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Adjustment of the underestimation of coronary artery calcification scoring and risk reclassification in low-dose coronary computed tomography angiography with Knowledge-based Iterative Model Reconstruction

Short title: CAC adjustment in low-dose IMR

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ABSTRACT

Background: Knowledge-based iterative model reconstruction (IMR) can reduce radiation exposure, but trend to underestimate coronary artery calcification score (CACS) on computed tomography. We aimed to adjust the impact of low-dose IMR on CAC scoring and risk reclassification.

Methods: From June 2016 to July 2018, two groups of patients (N = 250 and N = 346) who underwent routine-dose (120kV, 50mA) CAC scan with filtered back projection (FBP) reconstruction were enrolled as training and testing group respectively. A low-dose (120kV, 20mA) scan with IMR reconstruction was performed at the same time. Agatston scores were calculated semi-automatically on the routine-dose FBP and low-dose IMR images. In the training group, a mathematical relationship between the CAC scores obtained from FBP and IMR was modeled by weighted least square method. In the testing group, adjusted IMR (ad-IMR) scores were calculated using the equation from the training group. Differences between ad-IMR and FBP scores, and consistency rates of risk categories by IMR/ad-IMR to FBP scores were analyzed.

Results: In the training group, CAC were underestimated by 26.0% ($P < 0.0001$) with low-dose IMR, the adjustment equation was Y = 17.45 + 1.14X (Y: FBP, X: IMR R^2 = 0.96). There was no difference between ad-IMR and FBP scores in testing group. Furthermore, the consistency rate of risk categories was significantly improved by ad-IMR scores (from 74.0% to 85.3%, $P < 0.001$), greater improvement was observed in patients with FBP score > 10 (91.6%).

Conclusion: The underestimation of CACS by low-dose scan with IMR reconstruction could be adjusted by mathematical adjustment. The impact on risk reclassification can be improved thereby facilitating further dose reductions.

Keywords: Coronary artery disease; Coronary artery calcification; Iterative reconstruction; Computed tomography angiography

INTRODUCTION

Coronary artery calcification (CAC) is a reliable indicator of the existence and progression of coronary artery disease (CAD).[1,2] And it can be detected by non-contrast computed tomography (CT) scan and quantified by several scoring methods.[3–5] As a strong independent predictive factor of adverse cardiovascular events,[6–9] Agatston score is the most widely used index in both research and clinical settings. Furthermore, the Agatston score could also help to improve clinical management of CAD. [10,11]

Although the radiation dose of coronary computed tomography angiography (CTA) was reduced by the development of image reconstruction technology, radiation exposure is still an important concern, especially with statements that recommend the use of CT for CAC assessment even for asymptomatic patients who are at low-to-intermediate cardiovascular risk.[12–14] Filtered back projection (FBP) has been widely used to reconstruct CT images in the past few decades, but unfortunately it requires relatively high tube voltage and current to achieve acceptable image quality and thus has limitations. Knowledge-based iterative model reconstruction (IMR) is now a widely-used image reconstruction algorithm, which enables lower radiation dose and at the same time ensures equivalent or even better image quality.[15–18] Previous studies have reported that IMR or other advanced modeled iterative reconstruction images might underestimate CAC score.[19–25] Recent research attempted to correct the impact of IMR on CAC scoring on the routine-dose scanning (120kV, 50mA).[25] However, the correction of low-dose IMR to “routine” dose FBP scoring was still unclear.

Therefore, we sought to establish an adjustment between the Agatston scores obtained from low-dose scan with IMR and routine-dose scan with FBP reconstructions to account for the impact of dose-reduced technique on CAC risk classification.

PATIENTS AND METHODS

Patients

This prospective study was conducted between June 2019 and July 2020，and was approved by the research ethics committee of Shengjing Hospital of China Medical University with written informed consent obtained from all participants. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Patients who were clinically indicated for coronary computed tomography angiography (CCTA) and also had a positive Agatston CAC score from routine radiation dose scans with FBP reconstruction were included in the study. The exclusion criteria were patients with a history of coronary artery bypass grafting (CABG), coronary artery stent implantation, or any other instrument implantation within the scan area. Patients with tachycardia, in non-sinus rhythm or arrhythmia were also excluded from this study.

