

Original Research Article

Study of cardiac manifestations in people living with HIV using echocardiography and association with CD-4 counts and other factors

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ABSTRACT

Background: As the AIDS related deaths have declined, due to introduction of ART, the survival of people living with HIV (PLWH) has increased, leading to increased prevalence of chronic conditions like cardiovascular diseases. India has the second highest burden of HIV-AIDS globally so there is a need for studying cardiovascular diseases in this population. Present study was undertaken to study the cardiac manifestations in people living with HIV using echocardiography and other tools and their correlation with CD4-counts and other factors.

Methods: A cross-sectional study was done on 200 patients divided into two equal groups based on HIV-ELISA status. Known cases of coronary heart disease, structural and valvular heart disease were excluded. Participants underwent basic investigations, chest X ray, ECG, TMT, NTProBNP and echocardiography. PLWH also had their CD4-counts measured. A statistical analysis was performed and the prevalence of cardiovascular abnormalities and presence of related associations was sought.

Results: 26% of PLWH showed abnormal echocardiography with prevalence odd's ratio of 3.16 when compared to non-HIV group. Diastolic dysfunction was the most common abnormality found. Older age (>50 years), presence of comorbidities, low CD4 counts, advanced WHO staging, non-intake of ART and presence of opportunistic infections were positively and significantly associated with echocardiographic abnormalities in PLWH.

Conclusions: There is high prevalence of cardiovascular diseases among PLWH. Echocardiography may be used as screening tool. Newer ART regimens and High CD4-counts seem to be cardioprotective. There is need for further prospective studies on larger scale to accurately determine associated risk factors.

Keywords: AIDS, Cardiovascular diseases, CD4-count, Echocardiography, HIV, PLWH

INTRODUCTION

Since its identification in the 1980s, HIV has had a devastating impact on global health, with over 40 million deaths worldwide.¹ As of recent estimates, approximately 23 Lacs people in India are living with HIV, with a national prevalence rate of around 0.22%. Even with such low prevalence India has the second highest HIV burden globally. The AIDS-related deaths have declined by 82.24% since 2010 leading to increased survival mainly attributed to the introduction of antiretroviral therapy (ART).² However, as the survival rates have increased, so

have the complexities of managing long-term health issues, particularly cardiovascular diseases (CVDs). The reported prevalence of cardiac involvement in such patients varies, with estimates ranging from 28% to 73%.³ Cardiac involvement can be over looked in HIV-positive patients, as the clinical features are frequently mistaken for noncardiac causes, such as pulmonary failure or secondary infection.³ The cardiac involvement may manifest as pericardial effusion, left ventricular dysfunction, myocarditis, dilated cardiomyopathy, endocarditis, pulmonary hypertension, malignant neoplasm, coronary artery disease and drug related cardiotoxicity.⁴ The cause

of this increased risk is likely multi-factorial: HIV associated immune dysfunction and inflammation, higher rates of traditional risk factors in PLWH (e.g., substance abuse), presence of opportunistic infections, adverse effects of ART including metabolic effects and higher prevalence of socio-economic disadvantage in this population.⁵⁻⁸ Understanding these mechanisms is essential for developing effective strategies for the prevention and management of cardiovascular disease in this vulnerable population.

While effective antiretroviral therapy (ART) has led to a reduction in relative risk, the overall burden of CVD among PLWH remains significant and continues to increase. A meta-analysis involving 793,635 individuals with a cumulative follow-up of 3.5 million person-years revealed that the global burden of HIV-associated cardiovascular disease (CVD) has tripled over the past 20 years.⁹

Several studies have demonstrated that lower CD4 counts are associated with an increased risk of CVD, emphasizing the importance of monitoring CD4 levels in HIV patients. A study involving virally suppressed HIV patients found that a major decline in CD4 count was associated with a heightened incidence of cardiovascular events, cancer and mortality within six months of the decline.¹⁰

As cardiac dysfunction is prevalent in this population and actual prevalence data is scarce, therefore the study was undertaken to detect the occurrence of symptomatic or asymptomatic cardiac involvement in HIV/AIDS cases using echocardiography and its correlation with CD4 cell counts and other factors. Early detection of cardiac involvement in HIV cases in pre-AIDS or AIDS phase of disease is important to prevent significant morbidity and mortality.

