Reliability of Coronary Artery Calcium Severity Assessment on Non-Electrocardiogram-Gated CT: A Meta-Analysis

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Objective: The purpose of this meta-analysis was to investigate the pooled agreements of the coronary artery calcium (CAC) severities assessed by electrocardiogram (ECG)-gated and non-ECG-gated CT and evaluate the impact of the scan parameters.

Materials and Methods: PubMed, EMBASE, and the Cochrane library were systematically searched. A modified Quality Assessment of Diagnostic Accuracy Studies-2 tool was used to evaluate the quality of the studies. Meta-analytic methods were utilized to determine the pooled weighted bias, limits of agreement (LOA), and the correlation coefficient of the CAC scores or the weighted kappa for the categorization of the CAC severities detected by the two modalities. The heterogeneity among the studies was also assessed. Subgroup analyses were performed based on factors that could affect the measurement of the CAC score and severity: slice thickness, reconstruction kernel, and radiation dose for non-ECG-gated CT.

Results: A total of 4000 patients from 16 studies were included. The pooled bias was 62.60, 95% LOA were -36.19 to 161.40, and the pooled correlation coefficient was 0.94 (95% confidence interval [CI] = 0.89–0.97) for the CAC score. The pooled weighted kappa of the CAC severity was 0.85 (95% CI = 0.79–0.91). Heterogeneity was observed in the studies (I² > 50%, p < 0.1). In the subgroup analysis, the agreement between the CAC categorizations was better when the two CT examinations had reconstructions based on the same slice thickness and kernel.

Conclusion: The pooled agreement of the CAC severities assessed by the ECG-gated and non-ECG-gated CT was excellent; however, it was significantly affected by scan parameters, such as slice thickness and the reconstruction kernel.

Keywords: Coronary artery calcium; Computed tomography; Reliability; Meta-analysis

INTRODUCTION

Coronary artery calcium (CAC) on electrocardiogram (ECG)-gated CT is an established marker for determining the risk of a cardiovascular event, and it has an incremental prognostic value compared to conventional risk factors [1,2]. Moreover, the CAC score determined using ECG-gated CT is effective for selecting optimal candidates for statin therapy [3,4]. With the increasing use of chest CT examinations, incidental findings of CAC during non-ECG-gated chest CT examinations, such as low-dose CT screening for lung cancer, are also increasing [5].

Although the primary indication for performing a chest CT is not to evaluate CAC, the importance of assessing CAC on non-ECG-gated chest CT examinations has been recognized. The presence and severity of CAC on chest CT are prognostic markers of future cardiovascular outcomes in various populations [6-9]. Therefore, the 2016 guidelines by the Society of Cardiovascular Computed Tomography (SCCT)/Society of Thoracic Radiology (STR) recommend that CAC should be evaluated and reported on all non-contrast chest
CT scans of patients aged ≥ 40 years with an estimation of severity as none, mild, moderate, or severe [10].

For a reliable assessment of CAC on non-ECG-gated CT scans, the agreement with ECG-gated scans should be thoroughly investigated. A previous meta-analysis included 1316 patients from five studies and reported a strong correlation between CAC scores on ECG-gated and non-ECG-gated CT scans. Moreover, an excellent agreement between ECG-gated and non-ECG-gated CT scans was observed with the four CAC severity categories [11]. In addition to ECG synchronization, there are other scan acquisition and reconstruction parameters—such as tube potential and current, slice thickness, and reconstruction kernel—that can affect the attenuation and volume of calcium. Consequently, these parameters influence the CAC score [12-14]. However, the impact of scan parameters on the agreement of the CAC scores of the ECG-gated and the non-ECG-gated CT scans has not been sufficiently investigated in a previous meta-analysis [11].

Therefore, the purpose of this meta-analysis was to investigate the pooled agreement of CAC severities determined using ECG-gated and non-ECG-gated CT scans and assess the impact of scan parameters.

**MATERIALS AND METHODS**

Our methods followed the recommendations of the preferred reporting items for systematic reviews and meta-analysis statements [15].

**Literature Search**

A systematic search of PubMed, EMBASE, and the Cochrane library was performed to identify studies published between January 1990 and August 1, 2019. The search terms are listed in Supplementary Materials 1.

