ORIGINAL ARTICLE

Diagnostic accuracy of zero Coronary Artery Calcium (CAC) score in a Malaysian cohort: A 20-year retrospective analysis

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ABSTRACT

Introduction: The Agatston coronary artery calcium (CAC) score is a widely used screening tool. However, its negative predictive value (NPV) in the Southeast Asian population, prone to premature non-calcified atherosclerosis, is not well defined.

Materials and Methods: We analysed paired data from 5,375 asymptomatic patients who underwent concurrent CAC scoring and Coronary CT Angiography (CCTA) at a tertiary center in Kuala Lumpur over 20 years. This cohort was selected to study plaque missed by CAC. A validated automated pipeline (weighted Cohen's Kappa = 0.978) was used to determine stenosis severity.

Results: Zero CAC yielded a negative predictive value of 76.1% for any plaque; 23.9% of calcium-negative patients harboured hidden atherosclerosis, including 3.5% with obstructive disease. While odds increased linearly with age (OR 1.22 per decade, p=0.004), missed disease peaked in males aged 40–44 and peri-menopausal women aged 55–59. These age groups represent a window during which lipid-rich plaques accumulate before calcifying.

Conclusion: Zero CAC can mask a "pre-calcific window" of active, radiolucent atheroma accumulation. Rather than a state of biological protection, this Zero CAC cohort harbours hidden risk driven by the same demographic engines as calcified disease, simply operating at an earlier phenotypic stage. Confirmatory CCTA is critical for high-risk younger males and peri-menopausal women to bridge this inherent diagnostic blind spot.

KEYWORDS:
Coronary artery calcium score; coronary computed tomography angiography; coronary artery disease; non-calcified plaque; diagnostic imaging

INTRODUCTION

In 1990, Agatston et al. introduced coronary artery calcium (CAC) scoring via computed tomography (CT) to non-invasively quantify atherosclerotic burden.[1] While a significant improvement over fluoroscopy, diagnostic sensitivity varies across age groups. Today, although the CAC score is a widely accepted screening tool, its reliance on calcification as the sole surrogate for atherosclerosis creates a "silent gap" or "pre-calcific window".[2-3]

This gap arises from the pathophysiology of atherosclerosis. Non-calcified plaques, composed of a lipid-rich necrotic core and fibrous cap, are radiolucent on non-contrast CT and invisible to the Agatston algorithm.[4-5] Calcification typically represents a late-stage healing response to chronic inflammation; thus, Zero CAC indicates "no calcified disease," not "no disease".[6-7] Consequently, vulnerable non-calcified plaques may proliferate undetected in patients mistakenly categorized as low-risk.

Despite this, large-scale Western trials such as SCOT-HEART[8] and PROMISE3 have heavily influenced the "power of zero" paradigm, prompting a 5 to 15 year "warranty period" for patients with Zero CAC.[9-10] However, emerging data suggest that the prevalence of non-calcified plaque may vary across populations.[11] Currently, there is a lack of large-scale data characterizing this disease burden in Southeast Asia, a population known for earlier disease onset and a severe cardiometabolic phenotype.[12-14]

To address this, we analysed 20-year retrospective data from 5,375 asymptomatic patients who underwent paired CAC and CCTA at a private medical centre in Kuala Lumpur, Malaysia. Contrasting with Agatston's foundational cohort,[1] we aim to leverage this large regional dataset to quantify the CAC "diagnostic blind spot" and identify demographic patterns missed by standard CAC screening.

MATERIALS AND METHODS

Study Design and Sample Population

This retrospective observational study analysed 5,375 patients who underwent paired CAC scoring and CCTA at a private medical centre in Kuala Lumpur, Malaysia. This cohort was selected to evaluate the prevalence of atherosclerosis missed by CAC. All included patients were asymptomatic per referral records, defined by the absence of documented chest pain, dyspnoea, Acute Coronary Syndrome (ACS), or positive stress testing.

Inclusion criteria:

- Adults aged ≥25 years;
- Patients who underwent both non-contrast CAC scanning and contrast-enhanced CCTA during the same imaging session.

Exclusion criteria were applied to focus strictly on native coronary atherosclerosis and included:

- Prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting);

This article was accepted: 06 July 2026
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- Incomplete imaging data (CAC or CCTA only);
- Reports lacking interpretable coronary findings.

