Deep Learning-Based Cardiovascular Risk Prediction Using Routine Mammograms

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Candidate's Declaration

I, Mu'Ath Ibrahim, hereby declare that the work contained within this thesis, titled *'Cardiovascular risk prediction using routine mammograms'*, is my own and has not been submitted to any other university or institution as part or whole requirement for any higher degree.

I confirm that I was the principal researcher of all the work included in this thesis, including the collaborative work published with multiple authors. I certify that the intellectual content of this thesis is my own and that all assistance received in preparing this thesis and all sources have been appropriately acknowledged. Additionally, I obtained ethical approval from the University of Sydney Human Ethics Committee for all relevant studies presented in this thesis.

I understand that, should a higher degree be awarded for this thesis, it will be lodged with the Director of University Libraries and made available for immediate use.

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Authorship attribution statement

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In cases where I am not the corresponding author for a published item, permission to include the published material has been obtained from the corresponding author.

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Publications and Presentation

- Ibrahim MA, Suleiman ME, Gandomkar Z, Tavakoli Taba A, Arnott C, Jorm L, Barraclough JY, Barbieri S, Brennan PC. Associations of breast arterial calcifications with cardiovascular disease. *J Womens Health*. 2023 May 1;32(5):529-45.

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- Ibrahim MA, Brennan PC, Suleiman ME, Rickard M, Arnott C, Barraclough JY, Tavakoli Taba A, Gandomkar Z. Factors associated with the presence and severity of breast arterial calcification: a deep learning-based assessment using screening mammography. *Can J Cardiol*. 2024. (Submitted, under review).

- Ibrahim MA, Brennan PC, Suleiman ME, Rickard M, Arnott C, Barraclough JY, Tavakoli Taba A, Gandomkar Z. A novel deep learning-based grading system for assessing breast arterial calcification for predicting cardiovascular events. *Radiol Cardiothorac Imaging*. 2024. (Submitted, under review).

Conference Papers

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Oral Presentations

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- Ibrahim MA, Gandomkar Z, Suleiman ME, Tavakoli Taba S, Brennan P. Automated Segmentation of Breast Arterial Calcification (BAC) Using Deep Learning for Predicting a Major Adverse Cardiovascular Event. Presented at: RANZCR Brisbane Annual Scientific Meeting; 2023**.** ***[Appendix A]***

- Ibrahim MA, Gandomkar Z, Suleiman ME, Yi J, Tavakoli Taba S, Brennan P. Deep Learning Analysis of Breast Arterial Calcifications: A Study on Predicting Cardiovascular Disease in Women. Presented at: SPIE Medical Imaging Conference; 2024**.** ***[Appendix B]***

- Ibrahim MA, Brennan PC, Suleiman ME, Rickard M, Tavakoli Taba A, Gandomkar Z. Cardiovascular Risk Prediction Using Routine Mammograms. Presented at: MIOPeG Meeting; 2024; The University of Sydney.

- Ibrahim MA, Gandomkar Z, Suleiman MA, Tavakoli Taba S, Brennan P. Deep Learning-Based Segmentation of Breast Arterial Calcification to Enhance Cardiovascular Risk Assessment in Women. Presented at: UKIO Conference; 2024. ***[Appendix C]***

Abstract

Aims

This thesis aims to develop an innovative deep learning-based framework for the automated detection and grading of breast arterial calcification (BAC) using routine mammograms. The framework is designed to enhance the assessment of BAC severity and its potential role as an independent predictor of cardiovascular disease (CVD) risk. By leveraging data from a woman's initial mammographic screening, the model categorizes BAC severity into low, moderate, or high-risk groups for adverse cardiovascular outcomes. This personalized approach seeks to provide a more accurate assessment of cardiovascular risk, thereby enhancing the utility of routine mammographic screenings.

Methods

A U-Net-based deep learning model was developed to segment BAC regions, utilizing two separate datasets: 1,270 women for training the segmentation model and 9,648 women for assessing cardiovascular outcomes. The initial training phase employed a fully supervised learning approach, which was subsequently refined using a semi-supervised learning technique with progressive pseudo-labelling. This method allowed the model to leverage a larger set of unlabelled mammograms, leading to improved segmentation accuracy. BAC severity was categorized using a four-level grading system—absent, mild, moderate, and severe—based on tertile thresholds of BAC area or normalized intensity.

To understand the relationship between BAC and cardiovascular risk factors, regression models were first applied to assess the influence of age, diabetes, hypertension, and smoking status on BAC severity. These models identified significant predictors and helped clarify how

these factors contribute to the presence and severity of BAC. Given the retrospective nature of the data, medication records served as proxies for conditions like diabetes and hypertension.

Subsequently, Cox Proportional Hazards models were employed to calculate adjusted hazard ratios (HR) for each BAC grade, providing insights into the association between different levels of BAC severity and the risk of adverse cardiovascular outcomes. This analysis allowed for an evaluation of BAC as an independent predictor of CVD risk, accounting for the identified cardiovascular risk factors.

Results

The deep learning model demonstrated strong segmentation performance, with the U-Net model achieving a Jaccard Similarity Coefficient of 0.585, precision of 0.711, and F1 score of 0.75 during the initial training phase. Incorporating semi-supervised learning improved these metrics to a Jaccard Similarity Coefficient of 0.602, precision of 0.77, and F1 score of 0.76, while maintaining a high accuracy of 0.99. The prevalence of BAC was 26.96% among 9,648 women, with rates increasing with age—from 10.32% in women aged 40-49 to 66.06% in those over 80. Regression analysis revealed that age (OR: 1.090 [95% CI: 1.082–1.097]), diabetes (OR: 1.232 [95% CI: 1.023–1.484]), and hypertension (OR: 1.198 [95% CI: 1.083–1.325]) were significant predictors of BAC severity, while smoking exhibited an inverse association (OR: 0.648 [95% CI: 0.514–0.817]). The Cox Proportional Hazards model indicated that severe BAC was associated with an adjusted HR of 1.654 (95% CI: 1.30–2.10), highlighting the strong relationship between higher BAC severity and increased cardiovascular risk.

Conclusion

This research presents a novel framework for the automated detection and grading of BAC, demonstrating the effectiveness of deep learning in enhancing cardiovascular risk assessment in women. The use of semi-supervised learning improved segmentation accuracy, while

regression models and Cox analysis provided insights into the relationship between BAC, traditional risk factors, and CVD outcomes. The findings support integrating BAC assessments into routine mammography, offering a valuable tool for personalized risk stratification and improving cardiovascular screening for high-risk populations.

Future research should focus on validating the proposed grading system across diverse populations and imaging platforms to ensure generalizability. Longitudinal studies are also needed to assess how BAC severity evolves over time and to examine whether changes in BAC are predictive of future cardiovascular events. Furthermore, combining BAC with other radiomic features and clinical biomarkers may offer a more comprehensive and precise risk prediction model to further support preventive strategies in cardiovascular care.

Chapter 1 Introduction

1.1 Background and Rationale

1.1.1 Overview of Cardiovascular Disease (CVD)

Cardiovascular Disease (CVD) is the leading cause of global mortality, responsible for more deaths than any other disease (1). It encompasses a range of conditions, including coronary artery disease (CAD), heart failure, stroke, and peripheral arterial disease. According to the World Health Organization (WHO), CVD accounts for approximately 17.9 million deaths annually, representing 31% of all global deaths (1). This significant burden affects populations in both developed and developing countries across a broad demographic spectrum (1). The impact of CVD is profound on both men and women. Men are generally at higher risk at a younger age, but post-menopausal women experience a sharp increase in risk, often surpassing that of their male counterparts (2). This gender disparity highlights the importance of understanding and addressing the unique aspects of CVD in women to improve prevention, diagnosis, and treatment strategies.

1.1.2 Challenges in Women's Health

One of the critical challenges in women's health regarding CVD is the under-recognition and misdiagnosis of symptoms (3). Women often present with atypical symptoms that differ from the classic signs seen in men, such as chest pain. Instead, women may experience symptoms like shortness of breath, nausea, back pain, or fatigue, which are often not immediately associated with CVD by either patients or healthcare providers (4). This can lead to delays in seeking care and in receiving appropriate diagnosis and treatment. Consequently, women tend to have higher morbidity and mortality rates from CVD compared to men (5). Studies have shown that women are less likely to receive timely and aggressive treatment for heart attacks, such as reperfusion therapy or coronary artery bypass surgery (6). They are also less likely to be prescribed preventive medications like statins and aspirin, contributing to poorer outcomes

(7). This disparity is compounded by systemic biases and a lack of awareness about the different ways CVD can manifest in women (8)

1.1.3 Limitations of Traditional Risk Assessment Tools

Traditional risk assessment tools for CVD, such as the Framingham Risk Score, are based on factors like age, cholesterol levels, blood pressure, smoking status, and family history (9). While these tools are valuable, they often underestimate the risk in women. This underestimation is due to the lack of gender-specific risk factors in these models. For instance, conditions like polycystic ovary syndrome (PCOS), pregnancy-related complications (e.g., preeclampsia), and menopause significantly affect cardiovascular risk in women but are not typically included in traditional risk assessments (10). Moreover, women often have different cholesterol profiles and experience the effects of hypertension differently than men, which are not always adequately reflected in standard risk models (11). This underscores the need for more effective and accessible assessment methods tailored specifically for women.

1.1.4 Opportunity for Integrated Screening

Mammography is a medical imaging technique that uses X-rays to create two-dimensional (2D) images for examining breast tissue, specifically to detect early signs of abnormalities, including breast cancer. The widespread practice of mammography for breast cancer screening presents a significant opportunity to integrate Breast Arterial Calcification (BAC) assessment into routine cardiovascular risk evaluation. Mammograms are already a standard practice for women, particularly those over 40, making it a convenient and non-invasive method to screen for additional health risks (12). BAC differs from breast calcifications in its nature and appearance. While BAC involves medial arterial calcifications in the mammary arteries and presents as tubular or parallel lines on mammograms, breast calcifications are primarily associated with glandular tissue and appear as punctate or amorphous densities (6). By incorporating BAC evaluation into mammographic screenings, healthcare providers can

identify women at higher risk for CVD early and more accurately. This integration could lead to more personalized and effective prevention strategies, potentially reducing the burden of CVD among women. For instance, women identified with BAC could be targeted for more aggressive risk factor modification, including lifestyle changes and pharmacologic interventions.

Recent studies have demonstrated that breast arterial calcification (BAC) is associated with a higher risk of cardiovascular diseases, such as myocardial infarction and stroke. A systematic review and meta-analysis found that women with BAC have a significantly increased risk of coronary artery disease (CAD), with an odds ratio of 2.39 (13). This highlights the potential of BAC as an independent predictor of cardiovascular events and supports its role in enhancing risk stratification. Mammography, already part of routine screening for women over 40, offers a cost-effective and non-invasive platform for BAC assessment. Unlike cardiac CT, it involves no additional radiation or specialized protocols. Integrating BAC evaluation into mammographic screening leverages existing infrastructure and enables early identification of high-risk women, allowing for timely intervention.

1.2 Key Aspects of the Topics

1.2.1 BAC

BAC was first identified as a clinical entity in the early 1980s when Baum et al. (14) discovered its association with diabetes mellitus. This study established a link between BAC and diabetes, indicating that calcifications observed in the breast during mammograms could be an indicator of underlying metabolic disturbances (14). Since this initial discovery, the clinical significance of BAC has been the subject of extensive research, with a growing body of evidence suggesting that BAC is not merely an incidental finding, but a marker of systemic vascular pathology (15).

The clinical implications of BAC have expanded beyond its association with diabetes to include various CVDs. The recognition of BAC as a potential marker for cardiovascular risk stems from its similarity to calcifications found in other parts of the arterial system, such as the coronary and peripheral arteries (16).

As research progressed, studies began to explore the correlation between BAC and traditional cardiovascular risk factors, including hypertension, hypercholesterolemia, chronic kidney disease, reproductive factors, and increased cardiovascular morbidity and mortality (17, 18, 19, 20, 21). Multiple meta-analyses have confirmed the association between BAC and cardiovascular diseases, establishing BAC as a potential marker for cardiovascular risk (13, 22, 23). For instance, Hendriks et al. (22) analysed 52 studies assessing the relationship between BAC and CVD/CAD, traditional cardiovascular risk factors, and reproductive factors. They reported that the prevalence of BAC is approximately 12.7% among women undergoing breast cancer screening. Their analysis revealed that increasing age (pooled odds ratio (OR) 2.98 [95% CI 2.31-3.85] for every 10 years), diabetes (pooled OR 1.88 [95% CI 1.36-2.59]), and having children as opposed to being nulliparous (pooled OR 3.43 [95% CI 2.23-5.27]) are factors associated with higher BAC prevalence. Conversely, smoking was linked to a lower prevalence of BAC (pooled OR 0.48 [95% CI 0.39-0.60]). The study found no significant associations between BAC and hypertension, obesity, or dyslipidemia. Despite the limited number of longitudinal studies (n = 3), BAC seems to be related to an increased risk of cardiovascular disease events, with adjusted hazard ratios for coronary heart disease ranging from 1.32 (95% CI 1.08-1.60) to 1.44 (95% CI 1.02-2.05).

1.2.2 Deep Learning in Medical Imaging

Deep learning (DL), a subset of machine learning, has revolutionized various fields, including medical imaging. DL models, particularly convolutional neural networks (CNNs), have demonstrated remarkable capabilities in image recognition and classification tasks (24). One

of the most prominent architectures used in biomedical image segmentation is U-Net that introduced by Ronneberger et al. (25). U-Net has become a standard for biomedical image segmentation due to its encoder-decoder structure with skip connections, which allows the model to capture both local and global contextual information effectively. In medical imaging, DL models have been applied to a variety of tasks, including the detection and segmentation of tumors, organ delineation, and disease classification (24). These models have shown a high degree of accuracy and consistency, often matching or surpassing human expert performance. The application of DL in detecting and quantifying BAC is a natural extension of these capabilities, offering a means to automate the assessment process and potentially improve cardiovascular risk stratification (26, 27, 28).

The implementation of DL for BAC detection and quantification offers several benefits. Automation of BAC detection reduces the reliance on manual assessments by radiologists, which can be time-consuming and subject to inter-reader variability. Automated systems can provide consistent evaluations, reducing the subjectivity inherent in human assessments. Moreover, DL models can process large volumes of imaging data efficiently, facilitating the integration of BAC assessment into routine mammographic screenings without additional workload for radiologists. Despite these advantages, there are significant challenges to address. One of the primary challenges is the need for large, annotated datasets to train DL models effectively. Annotating medical images is a labor-intensive process that requires expert knowledge, making it difficult to compile sufficiently large datasets.

1.2.3 Current Research

Recent studies continue to underscore the importance of BAC as a significant cardiovascular risk enhancer. Iribarren et al. (29) conducted a comprehensive study involving 5059 postmenopausal women undergoing routine mammographic screenings to evaluate BAC as an independent predictor of CVD. BAC was quantified using a novel densitometry method,

estimating a continuous BAC mass score (in milligrams) from digital mammograms (30, 31). The study Iribarren et al found that 26% of the women had detectable BAC (>0 mg). The analysis revealed that the presence of BAC was significantly associated with an increased hazard of incident atherosclerotic cardiovascular disease (ASCVD) and global CVD events. Specifically, women with BAC had a 1.51-fold higher risk of developing ASCVD (95% CI, 1.08–2.11; p = 0.02) and a 1.23-fold higher risk of global CVD (95% CI, 1.002–1.52; p = 0.04) compared to women without BAC. The study's use of a continuous BAC mass score rather than a categorical grading system highlights the need for standardized BAC quantification methods, as the lack of standardization complicates the comparison of results across studies and hampers the development of universally applicable clinical guidelines.

In another recent study, Lee et al. (32) investigated the association between BAC and ASCVD within an Australian cohort consisting of 1020 women with a mean age of 60 years. BAC was assessed manually by radiologists and categorized based on the presence or absence of calcifications, without detailed quantification. The study found that 18% of the participants had detectable BAC. The univariate analysis demonstrated a significant association between BAC presence and ASCVD, with a hazard ratio (HR) of 1.96 (95% CI: 1.29–2.99). However, after adjusting for other risk factors such as age, diabetes and hypertension, the association was attenuated, resulting in an HR of 1.37 (95% CI: 0.88–2.14). This study reinforces the clinical value of BAC in cardiovascular risk stratification but also highlights the limitations of using a simple presence/absence approach without detailed quantification.

The differences in the results of these two studies highlight the importance of grading BAC severity and the impact of sample sizes on research outcomes. The lack of standardized grading methods for BAC quantification poses a significant challenge in achieving consistent and comparable results across studies.

1.3 Knowledge Gap

1.3.1 Lack of Standardized Methods for BAC Detection and Quantification

The assessment of BAC faces significant challenges due to the absence of standardized methods for its detection and quantification. Traditional imaging techniques, such as mammography, rely heavily on the subjective interpretation of radiologists, which can be both time-consuming and resource intensive. This reliance introduces considerable variability in BAC detection and grading, as interpretations can differ widely among radiologists based on their perceptual skills and experience. Consequently, the consistency of BAC assessments and their correlation with cardiovascular risk is significantly affected by differences in radiologists' training and expertise. Various grading systems, such as the 3-point, 4-point, and 12-point scales, have been proposed (6), each evaluating BAC based on factors like calcium density, the length of calcified vessels, and the number of affected vessels. However, there is no consensus on the most accurate and clinically relevant method for BAC quantification, leading to discrepancies in risk stratification and complicating the establishment of standardized criteria for BAC evaluation.

Efforts to develop more objective assessment tools have resulted in several automated methods aimed at enhancing BAC detection and quantification. For instance, Ge et al. (33) utilized a combination of image filtering techniques and k-segments clustering to detect BAC, though their method struggled with highly curved shapes. Similarly, Cheng et al. (34) employed a two-step method using a tracking algorithm and a linking algorithm, which achieved high sensitivity and specificity but faced challenges with varying breast compositions. Another approach by Molloi et al. (30) introduced a semi-automated method using full-field digital mammography to measure calcification area and density, providing a more consistent assessment. Despite its potential for reducing subjective bias, this method has not been widely adopted and remains

underexplored in diverse clinical settings due to its dependence on imaging quality and radiologist input.

To address these challenges, the development of standardized and automated systems for BAC detection and quantification is urgently needed. Advances in imaging technology and computer-aided detection systems could enhance the consistency and reproducibility of BAC evaluations by minimizing inter-observer variability. Establishing such standardized methods would facilitate more accurate risk stratification and improve the clinical application of BAC assessments.

1.3.2 Limitations in Deep Learning Models and the Need for Comprehensive Validation

DL has shown significant potential in automating image analysis tasks, including BAC detection and quantification. Studies have demonstrated that DL algorithms can achieve performance comparable to, or even surpassing, that of human experts (27, 28). However, these models face limitations that affect their generalizability and robustness. Most are trained on small, homogeneous datasets, which limits their applicability to diverse populations and various imaging conditions. This restriction can introduce biases, reducing the models' performance in real-world clinical settings (6).

Moreover, the validation of these models is often conducted in controlled environments using data from specific types of mammography machines. This narrow focus limits their application in diverse clinical settings with varying imaging technologies and patient demographics. Performance can vary significantly depending on the resolution and contrast of mammography images, posing challenges for consistent BAC assessments across different platforms (6). Enhancing the generalizability and robustness of DL models for BAC detection requires training on larger, more diverse datasets and validating them across various imaging platforms

and clinical environments. Techniques like transfer learning could improve model performance across different imaging conditions with minimal retraining.

1.3.3 Need for Enhanced Grading Systems Incorporating BAC Extent and Intensity

Current BAC grading systems are often overly simplistic, relying on binary classifications or basic categorical scales that fail to capture the nuanced risk associated with varying levels of BAC severity (6). These limitations reduce the effectiveness of BAC as a predictive tool for cardiovascular risk. To address this, a more comprehensive grading system is needed, one that accounts for both the extent and intensity of calcifications. Developing such sophisticated grading systems requires extensive research to establish detailed criteria that accurately reflects the relationship between BAC severity and cardiovascular risk. Advanced imaging techniques and algorithms capable of assessing BAC area and intensity with greater precision are crucial for creating these grading systems. Additionally, testing this new grading system on large cohorts is essential to determine if it provides added value and deeper insights into the association between BAC severity and both cardiovascular events and traditional risk factors. This comprehensive evaluation can help develop a framework that not only detects and grades the severity of BAC but also predicts cardiovascular risk more effectively. Moreover, these systems must be validated across diverse clinical settings to ensure their robustness and applicability to different patient populations and imaging platforms. Addressing these gaps will substantially improve the reliability, consistency, and clinical utility of BAC as a marker for cardiovascular disease risk. Continued research and innovation are essential to developing standardized, objective, and robust methods for BAC assessment, thereby enhancing its role in predicting and managing cardiovascular health in women.

1.4 Aims and Objectives of the Thesis

Aim

The primary aim of this thesis is to develop a novel deep learning framework capable of automatically detecting and grading breast arterial calcifications (BAC) on mammograms, thereby improving cardiovascular risk prediction for women. This model aims to enhance the utility of routine mammographic screenings by providing an additional assessment for cardiovascular health.

Objectives

1. Comprehensive Literature Review

The first objective is to systematically review existing research on the association between BAC and cardiovascular disease (CVD). This includes examining current methods for BAC detection and grading on mammograms, identifying key challenges, and highlighting inconsistencies in assessment approaches. A critical analysis of these limitations will provide the foundation for developing more advanced and standardized methods for BAC evaluation.

2. Development of a Semi-Supervised Deep Learning Model for BAC Segmentation

The second objective is to design and implement a semi-supervised deep learning model tailored for the segmentation of BAC on mammograms. This model will address limitations seen in current methodologies, such as reliance on small, homogeneous datasets and variability in imaging equipment. By training the model on diverse mammogram datasets from multiple sources, the goal is to enhance its robustness, generalizability, and clinical applicability.

3. Evaluation of BAC's Association with Traditional Cardiovascular Risk Factors

The third objective is to investigate the relationship between BAC and established cardiovascular risk factors, including age, hypertension, diabetes, and smoking. Unlike previous studies that primarily focused on BAC presence, this thesis will examine BAC severity within a larger and more diverse cohort. By doing so, it aims to provide a more comprehensive understanding of BAC's role in cardiovascular risk prediction.

4. Development and Validation of a Novel BAC Grading System

The final objective is to introduce a new grading system for BAC that integrates both the area and intensity of calcifications. This system aims to offer a more precise and clinically useful measure of BAC severity, going beyond conventional binary or categorical classifications. The effectiveness of this grading system will be rigorously validated in large-scale datasets to assess its potential for improving cardiovascular risk stratification.

1.5 Thesis Structure

To systematically address these objectives, the thesis is organized into six chapters, each building on the previous ones to provide a cohesive and comprehensive exploration of the topic.

1.5.1 Chapter One – Introduction:

1. Comprehensive Literature Review

This chapter provides a detailed overview of the thesis topic, outlining the rationale behind the study and the need for improved BAC detection and grading systems. It introduces the key

aims and objectives of the research and sets the stage for the subsequent chapters. The introduction establishes the context of cardiovascular disease in women and the potential role of BAC as a predictive marker for cardiovascular risk, highlighting the significance of integrating BAC assessment into routine mammographic screenings.

1.5.2 Chapter Two – Literature Review:

This chapter delves into existing research on BAC and cardiovascular risk, identifying gaps and opportunities for further study. It reviews the historical context of BAC detection and its clinical implications, emphasizing the challenges in current methods and the need for more sophisticated grading systems. Additionally, the chapter examines the application of DL in medical imaging, particularly focusing on its potential to enhance BAC assessment. The review provides a critical analysis of previous studies, setting the foundation for the development of the proposed model and grading system.

1.5.3 Chapter Three – Semi-supervised Deep Learning-based Model for Segmentation of the Breast Arterial Calcification on Mammograms:

This chapter presents the detailed development and validation process of the semi-supervised DL model for BAC segmentation. It covers the methodology in-depth, including data collection, preprocessing, model architecture, and training procedures. The chapter also evaluates the model's performance, comparing it with existing methods to highlight its advantages and improvements. The goal is to demonstrate the model's capability to accurately identify and quantify BAC across a wide range of mammographic images.

1.5.4 Chapter Four – Exploring the Association of BAC and Traditional Cardiovascular Risk Factors:

This chapter investigates the relationships between BAC and traditional cardiovascular risk factors such as age, hypertension, diabetes, and smoking. It provides a statistical analysis and

interpretation of the data, discussing the implications of these associations for risk stratification and prevention strategies. The chapter aims to confirm and clarify the role of BAC as a marker for cardiovascular risk by exploring its correlations with well-known risk factors in diverse populations.

1.5.5 Chapter Five – A Novel Deep Learning-based Grading System for Assessing Breast Arterial Calcification on Mammograms as an Independent Risk Factor for Predicting Adverse Cardiovascular Events:

This chapter introduces the new BAC grading system developed in the thesis. It explains the criteria for grading based on both the extent and intensity of calcification, providing a detailed framework for assessing BAC severity. The chapter demonstrates the grading system's predictive power for cardiovascular risk assessment through rigorous testing and validation among large cohorts of women. The results are expected to show how this advanced system enhances the prediction of cardiovascular events compared to traditional methods.

1.5.6 Chapter Six – Discussion and Conclusion:

The final chapter summarizes the key findings of the study, providing a comprehensive discussion of the results and their implications. It addresses the limitations of the research and suggests potential areas for future work. The chapter also outlines the practical implications of the findings for clinical practice and public health, emphasizing how the new BAC detection and grading systems can enhance cardiovascular risk prediction and management in women.

The Vancouver referencing style is used consistently throughout the thesis, except for Chapters 2 to 5, which include papers that are published or submitted (and under review). These papers appear exactly as they do (or will) in their online versions. Each main chapter begins with a 'Chapter Introduction' that links it to the previous chapter and outlines upcoming content. Publication details follow each 'Chapter Introduction.

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Chapter 2 Literature Review

2.1 Chapter 2 Introduction

This chapter builds on the findings of the published work: Ibrahim MA, Suleiman MA, Gandomkar Z, Tavakoli Taba A, Arnott C, Jorm L, Barraclough JY, Barbieri S, Brennan PC. Associations of Breast Arterial Calcifications with Cardiovascular Disease. Journal of Women's Health. 2023 May 1;32(5):529-45.

The chapter begins by examining the prevalence, detection, and physiological significance of BAC as identified through mammographic imaging. It explores the association of BAC with systemic cardiovascular conditions and evaluates its utility as a diagnostic marker in various clinical contexts. The limitations of existing studies, including variability in BAC detection methods and population diversity, are also highlighted, offering a critical lens for future research.

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Associations of Breast Arterial Calcifications with Cardiovascular Disease

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Abstract

Cardiovascular diseases (CVD), including coronary artery disease (CAD), continue to be the leading cause of global mortality among women. While traditional CVD/CAD prevention tools play a significant role in reducing morbidity and mortality among both men and women, current tools for preventing CVD/CAD rely on traditional risk factor-based algorithms that often underestimate CVD/CAD risk in women compared with men. In recent years, some studies have suggested that breast arterial calcifications (BAC), which are benign calcifications seen in mammograms, may be linked to CVD/CAD. Considering that millions of women older than 40 years undergo annual screening mammography for breast cancer as a regular activity, innovative risk prediction factors for CVD/CAD involving mammographic data could offer a gender-specific and convenient solution. Such factors that may be independent of, or complementary to, current risk models without extra cost or radiation exposure are worthy of detailed investigation. This review aims to discuss relevant studies examining the association between BAC and CVD/CAD and highlights some of the issues related to previous studies' design such as sample size, population types, method of assessing BAC and CVD/CAD, definition of cardiovascular events, and other confounding factors. The work may also offer insights for future CVD risk prediction research directions using routine mammograms and radiomic features other than BAC such as breast density and macrocalcifications.