**Study Selection**

Two radiologists experienced in meta-analyses (4- and 7-year experiences in cardiothoracic radiology) independently reviewed articles from PubMed, EMBASE, and the Cochrane library. Figure 1 shows the literature review process of this meta-analysis.

The eligibility criteria used at the full text level included studies that evaluated CAC on non-enhanced non-ECG-gated CT covering the thorax, used ECG-gated CT as a reference standard, and assessed the agreement between ECG-gated and non-gated CT. Studies were excluded if they used the index test other than non-ECG-gated CT, used no reference

![Fig. 1. Flowchart of the literature review process. CAC = coronary artery calcium, ECG = electrocardiogram](image-url)
standard, focused on only the prognosis of CAC on non-ECG-gated CT, reported only the prevalence of CAC on non-ECG-gated CT, reported data that were not extractable, or concentrated on unrelated topics and phantom studies.

**Data Extraction**

The data were independently extracted by two investigators. The extracted parameters included the following: 1) article information and patient characteristics; 2) CAC scoring method (Agatston score, ordinal score, or visual assessment) and scan protocol of ECG-gated and non-ECG-gated CT (CT scanner type, slice thickness, reconstruction kernel, tube potential [kVp], and tube current-time product [mAs]); 3) study outcomes, with focus on the agreement between the CAC scores of ECG-gated and non-ECG-gated CT (mean bias and limits of agreements [LOA] for CAC scores, correlation coefficients, kappa values of category agreement for CAC severity, and frequency of severity differences with 2 or more categories between ECG-gated and non-ECG-gated CT, the sensitivity and specificity for detecting CAC on non-ECG-gated CT, and prevalence of CAC on ECG-gated CT); and 4) time interval between non-ECG-gated and ECG-gated CT scans.

The severity of CAC was categorized into four types according to the Agatston score as follows: “none” = 0, “mild” = 1–100, “moderate” = 100–400, and “severe” > 400. For studies that used different criteria, other than the Agatston score, to assign severity, the cases were re-categorized to align with these criteria [13,16,17]. For studies that used other CAC scoring methods, such as artery-based scoring or visual assessment, the categories of CAC severity were used as presented in those studies [14,18-21].

Subgroups were formed according to the slice thickness, kernel, and radiation dose of non-ECG-gated CT. Two subgroups based on slice thickness were as follows: one group used a slice thickness that was different from those used in ECG-gated CT (≤ 2 or 5 mm) and the group used slice thickness that was similar to that used in ECG-gated CT (2.5 or 3 mm). We additionally divided the slice thickness subgroups into thin slice thickness (≤ 2 mm) and thick slice thickness (5 mm) groups. Based on the kernel, the “smooth” or “sharp” subgroups were created. As the specific name of a reconstruction kernel varies by vendor, the kernels referred to as “standard,” “medium,” or “soft tissue” were assigned to the smooth kernel group. The “low-dose” and “standard dose” subgroups were based on the radiation dose. When the dose of the non-ECG-gated CT was less than 65 mAs, it was assigned to the low-dose group.

**Quality Assessment**

Two independent investigators performed the quality assessments of the studies using a modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [22].

**Statistical Analysis**

The pooled bias and 95% LOA from the included studies were estimated [23]. The pooled correlation coefficient of the CAC scores and the pooled agreement for the CAC severity categories were analyzed [24]. Heterogeneity was assessed, and publication biases were demonstrated with funnel plots [25-27]. The detailed statistical methods are summarized in Supplementary Materials 2.

**RESULTS**

**Study Characteristics**

From the literature search, a total of 4000 patients from 16 studies were included in this meta-analysis [12-14,16-21,28-34]. Table 1 summarizes the study characteristics, CAC scoring method, and technical considerations for the non-ECG-gated CT scans.

