



Hyperhomocysteinemia Outperforms CD4 Count and Framingham Risk Score in Detecting Subclinical Coronary Atherosclerosis Based on Agatston Scoring, and Cardiac Morbidity in Human Immunodeficiency Virus Patients on Antiretroviral Therapy: A Cross-sectional Study from Northern India

Ajeet Kumar Chaurasia¹*, Shreya Dastidar², Poonam Gupta^{3*}, Abhishek Sachdeva⁴, Sharad Varma⁵

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[Visual Abstract](#)

ABSTRACT

Background: People living with HIV have increased cardiovascular risk despite antiretroviral therapy, and conventional risk tools like the Framingham Risk Score may underestimate subclinical coronary disease. Coronary artery calcium (CAC) scoring is a validated marker of subclinical atherosclerosis, while prior HIV imaging studies show appreciable plaque burden even among patients categorized as low risk by traditional models. Alongside, hyperhomocysteinemia is increasingly recognized as a potentially modifiable cardiovascular risk factor in HIV patients as a consequence of chronic inflammation, micronutrient deficiencies, and long-term antiretroviral therapies.

Objectives: To evaluate whether serum homocysteine outperforms current CD4 count and Framingham Risk Score in identifying subclinical coronary atherosclerosis and cardiac morbidity in treated people living with HIV.

Materials and methods: This cross-sectional analytical study enrolled 211 adults with HIV on antiretroviral therapy at a tertiary care hospital in Prayagraj, India, from March 2025 to March 2026 and assessed coronary artery calcification by noncontrast cardiac CT using Agatston scoring, along with electrocardiography, treadmill testing (TMT), and echocardiography. Serum homocysteine, CD4 count, fasting lipid profile, vitamin B12, and folate were measured. Data were analyzed using advanced software (SPSS v25.0), and associations were examined using correlation analysis, Chi-square testing, ANOVA, and regression methods.

Results: The mean age of the cohort was 41.7 years, and 81% of participants remained in the low Framingham risk category despite a substantial burden of coronary artery calcification (31% had a positive CAC score) and cardiovascular dysfunction (28.4% had detectable echocardiographic abnormalities). Serum homocysteine showed a moderate positive correlation with CAC score ($r = 0.403$, $p < 0.001$), whereas CD4 count had neither a significant correlation with CAC score ($r = -0.039$, $p = 0.575$) nor with echocardiographic cardiovascular dysfunction ($r = -0.003$, $p = 0.969$). Hyperhomocysteinemia independently predicted CAC positivity after adjustment for confounders, with an odds ratio of 7.26, while vitamin B12 deficiency showed a weaker association, with an odds ratio of 2.36; age, sex, and ART duration were not significantly associated in the model. Framingham Risk Score did not meaningfully track with homocysteine, coronary calcium burden, or immune status in this study.

Conclusion: Serum homocysteine appears to be a stronger marker of subclinical coronary atherosclerosis than current CD4 count or Framingham Risk Score in treated people living with HIV. Incorporating homocysteine, vitamin B12 status, and selective coronary calcium assessment may improve cardiovascular risk stratification in HIV care, particularly in populations where conventional risk scores may underestimate disease burden.

Keywords: Agatston score, CD4 count, Coronary artery calcium, Framingham Risk Score, Human immunodeficiency virus, Hyperhomocysteinemia, Subclinical atherosclerosis.

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INTRODUCTION

As survival improves with antiretroviral therapy, cardiovascular disease has emerged as an important contributor to long-term morbidity in people living with HIV (PLHIV).¹ Imaging studies have shown that subclinical atherosclerosis and coronary plaque are common in HIV, even in those patients who appear to be at low risk according

to conventional cardiovascular morbidity prediction tools.² This environment is marked by ongoing inflammation, damage to blood vessels, and accelerated atherosclerosis. These factors then lead to both ischemic and nonischemic heart disease.³

