RESEARCH

Echocardiographic Profile of Human Immuno deficiency Virus (HIV) Infected Patients: A hospital based study in North-East India

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Abstract:

Context: Cardiovascular illness is common in patients with HIV infection, particularly in the later course of disease. Cardiovascular abnormalities in people living with HIV disease (PLHIV) often go unrecognized or untreated resulting in increased cardiovascular related morbidity and mortality and reduced quality of life. The prevalence of cardiac involvement in PLHIV has been reported to range between 28 to 73%. However, the incidence of symptomatic heart failure in HIV positive patients is 8-10%.Recognizing cardiac dysfunction early is crucial for prompt medical therapy and potentially postpone irreversible heart dysfunction. **Methods and Material:** This was a hospital-based cross-sectional study undertaken at the Centre of Excellence (CoE) ART Centre, Department of Medicine, Regional Institute of Medical Sciences, Imphal. The study included patients infected with the human immunodeficiency virus, both treatment-naïve and those undergoing antiretroviral therapy, who attended the Medicine outpatient department at the Centre of Excellence ART Centre, RIMS, and to those admitted to the Medicine wards. A 12-lead electrocardiogram and 2D echocardiography were performed using the SONOACE X8 echocardiography machine, Version 2.03.00, M345-E20300-00, and its association with CD4 count and WHO clinical staging , was assessed . **Result:** A total of 156 HIV-positive patients of age more than 18 years , attending the Medicine Outpatient Department at the Centre of Excellence ART Centre, RIMS, and those hospitalized to the Medicine wards, were recruited in the research during **a 12-month period, having** satisfied the inclusion criteria. The highest proportion of participants was in the age range 41–50 years at 39.7%, followed by 51 –60 years at 26.9%, and the lowest was in the over 60 years group at 7.1%. The study population had a nearly equal gender distribution, with males constituting 51% (79) and females 49% (77). Among the 156 patients, about 61.5% with a CD4+ level below 200 and 57.4% with a CD4+ count between 200 and 350 had cardiac symptoms. A statistically significant relationship exists between low CD4+ count and cardiac problems. The majority of patients with a CD4 cell count below 200 per mm³ exhibited left ventricular diastolic dysfunction (LVDD) compared to those with a CD4 cell count beyond 200 per mm³. Hypokinesia of the left ventricle, mitral regurgitation, pulmonary arterial hypertension (PAH), regional wall motion abnormality (RWMA), heart failure with preserved ejection fraction (EF), heart failure with reduced EF, and dilated cardiomyopathy were more prevalent in patients with a CD4 cell count below 200 per mm³ compared to those with a count above 200 per mm³ . **Conclusions:** HIV-infected people exhibit an increase in echocardiographic abnormalities as the CD4 level declines. We should prioritize the early initiation of ART in HIV-infected patients to enhance the quality of life for those living with HIV/AIDS.

INTRODUCTION

HIV is a pandemic disease which had already affected 34 million people worldwide up until 2010.[1] As of 2009, it was estimated that 2.4 million people were living with HIV in India.[2] Manipur shows 1.43%-estimated adult HIV prevalence among 15–49 years, which is higher than the national average.[3]

HIV infection virtually involves every system, including hematologic, central nervous system, respiratory system, and cardiovascular system. The cardiac involvement in HIV-infected patients can occur due to a variety of causes like HIV infection itself, opportunistic infections caused by viruses, fungi, and protozoa, side effects of anti retro- viral drugs, and a combination of these factors. Direct infection of target tissue with HIV, inflammation and immune suppression secondary to HIV infection, and common comorbidities such as alcohol and drug abuse may all contribute to impairment of cardiac function. HIV is known to infect myocytes but is not found to be abundant or highly multiplicative in these cells.[4]

Cardiovascular illness is common in patients with HIV infection, particularly in the later course of disease. The prevalence of cardiac involvement in HIV infection has been reported to range from 28% to 73%.[5] At the beginning of the HIV epidemic, heart muscle disease was the dominant cardiac complication of HIV infection in the developed world, and tuberculous pericarditis (incidence as high as 11% per year) was the most important cardiac manifestation of the disease in Africa.[6] In a study, cardiovascular diseases (CVDs) have attributed up to 20% of mortality in HIV- infected patients.[7] With