Two studies reported agreement between the non-ECG-gated CT scans with varying slice thickness and the ECG-gated CT scans with a 3-mm slice thickness [12,14]. The results of the non-ECG-gated scans with the same slice thickness as the ECG-gated CT scans (3 mm) were used as representative values for the pooled agreement analysis for the entire population to avoid patient duplication. For the subgroup analysis of slice thickness, data from each slice thickness were considered differently (slice thickness of Huang 1:3 mm, Huang 2:5 mm; Slice thickness of Kim 1:2.5 mm, Kim 2:1 mm, Kim 3:5 mm). Wan et al. [13] reported results from two different kernels (soft tissue vs. sharp kernel) in the same study population. Therefore, data from the soft tissue kernel subgroup were used for the pooled analysis to avoid duplication. The soft tissue and sharp kernel data were used in the subgroup analysis (Wan 1 and 2, respectively) [13]. For the ECG-gated CT scans, most of the studies used a uniform established scan protocol (120 kVp acquisition, reconstruction with 2.5 mm or 3 mm slice thickness, and soft tissue or medium kernel) and applied Agatston scoring to the CAC grading.
## Table 1. Study Characteristics, CAC Grading Method and CT Scan Protocols

| Author | Journal | Study Design | Study Sites (Countries) | Inclusion Number of Patients in Analysis | CAC Grading Method on Non-ECG-Gated CT | Agatston Score (Non-ECG-Gated CT) | Time between Non-ECG-Gated and ECG-Gated CT | CT Scanner | Slice Thickness (mm) | Reconstruction Kernel | Use of Iterative Reconstruction Method | Tube Current-Product (mAs) | Non-ECG-Gated CT | ECG-Gated CT | Non-ECG-Gated CT | ECG-Gated CT | Non-ECG-Gated CT | ECG-Gated CT | Tube Current-Product of Non-ECG-Gated CT (mAs) |
|--------|---------|-------------|-------------------------|------------------------------------------|----------------------------------------|-------------------------------------|-----------------------------------------------|----------------|-------------------|-----------------|------------------|-----------------------|---------------------------|---------------|----------------|---------------|---------------|----------------|---------------|----------------|----------------|
| Kim [12] | AJR | Prospective | Korea | Lung cancer screening | 128 128 ± 0 | 52 ± 7 | Agatston score | NR | NR | NR | 40-MDCT | 2.5 | 2.5 | NR | NR | NR | NR | NR | NR | NR | 30 |
| Mu [34] | AJR | Prospective | Taiwan | Lung cancer screening | 483 320 ± 16 | 62 ± 12.2 | Agatston score | NR | NR | NR | Same day | 16-MDCT | 3 | 3 | Smooth soft tissue | Medium soft tissue | FBP | NR | 16.0 ± 2.7 |
| Einstein [20] | JACC | Retrospective | United States | Patients performing hybrid SPECT/CT or SPECT/CT | 402 255 ± 277 | NR | Visual assessment (6 points scale) | NR | NR | NR | Same day | 16-SPECT/CT to 64-CT/CT | NR | NR | NR | NR | NR | NR | NR | 47, 18 or 16.5 |
| Budoff [20] | Circulation: Cardiovascular Imaging | Prospective | United States | Lung screening (300-600 ms, I131) | 50 | NR | NR | Agatston score | Mean 353.6 (95% CI = 1600–538.8) | Mean 277.1 (95% CI = 1366–413.8) | NR | 64-MDCT | 2.5 | 2.5 | NR | NR | NR | NR | NR | NR | 215 |
| Ketch [33] | Int J Cardiol | Retrospective | Italy | Lung cancer screening | 163 127 ± 6 | 51 ± 9 | Ordinal (athyroid-based)* | NR | NR | NR | Same day | 16 or 64-MDCT | 5 | 3 | b60f (medium) | b30f (medium) | FBP | FBP | Reference | 160 |
| Huang [14] | Eur Radiol | Retrospective | Taiwan | Lung cancer screening | 569 236 ± 135 | 54 ± 12.1 | Agatston score | Mean 353.6 (95% CI = 1600–538.8) | Mean 277.1 (95% CI = 1366–413.8) | NR | 64-MDCT | 2.5 | 2.5 | NR | NR | NR | NR | NR | NR | 215 |
| Ancal [16] | Eur Radiol | Retrospective | Italy | Lung cancer screening | 60 30 ± 30 | 73 ± 4.7 | Agatston score | Mean 166.0 (95% CI = 101–251.6) | Mean 104.8 (95% CI = 61–147.0) | NR | 64-MDCT | 5 | 3 | b30f (medium soft tissue) | b30f (medium soft tissue) | FBP | FBP | 30 |
| Kim [21] | Int J Cardiol | Retrospective | United States | Lung cancer screening | 117 97 ± 20 | 53 ± 8.5 | Visual assessment | NR | NR | NR | Same day | 64 or 128-MDCT | 5 | 3 | b60f (sharp) | b30f (medium) | FBP | FBP | 30 |
| Nutt [32] | Eur Radiol | Retrospective | France | Smokers older than 40 years of age in a variety of clinical situations | 185 116 ± 69 | 57 ± 11.5 | Agatston score | Mean 204.0 (range 64–497.5) | Mean 164.8 (range 0–498.9) | NR | 128-dual source CT | 3 | 3 | I50 (medium-smooth) | I50 (medium-smooth) | IR | IR | 65 |
| Bailey [28] | PLoS ONE | Retrospective | United States | Routine clinical population | 66 61 ± 65 | 65 (9847)† | Agatston score | Mean 160.8 (range 2–496.5) | Mean 111.4 (range 0–496.9) | NR | 16-MDCT | 2 | 3 | NR | NR | FBP | NR | 11.5–16.1 |
| Chandra [30] | Clin Imaging | Retrospective | China | Multicenter ABD1 Cohort: Study participants | 108 | NR | 55 ± 12 (50–66)† | Agatston score | Mean 114.5 (range 10–620) | Mean 88.4 (range 4.1–521.0) | NR | 64-MDCT | 2.5 | 2.5 | 2.5 | NR | NR | NR | NR | 250 mA or 125 mAs |
| Acorn [18] | Acad Radiol | Retrospective | United States | Self-referral or physician-referred patients | 222 166 ± 62 | Median 80 | Ordinal (athyroid-based)* | NR | NR | NR | Same day | 64-MDCT | 2.5 | 2.5 | Standard | Standard | NR | NR | 32–200 |
| Man [13] | Int J Cardiol | Prospective | Taiwan | Lung cancer screening | 50 36 ± 14 | Mean 68.5 | Agatston score | 955 ± 183.8 (PET/CT filter) Mean 1048 ± 195 (PET/CT filter) | 1085 ± 189.5 (PET/CT filter) | Same day | 320-slice whole-body detector | 3 | 3 | FD22 (soft tissue), FD22 (hard tissue) | FD22 (soft tissue) | Hybrid algorithms | Hybrid algorithms | 20–45 |
| Ben [31] | Clin Imaging | Prospective | China | Combination of participants who had CAC | 102 66 ± 36 | 63 ± 9 | Agatston score | NR | NR | NR | 256-MDCT | 2.5 | 2.5 | NR | NR | NR | NR | 50 mA |
| Christiansen [17] | JACC | Retrospective | United States | Routine clinical population | 87 74 ± 43 | 63 (70–68)† | Agatston score | 133.0 (165–370.5) | 79.7 (11–346.3)† | Median | 10 months | 128-MDCT | 1.25 | 3 | NR | NR | NR | NR | NR | 20 |
| Chen [30] | Radiol | Prospective | China | CT for lung cancer screening or routine physicals | 1318 912 ± 466 | Mean 58.4 | Agatston score | Mean 243 (range 0–980) | Mean 257 (range 0–3222) | Same day | 256-slice whole-body detector | 1.25 | 1.25 | NR | NR | NR | NR | 320 mA |