METHODS

This cross-sectional analytical study was conducted at Maharani Laxmi Bai Medical College, Jhansi, to compare the prevalence of cardiovascular diseases (CVD) in people living with HIV (PLWH) versus HIV-negative controls. Participants were recruited from both OPD and inpatient settings over the course of 14 months (May, 2023 to June, 2024). The study population was divided into two groups: Group A (HIV ELISA positive) and Group B (HIV ELISA negative), each comprising 100 patients, selected via random sampling. Group B patients were appropriately age and sex matched to Group A. All participants >18 years of age who gave informed consent were included in the study. Known cases of coronary, structural or valvular heart diseases were excluded.

All participants were assessed clinically by detailed history and physical examination. Blood routine investigations along with NTProBNP were done. Screening of opportunistic infections and measurement of CD-4 counts was done in Group A patients. An ECG, TMT

and chest X-ray PA-view were taken to look for any major abnormality and cardiomegaly.

All patients were examined using quantitative M-mode and two-dimensional transthoracic echocardiography, along with colour flow Doppler assessments. Each two-dimensional echocardiographic evaluation included parasternal long and short axis and apical two and four chamber views. The left atrial (LA) dimensions, left ventricular (LV) end systolic and end diastolic dimensions, right ventricular (RV) end diastolic dimensions and LV fractional shortening (FS) were obtained as per conventions of American Society of Echocardiography. LV volumes were measured and ejection fraction (EF) was calculated using Simpson's method. Diastolic dysfunction was defined according to pulse wave Doppler parameters. Diastolic dysfunction was categorized into 3 grades, grade 1 defined as E/A ratio <0.75, grade 2 defined as E/A ratio >1, deceleration time (DT) <140 ms and grade 3 defined as E/A ratio >2, DT <140 ms.

Statistical analysis of data was performed using SPSS Version 20.0. P value of <0.05 was considered statistically significant.

RESULTS

Total 200 patients were studied, divided into two equal groups: Group A (PLWH) and Group B (non-PLWH). Each group had 60 males and 40 females with similar mean age of presentation in both groups (Table 1). The mean BMI was quite lower in Group A (19.56 ± 2.68) compared to Group B (22.85 ± 3.87) ($p < 0.05$) (Table 1).

Both groups reported similar trend of substance abuse, with no significant differences in alcohol, smoking or tobacco use (Table 2).

Frequency of abnormalities in Chest X-ray, ECG, TMT and NTProBNP were similar in both groups ($p > 0.05$). However, echocardiography abnormalities were significantly higher in Group A at 26% compared to 10% in Group B ($p = 0.003$) with prevalence odd's ratio (POR) of 3.16 (Table 3).

The distribution of echocardiography abnormalities in Group A shows that the most common abnormality was diastolic dysfunction seen in 15 cases followed by LVH, LV systolic dysfunction, valvular abnormalities and pericarditis which were found in 14, 6, 6 and 2 cases, respectively. RWMA was only seen in 1 case (Figure 1).

Among Group A, 26 patients were at least 50 years old and had increased occurrence of echocardiographic abnormalities as compared to younger patients with statistically significant p value of 0.029 (Table 4).

In Group A, all patients with systemic hypertension (4 cases) or diabetes mellitus (3 cases) also had some abnormality in echocardiography. Out of 6 cases of

dyslipidemia, 5 had abnormal echocardiography (p -value<0.05) (Figure 2).

On comparing CD4 counts between participants with normal and abnormal echocardiographs in Group A (PLWH), the mean \pm SD CD4 count was higher in the normal group (422.71 ± 183) compared to the abnormal group (386.65 ± 282), but this difference was not statistically significant ($p=0.46$). However, only 8% of patients with normal echocardiograph had CD4 counts below 200, while in abnormal group this proportion is 31%, which was statistically significant (p value=0.009), indicating a higher proportion of low CD4 counts in those with abnormal echocardiographs (Table 5 and Figure 3).

