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ORIGINAL ARTICLE

Serum Angiotensin-Converting Enzyme as a Non-Invasive Biomarker for Identifying Vulnerable Coronary Plaques by Coronary CT Angiography in Patients Presenting with Chronic Coronary Syndrome

MD. MOSTOFA KABIR[1], DIN-E-MUJAHID MOHAMMAD FARUQUE OSMANY[2], LOHANI MD. TAZUL ISLAM[2], MD. FAKHRUL ISLAM KHALED[2], MOHAMMAD WALIDUR RAHMAN[2], DEBBROTO SAHA[1], MOHAMMAD ATAULLAH[3], NUSSART MARIAM[1], TAREKUL ISLAM[1], JAHIDUL ISLAM[1], NAZRUL ISLAM[4], MOHAMMAD SAFIUDDIN[2], MOHAMMED SHAHIDUL HOQUE[2]

[1]Department of Health Services, Directorate General of Health Services (DGHS), Dhaka, Bangladesh, [2]Department of Cardiology, Bangladesh Medical University, Dhaka, Bangladesh, [3]National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh, [4]Department of Radiology, Bangladesh Medical University, Dhaka, Bangladesh

Address of Correspondence: Dr. Din-E-Mujahid Mohammad Faruque Osmany , Associate Professor, Department of Cardiology, Bangladesh Medical University, Dhaka, Bangladesh Email: osmany@bsmmu.edu.bd

Abstract

Introduction: *Cardiovascular disease (CVD) remains the leading cause of premature death worldwide, accounting for approximately 20.5 million deaths annually. Chronic coronary syndrome (CCS) is characterized by a chronic mismatch between myocardial oxygen supply and demand, most commonly resulting from atherosclerotic coronary obstruction. Vulnerable coronary plaques, defined by high-risk morphological features on coronary computed tomography angiography (CCTA), are major precursors of acute coronary events. Angiotensin-converting enzyme (ACE), a key component of the renin–angiotensin system, is abundantly expressed in atherosclerotic lesions and macrophages; however, its clinical utility as a serum biomarker for coronary plaque vulnerability has not been previously investigated.*

Aim of the Study: *To evaluate serum ACE as a non-invasive biomarker for identifying vulnerable coronary plaques in patients with chronic coronary syndrome using CCTA as the reference standard.*

Methods: *This cross-sectional study enrolled 30 consecutive adult patients with CCS who underwent CCTA at Bangladesh Medical University (BMU) and Ibrahim Cardiac Hospital & Research Institute, Dhaka, Bangladesh (August 2023–September 2025). Plaque morphology was assessed on a 128-slice SIEMENS SOMATOM CT scanner with ECG-gating. Vulnerable plaque was defined by the presence of at least one high-risk CCTA feature: low-attenuation plaque, positive remodeling, spotty/microcalcification, or napkin-ring sign. Serum ACE activity was measured within 48 hours of CCTA using the kinetic FAPGG hydrolysis method on a Siemens Atelica Solution analyzer. Participants were equally divided into vulnerable-plaque (n=15) and non-vulnerable-plaque (n=15) groups. Diagnostic performance was assessed by receiver operating characteristic (ROC) curve analysis.*

Results: *Among 30 patients with chronic coronary syndrome, 15 had vulnerable coronary plaques and 15 had non-vulnerable plaques on CCTA. Baseline demographic and cardiovascular risk factors were comparable between the groups, with no statistically significant differences observed (all $p>0.05$). Serum ACE levels were significantly higher in patients with vulnerable plaques compared with those with non-vulnerable plaques (40.02±21.54 vs. 12.56±7.27 U/L, $p<0.001$). Median serum ACE levels were also markedly elevated in the vulnerable plaque group [36 (24–55) vs. 11 (7–17) U/L, $p<0.001$]. ROC analysis demonstrated excellent discriminatory performance of serum ACE for identifying vulnerable plaque, with an area under the curve (AUC) of 0.889 (95% CI: 0.769–1.000, $p=0.001$). A serum ACE cut-off value of ≥20.50 U/L provided the optimal diagnostic performance, yielding a sensitivity of 93.33%, specificity of 86.67%, positive predictive value of 87.50%, negative predictive value of 92.86%, and overall accuracy of 90.00%.*