Coronary artery calcium measured by noncontrast CT is an established marker of cumulative coronary atherosclerotic burden and future cardiovascular events, quantified

based on Agatston scoring. A score of zero indicates an extremely low short-term risk of cardiovascular events, whereas higher scores are associated with progressively increasing risk. Interpretation: 0: No detectable coronary calcification; 1–99: Mild calcification; 100–399: Moderate calcification; ≥ 400 : Severe calcification.⁴

Traditional models such as the Framingham Risk Score (FRS), used for prediction of 10-year risk of CVD (low = $<10\%$ risk, moderate = $10\text{--}20\%$ risk, and high = $>20\%$ risk), do not account for persistent immune activation, chronic inflammation, ART-related metabolic effects, or HIV-specific biology, which may limit their performance in this population.⁵

Homocysteine is biologically plausible as a vascular risk marker because it is linked to oxidative stress, endothelial dysfunction, inflammation, and thrombosis.⁶ In treated HIV populations, hyperhomocysteinemia may additionally reflect nutritional deficits, antiretroviral-related metabolic disturbance, and chronic inflammatory activation, making it a potentially useful integrative biomarker of vascular risk.⁷

¹Professor, Department of Medicine, MLN Medical College; ²Junior Resident, Department of General Medicine, Moti Lal Nehru Medical College; ³Professor and Head, Department of Medicine, MLN Medical College and SRN Hospital; ⁴Associate Professor, Department of Cardiology, MLN Medical College; ⁵Senior Medical Officer, Department of General Medicine, Moti Lal Nehru Medical College, Prayagraj, Uttar Pradesh, India; *Corresponding Author

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AIMS AND OBJECTIVES

Aims

To evaluate whether serum homocysteine outperforms current CD4 count and Framingham Risk Score in identifying subclinical coronary atherosclerosis and cardiac morbidity in treated people living with HIV in Northern India.

Objectives

To estimate the prevalence of subclinical coronary atherosclerosis based on coronary artery calcification by Agatston scoring in PLHIV patients on ART.

To estimate the prevalence of cardiovascular dysfunction based on echocardiography and TMT abnormalities in PLHIV patients on ART.

To assess the correlation of CAC scoring and cardiovascular dysfunction with hyperhomocysteinemia, current CD4 counts, and Framingham Risk Score in PLHIV patients on ART.

MATERIALS AND METHODS

This was a hospital-based cross-sectional analytical study conducted at Swaroop Rani Nehru Hospital, Prayagraj, a tertiary care center in Northern India. In this study, 500 adults, as shown in Figure 1, with HIV infection receiving antiretroviral therapy who were willing to participate were included after informed consent. Following the application of exclusion criteria, 197 adults were excluded who were critically ill or had preexisting diabetes or other comorbidities like malignancies, chronic kidney disease, and chronic liver disease. A total of 303 patients filled out the questionnaire, of whom 211 patients were willing to undergo the required diagnostic procedures. The study was largely based on clinically stable patients and was representative of PLHIV on ART attending

the hospital during the study period. Proper Institutional Ethics Committee approval was obtained from the institute, Moti Lal Nehru Medical College, Prayagraj (Ethics Committee Registration No. ECR/922/inst/UP/RR-22 issued under New Drugs and Clinical Trial Rules, 2019), dated 21st March 2025.

Inclusion Criteria

All PLHIV patients above 18 years of age who were on ART, attending the hospital during the study period, and willing to participate in the study.

Exclusion Criteria

Those patients who were critically ill, had preexisting diabetes mellitus, malignancies, chronic kidney disease, chronic liver disease, were pregnant or lactating, had newly diagnosed HIV and were not on ART, or were unwilling to undergo the required diagnostic procedures were excluded.

Data Collection Tools and Procedure

All participants underwent structured clinical evaluation, electrocardiography, treadmill testing (TMT), two-dimensional echocardiography, and noncontrast cardiac CT for CAC assessment using the Agatston method. Serum homocysteine, CD4 count, fasting lipid profile, vitamin B12, folate, and other metabolic variables were measured by standard laboratory methods used at the institution. Coronary artery calcification was categorized by Agatston score, with CAC >0 considered calcification positive. Hyperhomocysteinemia was defined in this study using a cutoff above 22 $\mu\text{mol/L}$, vitamin B12 deficiency as <180 pg/mL, and folate deficiency as 2 ng/mL or lower.