No experimental interventions were performed. All data were derived from routine clinical care as detailed in Figure 1C.

Imaging Acquisition and CCTA Status Classifications
Scans were acquired using multidetector CT systems (≥64-slice), initially utilizing the 64-slice GE LightSpeed VCT and later transitioning to the 128-slice GE Optima CT660 (GE Healthcare, USA). All imaging adhered to evolving institutional cardiac CT Standard Operating Procedures throughout the 20-year study period.15 While scanner generations evolved, interpretation criteria remained consistent.

Step 1: Non-Contrast CT for Calcium Scoring
A non-contrast scan quantified coronary artery calcium burden using the Agatston method.[1] Scores were categorized:
- **0 (Zero):** No identifiable calcification.
- **1–100 (Mild):** Minimal atherosclerotic burden.
- **101–400 (Moderate):** Significant burden.
- **>400 (Severe):** Extensive burden, often correlating with high probability of ischemia.

Step 2: Contrast-Enhanced CCTA
Contrast-enhanced CCTA was performed with target heart rate ≤70 bpm; beta-blockers were administered as needed. Iodinated contrast medium was administered using a weight-adapted protocol: Ultravist 370 (Bayer Healthcare, Germany) for patient weight ≥80 kg and Xenetix 350 (Guerbet, France) for patient weight <80 kg.

CCTA images were reconstructed and interpreted by a Malaysia Medical Council–certified senior consultant radiologist, consistent with Society of Cardiovascular Computed Tomography (SCCT) guidelines,16 where disease severity was determined by the maximal luminal narrowing observed in any major epicardial vessel (Left Main, Left Anterior Descending, Left Circumflex, or Right Coronary Artery). Under this framework, patients were categorized as having **Normal Coronaries** (0% stenosis with a fully patent lumen), **Non-Obstructive CAD** (1%–49% stenosis with identifiable plaque), or **Obstructive CAD** (significant burden causing ≥50% luminal stenosis).

Automated Extraction Pipeline
An automated extraction pipeline was constructed using Python (version 3.9.11) with regular expression library (regex). The system operates by identifying specific linguistic patterns to categorize radiologist findings according to the classifications defined in Figure 1B. The high-level processing flow is defined as follows:

Radiologist Findings (Clinical Notes) → **Extraction Pipeline** (RegEx Algorithm) → **CCTA Status Classification** (Normal, Non-Obstructive, Obstructive, Outlier)

Text patterns were derived from SCCT reporting guidelines[16] and historical radiologist reporting syntax. Five functional categories processed raw findings into final classifications:

a) **Anchors Terms (A)**
Quantitative severity descriptors are only valid when syntactically linked to a predefined target clinical concept nouns set: "Stenosis", "Narrowing", "Obstruction", "Plaque".
Example: "Mild calcified plaque burden with mild (25-49%) luminal stenosis" → Extracted Anchor Term (A): {Plaque, Stenosis}

b) **Stenosis Severity Terms (K)**
An ordinal taxonomy of severity descriptors mapped to integer values (0-100%) based on SCCT reporting guidelines16 as shown in Figure 1B, where keywords took precedence over numeric ranges.
Example: "Severe calcified plaque burden with severe (70-99%) luminal stenosis" → Extracted Stenosis Severity Term (K): {Severe, 70-99%} Logic: Keywords take precedence over numeric ranges. → Final Value: 70%

c) **Exclusion terms (E)**
A comprehensive set of patterns used to remove false positives and non-target findings. This category unifies four specific filtering logic gates:

i. **Anatomical Exclusion:** Removes findings from non-coronary structures (e.g., "Aorta", "Mitral Valve").
Example: "The calcium plaque initially identified... located predominantly in the aorta rather than in the LMS" → Action: The presence of the exclusion keyword "aorta" invalidates the findings in this sentence, preventing the calcium burden from being incorrectly assigned to the Left Main Stem (LMS).

ii. **Contextual Disambiguation:** Neutralizes size descriptors that mimic severity terms (e.g., "Small vessel").
Example: "The left main coronary artery (LM) is a medium size vessel and bifurcates in LAD and LCX." → Action: Phrase "medium size vessel" is neutralized to prevent false-positive sizing.