Conclusion: *Serum ACE is significantly associated with vulnerable coronary plaque in patients with chronic coronary syndrome. It shows strong potential as a non-invasive biomarker for plaque vulnerability and may enhance cardiovascular risk stratification in clinical practice.*

Keywords: *Chronic coronary syndrome, Angiotensin-converting enzyme, Vulnerable plaque, Coronary CT angiography, Atherosclerosis*

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Introduction

The leading cause of premature death globally for decades is Cardiovascular disease affecting the functioning of the heart or blood vessels. CVD remains a major cause of premature death which accounts for 20.5 million deaths per year.[1] Ischemic heart disease is the major cause of cardiovascular death, which accounts for 10.6% of all to death and more than 50% of cardiovascular mortality.[2] In Bangladesh, exact prevalence of CAD is unknown. Very few number of small-scale epidemiological studies show CAD prevalence 1.85% to 3.4% in rural and 19.6% in urban samples of working professionals.[3] The prevalence of CAD in our country is seems to be rising.[4] Chronic coronary syndrome (CCS) is described as a pathological condition caused by a chronic or repetitive mismatch between supply and demand in myocardial oxygen consumption. Atherosclerotic obstruction of the coronary arteries is the most common cause of ischemia and others are microvascular dysfunction, vasospasm, congenital anomalies, or non-atherosclerotic myocardial injuries.[5] During the study of the renin-angiotensin system (RAS), Angiotensin-converting enzyme (ACE)- a zinc-dependent di-carboxypeptidase with two catalytic domains was initially discovered in 1953.[6] It is expressed in various tissues, but especially in the lungs, kidneys, testes, duodenum, choroid plexus, and placenta.[7] Whereas serum levels among individuals are affected by genetic polymorphisms, individual adult serum ACE levels are thought to be stable. [8] Recent studies suggest that ACE regulates macrophage function, in addition to its role in blood pressure management through the renin-angiotensin system.[9] Lesional macrophages in human atherosclerosis produce significant levels of ACE, although its role in atherosclerosis-associated inflammation remains unclear. [10] Although atherosclerosis is associated with older age, lipids enter blood vessel walls and are removed by macrophages throughout life. Lack of lipid clearance and the development of macrophage foam cells are significant pathologic hallmarks of atherosclerotic lesions.[11] Coronary computed tomography angiography is a more efficient risk-stratification tool than ischemia testing. It can inform decision-making for individuals with severe CAD who may benefit from an invasive approach. Advanced quantitative plaque assessments on coronary computed tomography angiography (CCTA) can track disease progression and changes in plaque morphology with high reproducibility.[12] Recent studies indicate a high correlation between plaque composition measured by quantitative computed tomography (CT) analysis and clinical events.[13] High-risk plaque characteristics include low attenuation plaque (attenuation density<30 HU serves as a marker of necrotic core), positive remodeling, napkin-ring sign, spotty calcification, minimum lumen area <4 mm2, and plaque burden e”70%. Therefore, we aimed to evaluate serum ACE as a non-invasive biomarker for identifying vulnerable coronary plaques in patients with chronic coronary syndrome.

Methods

This cross-sectional study was conducted in the Department of Cardiology, Bangladesh Medical University (BMU), Dhaka, Bangladesh, from August 2023 to September 2025. Consecutive adult patients with chronic coronary syndrome (CCS) who underwent coronary computed tomography angiography (CCTA) at the Department of Radiology and Imaging, BMU, and Ibrahim Cardiac Hospital & Research Institute (ICHRI) were enrolled. Coronary plaque morphology was assessed using a SIEMENS SOMATOM Definition AS 128-slice CT scanner with ECG-gated acquisition and intravenous contrast administration. Images were independently interpreted by an experienced cardiologist and radiologist according to a standardized protocol. Vulnerable plaque was defined by the presence of at least one high-risk feature, including low-attenuation plaque, positive remodeling, spotty/micro-calcification, or napkin-ring sign. Participants were categorized into vulnerable-plaque and non-vulnerable-plaque groups based on CCTA findings. Detailed demographic and clinical data were collected using a predesigned semi-structured questionnaire. Within 48 hours of CCTA, venous blood samples were obtained for measurement of serum angiotensin-converting enzyme (ACE) activity in the Department of Biochemistry and Molecular Biology, BMU. Serum ACE was measured using the Siemens Atelica Solution analyzer with ACE Liquid Reagent (Sentinel Diagnostics) based on the kinetic hydrolysis of N-[3-(2-furyl)acryloyl]-L-phenylalanylglycylglycine (FAPGG). Statistical analysis was performed using SPSS version 27. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequency and percentage. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher’s exact test for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminatory performance of serum ACE levels for identifying vulnerable plaque and to determine the optimal cutoff value. A two-tailed p-value <0.05 was considered