Statistical Analysis

The study used SPSS version 25 for data analysis. Associations were examined using

Chi-squared tests, Pearson and Spearman correlation coefficients, ANOVA or Kruskal–Wallis tests where appropriate, and multivariable regression methods. A two-sided *p*-value below 0.05 was considered statistically significant in the thesis analysis.

RESULTS

Baseline Profile

The mean age of the study population was 41.7 years. CD4 distribution suggested that only 6.6% of participants had severe immunosuppression, with CD4 below 200 cells/ μL , while 51.7% had CD4 200 to 500 cells/ μL and 41.7% had CD4 above 500 cells/ μL .

Metabolic Profile

A high metabolic burden was present in this study. Lipid abnormalities were documented in 78.7% of participants, with low HDL in 61.6% and high triglycerides of at least 150 mg/dL in 54.5%, yet no statistically significant CAC/CVD association ($p > 0.05$) was observed. Vitamin B12 deficiency was present in 30.8% and folate deficiency in 16.6%, as shown in Table 1.

Patients with B12 deficiency combined with hyperhomocysteinemia showed the highest burden of CAC: 51.9% had elevated CAC (38.5% mild + 13.5% moderate), whereas patients with B12 deficiency alone (without hyperhomocysteinemia) had a lower CAC burden: only 15.4% had mild CAC. This further emphasizes that B12 deficiency synergized with hyperhomocysteinemia for CAC ($\chi^2 = 18.74$, $p = 0.001$), as shown in Table 2 and Figure 2, although its association with CAC alone was not significant.

Coronary Calcium and Biomarker Associations

Among all the study subjects, as shown in Table 3, 31% had detectable coronary

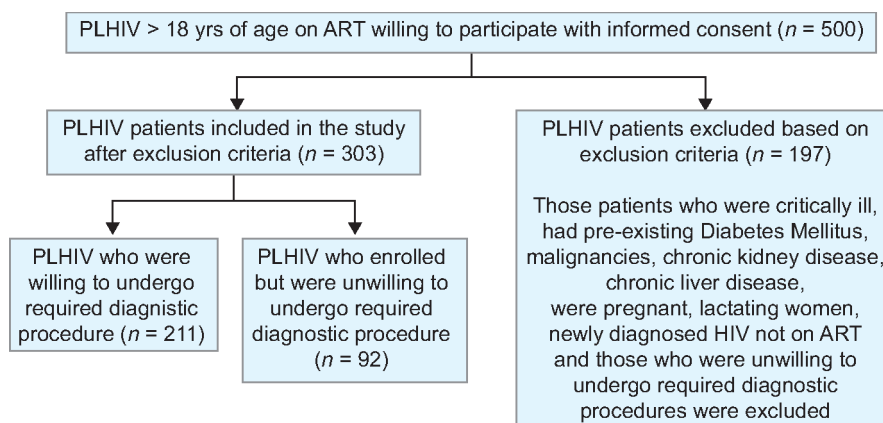


Fig. 1: A flowchart detailing recruitment of participants

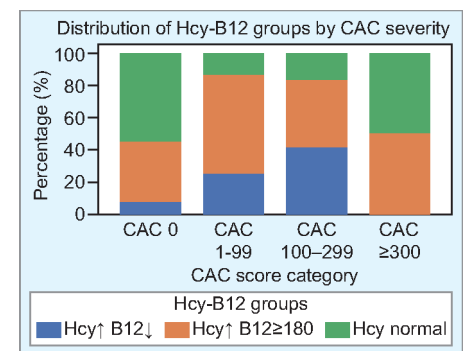


Fig. 2: Distribution of homocysteine groups across CAC severity categories, showing enrichment of hyperhomocysteinemia with increasing coronary calcium burden