In order to establish a mathematical model between FBP and IMR CAC scores and evaluate its efficacy, we divided all enrolled patients into training and testing groups in chronological order. Training group was recruited from June 2019 to May 2020, while testing group was recruited from May 2020 to July 2020.

Image acquisition and reconstruction

Patients clinically indicated for CCTA first underwent a routine non-contrast-enhanced CAC scan (120 kVp, 50 mAs) on a 256-slice CT scanner (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA).[23] Scans were prospective electro-cardiogram (ECG) triggered at 75% of R-R interval. Additionally, patients with a non-zero Agatston score also underwent a low dose scan (120 kVp, 20 mAs). If the patient's weight was over 90 kilograms (KG), we adjusted the tube current to 80 mAs for routine dose scan and 30 mAs for low dose scan. FBP reconstruction with Cardiac Standard kernel were used for routine dose scan, and Body Soft Tissue (recommended by the manufacturer) were used in IMR reconstruction for low dose scan. Other scan parameters were kept the same, including collimation: 0.625 mm × 128, rotation time: 270 ms, FOV: 200mm. Oral beta-blockers (metoprolol tartrate 25–50 mg) were administered, if the heart rate was above 70 bpm. Axial images were reconstructed at 2.5 mm slice thickness. Computed tomographic dose index (CTDI)

and dose length product (DLP) were recorded while scanning. Effective dose (ED) was calculated by equation: ED = DLP × k (where k is an absorption coefficient for chest, k = 0.014mSv × mGy^{-1} × cm^{-1}).[26]

CAC score measurements

Agatston scores were measured on the same workstation (Heartbeat CS, Extended Brilliance Workspace v3.5.0.2254, Philips Healthcare, Cleveland). Coronary artery plaques with an area of ≥ 1 mm^2 and a density of greater than 130 Hounsfield Units (HU) were identified by the software, and modified by the same radiologist with 5 years' experience if necessary. Then the CAC Agatston scores were calculated automatically. For assessing inter-observer variability, 35 patients were randomly chosen from overall subjects, and assigned to another experienced radiologist to measure the CAC score on both FBP and IMR images.

Patients were classified into different risk categories based on the CAC score value: no risk (0), low risk (1–10), low-intermediate risk (11–100), intermediate risk (101–400) and high risk (> 400).[27]

Statistical analysis

Statistical analysis was performed using commercially available software SPSS 20.0 (IBM Corp., Chicago, USA). The continuous variables were described by mean ± standard deviation. Categorical variable was expressed as percentage. $P < 0.05$ was considered statistically significant.

Inter-observer variability was assessed using the intraclass correlation coefficient (ICC). In the training group, paired-samples t-test was used to evaluate the differences between FBP and IMR CAC scores. To correct the heteroscedasticity, weighted least square method was applied to establish a linear regression between FBP and IMR CAC values.

In the testing group, adjusted-IMR (ad-IMR) scores were calculated with the equation which resulted from linear regression of training group, and paired-samples t-test was used to evaluate their differences with FBP scores. CAC risk categories of IMR,

ad-IMR and FBP scores were classified for each patient. Consistency rates of risk categories between IMR and FBP scores, and consistency rates between ad-IMR and FBP scores, were calculated separately. Difference in the consistency rates was analyzed by McNemar Test.

RESULTS

General features and inter-rater agreement

250 and 346 patients were recruited for training and testing groups respectively. Details of patients' characteristics are shown in Table 1. There was no difference in patients' age, gender and body mass index (BMI) between the two groups. ED was 60% lower in low-dose scan than that of routine-dose scan (ED: 0.26 ± 0.03 mSv & 0.65 ± 0.08 mSv).

