIPS), which was used to identify and score any calcium in the four main coronary arteries, the left main (LM), left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA), based on established minimum attenuation values. The Agatston score was generated by summing the scores of all lesions, which were derived by multiplying the lesion area by density in Hounsfield units.[5] All identified plaque was manually evaluated by an investigator to exclude non-coronary artery calcium.

2.5. CAC assessment by ordinal scoring

Two readers, thoracic radiologists with 20 and 4 years of experience, independently reviewed the ECG-gated and non-gated scans. Readers were blinded to the Agatston scores. The gated and the non-gated studies were scored at a one-week interval in random order.

Visual assessment of CAC was performed via ordinal scoring. Each of the four main coronary arteries was identified. Calcium was scored by the thoracic radiologists as 0, 1, 2, or 3 to correspond to absent, mild, moderate, or severe CAC in each vessel. Mild CAC was defined as involvement of less than one third of the vessel length (Fig. 1), moderate as involvement of one to two thirds of the vessel length (Fig. 2), with severe coronary artery calcium defined as involvement of greater than two thirds of the vessel length (Fig. 3). The scores were summed to yield ordinal scores of 0–12 for each scan.[34,36] The total ordinal scores were then categorized as 0, 1–3, 4–5, and $\geq$6.

2.6. Statistical analysis

A binary scale was used to classify the ECG-gated exams as to the presence or absence of CAC (Agatston score of 0 versus Agatston score > 0). The sensitivity, specificity, positive predictive value, and negative predictive values were determined for the total ordinal score of zero. The inter-reader agreement for the detection of CAC by ordinal scoring was determined with Cohen's kappa coefficient.

The correlation between the ordinal and Agatston scores was determined with Pearson's correlation coefficient. The exams were then grouped by ordinal score ranges of 0, 1–3, 4–5, and $\geq$6. The median, mean, absolute minimum, and absolute maximum

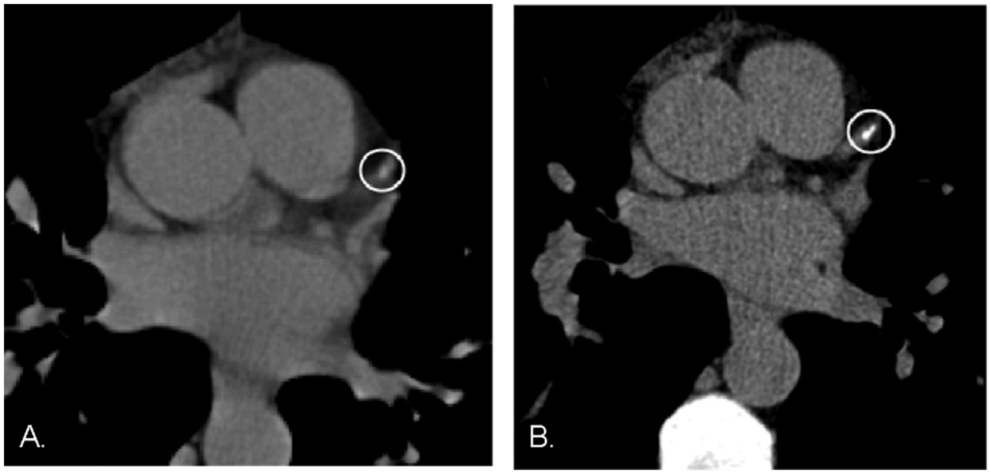

Fig. 1. Ordinal Score of 1. 54 year old man presenting for screening exam, with true positive coronary artery calcification (CAC) in the distribution of the left anterior descending (LAD, circled) coronary artery on same-day routine non-gated chest CT (**A**) and ECG-gated coronary CT (**B**). **A**, Routine non-ECG gated chest CT shows CAC involving less than one third the vessel length, corresponding to an ordinal score of 1 in the LAD. **B**, ECG-gated coronary CT shows the same focus of CAC involving the LAD.