statistically significant. Ethical approval was obtained from the Institutional Review Board of BMU, and written informed consent was obtained from all participants prior to enrollment.

Inclusion criteria:

- Age ≥18
- Patients with chronic coronary syndrome undergoing coronary CT angiography.

Exclusion criteria:

- Patients with HF.
- H/O MI.
- Revascularization within six months.
- Acute and Chronic renal disease.
- Patient who got ACEI or ARB within 6 weeks.
- Sarcoidosis.
- Active Tuberculosis.

Results

The baseline characteristics were comparable between the two groups. Diabetes mellitus (53.3% vs. 33.3%) and dyslipidemia (40.0% vs. 20.0%) were more frequent among patients with vulnerable plaques; however, none of the demographic or cardiovascular risk factors showed a statistically significant association with plaque vulnerability (all $p>0.05$).

Serum ACE levels were significantly higher in patients with vulnerable plaques than in those with non-vulnerable plaques (40.02±21.54 vs. 12.56±7.27 U/L; $p<0.001$). Median ACE levels were also markedly elevated in the vulnerable plaque group [36 (24–55) vs. 11 (7–17) U/L].

Table-I

Baseline Characteristics of Study Participants According to Coronary Plaque Morphology (N=30).

Variables	Non-vulnerable Plaque (n=15)	Vulnerable Plaque (n=15)	P value
Age (years)			0.525ns
32–41	4 (26.7)	1 (6.7)	
42–51	4 (26.7)	6 (40.0)	
52–61	5 (33.3)	5 (33.3)	
62–71	2 (13.3)	2 (13.3)	
e”72	0 (0.0)	1 (6.7)	
Male sex	13 (86.7)	11 (73.3)	0.650ns
Female sex	2 (13.3)	4 (26.7)	
Overweight/Obese	11 (73.3)	12 (80.0)	1.000ns
Diabetes mellitus	5 (33.3)	8 (53.3)	0.269ns
Dyslipidemia	3 (20.0)	6 (40.0)	1.000ns
Smoking	8 (53.3)	5 (33.3)	0.182ns
Family history of premature CAD	9 (60.0)	7 (46.7)	0.464ns
Previous PCI/CABG	2 (13.3)	2 (13.3)	1.000ns

Table-II

Serum ACE Levels According to Coronary Plaque Morphology (N=30)

Variable	Non-vulnerable Plaque (n=15)	Vulnerable Plaque (n=15)	P value
Serum ACE (U/L), Mean ± SD	12.56 ± 7.27	40.02 ± 21.54	<0.001s
Serum ACE (U/L), Median (IQR)	11 (7–17)	36 (24–55)	<0.001s

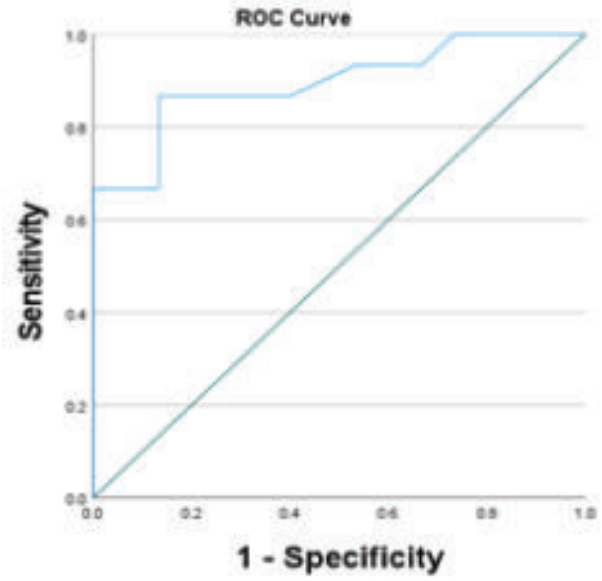

Figure 1: *Receiver operating characteristic (ROC) curves of diagnostic performance of serum ACE level in differentiating vulnerable from non-vulnerable coronary plaque (N=30)*

