Original Article | Cardiovascular Imaging

eISSN 2005-8330
https://doi.org/10.3348/kjr.2020.1047
Korean J Radiol 2021;22(7):1034-1043

Korean Journal of Radiology
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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 (I^2 > 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

Received: August 23, 2020 **Revised:** November 9, 2020
Accepted: December 1, 2020
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2018R1C1B6007251).
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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

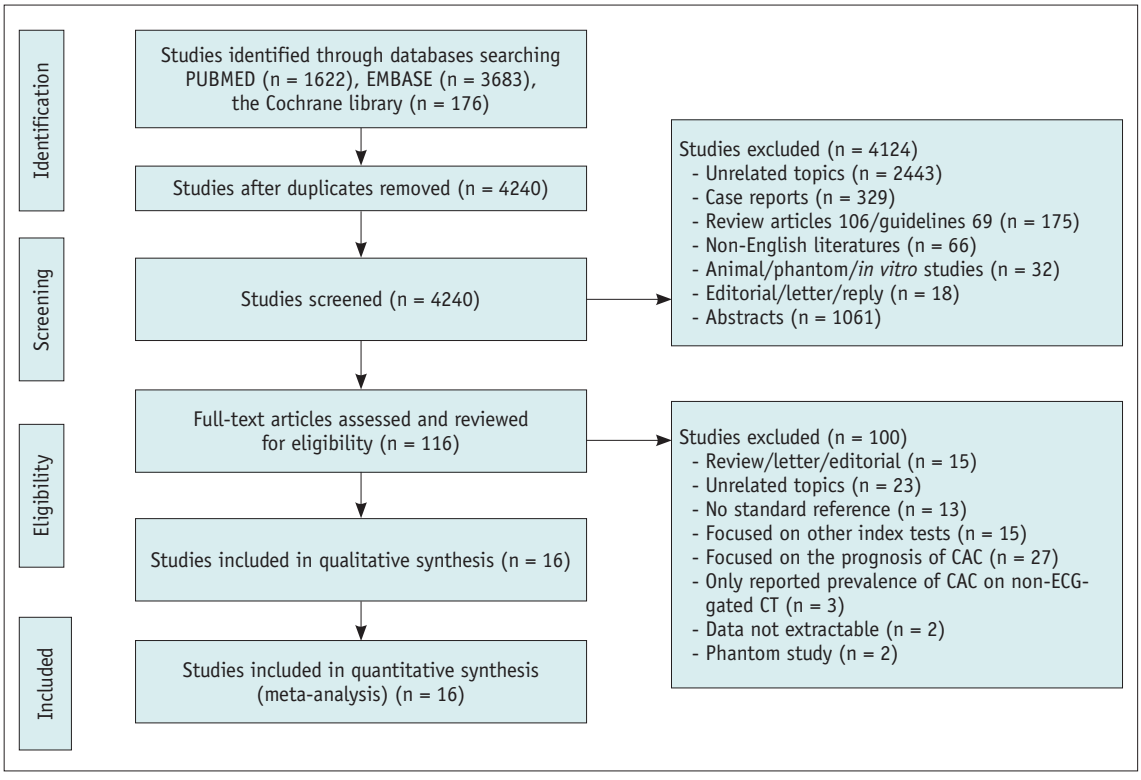

Fig. 1. Flowchart of the literature review process. CAC = coronary artery calcium, ECG = electrocardiogram

https://doi.org/10.3348/kjr.2020.1047

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.