*Scoring system that was suggested by Kirsch et al. [33], †Scoring system that was suggested by Huang et al. [14], ‡Scoring system that was suggested by Shemesh et al. [7], §Data indicate median with 25th to 75th percentile in parentheses, ‡Hybrid algorithms means using 50% filtered back projection and 50% iterative reconstruction. CAC = coronary artery calcium, CI = confidence interval, ECG = electrocardiogram, FBP = filtered back projection, HU = Hounsfield unit, IR = iterative reconstruction, MDCT = multi-detector CT, NR = not reported, PET = positron emission tomography, SD = standard deviation, SPECT = single-photon emission CT.
Agreement of the CAC Scores and the Severity Grading of Non-ECG-Gated Chest CT and ECG-Gated Cardiac CT

The pooled prevalence of CAC on ECG-gated CT was 76.24% (95% confidence interval [CI] = 68.71–83.56) (Supplementary Fig. 1). The bias and LOA values for the CAC score (non-ECG-gated CT relative to ECG-gated CT) were evaluated in 7 studies. The pooled bias was 62.60, with a 95% LOA of -36.19 to 161.40 (Fig. 2A). The pooled correlation coefficient was 0.94 (95% CI = 0.89–0.97) in 10 studies (Fig. 2B). The pooled sensitivity and specificity of non-ECG-gated CT for the detection of CAC were 93.6% (95% CI = 89.2–96.2) and 96.6% (95% CI = 91.4–98.7), respectively (Fig. 2C). For the CAC severity categorization, the pooled weighted kappa was 0.85 (95% CI = 0.79–0.91) in 12 studies (Fig. 2D). The pooled proportion of cases with a difference of ≥ 2 categories was 0.23% (95% CI = 0.05–12.59) (Supplementary Fig. 1). The correlation coefficients and weighted kappa of the studies showed significant heterogeneity ($I^2 > 50\%$, $p < 0.1$).