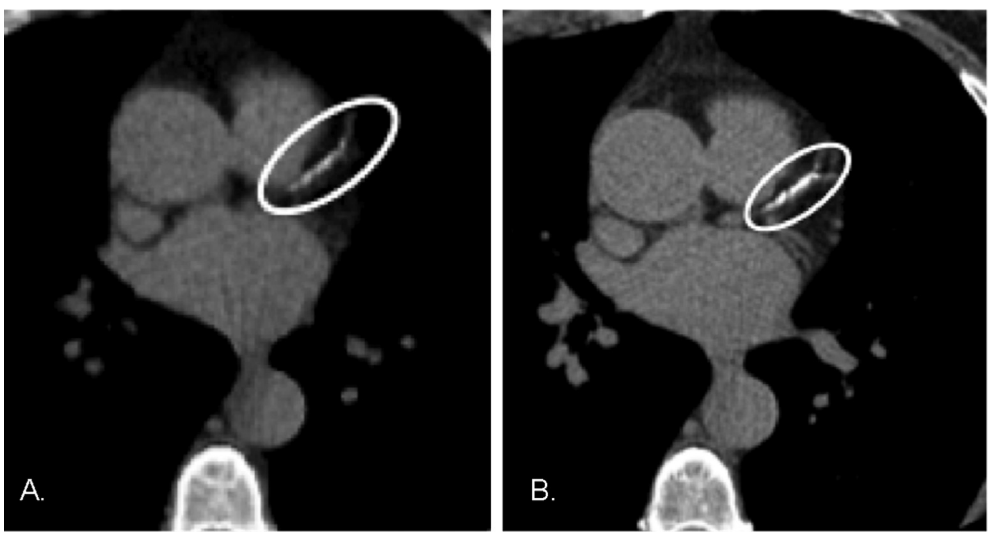

Fig. 2. Ordinal Score of 2. 66 year old woman presenting for screening exam, with CAC in the distribution of the LAD (circled) on same-day routine non-gated chest CT (**A**) and ECG-gated coronary CT (**B**). Additional CAC in the left main and right coronary arteries is not shown. **A**, Routine non-ECG gated chest CT shows CAC involving 1/3 to 2/3 the vessel length, corresponding to an ordinal score of 2 in the LAD. **B**, ECG-gated coronary CT shows a similar extent of CAC involving the LAD.

Agatston scores were generated for each ordinal score range.

The prevalence of CAC by coronary artery was evaluated for single vessel coronary artery disease, multi-vessel coronary artery disease, and overall, with exclusion of false positive ordinal scores. The inter-reader agreement for the assignment of CAC for each vessel was determined with Cohen's kappa coefficient.

3. Results

The prevalence of an Agatston score greater than zero on gated cardiac CT exams was 38.3% (85/222 patients). Table 1 depicts the severity of CAC burden by sex for Agatston and ordinal scores, with Fig. 4 showing the distribution of Agatston score ranges within our cohort. Our population was 72.7% male, with males and females well matched for age.

The inter-reader agreement for the presence (total ordinal score ≥ 1) or absence (total ordinal score $= 0$) of CAC on non-gated routine chest CT was excellent (kappa $= 0.96$). The negative predictive value of an ordinal score of zero on routine chest CT was 91.6% (95% confidence interval: 85.1–95.9%).

Within our cohort, there were 3 false positives and 13 false negatives. Of the false negatives, 12 were missed by both readers. The average Agatston score on the false negative exams was 6.6, with a minimum Agatston score of 1 and maximum Agatston of 17. Further, all misses were on 5 mm slice thickness scans, with none on the 23 routine exams for which 2.5 mm thickness slices were available. There were 3 false positives, assigned once each to the left main, left anterior descending, and right coronary arteries, which upon review corresponded to motion-related artifact.

We found very strong correlation (Pearson correlation $R = 0.811$, $p < 0.01$) between total ordinal scores and the Agatston scores, as illustrated in Fig. 5. Total ordinal score ranges of 0, 1–3, 4–5, and ≥ 6 correlated with progressively increasing mean Agatston scores, shown in Table 2. A total ordinal score of zero corresponded to a mean Agatston score of 0.52, and maximum missed Agatston score of 17. Ordinal scores ≥ 6 corresponded to a mean Agatston score of 1925.4, with a minimum Agatston score of 406, yielding a 100% positive predictive value for an ordinal score of 6 or greater to