https://doi.org/10.3348/kjr.2020.1047

Table 1. Study Characteristics, CAC Grading Method and CT Scan Protocols

First Author	Journal	Study Design	Study Sites (Countries)	Patient Description	Included Number of Patients in Analysis	Sex (Male: Female)	Age, Years (Mean ± SD)	CAC Grading Method on Non-ECG-Gated CT	Agatston Score (Mean ± SD)		Time between Non-ECG-Gated and ECG-Gated CT	CT Scanner	Slice Thickness (mm)		Reconstruction Kernel		Use of Iterative Reconstruction Method		Tube Current-Product of Non-ECG-Gated CT (mAs)
									Non-ECG-Gated CT	ECG-Gated CT			Non-ECG-Gated CT	ECG-Gated CT	Non-ECG-Gated CT	ECG-Gated CT	Non-ECG-Gated CT	ECG-Gated CT	
Kim [12]	Am J Roentgenol	Prospective	Korea	Lung cancer screening	128	128:0	52 ± 7	Agatston score	NR	NR	NR	40-MDCT	1/2.5/5	2.5	NR	NR	NR	NR	30
Wu [34]	Am J Roentgenol	Prospective	Taiwan	Lung cancer screening	483	320:163	62.2 ± 13.2	Agatston score	NR	NR	Same day	16-MDCT	3	3	Smooth soft tissue	Medium soft tissue	FBP	NR	16.0 ± 2.7
Einstein [20]	J Am Coll Cardiol	Retrospective	United States	Patients performing hybrid PET/CT or SPECT/CT	492	215:277	NR	Visual assessment (6 points scale)	NR	NR	Same day	16-SPECT/CT 16-PET/CT 64-PET/CT	NR	NR	NR	NR	NR	NR	47, 18 or 16.5
Budoff [29]	J Cardiovasc Comput Tomogr	Prospective	United States	Lung screening (COPDGene subcohort)	50	NR	NR	Agatston score	Mean 353.6 (95% CI = 169.0–538.2)	Mean 277.1 (95% CI = 136.4–417.8)	NR	64-MDCT	2.5	2.5	NR	NR	NR	NR	215
Kirsch [33]	Int J Cardiovasc Imaging	Retrospective	United States	Health screening	163	127:36	51 ± 9	Ordinal (artery-based)*	NR	NR	Same day	16 or 64-MDCT	5	3	b40f (medium)	b35f (medium)	FBP	FBP	Reference 180
Huang [14]	Eur Radiol	Retrospective	China	Lung cancer screening	369	234:135	54.9 ± 12.1	Ordinal (artery-based)†	NR	Median 28.4 (range 1.1–3,042.3)	Same day	16-MDCT	3 and 5	3	b20 (medium smooth soft tissue)	b35f (medium soft tissue)	FBP	FBP	30
Arcadi [16]	World J Radiol	Prospective	Italy	Lung cancer screening	60	30:30	73.4 ± 7.1	Agatston score	428 ± 776	481 ± 854	NR	64-MDCT	5	3	b30f (medium smooth)	b35f (medium)	FBP	FBP	20
Kim [21]	Int J Cardiovasc Imaging	Retrospective	Korea	Lung cancer screening	117	97:20	53.4 ± 8.5	Visual assessment	NR	Mean 166.0 (range 0.4–3719.3)	Same day	64 or 128 MDCT	5	3	b60f (Sharp)	b35f (medium)	FBP	FBP	30
Hutt [32]	Eur Radiol	Prospective	France	Smokers older than 40 years of age in a variety of clinical situations	185	116:69	57 ± 11.5	Agatston score	Median 240.3 (range 0–4967.9)	Median 244.8 (range 0.4–4968)	NR	128-dual source CT	3	3	I30 (medium-smooth)	I30 (medium-smooth)	IR	IR	65
Bailey [28]	PLoS ONE	Retrospective	United States	Routine clinical population	66	61:5	65 (58–67)§	Agatston score	160 (14–441)§	NR	Median 7 months	16-MDCT	2	3	NR	NR	FBP	NR	11.5–16.1
Chandra [19]	PLoS ONE	Prospective	United States	Multicenter AIDS Cohort Study participants	108	NR	55.2 (50.4–59.9)§	Ordinal (artery-based)*	NR	NR	21.8 ± 400.3 days	64-MDCT	2.5, 3.0	2.5 or 3	b31f (medium smooth)	NR	FBP	NR	250 mA or 125 mAs
Azour [18]	J Cardiovasc Comput Tomogr	Retrospective	United States	Self-or physician-referred patients	222	160:62	Median 50	Ordinal (artery-based)‡	NR	NR	Same day	64-MDCT	2.5 or 5	2.5	Standard	Standard	NR	NR	32–200
Wan [13]	Int J Cardiol	Prospective	Taiwan	45 to 85 years old with visible CAC on routine chest CT	50	36:14	Mean 68.5	Agatston score	955.5 ± 183.8 (FC02 filter) 1048.4 ± 190.5 (FC08 filter)	1085.0 ± 189.5	Same day	320-row wide detector CT	3	3	FC02 (soft tissue), FC08 (sharp)	FC12 (soft tissue)	Hybrid algorithm‖	Hybrid algorithm‖	20–45
Fan [31]	Clin Imaging	Prospective	China	Consecutive participant who had CAC	102	66:36	63 ± 9	Agatston score	NR	NR	NR	256-MDCT	2.5	2.5	NR	NR	IR	NR	50 mA
Christensen [17]	J Am Heart Assoc	Retrospective	United States	Routine clinical population	87	74/13	63 (57–68)§	Agatston score	133.0 (19.5–370.5)§	79.7 (11–345.6)§	Median 10 months	128-MDCT	1.25	3	NR	NR	NR	NR	20
Chen [30]	Acad Radiol	Prospective	China	CT for lung cancer screening or routine physicals	1318	912:406	Mean 58.4	Agatston score	Median 243 (range 0–5538)	Median 257 (range 0–5213)	Same day	256-row, wide detector CT	1.25	1.25	NR	NR	IR	IR	Automatic tube current modulation for obtaining a preset noise index of 20 HU