Keywords: cardiovascular disease, coronary artery disease, breast artery calcifications, mammograms, women

Background

Cardiovascular disease (CVD), including coronary artery disease (CAD), continues to be the leading cause of global mortality in both men and women, with women at a greater risk of stroke than men.[1] Based on recent statistics from the United States, cardiovascular mortality has recently increased by 1% annually in women aged £55 years, and globally, about 20% of ischemic heart disease events in women occur in the absence of the traditional cardiovascular risk factor.[2,3] Suboptimal prevention of CVD in women, due to many factors including underdiagnosis, undertreatment, system bias, and poorly identified gender-specific risk factors, is of great concern,[4–6] particularly since women often present later with symptoms of CVD/CAD compared with men. CVD/CAD symptoms in women are often ''atypical'' unclear or nonspecific compared with traditional symptoms in men.[7]

To identify those at high risk of CVD, current techniques rely on risk factor-based algorithms; however, these algorithms perform poorly in women and often underestimate CVD/CAD risk in women.[8] Furthermore, women are less likely than men to have CVD screening or seek help from a general practitioner, while it has been demonstrated, medical practitioners may be less inclined to screen women for CVD compared with men.[7] Hence, additional approaches beyond

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the traditional medical practitioner led risk factor-based algorithms are required to engage women in cardiovascular (CV) screening and identify women who might be at risk of CVD and most likely to benefit from preventative medical therapy and close monitoring. It is clear that a novel and gender-specific risk assessment strategy is required.

In 1995, Moshyedi et al.[9] demonstrated an association between breast arterial calcification (BAC) and CVD/CAD risk factors in women younger than 59 years. Since then, several studies have explored this association, and the majority have confirmed a positive relationship between BAC and CVD/CAD.[10–26] These studies, however, had limitations relating to sample size, biased populations, CVD events definitions, unknown confounding variables, and variation of the methods used for identifying and quantifying BAC on mammograms. In this review, we focus on some of these limitations in using BAC to determine the risk of CV events and offer insights for future research directions on CV risk prediction using routine mammograms and other radiomic features.

What is BAC?

BAC is a form of medial arterial calcification (MAC), known as Mo¨nckeberg sclerosis, affecting the entire circumference of the mammary vessel and decreasing arterial compliance.[27,28] It can be referred to as peripheral arterial arteriosclerosis, which occurs due to the loss of elasticity of the arteries making them hardened and thick.[29,30] MAC, or Mo¨nckeberg sclerosis,[31] refers to vascular calcification of the medial layer of the vascular wall and mostly affects peripheral arteries with an inclination to be observed in muscular arteries causing loss of elasticity.[32–34] MAC reflects a process of active calcification resembling bone formation and is often associated with aging, diabetes, and end-stage kidney disease.[35]

BAC commonly occurs in small to medium size muscular arteries, including small arterioles;[4,27,36] however, O'Neill and Adams[36] suggested no relationship between artery size and its susceptibility to calcification. Given the small sample size of 19 patients in the study,[36] further data are required to understand the relationship between artery size and the presence of BAC and a potential association should not at this stage be ruled out. Specifically, future studies focusing on the influence of vessel size, type, and other anatomical factors on susceptibility to calcification are needed.[37]

BAC can be detected on a mammogram by the presence of parallel lines or tubular tracks;[38,39] however, its identification is still a challenging task for various reasons including differences in size and shape of the lesion, as well as varying contrast of images.[38,40] Also, the nonuniformity in the calcium density within arteries results in topological complexity of BAC lines.[2,41] As illustrated in Figure 1, BAC can exhibit as disconnected, strongly connected, thin, or overlapping lines.[40] Furthermore, BAC is not always clearly visible, resulting in a breast with normal appearances.[41]

Prevalence of BAC

The prevalence of BAC in mammography is inconsistent and depends on the study population. Pooled analysis of data from 18 studies conducted in a general population yielded a prevalence estimate of 12.7% (95% confidence interval [CI] 10.4%–15.1%).[42] Among different predictors, age is the most explored factor. Reddy et al.[43] conducted a cross-sectional study of 1,905 females with a mean age of 57.6 years: the participants were divided into five age groups, 35–44, 45–54, 55–64, 65–74, and 75–90 years, and the prevalence of BAC among these age groups was shown to be 3.9%, 15.1%, 31.8%, 55.7%, and 54.4%, respectively. According to a meta-

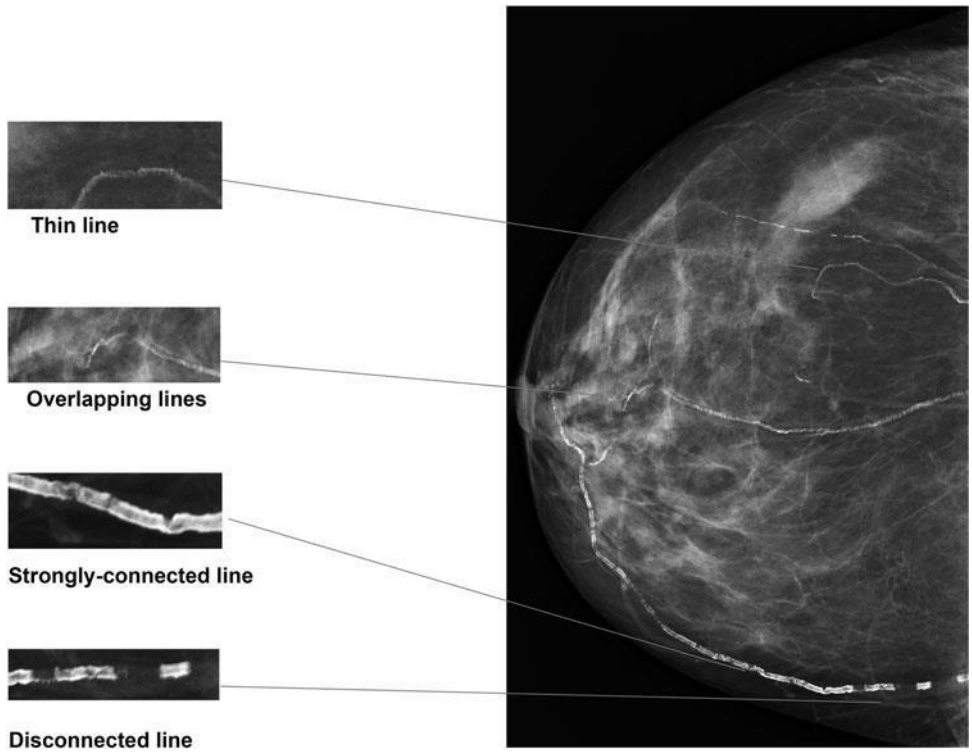

FIG. 1. Examples of different appearances of BACs. BAC, breast arterial calcification.

analysis of 10 studies,[42] age is a significant determinant with an odds ratio (OR) of 2.98 (95% CI 2.31–3.85) for every 10 year increase.[42]

Reproductive and hormonal factors also affect the prevalence of BAC. A meta-analysis of seven studies found that parous women had an OR of 3.43 for the presence of BAC compared with nonparous women.[42] Moreover, number of children and breastfeeding have found to be positively associated with the presence of BAC.[42] BAC is more common after menopause and less frequent in women receiving hormone replacement therapy.[44] Race is also another important risk with BAC prevalence reported highest among Hispanics (35%), followed by African Americans (25%), Caucasians (24%), and finally Asians (7%).[43]

Association Between BAC and CVD

BAC is generally considered a benign finding in mammograms. It has been known to radiologists for a long time; however, little clinical significance was linked to it until 1980 when researchers discovered an association between the presence of BAC and diabetes mellitus.[45] Since that time, multiple studies have been conducted to evaluate the association between BAC and other diseases such as CVD or CAD. Iribarren et al.[46] conducted a study on 5,059 postmenopausal women (with no symptoms of CVD/CAD) aged between 60 and 79 years who underwent breast screening from October 2012 to February 2015.

BAC was present in 26% of these women. To investigate the relationship between BAC and atherosclerotic cardiovascular disease (ASCVD) and global CVD, the authors performed a follow-up after 6.5 years and found that the presence of BAC was strongly associated with ASCVD and global CVD with increased hazard ratios (HRs) of 1.51 (95% CI 1.08–2.11; $p = 0.02$) and 1.23 (95% CI 1.002–1.52; $p = 0.04$), respectively. One major issue of this study is that its findings may not be generalizable to women younger than 60 years.

To date, most studies have confirmed a positive relationship between BAC and CVD/CAD;[10–26] however, one should acknowledge that a sma$_4$ll$_7$ n$_4$u$_9$mber of other studies have failed to show a relationship. The studies included in this review article is summarized in Table 1. In this section, we briefly review the studies investigating the association between BAC and (1) coronary artery calcium (CAC)/subclinical CAD, (2) peripheral arterial disease, (3) stroke, and (4) cardiovascular mortality. Differences in the conclusions from these studies may be related to study design, the number of participants, age of participants, methods of assessing BAC, and detecting CVD. Some of the key issues regarding these studies are discussed below.

BAC and CAC/subclinical CAD

Although the etiology of coronary arterial calcification is predominantly intimal which differs from BAC, that strictly involves medial calcification,[50] several studies have suggested that there is a correlation between the presence of BAC and CAC scoring.[24,50–55] CAC scoring is considered one of the most promising methods for identifying the risk of experiencing a CAD event; however, the high cost and radiation exposure associated with the use of computed tomography (CT) to establish CAC scores are two major disadvantages preventing CAC scoring from being implemented on a wide scale.[4] Interestingly, however, millions of women undertake breast screening mammograms every year across the world while some of these also undergo CAC scoring for CAD screening. This provides an excellent opportunity to explore potential associations between BAC and CAC that could enable a sex-specific method for predicting the risk of CAD in asymptomatic women with low cost and no extra radiation exposure.[56]

To date, the potential association between BAC and CAC has been confirmed: Maas et al.[50] conducted a prospective study among 499 women with follow-up period between 6 and 11 years and found a positive relationship between the presence of BAC and the development of CAC >0 with an adjusted OR of 2.0 (95% CI 1.03–3.86); Chadashvili et al.[52] conducted a small retrospective study of 145 women and used CAC score >11 as the measurement outcome of CAD and found an adjusted OR of 4.53 (95% CI 2.04–10.08) for patients with BAC; Newallo et al.[53] investigated the relationship between BAC and CAC score >100 among 204 African American women and showed a significant association with an OR of 7.66 (95% CI 2.75–21.29); Matsumura et al.[55] used CAC score >400 as assessment outcome in their cross-sectional study among 202 women and found a strong link between CAC and BAC with an OR of 22.6 (95% CI 2.1–237.1).

It is important to note that these previous studies simply focused upon the presence or absence of BAC but not the severity of BAC. When semiquantitative techniques were used to measure the extent of BAC in, for example, 2,100 asymptomatic women, a positive relationship between the severity of BAC with CAC score >0 was found with an OR of 2.87 (95% CI 1.67–4.93).[24] Margolies et al.[54] conducted a retrospective study of 292 women using semiquantitative methods and showed a positive relationship between BAC and CAC score >0 with an adjusted OR of 3.2 (95% CI 1.8–5.9). It is important to acknowledge another study[57] that found no significant association between BAC severity and CAC score; however, this study only included a small number of symptomatic women ($n = 150$).

Coronary Artery Disease-Reporting and Data System (CAD-RADS) is another approach to reporting CT angiography and serves as clinical management guidelines of CAD.[58] It has grading systems ranging from 0 to N, where a CAD-RADS score from 0 to 2 indicates no CAD, and a CAD-RADS score ‡3 indicates CAD.[58,59] Kelly et al.[59] conducted a study to evaluate the association between the presence and severity of BAC with CAD-RADS ‡3 on 104 women who reported chest pain (aged between 50 and 65 years) and underwent both a coronary CT angiography (CCTA) and a breast screening.

The study concluded that the presence and severity of BAC linked with CAD-RADS ‡3 in asymptomatic women. To evaluate if the previous study's findings can be generalized to the broader screening mammograph population, Huang et al.[60] performed a study on 213 asymptomatic women aged between 40 and 85 years to investigate the relationship between BAC and CAD-RADS based on deep learning (DL)-CT angiography. In their multivariate analysis, they found that the presence of BAC is significantly associated with CAD-RADS ‡3 with an OR of 10.22 (95% CI 2.86–36.49, $p < 0.001$).

BAC and peripheral arterial disease

Peripheral arterial disease (PAD) is a progressive and debilitating form of CVD, which is often only diagnosed when a

Table 1. Summary of Studies Investigating the Association Between Breast Arterial Calcification with Cardiovascular Diseases/Coronary Artery Disease and Other Diseases

Author (year)	*Study design (sample size)*	*Age (mean), years*	*Outcome*	*Outcome measurement method*	*BAC% (assessment method)*	*Main results*
Baum (1980)[45]	CS (319)	—	DM	Medical records	11.6 (P/A)	BAC was associated with DM
Sickles (1985)[111]	CS (500)	—	DM	Self-reported Medical records	9.6 (P/A, grading)	A weak association between BAC and DM
Moshyedi (1995)[9]	CS (182)	39–92 (64)	CAD	Angiogram (stenosis ‡50%)	33.5 (P/A)	BAC was associated with CAD in diabetic women younger than 59 years
van Noord (1996)[69]	CS (12,239)	50–69 (58)	MI, TIA/stroke, CV risk factors	Self-reported	9.1 (P/A)	BAC was associated with MI, TIA/stroke, CV risk factors
Kemmeren (1998)[70]	Retrospective (12,239)	50–68	CV mortality	Laboratory tests Medical records	9 (P/A)	BAC was associated with the risk of CV mortality, especially in diabetics women
Crystal (2000)[10]	CS (865)	(65 – 8) BAC+ (54 – 9) BAC-	Prevalence of ASCVD, CV risk factors	Self-reported	17.6 (P/A)	BAC was associated with and ASCVD and CV risk factors and inversely with smoking
Pecchi (2003)[51]	CS (74)	>65	Coronary calcium, hypertension, DM	MSCT Medical records	59.5 (P/A, grading)	BAC is strongly associated with coronary calcium
Iribarren (2004)[66]	Cohort (12,761)	40–79	CAD, ischemic stroke, TIA, heart failure, hemorrhagic stroke	Medical records Self-reported	3.3 (P/A)	BAC was strongly associated with CAD, ischemic stroke, and heart failure but not strongly with TIA and hemorrhagic stroke
Henkin (2003)[49]	Retrospective (319)	50–70	Incident CAD, CAD risk factors	Angiogram Medical records	41 (P/A)	BAC was associated with CAD risk factors but not with angiographically CAD
Markopoulos (2004)[65]	Prospective (420)	41–75	Systemic vascular disease	Medical records Ultrasound	11 (P/A)	BAC was significantly associated with systemic vascular disease
Cetin (2004)[11]	CS (2,400)	32–75	Prevalent of hypertension	Self-reported Medical records	9.1 (P/A)	BAC was associated with hypertension
Maas (2004)[113]	CS (600)	(70 – 6) BAC+ (67 – 6) BAC-	Prevalence of CV risk factors	Medical records	23 (P/A, grading)	BAC associated with CV risk factors and with the number of given births
Maas (2006)[114]	CS (1,699)	49–70	Prevalence of various CV risk factors, pregnancy/lactation	Self-reported	11.4 (P/A)	BAC was associated with pregnancy and lactation but not with CV risk factors
Dale (2006)[63]	Retrospective (121)	40–97 (72)	Prevalence of various PAD	Medical records	19 (P/A)	BAC was associated with an increased prevalence of PAD
Taxskin (2006)[12]	CC(BAC) (985)	>40	Various CV risk factors	Medical records	7.9 (P/A)	BAC was associated with CV risk factors, especially in premenopausal women
Kataoka (2006)[113]	CS (1,590)	>55	Prevalent CAD	Self-reported	16 (P/A)	BAC was associated with CAD but not with stroke in postmenopausal women

(*continued*)

Table 1. (Continued)

Author (year)	*Study design (sample size)*	*Age (mean), years*	*Outcome*	*Outcome measurement method*	*BAC% (assessment method)*	*Main results*
Topal (2007)[14]	CS (123)	40–77 (56.8 – 9.5)	Incident CAD	Angiogram (>50% stenosis)	39.8 (P/A, grading)	BAC was associated with severe CAD
Maas (2007)[50]	Prospective (499)	49–70	CAC >0, CV risk factors, pregnancy/lactation	CT cardiac Medical records	12 (P/A)	BAC was associated with CAC, pregnancy, and lactation but not with CV risk factors
Fiuza Ferreira (2007)[15]	CS (131)	(61.1)	Incident CAD	Angiogram (any % stenosis)	39.7 (P/A, grading)	BAC was strongly associated with CAD
Dale (2008)[17]	CS (1,000)	23–93	Prevalence of CAD and DM	Self-reported	16.1 (P/A)	BAC was significantly associated with CAD and DM
Dale (2008)[16]	CS (819)	23–93	Prevalence of CAD	Angiogram Self-reported	10.5 (P/A)	BAC was significantly associated with CAD in women with no history of CAD
Yildiz (2008)[82]	CC(BAC) (54)	(60 – 6) BAC+ (63 – 7) BAC-	C-IMT value	Ultrasonographic	10.2 (P/A)	BAC was strongly associated with C-IMT
Rotter (2008)[68]	CS (1,919)	25–96.7 (56 – 12.7)	Prevalence of ASCVD	Self-reported	14 (P/A)	BAC was associated with CV risk factors and CV morbidity
Pidal (2009)[115]	CC(BAC) (136)	45–65 (57) BAC+ (55) BAC-	Prevalence of CV risk factors	Self-reported Laboratory tests	8.36 (P/A, grading)	The presence of BAC was significantly associated with clinical and biochemical factors associated with CV risk
Oliveira (2009)[18]	CC(CAD) (80)	(64.65) case (63.88) control	Incident CAD, CV risk factors	Angiogram (any % stenosis) Medical records	79 (grading)	BAC was associated with an incident of CAD, hypertension, and a family history of CAD but not with DM and smoking
Ferreira (2009)[19]	CS (307)	(55.2 + 6.8)	Prevalence of CVD	Self-reported Medical records	6.8 (P/A)	BAC was associated with the prevalence of CVD
Sarrafzadegann (2009)[116]	CS (84)	<55	Prevalence of CAD, CV risk factors, and C-IMT	Angiogram Echocardiography Ultrasound Self-reported	7.1 (P/A)	No significant association between the presence of BAC and CAD, CV risk factors, and C-IMT
Dale (2010)[117]	CC(DM) (1,609)	24–93	DM	Self-reported Medical records	36.5 (P/A)	BAC was significantly associated with DB
Penugonda (2010)[47]	CS (94)	(66.7)	Incident CAD, CV risk factors, acute CV events, MI	Angiogram Medical records	60.6 (P/A)	No association between BAC and CV risk factors, CAD, or acute CV events
Zgheib (2010)[48]	CC(CAD) (172)	64.3	Incident CAD	Angiogram	33.1 (P/A, grading)	No correlation between BAC and CAD
Schnatz (2011)[67]	Prospective (1,454)	(56.3 – 12.1)	Incident CAD and stroke	Self-reported	16.3 (P/A)	BAC was associated with CAD and stroke incidents

(*continued*)

Table 1. (Continued)

Author (year)	*Study design (sample size)*	*Age (mean), years*	*Outcome*	*Outcome measurement method*	*BAC% (assessment method)*	*Main results*
Akinola (2011)[118]	CS (54)	(60 – 10) BAC+ (51 – 7) BAC-	Prevalence of CV risk factors	Self-reported Laboratory tests	20 (P/A)	No association between BAC and CV risk factors
Sedighi (2011)[20]	CC(BAC) (204)	46–75	History of CAD, CV risk factors C-IMT	Self-reported Carotid ultrasound	14.7 (P/A)	BAC was associated with C-IMT, CAD, and hypertension but not with DM and HL
Duhn (2011)[28]	CC(ESKD) (142)	32–85	Prevalence of PAC, ESKD, CKD	Medical records	40 P/A	BAC was associated with MAC, ESKD, and advanced CKD
Hekimog˘lu (2012)[21]	CS (55)	(63)	Prevalence of CAD and CV risk factors	Angiogram (stenosis ‡50%)	41.8 (P/A)	BAC was strongly associated with CAD and CV risk factors
Zafar (2013)[119]	CS (200)	18–79 (57 – 13) BAC+ (44 – 11) BAC-	Prevalence of hypertension, pregnancy, lactation, weight	Self-reported Medical records Laboratory tests	13.5 (P/A)	BAC was associated with hypertension, pregnancy, and lactation but not with women's weight
Bae (2013)[103]	CC(BAC) (202)	41–78 (58.9)	10-Year CAD risk, MS	Medical records Laboratory tests	N/A (P/A, grading)	The presence and severity of BAC were associated with MS and risk of CAD
Matsumura (2013)[55]	CC(BAC) 202)	(60) BAC+ (58) BAC-	CAC >400	MSCT	48.5 (P/A)	A strong association between the presence of BAC and CAC score
Moradi (2014)[57]	CS (150)	(68 – 6) BAC+ (54 – 8) BAC-	CAC >0	CTCA	23 (grading)	The presence and severity of BAC have no significant correlation with CAC
Nasser (2014)[99]	CS (211)	(62.1)	Prevalence of BMD	Dual-energy X-ray absorptiometry	18 (P/A)	No correlation between the presence of BAC and BMD
Yildiz (2014)[119]	CS (310)	40–73 (55.9 – 8.4)	Prevalence of MS, hypertension	Medical records Self-reported	39.9 (P/A)	BAC was associated with MS and hypertension
Yag˘tu (2015)[120]	CC(BAC) (80)	39–86	Prevalence of carotid plaque	Doppler ultrasonography	N/A (grading)	BAC was correlated with an increased prevalence of carotid plaque
Karm (2015)[23]	CS (198)	(65)	Incident CAD and CV risk factors	Angiogram Medical records	41.4 (P/A)	BAC was associated with CAD and CV risk factors and inversely associated with smoking
Abou-Hassan (2015)[64]	Cohort (202)	(62 – 11) BAC+ (53 – 12) BAC-	Prevalence and new incidence of PAD	Laboratory tests Medical records	58.4 (P/A)	BAC was strongly associated with PAD and new incidence of PAD in ESRD women
Mostafavi (2015)[78]	CS (100)	(65.3)	Incident CAD	CTCA	12 (grading)	The presence of BAC was associated with CAD
Newallo (2015)[53]	Retrospective (204)	46–59 (52.5)	CAC >100 (Incident CAD)	CT cardiac CTCA	20.6 (grading)	BAC was associated with increased CAC, atherosclerosis, and CAD

(*continued*)

Table 1. (Continued)

Author (year)	*Study design (sample size)*	*Age (mean), years*	*Outcome*	*Outcome measurement method*	*BAC% (assessment method)*	*Main results*
Chadashvili (2016)[52]	Retrospective (145)	(56) BAC+ (61) BAC-	CAC >11 CAD risk factors	CT cardiac Medical records	25.5 (P/A)	BAC was significantly associated with CAC and not significant with HL, hypertension, smoking, CAD, and a family history of CAD
Margolies (2016)[54]	Retrospective (292)	(61.5 – 10.8)	CAC >0 CV risk factors	CT cardiac Medical records	42.5 (grading)	BAC was associated with CAC, equivalent to FRS and PCE, for identifying CV risk factors
Fathala (2017)[79]	Retrospective (435)	(58)	MI	MPS	59 (P/A, grading)	No association between the presence/severity of BAC and MI on stress MPS
Ronzani (2017)[121]	CS (312)	(55.9)	Hypertension, CKD, DM glomerular filtration rate	Self-reported Medical records	23 (P/A)	BAC was correlated with hypertension, DM, CKD, and low glomerular filtration rate
Ruzˇicˇicˊ (2018)[84]	CS (102)	(62)	Prevalence of CAD	Angiography Medical records	63.7 (grading)	BAC quantification was associated with the prevalence of CAD
Hendriks (2017)[71]	Cohort (163)	(56.6 – 11.1)	CV and all-cause mortality	Medical records	3.7 (P/A)	The presence of BAC on CT was associated with CV and all-cause mortality
Kelly (2018)[59]	Retrospective (104)	(58.93)	CAD-RADs ‡3	CTCA	14 (grading)	BAC was associated CAD-RADs score ‡3 and increased future CVD/CAD incidents
Hanafi (2018)[83]	CC(CAD) (60)	(52)	Prevalence of CAD	CTCA	60 (P/A, grading)	The presence and severity of BAC were associated with CAD
Fathala (2018)[86]	Retrospective (307)	49–70	CAC score, CAD risk factors	CT Medical records	46.3 Grading	BAC was strongly correlated with CAC and CAD risk factors, including CKD
Iribarren (2018)[62]	CS (3,800)	60–79	Incident PAD	ABI test	28.1 (P/A grading)	BAC was associated with PAD
Soylu (2019)[85]	CS (404)	(67 – 9) BAC+ (54 – 9) BAC-	Aortic calcification, CAC	Thoracic CT	30.4 (P/A, grading)	The presence and severity of BAC were associated with aortic calcification and CAC
Yoon (2019)[24]	CS (2,100)	(52 – 7)	CAC >0, CAP, risk of ASCVD	CTCA Medical records	9.5 (Grading)	BAC was associated with the presence of PAD, CAC >0, and risk of ASCVD
McLenachan (2019)[25]	CS (405)	(59 – 8)	CV risk factors, CAC, CAD	CTCA Medical records	23 (Grading)	BAC was associated with CAC and CV risk factors, but the diagnostic accuracy of BAC to identify CAD or obstructive CAD is poor

(*continued*)

Table 1. (Continued)

Author (year)	*Study design (sample size)*	*Age (mean), years*	*Outcome*	*Outcome measurement method*	*BAC% (assessment method)*	*Main results*
Sankaran (2019)[122]	CC(BAC) (100)	(59) BAC+ (51) BAC-	C-IMT	Ultrasound	N/A (grading)	BAC was associated with C-IMT
Huang (2020)[60]	CS (213)	(58 – 8.6)	CAD-RADS ‡3 CV risk factors	CTCA Medical records	10.3 (P/A)	BAC was correlated with CAD-RADS ‡3 and CV risk factors
Iribarren (2020)[98]	CS (1,273)	60–79 (67)	BMD	Dual-energy X-ray absorptiometry	29.8 (P/A grading)	No association between the presence and severity of BAC and low BMD
Seifi (2020)[26]	CS (60)	(49.52 – 8.83)	CAC	CTCA (various calcium scores)	83.3 (Grading)	The presence and severity of BAC were associated with CAD
Iribarren (2021)[101]	CS (3,913)	60–79 (67 – 5) BAC+ (65 – 4) BAC-	Cognitive impairment, dementia	Cognitive tests Medical records Self-reported	28.2 (P/A, grading)	No association between the presence or grading of BAC and cognitive impairment or development of all-cause dementia
Shobeiri (2021)[80]	CS (400)	(59 – 8) BAC+ (55 – 7) BAC-	Prevalence of MI, CV risk factors, history of CVD	Echocardiography Self-reported	15.2 (P/A)	BAC was associated with the prevalence of MI, CV risk factors, and a history of CVD
Iribarren (2022)[46]	Prospective (5,059)	60–79	Incident ASCVD and global CVD	Medical records Self-reported	26.5 (P/A, grading)	BAC was associated with incident ASCVD and global CVD

ASCVD, atherosclerotic cardiovascular disease; BAC, breast arterial calcification; BMD, bone mineral density; CAC, coronary artery calcium; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease-Reporting and Data System; CC, case–control; CCAP, calcified carotid artery plaque; C-IMT, carotid intima-media thickness; CKD, chronic kidney disease; CS, cross-sectional, CTCA, computed tomography coronary angiography; CV, cardiovascular; CVD, cardiovascular diseases; DM, diabetes mellitus; ESRD, end-stage renal disease; FRS, Framingham Risk Score; HL, hyperlipidemia; HRT, hormone replacement therapy; MI, myocardial ischemia; MPS, myocardial perfusion scan; MS, metabolic syndrome; MSCT, multislice computed tomography; N/A, not applicable; OCA, oral contraceptive agent; P/A, presence/absence; PAC, peripheral arterial calcification; PAD, peripheral arterial disease; PCE, the 2013 Cholesterol Guidelines Pooled Cohort Equations.

patient becomes symptomatic, resulting in underestimation of disease burden and delays in early intervention.[61] Iribarne et al.[62] conducted an extensive study (n = 3,800) of menopausal women aged between 60 and 79 years to assess the association between BAC and PAD. They use the ankle–brachial index (ABI) as a measuring metric of PAD. An ABI <0.9 is considered a low ABI and indicates the presence of PAD, an ABI between ‡0.9 and <1.3 is normal and no PAD, and an ABI ‡1.3 is a high ABI and indicates stiff arteries. Their result showed that the presence of BAC is significantly associated with ABI <0.9 with an adjusted OR of 1.36 (95% CI 0.99–1.85; p = 0.05). Also, they found no correlation between the presence and severity of BAC with ABI ‡1.3. The main drawback of this study is that the findings may not generalize to younger women.