Table 1: Baseline study parameters

Variable	Mean $\pm$ SD	Median (IQR)	Range
Age (years)	41.7 $\pm$ 11.4	42 (34–50)	20–59
CD4 count (cells/ μ L)	476.5 $\pm$ 213.4	456 (321–615)	185–898
Homocysteine (μ mol/L)	27.3 $\pm$ 13.5	24.6 (19.3–32.6)	7.4–82.2
CAC score	31.2 $\pm$ 66.2	0 (0–20)	0–319
FRS10-year (%)	6.12 $\pm$ 5.28	4.50 (1.50–9.40)	0.50–29.40
HbA1c (%)	4.84 $\pm$ 0.81	4.80 (4.40–5.20)	3.00–12.70
Vitamin B12 (pg/mL)	310.2 $\pm$ 242.9	267 (168–392)	83–1492
Folate (ng/mL)	5.5 $\pm$ 4.5	4.2 (2.9–6.1)	0.1–20.0
Total cholesterol (mg/dL)	155.8 $\pm$ 37.5	154 (132–178)	78–260
LDL (mg/dL)	83.9 $\pm$ 38.3	78 (56–105)	1–206
HDL (mg/dL)	42.2 $\pm$ 17.1	39 (29–53)	14–86
Triglycerides (mg/dL)	167.4 $\pm$ 55.7	164 (123–203)	69–432

Table 2: Association of homocysteine with CAC scoring

Homocysteine group	CAC = 0, n (%)	CAC > 0, n (%)	Total	χ^2	p-value
Hyper-Hcy + low B12	10 (37.0%)	17 (63.0%)	27	34.27	<0.001*
Hyper-Hcy + normal B12	55 (59.1%)	38 (40.9%)	93		
Normal Hcy	81 (89.0%)	10 (11.0%)	91		

*Highly statistically significant association ($\chi^2 = 34.27$, $p < 0.001$)

Table 3: CAC scoring distribution indicating subclinical atherosclerosis

CAC category (Agatston)	Number of patients	Percentage
0 (no calcification)	146	69%
1–99 (mild)	51	24.2%
100–299 (moderate)	12	5.7%
≥ 300 (severe)	2	1%

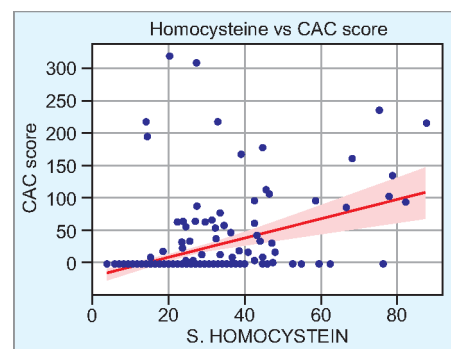


Fig. 3: Scatter plot showing a moderate positive correlation between serum homocysteine and CAC score ($r = 0.403$, $p < 0.001$). Higher homocysteine levels are associated with progressively higher coronary calcium burden

calcification (CAC > 0), indicating subclinical atherosclerosis.

Serum homocysteine demonstrated a moderate positive correlation with CAC score ($r = 0.403$, $p < 0.001$), as shown in Table 2 and Figure 3, indicating a clinically relevant relationship between rising homocysteine levels and increasing coronary calcium burden.

In contrast, CD4 count, as shown in Table 4 and Figure 4, showed no correlation with CAC

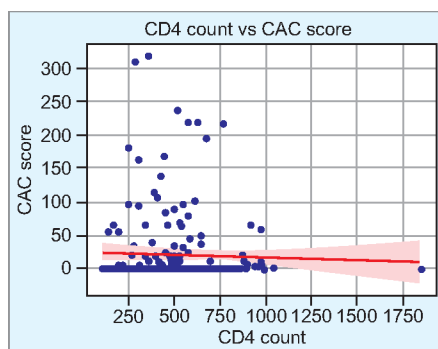


Fig. 4: Lack of association between CD4 and CAC: Distribution of CAC according to CD4 categories, showing no significant association between current CD4 count and CAC positivity

score ($r = -0.039$, $p = 0.575$). Across CD4 strata, CAC positivity was strikingly similar: 28.6% in those with CD4 below 200 cells/ μ L, 31.2% in those with CD4 200 to 500 cells/ μ L, and 30.7% in those with CD4 above 500 cells/ μ L, with no statistically significant association (Chi-square = 0.04, $p = 0.980$). These data suggest that current immune status does not discriminate calcific coronary plaque burden in treated HIV patients.