The ROC curve demonstrates good discriminatory ability of serum ACE levels for identifying vulnerable coronary plaque, with the curve lying well above the diagonal reference line. The area under the curve (AUC) .889 indicates acceptable accuracy, and the optimal cut-off was identified at the point with the highest Youden Index, providing the best balance of sensitivity and specificity

Table-III

Receiver Operating Characteristic (ROC) Analysis of Serum ACE for Identifying Vulnerable Coronary Plaque

Parameter	Value
Area Under the Curve (AUC)	0.889
Standard Error	0.061
95% Confidence Interval	0.769–1.000
P value	0.001

The ROC analysis showed that serum ACE level had a strong discriminatory power for identifying vulnerable coronary plaque, with an AUC of 0.889 (SE = 0.061, 95% CI: 0.769–1.000, p = 0.001). This indicates excellent accuracy, and the optimal cut-off (corresponding to the highest Youden Index) provided the best balance of sensitivity and specificity.

A cut-off value of e”20.50 U/L showed the highest Youden index (0.73) with 93.33 % sensitivity and 86.67% specificity. In addition, the accuracy was 90%. Moreover, the cut-off value of S.ACE e”20.50 U/L showed, PPV and NPV of 87.50% and 92.86%.

The diagnostic evaluation showed that serum ACE level was a highly effective marker for identifying vulnerable coronary plaque. Sensitivity and negative predictive value were both above 90%, indicating that most patients with vulnerable plaque were correctly detected and that a negative test reliably excluded vulnerability. Specificity and positive predictive value were also high, showing good

Table-IV

Determination of Optimal Serum ACE Cut-off Values for Identifying Vulnerable Coronary Plaque

Serum ACE Cut-off (U/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Youden Index
≥17.50	86.67	80.00	81.25	85.71	83.30	0.66
≥20.50	93.33	86.67	87.50	92.86	90.00	0.73
≥23.50	80.00	86.67	85.71	81.25	83.30	0.66

Table-V

Diagnostic Performance of Serum ACE at the Optimal Cut-off (e”20.50 U/L) for Identifying Vulnerable Coronary Plaque

Diagnostic Parameter	Value (%)	95% Confidence Interval
Sensitivity	93.33	68.05–99.83
Specificity	86.67	59.54–98.34
Positive Predictive Value (PPV)	87.50	65.67–96.24
Negative Predictive Value (NPV)	92.86	65.95–98.87
Accuracy	90.00	73.47–97.89

ability to correctly classify non-vulnerable cases and confirm vulnerability when the test was positive. Overall diagnostic accuracy was 90%, confirming that serum ACE performed as a robust discriminator between vulnerable and non-vulnerable plaque groups.

Discussion

This cross-sectional study included 30 patients with chronic coronary syndrome (CCS). Plaque characterization was performed by coronary CT angiography (CCTA), and patients were equally divided into a vulnerable plaque group (n=15) and a non-vulnerable plaque group (n=15). Serum ACE levels were measured in all participants at the Department of Biochemistry, Bangladesh Medical University (BMU), Dhaka, Bangladesh.

The mean age of participants was 51.9±11.0 years, with the majority falling within the 42–61-year age group (Table 1). This reflects the well-recognised tendency toward earlier onset of coronary artery disease (CAD) in South Asian populations compared with their Western counterparts, where onset typically occurs a decade later, as reported by Chowdhury et al. (2018).[4] Male predominance was evident, with 80% of participants being men, consistent with the well-documented gender disparity in CAD burden described by Kuneman et al. (2021). [13] Nearly half of all participants were current or ex-smokers (43.3%), reflecting the high prevalence of tobacco use in a study by Gallucci et al. (2020).[14]

Conventional cardiovascular risk factors were frequently represented in this cohort. Diabetes mellitus was present in 43.3% of participants, dyslipidaemia in 30.0%, and a family history of premature CAD in 53.3% (Table 1), consistent with the increasing metabolic risk burden in Bangladesh described by Bhuiyan et al. (2025).[15] The high prevalence of family history of premature CAD underlines the importance of genetic predisposition in South Asian populations, as highlighted by Volgma et al. (2023).[16] Importantly, none of the conventional demographic or cardiovascular risk factors demonstrated a statistically significant difference between the vulnerable and non-vulnerable plaque groups (all $p>0.05$), confirming that both groups were well-matched at baseline.