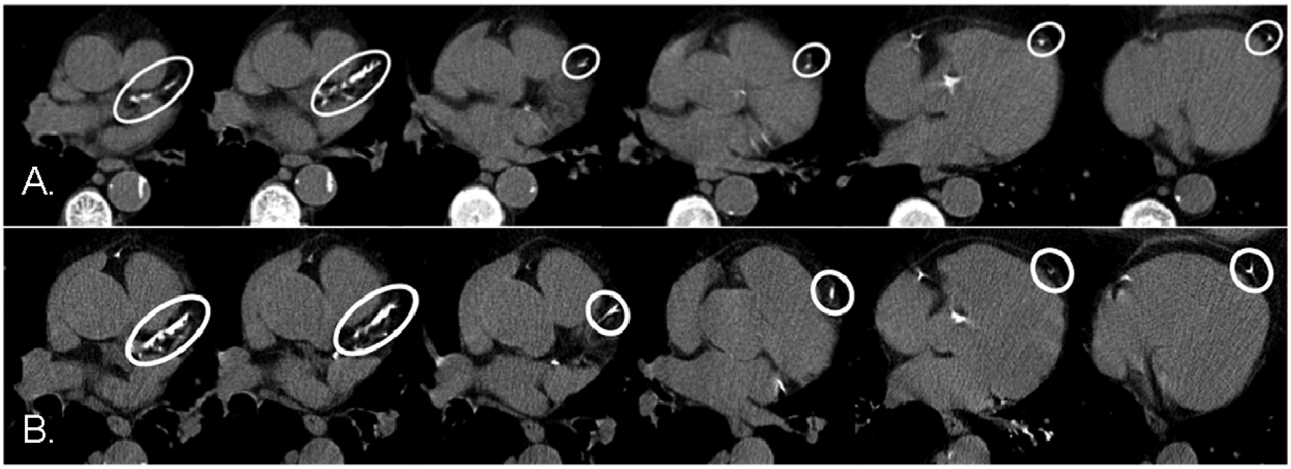

Fig. 3. Ordinal Score of 3. 79 year old man presenting for screening exam, with CAC in the distribution of the LAD (circled) on same-day routine non-gated chest CT (**A**) and ECG-gated coronary CT (**B**). Also seen is CAC in the left circumflex and right coronary arteries, as well as atherosclerotic calcification of the descending thoracic aorta. **A**, Routine non-ECG gated chest CT shows CAC involving greater than 2/3 the vessel length, corresponding to an ordinal score of 3 in the LAD. **B**, ECG-gated coronary CT shows the similar appearance of CAC in the LAD.

Table 1
Summary of CAC burden according to sex.

Parameter	Men (n = 160)	Women (n = 62)
Age (y)		
Median	50	50
Mean ± SD	51.7 ± 11.3	51.7 ± 12.4
Agatston score		
0	88 (55)	49 (79)
1–100	37 (23.1)	8 (12.9)
101–400	18 (11.3)	4 (6.5)
≥400	17 (10.6)	1 (1.6)
Ordinal score		
0	197[a] (61.6)	108[a] (87.1)
1–3	88 (27.5)	20 (16.1)
4–5	8 (2.5)	4 (3.2)
≥6	27 (8.4)	1 (0.81)

Except where indicated, data is provided in numbers of patients, with percentages in parentheses.
[a] Refers to number of ordinal scores within each interval, as each participant's non-gated exam was scored by two radiologists.

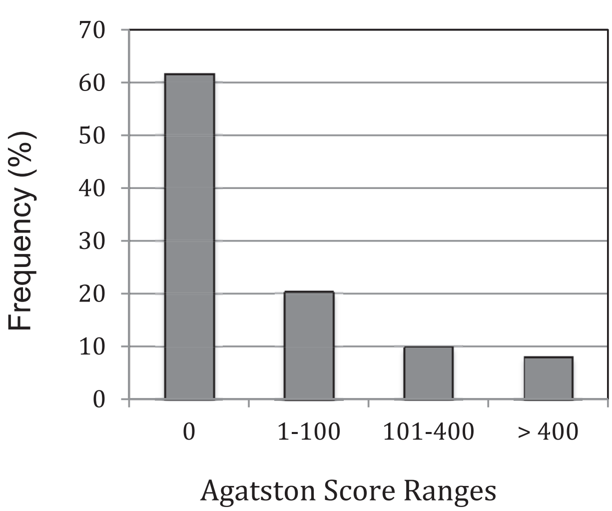

Fig. 4. Bar chart shows the frequency of Agatston scores within our cohort.

