# Coronary Artery Calcium Score as a Potential Non-Invasive Marker for Pulmonary Artery Hypertension

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## ABSTRACT

***Background:*** *Early prediction of cardiac dysfunction is crucial in preventing the progression to heart failure and associated complications. To achieve this, the utilization of clinical indicators, molecular and pathological markers, and non-invasive evaluation methods has gained significant interest. One potential predictive tool that can be measured through non-invasive imaging modalities is the coronary artery calcium (CAC) score. Recent studies have extensively examined the correlation between coronary atherosclerotic plaque calcium score and cardiac dysfunction. However, data are scarce regarding the usefulness of the calcium score in predicting pulmonary artery hypertension, which is a known consequence of ventricular dysfunction.* ***Methods****: A total of 167 patients with suspected coronary artery involvement were included in the study. Before performing CT angiography, the score of CAC was measured in all patients based on their CT results. The CAC value was calculated using Vitrea software. The CAC score of each coronary artery, as well as the total CAC score (by summing the scores of each artery), was determined based on the Agatston method. Then the patients were subjected to CT angiography, and the value of pulmonary artery pressure or PAP, as well as the pulmonary artery dilatation, was measured based on the results of CT angiography.* ***Results:*** *The average CAC score in the two groups with and without PAH was 107.57 ± 268.60 and 35.47 ± 93.98, respectively, which indicated a significant difference between the two groups (P value 0.011). Accordingly, the number of cases with a positive CAC score in the two groups with and without PAH was 24 (49.0%) and 47 (39.8%), respectively, which showed a significant difference between the two groups (P = 0.046). There was a significant correlation between CAC score and PAH. Based on the analysis of the area under the ROC curve, CAC score evaluation had a high ability to predict PAH in women and in patients over 50 years old.* ***Conclusion:*** *The measurement of CAC score could be incorporated as a predictive index for the increase of pulmonary artery pressure and the occurrence of PAH. However, this predictive value is more evident in women and in older patients.*

***Keywords:*** *Coronary Artery Calcium Score, Non-Invasive Marker, Pulmonary Artery Hypertension.*

## INTRODUCTION

The coronary artery calcium score, known as CAC, plays an important role in assessing and categorizing cardiovascular risk levels. The effectiveness of quantifying CAC using non-contrast-enhanced, electrocardiographically gated CT was initially highlighted by Agatston and colleagues in 1990.[1] Subsequent research has consistently demonstrated a strong correlation between CAC scores and the likelihood of experiencing significant cardiovascular events, including heart disease-related deaths and non-fatal acute myocardial infarctions.[2-4]

Based on data from the American Heart Association, six large studies involving 27,622 asymptomatic patients revealed a notable increase in the risk of cardiovascular events among individuals with a positive coronary artery calcium (CAC) score. Specifically, patients with a CAC score ranging from 100 to 400 had a relative risk approximately 4.3 times higher, while those with scores between 401 and 999 faced a risk about 7.2 times greater. For patients with scores exceeding 1000, the risk escalated to around 10.8 times higher.[5] The correlation between CAC scores and various functional and structural parameters of the left and right ventricles has attracted considerable interest at both anatomical and physiological levels. Studies have demonstrated that the presence and extent of coronary artery calcification are linked to atherosclerosis severity and the subsequent risk of ischemic heart disease.[6] Notably, diastolic dysfunction, which is often the initial cardiac impairment in ischemic heart disease, has been associated with CAC scores in multiple studies.[7-10] Parameters of diastolic function, such as left atrial volume index, average E/e', and left ventricular mass index in echocardiography, have shown correlations with the CAC score.[11]

Pulmonary hypertension is characterized by a mean pulmonary artery pressure of 25 mm Hg or higher at rest, as detected through right heart catheterization.[12] This condition is classified into five distinct groups based on pathophysiological, clinical, and therapeutic factors: pulmonary arterial hypertension, pulmonary hypertension related to left-sided heart issues, pulmonary hypertension associated with lung disease or hypoxia, chronic thromboembolic pulmonary hypertension, and pulmonary hypertension with uncertain or multiple causative factors.[13]