The most important and novel observation of this study was that serum ACE levels were significantly higher in patients with vulnerable plaques compared with those with non-vulnerable plaques (40.02±21.54 vs. 12.56±7.27 U/L; $p<0.001$).[17]

No prior published studies have directly investigated the relationship between serum ACE levels and CCTA-defined plaque morphology. However, indirect evidence supports biological plausibility. Cao et al. (2023) demonstrated that ACE is abundantly expressed in atherosclerotic lesions.[12]

The present results extend this evidence base by providing the first clinical demonstration that elevated serum ACE levels are directly associated with vulnerable coronary plaque morphology on CCTA. Unlike conventional cardiovascular risk factors, which showed no statistically significant difference between the two plaque groups in this study (Table 1), serum ACE emerged as a distinct biochemical marker of vulnerability. This suggests that ACE measurement may capture vascular inflammatory and remodeling biology not reflected by standard risk factor profiling, and that it may therefore serve as a promising adjunct biomarker to imaging in identifying patients at heightened risk of acute coronary events.

Serum ACE level demonstrated strong discriminatory ability for differentiating vulnerable from non-vulnerable coronary plaques on ROC curve analysis. The AUC was 0.889 (95% CI: 0.769–1.000; $p=0.001$), indicating excellent diagnostic performance (Figure 1 and Table 5). At the optimal cut-off of e”20.50 U/L, identified by the Youden index ($J=0.73$), serum ACE achieved a sensitivity of 93.3% (95% CI: 68.05–99.83%), specificity of 86.7% (95% CI: 59.54–98.34%), positive predictive value of 87.5%, negative predictive value of 92.9%, and an overall diagnostic accuracy of 90.0%. Elevated ACE activity at this threshold promotes angiotensin II formation, contributing to endothelial dysfunction, oxidative stress, and destabilization of atherosclerotic plaques. Previous studies have similarly reported higher ACE activity in patients with acute coronary syndromes and plaque rupture, supporting its value as a surrogate marker of plaque instability (Hoshida et al., 2001).[18]

This study provides important exploratory evidence that serum ACE may serve as a clinically accessible biomarker of coronary plaque vulnerability in patients with CCS. Serum ACE measurement is inexpensive, widely available, and technically straightforward, offering a potential advantage over advanced imaging techniques in resource-limited settings such as Bangladesh. If validated in larger, multicentre, prospective cohorts, serum ACE measurement at the identified cut-off could become a cost-effective adjunct to CCTA for non-invasive risk stratification and early identification of patients at risk of acute coronary events. The present study should, however, be interpreted within the context of its limitations, including the modest

sample size and single-centre cross-sectional design, which preclude causal inference and limit generalisability. Future studies with longitudinal follow-up and larger cohorts are warranted to confirm these findings and to evaluate whether ACE-guided risk stratification translates into meaningful improvements in clinical outcomes.

Limitation Of The Study:

The modest sample size, single-centre cross-sectional design, and absence of longitudinal follow-up limit the generalizability of the findings and preclude causal inference

Conclusion

Serum ACE levels are significantly associated with vulnerable coronary plaque morphology in patients with chronic coronary syndrome. Serum ACE demonstrated excellent diagnostic performance for identifying plaque vulnerability and may serve as a simple, non-invasive, and cost-effective biomarker for risk stratification, particularly in resource-limited settings.

Recommendation

Further large-scale, multicenter prospective studies are recommended to validate serum ACE as a diagnostic and prognostic biomarker for coronary plaque vulnerability. Future research should also explore its integration with imaging and other biomarkers to improve risk prediction models, especially in resource-limited settings.

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