

Association of Breast Vascular Calcification with Atherosclerosis in the Common Carotid Artery and Its Impact on Coronary Artery Disease

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ABSTRACT

Introduction: Breast Arterial Calcification (BAC) seen on mammograms may indicate systemic atherosclerosis, including changes in carotid arteries and coronary arteries. This study explores whether BAC can be a marker of cardiovascular risk by examining its association with carotid intima-media thickness (IMT) and coronary calcium scores.

Data and Methods: This case-control study was conducted at TUTH, Kathmandu, involving 200 women from June 2019 to November 2020. Cases (n=100) had BAC on mammograms, while controls (n=100) did not. Carotid IMT was measured with ultrasound, and coronary calcium scores were assessed with CT scans. The Agatston CT scoring system was adopted for calculating the coronary calcium score. Statistical tests were used to compare groups.

Results: Women with BAC had significantly higher carotid IMT and coronary calcium scores than controls ($p < 0.05$). A positive correlation was found between BAC severity and carotid IMT. Odds ratio analysis showed a strong link between BAC and atherosclerosis.

Conclusion: BAC is associated with higher carotid IMT and coronary calcium scores, suggesting it could be a non-invasive marker for cardiovascular risk. Including BAC in mammogram reports may help identify at-risk patients early for further evaluation.

Keywords: Breast Arterial Calcification; Carotid Intima-Media Thickness; Atherosclerosis; Coronary Calcium Score; Cardiovascular Risk; Internal Mammary Artery; Atherosclerotic Cardiovascular Disease; Low Density Lipoprotein; Cerebrovascular Disease; Tram Track Calcifications; Mammogram; Agatston CT Coronary Calcium Scoring System.

1. Introduction

Mammography is a widely utilized imaging modality for the screening and diagnosis of various breast pathologies. Among the findings observed on mammograms, vascular calcifications are a significant subset, often manifesting as tram-track calcifications of the internal mammary artery [1]. While typically considered benign, these calcifications may reflect broader systemic vascular changes associated with conditions such as renal disease, coronary arterial disease, hyperparathyroidism, liver disease, and calciphylaxis [2-4].

Atherosclerosis, a chronic inflammatory condition characterized by vessel wall remodeling and oxidized LDL deposition, is a prominent cause of vascular calcification, particularly in the older population [5]. Atherosclerosis serves as an independent predictor of several severe health conditions, including acute coronary syndromes [6], cerebrovascular accidents [7], chronic kidney disease [8], and peripheral vascular disease [9]. This process involves thickening and stiffening of vascular walls, often evidenced by an increased intima-media thickness (IMT) and plaque formation in arteries like the carotid [10]. The internal mammary artery, frequently involved in breast arterial calcification (BAC), may also exhibit changes akin to those seen in carotid atherosclerosis [11]. Furthermore, BAC has been associated with higher estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk, with women exhibiting both BAC and coronary arterial calcifications (CAC) showing the highest risk (13.30%) [12]. The concurrent occurrence of atherosclerosis in the internal mammary, coronary and common carotid arteries raises the possibility of a shared pathophysiological spectrum. Given that common carotid arteries

can be readily assessed using ultrasound and Doppler imaging, a potential association between BAC observed on mammography and carotid intima-media thickness could provide valuable insights into cardiovascular health. The concurrent evaluation of coronary calcium score helps us to predict coronary artery diseases in patients with BAC. Limited data exist regarding this association in the Nepali population, where cardiovascular disease poses a significant public health challenge. Establishing BAC as a non-invasive marker for systemic atherosclerosis could facilitate the early identification of patients at risk for cardiovascular, cerebrovascular, and renal complications.

In this study, we aim to evaluate atherosclerotic features in patients with BAC detected on mammography and compare them with a control group without vascular calcifications. By examining the association between BAC and carotid intima-media thickness, we seek to determine whether BAC can be effectively utilized as a predictive marker for atherosclerosis and its related systemic complications [8]. In the recent report by Suh and Yun, et al; there was good agreement between readers for the BAC score (intraclass coefficient = 0.71, 95% confidence interval [CI]: 0.60–0.79) and substantial agreement for the presence of BAC ($\kappa = 0.76$, $p < 0.001$) [7].

1.1. Objectives of the Study

1.1.1. General objective

Vascular calcification in breast and its association with atherosclerosis in common carotid artery and its impact on coronary artery disease.

1.1.2. Specific objectives

- (1) To score BAC in a mammogram.
- (2) To measure the mean intima media thickness of the bilateral common carotid artery in cases and controls.
- (3) To correlate the BAC score with the mean IMT of carotid arteries.
- (4) To calculate the mean coronary calcium score in CT.
- (5) To find a relation between the BAC density and the coronary calcium score.