Furthermore, three more studies with smaller populations focusing on populations greater than 100 women have shown a clear association between BAC and PAD, where BAC can be used as a marker of peripheral arterial disease: Dale et al.[63] conducted a study on 121 women who underwent both mammography and have history of PAD, retrieved from their medical records, and found a significant relationship between the presence BAC and PAD with an OR of 3.09 (95% CI 2.1–4.7); Abou-Hassan et al.[64] conducted a study on 202 women with end-stage renal disease (ESRD) and identified a strong correlation between BAC and PAD with an OR of 4.56 (95% CI 1.20–17.3); Markopoulos et al.[65] in 110 women also identified a strong relationship between BAC and PAD (femoral and carotid disease). These works suggest that BAC may reflect an individual's risk of MAC; however, given the paucity of studies, small sample sizes,[63–65] and heterogeneous study populations, there may be confounders. Therefore, a large prospective study is needed to confirm the association of BAC with systemic arteriosclerosis or peripheral arterial disease.

BAC and stroke

Several studies have shown that the presence of BAC is a marker of the incidence and prevalence of stroke.[10,13,50,66–69] While most of these studies looked at stroke as part of the definition of CVD/CAD or as a secondary outcome,[27] only one cohort study[66] focused specifically on the association between BAC and stroke. Iribarren et al.[66] studied a population of 12,761 women all of whom had attended multiphasic health checkups and screening mammography. Such multiphasic checkups gather comprehensive medical and laboratory tests results as well as patient histories, all of which are used to assess a variety of outcomes, including ischemic stroke, hemorrhagic stroke, and transient ischemic attack (among other CVD-related outcomes).

All these patient data were extracted from the beginning of 1971 until the end of 2000 with a median follow-up period of 24.8 years. The authors found a positive relationship between BAC and ischemic stroke, hemorrhagic stroke, and transient ischemic attack with an age-adjusted HR of 1.41 (95% CI 1.1–1.8), 1.43 (95% CI 0.79–2.60), and 1.44 (95% CI 0.77–2.70), respectively. Iribarren et al.[46] investigated the association between BAC and global CVD in 5,035 postmenopausal women. They included ischemic stroke and hemorrhagic stroke as part of the definition of global CVD. The authors found that the prevalence of ischemic stroke and hemorrhagic stroke is higher among women with BAC compared with those without and statically significant with a p value of 0.048.

Schnatz et al.[67] studied 1,454 individuals, where the relationship between the BAC and stroke was reported as a secondary outcome. The authors used a self-reported survey to understand patient history, including self-reported personal history of CAD, and concluded that BAC was a significant indicator of increased risk of CAD and stroke. However, the study did not specify differences between ischemic and hemorrhagic strokes. The relationship between BAC and stroke has been confirmed in other cross-sectional studies[10,13,68,69] involving self-reporting of stroke: Kataoka et al.[13] and van Noord et al.[69] reported adjusted ORs for stroke of 2.02 (95% CI 0.61–6.69) and 1.4 (95% CI 1.1–1.9), respectively, for patients with BAC; Crystal et al.[10] and Rotter et al.[68] showed a significant relationship between BAC and stroke with crude ORs of 4.9 and 4.4, respectively; Shah et al.[27] in their meta-analysis involving 7 investigations studied 30,673 participants and found that 5 of these studies reported a statistically strong association between BAC and stroke concluding that BAC could serve as a predictor of stroke.

BAC and cardiovascular mortality

Kemmeren et al.[70] investigated the relationship between BAC and CVD mortality in a population of 12,084 women aged 50–68 years who underwent breast screening mammography and were followed up for a period of 16–19 years. The authors found that BAC was associated with CVD and CAD mortality with HRs of 1.22 and 1.36, respectively. In addition, the study showed that diabetic women with BAC have a higher risk of CVD and CAD mortality compared with those individuals with BAC but nondiabetic with HRs of 1.71 and 1.76, respectively. The association between BAC and CVD mortality was also investigated in the study of Iribarren et al.,[46] which showed a strong association between BAC and the prevalence of CVD mortality among postmenopausal women.

Hendriks et al.[71] conducted a study on 163 women who underwent CT scans to investigate the associations of BAC, splenic, and internal and external iliac arteries with CVD-related and non-CVD-related mortality; however, the number of women who had BAC in this study was very small (n = 6). The authors found a strong association between BAC on CT and CVD mortality and total mortality with age-adjusted HRs of 12.30 (95% CI 2.84–53.37) and 4.67 (95% CI 1.57–13.88), respectively.[71]

Literature focusing on the relationship between BAC and CVD/CAD mortality is scarce; however, several studies suggested that calcification of arteries from different parts of the body such as the pelvis, thigh, and spleen can increase the risk of CVD mortality.[34,72–74] MAC in the pelvis and thigh in ESRD patients was found to be a strong independent predictor of cardiovascular mortality.[34] Furthermore, MAC in femoral arteries among diabetic patients was also found to have a strong association with mortality from CVD and CAD.[75] These results are understandable as MAC causes reduced elasticity in the arteries, increasing systolic blood pressure and reducing diastolic blood pressure, which in turn may lead to increased cardiac afterload, hypertrophy, and increased risk of myocardial infarction and heart failure.[72,74]

Methodological Heterogeneity

Limited sample size

Although many studies have demonstrated an association between BAC and CVD/CAD, there are a few studies that have reported no relationship between BAC and CVD/CAD. For example, two studies conducted by Penugonda et al.[47] and Zgheib et al.[48] investigated the relationship between BAC and CVD/CAD and reported that BAC is not associated with CVD/CAD. However, the sample sizes were very small in both studies with only 94 in Penugonda et al.[47] and 104 in Zgheib et al.[48] Furthermore, Moradi et al.[57] studied the association between BAC and CAC scores and the severity of coronary artery stenosis and found no association. Again, the number of participants in this study was relatively small, with only 150 participants. These conflicting results around the association between BAC and CVD/CAD have highlighted the need for a larger sample size or robust systematic reviews to increase study power and thus give a better understanding of the association between BAC and CVD/CAD.

Since 2014, five systematic reviews and meta-analyses have been performed, providing insight into the correlation between BAC and CVD/CAD.[4,8,27,76,77] Lee et al.[8] included 31 studies (n = 35,583) in their meta-analysis defining CAD as any CV events that were reported by participants, retrieved from medical records, or obtained through direct diagnostic procedures, such as coronary angiography, myocardial perfusion scan, and CT. Their results suggested a strong association between BAC and CAD with a pooled OR of 2.61 (95% CI 2.12–3.21).[8] Mohammed et al.[76] included 18 studies in their meta-analysis with a total of 33,494 women, and they found a significant relationship between BAC and CAD with a crude OR of 2.14 (95% CI 1.63–2.81). In addition, they were able to extract the adjusted OR for 10 studies, and the relationship between BAC and CAD for these 10 studies was still significant with an adjusted OR of 2.39 (95% CI 1.68–3.41).

A further meta-analysis by Hendriks et al.[77] analyzed the medical history and records used in 52 studies assessing the relationship between BAC and CVD/CAD, traditional CV risk factors, and reproductive factors. The authors reported that BAC was linked to the increased risk of CVD with adjusted HRs ranging between 1.32 (95% CI 1.08–1.60) and 1.44 (95% CI 1.02–2.05). However, the authors acknowledged that the diversity of study designs and scarcity of longitudinal studies, which make the conclusions less certain. Even with these reviews, however, it is still unclear if BAC measurements can be used reliably as a screening tool for CAD in asymptomatic women since the previous work was predominantly of cross-sectional design and did not specifically target a primary prevention cohort.

Biased populations

There are similar studies that found positive[78] or no relationship[25] between BAC and CAD, but many of these were limited by selection bias, which makes generalizing results from symptomatic to asymptomatic patients difficult. An ideal method of investigating the relationship between BAC and CAD would only involve asymptomatic women undergoing routine screening mammograms and direct diagnostic procedures such as coronary angiography and CT angiography for diagnosis of CAD.[27] However, it is extremely difficult to perform or find both routine mammogram and coronary imaging data on a primary prevention cohort since direct diagnostic procedures of CAD are expensive, generally involve ionizing radiation and risk, and not being covered by private health insurance in many countries. Therefore, medical practitioners usually do not refer patients for these procedures unless they have symptoms of CAD.

Mostafavi et al.[78] performed a cross-sectional study among 100 women undergoing CT angiography and concluded that BAC is associated with CAD. However, this study had two major limitations: the number of participants was very small, and most participants had intermediate to high CVD risk. In contrast, McLenachan et al.[25] conducted a cross-sectional study among 405 women and their study showed that BAC was not an adequate indicator of the presence of CAD on CT angiography. However, a significant portion of the studied population suffered from typical angina episodes, which means that the conclusion of this work was again limited to symptomatic women. Furthermore, Fathala et al.[79] investigated the relationship between BAC and myocardial ischemia on stress myocardial perfusion scanning by conducting a study on 435 women divided into 2 groups: 177 without BAC and 255 with BAC.

Their results showed no relationship between myocardial ischemia and BAC. Again, selection bias was a major limitation of this study, where the prevalence of CAD and BAC among the participants was high. Also, the prevalence of BAC in this study was significantly high (59%), especially compared with the prevalence of 15.2% in the study of Shobeiri et al.,[80] which was conducted on 400 women and reported a positive relationship between BAC and myocardial ischemia. Yoon et al.,[24] however, found a positive relationship between BAC and CAD and that the severity of BAC was strongly associated with CAD. Their study was conducted on 2,100 Korean women who underwent mammography and CT angiography as part of health checkup in Korea every 2 years: thus focusing on women without symptoms of CAD potentially yielding more generalizable findings.

Two early meta-analyses[22,81] assessing the association between BAC and CAD showed a positive relationship between BAC and CVD or CAD with ORs of 3.86 (95% CI 3.24–4.59) and 1.59 (95% CI 1.21–2.09), respectively. However, it has been highlighted that the populations studied in these two meta-analyses[22,81] were biased as the selection criteria were limited to studies that used coronary angiography as a measurement tool of CAD.[8] Coronary angiography is usually undertaken in patients who have a higher likelihood of CVD/CAD based on symptoms; hence, it could be inaccurate to conclude from these data that BAC is useful as a screening tool for CVD/CAD on asymptomatic women without prior CVD events or symptoms.

Definition of CV events

Differences in the methods used to identify and measure CVD/CAD outcomes are apparent across studies investigating the association of BAC. CAD and CVD definitions ranged from major adverse cardiovascular events (MACE) outcome including stroke, myocardial infarction, peripheral vascular disease arterial ischemia, and CVD mortality to the presence of CAD on coronary imaging. Others only included one CV outcome, a subgroup of CV outcomes, or only CVD mortality, which may have led to an underestimation of the association between BAC and CVD/CAD.

In addition, methods for determining the presence of CAD differed among studies, including self-reporting, coronary angiography, CT, and carotid intima-media thickness ultrasound test, which is a well-known predictor of CAD and cardiovascular morbidity and mortality.[82] Lee et al.[8] in their meta-analysis demonstrated that the association between BAC and CVD/CAD was strongest when based on CT, self-reporting may be inaccurate and biased, and invasive coronary angiography can underestimate calcification and nonobstructive coronary plaque burden. The ORs were 2.16 (95% CI 1.83–2.55), 2.14 (95% CI 1.40–3.29), and 3.90 (95% CI 2.53–6.03) for self-reporting, coronary angiography, and CT, respectively.

Differences when considering confounding factors

BAC and CAD increase with advancing age, making age a major confounding factor when exploring associations between the two clinical conditions. Most studies, including recent systematic reviews and meta-analyses,[4,8,27,76,77] have shown that the BAC/CAD association remains significant after stratifying or adjusting for age. However, Henkin et al.[49] argued that this association might also be due to other confounding variables associated with CAD risk and reported that the association of BAC and CAD, after adjusting for other CV risk factors including age, diabetes, and hypertension, to be diminished to a multivariate-adjusted OR of 0.96 (95% CI 0.56–1.64). This result is incongruent with other multivariate analyses,[10,15,18,23,53,68] which still reported a robust independent relationship between BAC and CAD after adjustment of confounding CV risk factors.

Several studies[54,55,64,78] controlled their findings based on smoking history—a significant risk factor for early onset and CV disease and still reported a strong association between BAC and CAD. However, Lee et al.[8] suggested that simply controlling for smoking may not be enough to draw a conclusion about this association and studies need to stratify their finding based on smoking history more robustly to test this association.

Differences in the BAC assessment methodologies

BAC is usually assessed manually by radiologists when reading mammograms as present or absent, which only allows classification of a primary prevention cohort of women into two CVD risk categories. The ability to assess BAC severity can improve the accuracy of predicting the risk of developing CVD in asymptomatic women using standard mammography and allows to classify patients into various CVD risk groups.[3] Several recent studies have proposed various methods for grading and assessing the severity of BAC, including a 3-point scale,[51] 4-point scale,[18,25,57,78,83–85] and 12-point scale.[54,79,86,87] Different criteria were considered for grading BAC in these studies such as the density of calcium, length of vessel, and number of affected vessels.[8]

Despite these efforts, the variation in grading scales indicates the absence of standardized criteria for quantifying BAC. Furthermore, there are other challenges preventing BAC assessment from being part of the clinical routine such as that radiologists may not have the adequate knowledge to assess BAC and it is time-consuming to do so. Thus, developing an automated method of detecting and quantifying BAC may help address these challenges. Several such approaches have been used: Ge et al.[88] proposed an automated classifier that combined a set of image filtering techniques with a k-segments clustering algorithm and showed that the proposed method can detect BAC and identified the calcified vessels.

However, this method cannot detect some common appearances of BAC such as highly curving shape. Cheng et al.[89,90] developed a two-step method using a tracking algorithm to detect the BAC paths, followed by a linking algorithm to connect and extract the generated paths of BACs from mammograms, demonstrating that BAC can be detected, and calcified vessels identified. The authors tested their method with 40 mammograms and achieved performance of 93.8 − 1.3% for sensitivity and 84.7 − 3.9% for specificity. However, the proposed method failed to deal with the variation of breast compositions where the distribution of fat and fibroglandular tissues differed in each breast.[41] Nonetheless, precise and automated method for detecting BACs in mammograms continues to be a task worth pursuing particularly if size, shape, and contrast can be taken into account.

DL in medical imaging is a rapidly growing research area used to predict, diagnose, and classify a disease for automated decision making. The application of DL in medical imaging is to assist computers extract features from medical images that may provide useful descriptions and characterizations of the data for a particular medical application. High-level features can be extracted by passing the features of medical images across number layers of the DL model, which are then transformed into useful outputs for this particular medical application.

Several recent studies have investigated the potential of applying DL for assessing BAC from digital mammograms and showed that DL algorithms can achieve or even outperform human experts in identifying BAC from mammograms, which is an encouraging step for predicting this CVD risk factor in women:[38,40,91] Wang et al.[38] proposed a DL model that identified BAC from mammograms at a level comparable to radiology experts but it required high computational cost; AlGhamdi et al.[40] proposed an automated model to detect BACs from mammograms called DU-Net and claimed that their model matched human expert performance; however, BAC was only described as present or absent with no grading presented; Guo et al.[91] developed a lightweight model named (Simple Context U-Net), which requires less computational cost compared with the traditional DL segmentation models, and can be integrated to identify, quantify, and measure the progression of BAC over time in women and showed accurate segmentation of BAC on routine screening mammograms.

However, their model only evaluated data from one institution and a single brand of scanners, which questioned the generalizability of their approach. As a result of the aforementioned limitations, none of these approaches has yet been deployed into clinical practice or validated against clinical outcomes in patients.

BAC Cardiovascular Risk Factors and Other Conditions

BAC cardiovascular risk factors

Several studies have suggested that there is an association between BAC and traditional cardiovascular risk factors, such as diabetes mellitus, hypertension, hypercholesterolemia, chronic kidney disease, and smoking.[11,20,28,92–94]

However, data supporting the association between BAC and some cardiovascular risk factors including hypertension and hypercholesterolemia are inconsistent.[42] To better understand the association between BAC and cardiovascular risk factors, Lee et al.[8] conducted a large meta-analysis of 59 studies and found a positive relation between BAC and diabetes mellitus, hypertension, and hypercholesterolemia with ORs of 2.17 (95% CI 1.82–2.59), 1.80 (95% CI 1.47–2.21), and 1.28 (95% CI 1.06–1.55), respectively.

Furthermore, another independent cardiovascular risk factor is chronic kidney disease (CKD) as women with CKD has higher CVD events compared with women without;[95] Hassan et al.[92] conducted a cross-sectional study and compared women with stage 3 CKD, stage 4 CKD, and ESRD against a control group of women without renal disease, all of which have had screening mammograms. The work found that women with stage 3 CKD, stage 4 CKD, and ESRD had a higher prevalence of BAC compared with the control group with ORs of 1.48 (95% CI 0.43–5.12), 1.99 (95% CI 0.82–4.80), and 1.97 (95% CI 0.98–3.97), respectively.

However, there is an inverse relationship between BAC and smoking,[8,27,42] this is not surprising given that peripheral vascular calcification, which is another form of arterial calcification of the media, is less prevalent among smokers,[4] although the reasons for this inverse relationship are still unknown.[42] One explanation could be that smoking is associated with a higher level of estrogen in postmenopausal women,[96] which is in line with a study from Schnatz et al.,[44] where they concluded that women who receive estrogen hormone replacement therapy have lower prevalence of BAC.

BAC and other conditions

Low bone mineral density (BMD) is a condition that often occurs concurrently with CVD/CAD and a shared number of risk factors, including age, hypertension, and smoking.[97] This link between BMD and CVD/CAD has motivated Iribarren et al.[98] to investigate if there is also an association between BAC and BMD. The authors conducted a study on 1,273 postmenopausal women who undertook dual-energy X-ray absorptiometry and screening mammography and found no relationship between the presence and severity of BAC with BMD. There was another study conducted by Nasser et al.[99] that also investigated the relationship between BAC and BMD among 211 postmenopausal women and found no correlation between the presence of BAC and BMD. However, both studies were cross-sectional studies that only focused on women aged 60 years and older. Therefore, prospective studies that include younger women are required to confirm and generalize this finding.

Cognitive impairment is another condition that has also been shown to coexist with CVD/CAD, where patients with known CAD have a 45% increased risk of developing cognitive impairment.[100] Therefore, Iribarren et al.[101] suggested that BAC can be linked with cognitive impairment and dementia. They measured the cognitive function of (3,913) postmenopausal women who also underwent breast screening. After a median follow-up of 5.6 years, their analysis showed that there is no association between the presence and severity of BAC and cognitive impairment or development of all-cause dementia.

The metabolic syndrome is a group of conditions that include insulin resistance, hypertension, excess body fat around the waist, impaired glucose tolerance, and dyslipidemia that usually occur together and increase the risk of CVD.[102] Bae et al.[103] performed a study on 202 women aged 41 and 78 years who underwent a screening mammogram to evaluate the relationship between the presence and severity of BAC and metabolic syndrome and found that the presence and the severity of BAC were associated with an increased risk of metabolic syndrome among women. Another study investigating the association between BAC and metabolic syndrome was conducted by Yildiz et al.[104] and found a positive relationship between BAC and metabolic syndrome.

Other Mammographic Features and CVD

Mammographic images contain additional features, some of which can be important risk factors not only for breast cancer but also for CVD. One such feature is breast density, which describes the amount of glandular tissue and fibrous connective tissue compared with the amount of fatty breast tissue[105] and appears radiopaque on the mammographic examination while the fatty breast tissue appears more radiolucent.[106] It is well known that women with higher breast density have a greater risk of breast cancer; however, a recent study has revealed that women with a higher percentage of fatty tissue in the breast (lower breast density) might have a higher risk of developing CVD with a HR of 3.483 (95% CI 1.476–8.257).[107]

Microcalcifications are another feature of mammographic images linked with CVD. These appear as small bright dots on the soft tissue background of the breast with a diameter of less than 1 mm.[108] They can be benign or a sign of malignant breast cancer. Microcalcifications in women are associated with increased age, a family history of breast cancer, and chronic renal failure.[109–111] In addition to breast cancer implications, Grassmann et al.[108] also found that microcalcifications were associated with increased risk for subsequent cardiometabolic diseases in women with a pre-existing condition of cardiometabolic diseases. Cardiometabolic diseases were defined in this study as CVD, diabetes mellitus, chronic renal failure, and other related conditions.

The authors found that the absolute risk of developing subsequent cardiometabolic disease in women with pre-existing conditions cardiometabolic over 5 years is 57.92% for women with microcalcifications compared with 51.81% for women without.[108] Furthermore, they found that women with cardiometabolic diseases and microcalcifications had a higher risk of cardiometabolic mortality with a HR of 1.79 (95% CI 1.24–2.58) than women with cardiometabolic diseases but without microcalcifications. However, the method used in this study to identify microcalcifications did not distinguish between BAC and microcalcifications and is possible as both were included as microcalcifications. Also, this study did not find any association between microcalcifications and cardiometabolic diseases in asymptomatic women.

Conclusions

Previous research indicates that BAC is strongly correlated with CVD/CAD, hypertension, and diabetes. However, most of these studies are cross-sectional studies with small sample

size and are not performed in a primary prevention cohort. Furthermore, the current methods of quantifying BAC and other mammographic features varied across these studies. Therefore, future research should focus more on: evaluating the association between BAC and all future CVD/CAD events for women without established CVD/CAD; stratifying the studies' findings based on different CAD risk factors such as smoking, hypertension, and diabetes mellitus; developing a standardized and automated approach to score or quantify BAC.

Furthermore, most of the existing studies predicting CVD/CAD events from mammographic appearances focus on BAC alone without consideration of other breast characteristics. Thus, future research should also focus on the relationship between CVD and other mammographic features such as breast density and macrocalcifications to confirm if they can also be used alongside BAC for predicting CVD/CAD.

Authors' Contributions

All authors have made equal contributions to this work, including conceptualization, methodology, writing the original draft, reviewing, and editing.

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Chapter 3 Semi-Supervised Deep Learning-Based Model for Segmentation of Breast Arterial Calcification on Screening Mammograms

3.1 Introduction

Building on the foundational discussion in the previous chapter, which underscored the importance of BAC as a potential biomarker for CVD risk, this chapter addresses the inherent limitations of manual BAC assessment, including subjectivity, inter-reader variability, and the considerable time required. These challenges highlight the need for automated methods capable of reliably identifying and quantifying BAC in clinical settings.

This chapter is based on the manuscript: Ibrahim MA, Brennan PC, Suleiman ME, Rickard M, Tavakoli Taba A, Gandomkar Z. *Semi-Supervised Deep Learning-Based Model for Segmentation of Breast Arterial Calcification on Screening Mammograms*, *Journal of Medical Imaging* (2024, under review). I, Mu'Ath Ibrahim, am the first author and was primarily responsible for the study design, data collection, model development, data analysis, interpretation of results, and drafting of the manuscript. Supervisors and co-authors contributed to the project through clinical expertise, study oversight, and critical manuscript review.

In this chapter, we present the initial phase of a three-part study on automated BAC assessment. Specifically, we describe a semi-supervised deep learning approach for BAC segmentation that leverages both annotated and unlabeled mammographic data. The proposed model employs progressive pseudo-labeling to enhance robustness and adapt to a variety of clinical environments. Grounded in a U-Net architecture well-suited for biomedical image segmentation, the method incorporates essential preprocessing strategies—including normalization, augmentation, and resizing—to optimize performance.

To address the lack of standardized protocols for BAC measurement, this chapter also introduces a novel BAC grading framework that stratifies calcifications into four severity levels according to the percentage of affected breast area. Validation against expert radiologist assessments demonstrates the model's potential to achieve human-level grading accuracy while significantly reducing evaluation time.

Overall, Chapter 3 serves as a critical link between the conceptual groundwork presented in the previous chapter and the subsequent sections, which will refine and expand upon this prototype for automated BAC assessment.

Semi-Supervised Deep Learning-Based Model for Segmentation of Breast Arterial Calcification on Screening Mammograms

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Abstract

Purpose:
Breast arterial calcification (BAC), detectable on routine mammograms, offers a promising independent risk factor for cardiovascular disease (CVD) risk stratification. However, current BAC assessment methods lack standardization and rely on subjective interpretations. This study introduces a semi-supervised deep learning (DL) model to automate BAC grading, enhance cross-system generalizability, and align with clinical consensus.

Approach:
A U-Net-based segmentation model was trained on 2560 annotated screening mammograms from seven vendors. A semi-supervised learning strategy employing progressive pseudo-labeling incorporated 6,000 unlabeled images to enhance model robustness. BAC severity was graded by thresholding the percentage area covered by BAC and benchmarked against radiologists' assessments using Canadian Society of Breast Imaging (CSBI) guidelines. Performance was evaluated using the Jaccard Similarity Coefficient (JSC) for segmentation, along with accuracy, precision, F1-score, and recall. For detecting clinically significant (Grade 3) BAC, sensitivity, specificity, and area under the curve (AUC) were assessed. Agreement with experts was evaluated using weighted kappa statistics.

Results:
The proposed model achieved a JSC of 0.614, an accuracy of 0.991, an F1-score of 0.756, a precision of 0.763, and a recall of 0.764. It demonstrated superior segmentation accuracy compared to the baseline U-Net model. Agreement with consensus radiologists was high, with a weighted kappa of 0.90, 95% CI = (0.70, 1.00). For clinically significant (Grade 3) BAC, the model achieved an AUC of 0.87, 95% CI = (0.72, 1.00), sensitivity of 0.80, and specificity of 0.93.

Conclusion:
The framework holds promise for clinical adoption, integrating into mammography workflows and improving women's cardiovascular risk stratification.

Keywords: Cardiovascular disease, Breast arterial calcification, Mammography, Women, Deep learning

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1. Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality in women worldwide [1]. Although widely utilized tools for CVD risk stratification exist, they often fail to capture unique sex-specific factors that influence women's cardiovascular health [2], resulting in underdiagnosis, undertreatment, and poorer outcomes [3]. As a result, there is growing interest in leveraging adjunctive biomarkers that can be readily incorporated into existing clinical workflows.

One such biomarker is Breast Arterial Calcification (BAC), which appears incidentally on routine mammograms performed for breast cancer screening [2]. BAC is associated with systemic arterial calcification and has been linked to an elevated risk of future cardiovascular events. By evaluating BAC severity on mammographic images, clinicians may gain insights into a woman's cardiovascular health status at little additional cost and without extra testing time. However, current methods for BAC assessment are often limited by subjectivity, relying on radiologists' interpretations that can vary based on experience and lack standardized criteria [2]. This subjectivity hinders consistent grading, reproducible risk stratification, and widespread clinical adoption.

Automated tools, including deep learning (DL)-based methods, have shown promise in addressing these challenges by automating the detection and quantification of BAC [4-7]. Nonetheless, such approaches often demand large, annotated datasets, and their performance may be constrained by training on images acquired from a single manufacturer's equipment. These limitations reduce both the robustness and generalizability of existing DL-based solutions.

In this work, we introduced a semi-supervised deep learning approach to improve BAC grading. By incorporating images from multiple vendors and employing progressive pseudo-labeling, our model aims to reduce annotation burden and enhance cross-system generalizability. This approach not only mitigates the challenges posed by limited data but also improves the robustness and applicability of the model across diverse clinical settings. Additionally, we proposed a grading system and investigated the magnitude of agreement between the grades produced by our proposed system and the grading schema outlined in the Canadian Society of Breast Imaging (CSBI) Position Statement on BAC reporting on mammography. This consensus guideline suggests classifying BAC into three grades and recommends that when mammography identifies Grade 3 BAC, the report should indicate the strong association with CVD and encourage correlation with cardiovascular risk factors. We benchmark the model's performance against expert radiologists' assessments and evaluate its sensitivity and specificity in detecting Grade 3 BAC, the most clinically significant category.