Pulmonary hypertension is increasingly being linked to left-sided heart failure, specifically heart failure with preserved ejection fraction. This condition is becoming more prevalent in individuals aged 65 years or older, affecting an estimated 5-10% of this population.[14] A study conducted by Kim et al.[15] In dialysis patients found a strong correlation was observed between the presence of vascular calcification and an enlarged left atrial diameter with pulmonary hypertension. These findings suggest that both of these factors independently contribute to the risk of developing pulmonary hypertension in dialysis patients, regardless of any existing myocardial dysfunction. Interestingly, research conducted both in vitro and in vivo has revealed that the presence of vascular calcifications in the pulmonary arteries could potentially contribute to the onset of pulmonary arterial hypertension (PAH). This process is believed to be mediated by the activation of hypoxia-inducible factor-1α through the expression of Runt-related transcription factor 2.[16] While visible pulmonary artery calcifications are uncommon in macroscopic in vivo imaging, similar mechanisms involving Runt-related transcription factor 2 are known to play a role in the calcification of other vascular regions, such as the coronary arteries.[17] Thus, it is plausible to suggest that there may exist an indirect link between coronary artery calcium (CAC) scores and the likelihood of developing pulmonary hypertension stemming from complications in the left heart.

Despite limited available data on the relationship between CAC and pulmonary hypertension and its predictive value for cardiovascular events, a study by Rossdale et al.[18] focusing on patients with systemic sclerosis demonstrated an association between CAC identified on thoracic CT scans and the presence of pulmonary hypertension. Notably, both factors were also found to be predictors of mortality. In this study, we aim to determine the relationship between CAC and pulmonary arterial hypertension in patients undergoing CT angiography.

## METHODS

This was a cross-sectional study that enrolled patients who were suspected of having coronary artery involvement and were candidates for CT angiography. Due to the retrospective methodology of the study, patients without information related to CT angiography results or coronary calcium score were excluded from the study. Also, all patients with a history of previous diagnostic or therapeutic interventions on coronary arteries, or with a history of treatment with calcium channel blockers, were excluded from the study. At last, 167 patients were considered eligible. Baseline information, including demographic characteristics and information related to risk factors for cardiac diseases, as well as systolic and diastolic function parameters (based on two-dimensional echocardiography), was extracted by reviewing the patient documents and entered into the study checklist.

### Ethical Statement

This study is approved by the ethics committee of Shahid Beheshti University of Medical Sciences.

### Measurement of CAC Score and Pulmonary Artery Pressure

Before performing CT, angiography, and based on CT results, the amount of CAC was measured in all patients. CAC value was calculated using Vitrea software. The calcium score of each coronary artery, as well as the total calcium score (by summing the scores of each artery), was determined based on the Agatston method. Then, the size of pulmonary artery dilatation was measured based on CT angiography results. Finally, the relationship between CAC and arterial diameter was evaluated. Pulmonary arterial hypertension was defined as PAP higher than 25 mmHg. An increase in the diameter of the pulmonary artery means a diameter above 29 mm in the main pulmonary artery and above 20 mm in the right and left pulmonary arteries.

### Statistical Analysis

The results for quantitative variables were expressed as mean and standard deviation (mean ± SD), and for categorical variables as percentages. Comparison between quantitative variables was performed using a t-test, while the comparison between categorical variables was conducted using the Chi-square test. Correlation between quantitative variables was tested using the Pearson or Spearman correlation test. To evaluate the diagnostic capability of CAC in predicting pulmonary arterial hypertension, the evaluation of the area under the ROC curve was used. SPSS version 20 and SAS version 9.1 were used for statistical analysis of data. A significance level of less than 0.05 was determined.