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improved clinical surveillance and treatment, more HIV-infected patients are living longer, and now more attention is being paid toward CVDs. The advent of combined antiretroviral therapy (ART) has changed the pat- tern of disease in developed countries where premature coronary artery disease and other manifestations of atherosclerosis are now the most common cardiovascular disorders in HIV- infected patients.[8]

Cardiovascular abnormalities are common in PLHIV but often go unrecognized or untreated resulting in increased cardiovascular related morbidity and mortality and reduced quality of life. The present study had been undertaken to study the prevalence of cardiovascular abnormalities in H I V positive patients in north-eastern part of Indian population and its association with CD 4 count and WHO stages of the disease.

MATERIAL and METHODS

The hospital-based observational cross-sectional study was carried out at the Regional Institute of Medical Sciences in Imphal, Manipur, a tertiary care center in northeastern India. Patients were included once they provided informed consent. The diagnosis was determined in accordance with NACO principles, and the staging followed WHO recommendations.9,10

The research lasted one year, from January to December 2020. The trial comprised HIV-positive individuals over the age of 18 who provided informed consent. The study excluded individuals who did not provide informed consent or had a history of ischemic, rheumatic, congenital heart disease, chronic renal disease, or chronic respiratory illness prior to HIV diagnosis. The convenient sampling strategy was employed to recruit participants until the sample size was attained. The independent variables included socio-demographic parameters such as age (years), gender (male/female), weight (kg), and so on. Outcome factors included 12 lead electrocardiogram findings, 2D-echocardiography findings, CD4+ count, WHO clinical stage, and so forth.

Data collection: All PLHIV patients, whether antiretroviral drug naïve or currently receiving antiretroviral treatment, who visited the CoE ART Centre, Department of Medicine, RIMS, Imphal, were recruited in the study upon satisfying the inclusion and exclusion criteria. An structured Performa was utilized for data collection. Ethical approval was obtained from the Research Ethics Board, RIMS, Imphal before the commencement of the project. Informed consent was obtained from each participant before their involvement in the study. The participants were assured of their anonymity during data collection, and the need of delivering accurate replies was underscored. A thorough clinical history, clinical examination, and investigation reports were collected from all individuals utilizing a uniform Performa. A thorough account of the signs and symptoms of cardiovascular failure was obtained. All patients had fundamental blood examinations (complete blood count, liver and kidney function tests), ECG, echocardiography, lipid profile, HbA1c, and chest X-ray (PA view) following the acquisition of written consent. Blood samples were collected to assess the CD4 count and HIV virus loads. The collected data were verified for completeness and documented accordingly.

Statistical analysis: SPSS (IBM) version 26 was used to enter and evaluate the gathered data. Descriptive statistics including mean, standard deviation, and percentages were used to summarize data on age, sex, smoking and tobacco usage, viral load, lipid profile, etc. The chi-square test and Fisher's exact test were utilized to examine the correlation between the result variables and relevant factors such as age, gender, and so on. The ANOVA test was utilized to ascertain the relationship between the mean CD4 count value and the cardiovascular result. One considered a P-value of less than 0.05 to be statistically significant .

RESULTS

The study included 156 HIV-positive patients who were either not taking antiretroviral medication or were already taking it. The patients were recruited from the Medicine Outpatient Department (OPD), the Centre of Excellence (CoE) Antiretroviral Treatment Centre (RIMS), and the Medicine wards at RIMS hospitals throughout the study period.

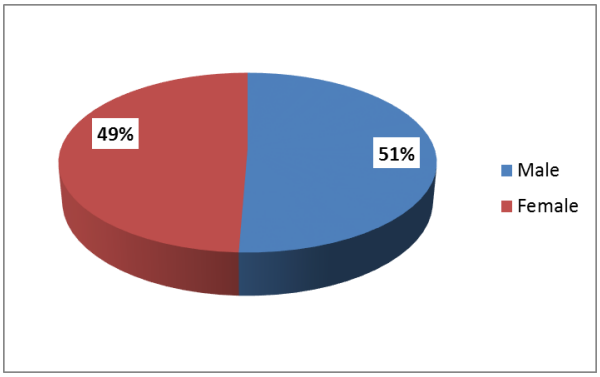

Fig.1. Gender wise distribution of the patients (N=156)

There were more or less equal distribution of gender among the study population with male 51% (79) and female 49% (77).