2. Data and Methods

2.1. Study Setting and Population

This is an analytical case-control study conducted at the Tribhuvan University Teaching Hospital (TUTH), Maharajgunj, Kathmandu, from June 2019 to November 2020. The primary aim was to evaluate the relationship between breast arterial calcification (BAC) detected on mammography and atherosclerosis, assessed through carotid intima-media thickness (IMT) and coronary artery calcium scores.

A total of 200 female patients referred for screening or diagnostic mammography due to various breast symptoms were included. Participants were selected using a non-probability sampling method and divided into two groups: 100 cases with vascular calcifications observed on mammograms (tram-line patterns in internal mammary arteries) and 100 controls without any such calcifications, matched for age and relevant clinical factors.

Adult women undergoing mammography were eligible. Women with observed BAC were cases, while women without BAC were controls. Women with post-operative breast changes, architectural distortion, or a history of hypertension, diabetes, or chronic kidney disease were excluded as they are independent risk factor for atherosclerosis and may confound the result.

2.2. Imaging Procedures

Mammograms were obtained using the Mammomat Fusion Unit in standard CC (craniocaudal) and MLO (mediolateral oblique) views. Images were reviewed to identify and grade BAC based on pattern, length, and density. Subsequently, ultrasonography of the neck was performed using a linear 7.5 MHz transducer to measure IMT 1 cm proximal to the carotid bifurcation bilaterally. Coronary calcium scoring was performed using non-contrast CT (NCCT) to assess coronary artery involvement. The Agatston scoring system was used to calculate the coronary calcium score. The measurement of IMT was done by different individuals and so was the coronary calcium score calculation.

2.3. Breast arterial calcification (BAC) score calculation on mammogram

Normal mammography with BAC would be categorized in the Breast Imaging Reporting and Data System (BI-RADS) as category 1 (negative) or 2 (benign finding). To calculate a BAC score, the number, length, and density of BAC are evaluated [1].

- The number of calcified vessels in both breasts are recorded. A vessel with calcification is counted as one if it is visible in both cranial-caudal and mediolateral-oblique views. If more than six vessels are visible in both CC and MLO view they are counted as six.
- The length of calcified segment is scored using a 4-step scale; 0, none; 1, less than 1/3; 2, between 1/3 and 2/3; and 3, more than 2/3 of the total visible vessel.
- The calcification density of the vessel in the densest segment is scored using 4-step scale; 0, none; 1, vessel wall calcification with clear visualization of the lumen and/or single wall calcification; 2, vessel wall calcification with clouding of the lumen; and 3, dense vessel wall calcification without visualization of the lumen.

To evaluate the severity of BAC, radiologists sum these three scores for each mammogram, and these BAC severity scores are categorized into three groups 0, 1 to 6, and 7 to 12; none, mild, and severe, respectively

2.4. CT Coronary calcium score calculation

The Agatston score quantifies coronary artery calcification by identifying areas of calcium on a CT scan, then multiplying the Hounsfield Units (HU) of the calcified area by its area and a density factor (1-4 based on HU range), and finally summing these weighted values for all calcified lesions to get the total score. This calculation is performed automatically by specialized software on the CT workstation.

Here's a breakdown of the calculation process:

a. Threshold Identification

The software identifies areas of calcification, defined as having a density of 130 HU or higher.

b. Density Factor

Each calcified lesion is assigned a density factor (1, 2, 3, or 4) based on its peak Hounsfield Units:

- **Factor 1:** 130–199 HU
- **Factor 2:** 200–299 HU
- **Factor 3:** 300–399 HU
- **Factor 4:** 400 HU or higher

c. Area Measurement

The software determines the area of each distinct calcified plaque.

d. Weighted Score Calculation

The area of each lesion is multiplied by its assigned density factor to get a lesion-specific score.

e. Summation

The total Agatston score is the sum of these weighted scores from all calcified lesions throughout the coronary arteries.

2.5. Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25. Mean IMT values for cases and controls were compared using an independent t-test. Odds ratios (ORs) were calculated to evaluate the association between BAC and atherosclerosis, including carotid and coronary artery involvement.

2.6. Ethical Considerations

The study adhered to ethical guidelines and was approved by the institutional ethics review board of Tribhuvan University Teaching Hospital (Reference Number: [80 (6-11) E2/076/077]). Written informed consent was obtained from all participants, and data confidentiality was strictly maintained.

3. Results

The ages of the participants ranged from 34 to 78 years, with an average age of 56 years for cases and 50 years for controls. As illustrated in Figure 1, the highest mean Left IMT was observed in the 70–80 years age group, while the highest mean Right IMT occurred in the 60–70 years age group. The lowest mean IMT was recorded in the 30–40 years age group. The mean IMT in the case group was significantly higher than in the control group, indicating the presence of atherosclerotic changes in the common carotid arteries.