## RESULTS

### Baseline Characteristics

A total of 167 patients were studied. The mean age of the patients was 52.01 ± 11.87 years (ranging from of 23 to 80 years), and in terms of gender distribution, 74 cases (44.3%) were male, and 93 cases (55.7%) were female. The overall average CAC score was estimated as 167.84 ± 56.63 (ranging from of 0 to 1584.6). Ninety-six cases (57.5%) had a zero score, and 71 cases (42.5%) were positive. The average RPA diameter was 18.46 ± 3.21 mm, the average LPA diameter was 17.53 ± 2.91 mm, and the average MPA diameter was 24.36 ± 3.59 mm; therefore, PAH was diagnosed in 29.3% of patients.

### Patients' Characteristics by PAH Status

**Table 2** summarizes the characteristics of patients divided based on the possible PAH diagnosis. In terms of gender distribution, men

**Table 1.** Baseline characteristics

| **Age (mean SD)** | **52.01±11.87** |
|---|---|
| Gender | |
| Men | 74 (44.3%) |
| Women | 93(55.7%) |
| Mean CAC score | 167.84±56.63 |
| CAC score | |
| Zero | 96 (57.5%) |
| Positive | 71 (42.5%) |
| Mean pulmonary artery diameter. | |
| MPA | 24.36±3.59 |
| RPA | 18.46±3.21 |
| LPA | 17.53±2.91 |

comprised 19 cases of PAH positive (38.8%) and 55 cases of PAH negative (46.6%). Meanwhile 30 cases (61.2%) and 63 cases (53.4%) were women in PAH positive and PAH-negative, respectively. No significant difference was observed between the two groups in terms of gender. The mean age was 55.92 ± 11.97 years in those with PAH and 50.39 ± 11.49 years in those without PAH; this difference between the two groups was significant (P=0.006). The difference between the two groups in terms of pulmonary artery diameter was significant (p < 001). The average CAC score in the two groups with and without PAH was 268.60± 107.57 and 93.98 ± 35.47, respectively (**Figure 1**). This difference was found to be significant (p=0.011). Accordingly, the rate of positive score cases in the two groups with and without PAH was estimated to be 24 cases (49.0%) and 47 cases (39.8%), respectively, which showed a significant difference between the two groups (P=0.046).

**Table 2.** Patients' characteristics per PAH status

| | With PAH | Without PAH | P-value |
|---|---|---|---|
| **Gender** | | | 0.353 |
| Men | 19 (38.8%) | 55 (46.6%) | |
| Women | 30 (61.2%) | 63 (53.4%) | |
| **Age** | 55.92±11.97 | 50.39±11.49 | 0.006 |
| **LPA** | 19.48±3.08 | 16.72±2.41 | <0.001 |
| **RPA** | 21.04±3.26 | 17.39±2.51 | <0.001 |
| **MPA** | 28.7±12.76 | 22.55±1.99 | <0.001 |
| **Mean CAC score** | 268.60±107.57 | 93.98±35.47 | 0.011 |
| **Positive CAC score** | 24 (49.0%) | 47 (39.8%) | 0.046 |