Subgroup Analysis

Table 2 and Supplementary Figures 2–4 show the pooled weighted bias with 95% LOA, correlation coefficients, and weighted kappa for the subgroup analyses. For the correlation coefficients, there were significant differences in heterogeneity between the subgroups based on the radiation dose of non-ECG-gated CT. However, the meta-regression showed that no factor significantly affected heterogeneity ($p > 0.05$). For the weighted kappa of the severity categorization, there was a significant difference in heterogeneity between the subgroups based on the reconstruction kernel.

Einstein et al. [20] did not provide information about slice thickness, and Azour et al. [18] reported data with mixed slice thicknesses (2.5 or 5 mm). Therefore, these two studies were not included in the subgroup analysis. Based on the slice thickness, Huang 1 and 2 and Kim 1, 2, and 3 were regarded as individual subgroups [12,14]. Chen et al. [30] applied the same thin slice thickness (1.25 mm) to both ECG-gated and non-ECG-gated scans, and it was considered as the same slice thickness subgroup. The same slice thickness (2.5 or 3 mm) was used for non-ECG-gated CT in 9 studies [12-14,19,29-32,34]. Different slice thicknesses were used in 8 studies: thinner slices ($≤ 2$ mm) in 3 studies [12,17,28] and thicker slices (5 mm) in 5 studies [12,14,16,21,33]. The studies that used the same slice thickness had higher correlation coefficients and weighted kappa than studies that used different slice thicknesses. However, those studies also had higher weighted bias values and wider LOAs (Table 2). When we analyzed the agreement between the CAC scores for the three slice thickness groups (same, thin, and thick subgroups), the pooled correlation coefficient was also highest in the same slice thickness subgroup (Supplementary Table 1). However, the weighted kappa was higher for the thick slice subgroup than the same thickness subgroup, and the weighted bias was lower for the thick slice subgroup than for the same thickness subgroup (Supplementary Fig. 5, Supplementary Table 1).

In the analysis of the reconstruction kernel subgroups, 8 of 16 studies did not report information about kernel type [12,14,17,19,20,28-31]. The data for Wan 1 and 2 were considered separate in this subgroup analysis [13]. Seven studies used a soft tissue or a smooth kernel for the non-ECG-gated CT, and ECG-gated CT [13,14,16,18,32-34], and two studies used a sharp kernel for non-ECG-gated CT and a smooth kernel for the ECG-gated CT [13,21]. Studies in the soft tissue or smooth reconstruction kernel subgroup had lower pooled bias values and higher weighted kappa values than those in the sharp reconstruction kernel subgroup. A statistical comparison of correlation coefficients could not be performed because only one study was included in the “different kernel” subgroup.

In the analysis of the non-ECG-gated CT radiation dose subgroups, 12 of 16 studies used low-dose protocols [12-14,16,17,20,21,28,30-32,34], and 4 studies used standard dose protocols [18,19,29,33]. Studies that used low-dose protocols showed higher pooled correlation coefficients and higher pooled weighted kappa values than those that used standard dose protocols. Only one study was included in the standard dose subgroup for the evaluation of bias for the ECG-gated and the non-ECG-gated scans, and it had a higher bias and wider LOA than studies that used low-dose protocols.

Quality of the Studies

A quality assessment of the included studies using QUADAS-2 is presented in Supplementary Figure 6. Most of the studies enrolled patients consecutively (15 of 16, 93.8%). The risk of bias in the index test domain was assessed as “unclear” in four studies (25%), and the risk of bias in the reference standard domain was assessed as “unclear” in 10 studies (62.5%) because there was no mention of whether non-ECG-gated and gated CT CAC scores were assessed without knowledge of the other measurement.
Fig. 2. Pooled agreement, correlation, and accuracies of non-ECG-gated CT compared to ECG-gated CT for CAC.