2. Materials and Methods

2.1 Dataset of Annotated Screening Mammograms

A total of 2,560 single-view mammographic images—comprising 1,318 craniocaudal (CC) and 1,242 mediolateral oblique (MLO) views—were acquired using 11 different scanner types from seven distinct manufacturers: Agfa (2.10%), FUJI (38.44%), HOLOGIC (10.56%), KONICA (7.74%), Philips (1.29%), Sectra (11.68%), and SIEMENS (28.20%). These images were assembled to serve as the primary training, validation, and testing dataset. To create paired images for analysis, the single-view images were concatenated, resulting in 1,280 bilateral mammographic images. This diversity was intentionally sought to evaluate the model's performance under varied imaging conditions and to support generalization across clinical settings. Image selection was performed by a dedicated medical imaging scientist specializing in mammography, while the presence of BAC was verified by a senior radiologist with over 30 years of experience.

All images underwent a rigorous annotation process using Label Studio software [8]. Initial segmentations were subsequently reviewed and confirmed by two senior radiologists to establish a robust ground truth. To standardize image inputs, several preprocessing steps were performed, including uniform resizing and pixel-value normalization to address variations in brightness and contrast.

2..2 Base Model Training

A U-Net architecture [9] was selected as the base model for BAC segmentation due to its proven effectiveness in biomedical imaging tasks. The U-Net structure, with its encoder-decoder and skip-connections design, is well-suited for capturing both coarse and fine details necessary to delineate calcifications.

The model was trained on resized full-sized images (1024 × 1024 pixels) and patches of size 512 × 512 pixels with an overlap of 386 pixels. Training on patches enabled the model to focus on localized

Features were enhanced to improve the model's ability to segment smaller and more intricate calcifications. Bilateral images were incorporated to address misclassification issues observed during single-view training, where the model occasionally misclassified artifacts at the edges of the image as BAC. By including bilateral images, the model learned to better distinguish true calcifications from artifacts at the boundaries of the combined views. Figure 1 illustrates how bilateral images were used to mitigate these issues.

Of the manually annotated dataset, 70% of the images were used for training, 20% for validation, and 10% for testing. The model was trained with a learning rate of 0.001 and binary cross-entropy as the loss function. This initial training phase established a strong baseline for subsequent refinements.

Data augmentation was applied exclusively to the training dataset to increase variability and robustness. Specifically, brightness adjustments were performed with a scaling factor of 0.2, pixel saturation with a factor of 0.3, and hue shifts up to 0.25. While no geometric perturbations such as flips, rotations, or scaling were applied, the use of intensity augmentations helped mitigate overfitting and improve the model's generalizability.

2.3 Semi-Supervised Learning with Progressive Pseudo-Labeling

To address the challenge of limited annotated data, we adopted a semi-supervised learning strategy that incorporated progressive pseudo-labeling, as inspired by prior work [10]. This approach enabled us to enhance the model's performance and generalizability by leveraging an additional dataset of 6,000 unlabeled mammographic images. Initially, we employed an entropy-based selection method to evaluate these unlabeled images. The trained base model generated predictions, and images with low entropy—indicating high-confidence predictions—were chosen for pseudo-labeling. By selecting only these most reliably predicted images for subsequent training iterations, we ensured that the added data would meaningfully improve the model's capabilities.

To maintain training quality and manage the large volume of unlabeled data, we introduced pseudo-labeled images incrementally, in small batches. This gradual approach allowed the model to steadily assimilate new information without being overwhelmed, thereby fostering a balanced and effective training regimen and continuously improving its segmentation performance.

Retraining on the combined annotated and pseudo-labeled dataset utilized a custom loss function blending binary cross-entropy and Jaccard loss. Binary cross-entropy provided fine-grained pixel-level differentiation between BAC and non-BAC regions, while Jaccard Similarity Coefficient (JSC) loss emphasized the spatial overlap between predicted segmentation masks and ground-truth labels. Integrating these losses encouraged the model not only to achieve high overall accuracy but also to precisely delineate the subtle, clinically significant BAC regions within the mammographic images.

This iterative process of pseudo-labeling and retraining continued until the model's performance met our predefined criteria for satisfactory segmentation quality. Each iteration enriched the training dataset with additional high-confidence pseudo-labeled images, progressively refining the model's

segmentation capabilities. Through this iterative methodology, we effectively leveraged both annotated and unlabeled data, significantly improving the model's accuracy, robustness, and adaptability to a wide range of clinical imaging conditions.

2.4 BAC Severity Grading

In addition to segmentation, we introduced a four-tier grading system based on the ratio of BAC area to the total breast area:

- **Absence:** BAC area < 0.2% of the total breast area
- **Mild:** BAC area between 0.2% and 1% of the total breast area
- **Moderate:** BAC area between 1% and 2.5% of the total breast area
- **Severe:** BAC area > 2.5% of the total breast area

This quantitative framework facilitated consistent severity assessments for both the model and expert radiologists.

2.5 Code and Model Availability

To facilitate transparency, reproducibility, and clinical translation, the full implementation of the proposed BAC segmentation and grading framework has been made publicly accessible via the following repository: https://github.com/muath111/BAC_Segmentation. The repository is systematically structured to reflect two complementary methodological pipelines—one based on resized whole mammographic images and the other on high-resolution image patches. These approaches were aligned with the training design described in this study, where the model was trained on resized full-sized images (1024 × 1024 pixels) and patches of size 512 × 512 pixels with an overlap of 386 pixels. Training on whole images allows for capturing global anatomical context, while patch-based learning enhances the model's ability to identify localized calcifications.

The whole-image pipeline encompasses image preprocessing, model training, validation, inference, and post-processing for the extraction of BAC-specific features. These features are used to compute both the relative area and intensity of calcifications, which form the basis of the proposed BAC severity grading system. The patch-based pipeline involves systematic preprocessing, data augmentation, model training, and evaluation using overlapping high-resolution patches. This approach supports the identification of subtle calcifications.

Both pipelines utilize a U-Net-based architecture and implement a semi-supervised learning approach via entropy-based progressive pseudo-labeli*n*g. This strategy enables the integration of confidently predicted labels from a large unlabeled mammogram pool into the training dataset, thereby improving robustness and generalizability.

This open-source repository provides pretrained model weights, implementation guidelines, and documentation to support adaptation to other mammography datasets, encouraging reproducibility and further clinical research. The trained weights for both the whole-image and patch-based models are also available within the repository to facilitate direct replication or transfer learning.

2.6 Validation Against Expert Radiologists

To assess the model's performance against clinical expertise, 20 bilateral mammographic images not used in training or initial validation were selected. These images represented a range of BAC severities as identified by our AI model, with five images allocated to each severity category. Three experienced

radiologists, who had not previously seen these images nor participated in establishing the ground truth or annotating the dataset, independently graded these images using the guidelines from the CSBI Position Statement on BAC reporting. This schema classifies BAC into three categories:

- **Grade 1:** Few punctate calcifications, no coarse or tram-track calcifications
- **Grade 2:** Coarse or tram-track calcifications in fewer than three vessels
- **Grade 3:** Severe coarse or tram-track calcifications affecting three or more vessels

For Grade 3 BAC, the CSBI recommends reporting the strong association with cardiovascular disease (CVD) and advising further correlation with CVD risk factors. By comparing our model's grading outcomes to the radiologists' assessments, we evaluated its alignment with clinical consensus and the potential utility of the model in guiding clinical decision-making. Although our proposed four-tier grading system is based on the proportion of BAC area relative to the total breast area, we hypothesized that this quantitative, percentage-based grading would still show a strong association with the CSBI grading system. We tested this hypothesis by assessing how closely the model's percentage-based grades correlated with the CSBI classification.

2.7 Evaluating the Model's Performance

To assess the performance of our semi-supervised deep learning model in segmenting BAC on mammograms, we employed a range of metrics, including accuracy, precision, recall, F1 score, and the Jaccard Similarity Coefficient (JSC).

- Accuracy measures the proportion of correct predictions across the entire image.
- Precision quantifies the proportion of correctly identified BAC regions among all predicted BAC regions.
- Recall reflects the proportion of actual BAC regions that were correctly identified.
- F1 score is the harmonic mean of precision and recall, balancing false positives and false negatives.
- JSC, also known as Intersection over Union (IoU), measures the overlap between the predicted segmentation mask and the ground truth. This metric is particularly important in our context, as BAC generally occupies only a small portion of the mammogram. Without emphasizing this specific overlap, a model might achieve deceptively high accuracy by primarily capturing non-calcified areas rather than the clinically significant BAC regions. A high JSC, therefore, indicates the model's ability to accurately delineate BAC boundaries, even when these areas are relatively minor within the larger image.

Observer agreement was quantified using weighted kappa statistics. Comparisons were made between each pair of human observers and between the observers and the AI model. By applying a majority voting scheme, an expert consensus was established for each case, enabling the calculation of overall percent agreement and the weighted kappa (AI vs. consensus).

Finally, given the clinical importance of identifying Grade 3 BAC, as outlined in the CSBI Position Statement on BAC reporting in mammography, we conducted a binary classification analysis focused on this category. In this scenario, we calculated:

- AUC (Area Under the Curve), which measures the model's ability to distinguish Grade 3 BAC from non-Grade 3 BAC cases across thresholds.
- Sensitivity, which is the proportion of Grade 3 BAC cases correctly identified by the model.

- Specificity, which is the proportion of non-Grade 3 BAC cases correctly excluded by the model.

These metrics collectively provide a comprehensive evaluation of the model's effectiveness in segmenting BAC and detecting clinically significant cases.

3. Results

3.1 Performance of the Proposed Segmentation Model

Initial evaluations of the U-Net model using both patch-based (512×512) and whole-image (resized to 1024×1024) training approaches showed promising performance (Table 1). For the patch-based approach, the U-Net achieved a JSC of 0.602, with an accuracy of 0.991, precision of 0.753, F1-score of 0.747, and recall of 0.756. Similarly, training on resized 1024×1024 images yielded comparable results, with a JSC of 0.590, accuracy of 0.990, precision of 0.772, F1-score of 0.759, and recall of 0.748. These results provided a solid baseline for further model enhancements.

Incorporating a semi-supervised learning strategy with progressive pseudo-labeling significantly improved performance. The patch-based model's JSC increased to 0.614, while maintaining an accuracy of 0.991. Additionally, the F1-score improved to 0.756, and recall rose to 0.764. For the whole-image model, modest gains were observed, with the JSC improving to 0.591, accuracy and precision remaining at 0.990 and 0.772, and slight increases in F1-score (0.760) and recall (0.750).

To visually validate the model's performance, Figure 1 (a, b, c) presents segmented mask outputs compared to ground truth from three manufacturers: Siemens, Hologic, and Fuji. The enhanced ability to capture the intricate details of BAC regions highlights the model's capability to deliver accurate and reliable assessments.

Table 1. Evaluation results of different models trained on patches and whole images. The metrics presented are Recall, Precision, Accuracy, F1-Score, and Jaccard Similarity Coefficient (JSC).

Model	***Recall (Whole)***	***Precision (Whole)***	***Accuracy (Whole)***	***F1-Score (Whole)***	***Jaccard (Whole)***	***Recall (Patch)***	***Precision (Patch)***	***Accuracy (Patch)***	***F1-Score (Patch)***	***Jaccard (Patch)***
Baseline	0.748	0.772	0.990	0.759	0.590	0.756	0.753	0.991	0.747	0.602
Semi-Supervised Model	**0.750**	0.772	0.990	**0.760**	**0.591**	**0.764**	**0.763**	0.991	**0.756**	**0.614**

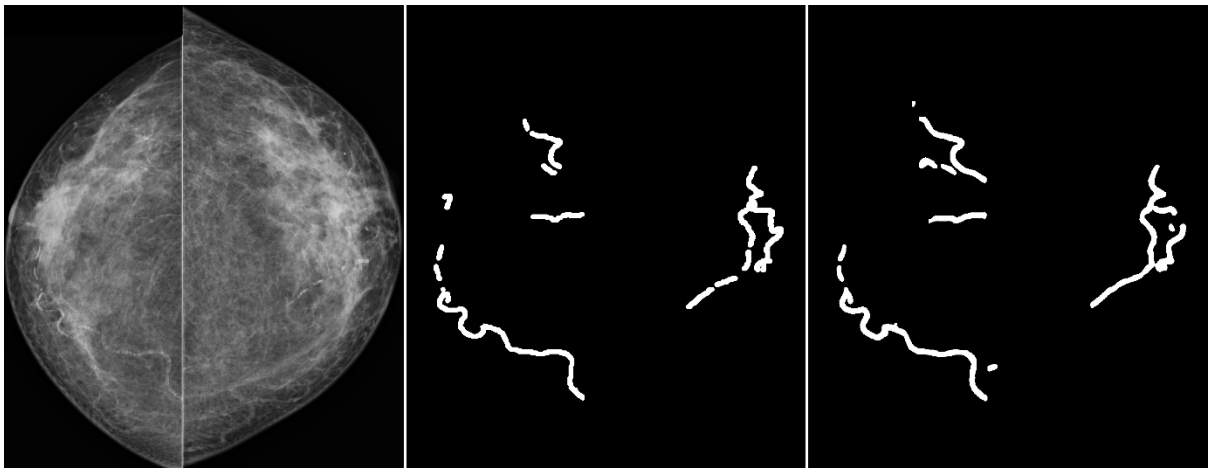
Columns labeled "Patch" represent results for models trained on 512×512 patches. Columns labeled "Whole" represent results for models trained on 1024×1024 whole images. Improvements from the baseline model are shown in bold.

Original mammogram Ground truth mask Predicted mask

(a)

Original mammogram Ground truth mask Predicted mask

(b)



Original mammogram Ground truth mask Predicted mask

(c)

Figure 1: Comparison of BAC segmentation for examinations from three vendors (i.e., (a) Siemens, (b) Hologic, (c) Fuji), including the original image, ground truth mask, and predicted mask.

3.2 Validation Against Expert Radiologists

Inter-observer and observer-to-model comparisons demonstrated strong agreement in grading BAC severity. Pairwise comparisons between the three radiologists yielded weighted kappa values of 0.88, 95% CI = (0.67, 1.00) (Observer 1 vs. Observer 2), 0.91, 95% CI = (0.73, 1.00) (Observer 1 vs. Observer 3), and 0.93, 95% CI = (0.77, 1.00) (Observer 2 vs. Observer 3), indicating high consistency among expert graders. When comparing each observer to the AI model, the weighted kappa values remained robust, at 0.85, 95% CI = (0.62, 1.00) (Observer 1 vs. AI), 0.95, 95% CI = (0.80, 1.00) (Observer 2 vs. AI), and 0.88, 95% CI = (0.66, 1.00) (Observer 3 vs. AI), further underscoring the model's ability to align with expert assessments. These results are detailed in Table 2.

By applying a majority-voting consensus among the radiologists, the AI model's weighted kappa against this consensus reached 0.90, 95% CI = (0.70, 1.00). In a binary classification scenario focused on detecting clinically significant (Grade 3) BAC based on CSBI position statement, the model achieved an AUC of 0.87, 95% CI = (0.72, 1.02), with a sensitivity of 0.80, 95% CI = (0.45, 1.00) and a specificity of 0.93, 95% CI = (0.81, 1.00).

Table 2. Inter-Observer and Observer-to-AI Agreement in BAC Severity Grading:

Comparison	**Weighted Kappa**	**95% Confidence Interval**
Observer 1 vs Observer 2	0.88	(0.67, 1.00)
Observer 1 vs Observer 3	0.91	(0.73, 1.00)
Observer 2 vs Observer 3	0.93	(0.77, 1.00)
Observer 1 vs AI Model	0.85	(0.62, 1.00)
Observer 2 vs AI Model	0.95	(0.80, 1.00)
Observer 3 vs AI Model	0.88	(0.66, 1.00)

4. Discussion

This study evaluated the performance of a semi-supervised DL model for the segmentation and quantification of BAC on mammograms. Unlike other models primarily focused on detecting the presence or absence of BAC [6, 11, 12], our approach provides detailed segmentation and quantification, allowing for a more comprehensive assessment of BAC extent and severity. Such a comprehensive assessment is particularly important given the emphasis on clinically significant BAC findings, as highlighted in the CSBI Position Statement, which underscores the importance of accurately identifying and reporting severe (Grade 3) BAC. By quantifying BAC rather than merely detecting it, our model provides critical insight into these severity levels.

Our findings demonstrate that a semi-supervised DL model can effectively leverage both annotated and unannotated data, improving generalizability and robustness. By incorporating images from multiple scanners and using progressive pseudo-labelling, our model overcame key limitations that often hamper generalization. In contrast, other models such as DU-Net (6) and DL-based model proposed in [12] provide strong detection performance but lack detailed segmentation and quantification. While SCU-Net (7) demonstrates promising results, it relies on single-vendor training, raising concerns about its adaptability to images from diverse vendors. Additionally, SCU-Net could not be directly assessed on

our diverse, multi-vendor dataset as the model is not publicly available, preventing us from evaluating its performance under the same conditions.

Our model provides detailed segmentation and quantification of BAC, essential for accurately assessing the extent and intensity of calcifications, offering a more comprehensive evaluation of cardiovascular risk compared to models focused solely on classification. By training on data from diverse vendors and using semi-supervised learning, our model demonstrates adaptability to different clinical settings, reducing the risk of overfitting and enhancing its utility across varied patient populations and imaging equipment. Clinically, integrating BAC assessment into routine mammographic screenings offers a unique dual-benefit modality, enabling clinicians to evaluate both breast cancer and cardiovascular risk simultaneously. Automated BAC segmentation and quantification can serve as an additional tool for early CVD risk identification, particularly in populations with limited access to comprehensive cardiovascular screening, thereby enhancing patient care and optimizing resource utilization.

A key strength of our study is the introduction and validation of a comprehensive BAC grading system, which assigns calcifications to four distinct categories—Absence, Mild, Moderate, and Severe—based on their extent within the breast. Unlike binary classification models that merely detect the presence or absence of BAC, our grading framework provides a refined stratification that more closely matches the granularity of expert radiologists' clinical judgment.

The robustness of this grading approach is reinforced by the high level of agreement observed between our model's output and expert radiologist assessments. Weighted kappa values of 0.85, 0.95, and 0.88, when comparing individual observers to the AI model, highlight that our automated classification does not merely approximate human performance—it closely parallels it. Achieving a weighted kappa of 0.90 against the consensus of three experienced radiologists further emphasizes the model's ability to produce clinically meaningful results. Moreover, the model's strong performance in detecting clinically significant Grade 3 BAC, as defined in the CSBI Position Statement, underscores its relevance in real-world clinical applications. The high AUC of 0.87, coupled with a sensitivity of 0.80 and a specificity of 0.93, indicates that the model not only recognizes severe calcifications that may warrant further cardiovascular risk assessment, but does so with an accuracy approaching that of expert readers. By providing an automated, standardized interpretation of BAC severity, this approach can streamline clinical workflows, reduce the subjectivity and variability associated with manual interpretations, and ultimately enhance patient care by identifying those who might benefit most from closer cardiovascular follow-up.

Despite the promising results, several challenges and limitations persist. While our dataset was sourced from multiple scanners and manufacturers, it was not evenly distributed, potentially introducing biases that may affect the model's generalizability to certain imaging systems or patient populations. Future research should focus on validating these findings in larger, more diverse datasets and clinical contexts. Additionally, exploring the model's ability to predict long-term cardiovascular outcomes would offer valuable insights into the prognostic value of BAC segmentation and quantification.

In conclusion, this study highlights the efficacy and versatility of a semi-supervised DL-based model for BAC segmentation and quantification. By capitalizing on both annotated and unannotated data, and training on images from varied sources, our model demonstrates enhanced robustness and utility across different clinical settings. The approach holds promise for integrating automated BAC assessment into routine mammographic screenings, potentially improving cardiovascular risk stratification and patient outcomes. Further research should aim to refine these methods, broaden their applicability, and firmly establish their role in clinical practice.

Disclosure:

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Code, Data, and Materials Availability:

Data related to this study will be made available upon reasonable request. Access to the de-identified dataset used for the analysis may be granted with proper institutional and ethical approvals.

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Chapter 4 Factors Associated with the Presence and Severity of Breast Arterial Calcification: A Deep Learning-Based Assessment Using Screening Mammography

4.1 Chapter 4: Introduction

While Chapter 3 outlined the development of a prototype deep learning model for BAC segmentation, Chapter 4 shifts focus to explore the factors associated with BAC presence and severity. This chapter investigates the role of metabolic, reproductive, and lifestyle determinants in BAC, providing insights into its clinical significance as an independent cardiovascular risk marker.

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Using data from a cohort of 9,648 women undergoing mammographic screening, BAC presence and severity were assessed through area-based and intensity-based grading systems. Statistical analyses, including logistic regression and multinomial logistic regression, were employed to identify predictors such as age, parity, smoking status, and medication use.

Building on the BAC segmentation framework introduced in Chapter 3, this chapter applies it to a large dataset to identify clinical and demographic predictors of BAC. These findings bridge critical gaps in understanding BAC as a non-invasive marker for cardiovascular risk, emphasizing its relevance in personalized risk assessment strategies.

Factors Associated with the Presence and Severity of Breast Arterial Calcification: A Deep Learning-Based Assessment Using Screening Mammography

Abstract

Background

Breast arterial calcification (BAC) is an emerging marker of cardiovascular health. While its presence has been widely studied, factors influencing BAC severity remain unclear. This study explores these relationships to evaluate BAC's potential as a marker of vascular health.

Methods:

A cohort of 9,648 women undergoing screening mammography were analyzed using a deep learning-based model to assess BAC presence and severity. BAC severity was quantified using both area- and intensity-based grading systems. Multinomial and ordinal logistic regression models were used to identify predictors of BAC presence and severity, including factors such as age, parity, body mass index (BMI), smoking and alcohol consumption, oral contraceptive use, and medication use as proxies for diabetes, hypertension, and hypercholesterolemia.

Results:

BAC was present in 27% of the cohort, increasing with age from 10.3% in women aged 40–49 to 66.1% in those over 80. Medication use diabetes (OR: 1.37, 95% CI: 1.05–1.81) use of antihypertensive and cardiovascular protective medications (OR: 1.46, 95% CI: 1.24–1.71) were associated with higher BAC severity. Parity (OR: 6.51, 95% CI: 4.03–10.53) was linked to severe BAC, while inverse associations were found with oral

contraceptive use (OR: 0.77, 95% CI: 0.64–0.93) and smoking (OR: 0.36, 95% CI: 0.22–0.61). No significant associations were found for BMI, alcohol consumption, or cholesterol-lowering medications.

Conclusion:

BAC is associated with metabolic disorders, particularly diabetes and hypertension, and these associations become stronger as BAC severity increases. These relationships persist independently of several factors, including age, reproductive, and lifestyle factors.

1- Introduction

Breast arterial calcification (BAC) is a form of medial arterial calcification that is frequently detected on screening mammograms [1]. Unlike other forms of vascular calcification, which can be challenging to distinguish non-invasively, BAC is uniquely identifiable and presents an opportunity to investigate its clinical significance. Despite its long-standing recognition by radiologists, the potential health implications of BAC were not well understood until a link with diabetes mellitus was identified in 1980 [2]. Since then, research has expanded to explore associations between BAC and factors such as age [3], chronic kidney disease[4, 5], metabolic syndrome [6], cardiovascular disease [7] and mortality [8]. Moreover, it may serve as a marker for systemic subclinical vascular disease, particularly microvascular dysfunction, which affects the architecture and function of small arteries and capillaries in organs such as the heart, brain, kidneys, lungs, and retina [9]. However, very few studies have assessed the relationship between the severity of BAC and cardiometabolic disease, or its potential role as an independent indicator of various health conditions.

Understanding the determinants of BAC is crucial for its effective use in clinical prediction models. Among these determinants, age is a well-established factor associated with the presence of BAC [1, 10]. However, even for age, the relationship between age and the severity or extent of BAC remains underexplored. Two notable meta-analyses by Hendriks et al. [1] and Lee et al. [10] have examined factors associated with BAC presence. Hendriks et al. [1] found that parous women non-smokers, and those with cardiovascular conditions, hypertension and diabetes, had higher odds of BAC presence, while hormone replacement therapy was linked to reduced prevalence of BAC. Similarly, Lee et al. [10] highlighted hypertension, diabetes, and hypercholesterolemia as significant risk factors, with smoking showing a protective effect against the presence of BAC.

While these studies provide valuable insights into the factors associated with BAC presence, they do not evaluate the relevance of BAC severity [11]. The majority of studies included in these meta-analyses relied on radiologists' subjective assessments, which were typically binary (presence or absence). This traditional approach fails to capture the varying degrees of calcification that may hold more nuanced clinical relevance. Although grading scales for BAC have been proposed, the lack of standardized quantification criteria remains a significant challenge, and manual assessments introduce variability and require specialized expertise.

Accordingly, this study utilized a previously developed and validated deep learning model [12], as described in Chapter 3, to evaluate both the presence and severity of BAC. Our objective was to rigorously identify associations between BAC severity and key reproductive, and lifestyle determinants, providing a detailed analysis of the factors influencing BAC within a large cohort.

2- Materials and Methods

This retrospective study leveraged two distinct datasets from Lifepool, a cohort of women enrolled in BreastScreen Australia, each dataset serving a specific role within the study design. The first, the SegModel dataset, comprised 1,094 mammograms (818 single lateral and 276 bilateral images) and was used to train and validate a deep learning model for segmenting regions of BAC. The second dataset included screening mammograms from 9,648 women, each linked to medical records, to explore factors associated with the presence and severity of BAC. The study was conducted with ethical approval, and informed consent was obtained from all participants.

Figure 1 summarizes the study design. The model development process is outlined in Step 1, where the SegModel dataset is divided into training (70%), validation (20%), and test sets (10%) to train a U-Net-based deep learning model for segmenting BAC regions. The trained U-Net is then evaluated for segmentation performance. Step 2 involves using the segmented BAC areas to investigate the factors associated with the presence and severity of BAC. These factors are derived from a dataset of potential determinants, including women's characteristics and clinical history. Two grading methods, intensity-based and area-based, are applied to the segmented regions. Statistical analyses, including adjusted odds ratio estimation for BAC presence, multinomial logistic regression, and ordinal logistic regression, are performed to identify associations between these determinants and BAC presence or severity. Two datasets used for developing the model (Step 1) and identifying the BAC determinant (Step 2) were non-overlapping.

2-1- Step 1: Automated Assessment of Breast Arterial Calcification

We proposed a deep learning-based approach to segment the BAC area using the SegModel dataset. The segmented model was then categorized based on the BAC area and intensity into a grade ranging from 0 to 3. Details about the training of our proposed model are provided in [12] and also described in Chapter 3.. Briefly, we trained a U-Net model [13], to segment BAC areas on mammograms. For model training, we used the **SegModel** dataset, which consists of 1,094 mammographic images acquired from machines made by seven different vendors. This collection includes 818 single lateral mammograms and 276 bilateral images. To ensure precision in image selection, an expert breast radiologist with over 30 years of experience verified the presence of BAC in the images. Subsequently, a medical imaging scientist used Label Studio software to annotate the BAC areas. These initial annotations were then reviewed by a radiologist to ensure accuracy and consensus on the identified BAC regions.

Before feeding the images into the U-Net model, they were pre-processed. This pre-processing included resizing the images to a standardized resolution, normalizing pixel values, adjusting image brightness, and applying various data augmentation techniques. These steps were essential for enriching the dataset and mitigating the risk of overfitting during the model training phase. The **SegModel** dataset was split into training (70%), validation (20%), and test sets (10%) for training and evaluating the U-Net model for BAC segmentation. We implemented a learning rate of 0.001 and used binary cross-entropy as the loss function.