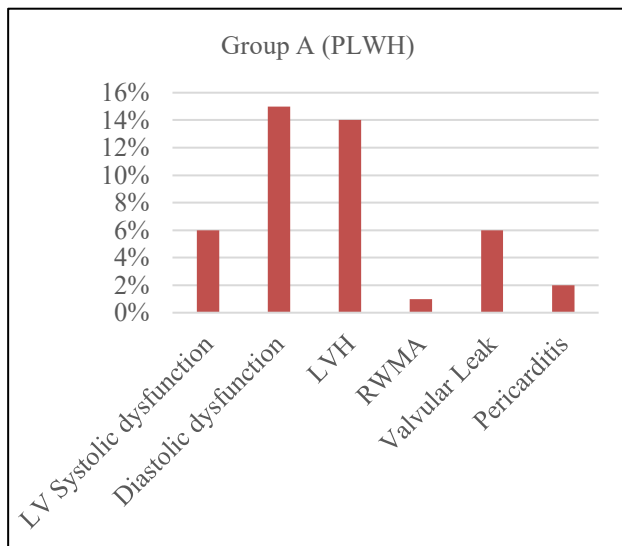


Figure 1: Distribution of echocardiography abnormalities in Group A.

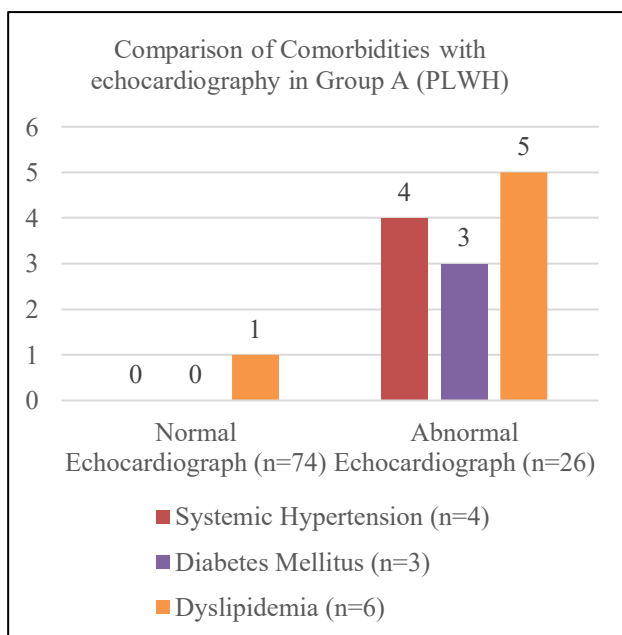


Figure 2: Comparison of comorbidities in Group A with normal vs abnormal echocardiography.