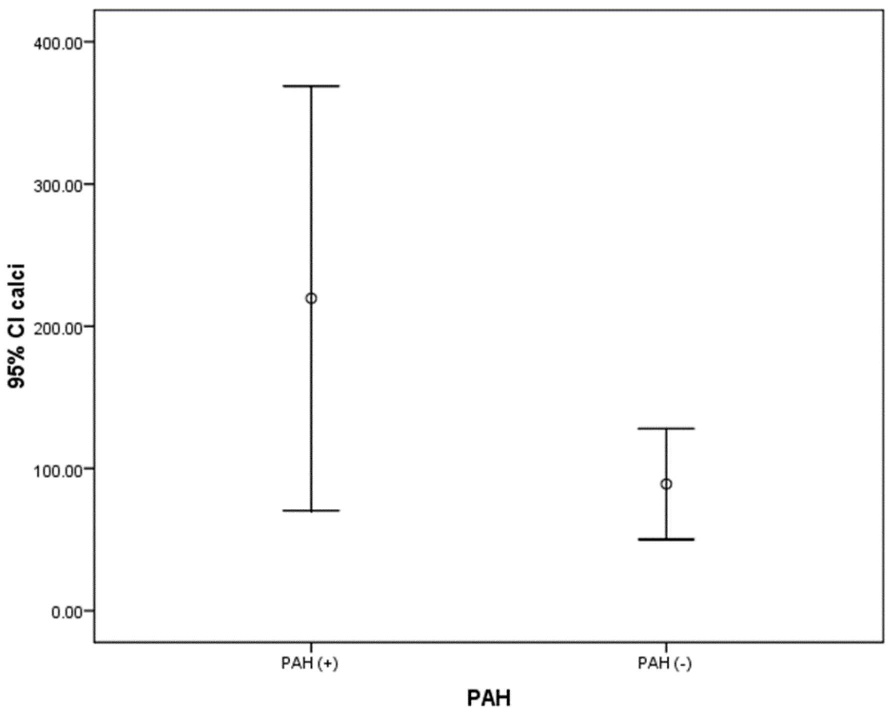


**Figure 1.** Mean CAC score in patients with and without PAH.

### Correlation Between Pulmonary Artery Diameter and CAC Score

**Table 3** discusses the correlation between pulmonary artery diameter and CAC score based on four subgroups. There was a significant direct correlation between CAC score with RPA (CC= 0.169, P = 0.029) and with MPA (CC= 0.293, P = 0.001), but CAC score with LPA had no significant correlation (CC= 0.081, P = 0.300). In the subgroup of women, there was a significant direct correlation between CAC score with RPA (CC= 0.243, P = 0.019) and with MPA (CC= 0.361, P = 0.001), but in the subgroup of men and patients under 50 years of age, no significant correlation was found between CAC and any of the PAs' diameters. In the group of patients over 50 years old, the only significant correlation was observed between CAC and MPA (CC=0.346, P = 0.001). The data above are illustrated in **Figures 2 and 3**.

### Diagnostic Value of a Positive CAC Score for the Prediction of PAH

Based on the analysis of the area under the ROC curve as portrayed in **Table 4**, CAC assessment in women and patients over 50 years old had a high value to predict PAH. While it did not reach the same statistically significant value in men and patients under the age of 50 (**Figure 4**).

**Table 3.** Correlation between pulmonary artery diameter and CAC score

| | Correlation coefficient | P-value |
|---|---|---|
| Men | | |
| **LPA** | 0.009 | 0.942 |
| **RPA** | 0.044 | 0.708 |
| **MPA** | 0.209 | 0.073 |
| **Women** | | |
| **LPA** | 0.131 | 0.210 |
| **RPA** | 0.243 | 0.019 |
| **MPA** | 0.361 | 0.001 |
| **Age < 50** | | |
| **LPA** | -0.013 | 0.905 |
| **RPA** | 0.020 | 0.858 |
| **MPA** | 0.037 | 0.742 |
| **Age> 50** | | |
| **LPA** | 0.089 | 0.415 |
| **RPA** | 0.158 | 0.145 |
| **MPA** | 0.346 | 0.001 |