We assessed BAC severity using two approaches: one based on area and the other on intensity, each employing a four-level grading system. The area-based approach classified BAC severity by the proportion of BAC-affected breast tissue, with grades defined as absent (BAC area below 0.2% of total breast area), mild, moderate, and severe. For BAC-present cases, area thresholds were set by dividing the distribution into tertiles, with the first tertile indicating mild severity, the second moderate, and the third severe. The intensity-based method focused on the average intensity of the segmented BAC regions. For each BAC-positive case, we calculated the mean intensity within the segmented area, normalizing these values by subtracting the scanner-specific mean and dividing by the standard deviation to account for scanner variations. The normalized intensities were then categorized as absent (below 0.2% BAC area), mild (first tertile), moderate (second tertile), and severe (third tertile).

2-2- Step 2: Identifying Factors Associated with The BAC Presence and Severity

2-2-1- BAC Determinants Dataset

We retrospectively retrieved mammographic examinations from 9,648 women who participated in a breast cancer screening program. Each subject underwent screening that produced a set of four images, capturing both the mediolateral oblique (MLO) and craniocaudal (CC) views for each breast. The women were recruited through the Lifepool Project and provided consent for their data to be used in research. These participants also completed questionnaires, giving us access to a wide range of variables, including age at screening, body mass index, alcohol consumption over the past year, smoking status, history of breast cancer and breast biopsy, chest radiotherapy, parity, use of oral contraceptives, hormone replacement therapy, and menopausal status. Since the dataset was

collected retrospectively, information on diabetes, hypercholesterolemia, and hypertension were not directly available. To address this, we linked the dataset of theses 9,648 women with electronic health records and used medication data as a surrogate indicator for these conditions. Participants were originally selected for a case-control study on major adverse cardiovascular events (MACE), which included all women with MACE and age-matched controls at a 1:2 ratio. This dataset was subsequently repurposed for the present study. Inclusion criteria comprised the availability of mammograms and linked medical and questionnaire data (see Chapter 5 for details).

2-2-2- Statistical analysis

To identify predictors associated with the presence and severity of BAC, we employed three statistical techniques, including logistic regression, multinomial logistic regression, and ordinal logistic regression.

Assessing Factors Associated with BAC Presence: Logistic regression was utilized to estimate adjusted odds ratios (ORs) for BAC presence, with BAC categorized as a binary outcome (present vs. absent). This analysis incorporated various predictors, including age, BMI, alcohol consumption, smoking status, history of breast cancer, history of chest radiotherapy, history of breast biopsy, parity, menopausal status, use of oral contraceptives, hormone replacement therapy, and medication usage (comprising medications for diabetes, high cholesterol, antiplatelets, and other cardiovascular protective drugs). ORs were computed, accompanied by 95% confidence intervals (CIs) and p-values to evaluate the statistical significance of each predictor.

Assessing Factors Associated with BAC Severity: To examine the factors influencing different levels of BAC severity, we applied both multinomial logistic regression and

the predictors' effects on the likelihood of experiencing mild, moderate, or severe BAC. Additionally, ordinal logistic regression was conducted to account for the ordered nature of BAC severity. This model evaluated the relationship between predictors and the cumulative odds of being in a higher severity category, providing a unified measure of association that reflects the cumulative impact of predictors across the severity spectrum of BAC.

All statistical analyses were conducted using Python with the statsmodels package, and significance was determined at a threshold of $p<0.05$. CIs were calculated to present a range of plausible effect sizes for each predictor.

3- Results

3-1- BAC Prevalence and Severity in the BAC Determinants Dataset

In this cohort of 9648 women, we observed a BAC prevalence of 26.96%. Figure 2 represents the distribution of BAC severity grades across various age groups. Overall, for both grading approaches in younger age groups (under 50 and 51-55), the vast majority of individuals fall into Grade 0 (89+%), with very few individuals showing higher grades of calcification. As age increases, in both grading approaches, there is a clear shift in the distribution, with a decreasing proportion of individuals in Grade 0 and a corresponding increase in the proportions in Grades 1-3. As an example for area-based grading, in the oldest age group (80+), only 33.94% of individuals remain in Grade 0, while the majority are distributed among the higher grades, with 37.33% falling into Grade 3 (i.e., severe). The data suggests a trend of increasing BAC severity with age, as the proportion of individuals with moderate to severe calcification (Grades 2 and 3) rises sharply in the older age groups (71-75, 76-80, and 80+).

3-2- Factors Associated with BAC Presence

Table 1 shows the key predictors associated with the presence of BAC. As anticipated, age was significantly higher in individuals with BAC (mean age 67.26 years) compared to those without BAC (mean age 62.41 years), with an OR of 1.083 (95% CI: 1.075 -1 .091, $p < 0.001$), indicating a substantial increase in BAC risk with advancing age. Parity emerged as another strong predictor, where parous women had more than double the odds of having BAC compared to nulliparous women (OR: 2.334, 95% CI: 1.896 - 2.873, $p < 0.001$). In contrast, being a current or former smoker was associated with a lower likelihood of BAC (current smokers: OR = 0.692, $p = 0.002$; ex-smokers: OR = 0.707, $p < 0.001$). The use of oral contraceptives was linked to decreased odds of BAC (OR=0.855, $p = 0.018$). Conversely, individuals on antiplatelet medications (OR = 1.156, $p = 0.020$) or other antihypertensive and cardiovascular medications (OR = 1.198, $p < 0.001$) showed an increased likelihood of BAC. Other factors, including BMI, alcohol consumption, history of breast cancer, chest radiotherapy, breast biopsy, postmenopausal status, hormone replacement therapy, and medications for diabetes or high cholesterol, did not demonstrate statistically significant associations with BAC presence.

3-3- Factors Associated with BAC Severity

Table 2 presents the results of the multinomial and ordinal logistic regression models assessing factors associated with the severity of BAC using an area-based method. In both

models, age was strongly associated with increasing BAC severity, with higher odds ratios observed as severity progressed, culminating in an OR of 1.138 for severe BAC in the multinomial model and 1.090 in the ordinal model. Smoking status exhibited an inverse association with BAC severity in both models, with current and former smokers having significantly lower odds of severe BAC. Parity was a robust predictor of BAC severity, particularly for severe cases, with an OR of 6.511 in the multinomial model and 2.543 in the ordinal model. The ordinal model generally supported the trends observed in the multinomial analysis, confirming the progressive relationship between age and parity with higher BAC severity. Additionally, the use of antiplatelet and cardiovascular protective medications was consistently associated with severe BAC in both models. In contrast, oral contraceptive use was inversely related to BAC severity, and BMI, alcohol consumption, and other medical history factors as listed in table 2 were not significant predictors in the ordinal model. Overall, the ordinal model aligned closely with the multinomial findings, reinforcing key associations across different severities of BAC.

Table 3 details the results of multinomial and ordinal logistic regression analyses examining factors linked to the intensity-based grading of BAC. Similar to the area-based grading approach, both models revealed that age was significantly associated with increasing BAC severity, with higher odds ratios as severity intensified. The multinomial model showed odds ratios of 1.045 for mild, 1.081 for moderate, and 1.132 for severe BAC, while the ordinal model demonstrated a continuous OR of 1.088, indicating a clear correlation between older age and more severe BAC. BMI exhibited a variable impact across the models. In the multinomial model, BMI was inversely related to mild BAC (OR = 0.989)

but positively associated with moderate and severe BAC. However, the ordinal model did not show significant results (OR = 1.005) for BMI. Smoking status demonstrated a significant negative association with BAC severity. Current smokers had lower odds of severe BAC in both models, with ORs of 0.400 in the multinomial model and 0.658 in the ordinal model. Former smokers also had reduced odds across all severity levels, underscoring the link between smoking and lower BAC severity. This relationship was measured by the mean intensity of the segmented BAC area. Parity was a significant predictor of BAC intensity, especially for severe cases. The multinomial model indicated odds ratios of 1.457 for mild, 2.087 for moderate, and 6.727 for severe BAC, while the ordinal model corroborated a high OR of 2.522, suggesting that higher parity is strongly associated with increased BAC severity. Medications for diabetes, high cholesterol, and cardiovascular protection had varied effects on BAC intensity. Antiplatelet use was consistently linked to more severe BAC, with ORs of 1.276 in the multinomial model and 1.178 in the ordinal model. Other antihypertensive and cardiovascular medications also showed significant positive associations with BAC severity. Overall, the ordinal model generally supported the multinomial findings, reinforcing the main associations, including the impact of age, parity, and smoking status on BAC severity as measured by its intensity.

3-4- Performance of the Segmentation Model

Using the test dataset, the segmentation model achieved a Jaccard Similarity Coefficient of 0.582 ± 0.031, which measures the overlap between the predicted and actual segmentation regions. The model's accuracy reached 0.996 ± 0.001. It also achieved a precision of 0.801

± 0.03, and a recall of 0.716 ± 0.041. The F1 score, a balance between precision and recall, was 0.756 ± 0.026.

Figure 3 visually illustrates this performance by presenting an example of the segmentation output alongside the ground truth, confirming the model's enhanced capability in segmenting the target regions accurately.

4- Discussion

Our study highlights significant associations between BAC presence and severity with key metabolic, reproductive, and lifestyle factors in women undergoing screening mammography. By focusing on BAC severity, rather than just its presence, we gained a more comprehensive understanding of BAC's associations with specific health factors. Adjusting for factors such as age, parity, smoking status, and medication use allowed us to control for potential confounders, providing clearer insights into these associations. Notably, diabetes and hypertension showed stronger associations with increasing BAC severity. Parity was independently linked to higher BAC severity, while an inverse relationship with smoking and oral contraceptive use became more pronounced with greater BAC severity.

As supported by previous studies [14-16], age emerged as a strong predictor of both BAC presence and severity. The prevalence of BAC increased markedly with age, from 10.32% in women aged 40–49 to 66.06% in those over 80, reflecting the natural progression of

arterial calcification as part of vascular aging. This highlights the need to consider BAC in age-related cardiovascular risk assessments.

A particularly noteworthy finding is the independent association between metabolic conditions, specifically diabetes and hypertension, and increased BAC severity. Women taking medications for diabetes exhibited higher adjusted odds of severe BAC (OR: 1.374 for intensity-based grading), and those on antihypertensive medications showed a similar association (OR: 1.457). The underlying pathophysiological mechanisms likely involve chronic hyperglycemia, leading to the accumulation of advanced glycation end-products, oxidative stress, and the osteogenic differentiation of vascular smooth muscle cells, which promote medial arterial calcification [17, 18]. Hypertension may contribute to this process through endothelial dysfunction and increased arterial wall stress [18].

While most of the literature supports these associations [14-16], there are some discrepancies. For example, a recent study by Lee et al.[19] involving 1020 Australian women found no association between BAC presence and diabetes or hypertension. Such differences could be attributed to variations in study design, sample size, or the focus on BAC's mere presence rather than its severity. In our study, assessing BAC severity allowed for stronger associations to be uncovered, underscoring the value of detailed evaluation in understanding BAC's clinical relevance.

Parity also emerged as a significant predictor of BAC severity, with parous women exhibiting substantially higher adjusted odds of severe BAC (OR: 6.511) as compared to nulliparous women, suggesting an independent association. The physiological and hormonal alterations during pregnancy, such as increased blood volume, altered lipid

metabolism, and endothelial adaptation may exert long-term effects on vascular health, potentially facilitating arterial calcification in later life [20]. These findings corroborate recent studies that underscore the importance of incorporating reproductive history into cardiovascular risk assessments [21-23] and reinforce the necessity for sex-specific risk assessment strategies [16]. Such considerations are pivotal for developing tailored approaches to cardiovascular disease prevention and management in women.

One particularly interesting finding in our study is the inverse association between oral contraceptive use and both the presence and severity of BAC. Women who had ever used oral contraceptive demonstrated lower odds of BAC presence, and this inverse trend continued with BAC severity, as oral contraceptive users with BAC showed reduced odds of developing severe calcification. Research on modern, low-dose oral contraceptives suggest they do not increase the risk of CVD and may even offer protective benefits, particularly for coronary artery health [24]. Supporting this, a large UK Biobank cohort study by Liu et al. [25] found no increased risk of CVD or all-cause mortality with oral contraceptive use, with some evidence of net benefit from long-term use. However, a recent systemic review by Fabunmi et al. [26] reported that oral contraceptive use is associated with an increase in traditional cardiovascular risk factors. Given that BAC has been increasingly linked to future cardiovascular events [14-16], the lower odds of BAC observed in oral contraceptive users in our study warrant further investigation. Importantly, while our findings highlight a potential relationship between oral contraceptive use and reduced BAC severity, it remains premature to infer any protective cardiovascular effects based on these data alone. Further research is essential to elucidate the complex interplay between oral

contraceptive use, BAC, and long-term cardiovascular outcomes, particularly in the context of other exogenous hormone exposures and reproductive factors.

An inverse association between smoking and BAC severity was observed. Current and former smokers had lower odds of severe BAC compared to non-smokers (OR: 0.364 for current smokers and OR: 0.545 for former smokers). This finding aligns with previous studies [14-16] and suggests that smoking may not promote medial arterial calcification as it does atherosclerotic intimal calcification. The mechanisms underlying this inverse relationship are not fully understood but may involve smoking-induced alterations in estrogen metabolism or differences in vascular calcification pathways [27, 28]. Despite this inverse association, smoking remains a well-established risk factor for cardiovascular disease due to its promotion of atherosclerosis and other deleterious vascular effects [29, 30]. This highlights a potential limitation in the use of BAC as a solitary predictor of cardiovascular risk, suggesting that BAC alone may not fully capture the complex interplay of risk factors in cardiovascular disease pathogenesis. Further research is needed to better understand the specific pathways through which smoking influences different types of vascular calcification and their implications for cardiovascular risk prediction.

No significant associations were observed between BAC presence and severity and factors such as BMI, alcohol consumption, postmenopausal status, hormone replacement therapy, cholesterol-lowering medications, history of breast cancer, radiotherapy, or breast biopsy

A key strength of this study lies in its large sample size and the objective evaluation of BAC using a validated deep learning model. By assessing both the presence and severity of BAC and adjusting for a wide range of confounders, we provide strong evidence for independent associations. Including BAC severity improves detection of significant relationships with

screening without additional burden on radiologists. However, several limitations exist. The retrospective design precludes causal inference, and the reliance on self-reported risk factors and medication data as proxies for clinical conditions may result in misclassification or incomplete capture of disease presence or severity. Furthermore, the lack of data on many traditional and non-traditional cardiovascular risk factors limits a comprehensive assessment of the broader cardiovascular risk profile. Incorporating BAC into mammography could enable earlier identification of women at increased cardiovascular risk, particularly given the burden of cardiovascular disease in women. Leveraging existing imaging techniques for risk stratification may improve outcomes through timely intervention. Future prospective studies are needed to validate these findings and clarify the relationship between BAC progression and cardiovascular outcomes. Investigating BAC's biological mechanisms may reveal therapeutic targets, while standardizing grading across platforms would enhance clinical implementation. Evaluating the cost-effectiveness and impact of BAC screening could inform policy and guideline development.

In summary, our study provides insights into the factors associated with BAC presence and severity, utilizing a novel deep learning-based model for BAC assessment. Age and parity emerged as significant factors related to BAC severity, with inverse associations observed with smoking and oral contraceptive use. Other determinants included the use of medications for diabetes, antiplatelets, and antihypertensive cardiovascular-protective medications. While our findings show strong associations between diabetes, antihypertensive medication use, and severe BAC, providing clinical recommendations for managing these conditions to lower BAC risk is beyond the scope of this study. Longitudinal studies are needed to assess whether improved metabolic control can slow

BAC progression and reduce cardiovascular risk, and to further validate BAC's prognostic utility across diverse health conditions.

Ethics Statement: The research reported in the review has adhered to the relevant ethical guidelines.

Patient Consent: The authors confirm that patient consent is not applicable to this article, because it is a retrospective study using de-identified data.

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Table 1. Predictors associated with the presence of Breast Arterial Calcification (BAC). Odds ratios (OR) with 95% confidence intervals (CI) and corresponding p-values are shown.

Predictors	***BAC Absent***	***BAC Present***	***Odds Ratio (95% CI, p-value)***
Age (Mean, STD)	62.41, 7.49	67.26, 7.64	**1.083 [1.075-1.091], p < 0.001**
BMI (Mean, STD)	26.0, 6.69	25.89, 9.08	1.003 [0.998-1.009], p = 0.26
If had a drink last year (#)	5722	2003	1.007 [0.895-1.133], p = 0.90
Being a current smoker (#)	444	98	**0.692 [0.548-0.875], p = 0.002**
Being an ex-smoker (#)	2661	782	**0.707 [0.637-0.784], p < 0 .001**
History of breast cancer (#)	25	11	0.894 [0.417-1.915], p = 0.772
History of chest radiotherapy (#)	87	31	0.854 [0.550-1.326], p = 0.48
History of breast biopsy (#)	995	417	1.118 [0.980-1.275], p = 0.09
Parous (#)	6373	2476	**2.334 [1.896-2.873], p < 0.001**
Postmenopausal (#)	6008	2316	1.000 [0.858-1.165], p = 0.99
Ever used oral contraceptives (#)	6066	2043	**0.855 [0.751-0.974], p = 0.018**
Ever used hormone replacement therapy (#)	3243	1347	1.012 [0.918-1.116], p = 0.81
Medications usage			

Medications for diabetes (#)	397	204	1.207 [0.995-1.463], p = 0.056
Medications for high cholesterol (#)	2087	949	0.970 [0.870-1.082], p = 0 .58
Antiplatelets (#)	1242	675	**1.156 [1.023-1.307], p = 0.02**
Other antihypertensive and cardiovascular protective medications (#)	2411	1162	**1.198 [1.080-1.329], p < 0.001**

Table 2. Predictors of breast arterial calcification (BAC) severity, as measured by area-based approach, using multinomial and ordinal logistic regression models.

	Multinomial logistic regression model			***Ordinal Model***
Predictors	***Mild***	***Moderate***	***Severe***	
Age	**1.038 [1.027-1.049]**	**1.083 [1.072-1.095]**	**1.138 [1.125-1.152]**	**1.090 [1.082-1.097]**
BMI	**1.01 [1.002-1.019]**	1.005 [0.997-1.013]	0.994 [0.985-1.002]	1.001 [0.996-1.006]
If had a drink last year	1.158 [0.961-1.395]	0.945 [0.792-1.128]	0.946 [0.792-1.13]	0.994 [0.886-1.115]

Being a current smoker	1.078 [0.8-1.453]	**0.568 [0.379-0.852]**	**0.364 [0.217-0.61]**	**0.648 [0.514-0.817]**
Being an ex-smoker	**0.804 [0.689-0.939]**	**0.766 [0.655-0.896]**	**0.545 [0.459-0.648]**	**0.686 [0.620-0.759]**
History of breast cancer	1.132 [0.383-3.347]	0.942 [0.313-2.837]	0.68 [0.189-2.447]	0.890 [0.427-1.854]
History of chest radiotherapy	0.855 [0.437-1.673]	0.914 [0.475-1.761]	0.809 [0.396-1.654]	0.854 [0.556-1.314]
History of breast biopsy	1.12 [0.92-1.363]	1.213 [0.999-1.473]	1.014 [0.82-1.255]	1.087 [0.956-1.236]
Parous	1.252 [0.964-1.626]	**2.782 [1.949-3.971]**	**6.511 [4.026-10.529]**	**2.543 [2.069-3.125]**
Postmenopausal	1.034 [0.825-1.295]	1.008 [0.797-1.275]	1.056 [0.822-1.357]	0.975 [0.839-1.132]
Ever used oral contraceptives	0.88 [0.719-1.076]	0.936 [0.767-1.142]	**0.767 [0.636-0.926]**	**0.840 [0.741-0.953]**
Ever used hormone replacement therapy	1.073 [0.926-1.244]	1.038 [0.894-1.205]	0.953 [0.817-1.112]	0.990 [0.900-1.089]
Medications usage				
Medications for diabetes	1.014 [0.75-1.371]	**1.371 [1.033-1.818]**	1.286 [0.964-1.715]	**1.232 [1.023-1.484]**

Medications for high cholesterol	1.048 [0.889-1.236]	0.928 [0.785-1.096]	0.954 [0.806-1.129]	0.955 [0.859-1.062]
Antiplatelets	1.063 [0.881-1.284]	1.129 [0.937-1.36]	**1.261 [1.052-1.513]**	**1.184 [1.052-1.333]**
Other antihypertensive and cardiovascular protective medications	**1.226 [1.048-1.434]**	1.05 [0.896-1.232]	**1.35 [1.149-1.586]**	**1.198 [1.083-1.325]**

Table 3- Predictors of breast arterial calcification (BAC) severity, as measured by intensity-based approach, using multinomial and ordinal logistic regression models.

	Multinomial logistic regression model			***Ordinal Model***
Predictors	***Mild***	***Moderate***	***Severe***	
Age	**1.045 [1.034-1.056]**	**1.081 [1.069-1.093]**	**1.132 [1.119-1.145]**	**1.088 [1.080-1.095]**
BMI	0.989 [0.982-0.997]	**1.012 [1.004-1.021]**	**1.01 [1.002-1.019]**	1.005 [0.999-1.010]
If had a drink last year	1.231 [1.016-1.491]	0.995 [0.834-1.188]	0.854 [0.718-1.017]	0.967 [0.862-1.085]

Being a current smoker	0.995 [0.731-1.354]	**0.612 [0.416-0.901]**	**0.400 [0.242-0.662]**	**0.658 [0.522-0.829]**
Being an ex-smoker	**0.779 [0.666-0.911]**	**0.692 [0.591-0.811]**	**0.639 [0.54-0.755]**	**0.699 [0.632-0.774]**
History of breast cancer	1.653 [0.65-4.205]	0.489 [0.112-2.135]	0.619 [0.173-2.216]	0.808 [0.388-1.683]
History of chest radiotherapy	0.823 [0.416-1.629]	0.962 [0.501-1.847]	0.781 [0.385-1.587]	0.853 [0.554-1.313]
History of breast biopsy	1.176 [0.968-1.428]	1.022 [0.834-1.253]	1.168 [0.951-1.433]	1.104 [0.972-1.255]
Parous	**1.457 [1.101-1.928]**	**2.087 [1.524-2.857]**	**6.727 [4.119-10.985]**	**2.522 [2.052-3.099]**
Postmenopausal	1.138 [0.899-1.44]	0.997 [0.79-1.26]	0.935 [0.735-1.191]	0.960 [0.827-1.115]
Ever used oral contraceptives	0.945 [0.769-1.163]	0.907 [0.746-1.102]	**0.745 [0.618-0.898]**	**0.832 [0.734-0.943]**
Ever used hormone replacement therapy	1.084 [0.934-1.258]	1.041 [0.897-1.207]	0.932 [0.8-1.087]	0.989 [0.899-1.088]
Medications usage				
Medications for diabetes	0.906 [0.644-1.275]	1.308 [0.992-1.724]	**1.374 [1.045-1.807]**	**1.253 [1.039-1.510]**

Medications for high cholesterol	0.908 [0.766-1.077]	1.053 [0.895-1.24]	0.972 [0.823-1.149]	0.972 [0.874-1.081]
Antiplatelets	1.07 [0.88-1.3]	1.106 [0.921-1.328]	**1.276 [1.066-1.526]**	**1.178 [1.047-1.326]**
Other antihypertensive and cardiovascular protective medications	1.039 [0.885-1.22]	1.159 [0.99-1.356]	**1.457 [1.241-1.712]**	**1.232 [1.114-1.364]**

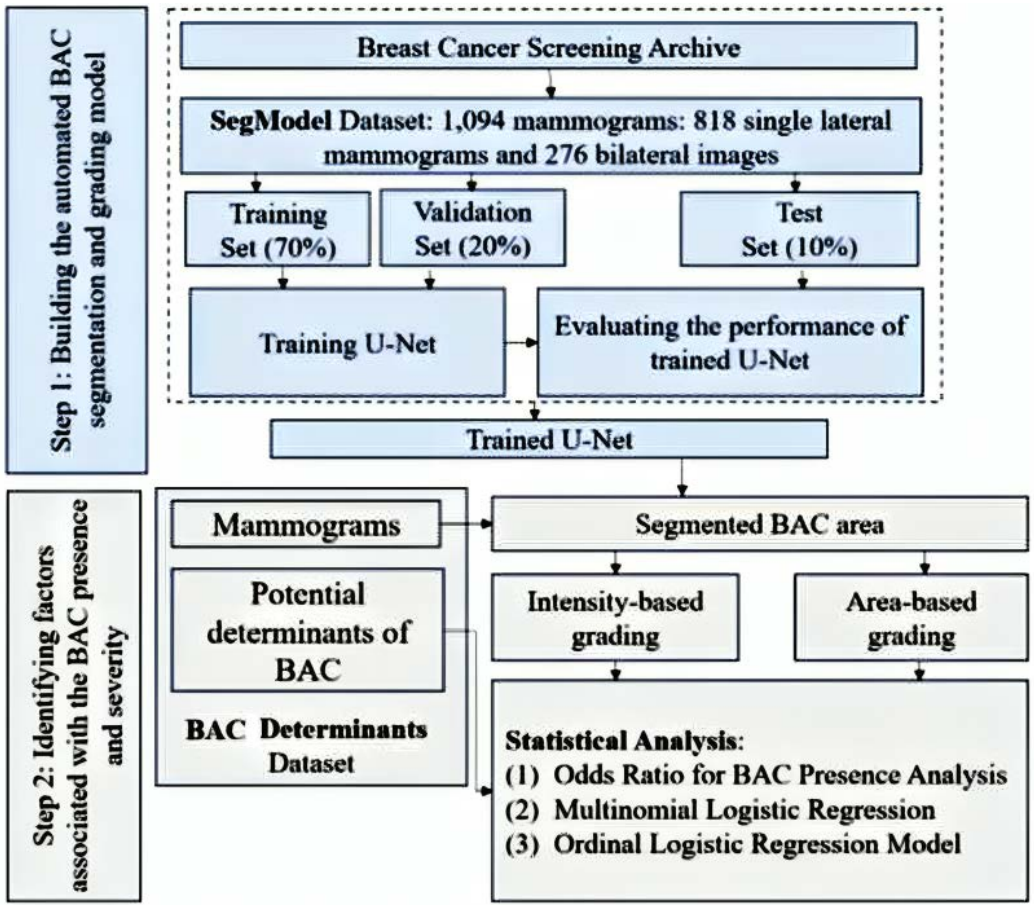

Figure 1. Flowchart depicting the study design for building the automated BAC segmentation and grading model and identifying factors associated with BAC presence and severity. In Step 1, the Breast Cancer Screening Archive dataset was divided into training (70%), validation (20%), and test sets (10%) to train and evaluate a U-Net model for BAC segmentation. In Step 2, the trained U-Net was applied to segment BAC areas, followed by grading the cases based on BAC intensity and area. Statistical analyses, including odds ratio analysis, multinomial logistic regression, and ordinal logistic regression, were conducted to identify potential determinants of BAC.