In multivariable analysis, hyperhomocysteinemia independently predicted CAC positivity, with an odds ratio

of 7.26 and a 95% confidence interval of 3.34–15.80, and the association was highly significant ($p < 0.001$), whereas vitamin B12 deficiency had a smaller association, with an odds ratio of 2.36. Age, sex, and ART duration were not significant, as shown in Table 5 and Figure 5. This pattern supports homocysteine as the most informative biomarker among the variables examined for calcific subclinical atherosclerosis in this study.

Cardiac Morbidity and Echocardiographic Findings

Prevalence of CVD was determined based on different investigative modalities. Abnormalities, as shown in Table 6 were led by echocardiography (28.4%), with LV diastolic dysfunction (9.5%) and hypertrophy (10.9%) predominant. Other abnormalities included valvular heart disease (MR/TR) (8.6%), dilated cardiomyopathy (0.9%), and heart failure with reduced ejection fraction (4.7%); TMT changes were rarer (2.36%). These findings suggest that subclinical cardiac remodeling is prevalent even in asymptomatic patients on stable ART.

Homocysteine did not show a significant relationship with echocardiographic cardiovascular dysfunction, with a correlation coefficient of -0.036 and $p = 0.606$. Likewise, the association between homocysteine category and cardiovascular dysfunction was not significant, with Chi-square = 1.25 and $p = 0.264$, as shown in Table 7.

CD4 count also did not predict echocardiographic cardiovascular

Table 4: Showing association between CD4 categories and CAC score

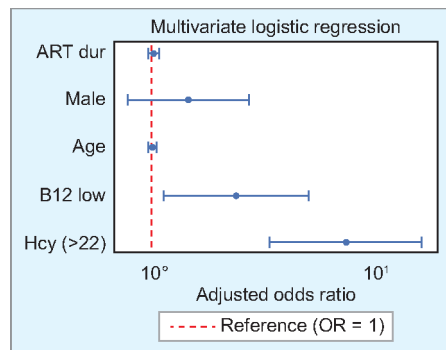
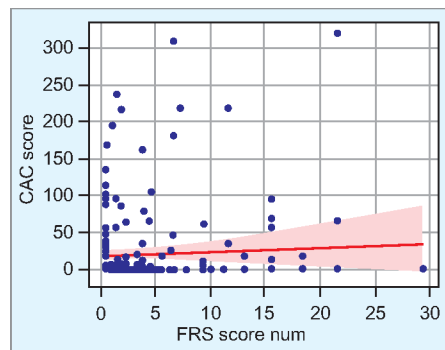
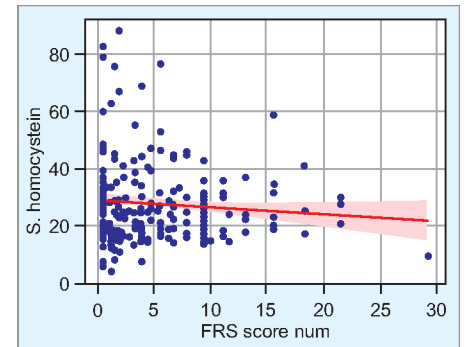
CD4 category	CAC = 0	CAC >0	Total	χ^2	p-value
<200	10 (71.4%)	4 (28.6%)	14	0.04	0.980 (not significant)
200–500	75 (68.8%)	34 (31.2%)	109		
>500	61 (69.3%)	27 (30.7%)	88		