iii. **Negation:** Identifies and excludes findings modified by negative qualifiers (e.g., "No evidence of").
Example: "No significant stenosis or plaque" → Action: Matches Negation Driver. Phrase "No significant" triggers null value (0%).

iv. **Artifacts:** Removes adjectives associated with image quality issues (e.g., "Motion artifact").
Example: "The calcium speck identified is likely an artifact" → Action: Matches Artifact keyword. The phrase is neutralized and excluded from scoring.

d) **Stenosis/Plaque type identifier terms (M)**
A hierarchical set of plaque composition descriptors are used: "Calcified","Mixed","Soft".
Example: "Severe non-calcified atherosclerotic plaque..." →Extracted (M): {Non-calcified}

e) **CCTA Status Classification (C):**
The final classification derived from the maximum stenosis value, mapped to one of three risk classes (Normal, Non-obstructive, Obstructive) as illustrated in Figure 1B.

The extraction pipeline executes a sequential processing routine (Figure 1). First, the raw text is normalized and segmented into sentences, preventing context leakage. The

engine then iterates through each sentence, applying the Exclusion Terms (E) to discard non-coronary, negated, or artifact-related statements. For remaining valid sentences, it extracts Stenosis Severity Terms (K) only if anchored to an Anchor Term (A). Stenosis/Plaque Type Identifier Terms (M) are extracted from non-negated sentences as supplementary metadata for qualitative review but were not utilized in the primary statistical analysis. Finally, the maximum severity value (Smax) detected across all valid segments is aggregated and mapped to SCCT stenosis grades, then to the final Clinical Category (C).

To illustrate this aggregation logic, consider a composite case based on the extraction definitions detailed above. If a patient report contains findings mapped to 25%, 0%, and 70% severity, the system computes the global maximum:
S_{max} = max (25, 0, 70) = 70%

This value is then processed through the clinical mapping logic:
1. **SCCT Grade:** 70% maps to Severe.
2. Clinical Output Category (C): Severe maps to Obstructive (Threshold ≥ 50%).
∴ Input (Radiologist Findings) → (Smax= 70%, SCCT Grade = {Severe}, C = {Obstructive})

The extraction pipeline was validated against a 350-report manual review, achieving excellent reliability (weighted Cohen's Kappa = 0.978; 100% sensitivity; 97.6% specificity in validation sample). This perfect sensitivity is inherent to the deterministic, rule-based design.

Statistical Analysis and Validation Protocol

Cohort Stratification and Demographics

Data aggregation and statistical analysis were performed using Python (pandas, scipy, statsmodels). The cohort was stratified by CAC status (Zero CAC vs. Positive CAC). Continuous variables (e.g., age) are presented as mean ± standard deviation (SD) and compared using independent samples t-tests. Categorical variables (e.g., sex) are presented as frequencies and percentages and evaluated using Pearson's Chi-square (χ^2) test of independence. To ensure statistical robustness for prevalence estimates, particularly in smaller subgroups, 95% confidence intervals (CI) for proportions were calculated using the Wilson Score Interval. Two-tailed p-values <0.05 were considered statistically significant.

Multivariable Predictive Modelling

To determine if age and sex serve as predictors of plaque in the absence of calcium, a multivariable binary logistic regression was performed on the Zero CAC cohort (n=1,382). Traditional cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, smoking) were incompletely documented in imaging reports and could not be included in multivariable modelling. The primary predictive model therefore focused on the high-fidelity demographic variables of Age and Sex, which were consistently recorded. This approach represents a demographic risk stratification model rather than a comprehensive clinical risk model. Results are reported as Odds Ratios (OR) with associated 95% CIs, with the explicit understanding that unmeasured confounding may influence estimates. A penalized (Firth-style) logistic regression was utilized to stabilize point estimates given the event rate.

Diagnostic Performance Metrics

Using CCTA classification as the reference standard,[11] diagnostic accuracy (Sensitivity, Specificity, Positive and Negative Predictive Values) was calculated for CAC scoring. A CAC>0 was defined as positive for calcification. CCTA classifications of "Normal," "Non-obstructive," and "Obstructive" were determined by the radiologist's clinical notes, where terms are utilized as defined in Figure 1B.