Table 1. Mean age of the patients (N=156)

Sl.no.	Particulars	Mean	Standard Deviation
1.	Age in years	46.35	10.36

The mean age of the study population was 46.35 ± 10.36 years.

Table 2. Distribution of the patients by Age (N=156)

Sl.no.	Age groups in years	No. of patients	Percentage (%)
1.	18-30	13	8.3
2.	31-40	28	17.9
3.	41-50	62	39.7
4.	51-60	42	26.9
5.	> 60	11	7.1
4.	Mean age ± SD in years	46.35 ± 10.36 years	

Maximum numbers of participants were in the age group 41 – 50years with 39.7% followed by 51 – 60 years (26.9%) and minimum in above 60 years group with 7.1%.

Table 3. Distribution of patients by WHO stage (N=156)

Sl.no.	WHO stage	No. of patients	Percentages (%)
1.	Stage I	107	68.6
2.	Stage II	34	21.8
3.	Stage III	14	9.0
4.	Stage IV	1	0.6

Maximum of the patient were in WHO stage I (68.6%) followed by Stage II (21.8%) and stage III (9%). Only 0.6% had WHO stage IV.

Table 4. Mean CD4 count and Weight (N=156)

Sl.no.	Characteristics	Mean	Standard deviation
1.	CD4 count in cells/mm^3	439.32	230.53
2.	Weight in kg	53.02	7.61

The mean CD4+ count of the patients was 439.32 ± 230.53cells/mm^3. The mean weight was53.02 ± 7.61 Kg

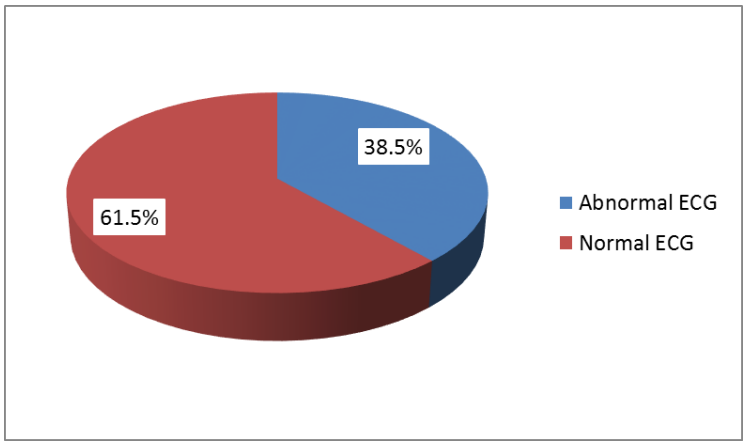

Fig.2. Distribution of patients by ECG findings (N=156)

Maximum of the patient had normal ECG findings. Only 38.5% (60) of the patients had abnormal ECG.

Table 5. Distribution of patients by abnormal ECG findings (N=60)

Sl.no.	ECG finding	No. of patients	Percentages (%)
1.	Myocardial Infarction	15	25.0
2.	Right Bundle Branch Block (RBBB)	4	6.7
3.	Left Bundle Branch Block (LBBB) and Left axis deviation	6	10.0
4.	Concentric LVH	8	13.3
5.	Atrial fibrillation	3	5.0
6.	Low voltage complex	4	6.7
8.	Sinus tachycardia	20	33.3

Maximum of the patients had sinus tachycardia (33.3%) followed by 25% Myocardial Infarction (ST/T changes), 10% LBBB 6.7% low voltage complexes, 6.7% RBBB and 5% Atrial fibrillation.