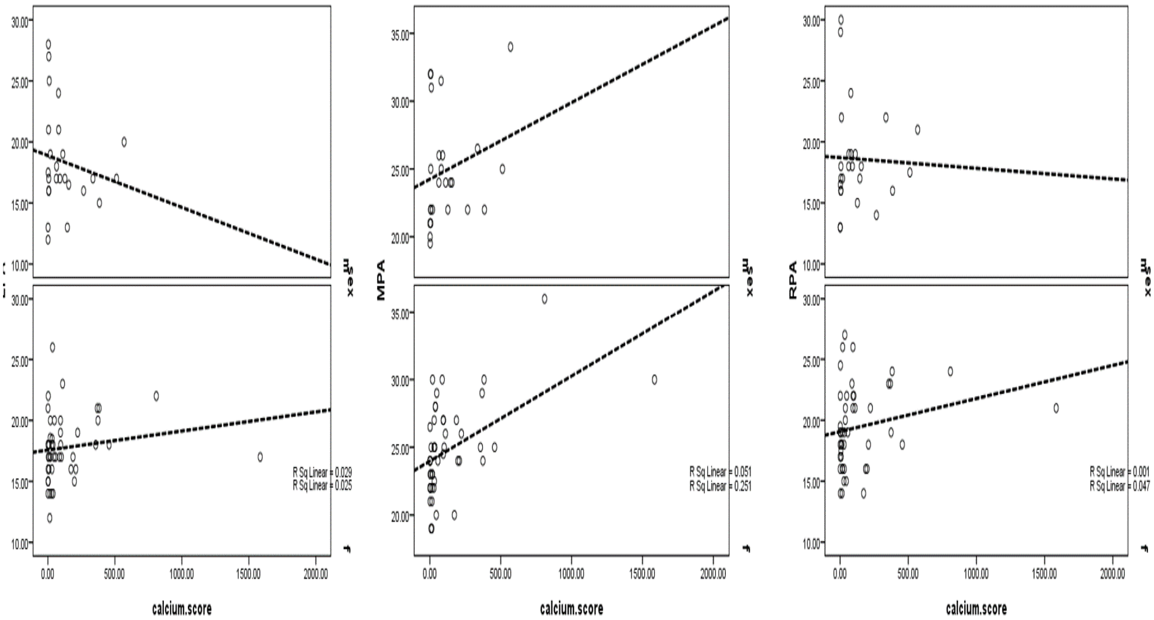


**Figure 2**. Linear correlation between CAC score and PAD in men and women.

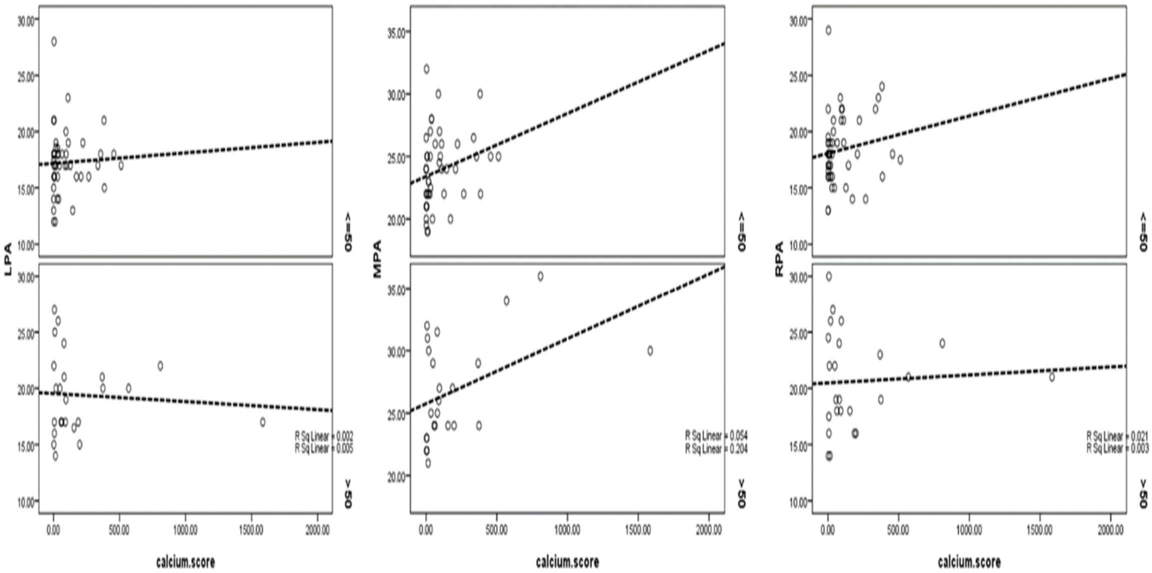

**Figure 3**. Linear correlation between CAC score and PAD according to age

**Table 4.** Diagnostic value of a positive CAC score for the prediction of PAH

| | Area under the ROC curve | Lower limit | Upper limit | P-value |
|---|---|---|---|---|
| Men | 0.566 | 0.328 | 0.804 | 0.600 |
| Women | 0.749 | 0.604 | 0.894 | 0.006 |
| Age<50 | 0.569 | 0.244 | 0.893 | 0.166 |
| Age>50 | 0.708 | 0.500 | 0.916 | 0.016 |