In this study, the metrics are defined as:
- True Positive (TP): CAC>0 and CCTA shows plaque
- False Positive (FP): CAC>0 but CCTA normal coronaries
- True Negative (TN): Zero CAC and CCTA normal coronaries
- False Negative (FN): Zero CAC but CCTA shows plaque

All metrics were computed with exact binomial 95% confidence intervals to assess the precision of CAC as a predictor for CCTA-defined atherosclerosis.

Clinical Discordance Analysis

A manual root-cause analysis of the 21 discordant outliers (0.4% of cohort) presenting with positive CAC scores but normal CCTA confirmed the CCTA interpretations were correct. These false-positive CAC readings were attributed to known non-contrast CT limitations, including motion artifacts (n=12), sub-resolution micro-calcifications (n=5), and mis-indexed extra-coronary calcification (n=4) located in the adjacent aorta, pulmonary trunk, or outside the vasculature.[16-18] This confirms discordance in this direction is driven by inherent specificity limitations rather than missed pathology.

RESULTS

Demographics

The baseline characteristics of the study population (N=5,375) are detailed in Table I. Patients with Zero CAC were significantly younger than those with positive scores (49.2 ± 9.9 vs. 58.4 ± 9.9 years, p<0.001). Male sex predominated across the cohort (69.5%), particularly within the positive CAC group (72.9% vs. 59.7% in the Zero CAC group, p<0.001). A small number of patients (n=21) had positive CAC, but no plaque detected on CCTA, reflecting differences in detection between calcium scoring and plaque visualization (refer Section 2.4.4 for explanation).

The association between CAC categories and CCTA-defined stenosis was highly significant (χ_2 = 1153.14, p<0.001), with higher scores correlating strongly with obstructive CAD, reaching 95.5% (95% CI: 93.7–96.7%) in the severe (>400) group. Conversely, among the Zero CAC cohort, CCTA identified 330 patients (23.9%; 95% CI: 21.7–26.2%) with plaque. Within this "blind spot," 281 patients (20.3%; 95% CI: 18.3–22.5%) had non-obstructive CAD and 49 (3.5%; 95% CI: 2.7–4.7%) harboured obstructive CAD (≥50% stenosis).

Diagnostic Performance Metrics

To quantify the reliability of CAC as a screening tool, diagnostic performance metrics were evaluated against CCTA classifications for Any Plaque and Obstructive CAD (Table II).

Table I: Overall demographics of CaC & CCTA Results

CAC Group	N	Age (years)	Male, n (%)	CCTA Classification		
				Positive CCTA (Any Plaque)	Non-Obstructive CAD (<50%), n (%)	Obstructive CAD (≥50%), n (%)
Zero CAC Score	1382	49.2 ± 9.9	825 (59.7%)	330 (23.9%) [21.7–26.2]	281 (20.3%) [18.3–22.5]	49 (3.5%) [2.7–4.7]
Positive CAC (>0)	3993	58.4 ± 9.9	2,912 (72.9%)	3,972 (99.5%) [99.2–99.7]	1,737 (43.5%) [42.0–45.0]	2,235 (56.0%) [54.4–57.5]
Mild (1-100)	2125	55.6 ± 9.4	1,510 (71.1%)	2,109 (99.2%) [98.8–99.5]	1,414 (66.5%) [64.5–68.5]	695 (32.7%) [30.8–34.7]
Moderate (101-400)	1119	60.0 ± 9.5	816 (72.9%)	1,116 (99.7%) [99.2–99.9]	291 (26.0%) [23.5–28.7]	825 (73.7%) [71.1–76.2]
Severe (>400)	749	63.5 ± 9.4	586 (78.2%)	747 (99.7%) [99.0–99.9]	32 (4.3%) [3.0–6.0]	715 (95.5%) [93.7–96.7]
Total Cohort	5375	56.0 ± 10.7	3,737 (69.5%)	4,302 (80.0%) [78.9–81.1]	2,018 (37.5%) [36.2–38.8]	2,284 (42.5%) [41.2–43.8]
Statistic	N/A	-29.51	84.46	3666.56	N/A	1153.14
P-Value (0 vs >0)	N/A	<0.001*	<0.001†	<0.001†	N/A	<0.001†

Data Presentation: Continuous variables are presented as mean ± standard deviation; categorical variables are presented as n (%) with [95% Wilson Score Confidence Intervals].
* Welch's t-test: Used for continuous comparison between Zero and Positive CAC group.
† Pearson's Chi-Square ($\chi 2$): Used for categorical comparisons between Zero and Positive CAC groups.
These comparisons are presented to characterize cohort differences and are not intended to imply causal inference.