Each patient got his/her own number with the randomizer of SPSS. Then the patients were arranged by these random numbers, and top 10% (35) patients were selected for the assessment of inter-rater agreement. FBP and IMR CAC agatston score measurements of these randomly selected patients were highly reproducible between the two CAC readers, with excellent inter-rater agreement for FBP CAC score (ICC = 0.997), IMR CAC score (ICC = 0.992).

Table 1. Patient characteristics

Patient data	Training Group	Testing Group	*P* Value
Patients(*n*)	250	346	
Male(*n*)	146	194	0.63
Age(year)	61.30±9.21	60.55±10.17	0.09
BMI (kg/m^2)	24.66±3.56	24.93±3.09	0.44
Smoker(n)	47.6%	41.3%	0.13
Diabetes Mellitus(n)	25.2%	29.2%	0.27
Hypertension(n)	27.6%	34.1%	0.11
LDL-C(mmol/L)	2.63±0.66	2.73±0.68	0.07

FBP CACs	314.66±426.30	303.40±509.33	0.77
IMR CACs	262.66±384.47	244.68±438.67	0.60

BMI: Body Mass Index; LDL-C: low-density lipoprotein cholesterol; FBP: Filtered Back Projection; IMR: Iterative Model-based Reconstruction; CACs: Coronary artery calcium score.

The correlation and adjustment between IMR and FBP CACs in training group

In the training group, there were significant differences between IMR and FBP CAC scores ($P < 0.001$). IMR scores were 26% (21.8%–30.2%) lower than FBP scores. General feature of CAC scores in training group are shown in Table 2. There was a strong linear correlation between IMR and FBP CAC scores in the overall subjects. However, the correlations between IMR and FBP CAC scores were variant among different risk categories, details were showed in Figure 1. The adjustment of IMR scores by linear regression was: Y = 17.45 + 1.14X (Y: FBP CACs, X: IMR CACs). The goodness-of-fit was excellent, with $R^2 = 0.96$ (Figure 2).