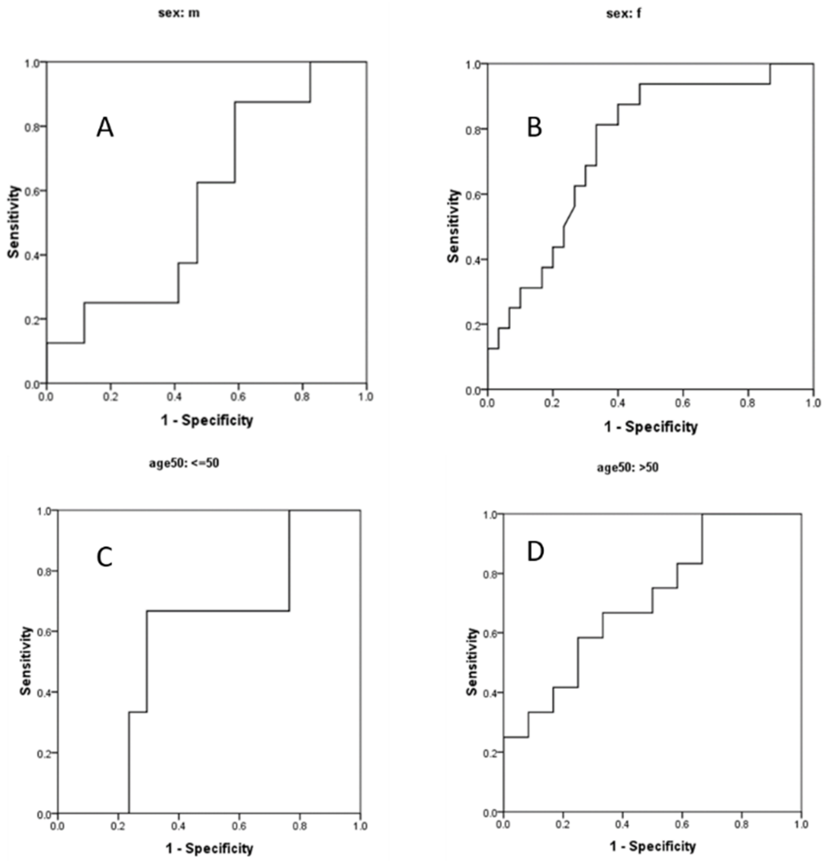


**Figure 4.** The area under the ROC curve for predicting PAH by evaluating the CAC in a) men, b) women, c) under age 50, and d) age over 50.

## DISCUSSION

The ability to predict cardiac dysfunction early on offers the potential for preventing heart failure. In this regard, there has been a particular focus on utilizing clinical indicators, as well as molecular and pathological markers, to assess the risk of heart failure through non-invasive methods. Non-invasive diagnostic techniques are now preferred over invasive procedures like right heart catheterization for detecting pulmonary artery hypertension (PAH).[19] Recent research has revealed that pro-inflammatory pathways play a significant role in the development of both vascular calcification and PAH. One such pathway involves IL-6, a cytokine associated with systemic inflammation, which is linked to both PAH and aortic calcification.[20,21]

Limited data is currently available on the correlation between calcium score and pulmonary arterial hypertension (PAH) in clinical settings. A recent investigation conducted by Rossdale et al (18). Explored this relationship in patients with systemic sclerosis, a condition known for its pro-inflammatory nature. Their study revealed a connection between coronary artery calcium (CAC) and PAH, which was also visible on computed tomography (CT) scans. Similarly, a separate study by Santhanam et al.[22] found a link between CAC and the diameter of the main pulmonary artery, but this association was influenced by the presence of hypertension. The authors suggested that the sensitivity and specificity of CT imaging may not be adequate to detect PAH in non-hypertensive individuals when compared to invasive methods like right heart catheterization.