Table II: Diagnostic Utility of CAC Score against Clinical Thresholds

Metric / Test Threshold	Any Plaque (> 0%) CAC > 0	Obstructive CAD (≥50%)		
		CAC > 0	CAC > 100	CAC > 400
Sensitivity	92.3% [91.5-93.1]	97.9% [97.2-98.4]	67.4% [65.5-69.3]	31.3% [29.4-33.2]
Specificity	98.0% [97.0-98.7]	43.1% [41.4-44.9]	89.4% [88.2-90.4]	98.9% [98.5-99.2]
Likelihood Ratio (LR+)	46.2	1.72	6.36	28.5
Likelihood Ratio (LR-)	0.08	0.05	0.36	0.69
PPV	99.5% [99.2-99.7]	56.0% [54.4-57.5]	82.4% [80.6-84.1]	95.5% [93.7-96.7]
NPV	76.1% [73.8-78.3]	96.5% [95.3-97.3]	78.8% [77.4-80.1]	66.1% [64.7-67.4]
Accuracy	93.5% [92.8-94.1]	66.4% [65.1-67.6]	80.1% [79.0-81.1]	70.2% [68.9-71.4]

Table III: Multivariable Predictors of Coronary Plaque

Feature	Model 1: Full Dataset Model (CAC Positive Prediction)	Model 2: Zero CAC Subset Model (CCTA Plaque Prediction)
Model Fit (LLR)	p<0.0001	p=0.0020
VIF (Age / Sex)	1.05/1.05	1.11/1.11
Intercept (β0)	-5.98	-2.35
Age (β1)	1.14 (p<0.001)	0.192 (p=0.004)
Age (OR per decade)	3.13 [2.88, 3.39]	1.21 [1.10, 1.34]
Male Sex (β2)	1.37 (p<0.001)	0.3952 (p=0.004)
Male Sex (OR)	3.94 [3.35, 4.62]	1.48 [1.13, 1.95]
Regression:	ln(p/(1-p)) = β0+β1(Age)+β2(Sex [Male])	

Diagnostic utility shifted significantly across clinical thresholds. When evaluating for obstructive CAD, utilizing a standard positive threshold of CAC>0 yielded a high sensitivity of 97.9% but a reduced specificity of 43.1%. Conversely, increasing the threshold to CAC>400 served as a highly specific metric, maximizing specificity (98.9%), PPV (95.5%), and yielding a strong LR+ of 28.5. However, when evaluating for the presence of any atherosclerotic plaque, Zero CAC yielded an NPV of only 76.1%. This low NPV implies that while the CAC score remains highly sensitive for calcified lesions, it has limited ability to detect active, non calcified plaque, particularly in younger Malaysian patients where metabolic risk factors drive early non calcified atheroma formation.[12,19]

Characteristics of Patients with Zero CAC Score but with Plaque

Age and male sex are significant independent predictors of coronary calcification within the study population. In the full cohort baseline, multivariable analysis (Model 1) identified age (OR 3.13 per decade; p<0.001) and male sex (OR 3.94; p<0.001) as strong independent predictors with negligible multicollinearity (VIF 1.05/1.05) as shown in Table III.

These variables also predict hidden non-calcified plaque in the Zero CAC subset, albeit with a notably attenuated age effect. Model 2 demonstrated a significant overall fit (LLR p=0.002) and identified both age (OR 1.21 per decade; p=0.004) and male sex (OR 1.48; p=0.004) as significant