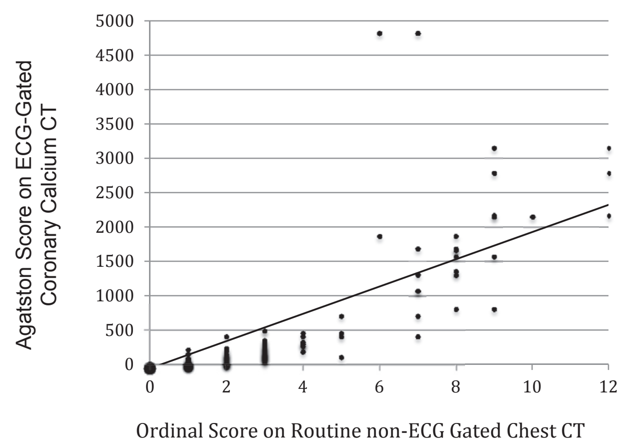

Fig. 5. Scatter plot shows the correlation of the ordinal and Agatston scores within our cohort.

correspond to an Agatston score above 400.

Evaluation of the distribution of CAC by coronary vessel revealed the majority of disease to involve the LAD, shown in Table 3. Among exams assigned a total ordinal score of one, by definition single vessel disease, the LAD was shown to be the initial vessel to demonstrate CAC in 91.7% of cases. The distribution of CAC assigned to each vessel was then examined according to reader, with the greatest discrepancy found in attribution of CAC to the LM versus LAD (Table 3). The inter-reader agreement in assigning LM CAC was 0.47, as compared to more robust measures for the LAD (k = 0.91), LCx (k = 0.72), and RCA (k = 0.79).

4. Discussion

We present findings of a community-based patient cohort who underwent routine non-contrast chest CT and also ECG-gated coronary calcium CT on the same date. Our population demonstrated a mean age of 51 years, 4 years younger than the age at which lung cancer screening would commence.[42] Our study is one of the first to evaluate the accuracy of a total ordinal score of zero, as well as the pattern and distribution of coronary artery calcium.

Table 2
Ordinal score ranges as a correlate to Agatston scores.

Ordinal score	Median Agatston score	Mean Agatston score	Standard deviation	Confidence interval (95%)	Lower bound	Upper bound	Absolute minimum Agatston score	Absolute maximum Agatston score
0	0	0.5	2.3	0.3	0.3	0.8	0	17
1–3	81	98.7	108.4	20.4	78.2	119.1	0	490
4–5	313.5	350.6	151.4	85.7	264.9	436.3	108	700
≥6	1673	1925.4	1075.8	398.5	1526.9	2323.9	406	4825

Table 3
Distribution of CAC by coronary artery.

CAC distribution	Left main	Left anterior descending	Left circumflex	Right coronary
Distribution of CAC in single and multi-vessel disease				
Single vessel disease (ordinal score = 1)	0[a]	91.7	4.2	4.2
Multi-vessel disease (ordinal score ≥ 2)	51.5	95.9	63.9	68.0
Overall (ordinal score ≥ 1)	34.5	94.5	44.1	46.9
Distribution of CAC assigned by each thoracic radiologist				
Reader 1	43 (31)	94.4 (68)	44.4 (32)	45.8 (33)
Reader 2	26 (19)	94.5 (69)	43.8 (32)	47.9 (35)
Kappa value	0.47	0.91	0.72	0.79

[a] Data is provided in percentages, with number of patients in parenthesis.

In our community-based population, we demonstrated the ordinal scoring of CAC on routine chest CT to accurately predict the Agatston score ranges derived from ECG-gated scans. This finding is consistent with multiple prior studies documenting CAC scoring on low-dose non-gated CT in lung cancer screening cohorts to be a reliable method of cardiovascular risk stratification.[20–22,33,34,36,43–45] Our study is one of the first to generalize these findings to a community-based population,[24,37,46] a group of potentially asymptomatic individuals, for whom cardiovascular risk information may not yet be clinically identified or suspected.

While it has been shown that the absolute CAC score predicts cardiovascular events better than age-adjusted percentiles,[6] it is also well established that CAC progresses with age, and is more commonly identified in males, with numerous studies having replicated these findings.[34,36]

In the Multi-Ethnic Study of Atherosclerosis (MESA) study, individuals with relatively low Agatston scores of 1–100 were shown to have 3 times the risk of any coronary event, highlighting the importance of scores greater than zero.[7] In asymptomatic patients, the absence of CAC corresponds to very low cardiovascular risk, and moreover, a zero score is a mitigating cardiovascular risk factor in smokers and diabetics.[47,48]

Agatston scores are typically accompanied by a percentile, which is based on the MESA demographic data.[49] Similarly, the ordinal CAC score should be interpreted in the context of an individual's age and gender, as “mild” CAC burden may not be “mild” for all patients (Table 4). For example, an ordinal score of 1 in a patient 45 years of age or younger would be considered unexpected/premature atherosclerosis, most often corresponding to a CAC burden at or above the 75th percentile for age- and gender-matched individuals. Identification of premature CAC would allow for early lifestyle modification and/or intervention, as the individual may otherwise be considered low risk via traditional stratification.