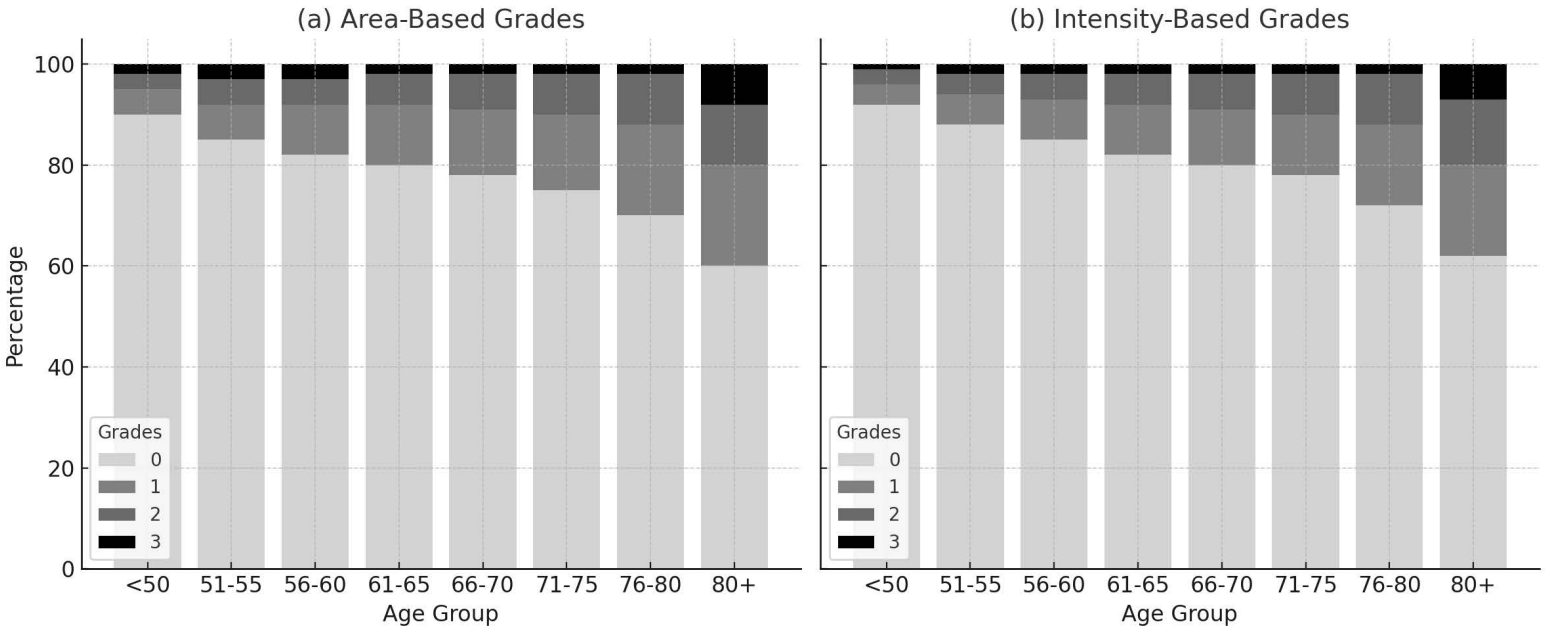

Figure 2. Stacked bar charts illustrate the distribution of Breast Arterial Calcification (BAC) severity grades across different age groups based on two grading methods: (a) Area-based grading and (b) Intensity-based grading. The x-axis represents the age groups, while the y-axis shows the percentage of individuals within each group assigned to one of four BAC severity grades: Grade 0 (no BAC), Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe). In both grading methods, there is a clear trend of increasing calcification severity with age. Younger age groups (<50, 51-55) show a predominant presence of Grade 0, indicating little to no BAC. As age increases, there is a noticeable shift toward higher BAC grades, particularly in the 71-75, 76-80, and 80+ age groups, where Grades 2 and 3 become more prevalent, suggesting greater severity of BAC with advancing age.

Figure 3. (a) The original mammography image, (b) the ground truth mask, and (c) the output of the segmentation model.

Chapter 5 A Novel Deep Learning-Based Grading System for Assessing Breast Arterial Calcification for Predicting Cardiovascular Events

5.1 Introduction

While Chapter 3 outlined the development of a prototype deep learning model for BAC segmentation, and Chapter 4 explored the factors associated with BAC presence and severity, Chapter 5 introduces the final stage of this research by validating the deep learning-based BAC grading framework as a predictive tool for cardiovascular risk stratification. This chapter focuses on establishing the relationship between graded BAC severity and cardiovascular outcomes, thereby reinforcing BAC's role as an independent biomarker for CVD.

This chapter builds on the findings of the under-review work: Ibrahim MA, Brennan PC, Suleiman ME, Rickard M, Arnott C, Barraclough JY, Tavakoli Taba A, Gandomkar Z. *A Novel Deep Learning-Based Grading System for Assessing Breast Arterial Calcification for Predicting Cardiovascular Events*. *Radiology: Cardiothoracic Imaging*. 2024. (Under review.) I, Mu'Ath Ibrahim, am the first author and was primarily responsible for the study conception, methodology design, data analysis, interpretation of the results, and drafting of the manuscript. Supervisors and co-authors contributed through clinical and methodological expertise, project supervision, and critical manuscript review.

Utilizing distinct datasets, this study evaluates the association between BAC severity and adverse cardiovascular events through hazard ratio analysis. The grading framework incorporates both area-based and intensity-based measures, providing a comprehensive assessment of BAC severity. Statistical analyses, including Cox proportional hazards models, are employed to determine the predictive value of BAC grades for cardiovascular outcomes. The results demonstrate that higher BAC grades are significantly correlated with an increased

risk of cardiovascular events, substantiating BAC's utility as an independent biomarker for CVD risk.

Building on the BAC grading framework introduced in Chapter 3, this chapter applies it to diverse populations to validate its predictive capability across different clinical settings. The integration of robust statistical methodologies ensures the reliability and generalizability of the findings. By linking graded BAC severity to tangible cardiovascular outcomes, this research bridges critical gaps in the current understanding of BAC as a non-invasive marker for cardiovascular risk, emphasizing its potential role in personalized risk assessment and preventive strategies.

Overall, Chapter 5 underscores the clinical utility of the BAC grading system in predicting cardiovascular outcomes and advocates for its integration into routine mammographic screenings. By establishing BAC as a key component of comprehensive cardiovascular risk assessment, this work contributes to the advancement of personalized medicine approaches in the early detection and management of CVD.

Radiology: Cardiothoracic Imaging

A novel deep learning-based grading system for assessing breast arterial calcification for predicting cardiovascular events

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A novel deep learning-based grading system for assessing breast arterial calcification for predicting cardiovascular events

Article Type

Original Research

Summary Statement

A deep learning-based grading system accurately detected and graded breast arterial calcification (BAC) on mammograms, demonstrating its potential as an independent predictor of cardiovascular risk in women.

Key Points

1. The U-Net model achieved a Jaccard Similarity Coefficient of 0.582, accuracy of 0.996, precision of 0.801, F1 score of 0.756, and recall of 0.716 in segmenting BAC.
2. BAC presence was associated with an increased cardiovascular risk, with an adjusted hazard ratio (HR) of 1.16 (95% CI: 1.10–1.23).
3. The combined grading system, integrating both area and intensity, showed that cardiovascular risk significantly increased with higher BAC severity, with a hazard ratio of 1.65 for severe BAC."

List of Abbreviations

1. BAC – Breast Arterial Calcification
2. CVD – Cardiovascular Disease
3. CAD – Coronary Artery Disease
4. MACE – Major Adverse Cardiovascular Events
5. HR – Hazard Ratio
6. U-Net – Convolutional Neural Network Model for Image Segmentation
7. MRI – Magnetic Resonance Imaging

8. CI – Confidence Interval
9. BMI – Body Mass Index
10. ACE – Angiotensin-Converting Enzyme

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Abstract

Purpose: This study proposes a deep learning-based framework for automated Breast arterial calcification (BAC) detection and severity grading, enhancing cardiovascular risk assessment in women.

Materials and Methods: This retrospective case-control study used two datasets: SegModel (1270 mammograms with BAC annotations) and MACEPred (3190 mammographic cases of women with major adverse cardiovascular events, plus 6458 controls). A U-Net segmentation model and Cox Proportional Hazards models were used to assess adjusted hazard ratios (HRs) for four BAC grading strategies: binary categorization, area-based grading (none, mild, moderate, severe), intensity-based grading, and a combined approach.

Results: The U-Net attained a Jaccard Similarity Coefficient of 0.582, accuracy of 0.996, precision of 0.801, F1 score of 0.756, and recall of 0.716 in segmenting BAC. The presence of BAC was associated with an adjusted HR of 1.16 (95% CI: 1.10 - 1.23). For the area-based grading system, HRs were 1.13 (95% CI: 1.06–1.20) for mild, 1.30 (95% CI: 1.18–1.45) for moderate, and 1.58 (95% CI: 1.15–2.18) for severe BAC grades. Intensity-based grading showed adjusted HRs of 1.08 (95% CI: 1.00–1.17) for mild, 1.10 (95% CI: 1.01–1.20) for moderate, and 1.18 (95% CI: 1.09–1.28) for severe grades. The combined approach demonstrated adjusted HRs of 1.102 (95% CI: 1.04–1.17) for mild, 1.249 (95% CI: 1.14–1.37) for moderate and 1.654 (95% CI: 1.30–2.10) for severe grades.

Conclusion: Our study presents a novel automated framework for BAC assessment that offers accessible and independent insights into cardiovascular risk in women.

Introduction

While coronary artery disease (CAD)-related deaths among women have decreased over three decades, this decline has stalled, with rising CVD mortality particularly noted within women under 55 (1). Notably, 20% of coronary incidents in women occur without primary risk factors (2). It is evident therefore women need access to comprehensive information about their CVD risk. Breast arterial calcification (BAC), often found incidentally during mammograms, results from calcification to the tunica media of the arterial wall. Its (non-breast) clinical significance was identified in 1980 when linked to diabetes (3) and studies since suggest a positive association between BAC and conditions like CVD and CAD (4), including the presence of atherosclerosis on computed-tomography coronary angiography (5). A recent cohort study of 5,059 postmenopausal women undergoing mammography confirmed these associations (6).

BAC assessment by radiologists is normally a manual process, followed by a present or absent categorization. This binary classification is prone to intra- and inter-reader variability (4) and fails to capture the full range of BAC appearances. Multiple grading scales (e.g., 3-point, 4-point, 12-point (5)) have been proposed, but the lack of standardized criteria for BAC quantification is a significant challenge. Manual assessment is also time-consuming and may not always be feasible due to limited expert availability (4).

Recent studies have explored deep learning (DL) approaches to assess BAC from digital mammograms, demonstrating DL's ability to segment BAC at levels comparable to or exceeding human experts (7-9). However, existing models are trained on limited annotated images, often from a single vendor, raising questions about their generalizability and these models have yet to be validated as independent risk predictors. Furthermore, segmented areas are not translated into an easy-to-communicate grading system that reflects incremental risk changes and potentially non-linearity in the relationship between BAC and cardiovascular risk. Additionally, the intensity of BAC areas varies, and it is unclear if combining segmentation area with intensity would enhance the grading system.

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In this study, we propose a novel DL framework to firstly automatically detect and segment BAC and secondly grade BAC severity. The outcomes could facilitate reproducible, independent, cost-effective and readily available CVD/CAD risk assessment in women undergoing breast screening as a matter of course. We compared grading systems based on area and intensity of segmentation and explored whether incorporating both adds value.

Materials and Methods

Dataset

This retrospective case-control study utilized two non-overlapping datasets—the SegModel and MACEPred Datasets—as illustrated in Figure 1. Both datasets were derived from Lifepool, a cohort comprising over 55,000 women participating in BreastScreen Australia who provided consent to enrol in this project. The SegModel Dataset was used to develop and evaluate a BAC segmentation model using the U-Net architecture. The MACEPred Dataset employed this model to establish a Cox proportional hazards model, assessing the effectiveness of the proposed deep learning-based BAC grading framework as an independent predictor of major adverse cardiovascular events (MACE). Using separate datasets prevented data leakage and potential bias in the results.

SegModel Dataset

In the development of the dataset, a medical imaging scientist specializing in mammography carefully selected 1270 mammographic images that depicted the presence of BAC from the Lifepool archive. The selection was made with consideration for the broad applicability of images across various medical imaging manufacturers and spatial resolutions. To ensure the accuracy of the selection, an expert radiologist with over three decades of experience verified the presence of BAC in the chosen images. The medical imaging scientist then utilized Label Studio software (10) for annotation. The initial expert radiologist and another senior radiologist then reviewed and confirmed the annotations to ensure their accuracy and establish consensus. Following verification, the images underwent a series of preprocessing steps including resizing to a uniform resolution, normalizing pixel values, adjusting

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brightness, and implementing various data augmentation techniques to enrich the dataset and prevent overfitting during the model training phase.

MACEPred Dataset

The dataset comprises 3190 mammographic cases from women who experienced extended major adverse cardiovascular events (MACE) and from 6458 women who had no such history (controls). These were matched based on their ages and the types of scanners used for image acquisition, resulting in a case-control ratio of approximately 1:2. Since both scanner type and women's ages can alter mammographic textural appearances, we ensured diverse representations in both case and control subsets.

Training the Segmentation Model

We chose the U-Net architecture for our base model, given its reputation for effectiveness in biomedical image segmentation (11). The U-Net's encoder-decoder structure with skip connections allows for capturing both local and global contextual information. 70% of the manually annotated images dataset was used for training (comprising both bilateral and unilateral annotations), 20% for validation, and the remaining 10% for testing. All images were resized 1024x1024 before feeding to U-Net. We set a learning rate of 0.001 and used custom loss function that blended binary cross-entropy and Jaccard loss as the loss function, optimized using the Adam optimization algorithm. We included both bilateral and unilateral annotations in our training dataset to provide our model with a comprehensive understanding of breast anatomy and BAC appearances. and to further enrich the model's understanding by offering global context. This approach aligns with clinical practice, where radiologists often consider information from both breasts when assessing mammograms.

Grading Breast Arterial Calcifications Severity

Four different strategies were employed to translate the area of segmented BAC into a grading system: (1) a **binary categorization**, (2) an **area-based four-scale grading** (absent, mild, moderate, and severe), (3) an **intensity-based four-scale grading**, and (4) a **combined approach integrating both area and intensity assessments**. As it is stated in Section 2-4, the BAC grades were fed into a Cox

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Proportional Hazards model and categorizing cases using a grading system can simplify the model, making it easier to interpret and communicate. Using a grading system to categorize cases rather using the total area of BAC as a continuous variable could also help with handling non-linearity in relationship between BAC severity and MACE risk and can mitigate the impact of extreme values (i.e. outliers) by grouping them into broader categories. The detailed grading system is provided in the supplementary material.

Statistical analysis

Four Cox Proportional Hazards models were constructed, one for each of the four grading approaches. All available risk factors, along with BAC grades, were included in the models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for each risk factor. A p-value of <0.05 was considered statistically significant. Adjustments were made for age to mitigate potential confounding effects, in accordance with guidelines recommended by Pearce (12), in addition to further adjustments for all additional variables available for the study participants. For ease of comparison with existing studies (6, 13), in the presented analysis, both age and BMI were treated as continuous variables. Please refer to the Supplementary Materials to see similar analysis when age and BMI are categorized into categories.

Results

The MACEPred cohort dataset consists of 3,190 women who experienced extended major MACE and 6,458 control women without such a history. The participants had an average age of 63.7 ± 7.8 years and were monitored over an average period of 6.09 years. The conditions classified as MACE were defined using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)**.** These conditions included angina pectoris, acute and subsequent myocardial infarction, current complications following acute myocardial infarction (ICD-10 scode I23*), other acute ischemic heart diseases (ICD-10 code I24*), chronic ischemic heart disease, cardiac arrest, heart failure, cerebral infarction (stroke, unspecified as hemorrhage or infarction), occlusion and stenosis of precerebral arteries (not resulting in cerebral infarction), occlusion and stenosis of cerebral arteries (not resulting in cerebral infarction), atherosclerosis, aortic aneurysm and dissection, other aneurysms and

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dissections, other peripheral vascular diseases, arterial embolism and thrombosis, and other disorders of arteries and arterioles. Additionally, any cardiovascular cause of death recorded in the National Death Index was considered a MACE. Further details on the specific ICD-10 codes and associated conditions are provided in supplementary materials. The characteristics of women included in the study are presented in Table 1.

Each of the **SegModel** and **MACEPred Dataset**s included screening examinations obtained from 11 different types of scanners produced by seven vendors, namely Agfa, Fuji, Hologic, Konica Minolta, Philips, Sectra Imtec Ab, and Siemens. By integrating diverse data sources comprehensively, we were able to evaluate the generalizability and performance of our DL-based grading system across various settings. Each screening examination comprised four images corresponding to left and mediolateral oblique (MLO) views, as well as cranial caudal (CC) views. For each participant, Body Mass Index (BMI), alcohol consumption, and current and former smoker status were collected using a survey. Using data linkage, information about medication uses for diabetes and high cholesterol, beta-blockers and calcium channel antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists, and Antiplatelets was also obtained. These medications can serve as surrogate variables for conventional CVD risk factors such as blood pressure, diabetes, or high cholesterol levels.

Performance of the Segmentation Model

To assess the performance of the trained model, a variety of performance metrics were utilized, including the Jaccard similarity coefficient, accuracy, precision, recall, and F1 score. These metrics are essential for evaluating the accuracy and completeness of the predicted segmentation masks and for comparing the predicted labels with the ground truth. The U-Net achieved a Jaccard Similarity Coefficient of 0.582, accuracy of 0.996, precision of 0.801, F1 score of 0.756, and recall of 0.716. To assess the performance of our proposed model, we benchmarked it against SCU-Net (7) and showed that. Figure 2 illustrates the effectiveness of our proposed model, presenting an example of the segmentation outputs alongside the ground truth.

Binary Categorization of Breast Arterial Calcification

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In the MACEPred dataset, the prevalence of BAC was found to be 26.96%, a figure consistent with existing literature for this age group (8), thereby confirming the representativeness of our study population. Initially, the Cox Proportional Hazard model, adjusted solely for age, evaluated the risk of MACE associated with the presence of BAC, defined by a threshold indicating BAC coverage of 0.2% or more of the breast area in mammograms. This model yielded an HR of 1.16 (95% CI: 1.10 - 1.23) for the presence of BAC above this threshold, indicating a 16% increased hazard for MACE when BAC is present. Subsequent adjustments for other CVD risk factors did not alter the significance of this finding, maintaining the HR at the same value, as detailed in Table 2.

Breast Arterial Calcification Severity Grading

Table 3 shows the adjusted HRs for various grading categories for area-based, intensity-based and combined approaches. As shown, when considering the area-based approach, after incorporating all available CVD risk factors adjusted HRs for mild, moderate, and severe BAC grades were determined to be 1.13 (95% CI: 1.06–1.20), 1.30 (95% CI: 1.18–1.45), and 1.58 (95% CI: 1.15–2.18), respectively. For intensity-based grading, with BAC “absent” serving as the reference category, the model yielded HRs of 1.08 (95% CI: 1.00–1.17) for mild, 1.10 (95% CI: 1.01–1.20) for moderate, and 1.18 (95% CI: 1.09–1.28) for severe. This consistent trend across BAC intensity grades suggests the potential of BAC intensity as an independent predictor of cardiovascular risk.

Discussion

Our study proposed a deep learning-based automated solution for segmenting BAC on mammograms from multiple vendors and translating the segmented areas into an easy-to-communicate, independent grading system. Our results show an association between BAC and increased risk for extended MACE, aligning with several previous studies (6, 14-16) that looked at BAC and CVD events. Training and validating our model on a multi-vendor dataset enhanced its generalizability and robustness compared to single-vendor models like Guo et al.'s SCU-Net (7). Our model outperforms SCU-Net in Jaccard similarity and F1 score, which are crucial for BAC segmentation, although SCU-Net shows slightly

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higher accuracy. Although it should be note that due to not cropping images to the breast area, accuracy metric could be skewed in (7).

Our study explores multiple grading strategies (binary, area-based, intensity-based, and combined). Unlike Wang et al. (8) and AlGhamdi et al. (9), who focused only on binary BAC detection, our model categorizes BAC into “mild,” “moderate,” and “severe.” Similar to the coronary artery calcium (CAC) score, which employs categories such as absent, minimal, mild, moderate, and extensive (19, 20) and indicates non-linear increments in HRs for cardiovascular events (21, 22), our study demonstrates similar non-linearity: from mild to moderate where HR increases from 1.10 to 1.25 compared with moderate to severe where HR increases from 1.25 to 1.65. Categorizing BAC severity simplifies risk communication and aids in modelling complex relationships more accurately than assuming a linear continuous variable.

This study offers important clinical implications. The BAC grading system, developed from routine screening mammograms, provides a non-invasive approach to improve cardiovascular risk stratification in women. Traditional risk models often underestimate risk in specific subgroups, such as younger or asymptomatic individuals. Deep learning–based automation enables integration into existing mammographic workflows, allowing opportunistic cardiovascular risk assessment during routine breast cancer screening. Such integration could support the early identification of women at increased risk and facilitate timely referral for preventive strategies. In settings where conventional risk scores may be insufficient, BAC assessment may enhance clinical decision-making. The use of AI also promotes consistency and scalability. However, prospective studies across diverse populations are needed to validate the grading system and assess whether changes in BAC severity over time reflect evolving cardiovascular risk. This evidence could support formal guideline inclusion and foster more tailored, gender-sensitive preventive care.

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In Iribarren et al.'s study (6), BAC was linked to a 1.51-fold heightened risk of atherosclerotic cardiovascular disease and a marginally increased HR of 1.23 for global CVD over a mean 6.5-year follow-up. For those with BAC>0, severity was categorized into tertiles. However, their study did not conclusively demonstrate a dose-response association with global CVD, possibly as a result of limiting the scope to postmenopausal women and did not encompass specific CVD events such as myocardial infarction. Furthermore, the analysis did not evaluate the number of calcified vessels, which correlates with the BAC coverage area.

It is imperative to acknowledge the study's limitations. One limitation is the lack of direct measurements of conventional risk factors such as blood pressure, diabetes, or high cholesterol levels. Instead, we relied on medication use as surrogate markers. In future studies, collecting these features directly could provide additional insights, particularly since retrieving medication information from existing medical health records is feasible and does not incur additional costs for implementing the model. The retrospective study design focused on women with an average age of 63: without a comprehensive analysis of a wider age group including younger or older women, the scope of our conclusions is restricted. However, given the cohort was retrieved from a screening archive, older and younger women were underrepresented. Moreover, our study included data from a single screening round; future research should prioritize longitudinal studies to explore the temporal relationship between BAC and CVD, including changes in BAC magnitude over time and its association with cardiovascular health. Finally, utilizing radiomic features and exploring detailed BAC characteristics beyond area and intensity can lead to a more refined cardiovascular risk assessment.

In conclusion, this study presents a novel framework that automates the detection and quantification of BAC, providing accessible and independent assessment of CVD risk in women. Our model's effectiveness was affirmed through testing across diverse scanner types and brands, with the inclusion of a new quantification method enhancing its clinical viability. Importantly, using the proposed grading system, as BAC severity increased, so did the HRs, indicating a significant rise in risk parallel to the increase in BAC severity and intensity. This underscores the potential of BAC as a valuable independent factor for predicting cardiovascular risk in women.

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Table 1: Characteristics of women Included in the study.

Characteristic	Case (N= 3190)	Control (N= 6458)
Age	63.2±7.6 $\bar{x}$	63.9±7.9 $\bar{x}$
BMI	26.5±9.9 $\bar{x}$	25.6±8.3 $\bar{x}$
If had a drink last year	2463 (77%)	5262 (81%)
Being a current smoker	255 (8%)	287 (4%)
Being an ex-smoker	1172 (37%)	2271 (35%)
Presence of BAC	949 (30%)	1652 (26%)
Medications usage		
Medications for Diabetes	321 (10%)	280 (4%)
Medications for High cholesterol	1252 (39%)	1784 (28%)
Beta blockers	284 (9%)	240 (4%)
Calcium channel antagonists	360 (11%)	409 (6%)
ACE inhibitors	754 (24%)	921 (14%)
Angiotensin II antagonists	825 (26%)	1070 (17%)
Antiplatelets	981 (31%)	936 (14%)

For all variables, the number of cases and their corresponding percentage of the total are presented, except for those marked with $\bar{x}$, where the mean ± standard deviation is reported.

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Table 2: Hazard Ratios (HRs) for cardiovascular disease (CVD) Risk Factors when using binary classification of cases based on the presence of Breast arterial Calcifications (BAC). The p-values for all risk factors are <0.05.

Characteristic	Case (N= 3190)	Control (N= 6458)	HR	%95 CI
Age	63.2±7.6 $\bar{x}$	63.9±7.9 $\bar{x}$	1.006	(1.00 - 1.01) ***
BMI	26.5±9.9 $\bar{x}$	25.6±8.3 $\bar{x}$	1.003	(1.00 - 1.01) *
If had a drink last year	2463 (77%)	5262 (81%)	0.875	(0.82 - 0.93) ***
Being a current smoker	255 (8%)	287 (4%)	1.845	(1.68- 2.03) ***
Being an ex-smoker	1172 (37%)	2271 (35%)	1.228	(1.16 - 1.30) ***
Presence of BAC	949 (30%)	1652 (26%)	1.164	(1.10 - 1.23) ***
Medications usage				
Medications for Diabetes	321 (10%)	280 (4%)	1.267	(1.16 - 1.38) ***
Medications for High cholesterol	1252 (39%)	1784 (28%)	1.128	(1.07- 1.20) ***
Beta blockers	284 (9%)	240 (4%)	1.463	(1.34 - 1.60) ***
Calcium channel antagonists	360 (11%)	409 (6%)	1.112	(1.03 - 1.21) **
ACE inhibitors	754 (24%)	921 (14%)	1.187	(1.12 - 1.26) ***
Angiotensin II antagonists	825 (26%)	1070 (17%)	1.178	(1.11 - 1.25) ***
Antiplatelets	981 (31%)	936 (14%)	1.578	(1.49 - 1.68) ***

* p-value<0.05 and >0.01

** p-value<0.01 and >0.001

*** p-value<0.001

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Table 3: Hazard Ratios (HRs) for cardiovascular disease (CVD) Risk Factors when using the area and intensity -based grading system for quantifying the presence and severity of the Breast arterial Calcifications (BAC). The p-values for all risk factors are <0.05. 95% Confidence Intervals (CI) are also presented.

	Area-based	Intensity-based	Combined	
Characteristic	**HR 95% CI**	**HR 95% CI**	**HR**	**95% CI**
Age	1.005 (1.00 - 1.01) **	1.006 (1.00 - 1.01) ****	1.006 (1.00 - 1.01) **	
BMI	1.003 (1.00 - 1.01) *	1.003 (1.00 - 1.01) ¶	1.003 (1.00 - 1.01) *	
If had a drink last year	0.875 (0.82 - 0.93) ***	0.875 (0.82 - 0.93) ***	0.875 (0.82 - 0.93) ***	
Being a current smoker	1.847 (1.68 - 2.03) ***	1.849 (1.68 - 2.03) ***	1.854 (1.68 - 2.03) ***	
Being an ex-smoker	1.232 (1.17 - 1.30) ***	1.227 (1.16 - 1.29) ***	1.233 (1.16 - 1.29) ***	
BAC Grading: Mild	1.126 (1.06 - 1.12) ***	1.077 (1.00 - 1.17) ¶	1.102 (1.04 - 1.17) **	
BAC Grading: Moderate	1.304 (1.18 - 1.45) ***	1.099 (1.01 - 1.20) *	1.249 (1.14 - 1.37) ***	
BAC Grading: Severe	1.584 (1.15 - 2.18) **	1.183 (1.09 - 1.28) ***	1.654 (1.30 - 2.10) ***	
Medications usage				
Medications for Diabetes	1.264 (1.16 - 1.40) ***	1.263 (1.16 - 1.38) ***	1.265 (1.16 - 1.38) ***	

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Medications for High cholesterol	1.129 (1.07 - 1.19) ***	1.127 (1.07 - 1.19) ***	1.128 (1.07 - 1.19) ***
Beta blockers	1.461 (1.34 - 1.60) ***	1.457 (1.33 - 1.59) ***	1.458 (1.33 - 1.59) ***
Calcium channel antagonists	1.109 (1.02 - 1.20) ***	1.109 (1.02 - 1.20) *	1.108 (1.02 - 1.20) *
ACE inhibitors	1.187 (1.12 - 1.26) *	1.185 (1.11 - 1.26) ***	1.185(1.11 - 1.26) ***
Angiotensin II antagonists	1.178 (1.11 - 1.25) ***	1.175 (1.11 - 1.25) ***	1.176 (1.11 - 1.25) ***
Antiplatelets	1.577 (1.49 - 1.68) ***	1.578 (1.49 - 1.68) ***	1.576 (1.49 - 1.68) ***

¶ p-value<0.1 and >0.05

* p-value<0.05 and >0.01

** p-value<0.01 and >0.001

*** p-value<0.001

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Figure 1: Overview of the study methodology illustrating dataset utilization, segmentation model construction, and integration into Cox proportional hazard analysis for evaluating the DL-based BAC grading.