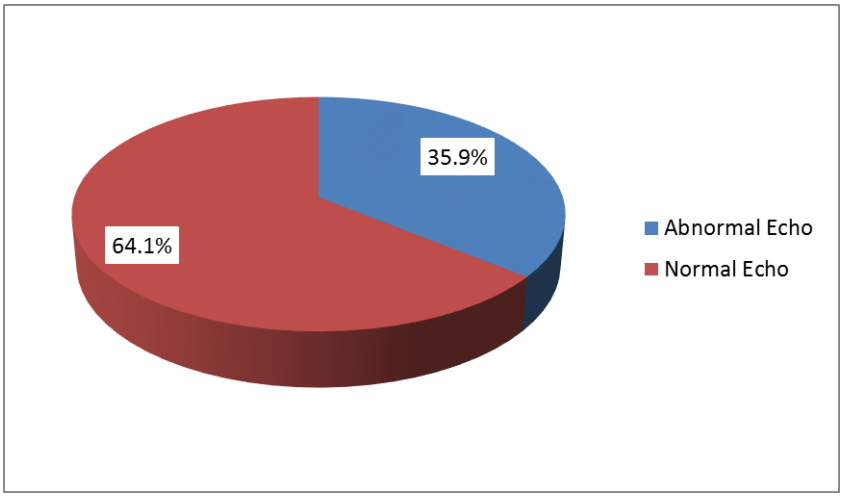

Fig. 3. Distribution of patients by Echo findings (N=156)

Maximum of the patient had normal Echo findings. Only 35.9% (56) of the patients had abnormal Echo findings.

Table 6. Distribution of patients by abnormal Echo finding (N=56)

Sl.no.	Echo finding	No. of patients	Percentages (%)
1.	Hypokinesia of Left Ventricle	8	14.2
2.	Pericardial effusion	4	7.1
3.	Mitral regurgitation	7	12.5
4.	Pulmonary arterial hypertension(PAH)	9	16.0
5.	Regional wall motion abnormality (RWMA)	6	10.7
6.	Concentric LVH	3	5.3
7.	LV Diastolic dysfunction(LVDD)	44	78.5
8.	Heart failure reduced EF	9	16.0
9.	Heart failure mid range EF	3	5.3
10.	Heart failure preserved EF	8	14.2
11.	Dilated Cardiomyopathy	12	21.4

Most common abnormal echo findings were LVDD (78.5%) followed by dilated cardiomyopathy (21.4%), heart failure with reduced EF (16%) and PAH (16%). Hypokinesia of Left Ventricle (14.2%) and Heart failure with preserved EF (14.2%) were also seen.

Table 7. The mean CD4 count and WHO stages of the patients (N=156)

Sl.no.	WHO stages	Mean value of CD4 count	Standard Deviation	P value
1.	WHO stage I	525.40	219.32	< 0.001
2.	WHO stage II	280.03	117.10	
3.	WHO stage III & IV	186.33	70.79	

The mean value of CD4 count was higher in WHO stage I (525.40 ± 219.32) in comparison to WHO stage II (280.03 ± 117.10) and WHO stage III&IV (186.33 ± 70.79). The difference was found to be statistically significant.

Table 8. Association between WHO stages and echo finding (N=156)

Sl.no.	WHO stages	Echo finding		P value
		Normal	Abnormal	
1.	Stage I	91 (91.0)	16 (28.6)	0.001
2.	Stage II	9 (9.0)	25 (44.6)	
3.	WHO stage III&IV	0 (0)	15 (26.8)	

Maximum of the patient with normal echo finding were from WHO stage I in comparison to WHO stage II, III & IV. Similarly most of the patient with abnormal echo finding were from Stage II,III& IV. The association between abnormal echo finding and WHO stage II,III& IV was found to be statistically significant.

Table 9. Association between Echo finding and CD4 Count (N=156)

Sl.no.	CD4 cell count	Echo finding		P value
		Normal	Abnormal	
1.	< 200	0 (0)	13 (23.2)	0.001
2.	200 -350	13 (13.0)	34 (60.7)	
3.	> 350	87 (87.0)	9 (16.1)	

All the patients with CD 4 Count < 200 had an abnormal finding in echo. Most of the patient with CD4 count > 350 had a normal finding in echo. The association between CD 4 cell count < 200 and CD 4 cell count 200-350 with abnormal echo finding was found to be statistically significant.