Table 4
Reporting of CAC on routine chest CT.

Ordinal Score	Coronary Artery Calcium	Criteria[+]	Probability of Cardiovascular Risk Relative to Age and Gender Matched Peers[+]
0	Absent	Total ordinal score of 0 in men over 55, and women over 65, years	Low
≥1	Present	Total ordinal score ≥ 1 in an individual ≤ 45 years	High
1-3	Mild	Total ordinal score ≥ 1 in any individual	Variable
4-5	Moderate		
≥6	Severe	Total ordinal score ≥ 6 in any individual	High

[+] Based on MESA demographic data.

The negative predictive value of a total ordinal score of zero on routine chest CT was over ninety percent in our cohort, missing only a few very small lesions, with a maximum missed Agatston score of 17. Similarly, in another community-based population, Kirsch et al. demonstrated the absence of CAC on routine chest CT to correspond to a maximum Agatston score of 19.[46] The absence of CAC by visual assessment on routine chest CT may at minimum accurately exclude severe coronary heart disease (Agatston score >400)[6] in men over 55, and women over 65 years in age, for whom an ordinal score of 1 is not considered high-risk based on MESA demographic data. Given the high negative predictive value demonstrated by ordinal scoring on routine CT, we believe this is a reliable method of identifying absent CAC, a marker of low cardiovascular risk. Reporting the absence of CAC may assist in medical management strategies employed by the physician and can obviate the need for dedicated CAC studies in certain patients.

Incorporating thinner sections (<5 mm) can improve the detection of CAC,[23] and strengthen the negative predictive value of a total ordinal score of zero. Similarly, the addition of maximum intensity projection (MIP) images in exam acquisition protocols may further increase the negative predictive value of the zero ordinal score. Calcium missed on routine 5 mm thickness non-gated chest CT is made more conspicuous by MIP images (Fig. 6), a potential topic for future investigation.

Knowledge of the pattern of CAC development may also aid in visual assessment. For example, since lesions are most often initially seen in the LAD,[50,51] the radiologist is more likely to be accurate in dismissing a questionable isolated LCx or RCA lesion on routine chest CT, rather than an isolated LAD lesion. As the greatest discrepancy in assigning CAC has been similarly found between the LM and LAD,[46] as in our study, these vessels should be evaluated with greater attention. Noting the diffusivity of CAC, whether single or multi-vessel disease, is an additional parameter shown to be predictive of coronary heart disease and cardiovascular events, with more diffuse disease correlating with worse outcomes.[52]

Beyond zero and relatively low Agatston scores, multiple studies have shown Agatston scores of 100–400 to correspond to 6–9 times greater mortality risk.[7,8,19] Agatston scores greater than the 400 benchmark are considered to correlate with high cardiovascular risk, with estimates of up to 12 times increased mortality risk.[6,19] Similarly, an ordinal score of 4 has been shown to be a significant predictor of cardiovascular death in a lung cancer screening population, irrespective of age, sex and pack-year smoking history.[36]

In our series, an ordinal score $\geq$6 corresponded to a minimum Agatston of 406. A comparison of ordinal versus Agatston scores in a predominately Caucasian, community-based population showed that a lower ordinal cut point of 3 corresponded to an Agatston score as high as 839, with an ordinal range of 4–6 corresponding to an Agatston range of 840-3100.[38] Larger scale studies will be necessary to validate a “severe” ordinal cut off score. An ordinal score of 6 is likely highly specific for severe CAC burden, with visual assessment in such cases not only precluding the need for dedicated calcium scoring exams, but alerting primary care providers to the presence of severe coronary artery disease. Based on the strong correlation between qualitative visual assessment and the