Figure 2: Segmented Breast Arterial Calcification (BAC) compared to the ground truth: (a) Original mammogram, (b) Ground truth mask, and (c) Segmented BAC area obtained from the proposed model.

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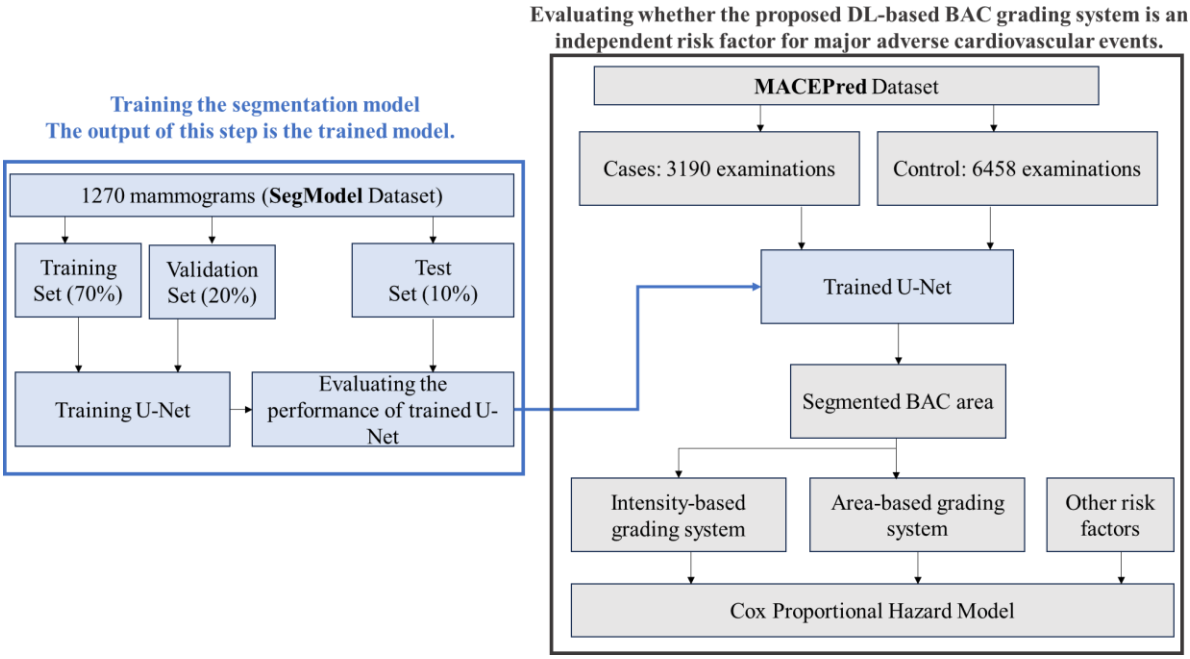

Figure 1: Overview of the study methodology illustrating dataset utilization, segmentation model construction, and integration into Cox proportional hazard analysis for evaluating the DL-based BAC grading.

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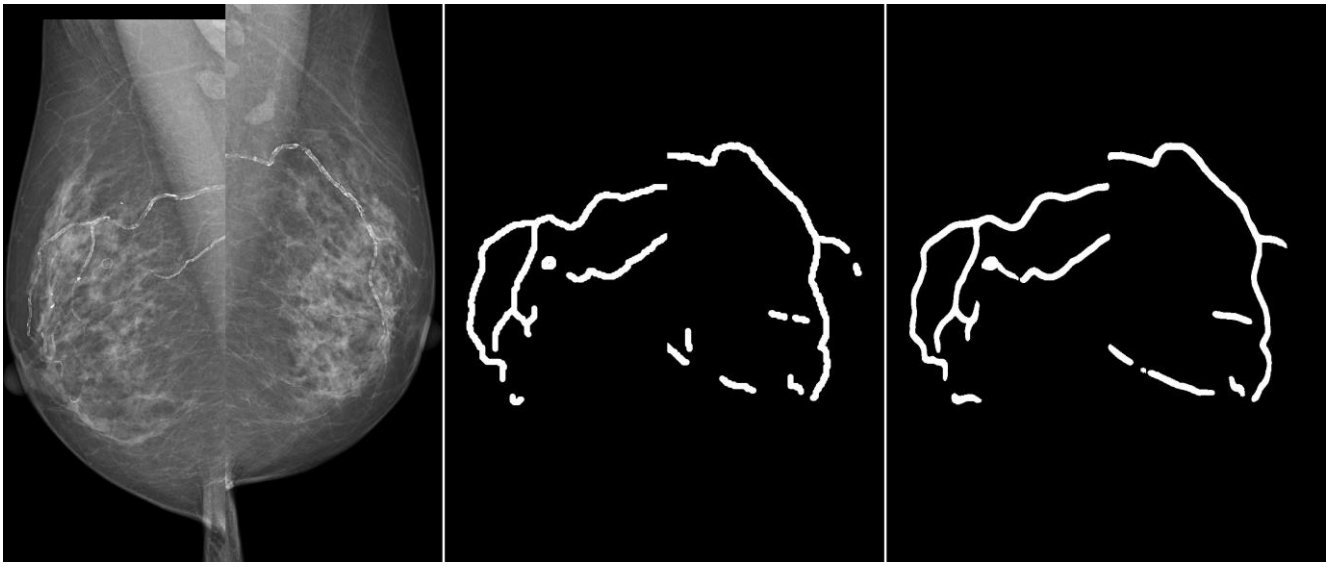

(a) (b) (c)

Figure 2: Segmented Breast Arterial Calcification (BAC) compared to the ground truth: (a) Original mammogram, (b) Ground truth mask, and (c) Segmented BAC area obtained from the proposed model.

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Grading Breast Arterial Calcifications Severity

The first strategy involved binary categorization of cases. Here, the percentage of breast occupied by BAC was extracted, and if the BAC area was below 0.002 of the total breast area, the case was classified as BAC absent; otherwise, it was considered present. This threshold was empirically set to exclude segmentation noise.

The second strategy introduced a four-scale BAC severity grading system based solely on area. This system yielded four grades: absent (representing BAC area below 0.002% of the total breast), mild (indicating cases with a BAC area between 0.002% and 0.01% of the total breast area), moderate (encompassing cases with a BAC area between 0.01% and 0.025% of the total breast area), and severe (indicating cases with a BAC area exceeding 0.025% of the total breast area). Each grade denoted an increasing severity of BAC presence.

The third strategy relied on the average intensity of the segmented BAC area. Firstly, the average intensity of the segmented area was calculated. Next, to account for variations in average intensity across different scanner types, we normalized the average intensity values by subtracting the mean and dividing by the standard deviation for each scanner. These normalized average intensity values were then categorized into four groups. The first group represented Absent, serving as the baseline, with a BAC area below 0.002% of the total breast area. The mild, moderate, and severe groups were determined by thresholding the normalized average intensity of BAC, using the first, second, and third tertiles, respectively.

The fourth strategy combined both area and intensity assessments. Building upon the area-based and intensity-based grading systems, this approach aimed to establish a unified grading system considering both factors simultaneously. The area-based grade served as the baseline, with adjustments (i.e., uprating) made based on intensity-based grades. For instance, if the area-based BAC grade was “mild” and the intensity-based grade suggested “mild”, the overall grade remained “mild”. However, if the intensity-based grade instead suggested “moderate” or “severe,” the overall grade of mild (from the area measure) was upgraded to “moderate.” Similarly, if the area-based BAC grade was “moderate” but the intensity-based grade was “severe,” the overall grade was assigned as “severe,” one level higher than the area-based grade. Otherwise, it remained “moderate”. Finally, if the BAC grade based on area was “severe”, regardless of the intensity grading, a grade of “severe” was assigned to the case. We selected the area as the baseline, as results from the second and third approaches indicated that the area-based grading approach provided a greater incremental effect as each grade level increased. Other approaches, such as considering the maximum value of two grading approaches or including both grades, were also explored, with results presented in the Supplementary Materials.

Supplementary Table 1. ICD-10 code definitions of Extended Major Adverse cardiovascular events and components

ICD-10 code	Description
I20*	Angina pectoris
I20*	Angina pectoris
I21*	Acute myocardial infarction
I21*	Acute myocardial infarction
I22*	Subsequent myocardial infarction
I22*	Subsequent myocardial infarction
I23*	Certain current complications following acute myocardial infarction
I23*	Certain current complications following acute myocardial infarction
I24*	Other acute ischaemic heart diseases
I24*	Other acute ischaemic heart diseases
I25*	Chronic ischaemic heart disease
I25*	Chronic ischaemic heart disease
I46*	Cardiac arrest
I50*	Heart failure
I50*	Heart failure
I63*	Cerebral infarction
I63*	Cerebral infarction
I64*	Stroke, not specified as haemorrhage or infarction
I64*	Stroke, not specified as haemorrhage or infarction
I65*	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I65*	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66*	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I66*	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I70*	Atherosclerosis
I70*	Atherosclerosis
I71*	Aortic aneurysm and dissection
I71*	Aortic aneurysm and dissection
I72*	Other aneurysm and dissection
I72*	Other aneurysm and dissection
I73*	Other peripheral vascular diseases
I73*	Other peripheral vascular diseases
I74*	Arterial embolism and thrombosis
I74*	Arterial embolism and thrombosis
I77*	Other disorders of arteries and arterioles
I77*	Other disorders of arteries and arterioles

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ICD-10 Codes defined by International Classification of Diseases, tenth revision (ICD-10) code World Health Organisation [1]

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Table 2: Hazard Ratios (HRs) for cardiovascular disease (CVD) Risk Factors, including categorized BMI and Age, using binary classification of cases based on the presence of Breast Arterial Calcifications (BAC). The p-values for all risk factors are <0.05.

Characteristic	Case (N= 3190)	Control (N= 6458)	HR	%95 CI
Age Group 1 VS Reference Age	1340 (42%)	2388 (37%)	1.08	(0.999 - 1.167) ¶
Age Group 2 VS Reference Age	1186 (37%)	2661(41%)	1.17	(1.078 - 1.27) ***
Age Group 3 VS Reference Age	221(07%)	543(8%)	1.134	(1.003 - 1.283) *
Reference Age	443 (14%)	866 (13%)	N/A	N/A
Underweight VS Normal weight	292 (9%)	454 (07%)	1.259	(1.146 - 1.383)
Overweight VS Normal weight	951(30%)	2083 (32%)	1.057	(0.991 - 1.128)
Obese VS Normal weight	1048 (33%)	1511 (23%)	1.212	(1.134 - 1.295)
Reference BMI Normal weight	899 (28%)	2410 (37%)	N/A	N/A
If had a drink last year	2463 (77%)	5262 (81%)	0.875	(0.82 - 0.93) ***
Being a current smoker	255 (8%)	287 (4%)	1.845	(1.68- 2.03) ***
Being an ex-smoker	1172 (37%)	2271 (35%)	1.228	(1.16 - 1.30) ***
Presence of BAC	949 (30%)	1652 (26%)	1.164	(1.10 - 1.23) ***
Medications usage				
Medications for Diabetes	321 (10%)	280 (4%)	1.22	(1.116 - 1.333) ***
Medications for High cholesterol	1252 (39%)	1784 (28%)	1.131	(1.069 - 1.196) ***
Beta blockers	284 (9%)	240 (4%)	1.461	(1.336 - 1.597) ***
Calcium channel antagonists	360 (11%)	409 (6%)	1.111	(1.025 - 1.204) *
ACE inhibitors	754 (24%)	921 (14%)	1.17	(1.1 - 1.244) ***
Angiotensin II antagonists	825 (26%)	1070 (17%)	1.155	(1.089 - 1.225) ***
Antiplatelets	981 (31%)	936 (14%)	1.562	(1.471 - 1.658) ***

¶ p-value<0.1 and >0.05
* p-value<0.05 and >0.01
** p-value<0.01 and >0.001
*** p-value<0.001

Age Categories:

- **Reference Age**: Age less than 55 years.
- **Age Group 1**: Age between 55 and 64 years.
- **Age Group 2**: Age between 65 and 74 years.
- **Age Group 3**: Age 75 years and above

BMI Categories:

- **Underweigh**t: BMI less than 18.5.
- **Normal weight**: BMI between 18.5 and 24.9.
- **Overweight**: BMI between 25 and 29.9.
- **Obese: BMI** 30 and above

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Table 3: Hazard Ratios (HRs) for cardiovascular disease (CVD) Risk Factors when using the area-based and intensity grading system for quantifying the presence and severity of Breast Arterial Calcifications (BAC). The p-values for all risk factors are <0.05. 95% Confidence Intervals (CI) are also presented. This includes both intensity and area in the same model.

Characteristic	HR	95% CI
Age	1.006	(1.002 - 1.009) **
BMI	1.003	(1.001 - 1.006) *
If had a drink last year	0.874	(0.823 - 0.928) ***
Being a current smoker	1.842	(1.676 - 2.025) ***
Being an ex-smoker	1.231	(1.167 - 1.299) ***
BAC Grading Area: Mild	1.177	(1.065 - 1.3) **
BAC Grading Area: Moderate	1.435	(1.211 - 1.701) ***
BAC Grading Area: Severe	1.747	(1.234 - 2.472) **
BAC Grading Intensity: Mild	1.003	(0.916 - 1.099) ¶
BAC Grading Intensity: Moderate	0.947	(0.838 - 1.071) ¶
BAC Grading Intensity: Severe	0.903	(0.78 - 1.046) ¶
Medications usage		
Medications for Diabetes	1.266	(1.159 - 1.382) ***
Medications for High cholesterol	1.129	(1.067 - 1.194) ***
Beta blockers	1.463	(1.338 - 1.599) ***
Calcium channel antagonists	1.11	(1.024 - 1.203) *
ACE inhibitors	1.188	(1.118 - 1.263) ***
Angiotensin II antagonists	1.179	(1.112 - 1.25) ***
Antiplatelets	1.58	(1.488 - 1.677) ***

¶ p-value<0.1 and >0.05
* p-value<0.05 and >0.01
** p-value<0.01 and >0.001
*** p-value<0.001

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Table 4: Hazard Ratios (HRs) for cardiovascular disease (CVD) Risk Factors when using the maximum value of area and intensity for quantifying the presence and severity of Breast Arterial Calcifications (BAC). The p-values for all risk factors are <0.05. 95% Confidence Intervals (CI) are also presented.

Characteristic	HR	95% CI
Age	1.006	(1.002 - 1.009) ***
BMI	1.003	(1.001 - 1.006) *
If had a drink last year	0.875	(0.824 - 0.93) ***
Being a current smoker	1.848	(1.681 - 2.031) ***
Being an ex-smoker	1.227	(1.163 - 1.294) ***
BAC Grading Combined: Mild	1.097	(1.02 - 1.181) *
BAC Grading Combined: Moderate	1.108	(1.018 - 1.205) *
BAC Grading Combined: Severe	1.191	(1.097 - 1.292) ***
Medications usage		
Medications for Diabetes	1.262	(1.156 - 1.378) ***
Medications for High cholesterol	1.127	(1.066 - 1.192) ***
Beta blockers	1.458	(1.333 - 1.594) ***
Calcium channel antagonists	1.109	(1.022 - 1.202) *
ACE inhibitors	1.185	(1.115 - 1.26) ***
Angiotensin II antagonists	1.175	(1.109 - 1.246) ***
Antiplatelets	1.58	(1.486 - 1.676) ***

* p-value<0.05 and >0.01
** p-value<0.01 and >0.001
*** p-value<0.001

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Chapter 6 Discussion and Conclusion

6.1 Chapter Introduction

Chapter 6 serves as the comprehensive discussion section of this thesis, summarizing the findings and their implications, addressing limitations, and proposing future research directions. The discussion is organized into four key sections:

- **Section I**: Provides a detailed summary of the major findings of the thesis, particularly focusing on the experimental studies from Chapters 3, 4, and 5.
- **Section II**: Discusses the clinical implications and impact of the developed model for enhancing CVD prevention in women, including recommendations based on the overall findings of the thesis.
- **Section III**: Explores the limitations of the work conducted in this thesis, addressing both methodological and practical constraints.
- **Section IV**: Finalizes the discussion by exploring future research directions and potential improvements for using mammograms in predicting CVD in women.

6.2 Section I: Summary and Major Findings

6.2.1 Accuracy of the DL Model:

The proposed DL model demonstrates significant advancements in automating BAC segmentation, addressing critical challenges that have long hindered the clinical application of BAC assessment. The model achieves robust performance metrics, including a Jaccard Similarity Coefficient (JSC) of 0.583, accuracy of 0.990, precision of 0.813, F1 score of 0.752, and recall of 0.70. These results indicate the model's ability to consistently identify and delineate BAC regions, overcoming limitations associated with small, irregular calcification

shapes and low contrast in mammographic images (1). High accuracy and precision minimize false positives, enhancing clinical reliability, while the recall metric reflects the model's capacity to capture true BAC regions, which is critical for accurate cardiovascular risk stratification. Detailed analysis of these performance metrics, including validation processes and dataset specifics, is provided in Chapter 3.

The model builds on limitations in traditional approaches, such as inconsistent manual evaluations and semiautomated methods. Manual assessments often classify BAC as present or absent, providing insufficient detail for nuanced risk stratification. semiautomated methods like Ge et al.'s (2) k-segments clustering struggled with highly curved calcifications, while Cheng et al.'s (3) two-step approach achieved high sensitivity and specificity on a small dataset (40 mammograms) but failed to address variability in breast composition. These shortcomings limited their applicability across different types of screening mammograms.

Our DL model bridges critical gaps in BAC analysis through an encoder-decoder architecture designed for precise segmentation of intricate BAC patterns. By training on a diverse dataset of 3,300 mammograms acquired from 11 scanner types spanning multiple manufacturers, the model achieves robust generalizability to varied imaging conditions and different screening mammogram types. This approach overcomes the limitations of smaller, homogeneous datasets, such as those used in SCU-Net (4). Unlike DU-Net (5), which focuses solely on detecting BAC presence, our model provides detailed segmentation and quantification, capturing both the extent and density of calcifications. This level of granularity enhances the reliability and consistency of cardiovascular risk assessments, making the model an invaluable tool in diverse screening workflows. By minimizing variability and improving accuracy, our DL model supports consistent and precise cardiovascular risk evaluations.

6.2.2 Integration of Semi-Supervised Learning:

The integration of semi-supervised learning into the model architecture successfully addressed the challenge of limited annotated data in medical imaging. Through a progressive pseudo-labelling strategy, 6,000 unlabelled mammograms were incorporated into the training process, resulting in significant enhancements to segmentation performance. For the 512x512 patch-based model, the JSC increased from 0.585 to 0.602, recall rose from 0.711 to 0.77, and the F1 score improved from 0.75 to 0.76. Similarly, the full-image model trained on resized 1024x1024 images saw an increase in JSC from 0.583 to 0.588, with recall improving from 0.701 to 0.747 and the F1 score rising from 0.752 to 0.757.

Compared to SCU-Net, which depends entirely on fully annotated datasets from single institutions, the semi-supervised framework demonstrated superior adaptability to varied imaging platforms and conditions. SCU-Net's limited generalizability was reflected in its lower JSC, while the patch-based model surpassed it with a JSC of 0.602. The semi-supervised approach reduced reliance on annotated data, streamlining resource-intensive preparation processes while achieving equal or better performance.

As detailed in Chapter 3, evaluations highlighted the complementary strengths of the two models. The patch-based model excelled in capturing fine-grained details, with higher recall and precision making it particularly adept at segmenting smaller or more intricate BAC regions. Conversely, the full-image model delivered consistent performance in maintaining contextual integrity, leveraging its broader field of view to enable comprehensive analysis of entire mammograms. These findings indicate that patch-based models are advantageous for detailed region-specific tasks, while full-image models are better suited for global evaluations requiring a holistic perspective.

Together, these results suggest that patch-based segmentation is ideal for applications demanding precise delineation of small calcifications, whereas full-image models are preferable for scenarios emphasizing structural relationships or overall mammographic interpretation. The integration of a semi-supervised learning strategy contributed to improved performance metrics for both models, with significant gains in JSC and recall. This enhancement balanced the system's sensitivity and specificity, reducing false positives while capturing a higher proportion of true BAC regions. Such outcomes underscore the robustness and versatility of the semi-supervised approach in addressing diverse imaging tasks.

6.2.3 Standardization of BAC Assessment:

The development of a DL model for BAC assessment represents a critical step towards standardizing its evaluation in clinical practice. Manual BAC assessments by radiologists are traditionally prone to significant intra- and inter-reader variability, as they rely on subjective interpretations and binary classification of presence or absence. This variability undermines the reliability of BAC as a cardiovascular risk marker. Furthermore, existing grading systems such as 3-point, 4-point, and 12-point scales lack standardization (1), complicating consistent quantification across clinical settings.

The proposed DL model directly addresses these issues by introducing an automated and uniform methodology for BAC detection and grading. Comparative analyses, as highlighted in the results section of Chapter 3, demonstrate the model's high inter-rater reliability, a key requirement for standardization. By leveraging advanced segmentation techniques, the model accurately identifies BAC with performance comparable to expert radiologists. Additionally, its grading framework incorporates both area- and intensity-based measures, enabling a more detailed and reproducible characterization of BAC severity.

This automated approach significantly reduces variability, enhances consistency, and provides a robust foundation for the integration of BAC assessment into CVD risk protocols. By delivering reproducible results, the DL model supports the establishment of universally accepted standards for BAC evaluation. Furthermore, automation streamlines the assessment process, minimizing the workload on radiologists and allowing scalable application across diverse healthcare settings.

The consistent and objective grading system employed by the DL model serves as a foundation for standardizing BAC assessment. By utilizing a systematic approach to quantify BAC based on area and intensity measures, the DL framework establishes a reproducible and uniform method for evaluating BAC severity. This grading system minimizes variability and ensures consistency across diverse clinical settings, positioning it as a benchmark for integrating BAC into cardiovascular risk stratification. As a step toward standardization, the DL-based system provides a robust, scalable, and actionable tool that supports the broader goal of incorporating BAC assessment into routine clinical practice for early cardiovascular risk detection.

6.2.4 Association Between BAC and CVD Risk Factors:

This study provides robust evidence of significant associations between BAC and key cardiovascular risk factors, underscoring the clinical relevance of assessing BAC severity rather than solely its presence. As detailed in Chapter 4, BAC prevalence increased sharply with age, rising from 10.3% in women aged 40–49 to 66.1% in those over 80. This pronounced trend reflects the progressive accumulation of vascular calcifications with age, positioning BAC as a marker of vascular aging and long-term cardiovascular stress.

Metabolic conditions such as diabetes and hypertension were robustly linked to higher BAC severity. Women with diabetes had a 37% greater likelihood of severe BAC, while those on

antihypertensive medications demonstrated a similar risk increase (OR: 1.46). These findings align with mechanisms involving chronic hyperglycemia and oxidative stress, which promote vascular calcification. Additionally, reproductive history was a key determinant, with parous women exhibiting a sixfold increased risk of severe BAC. Conversely, oral contraceptive use (OR: 0.77) and smoking (OR: 0.36) were inversely associated with severe BAC, highlighting potential hormonal effects and the specificity of medial calcification pathways distinct from intimal calcification.

The relatively large sample size of 9,648 women and the application of severity-based grading in this study effectively addressed the inconsistencies noted in prior research, as discussed in the literature review in Chapter 2. While most previous studies identified associations between BAC and cardiovascular risk factors, their findings were often inconsistent and variable, largely due to limitations such as small sample sizes and the reliance on binary presence measures. By incorporating a severity-based grading approach, this study was able to capture the gradations of calcification, revealing stronger and more consistent associations with cardiovascular risk factors. This methodology provided a more comprehensive understanding of BAC as an integrative marker of cardiovascular risk, emphasizing that the severity of calcification offers greater clinical relevance than its mere presence.

6.2.5 BAC as an Independent Risk Factor for CVD events:

As demonstrated in Chapter 5, BAC is an independent predictor of cardiovascular events, with its predictive power enhanced through the use of severity-based grading systems. The presence of BAC was associated with a 16% increased risk of cardiovascular events, but severity-based gradations provided greater differentiation. For example, mild, moderate, and severe BAC were associated with HRs of 1.13, 1.30, and 1.58, respectively, using area-based grading. Similarly, intensity-based grading showed HRs of 1.08, 1.10, and 1.18 for the same severity levels.

The combined grading system, which integrates area and intensity, demonstrated superior predictive value. This approach captured the non-linear relationship between BAC severity and cardiovascular risk, with hazard ratios of 1.102 for mild, 1.249 for moderate, and 1.654 for severe BAC. By combining the physical extent (area) and biological intensity of calcification, this method accounted for both structural and compositional aspects of vascular calcification, providing a more comprehensive risk assessment.

The non-linear nature of the relationship between BAC and cardiovascular risk highlights the limitations of binary presence measures. For instance, studies that rely solely on presence often underestimate the clinical significance of BAC. The introduction of grading thresholds, as used in this study, resolves this limitation by aligning risk stratification with the progressive nature of BAC severity. Moreover, the combined approach demonstrated its utility in refining cardiovascular risk predictions, making it particularly valuable in clinical settings where personalized interventions are prioritized.

These findings suggest that integrating BAC severity into cardiovascular risk models can improve stratification and facilitate targeted prevention strategies. The use of combined area- and intensity-based grading offers a standardized framework for evaluating BAC, enhancing its applicability as a non-invasive marker of cardiovascular health.

6.3 Section II: Clinical Implications and Recommendations

6.3.1 Improved Precision in CVD Risk Assessment

The inclusion of BAC into CVD risk assessment frameworks offers a complementary, sex-specific enhancement to traditional models. Traditional risk scores, such as the Framingham Risk Score or ASCVD calculators, have long served as valuable tools in estimating cardiovascular risk (1). However, their reliance on generalized metrics often fails to capture

the nuances of sex-specific risk factors, leading to an underestimation of cardiovascular risk in women, particularly younger women or those presenting with atypical symptoms (1). By incorporating BAC, which is a marker visible on routine mammograms and associated with increased cardiovascular risk, clinicians gain an additional layer of precision tailored specifically to women.

This integration can significantly improve the identification of women at elevated cardiovascular risk, especially those who may appear low risk based on traditional algorithms alone. BAC does not replace traditional metrics such as blood pressure, lipid profiles, or diabetes status; instead, it serves as a supplementary marker that strengthens overall risk stratification. Women identified with BAC can receive targeted interventions, including lifestyle changes like improved diet and exercise, earlier initiation of preventive therapies like statins or antihypertensives, and more frequent cardiovascular monitoring. As such, BAC fills a critical gap in current strategies by offering a gender-specific, accessible tool for refining cardiovascular risk assessment and supporting early, personalized care for women.

6.3.2 Dual-Function Mammographic Screenings

Mammographic screenings are widely implemented for breast cancer detection and represent a cornerstone of preventive health care for women. Leveraging this existing infrastructure to simultaneously assess cardiovascular risk through BAC analysis offers a dual-purpose approach that enhances the utility of these screenings. This improvement does not require additional diagnostic tools, patient time, or exposure to radiation, thereby providing a cost-effective method for identifying two of the leading causes of mortality in women: breast cancer and CVD (1).

This dual-function screening model presents multiple benefits. Clinically, it improves efficiency by enabling healthcare providers to address two major health concerns during a single imaging session. Significant BAC findings, identified alongside potential breast abnormalities, can trigger timely cardiovascular evaluations. These findings allow earlier initiation of preventive interventions, which could reduce the incidence of CVD. Moreover, integrating BAC assessments into routine mammography ensures broader population coverage, particularly among women who may not undergo separate cardiovascular screenings due to financial or systemic barriers. This approach enhances health equity, enabling at-risk populations to receive crucial preventive care during routine check-ups.

6.3.3 Standardized and Objective BAC Grading

Traditional methods of assessing BAC are manual and highly dependent on the subjective judgment of radiologists, which introduces variability and limits their reliability in clinical practice. The DL model proposed for BAC evaluation eliminates this variability by providing an automated, standardized framework for assessing the presence and severity of calcification. By quantifying BAC based on area and intensity, the DL model enhances the consistency of assessments and improves the stratification of cardiovascular risk.