The findings reveal a progressive increase in IMT with the severity of BAC, with the highest left IMT (LIMT) observed in the BAC 3 group, significantly exceeding the right IMT (RIMT) as seen in Figure 2. In the BAC1 and BAC2 groups, LIMT and RIMT values were similar, but a gradual increase in IMT was evident as BAC density

progressed. The carotid arteries of the case group showed more evidence of thickening, which correlated with the severity of BAC observed in mammography (BAC 1, BAC2 and BAC3 indicate increasing severity of breast arterial calcification).

The coronary calcium as seen in the CT scan was more in a patient with breast arterial calcification than their controls. The coronary calcium score showed a progressive increase with higher BAC grades as seen in Figure 3. Patients with BAC Grade 1 exhibited a mean coronary calcium score of 200, which increased substantially to 389 in BAC Grade 2 and peaked at 450 in BAC Grade 3. These findings suggest that patients with more severe BAC, as observed on mammography, are likely to have greater coronary calcification.

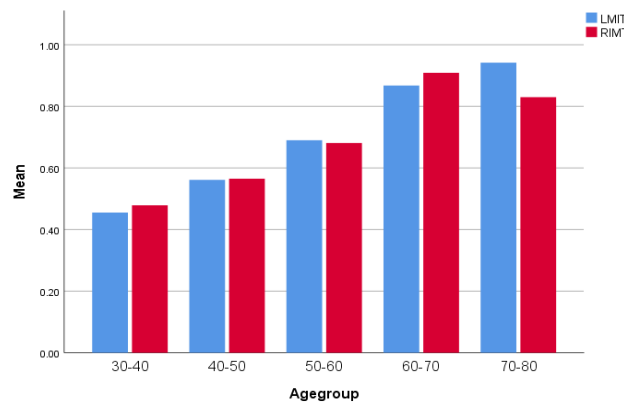


Figure 1. Mean IMT of right and left CCA in different age groups

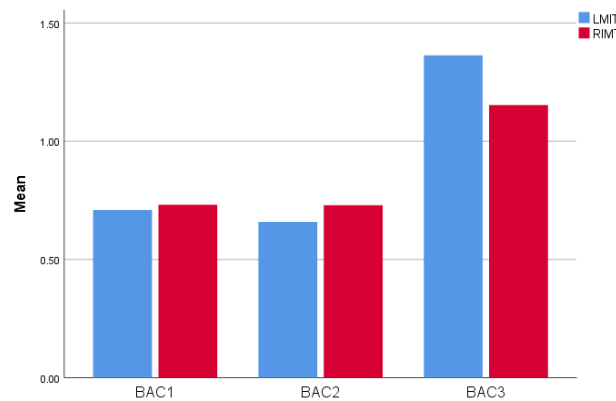


Figure 2. Mean Carotid Artery Intima-media Thickness in comparison to density of BAC

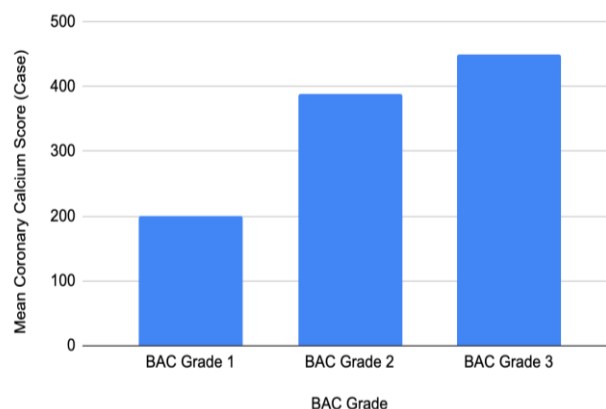


Figure 3. Mean Coronary Calcium Score in comparison to density of BAC

The independent t-test, tested at a significance level of 0.05, revealed a statistically significant difference in the mean IMT between the two groups ($p < 0.05$) (Table 1). The analysis revealed significant associations ($p = 0.000$) between BAC and the IMT of carotid arteries, with 95% confidence intervals of 0.14–0.29 and 0.11–0.30 for RIMT and LIMT, respectively.

Table 1. Association Between BAC and IMT

Parameter	Mean Difference	p-value	95% Confidence Interval
RIMT	0.2194	0.000	0.14–0.29
LIMT	0.20667	0.000	0.11–0.30

The odds ratio (OR) confirmed a strong association between breast arterial calcification and increased carotid intima-media thickness (Table 2). Specifically, individuals with BAC demonstrated a higher likelihood of having increased carotid intima-media thickness ($IMT > 1$ mm) in both the left and right common carotid arteries (CCA) on CT scans. In the left CCA, the odds of $IMT > 1$ mm were 7.8 times higher among cases compared to controls, while in the right CCA, the odds were 5.4 times higher. These findings suggest that BAC may serve as a reliable marker for systemic atherosclerosis and coronary artery disease.