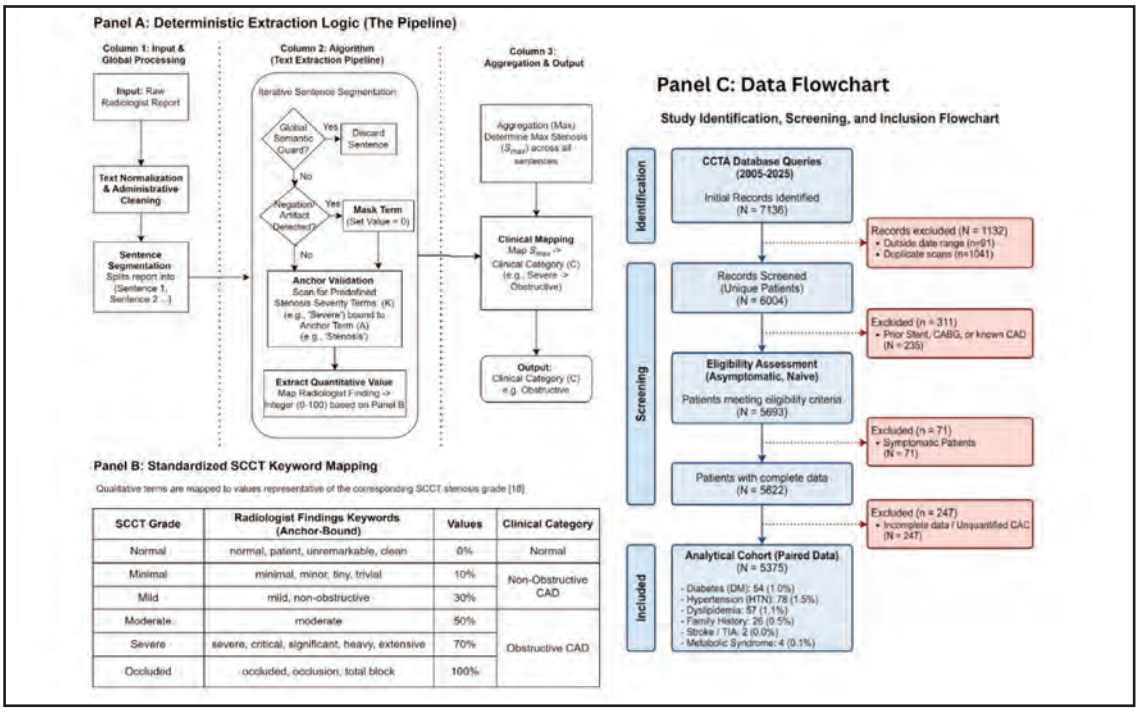

Fig. 1: Automated text extraction pipeline. (A) Processing workflow transforms raw radiology text into CCTA status classifications through normalization, filtering, and severity aggregation. (B) Keyword mapping table converts clinical descriptors to standardized SCCT stenosis grades. (C) Study cohort data flow: systematic attrition of the initial 7,136 records to the final analytical cohort of 5,375 asymptomatic patients, excluding duplicate scans and symptomatic cases
(Cardiovascular risk factor data incomplete; not included in analysis)