Table 5: Multivariate logistic regression model

Variable	OR	95% CI lower	95% CI upper	p-value
Homocysteine (>22 $\mu\text{mol/L}$)	7.26	3.34	15.80	<0.001
Vitamin B12 (<180 pg/mL)	2.36	1.12	4.98	0.023
Age (year)	1.02	0.99	1.05	0.248
Male vs female	1.45	0.78	2.71	0.243
ART duration (per year)	1.01	0.96	1.07	0.684

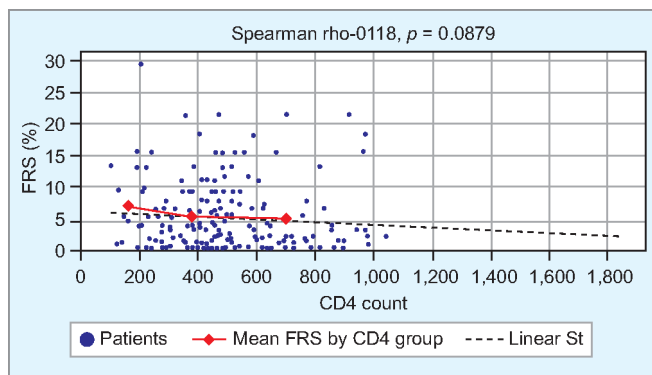
Table 6: Distribution of different 2D echocardiographic findings

Echo abnormality	Count	Percentage
Left ventricular hypertrophy	23	10.9%
LV diastolic dysfunction	20	9.5%
Reduced ejection fraction (EF <55%)	10	4.7%
Mild mitral regurgitation	9	4.3%
Mild tricuspid regurgitation	9	4.3%
LV systolic dysfunction	4	1.9%
Dilated cardiomyopathy	2	0.9%

**Fig. 5:** Multivariate logistic regression: Hyperhomocysteinemia independently predicts CAC positivity after adjustment for confounders. (OR = 7.26) Vitamin B12 deficiency: OR = 2.36 (weaker effect). Age, sex, and antiretroviral therapy (ART) duration: nonsignificant (ORs cluster near 1.0)**Fig. 6:** Scatter plot showing no linear correlation of CAC scores with Framingham Risk Score (FRS). Low FRS (<10) dominates all CAC groups (83–92%), with only scattered intermediate/high FRS cases**Fig. 7:** Scatter plot showing no linear correlation of serum homocysteine with FRS ($p = 1.21$)

dysfunction. The correlation between CD4 count and echo abnormalities was -0.003 with $p = 0.969$, and the categorical association between CD4 groups and echo abnormalities was not significant, with Chi-square = 1.89 and $p = 0.390$, as shown in Table 8.

These findings indicate that the strongest signal in the dataset relates specifically to calcific coronary atherosclerosis rather than to the broader composite of cardiac structural or functional abnormalities on echocardiography.

**Fig. 8:** Scatter plot showing an association between CD4 count and FRS, showing a weak negative trend with no significant correlation ($n = 211$). Spearman $\rho = -0.118$ ($p = 0.0879$) indicates that higher CD4 counts are associated with slightly lower FRS, but this falls short of statistical significance ($p > 0.05$)

Framingham Risk Score Performance

The study analyzed that most participants (81% of patients) remained in the low Framingham risk category despite detectable coronary calcium in a substantial subset. Visual and tabulated analyses in the study also showed no meaningful relationship between Framingham Risk Score and CAC burden, homocysteine levels, or CD4 count, as shown in Figures 6 to 8.

This discordance is consistent with prior HIV literature suggesting that conventional risk equations can miss clinically relevant subclinical vascular disease in PLHIV on ART.

Table 7: Association between homocysteine groups and Echo abnormalities

Hcy (>22)	Normal Echo	Abnormal Echo	p-value
≤22	61	30	$\chi^2 = 1.25$ $p = 0.264$
>22	90	30	(not statistically significant)

Table 8: Association of Echo abnormalities with CD4 count

CD4 category	CVD absent	CVD present	Total	χ^2	p-value
<200	3 (21.4%)	11 (78.6%)	14	1.89	0.390
200–500	44 (40.4%)	65 (59.6%)	109		(not significant)
>500	34 (38.6%)	54 (61.4%)	88		

DISCUSSION

The present cross-sectional analytical study systematically examined the correlations between CD4 count, serum homocysteine levels, and markers of cardiovascular disease—specifically, echocardiographic cardiovascular dysfunction and coronary artery calcification (CAC) quantified by Agatston scoring—in 211 PLWHA receiving a fixed-dose combination antiretroviral therapy (ART) regimen of TLD (tenofovir, lamivudine, dolutegravir).