Table 2. Odds ratio Calculation

	Left CCA IMT >1mm	Left CCA IMT <1mm	Right CCA IMT >1mm	Right CCA IMT <1mm
Cases	7	47	5	49
Controls	1	53	1	53
Odds Ratio	7.8	-	5.4	-

4. Discussion

Cardiovascular disease is often associated with systemic arterial disease, and arterial calcifications are recognized as important markers of atherosclerotic disease, indicating a potential future cardiovascular risk. While a considerable number of studies have explored the relationship between cardiovascular disease and breast arterial calcification (BAC), limited research has specifically examined the association between carotid intima-media thickness (C-IMT) and BAC. Thus, in addition to the cardiovascular risk, the cerebrovascular risk as reflected by CCA IMT is studied in our study. This study aimed to fill this gap and explore the potential link between vascular calcifications in the breast and atherosclerosis in the common carotid artery, as measured by C-IMT.

In the present study, we observed that vascular calcifications seen in mammograms are likely reflective of systemic atherosclerosis, including changes in the common carotid artery. Our results showed that patients with BAC had a significantly higher C-IMT as well as a higher coronary calcium score compared to those without BAC, indicating that breast arterial calcifications may indeed be a marker of atherosclerosis elsewhere in the body, particularly in the carotid and coronary arteries. The positive correlation between the severity of BAC and C-IMT strengthens this hypothesis, with higher BAC scores associated with higher C-IMT values and higher CT coronary calcium score. This suggests that the severity of vascular calcifications in the breast might reflect the degree of atherosclerotic changes in the common carotid arteries, and potentially in coronary arteries as well.

Our study findings align with previous research, such as the study by Ingole et al., which also demonstrated a higher C-IMT in individuals with BAC, supporting the idea that BAC could be used as an indirect marker of systemic atherosclerosis [13].

This study also showed a significant association between BAC and C-IMT score ($p < 0.05$), which supports the utility of C-IMT measurement as a tool to detect early atherosclerotic changes. This connection between BAC and carotid artery changes is important, as it could serve as a practical means of assessing cardiovascular risk in women, given that mammograms are routinely performed and breast arterial calcifications are common findings.

Moreover, while BAC is typically considered a benign finding in mammography, recent perspectives suggest that these calcifications could be suspicious markers for atherosclerosis. Therefore, mammogram reports should include mention of BAC, particularly as it could prompt timely screening and interventions for cardiovascular and cerebrovascular diseases, potentially reducing the risk of atherosclerosis-related complications in women.

5. Limitations

The sample size may be limited, potentially restricting the generalizability of findings to broader populations with varying demographics or clinical presentations. Additionally, differences in modality, technology, protocols, and resolution across institutions may impact diagnostic accuracy and reproducibility. The study's findings may also reflect regional and ethnic characteristics that may not apply to other populations. The mean IMT were taken by different observers and there is a possibility of interobserver variability.

6. Conclusion

In conclusion, the results of our study show a significant association between breast arterial calcification and atherosclerosis, as reflected by increased C-IMT and CT coronary calcium score. We recommend that vascular calcifications in the breast, observed in routine mammograms, be recognized as potential indicators of systemic atherosclerosis and be included in mammographic reports to guide further cardiovascular risk assessment and early intervention. Further studies are necessary to validate these findings and explore the broader clinical implications of BAC as a predictor of cardiovascular risk.

7. Future Suggestions

- 1) Breast arterial calcification can serve as a marker of systemic atherosclerosis and may be associated with atherosclerotic changes in other vascular territories, including the coronary, carotid, cerebral, and peripheral arteries.
- 2) The presence of breast arterial calcification on a mammogram should prompt further evaluation for cardiovascular and coronary artery disease. Early screening may help reduce morbidity and mortality from these conditions.
- 3) Similarly, coronary artery calcification may also reflect underlying atherosclerosis in the cerebral and peripheral arteries, underscoring the importance of comprehensive vascular screening.

4) In summary, breast arterial calcification (typically involving the internal mammary arteries) is an indicator of systemic atherosclerosis, and its detection warrants consideration of screening for atherosclerosis in other arterial regions.

Declarations

Source of Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare that they have no competing interests related to this work.

Consent for publication

The authors declare that they consented to the publication of this study.

Authors' contributions

Both the authors took part in literature review, analysis, and manuscript writing equally.

Availability of data and materials

The corresponding author is the custodian of the materials presented in this paper; the data are available upon reasonable request.

Ethical Approval

This research was approved by IRC, Institute of Medicine, TU Teaching Hospital with reference no of 80(6-11) E2 076/77 on September 1, 2019.

Institutional Review Board Statement

Not applicable for this study.

Informed Consent

All participants in this study voluntarily gave their informed consent prior to their involvement in the research.

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