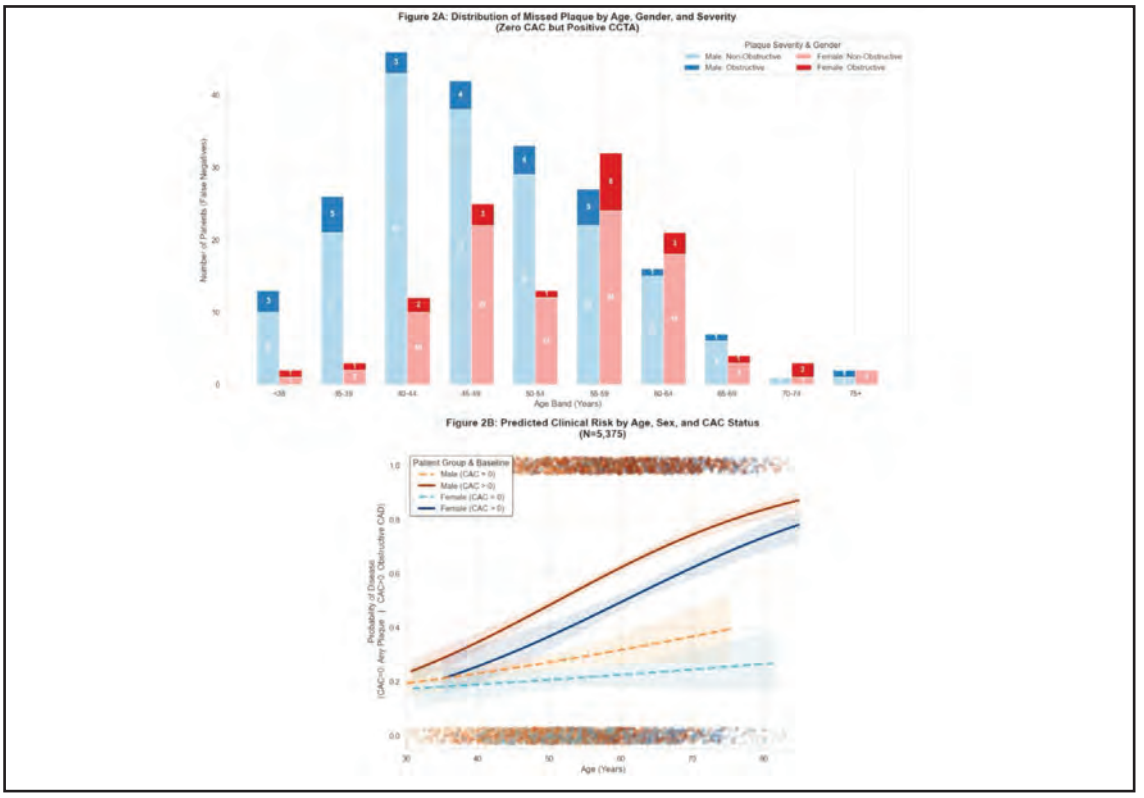

Fig. 2: CAD Distribution and Predicted Risk (A) Prevalence of Missed Plaque by Age and Sex: CCTA-derived characterization of the Zero CAC cohort, showing the distribution of non-obstructive versus obstructive disease. (B) Predicted Probability of CAD: Multivariable logistic regression curves comparing the risk of Any Plaque in Zero CAC patients (dashed lines) against Obstructive CAD in CAC>0 patients (solid lines). Note the distinct risk trajectories for Zero versus non zero CAC scores across age deciles

independent predictors (VIF 1.11/1.11) of hidden plaque. The reduction in the age coefficient (β1=0.192) indicates a less dominant age-driven trajectory in the Zero CAC cohort compared to the full-cohort baseline. While the male sex effect remained a strong risk driver (OR 1.48).

The Zero CAC cohort with plaque exhibited a distinct age-sex dimorphism (Figure 2A). Males predominated (68.9%) and demonstrated earlier disease onset, with non-obstructive CAD peaking in the 40 – 44 year band. Females showed delayed onset, clustering in the 55 – 59 year band. Risk followed a sustained linear escalation across the observed age spectrum (Figure 2B) without an apparent biological threshold, reflecting continuous plaque accumulation throughout the pre-calcific window.

Within this "blind spot," obstructive CAD was identified in 49 patients (3.5%). This hidden cohort was descriptively middle-aged (51.3 ± 11.2 years) and evenly distributed between sexes (55.1% male). These findings indicate that while Zero CAC is generally reassuring, a minority of patients harbour obstructive disease requiring confirmatory CCTA for detection.[20]

DISCUSSION AND CONCLUSION

While Zero CAC as a diagnostic gatekeeper is well-validated in Western populations,[3,8,10] its role as a clinical gatekeeper is increasingly contested in the Southeast Asian context. In this cohort, 23.9% of patients with Zero CAC had non-calcified plaque, with a 3.5% prevalence of hidden obstructive CAD. This burden of non-calcified disease is substantially higher than rates reported in major Western registries such as CONFIRM.[11]

This disparity highlights a notable finding driven by Malaysia's high cardiometabolic burden. With metabolic syndrome prevalence reaching 43% in adults under 40,[19,21] this milieu accelerates the formation of lipid-rich, non-calcified atheromas before osteogenic calcification becomes detectable on non-contrast CT.[22-24] Consequently, the traditional 5–15 year "warranty period" for Zero CAC is effectively reduced in this context.[9,10,14,24] These findings identify younger males and peri-menopausal women as high-yield groups for confirmatory CCTA, where Zero CAC score provides insufficient clinical reassurance.[12-13,25-26]

Association between Age and Plaque Development

The age gap between zero and positive CAC patients (49.2 vs. 58.4 years) reflects a well-characterised stage of atherosclerosis in which lipid-rich plaque accumulates prior to osteogenic calcification.[5,7] Aging subsequently drives calcific conversion, transitioning older patients into positive CAC cohorts and sequestering potential false negatives within younger groups where soft-plaque formation is most active.[27] While Western guidelines typically cite a 5–15 year "warranty period" for a zero score,[9-10] the 23.9% prevalence of non calcified plaque in our Zero CAC group suggests that this warranty is less reliable in this population. Consistent with Malaysia's metabolic syndrome burden clustering in adults under 40,[19,21] a milieu that accelerates lipid rich atheroma formation before calcification occurs.[14,24]