*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

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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] = 48.71–91.56) (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 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

https://doi.org/10.3348/kjr.2020.1047

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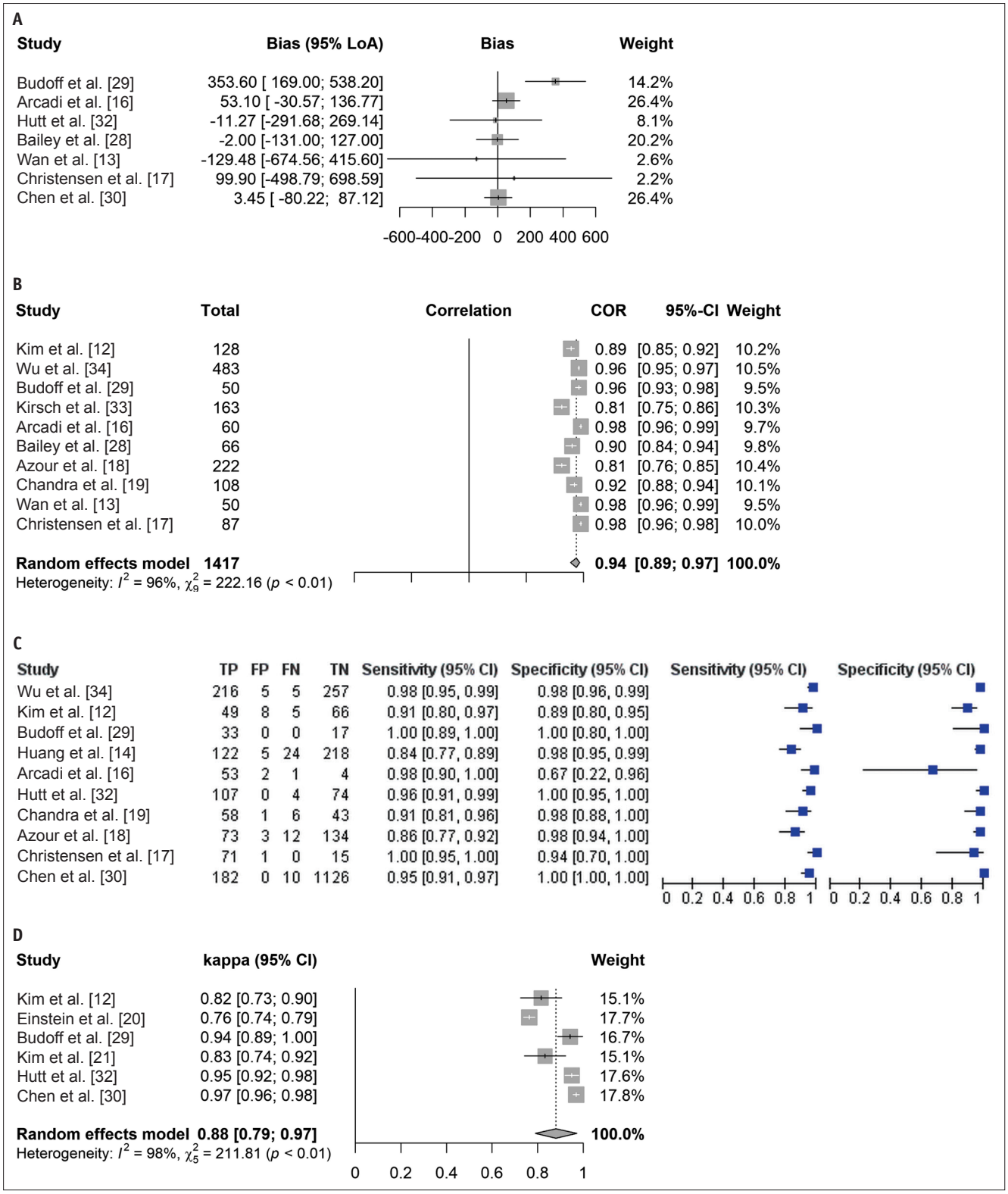