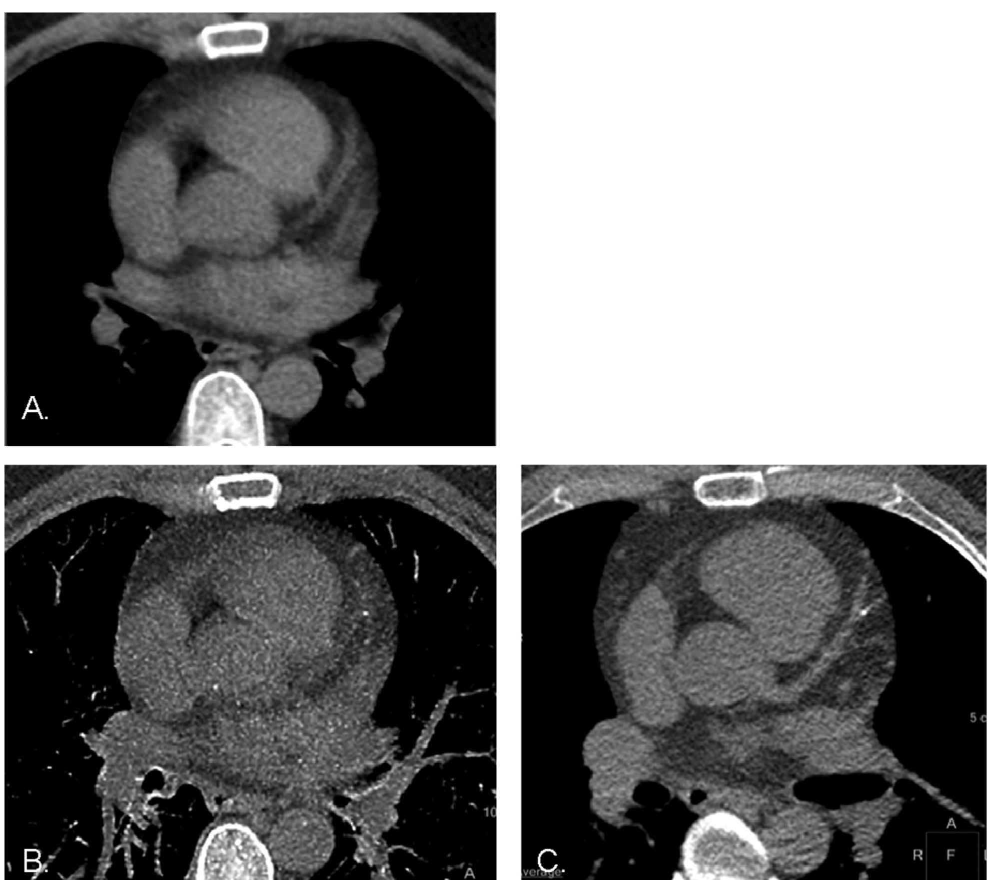

Fig. 6. MIP images and CAC conspicuity. 43 year old man presenting for screening exam. **A**, Routine non-ECG gated chest CT shows no CAC. **B**, The same non-ECG gated routine chest CT reformatted utilizing 10 mm MIP images makes the small focal calcification of the mid-LAD/proximal D1 more conspicuous. **C**, The corresponding ECG-gated CAC CT clearly demonstrates the focal calcification corresponding to the Agatston score of 17.

quantitative Agatston score, it may be reasonable for radiologists to incorporate a subjective "mild," "moderate, "or "severe" assessment of plaque burden in radiologic reports (Table 4), as well as notation of the affected vessels, particularly in single vessel disease.

4.1. Limitations

There were two main limitations in this study. Due to its retrospective nature, no outcome measures for the ordinal scores were available, though this relation has been previously demonstrated.[36–38] We also did not include traditional cardiovascular risk factor analyses, which in clinical practice may not be readily available to radiologists, and which have proven inferior to CAC score in prognostic capability.[6–11] Variability in patient heart rate as well as slice thickness may also influence the visual CAC assessment, which was not included in our study. Future studies may address the prognostic nature of interval progression of ordinally scored CAC, as rapid CAC progression is clinically relevant and worthy of radiologic mention.[53]

5. Conclusion

The ability to perform accurate calcium scoring on nongated chest CT allows for the application of calcium scoring to a broader cross-section of the population, including those with clinically unsuspected cardiovascular disease. This may lead to the study of groups not previously reached by dedicated calcium scoring, and may elucidate the role of calcium scoring in evaluating cardiovascular risk and treatment.

As a result of our findings, we recommend that radiologists systematically report the presence or absence of CAC on all routine non-contrast chest CT exams. Reporting the subjective assessment of plaque burden provides a robust surrogate for the Agatston score. Ordinal scoring is a simple, reproducible, and non-invasive measure that may reliably alert physicians to the severity of CAC, distinguishing high- and low-risk patients, with substantial clinical implications at no additional cost or radiation to the patient.

Conflict of interest

The authors declare that they have no conflict of interest.

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