Hyperhomocysteinemia ($\geq 22 \mu\text{mol/L}$) was strikingly prevalent in this study of PLHIV on ART, with a mean serum level of $27.3 \pm 13.5 \mu\text{mol/L}$ (median, $24.6 \mu\text{mol/L}$). This high burden underscores hyperhomocysteinemia as a major, potentially modifiable cardiovascular risk factor in this population, far exceeding general Indian population mean values (typically $11.46 \pm 2.56 \mu\text{mol/L}$ in males and $11.41 \pm 2.48 \mu\text{mol/L}$ in females)⁸ and aligning with HIV-specific metabolic disruptions.^{6,7}

Pearson correlation between hyperhomocysteinemia and CAC scoring confirmed a highly statistically significant moderate positive linear relationship ($r = 0.403$, $p = 0.001$), indicating a dose–response effect: higher hyperhomocysteinemia levels corresponded to progressively elevated CAC scores, suggesting causality. Multivariate logistic regression further established independence (OR = 7.26, 95% CI, 3.34–15.80, $p = 0.001$), with minimal B12 confounding (3.7% coefficient change; Hosmer-Lemeshow $p = 0.45$, c-statistic = 0.78). Kullo et al.⁹ demonstrated an Hcy-CAC association ($p = 0.01$) independent of age, sex, and smoking in 1,071 hypertensives, particularly at intermediate Framingham risk ($p = 0.003$), mirroring our study's low FRS (mean, 6.12). Sun et al. confirmed Hcy as an independent predictor of calcified plaques (OR = 1.668, $p = 0.037$) in asymptomatic CTA patients.¹⁰

The lack of association of current CD4 count with cardiovascular dysfunction and coronary atherosclerosis is important.

These null results challenge early HIV-CVD paradigms but align with ART-era shifts. Literature shows discordance: Mishra et al. linked CD4 <200/ μL to echo abnormalities (52% prevalence) in untreated/advanced HIV, but our suppressed study population (mean ART duration, 7.4 years) decouples immunity from outcomes.¹¹ Gupta et al.¹² found low CD4 predicted cIMT (mean, 332 cells/ μL) in younger PLWHA, yet post-ART recovery negated this. Mangili et al. (2010)¹³ tied nadir/low CD4 to mortality (HR *via* cIMT), but current CD4 failed, echoing our findings. Jachymek et al.¹⁴ found plaques in 26.5% of suppressed PLWHA despite high CD4. Mechanistically, pre-ART HIV depletes CD4 *via* gp120-mediated apoptosis/inflammation, driving monocyte activation, macrophage foam cells, and plaque. ART restores counts (>500 signals viral control), but residual risks persist *via* immune senescence (T-cell exhaustion), microbial translocation (sCD14), and ART dyslipidemia— independent of current CD4.¹⁵

The poor performance of Framingham Risk Score in this study, with null correlation, also has practical implications. Because traditional scores were developed outside HIV populations, they may underweight the contribution of chronic inflammation, ART-related dysmetabolism, and HIV-specific vascular risk, thereby classifying many patients as low risk despite imaging evidence of coronary atherosclerosis. Literature echoes this: Korten et al.¹⁶ found poor agreement across FRS/D:A:D/ASCVD in 527 PLWHA ($\kappa = 0.55$ –0.80), with 20–36% statin-eligible despite low FRS. Pereira et al.¹⁷ reclassified 43% *via* CAC (23.5% low-FRS had CAC >0). Raggi and Corwin¹⁸ critiqued FRS for ignoring HIV inflammation. Our low FRS yet 31% CAC/28.4% CVD prevalence matches: traditional factors (age/smoking/lipids) underperform versus HIV-specific factors (Hcy OR = 7.26).