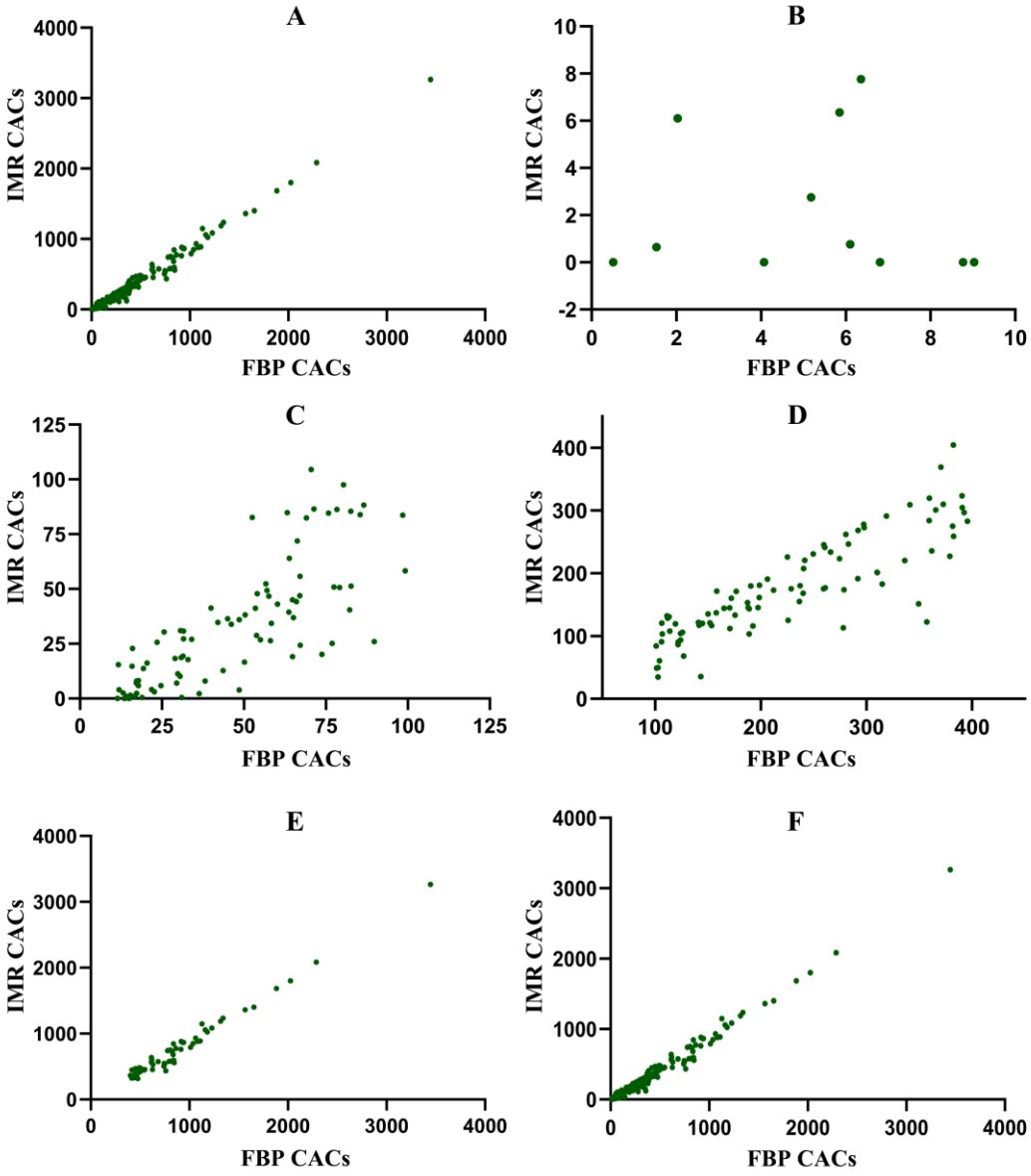

Figure 1. The correlation between FBP CACs and IMR CACs in training group. The correlation between FBP CACs and IMR CACs of overall patients (A) was excellent (r = 0.99, P < 0.001). However, the correlation was poor (r = –0.07, P = 0.84) in patients with FBP score ≤ 10 (B). With the increasing of FBP scores, the correlations became stronger. The correlation coefficients were 0.78 (P < 0.01) for 11–100 (C), 0.86 (P < 0.01) for 101–400 (D) and 0.99 (P < 0.01) for over 400 (E). The correlation coefficient was 0.99 (P < 0.01) when patients with FBP score ≤ 10 were excluded (F). FBP: Filtered Back Projection; IMR: Iterative Model-based Reconstruction; CACs: Coronary artery calcium score.

183 **Table 2.** Details of CAC scores and risk categories in training and testing group.

	Risk categories	No	Low	Low-intermediate	Intermediate	High
FBP CACs	Patients(*n*)	0	11	88	90	61
(training)	Scores	-	5.11±2.82	46.5±24.6	228.9±93.5	883.9±526.1
IMR CACs	Patients(*n*)	8	27	74	86	55
(training)	Scores	0	4.13±2.97	46.6±25.2	46.6±25.2	812.4±500.0
FBP CACs	Patients(*n*)	0	24	120	133	69
(testing)	Scores	-	4.27±2.65	44.6±25.3	217.0±96.1	1024.1±778.2
IMR CACs	Patients(*n*)	20	32	123	119	52
(testing)	Scores	0	3.60±2.69	49.8±25.5	217.8±96.1	1009.8±729.8