Fig. 2. Pooled agreement, correlation, and accuracies of non-ECG-gated CT compared to ECG-gated CT for CAC.
A. Bias with 95% LOA for CAC score (non-ECG-gated CT – ECG-gated CT). **B.** Correlation coefficient (r) of CAC score. **C.** Sensitivity and specificity for the detection of CAC. **D.** Weighted 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

https://doi.org/10.3348/kjr.2020.1047

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

Subgroup	Slice Thickness				Reconstruction Kernel				Radiation Dose			
Parameters	Same	Different	*P**	*P*†	Medium	Sharp	*P**	*P*†	Low-Dose CT	Standard Dose	*P**	*P*†
Bias (95% limits of agreement of CAC score)	89.411 (-110.292, 289.114) (n = 4)	7.804 (-27.963, 43.57) (n = 3)	N/A	N/A	-8.1 (-89.682, 73.481) (n = 3)	-36.64 (-498.523, 425.243) (n = 1)	N/A	N/A	20.999 (-6.029, 48.026) (n = 6)	353.6 (169.0, 538.20) (n = 1)	N/A	N/A
Correlation coefficients of CAC score (95% CI)	0.949 (0.89, 0.977) (n = 5)	0.919 (0.777, 0.972) (n = 6)	0.354	0.385	0.939 (0.77, 0.985) (n = 5)	0.985 (0.974, 0.992) (n = 1)	N/A‡	N/A‡	0.958 (0.909, 0.981) (n = 6)	0.892 (0.669, 0.967) (n = 4)	0.048	0.082
Weighted kappa for CAC severity categorization (95% CI)	0.872 (0.795, 0.948) (n = 9)	0.819 (0.743, 0.895) (n = 3)	0.160	0.463	0.909 (0.832, 0.985) (n = 4)	0.837 (0.748, 0.926) (n = 2)	0.004	0.290	0.855 (0.789, 0.922) (n = 8)	0.835 (-0.224, 1.894) (n = 2)	0.821	0.845

*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

[12-14,19-21,29,30,32,33]. 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 [12,16,29,31,32]; concerns regarding applicability were rated as "low" in all domains.

Publication Bias

Supplementary Figure 7 presents funnel plots of the prevalence of CAC, the bias of CAC scores, and weighted kappa values for CAC categorization. The results showed symmetric funnel plots without significant publication bias ($p > 0.05$).

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 for non-ECG-gated scans [11]. However, the previous meta-analysis did not consider variations in CT technical parameters, such as slice thickness, reconstruction kernel, or radiation dose, probably because only a small number of studies were included. However, these factors can significantly affect CAC scoring. A few recent studies emphasized the importance of these technical factors when performing CAC scoring for non-gated chest CT [13,17,35]. In contrast to the previous meta-analysis, a recent study using thin slices (1.25 mm) reported a tendency to overestimate CAC scores for non-ECG-gated chest CT [17].

In this meta-analysis, more studies were included. The overall pooled bias for CAC scoring was low (62.6), and the agreement of the CAC severity categories was excellent (0.85, 95% CI = 0.79–0.91); these values are lower than those reported in the previous meta-analysis. However, a significant inter-study heterogeneity was present, which resolved in the subgroup analyses of the reconstruction kernel used for non-ECG-gated CT. Our study results may

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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

 https://doi.org/10.3348/kjr.2020.1047

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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