Sex and Age Patterns in Non-Calcified Plaque

The 23.9% of Zero CAC patients harbouring hidden plaque exhibited a distinct sex dimorphism in disease onset, marking a critical "pre-calcific window". In men, non-obstructive CAD volume peaked in the 40–44 year band (n=43), whereas females demonstrated a delayed clustering in the 55–59 band (n=8 obstructive cases). This early male peak is consistent with fibrofatty atheroma formation driven by high regional prevalence of metabolic syndrome in adults under 40.[19,21] As these lesions age, they undergo osteogenic hardening and shift patients into calcified cohorts.[7,20] In women, the 55–59 clustering aligns with the post-menopausal loss of hormonal cardioprotection.[28]

Notably, the independent male sex effect (OR 1.48) confirms this dimorphism persists after adjusting for age, reinforcing that male sex is a distinct risk driver for non-calcified burden in this setting. Both patterns diverge from broader Asian registry data, where Zero CAC cohorts typically demonstrate later onset and lower non-calcified plaque prevalence.[24,29] While the magnitude of the age effect appeared smaller in Zero CAC patients (OR 1.21 vs. 3.13 per decade). This suggests that a zero score identifies patients with delayed calcification rather than a fundamentally different biology of aging. The reduced age coefficient indicates that in this "blind spot," plaque formation is likely accelerated by unmeasured metabolic stressors and genetic predisposition rather than chronological aging alone. Consequently, these findings identify Malaysian males under 50 and peri-menopausal women as high-yield groups for confirmatory CCTA, where Zero CAC provides insufficient clinical reassurance.

Diagnostic Performance and Clinical Significance

While CAC scoring shows high sensitivity (97.9%) for detecting obstructive CAD, its specificity is limited (43.1%) largely due to blooming artifacts where dense calcification exaggerates stenosis severity.[1,16,18] More clinically important is the 76.1% NPV for Any Plaque: 23.9% of patients with zero calcium had non-calcified plaque missed by CAC alone. Detecting this non-calcified burden matters because, as the SCOT-HEART trial demonstrated, identifying subclinical atherosclerosis enables preventive therapies that reduce cardiovascular events.[8]

The number needed to scan (NNS) with CCTA to detect one obstructive case in the Zero CAC cohort is 29. This does not justify routine CCTA for all Zero CAC patients, as CCTA involves radiation and contrast, but supports its use when metabolic risk factors or clinical suspicion suggest higher pretest probability. CAC scoring remains a useful filter for calcified disease, but CCTA adds prognostic value in younger patients where plaque may still be non-calcified.

LIMITATIONS

This single-centre retrospective study excluded documented symptomatic patients and prior revascularization, but undocumented symptoms and referral bias remain inherent limitations. Although patients were classified as asymptomatic based on referral documentation, same-session CAC and CCTA suggests possible undocumented symptoms or higher clinical suspicion, which may

overestimate plaque prevalence in a truly asymptomatic population. Data on traditional cardiovascular risk factors were incomplete and not included in multivariable modelling, which was restricted to age and sex. Residual confounding factors such as differential smoking rates (NHMS 2023: 44.2% male vs. 1.1% female) may explain observed associations rather than true sex-specific biology. The subgroup of Zero CAC patients with detectable plaque (n=330) limits the statistical power for granular analyses. These results should be interpreted as hypothesis-generating demographic patterns rather than causal predictors.

CONCLUSION

In this analysis of 5,375 Malaysian patients, a Zero CAC score effectively ruled out obstructive stenosis (NPV 96.5%) but missed atherosclerotic plaque in 23.9% of calcium-negative patients, including 3.5% with obstructive disease. Multivariable analysis confirmed that age and male sex remain significant predictors.

These findings demonstrate a critical "diagnostic gap." While a Zero CAC score provides strong reassurance, it does not guarantee the absence of disease, as the odd of hidden plaque climbs continuously by 22% every decade. Ultimately, clinicians must recognize the limitations of CAC screening, where radiolucent atheroma escapes detection.

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