The synergistic effect of hyperhomocysteinemia and vitamin B12 deficiency on subclinical coronary

atherosclerosis further suggests that nutritional and metabolic pathways influencing homocysteine may be clinically relevant in ART-treated HIV care, as mirrored in literature on B12-homocysteine interplay (Dinavahi and Falkner).¹⁹

An important nuance is that homocysteine was linked to CAC rather than to echocardiographic cardiovascular dysfunction. This may indicate that homocysteine is more useful as a marker of subclinical coronary plaque burden than of the broader spectrum of myocardial, valvular, or functional abnormalities encountered in HIV.

Limitations

Our study, being a cross-sectional study, failed to establish causality and temporal association of hyperhomocysteinemia with coronary atherosclerosis with certainty and could not assess progression and regression with interventions. The sample size being 211 and the study population being limited to a particular city reduced the generalizability to a wider population, especially different ethnic or regional groups within India. Third, a noninvasive cardiac CT imaging method was used for detecting coronary atherosclerosis instead of invasive coronary angiography, which only enabled identification of calcific plaques, while noncalcific plaque burden remained undiagnosed. Fourth, comparison with matched HIV-negative controls would have given a clearer picture of enhanced atherosclerosis in PLHIV.

CONCLUSION

Among treated adults with HIV in this tertiary-care cohort, serum homocysteine showed the clearest association with Agatston-based CAC burden, whereas current CD4 count and Framingham Risk Score performed poorly as markers of subclinical coronary atherosclerosis. These findings support

consideration of homocysteine, together with vitamin B12 assessment and selective CAC imaging, for more refined cardiovascular risk stratification in treated HIV populations.

RECOMMENDATIONS

Based on the study findings, hyperhomocysteinemia emerged as the principal modifiable predictor of coronary artery calcification in PLHIV receiving long-term antiretroviral therapy, whereas current CD4 count and FRS did not appear useful for cardiovascular risk stratification. Therefore, we recommend routine screening of serum homocysteine and vitamin B12 levels in all people living with HIV, irrespective of immunological status or conventional cardiovascular risk profile. Individuals with abnormal results should receive targeted B-vitamin supplementation, and statin therapy should be considered based on CAC scoring rather than CD4-based stratification. Cardiovascular assessment with 2D echocardiography should be used alongside metabolic evaluation to identify subclinical left ventricular hypertrophy and diastolic dysfunction at an early stage. In resource-limited settings such as India, this cost-effective approach, which prioritizes homocysteine assessment for initial triage, may support precision intervention and reduce cardiovascular morbidity by focusing on metabolic risk pathways rather than immunologic monitoring alone. Updated national HIV guidelines should incorporate HIV-specific metabolic biomarkers to improve cardiovascular prevention in the antiretroviral therapy era.

ETHICS APPROVAL

Proper Institutional Ethics Committee approval was obtained from Moti Lal Nehru Medical College, Prayagraj (Ethics Committee Registration No. ECR/922/inst/UP/RR-22 issued under New Drugs and Clinical Trial Rules, 2019), dated 21 March 2025.

CONSENT TO PARTICIPATE

All patients were informed about the study, and proper consent was obtained after explaining the advantages and risks to the patient.

DATA AVAILABILITY

Data transparency is maintained.

CODE AVAILABILITY (SOFTWARE APPLICATION OR CUSTOM CODE)

Microsoft Word.

AUTHOR CONTRIBUTIONS

AKC and SD chose the topic and planned the execution. All authors conducted the investigative part and collected data. AKC, SD, and PG wrote the main manuscript. AKC, SD, PG, AS, and SV prepared tables and figures and contributed to the discussion. All authors reviewed the manuscript. All authors contributed equally.

ORCID

Ajeet Kumar Chaurasia  <https://orcid.org/0009-0008-3887-9731>

Poonam Gupta  <https://orcid.org/0009-0007-8473-9492>

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