184 FBP: Filtered Back Projection; IMR: Iterative Model-based Reconstruction; CACs:

185 Coronary artery calcium score.

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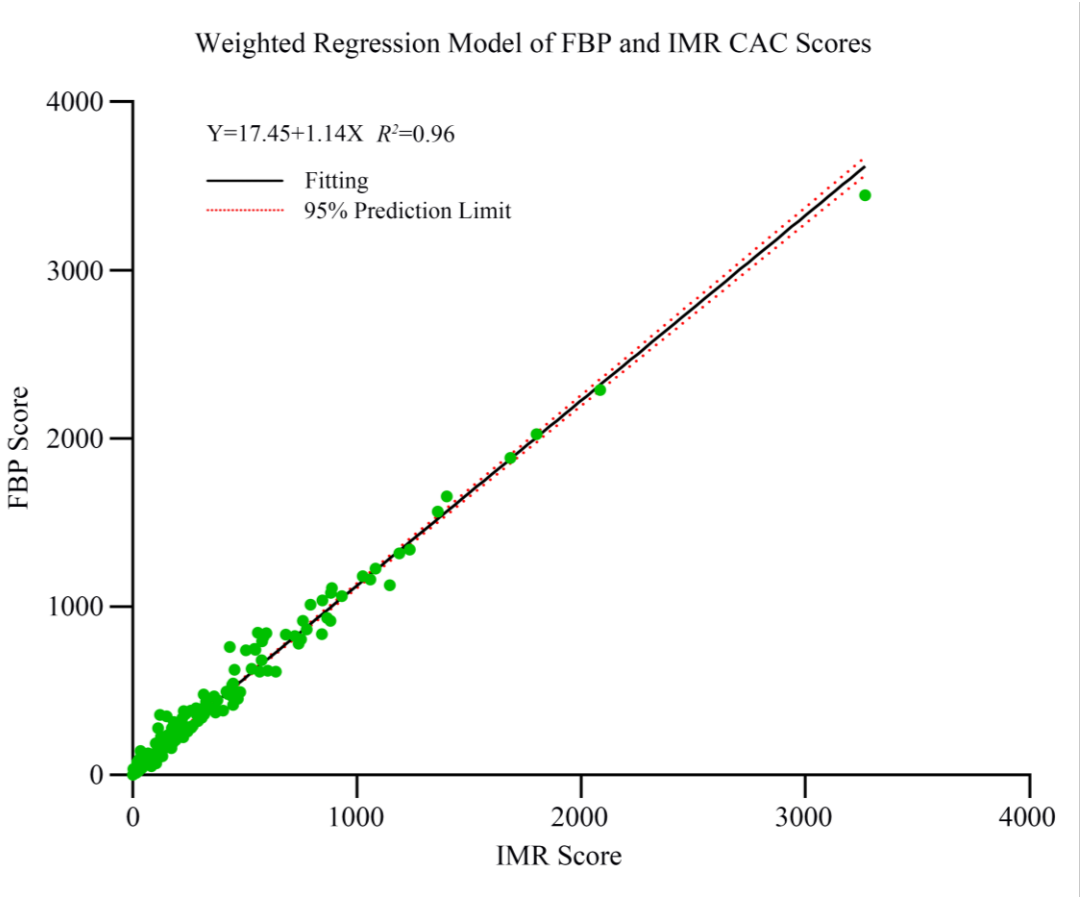