A. Bias with 95% LOA for CAC score (non-ECG-gated CT – ECG-gated CT).

B. Correlation coefficient (r) of CAC score.

C. Sensitivity and specificity for the detection of CAC.

D. Weighted kappa for the categorization of CAC severity.

CAC = coronary artery calcium, CI = confidence interval, COR = correlation coefficient, ECG = electrocardiogram, FN = false negative, FP = false positive, LOA = limits of agreement, TN = true negative, TP = true positive.
The risk of bias in the flow and timing domain was assessed as unclear in 5 studies (31.3%) because of the absence of a time interval [12, 16, 19, 21, 31, 32]; concerns regarding applicability were rated as “low” in all domains.

**DISCUSSION**

From our meta-analysis, the CAC scores on non-ECG-gated CT show a pooled bias of 62.6 and a strong correlation with the CAC scores on ECG-gated CT, and the agreement for the categorization of CAC severity is excellent between the two modalities. CAC scores vary with the scan protocol, and the agreement between the CAC categories is better when the CT reconstructions use the same slice thickness and kernel.

A previously reported meta-analysis showed a strong correlation (0.94; 95% CI = 0.89–0.97) between the CAC scores of the ECG-gated cardiac CT and non-ECG-gated chest CT and an excellent agreement for the four categories of CAC severity (0.89; 95% CI = 0.82–0.96), despite the 8.8% false negatives and the 19.1% underestimation of high CAC scores on non-ECG-gated scans [11]. However, these technical parameters, such as slice thickness, reconstruction kernel, or radiation dose, probably because of the absence of a time interval [12, 16, 19, 31, 33].

In contrast to the previous meta-analysis, more studies were included. The overall pooled bias for CAC scoring was low (62.6), and the agreement between the CAC categories is excellent between the two modalities. CAC scores vary with the scan protocol, and the agreement between the CAC categories is better when the CT reconstructions use the same slice thickness and kernel.

**Table 2. Agreement of CAC Score and Severity between ECG-Gated CT and Non-ECG-Gated CT in a Subgroup Analysis**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Slice Thickness</th>
<th>Reconstruction Kernel</th>
<th>Radiation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Same</td>
<td>Different</td>
<td>P*</td>
</tr>
<tr>
<td>Bias (95% limits of agreement of CAC score)</td>
<td>89.411 (-110.292, 289.114) (n = 4)</td>
<td>7.804 (-27.963, 43.57) (n = 3)</td>
<td>N/A</td>
</tr>
<tr>
<td>Correlation coefficients of CAC score (95% CI)</td>
<td>0.949 (0.89, 0.977) (n = 5)</td>
<td>0.919 (0.77, 0.972) (n = 6)</td>
<td>0.354 0.358 (0.77, 0.985) (n = 5)</td>
</tr>
<tr>
<td>Weighted kappa for CAC severity categorization (95% CI)</td>
<td>0.872 (0.795, 0.948) (n = 9)</td>
<td>0.819 (0.743, 0.895) (n = 3)</td>
<td>0.160 0.463 (0.832, 0.985) (n = 4)</td>
</tr>
</tbody>
</table>

*p value for difference of heterogeneity between two subgroups (Cochran’s Q test), †p value for meta-regression, ‡Not assessable because only one study was assigned to the subgroup. CAC = coronary artery calcium, CI = confidence interval, ECG = electrocardiogram, n = number of studies, N/A = not assessable.
indicate that technical parameters affect CAC scoring. A sharp kernel makes the image sharper and noisier, increasing the calcium attenuation and CAC score [36]. Low-dose acquisition with a reduced tube current generates images with higher noise that cannot be differentiated from calcium, and this increases the CAC score. Thinner slices tend to increase the detection of CAC and result in higher CAC scores [35,37]. However, our pooled analysis for weighted bias during the subgroup analysis of slice thickness showed an inverse relationship; this result may be attributable to the small number of eligible studies that reported differences in CAC scores. Moreover, the weighted bias of CAC score for the subgroup analysis of the reconstruction kernel and the radiation dose were also limited because only one study was assigned to the subgroup. In the subgroup analysis of radiation dose, the agreement and correlation coefficient were higher for the low-dose protocols than the standard dose protocols, but this result should be interpreted with caution because only a small number of studies were included for the standard dose protocols. The scan protocols of non-ECG-gated chest CT vary according to the scan indication, vendor, or institution. Therefore, it may be more important to properly categorize and report the CAC severity detected by non-ECG-gated CT than measure CAC scores because the prognostic value of CAC severity detected by non-ECG-gated CT for future mortality or major cardiovascular events has been demonstrated [6-9].