The proposed grading system categorizes BAC severity into absent, mild, moderate, and severe levels, allowing for a more nuanced interpretation of cardiovascular risk. This standardization facilitates comparisons across institutions, enabling the development of universally accepted guidelines for integrating BAC into CVD screening protocols. Additionally, the automation of BAC grading significantly reduces the burden on radiologists and enhances the scalability of the model in clinical settings. The DL model's adaptability to different imaging systems further underscores its potential for widespread application, ensuring that women undergoing

mammography benefit from consistent, high-quality evaluations irrespective of location or resources.

6.3.4 Recommendations for Policy and Clinical Guidelines

The growing body of evidence supporting the role of BAC as an independent marker for cardiovascular risk highlights the need for its inclusion in national and international clinical guidelines. Policies advocating for routine BAC assessment during mammographic screenings can significantly enhance the early detection of CVD in women, a population historically underrepresented in cardiovascular risk research and intervention programs.

To achieve this integration, clinical guidelines should be updated to mandate the evaluation of BAC as a standard practice in CVD screening. Such updates would align with broader preventive health initiatives, emphasizing early detection and risk stratification. Moreover, professional training programs should be implemented to educate clinicians and radiologists on the significance of BAC findings and their implications for cardiovascular health. Awareness campaigns aimed at the public could further encourage women to participate in dual-purpose mammographic screenings, highlighting their expanded benefits. Finally, ongoing research and investment in BAC-related technologies, such as deep learning models, are critical for validating their effectiveness in diverse populations and refining their predictive capabilities. By adopting these measures, healthcare systems can ensure that BAC becomes an integral component of comprehensive cardiovascular care for women.

6.4 Section III: Limitations

Despite the promising results, the study has several limitations that need to be addressed in future research.

6.4.1 Unbalanced Data:

While the model showed high accuracy, its generalizability across diverse populations and different types of mammography equipment requires further validation as the images were not balanced among all scan types. The dataset used in this study predominantly consisted of images from a limited range of mammography equipment, which may not represent the diversity of devices used in clinical practice. This limitation could affect the model's performance when applied to images from different types of mammography equipment. Further validation with a more diverse dataset, including images from various types of mammography equipment and a broader demographic, is necessary to ensure the model's robustness and applicability. Ensuring a balanced dataset that represents a wide range of equipment and patient demographics will help improve the model's accuracy and reliability in real-world settings. Chapter 3 discussed the dataset composition and the potential biases introduced by the over-representation of certain screening types. The study highlighted the need for more comprehensive datasets that include a variety of mammographic systems to ensure the model's applicability across different clinical environments. Addressing this limitation will be crucial for deploying the model in diverse healthcare settings.

6.4.2 Longitudinal Studies:

The study primarily focused on single round mammograms. Longitudinal studies are needed to monitor the progression of BAC over time and its impact on cardiovascular health. Monitoring BAC progression over time can provide deeper insights into its role as a predictive marker for cardiovascular events. Longitudinal data would allow for the assessment of how changes in BAC correlate with the development of cardiovascular diseases, enhancing the predictive power of BAC assessments. Longitudinal studies would also help in understanding the natural history of BAC and its progression, which is crucial for developing effective

prevention and intervention strategies. Chapter 4 emphasized the importance of longitudinal data in understanding BAC dynamics. The study proposed a framework for conducting longitudinal research, including the design of follow-up studies to track BAC changes and their association with cardiovascular outcomes. This approach will provide a more comprehensive understanding of BAC's role in cardiovascular health.

6.4.3 Limited Data on Clinical Conditions

The study used surrogate indicators for conditions such as diabetes, hypertension, and high cholesterol based on medication use. Having actual data on these conditions in women would improve the accuracy of the findings. Actual clinical data on the presence and severity of these conditions would provide a more accurate basis for evaluating their association with BAC. Understanding the full impact of these conditions and their treatments on BAC would help in refining the model's predictive capabilities. This approach would ensure that the associations observed are not merely due to medication effects but reflect the true relationship between BAC and these conditions. In Chapter 4, the study acknowledged the limitations of using medication use as a surrogate for clinical conditions. The study recommended incorporating more detailed clinical data, including diagnostic information and treatment histories, to improve the accuracy of the analyses. This will help in better understanding the interplay between BAC and cardiovascular risk factors.

6.4.4 Absence of Broader Traditional Risk Factors

While the model has shown high accuracy, it lacks consideration of several traditional risk factors that could further enhance its predictive capability for BAC. Factors such as the number of childbirths and breastfeeding history were not included, despite evidence linking these factors to BAC (1). Additionally, critical cardiovascular risk factors, such as family history of

cardiovascular disease, physical activity levels, dietary habits, psychosocial stress, socioeconomic status, ethnicity, specific lipid profiles (e.g., LDL and HDL cholesterol), and chronic kidney disease (CKD) are absent from the dataset. These factors are known to contribute to cardiovascular risk and could play a significant role in BAC development and severity (6, 7).

Incorporating this broader range of medical, lifestyle, and traditional cardiovascular risk data would provide a more comprehensive understanding of the factors influencing BAC progression. Examining these additional variables could reveal new insights into the complex interplay between reproductive health, lifestyle behaviors, and vascular health, offering a more nuanced view of BAC's role in cardiovascular disease risk. The study in Chapter 4 underscores the potential impact of these traditional risk factors on BAC, suggesting that a more holistic dataset could improve the model's robustness and applicability in diverse clinical settings.

6.5 Section IV: Future Directions

Future research should aim to address the limitations identified in this study and explore new avenues for enhancing the predictive power of BAC assessments.

6.5.1 Longitudinal Studies:

Conducting longitudinal studies to monitor BAC progression over time and its relationship with CVD outcomes. Longitudinal data would provide valuable insights into how BAC evolves over time and its correlation with cardiovascular events. Enhancing the model with temporal data would improve its ability to predict long-term cardiovascular risks. Longitudinal studies would also help in understanding the progression of BAC and its impact on cardiovascular health, aiding in the development of more effective prevention and intervention strategies. Future research should focus on designing and implementing longitudinal studies that track

BAC changes over several years. This approach will provide a deeper understanding of BAC dynamics and their implications for cardiovascular health. Such studies could involve regular mammographic screenings and detailed clinical follow-ups to assess the development of cardiovascular conditions.

6.5.2 Validation Across Diverse Populations:

Validating the deep learning model across diverse populations and clinical settings is essential to ensure its robustness and broad applicability. Including a wider range of demographic groups—such as varied ethnicities, age groups, and geographic regions—will help the model perform effectively for a broader patient population. Literature indicates that BAC prevalence varies significantly across racial groups, with the highest prevalence reported among Hispanics (35%), followed by African Americans (25%), Caucasians (24%), and Asians (7%) (8). These differences underscore the importance of testing the model across diverse racial and ethnic groups to capture these variations accurately.

To ensure the model's generalizability, future studies should incorporate images from various types of mammography equipment and involve patients from different demographic backgrounds. Understanding how BAC manifests in distinct groups will enhance the model's reliability and support its adoption in various clinical settings. Collaborating with multiple healthcare institutions can facilitate the collection of such diverse datasets, strengthening the model's robustness and effectiveness across populations and clinical environments.

6.5.3 Exploring Relationships with Other Mammographic Features:

Investigating the association between BAC and other mammographic features such as breast size, breast density, and microcalcifications offers the potential to develop integrated risk assessment tools that enhance predictions for both breast cancer and cardiovascular diseases.

Literature suggests that features like microcalcifications and high breast density may correlate with an increased risk of cardiovascular events【9,10】, underscoring the potential value of combining these indicators with BAC for a more comprehensive health assessment. Understanding the interactions between multiple mammographic features and their links to health outcomes would strengthen the model's predictive accuracy.

While breast density and size may influence image characteristics, they likely have minimal impact on BAC intensity, as arterial calcifications are highly radiopaque and visually distinct from surrounding soft tissue. In this study, breast size was accounted for by expressing BAC severity as a percentage of the affected area rather than using absolute values. However, technical factors such as exposure settings and vendor-specific post-processing algorithms can significantly affect image contrast and the perceived intensity of BAC. To mitigate this variability, normalising BAC intensity relative to the background of adjacent fat or glandular tissue may offer a more robust measure of contrast. This strategy could reduce the influence of both anatomical and technical differences across patients and imaging platforms, supporting more consistent BAC grading. Future studies should explore the combined impact of multiple features such as BAC, elevated breast density, and microcalcifications on cardiovascular risk prediction, ultimately contributing to more holistic and integrated assessments of both cardiovascular and oncological health.

6.5.4 Incorporating Dynamic BAC Assessments

Dynamic BAC assessments, tracking temporal changes in BAC size, density, and distribution, could provide deeper insights into cardiovascular risk. Such an approach would improve the model's ability to monitor BAC progression and identify critical periods for intervention, aiding in developing personalized, time-sensitive prevention strategies.

6.5.5 Integration with Broader Risk Factors

Incorporating traditional cardiovascular risk factors (e.g., cholesterol levels, physical activity, genetic markers) with BAC assessments could enhance predictive models by creating multifactorial risk profiles. This integration would allow for more personalized CVD risk assessments, leading to more targeted and effective prevention strategies for individual patients.

6.5.6 Automated Reporting Systems:

Develop automated reporting systems that integrate BAC assessments with clinical decision support tools to aid radiologists and clinicians in risk stratification and management. Automated systems could streamline the reporting process, reduce errors, and provide timely risk assessments for clinicians. Ensuring that these systems integrate seamlessly into existing clinical workflows is essential for their successful adoption. Automated reporting systems would enhance the efficiency and accuracy of BAC assessments, improving patient care and outcomes. Future studies should focus on developing and testing automated reporting systems that incorporate BAC assessments into clinical workflows. These systems could provide real-time risk assessments and decision support for clinicians, facilitating timely and informed interventions. Developing user-friendly interfaces and ensuring seamless integration with existing electronic health records will be crucial for the successful implementation of these systems.

6.6 Conclusion

The development of a DL-based model for detecting, segmenting, and BAC represents a significant advancement in CVD risk assessment, particularly for women. This innovation addresses critical limitations of traditional risk assessment tools, which often fail to account for

gender-specific factors and tend to underestimate women's cardiovascular risk. By leveraging BAC as a biomarker, this model provides an objective, consistent, and automated approach to evaluating cardiovascular risk, enhancing precision and supporting early, targeted interventions.

Integrating BAC assessment into routine mammographic screenings transforms these examinations into dual-purpose diagnostic tools, addressing both breast cancer and cardiovascular health without additional costs or radiation exposure. The model demonstrated high reliability and alignment with expert radiologists in grading BAC severity, using both area- and intensity-based methods. These grading systems showed strong associations between BAC severity and cardiovascular risk, underscoring the clinical utility of BAC as an independent biomarker for adverse cardiovascular outcomes.

This approach offers substantial benefits by optimizing existing healthcare infrastructure and improving access to comprehensive risk assessment for women. By identifying at-risk individuals earlier, the model supports timely preventive measures, including lifestyle interventions, medical therapies, and closer monitoring, which are critical for reducing the burden of cardiovascular disease.

Future efforts should focus on expanding the integration of BAC assessments with other cardiovascular biomarkers to create more holistic and personalized risk profiles. Validation across diverse populations and further integration into clinical guidelines and screening protocols will ensure broader adoption and maximize its impact. The adoption of BAC as a routine part of cardiovascular risk assessment has the potential to significantly improve healthcare outcomes by addressing the unique health challenges faced by women, reducing mortality from both breast cancer and cardiovascular disease. This dual-purpose innovation represents a major step forward in advancing preventive healthcare for women globally.

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Appendix A

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Automated Segmentation of BAC Using Deep Learning for Predicting CVD

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Purpose: The purpose of this study is to enhance the accuracy of breast arterial calcification (BAC) segmentation on screening mammograms while reducing the reliance on extensive manual annotations, and minimizing the costs and time associated with manual segmentation. The study aims to contribute to the early detection of cardiovascular diseases in women and improve risk assessment for preventive measures [1].

Methods and Materials: The study used data from the Lifepool registry, which contains records of 54,000 Australian women who underwent routine screening mammograms. For the first phase, 4,300 cases were manually annotated by a medical imaging scientist and validated by a highly experienced radiologist in reading mammograms. The annotation process involved locating BAC on mammograms and determining its boundaries using the process suggested by Al Ghamdi et al.[2] These cases contained approximately 27,000 digital mammograms, with BAC present in 3,330 mammograms. To analyze the unannotated mammography images, we propose a semi-supervised deep learning approach that leverages both labeled and unlabeled data to improve the accuracy of BAC segmentation. Our approach combines the U-net architecture, a well-established deep learning method specifically designed for medical image segmentation, with semi-supervised learning technique [3,4]. The process involves constructing an initial training dataset from available labelled mammography images and training the proposed model accordingly. Through an iterative procedure, the trained model is assessed on subsets of randomly chosen mammography images from the unlabelled dataset, generating data with synthetic labels known as pseudo-labelled data. This data is employed to expand the training dataset, allowing for model fine-tuning using the larger dataset. The iterative procedure continues until all unlabelled data is included, ultimately enhancing the model's performance in the segmentation task by merging labelled and model-generated pseudo-labelled data. We evaluated our approach on a dataset of mammography images from 100 women and demonstrated that our method outperforms human experts and other related methods for BAC segmentation.

Results: The experimental results of the proposed model reveal a precision of 66%, a recall rate of 79%, an accuracy of 98%, a Jaccard similarity index of 0.56, and an F1 score of 0.72 for the detection and segmentation of BAC from mammograms.

Conclusion: Our proposed model can accurately segment BAC in unannotated mammography images, providing valuable insights into the early detection of cardiovascular diseases in women.

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Appendix B

Deep Learning Analysis of Breast Arterial Calcifications: A Study on Predicting Cardiovascular Disease in Women

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ABSTRACT

Breast arterial calcifications (BAC) are increasingly recognized as indicative markers for cardiovascular disease (CVD). In this study, we manually annotated BAC areas on 3,330 mammograms, forming the foundational dataset for developing a deep learning model to automate assessment of BAC. Using this annotated data, we propose a semi-supervised deep learning approach to analyze unannotated mammography images, leveraging both labeled and unlabeled data to improve BAC segmentation accuracy. Our approach combines the U-net architecture, a well-established deep learning method for medical image segmentation, with a semi-supervised learning technique. We retrieved mammographic examinations of 6,000 women (3,000 with confirmed CVD and 3,000 without) from the screening archive to allow for a focused study. Utilizing our trained deep learning model, we accurately detected and measured the severity of BAC in these mammograms. Additionally, we examined the time between mammogram screenings and the occurrence of CVD events. Our study indicates that both the presence and severity (grade) of BAC, identified and measured using deep learning for automated segmentation, are crucial for primary CVD prevention. These findings underscore the value of technology in understanding the link between BAC in mammograms and cardiovascular disease, shaping future screening and prevention strategies for women's health.

Keywords: Cardiovascular disease, Breast arterial calcification, Mammography, Women, Deep learning

1. INTRODUCTION

Cardiovascular disease (CVD) continues to be the leading cause of death worldwide, impacting both men and women. Recent data highlight a growing disparity in its effects on women [1]. In the United States, stroke is now the third leading cause of death in women, compared to ranking fifth in men [2]. Furthermore, women often experience worse outcomes after myocardial infarctions, despite presenting with less severe coronary artery disease [3]. Alarmingly, there has been an increase in CVD mortality among women under the age of 55[4]. These trends underscore the critical need for women to be more aware of their individual risk factors for CVD.

Breast arterial calcification (BAC), a common incidental finding in mammographic screenings, has been increasingly recognized for its potential as a CVD marker [5]. The clinical significance of BAC, however, was not fully appreciated until its correlation with diabetes mellitus was identified in the 1980s [6]. Subsequent research has suggested a positive association between BAC and CVD, as well as coronary artery disease [5].

The traditional approach to BAC assessment, typically conducted manually by radiologists, categorizes women into a binary risk framework for CVD. This oversimplification has spurred the development of more nuanced grading scales. Despite these advances, a standardized approach to BAC quantification remains elusive. Moreover, manual assessment poses challenges in terms of time efficiency and consistency.

Three recent studies have examined the potential of Deep Learning (DL) in assessing breast arterial calcification (BAC) from digital mammograms. These studies have demonstrated that DL algorithms can match or even surpass human experts in identifying BAC, representing an encouraging advancement in predicting this cardiovascular disease risk factor in women. However, there are still limitations to be addressed. Wang et al. [7] proposed a DL model that achieved

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comparable BAC identification performance to radiology experts but required high computational resources. Al Ghamdi et al. [8] introduced an automated model called DU-Net, claiming it matched human expert performance; however, it only classified BAC as present or absent without grading. Guo et al. [9] developed a lightweight DL model that reduced computational costs compared to traditional segmentation models. Nevertheless, their evaluation was limited to data from a single institution and one brand of scanners, raising concerns about generalizability.

To address these gaps, we propose a novel framework employing DL and semi-supervised learning for the automated detection and quantification of BAC. This model aims to facilitate independent and accessible assessment of CVD/CAD risk in women, validated on a cohort of 6000 women who underwent mammographic screening using a variety of scanner types and brands.

2. METHODS

2.1 Cohort

This retrospective case-control study involves a total of 6000 women, equally divided into two groups of 3000 each. One group comprises women who experienced cardiovascular disease CVD events, and the other consists of women without such events, maintaining a balanced 1:1 ratio. Each participant underwent a mammogram with four different imaging views. The average time from the screening to the onset of CVD events was approximately 71.5 months.

2.2 BAC Assessment

In the context of enhancing diagnostic methodologies for BAC detection from mammograms, this section delineates the development and validation of a deep learning (DL) model tailored for the automated assessment and segmentation of BAC. The model's robustness and adaptability are ensured by utilizing a dataset comprising mammographic images produced by various scanners across a spectrum of manufacturers.

A comprehensive selection process was undertaken, involving the curation of 3300 mammographic images (consisting of samples from both CC and MLO views) demonstrative of BAC. This selection was executed by an experienced medical imaging scientist and subsequently validated by an expert radiologist. The BAC presence in these images was annotated utilizing the Label Studio software [10], with a senior radiologist corroborating these annotations. Preprocessing procedures included the standardization of image size, normalization of pixel values, adjustments in brightness, and the application of a range of data augmentation techniques to enhance model training efficacy.

The model's architectural foundation was based on the U-Net framework, renowned for its effectiveness in medical image segmentation [11]. The training protocol was structured with 80% of the dataset dedicated to model training, while 10% was allocated for validation purposes and the remaining 10% for testing. The initial training phase was conducted with a learning rate of 0.001, employing binary cross-entropy as the primary loss function.

To further augment the training data pool, a novel approach was adopted wherein unlabelled mammogram images were integrated into the training process. This integration was facilitated through a progressive pseudo-labelling method, inspired by the research conducted by Fan et al [12]. This method involved the selective incorporation of images that the model predicted with high confidence for pseudo-labelling, followed by a refinement process to ensure accurate segmentation. The expanded dataset thus obtained was then utilized for further training of the model. This phase of training employed a customized loss function, which was a hybrid of binary cross-entropy and Jaccard loss, to enhance the model's generalization capacity.

2.3 Statistical analysis

The study utilized Cox Proportional Hazards to estimate hazard ratios (HR) and 95% confidence intervals (CI) for understanding the relationship between BAC) and CVD events over time. Age adjustments were made following BMJ guidelines [13], despite initial age matching in the case-control groups.

Additionally, the study analyzed BAC features from segmented areas, focusing on a three-tier BAC Grade system. This system classifies BAC severity into Grade 1 (mild), Grade 2 (moderate), and Grade 3 (severe), offering insights into the varying impact of BAC on MACE risk.

3. RESULTS

3.1 Segmentation and Classification Performance

To gauge the effectiveness of the models in segmentation and classification, various key metrics were used. These included the Jaccard Similarity Coefficient (Intersection over Union), along with accuracy, precision, recall, and the F1 score. These metrics are essential in evaluating how accurately the models predict segmentation masks and how closely the predicted labels align with the actual data (ground truth). Figure 1 demonstrates the effectiveness of the proposed model by displaying segmentation outputs next to the ground truth, affirming the model's enhanced performance.

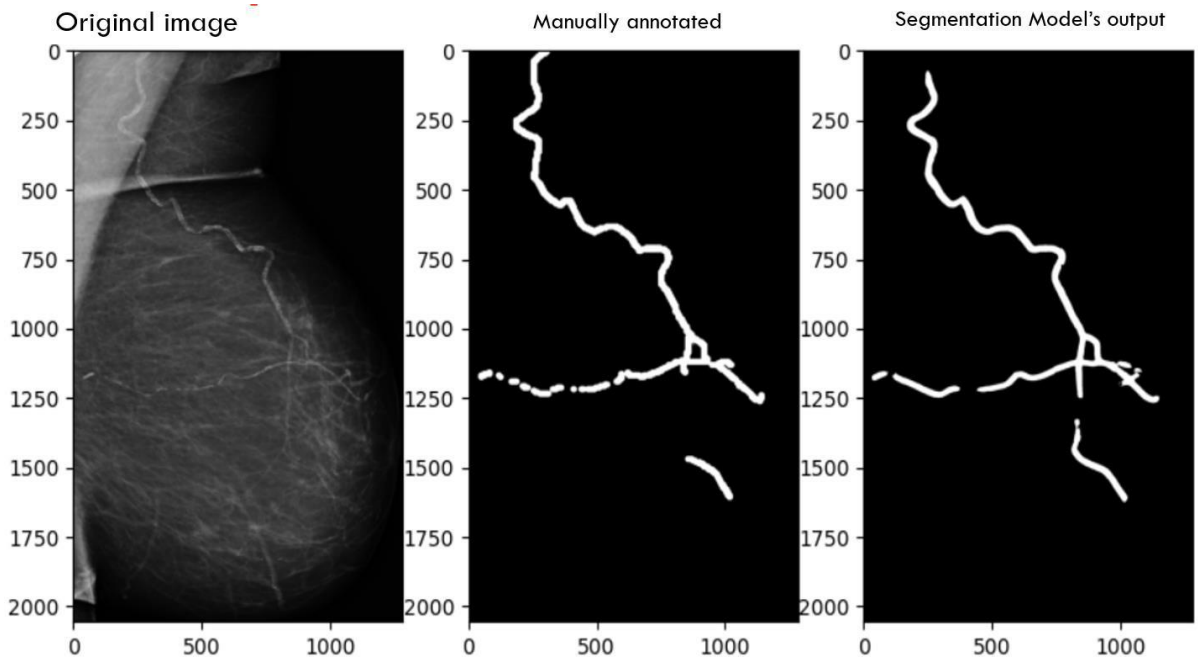

Figure 1: Illustrations of the predicted outcomes for BAC in comparison to the actual ground truth. Sequentially from left to right: the original mammography image, the ground truth mask, and the result of the prediction.

Initial tests showed promising results. The U-Net model, when trained on 512x512 pixel patches, achieved a Jaccard Similarity Coefficient of 0.585, accuracy of 0.991, precision of 0.81, an F1 score of 0.75, and recall of 0.711. When the U-Net model was trained on resized 1024x1024 pixel images, it scored similarly, with a Jaccard Coefficient of 0.583, accuracy of 0.990, precision of 0.813, an F1 score of 0.752, and recall of 0.701. These findings provided baseline performance metrics for the study, as shown in Table 1.

Subsequent improvements were noted upon implementing a semi-supervised learning approach with progressive pseudo labelling. The 512x512 patch-based model saw an increase in its Jaccard Coefficient to 0.602, while maintaining an accuracy of 0.991. Its precision rose to 0.77, F1 score to 0.76, and recall to 0.77. The model trained on 1024x1024 images also improved, with its Jaccard Coefficient increasing to 0.588, precision to 0.77, F1 score to 0.757, and recall to 0.747, while keeping an accuracy of 0.990. These improvements are visually presented in Figure 1, showcasing the segmented masks produced by the model and their comparison to the ground truth.

Furthermore, as Table 1 illustrates, the performance of the proposed model was compared with that of SCU-Net. This comparison revealed that the proposed model surpassed SCU-Net in several critical metrics, highlighting its superior segmentation and classification capabilities.

Table 1. Assessment of Segmentation Model Performance for Patches and Whole Images

Models	Recall		Precision		Accuracy		F1- Score		Jaccard	
U-Net	**0.701**	0.711	**0.813**	0.810	**0.99**	0.991	**0.752**	0.750	**0.583**	0.585
Proposed Model	**0.747**	0.770	**0.77**	0.770	**0.99**	0.991	**0.757**	0.760	**0.588**	0.602
SCU-Net	**0.778**	0.789	**0.682**	0.708	**0.98**	0.997	**0.698**	0.729	**0.569**	0.581

Note: The columns in regular font indicate models trained using patches. Columns in bold represent models trained on entire images.

3.2 Statistical Analysis Results

The prevalence of BAC in the population under study was found to be approximately 27%, which resonates with the percentages reported in similar age groups within the existing literature [5]. Our investigation into the relationship between BAC and CVD revealed a notable association. Specifically, the presence of BAC corresponded to a 12% heightened risk of developing CVD, as indicated by the Hazard Ratio (HR). A deeper analysis, considering the severity of BAC, uncovered a progressively increasing risk of CVD. Mild BAC (Grade 1) was linked to an 11% increased risk (HR: 1.11), moderate BAC (Grade 2) to a 26% increase (HR: 1.26), and severe BAC (Grade 3) led to a significant 161% increase in risk (HR: 2.61). This trend underscores the escalating cardiovascular threat posed by more severe levels of BAC. For a detailed breakdown, Table 2 presents the hazard ratios (HR) along with the 95% confidence intervals (CI) for both the presence and absence of BAC, as well as its varying severity.

Table 2. Evaluation of Hazard Ratios and Confidence Intervals for BAC

Variable	Hazard Ratio	95% CI	P-Value
BAC presence/absence	1.12	1.03 – 1.21	0.01
BAC_ Mild	1.11	1.02 - 1.20	0.01
BAC_ Moderate	1.26	1.00 - 1.60	0.05
BAC_ severe	2.61	1.23 - 5.51	0.01

4. CONCLUSION

This study highlights the role of BAC as a crucial indicator of elevated risk for CVD/CAD in women. By leveraging cutting-edge deep learning and semi-supervised learning techniques, we developed an automated framework for the detection and measurement of BAC, thereby improving the assessment of CVD/CAD risk in women. This model demonstrates effectiveness across various scanner technologies and incorporates a new quantification approach, enhancing its relevance in clinical settings. The clear correlation between the severity of BAC and the rise in hazard ratios underscores the importance of BAC as a key biomarker for cardiovascular risk prediction in women, offering significant benefits in the precise evaluation and management of CVD in female populations.

Declaration: The authors declare that this is an original and new work and that this has not been submitted for publication.

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Appendix C

J2.5 Deep learning-based segmentation of breast arterial calcification to enhance cardiovascular risk assessment in women

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Background: Cardiovascular disease (CVD) is a leading cause of death globally, with a significant impact on women (Ibrahim et al., 2023). Breast Arterial Calcification (BAC), identifiable through mammography, is a promising marker for CVD risk(Bui and Daniels, 2019). Traditional manual methods for BAC assessment are inefficient, requiring substantial time and resources. Existing deep learning approaches for BAC segmentation have been limited by small datasets and the use of mammograms from a single brand of scanners or manufacturers, lacking clinical validation for CVD prediction (Ibrahim et al., 2023). This study introduces a deep learning model designed to segment BAC and assist in predicting the risk of CVD in women.

Method: A deep learning model was developed, harnessing a dataset of 2500 mammograms, where BAC was present in each image. A subsequent case-control study of over 7000 women evaluated the model's effectiveness in CVD risk

prediction, employing the Cox proportional hazards model to analyse the association between BAC presence/severity and CVD risk.

Results: The model achieved notable performance metrics: Jaccard similarity of 0.567, accuracy of 0.991, Precision of 0.755, F1-score of 0.739, and Recall of 0.727, confirming its capability in accurately identifying and grading BAC. Additionally, the Cox proportional hazards model analysis revealed a significant association between BAC severity and an increased risk of CVD in women.

Conclusion: This research provides a validated deep learning framework for automated BAC segmentation, offering a novel method for CVD risk assessment in women.

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