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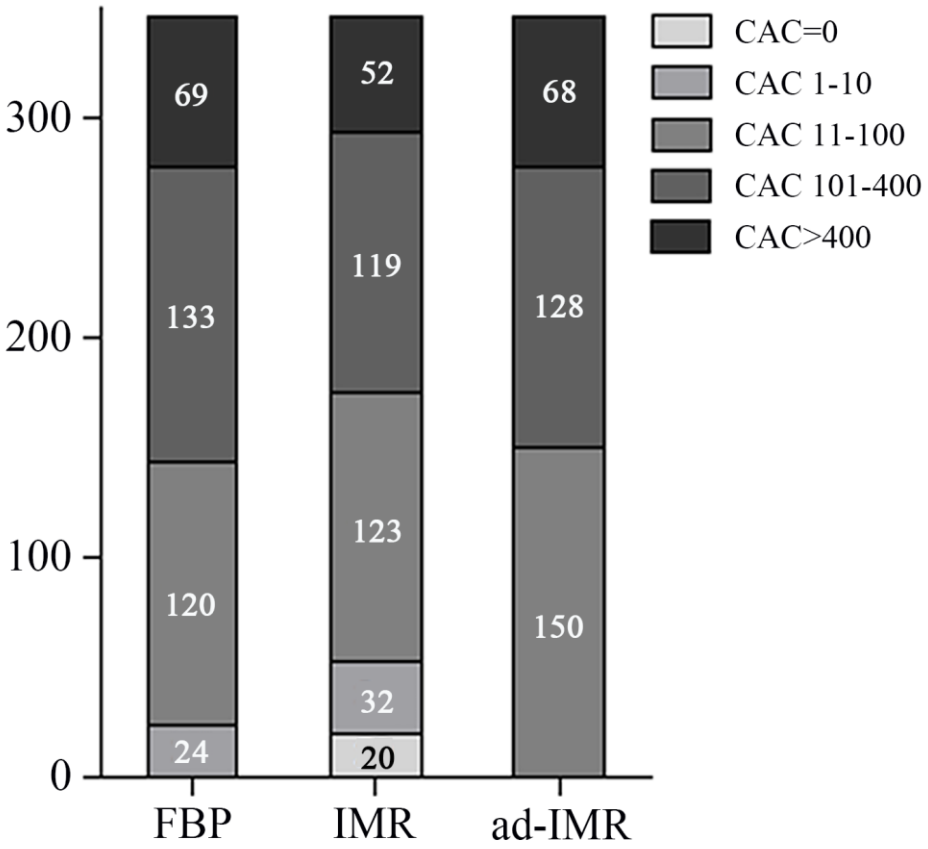
Figure 2. The linear regression of FBP CACs and IMR CACs. Weighted least square method was used to establish the mathematical model between FBP and IMR CAC scores in the training group. Correlation coefficient was 0.9919 and equation was Y = 17.45 + 1.14X (Y: FBP, X: IMR R^2 = 0.96). FBP: filtered back projection; IMR: iterative model reconstruction; CAC: coronary artery calcification.

Adjustment of CACs and risk reclassification in testing group

General features of CAC scores in testing group are shown in Table 2. There was no significant difference between ad-IMR and FBP scores in the testing group (mean difference 7.0, 95% CI [–1.9–16.0], P = 0.12). Risk categories with FBP, IMR and ad-IMR CAC scores were analyzed (Figure 3). Consistency rate between IMR and FBP risk categories was 74.0%. After adjustment the consistency rate improved to 85.3% with ad-IMR scores (difference 11.27%, 95% CI [6.23%–15.43%], P < 0.001). As the correlation between IMR and FBP CACs was poor when FBP score ≤ 10 (Figure 1B), further analysis of the consistency rate was performed in patients with FBP score > 10 and resulted in greater improvement in risk classification (from 76.4% to 91.6%, difference 15.22%, 95% CI [10.70%–18.35%], P < 0.001) (Figure 4).



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206 **Figure 3.** The risk categories of FBP, IMR and ad-IMR CAC scores of overall
207 subjects in testing group. The details of risk categories with FBP/IMR/ad-IMR scores
208 were shown, IMR score would make risk categories be underestimated as compared
209 to FBP scores, and this effect could be partially eliminated after adjusting by linear
210 regression. IMR: iterative model reconstruction; ad-IMR: adjusted IMR CAC scores;
211 CAC: coronary artery calcification; FBP: filtered back projection.