Table 10. Association between WHO stages and echo finding (N=156)

Sl.no.	Echo finding	WHO stages			P value
		Stage I	Stage II	Stage III&IV	
1.	LVDD	15 (14.2)	18 (52.9)	11 (73.3)	<0.001
2.	Hypokinesia LV	0 (0)	2 (5.9)	6 (40.0)	< 0.001
3.	Pericardial effusion	2 (1.9)	2 (5.9)	0 (0)	0.498
4.	Mitral regurgitation	1 (0.9)	2 (5.9)	4 (26.7)	0.001
5.	PAH	2 (1.9)	4 (11.8)	3 (20.0)	0.003
6.	RWMA	1 (0.9)	1 (2.9)	4 (26.7)	0.001
7.	Concentric LVH	1 (0.9)	2 (5.9)	0 (0)	0.232
8.	Heart failure pEF	1 (0.9)	5 (14.7)	2 (13.3)	0.001
9.	Heart failure mid EF	1 (0.9)	0 (0)	2 (13.3)	0.048
10.	Dilated cardiomyopathy	3 (2.8)	6 (17.6)	3 (20.0)	0.003
11.	Heart failure rEF	1 (0.9)	6 (17.6)	2 (13.3)	0.001

Maximum of the patient in WHO stage III&IV were having LVDD in comparison to WHO stage I and stage II. Similarly hypokinesia LV, mitral regurgitation, PAH, RWMA, heart failure pEF, mid EF, rEF and dilated cardiomyopathy were more commonly seen in WHO stage III&IV in comparison to WHO stage I. These differences were found to be statistically significant.

Table 11. Association between CD4count and echo finding (N=156)

Sl.no.	Echo finding	CD 4 cell count per mm^3			P value
		< 200	200-350	> 350	
1.	LVDD	10 (76.9)	27 (57.4)	7 (7.4)	< 0.001
2.	Hypokinesia LV	5 (38.5)	3 (6.4)	0 (0.0)	< 0.001
3.	Pericardial effusion	0 (0)	3 (6.4)	1 (1.0)	0.174
4.	Mitral regurgitation	2 (15.4)	4 (8.5)	1 (1.0)	0.012
5.	PAH	3 (23.1)	5 (10.6)	1 (1.0)	0.001
6.	RWMA	4 (30.8)	2 (4.3)	0 (0.0)	<0.001
7.	Concentric LVH	0 (0)	2 (4.3)	1 (1.0)	0.424
8.	Heart failure pEF	4 (30.8)	4 (8.5)	0 (0)	<0.001
9.	Heart failure mid EF	1 (7.7)	1 (2.1)	1 (1.0)	0.162
10.	Dilated cardiomyopathy	3 (23.1)	8 (17.0)	1 (1.0)	< 0.001
11.	Heart failure rEF	4 (30.8)	5 (10.6)	0 (0)	<0.001

Maximum of the patients withCD 4 cell count less than 200 per mm^3were having LVDD in comparison to CD 4 cell count more than 200 per mm^3. Similarly hypokinesia LV, mitral regurgitation, PAH, RWMA, heart failure pEF, rEF and dilated cardiomyopathy were more commonly seen in patients with CD 4 cell count less than 200 per mm^3in comparison to those above 200 per mm^3. These differences were found to be

DISCUSSION

A total of 156 people infected with HIV were included in the trial. Of these, 51% were male and 49% were female. Njoku PO et al[11]. reported a comparable study result indicating a roughly equal gender distribution within their HIV-positive cohort.Hakim JG et al[12]. reported a research population including 51% male and 49% female, which aligns with the findings of this study. Singh A et al[13]. stated that 66.7% of their research sample was male, whereas 33.3% was female. Consequently, several research have mostly included males in the study group, whereas only a limited number have demonstrated a somewhat equal gender distribution among their HIV-positive participants.