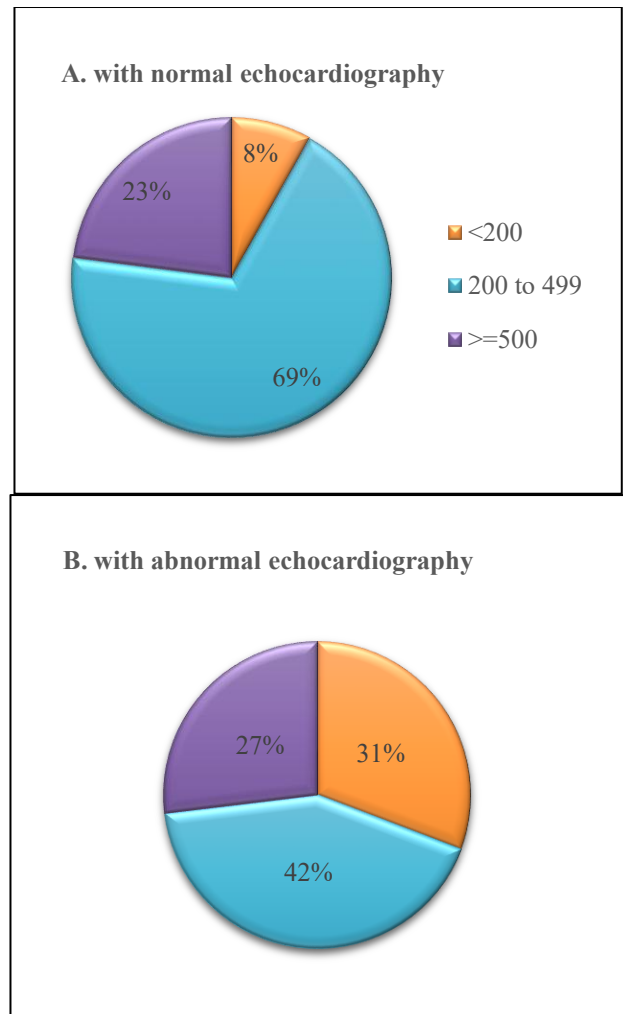


Figure 3: Proportion of CD4 Counts in Group A compared among those with (A) normal vs (B) abnormal echocardiography.

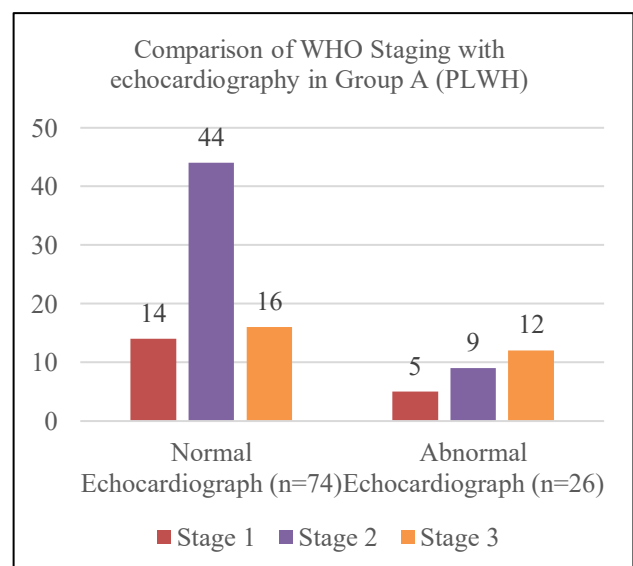


Figure 4: WHO Staging of HIV-AIDS in Group A (PLWH) compared among those with normal vs abnormal echocardiography.

In our study, 19 patients were in WHO Stage 1, 53 were in WHO Stage 2 and 28 were in WHO Stage 3. The proportion of cases that had abnormal echocardiography were 26.3% (5 out of 19), 16.9% (9 out of 53) and 43.8% (12 out of 28), respectively.

This result was statistically significant with p value of 0.041 (Figure 4). On comparing ART intake duration and echocardiography, the mean duration was slightly higher in the normal group (4.94 years) compared to the abnormal group (4.63 years), but was not statistically significant ($p=0.76$).

However, a greater proportion of participants with abnormal echocardiographs reported no ART intake (19% versus 4%). Furthermore, only 69% of those with abnormal echocardiographs had been on ART for at least one year, compared to 92% in the normal group (p value=0.014) (Table 6). Opportunistic infections are found in 26 participants, among them, 14 had normal echocardiographs while 12 had abnormal echocardiographs. While out of 74 participants without any opportunistic infection, majority (60) had normal echocardiographs while only 14 had abnormal ones ($p<0.05$) (Table 7).

Table 1: Demographic characteristics of both the groups.

Characteristic	Group A (PLWH) (n=100)	Group B (Non-PLWH) (n=100)
Age (Mean±SD)	41.71±12.58	41.67±12.51
Sex (Male:Female)	60:40	60:40
BMI (Mean±SD)	19.56±2.68	22.85±3.87
	t (198)=-5.73, $p<0.00001$	

Table 2: Comparison of substance abuse among both the groups.

Substance abused	Group A (PLWH) (n=100)	Group B (Non-PLWH) (n=100)	P value
No Substance abuse	66	62	0.55
Smoking	24	26	0.74
Alcohol	11	12	0.82
Tobacco chewing	32	29	0.65

Table 3: Comparison of cardiovascular abnormalities in both the groups.