However, most studies have not examined the relationship between calcium score and PAH directly; instead, the indices observed were severity of coronary artery involvement, severity of cardiac ischemia, and ventricular dysfunction, all of which could eventually lead to PAH.[13] In a study by Kim et al.[15] the connection between vascular calcification (VC) and PAH in end-stage renal disease patients undergoing dialysis was explored. The results revealed an independent link between VC and PAH, as well as left atrium volume (a parameter associated with diastolic dysfunction) and PAH. These findings further support the idea that coronary artery calcium (CAC) may contribute to PAH through both direct and indirect pathways.

Moreover, Maragiannis et al.[11] demonstrated that a positive calcium score in the coronary arteries was linked to impaired relaxation of the heart during diastole, as evidenced by echocardiography parameters such as left atrium volume index, average E/e ratio, and left ventricle mass. This finding aligns with Dykun et al.'s[10] study, which found a weak association between calcium score and left ventricle size. Similarly, Osawa et al.[7] we conducted a study on older patients and found that those with diastolic dysfunction had significantly higher average calcium scores compared to their counterparts without diastolic dysfunction. This relationship remained significant even after considering other factors that could influence the results. Sharma et al.[23] also found similar results, showing that atherosclerosis and calcium score were associated with subclinical left ventricular dyssynchrony, independent of age and left ventricular mass.

However, the independent nature of this association is still a matter of debate. Jamiel et al. (9) initially observed a direct correlation between coronary artery calcification and indicators of diastolic dysfunction, but this correlation weakened when adjusting for factors like age, hypertension, dyslipidemia, and diabetes mellitus initially observed. Additionally, Eleid et al.[24] found no association between calcium score and left ventricular dysfunction in asymptomatic patients. One possible explanation for these conflicting results is that the participants in these studies had fewer risk factors compared to those discussed earlier, and the proportion of women was relatively low at only 14%.

Women are often at a higher risk of adverse cardiovascular events compared to men, with even lower levels of coronary artery calcium (CAC) considered a significant risk factor for women.[25] This gender disparity is thought to be linked to the smaller size of coronary arteries in women, meaning that the same amount of atherosclerosis or calcium buildup could block a larger area in a woman's arteries compared to a man's, leading to more severe outcomes.[26]

Consequently, women with higher CAC scores may be more susceptible to ischemic heart disease (IHD) with structural complications that can result in left ventricular (LV) dysfunction and potentially pulmonary arterial hypertension (PAH). Our study found a significant association between CAC score and PAH in women aged 55 and older, highlighting the impact of age as an independent risk factor for atherosclerosis. It can be inferred that older women, particularly in the postmenopausal state with hormonal dysregulation, may experience more severe outcomes.[27]

The presence of calcified atherosclerotic plaque may contribute to ventricular dysfunction, ultimately leading to an increase in pulmonary artery pressure and the development of PAH over time. This association should be considered in conjunction with other risk factors such as gender and age. While further research is warranted to confirm these findings, CAC scoring holds promise as a non-invasive tool with reasonable accuracy and sensitivity for predicting the onset of PAH, particularly in women and older individuals.

There are a few limitations to consider in this study. Since the invasive nature of right heart catheterization was a concern, CT angiography was utilized to assess PAH. Consequently, pulmonary artery diameter was used as a proxy for pulmonary artery pressure, potentially impacting the accuracy of PAH diagnosis and explaining the lack of correlation between CAC score and left PA diameter. Further investigations employing right heart catheterization may be necessary to better understand the relationship between PAH and CAC score. Additionally, this study was cross-sectional, with a limited study population, and the data on CAC score were extracted from patients' medical records, which may limit the study's ability to establish a causal link.

## CONCLUSION

The findings suggest that the CAC score may serve as a valuable predictive indicator for the enlargement of pulmonary artery diameter and the development of PAH, particularly in women and older patients. Considering these results, it is recommended to consider incorporating CAC score measurement alongside molecular and echocardiographic markers in the assessment of PAH. Further research is warranted to validate these findings and explore the potential clinical implications of utilizing the CAC score as a predictive index for PAH.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## FUNDING

None.

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