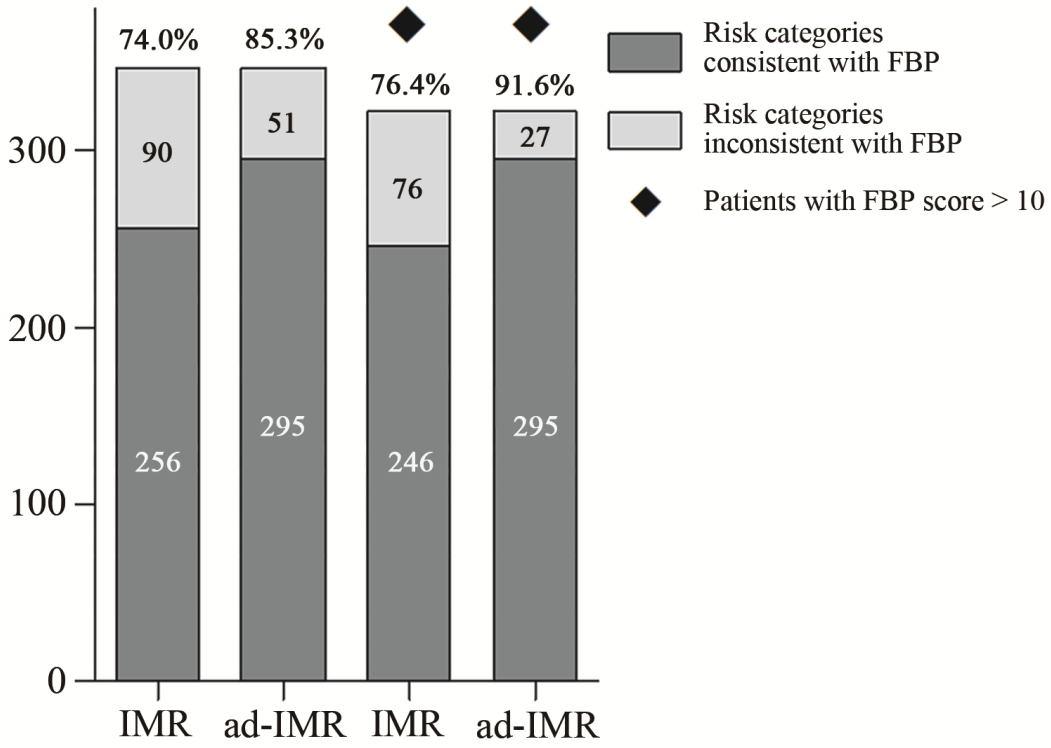

Figure 4. The consistency rates of CAC risk categories with IMR and ad-IMR scores when comparing to FBP scores. The consistency rate of CAC risk categories between IMR and FBP CAC scores was significantly improved by adjustment with linear regression (from 74.0% to 85.3%). And the consistency rate was further improved (up to 91.6%) when excluding patients whose FBP score ≤ 10. ◆: Patients with FBP CAC score > 10. IMR: iterative model reconstruction; ad-IMR: adjusted IMR CAC scores; FBP: filtered back projection.

90 patients were reclassified in the testing group while using IMR CAC scores, 84 of them were moved to a lower category level than FBP CACs, and the rest 6 patients were moved into two levels lower. However, after adjusting (i.e., ad-IMR), 53 of these 84 and all of the rest 6 patients were correctly classified into the FBP CACs category. At the same time, 20 patients who were in the same risk category with both IMR and FBP scores had their risk pushed to a higher category with ad-IMR (overestimation). Totally, there were 51 patients had a different risk category with ad-IMR and FBP

scores in overall subjects. After excluding patients whose FBP CAC score was ≤ 10, there were only 27 patients' categories were different with FBP scores after adjusting (i.e., ad-IMR), while the number was 76 with original IMR scores (Figure 3).

DISCUSSION

In current study we found that after adjustment by equation resulting from linear regression with weighted least square method, the ad-IMR score with low-dose CT became comparable with FBP score. Thus, the consistency rate between ad-IMR and FBP CAC risk categories was significantly improved by 11.27% (from 74.0% to 85.3%). Moreover, the improvement was much greater in patients with Agatston scores > 10 (from 76.4% to 91.6%).