Cardiovascular abnormalities	Group A (PLWH) (n=100)		Group B (Non-PLWH) (n=100)		P value
	Present	Absent	Present	Absent	
X Ray abnormalities (cardiomegaly)	8	92	2	98	0.10
ECG abnormalities	16	84	9	91	0.13
Abnormal TMT	13	87	10	90	0.51
Raised NTProBNP	17	83	16	84	0.85
Echocardiography abnormalities	26	74	10	90	0.003

Table 4: Comparison of age with echocardiographic abnormality in Group A.

Age group (in years)	Normal echocardiograph (n=74)	Abnormal echocardiograph (n=26)
<50 (n=74)	59	15
≥50 (n=26)	15	11
P value	$p=0.029$	

Table 5: Comparison of CD4 Counts with echocardiography in Group A.

CD4 counts	Normal echocardiograph (n=74)	Abnormal echocardiograph (n=26)
Mean (±SD)	422.71 (±183)	386.65 (±282)
	t (98)=0.744, $p=0.46$	
<200 (n=14)	6 (8%)	8 (31%)
200-499 (n=62)	51 (69%)	11 (42%)
≥500 (n=24)	17 (23%)	7 (27%)
P value	0.0092	

Table 6: Comparison of duration of ART with echocardiographic abnormality in Group A.

Duration of ART intake (years)	Normal echocardiograph (n=74)	Abnormal echocardiograph (n=26)
Mean (\pmSD)	4.94 (\pm 4.03)	4.63 (\pm 5.11)
	t (98)=0.308, p=0.76	
No intake (n=8)	3 (4%)	5 (19%)
<1 year (n=6)	3 (4%)	3 (12%)
\geq1 year (n=86)	68 (92%)	18 (69%)
P value	0.014	

Table 7: Comparison of presence of opportunistic infections with echocardiographic abnormality in Group A.

Opportunistic infection	Normal echocardiograph (n=74)	Abnormal echocardiograph (n=26)
Present (n=26)	14	12
Absent (n=74)	60	14
P value	0.0064	

DISCUSSION

Outcomes of ECG, CXR, TMT, NTPROBNP and 2D echocardiography

Frequency of cardiomegaly in chest X-ray and ECG abnormalities were not statistically significant when compared among both groups with p value of 0.10 and 0.13 respectively. This is similar with the result obtained in the Knudsen et al, study where there was no difference in prevalence of major ECG abnormalities between PLWH and controls (p=0.987).¹¹ Difference in TMT and NTproBNP was also not statistically significant when compared among both groups with p value of 0.51 and 0.85, respectively. Further studies are needed to ascertain the value of these tests in HIV population.

Abnormal echocardiography was found in 26 patients in Group A (PLWH) compared with 10 patients in Group B (non-PLWH), this result was statistically significant with p value of 0.003. It shows there is positive correlation between HIV serostatus and abnormal echocardiography. This association had also been found in numerous studies namely Shah et al, study where it was concluded that PLWH are twice as likely to develop cardiovascular disease when compared to general population.⁹

This high prevalence of diastolic dysfunction in our study is supported by Reinsch et al, study and Cerrato et al study where diastolic dysfunction was found in 48% and 43% of the subjects, respectively.^{12,13}

Associations of abnormal echocardiography in group A

In our study, older patients (\geq 50 years), had increased frequency of abnormal echocardiography which was statistically significant with p value=0.029. Similar findings were seen in Woldeyes et al, study where Age \geq 50 years was associated with increased odds of multiple cardiac abnormalities.¹⁴

Similarly, in our study, presence of co-morbidities like hypertension, diabetes and dyslipidemia was also positively associated with abnormal echocardiography with significant p value $<$ 0.05. Similar findings were noted in E. Woldeyes et al, (2022) where high blood pressure and high fasting blood glucose were associated with echocardiographic abnormalities.¹⁴