The mean age of the study population was 46.35 ± 10.36 years, with the majority of participants aged 41 to 50 years (39.7%), followed by those aged 51 to 60 years (26.9%), and the least represented group being individuals above 60 years at 7.1%. Ding Yet al[14] found a mean age of 44.3 ± 14.0 years in their research population, with the highest prevalence in the age groups of 30 to 44 years and 45 to 59 years, which aligns with the findings of our investigation. Nakaranurack C et al[15]. reported a mean age of 45.5 ± 8.3 years in their research population, which aligns with the findings of this investigation. Consequently, several investigations indicated that the majority of their patients were aged between 41 and 50 years, aligning with the findings of this study. In our study, the majority of patients were classified as WHO stage I (68.6%), followed by stage II (21.8%) and stage III (9%). Merely 0.6% exhibited WHO grade IV. Sivasubramanian B et al[16]. observed that the majority of their study population was in WHO stage III at 53%, followed by 41% in WHO stage IV. Singh A et al13. revealed that the highest proportion of their patients were in clinical stage IV (40%), followed by stage III (35.7%), stage II (14.3%), and just 10% were in stage I, respectively

In our analysis, the majority of patients had a mean CD4+ count of 439.32 ± 230.53 cells/mm^3. The average weight was 53.02 ± 7.61 kg. Ding Y et al14. revealed in their study that the majority of individuals (65.7%) had > 350 cells/mm^3. Njoku PO et al[11]. observed a mean CD4 cell count of 408.43 ± 221.62 cells/mm^3 among their research group on HAART, which aligns with the findings of this study. Womack JA et al17 found a mean CD4 count of 468±352 cells/mm^3 in their research group, which aligns with the findings of this investigation. In our investigation, aberrant ECG findings were seen in 38.5% of cases. Sinus tachycardia was observed in 33.3%, followed by myocardial infarction (ST/T alterations) at 25%, low voltage complexes at 6.7%, atrial fibrillation at 5%, left bundle branch block (LBBB) at 10%, and right bundle branch block (RBBB) at 6.7%. Ding Y et al[14]. observed a 35.3% prevalence of aberrant ECG findings among their HIV-positive patients, which aligns with the findings of this investigation. Kumar PS et al[18]. observed a 20% incidence of aberrant ECG findings in their research population, with the majority being sinus tachycardia (16%) and low voltage complexes (0.5%). According to Mishra TK et al[19], aberrant ECG findings were seen in 54.5% of the study group. Sinus tachycardia accounted for 45.8% of these findings, with low voltage QRS complex (23.8%) and ST-T wave alterations (20.2%) following closely behind. Chaudhary S et al20 identified a 49.3% incidence of abnormal ECGs among their research population. Consequently, a significant majority of studies showed aberrant ECGs, with sinus tachycardia identified as the predominant ECG abnormality in HIV patients, followed by ST alterations, consistent with the findings of this study. The majority of patients in our research had normal echocardiographic findings, with just 35.9% (56) presenting aberrant results. The highest prevalence of aberrant echocardiographic findings was observed in left ventricular diastolic dysfunction (78.5%), followed by dilated cardiomyopathy (21.4%), heart failure with decreased ejection fraction (16%), and pulmonary arterial hypertension (16%). Hypokinesia of the left ventricle (14.2%) and heart failure with maintained ejection fraction (14.2%) were also seen. Sivasubramanian B et al[16] revealed that among their HIV-positive study group, 6% had coronary artery disease, 10% had dilated cardiomyopathy, and 6% presented with pericardial effusion. Hakim JG et al[12] reported Echocardiographic abnormalities in 50% of their study population where dilated cardiomyopathy was found in 9%, left ventricular dysfunction in 22%. Right ventricular enlargement was found in 9% patients, pericardial effusion in 19% of the patients. Singh A et al[13] reported echocardiographic abnormalities in 55.7% of their cases. Out of which reduced EF (<50%) was seen in 22.8% and reduction in FS(<30%) in 48.6% of cases. Pericardial effusions in 17.4% while pulmonary artery hypertension in 11.4% of cases. Dilated cardiomyopathy and diastolic dysfunction was found in 8.5% of cases. Kumar PS et al18 detected diastolic dysfunction in 33%, pericardial effusion in 12%, dilated cardiomyopathy in 5%, systolic dysfunction in 9% and pulmonary hypertension in 8%. Mishra TK et al[19] identified abnormal echocardiographic findings in 52% of their study group. The most prevalent condition was LVDD at 39%, followed by valve regurgitation at 30.5%, reduced FS (<30%) at 32%, dilated cardiomyopathy at 12%, and pericardial effusion at 7%. Chaudhary S et al20 observed a 52.1% incidence of aberrant echocardiographic findings in their investigation. Nzuobontane D et al[21] reported 23.3% prevalence of dilated cardiomyopathy, 20% prevalence of pericardial effusion, and 6.7% prevalence of mitral valve prolapse within their research cohort. Consequently, the majority of investigations have shown a significant proportion of their study group exhibiting aberrant