Our findings about the underestimation in CAC agatston score with low-dose IMR are consistent with previous *in vivo* studies.[22–25] The reason for underestimation was that IMR could lessen the blooming artifacts and make plaque boundaries much clearer,[24] thus reducing the CAC area and scores. But we observed greater CAC underestimation in current study. There were two potential reasons for this difference: first, we performed two scans in each patient with different tube current (50 mAs for FBP and 20 mAs for IMR) in contrast to the work of Szilveszter [22] and Oda [24] where fixed tube currents (30 mAs and 32mAs respectively) were used; secondly, the extent of patients' CAC was more severe than reported in den Harder's study.[23]

To the best of our knowledge, this is the first study to develop the consensus adjustment equation for Agatston score between low-dose IMR and routine-dose FBP algorithm. Caruso *et al.*[28] tried to get the correction factor for CAC scoring using advanced modeled iterative reconstruction (ADMIRE), but they performed single scan with fixed tube voltage/current (120 kV, 80 mAs) instead of two scans with routine and reduced radiation dose. Similar study was conducted by Pan *et al*.[25] more recently to adjust the impact of IMR on CAC scoring, the correction was established at a fixed radiation dose (120 kV, 50mAs). Since IMR could help to further reduce the radiation dosage of CAC detection in compare with FBP, the adjustment between low-dose IMR and routine-dose FBP thought to be crucial on this issue. With the

results of present study, the underestimation of CAC by low-dose IMR would be adjusted and the risk classification could be more consistent to routine-dose FBP scores (85.3% for overall subjects and 91.6% for patients CACs > 10). However, the adjustment might not be suitable for no or low risk patients (CACs ≤ 10). The poor correlation between FBP and IMR scores within such patients (r = –0.07, P = 0.84) might be the reason for this weakness. The hypothesis to explain this was that inter-scan variation might be greater in patients with low CAC scores. In other words, the smaller CAC particle was, the greater variation might be existed between different scans. With the increasing of CAC scores, it's the reconstruction algorithm rather than inter-scan variation that affect CAC scoring.

For clinical application, it was low-intermediate and intermediate risk patients (CAC scores 11–400) rather than no-low or high-risk patients (CAC scores 0–10 or >400) that their drug prescription might be depend on CAC scores. Researches showed that there was a lower number needed to treat (NNT) with statins to prevent one cardiovascular event and a greater net benefit for aspirin intaking in CAC > 100 patients, regardless of traditional risk factors.[10,11] In our study, 31 patients with FBP score > 100 were underestimated to the lower category by IMR. After adjustment, 21 of them were re-categorized to be consistent with FBP categories. Thus, by adjusting via linear regression for low-dose scans that used IMR (i.e., ad-IMR), it is possible to arrive at appropriate therapeutic decisions for these patients who could otherwise be missed.

This adjustment of IMR scores could not only improve the risk classification but also facilitate the comparison of CACs data during follow-up. CAC is not a one-shot assessment but a progressive indicator for myocardial infarction and all-cause mortality.[2] As the progression of CAC quantified by Agatston score might be 20% to 25% per year [29] (or 16–39 increasing of Agatston score values during a 3–5 years' follow-up[30]), a 26.0% underestimation of CACs with IMR might completely neutralize it. According to our data, there was no difference between low-dose ad-IMR and routine-dose FBP scores in testing group (mean difference 7.0, 95% CI [–1.9–16.0], P = 0.12). Thus, the adjustment could make low-dose IMR scores be

more comparable with FBP scores in CAC follow-up.

There are some limitations in our study. First, since we scanned twice in each patient, inter-scan variation was inevitable to reduce the accuracy of our results, particularly in the patients with CACs < 10. Second, this was a single center study using the technology developed by a single vendor, which isn't suitable to other vendors. Third, as agatston score is the cornerstone of CAC risk classification, we didn't assess the consistency of mass or volume score in this work. At last, the efficacy of the equation has not been tested by clinical outcomes, further prospective follow-up studies need to be performed.

CONCLUSION

The underestimations to the Agatston coronary artery calcification (CAC) score with the use of advanced iterative model reconstructions (IMR) at low radiation dose CAC CT can be adjusted via linear regression thus making the risk classification (using ad-IMR) more consistent in line with "routine-dose" CAC scans with FBP reconstructions, thereby facilitating further radiation dose reduction of CAC scanning without compromising its clinical application.

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Ethics Approval and Consent to Participate

This study was approved by the research ethics committee of Shengjing Hospital of China Medical University (NO. 2019PS392K).

Conflict of Interest

None declared.

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