In our study, mean (\pm SD) of CD4 Counts in patients with normal echocardiography and abnormal echocardiography were 422.71 (\pm 183) and 386.65 (\pm 282), respectively. Although, this figure was lower in the abnormal group, it was not statistically significant with p value of 0.46. However, only 8% (6 cases out of 74) participants in normal group had CD4 counts less than 200 while the same was 31% (8 cases out of 26) in abnormal group, indicating a much higher proportion of low CD4 counts in those with abnormal echocardiography. This result was statistically significant with p value=0.09. This result was consistent with Aggarwal et al, (2009) study where the mean (\pm SD) of CD4 counts in normal and abnormal group was 116 \pm 95.89 and 61.68 \pm 34.16. They also found that the proportion of cases with low CD4 counts had higher echocardiographic abnormalities but they used the cut-off of 100 cells/mm³.¹⁵ Reddy et al, study also found the same result with cut-off of 200 cell/mm³ similar to our study.¹⁶

In our study, higher WHO staging was found to be positively associated with echocardiographic abnormalities which was statistically significant with p value of 0.041. Similar findings were also seen in Chaudhary et al, study where there was positive correlation of WHO staging and cardiac abnormalities.¹⁷

In our study, majority of patients were on ART for at least a year (86 out of 100), 6 patients took ART for less than 1 year and only 8 patients had never taken ART before the study. Out of those, echocardiographic abnormalities were found in 20.9% (18 out of 86), 50% (3 out of 6) and 62.5% (5 out of 8), respectively. This distribution was statistically

significant with p value of 0.014. This finding is in stark contrast with Islam et al, study where the pooled Relative risk of ART use was 1.52 and pooled annual relative risk was between 1.04 to 1.11 depending upon the class of drug.¹⁸ The point to be noted is that this meta-analysis included studies before 2010 when older drugs like lopinavir/ritonavir and abacavir were used and those drugs were apparently associated with increased cardiovascular risk. In our study, all participants had been taking newer regimen of Tenofovir (TDF 300 mg) +Lamivudine (3TC 300 mg) +Dolutegravir (DTG 50 mg) as per latest NACO guidelines. This regimen therefore seems protective with lower risk of cardiac abnormalities as compared to treatment naïve group. Further prospective studies are needed to verify this association.

In our study, presence of opportunistic infections was positively and significantly associated with echocardiographic abnormalities (p value<0.05). This was consistent with Aggarwal et al study in which abnormal echocardiographic findings were associated with clinically apparent opportunistic infections.¹⁵

Our study being a single centre cross-sectional study is limited by the inability to make causal inferences between echocardiographic abnormalities and HIV status and have limited number of cases that may not accurately represent the actual population. Therefore, a large multi-centric prospective study is needed to accurately assess the current impact of HIV-AIDS on cardiovascular health and finding associated risk factors.

CONCLUSION

Study found that 26% of PLWH showed abnormal echocardiographic results, which was significantly higher than in the non-HIV group, highlighting a strong correlation between HIV status and cardiac abnormalities. The prevalence odd's ratio of echocardiographic abnormality was found to be 3.16, suggesting that PLWH are thrice as likely to have cardiac abnormalities when compared to general population. Study also demonstrated the paradigm shift from systolic dysfunction to diastolic dysfunction in the ageing HIV population, as diastolic dysfunction was more prevalent (15%) than systolic dysfunction (6%).

Study also explored associations between echocardiographic abnormalities and various factors. Older age (>50 year) and presence of comorbidities like hypertension and diabetes were significantly associated with echocardiographic abnormalities. The study also found that low CD4 counts, advanced WHO staging of the disease and presence of opportunistic infections were more common in those with abnormal echocardiography, reinforcing the connection between immune status and cardiac health. The findings also indicated that newer antiretroviral drugs may offer protective benefits against cardiac abnormalities, contrasting with studies done with older treatment regimens.

Study suggests that PLWH are at increased risk for cardiac diseases and therefore, require early screening for such diseases to reduce overall mortality and morbidity and to improve quality of life. In this regard, our study found that echocardiography is an excellent tool when used as screening method to detect early cardiac abnormalities and therefore may be used for regular cardiovascular assessments in this population, although further prospective studies are needed to accurately assess cardiac health and associated risk factors in the ageing population of people living with HIV.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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