echocardiographic findings, with left ventricular diastolic dysfunction being the most prevalent, followed by dilated cardiomyopathy. Our investigation identified a statistically significant link between low CD4+ count and cardiac abnormalities. Approximately 77% of patients with a CD4+ level below 200 and 66% with a CD4+ count under 350 had cardiac problems. The risk of cardiac problems is greatest in people with significantly weakened immune systems (CD4+ count < 200).The risk of cardiac problems remains substantial in individuals with moderately impaired immune systems (CD4+ count between 200-350). Kumar PS et al[18] conducted a similar study indicating that lower CD4+ counts correlated with a higher prevalence of cardiac dysfunction, with a statistically significant association observed for systolic dysfunction. Additionally, lower CD4 counts were significantly linked to the presence of pericardial effusion, and 20% of patients exhibited ECG abnormalities. Our investigation revealed cardiac anomalies in 23.4% of individuals in WHO stage 1, 47.1% in WHO stage 2, and 66.7% in WHO stages 3 and 4 combined. The link between WHO staging and cardiac abnormalities was statistically significant, indicating a substantial relationship between the severity of HIV infection (as assessed by WHO staging) and the occurrence of cardiac abnormalities. The research indicates that an increase in the severity of HIV infection, as assessed by WHO staging, correlates with a heightened chance of cardiac abnormalities. The disparity in cardiac abnormality rates between WHO stages 1 and 2 was substantial, with a much greater incidence of cardiac abnormalities in WHO stage 2. WHO stages 3 and 4 combined reveal an even greater frequency of cardiac problems, suggesting that the most advanced stages of HIV infection are linked with the greatest pericardial effusion which fits our study result. Trinath Kumar Mishra et al[19] found a significant correlation with CD4 count , WHO illness stage with Cardiovascular abnormalities in the form of ECG and ECHO results in 54.5% and 52% of patients, respectively.

CONCLUSION

The incidence of HIV infection is evenly spread between males and females, with a higher prevalence in the age group of the 40s. The average age of the participants in the study was 46.35 years with a standard deviation of 10.36 years. The majority of them were classified under WHO stages I and II. The average CD4+ count of the individuals was 439.32 cells/mm3 with a standard deviation of 230.53 cells/mm3. Abnormal electrocardiograms were observed in 38.5% of the patients, with sinus tachycardia being the most common (33.3%), followed by myocardial infarction (ST/T changes) in 25% of cases. Additionally, low voltage complexes, atrial fibrillation, left bundle branch block (LBBB), and right bundle branch block (RBBB) were also identified. Abnormal echocardiograms were present in 35.9% (56) of the patients, with left ventricular diastolic dysfunction (LVDD) being the most prevalent at 78.5%, followed by dilated cardiomyopathy at 21.4%. Other findings included heart failure with reduced ejection fraction (EF), pulmonary arterial hypertension (PAH), hypokinesia of the left ventricle, and heart failure with preserved EF. Cardiomegaly was observed in 10% of patients in the Chest X-ray findings. The average CD4 count was found to be lowest in patients at WHO stage III & IV. Patients with severely compromised immune systems (CD4+ count < 200) have the highest risk of cardiac abnormalities. Even patients with moderately compromised immune systems (CD4+ count between 200-350) still have a significant risk of cardiac abnormalities. There are significant differences in the rates of cardiac abnormalities between WHO stages 1 and 2, with a notably higher prevalence in WHO stage 2. The combination of WHO stages 3 and 4 displays an even higher prevalence of cardiac abnormalities, indicating that the most advanced stages of HIV infection are linked to the highest risk of cardiac complications .

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