However, the recommendations for selecting optimal populations and reporting details for non-ECG-gated CT remain controversial. For example, SCCT/STR recommends reporting CAC on all non-contrast chest CT scans, regardless of CT indication in patients aged ≥ 40 years, with categories of none, mild, moderate, or severe. However, the American College of Radiology National Radiology Data Registry’s Lung Cancer Screening Registry limits the reporting of CAC within the registry to only moderate to severe CAC for low-dose CT screening for lung cancer [38]. Several grading methods have been suggested for the assessment of CAC severity (e.g., visual assessment, ordinal artery-based scoring, segment-based scoring, and Agatston scoring) [6,7,39]; however, the current guideline does not limit the methods used to analyze CAC on chest CT [10]. The clinical indications of studies included in this meta-analysis were heterogeneous and the CAC grading methods used in the non-ECG-gated chest CT varied: ten used the Agatston scoring method, four used the artery-based scoring method, and two used visual assessment.

To date, the management of CAC detected by non-gated chest CT lacks consensus. Even when CAC is detected on ECG-gated CT, the recommendations for risk assessment and guidelines for clinical management (i.e., selecting candidates for statin therapy) vary [3,40]. Some recommend that statin therapy should be initiated when the Agatston score is > 100 (moderate to severe CAC) for ECG-gated CT, and the cardiovascular risk is uncertain [3]. In contrast, others recommend that statin therapy should be initiated when the Agatston score is > 0 [4]. Therefore, the management of CAC detected by non-gated chest CT depends on the discretion of a physician or the patient. Our results suggest that reporting and interpreting Agatston scores on non-ECG-gated CT scans with the same cutoffs as those used for ECG-gated CT, without considering the scan protocol, may lead to the misclassification of CAC severity, even though the cases of misclassification by more than 2 categories were extremely rare.

Our study has several limitations. We acknowledge that CAC assessment by non-ECG-gated CT is most reliable when the same acquisition and reconstruction protocol for ECG-gated CT is applied. However, thin-slice (≤ 1.5 mm) images with sharp kernel reconstruction are typically recommended for lung nodule assessment [41], and performing additional image reconstructions for CAC evaluation may not be practical. To minimize the effect of variability in scan protocols, an atlas-based approach that uses representative non-ECG-gated CT images for each CAC category or a deep learning approach to CAC quantification and severity classification could help optimize CAC grading [41,42]. Second, we could not analyze the effect of CAC grading methods for non-ECG-gated CT on the agreement because most of the studies applied quantitative Agatston scoring, and only a few studies used artery-based grading or visual assessment. Third, the effects of other technical factors, such as the use of an iterative reconstruction or low kVp acquisition, could not be analyzed because such techniques were rarely used in the included studies. Finally, we did not assess the impact of the scan parameters for non-ECG-gated CT on the prognosis of CAC because we focused on the agreement between its CAC scores and severity and those of ECG-gated CT.

In conclusion, the pooled agreement of CAC severities assessed by ECG-gated CT and non-ECG-gated CT was excellent. However, the agreement was significantly affected by the scan parameters, including the slice thickness and
reconstruction kernel. Understanding the factors that affect CAC assessment and comprehensively evaluating the severity of CAC detected by non-ECG-gated CT will facilitate effective patient management.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1047.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conseptualization: Jin Young Kim, Young Joo Suh. Data curation: Jin Young Kim, Young Joo Suh. Formaly analysis: Kyunghwa Han, Young Joo Suh. Funding acquisition: Young Joo Suh. Investigation: Jin Young Kim, Young Joo Suh. Methodology: Jin Young Kim, Young Joo Suh, Kyunghwa Han. Supervision: Byoung Wook Choi, Young Joo Suh. Writing—original draft: Jin Young Kim, Young Joo Suh. Writing—review & editing: Byoung Wook Choi, Kyunghwa Han, Byoung Wook Choi.

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