__Original Research Article__

THE CHEST RADIOGRAPHIC FINDINGS AND THE VIRAL LOAD IN ADULT PATIENTS WITH HIV/PTB CO-INFECTION.

Abstract

INTRODUCTION: The human immunodeficiency virus (HIV) infection continues to modify the radiographic pattern of pulmonary tuberculosis (PTB). There is an increase in the prevalence and transmission of multidrug-resistant and drug-resistant MTB strains worldwide. **AIM:** To determine the relationship between the chest radiographic findings of patients with HIV/PTB co-infection and the viral load. **METHODS:** This is a prospective study of 112 HIV/PTB co-infected subjects using chest radiographs at full inspiration and the viral load. **RESULTS:** There were 112 Nigerian subjects with HIV/PTB co-infection, of which 79 (70.5%) had viral load > 10,000 copies/ml, 41(36.6%) were females, and 38(33.9%) were males. Plasma viral load of 20-10,000 copies/ml showed 28(25%) subjects, males and females 14 (12.5%) respectively. While viral load of < 20copies/ml showed females 4(3.5%) and males 1(0.9%). For normal radiographs, viral load > 10,000 copies/ml was seen in 13 (11.6%) subjects, none in subjects with < 20 copies/ml with a p-value = 0.459. Opacities were seen in 60 (53.6%) of subjects with viral load > 10,000 copies/ml and 4 (3.6%) of subjects with viral load < 20 copies/ml with a p-value= 0.670. There was no significant relationship between the zonal distribution of opacities and the chest radiographic findings with the subjects' viral load categories. **CONCLUSION:** The chest radiographic findings did not show any significant differences in appearance in the different viral load categories of the subjects.

KEYWORDS: Viral load, copies/ml, subjects, HIV, PTB

INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease caused by closely related gram-positive, acid and alcohol-fast bacteria known as the *Mycobacterium tuberculosis* complex. It most commonly affects the lungs resulting in pulmonary tuberculosis.[1] The human immunodeficiency virus (HIV) infection continues to modify the radiographic pattern of pulmonary tuberculosis (PTB). Various strains, new mutants, and super-infection patterns of the HIV may cause PTB to be radiographically present in unusual and undocumented ways. Tuberculosis is a major global health problem and one-fourth of the world's population is infected with the disease.[2] The current pattern of manifestations of PTB in the face of the ever-evolving dynamics of HIV and the increasing transmission of multi-drug resistant (MDR) pulmonary TB should be known. TB is transmitted from person to person via inhalation of droplets (aerosols) containing a critical dose of bacilli from the throat and lungs of patients with active pulmonary tuberculosis and importantly those with cavities.

Pulmonary tuberculosis is classified as primary or post-primary tuberculosis. In primary tuberculosis, radiographic signs occur around the time of inoculation. These include mediastinal lymphadenopathy, middle and lower lung involvement, and pleural effusion. Post-primary pulmonary tuberculosis is the most common type in adults. It is due to the reactivation of a latent primary infection (up to 90%) or less commonly following a repeat infection of a previously sensitized host. It usually presents with exudative inflammation. There is an initial involvement of the apical and posterior segment of the upper lobe or the superior segment of the lower lobe.[3,4] Radiographic findings are atypical in the immuno-compromised and resemble the primary type. Atypical distribution of the disease entails the involvement of the anterior segment of the upper lobe, the basal segments of the lower lobe, the right middle lobe, and the lingular segments. Other atypical patterns are diffuse lung infiltrates, mid-zone predilection, bilateral lung involvement, interstitial nodules, pleural effusion, mediastinal or hilar lymphadenopathy, and normal radiograph of the lung.[5] Human immunodeficiency virus (HIV) is a blood-borne virus; typically transmitted via sexual intercourse, shared intravenous drug paraphernalia, and mother-to-child transmission (MTCT). HIV disease is caused by infection with HIV 1 or HIV 2 which are retroviruses.[6] Patients may present with the signs or symptoms of any of the stages of the HIV infection which are features of the presenting infection or illness. There may be a benign asymptomatic phase, generalized lymphadenopathy, opportunistic malignancies, etc.[7]

HIV disease staging and classification systems are indispensable tools in the management and monitoring of the HIV pandemic. The two main classification systems in use are the Center for Disease Control (CDC) classification system,[8, 9] revised in 1993, and the WHO clinical staging for HIV/AIDS for adolescents and adults revised in 2007.[7]

The CDC categorization is based on the lowest documented CD4+ cell count and previously diagnosed HIV-related conditions. The Revised (2007) WHO clinical staging for HIV/AIDS for adults/adolescents [7] has four stages. The Revised (2007) WHO clinical staging system is more practical, especially in settings where CD4+ cell count testing may not be readily available. About one-third of the world population is infected with tuberculosis but does not currently have an active infection (latent TB).[10] HIV infection increases the risk of TB 20-fold compared with HIV seronegative individuals in high HIV prevalence countries. In 2016, there were 2.5 million new cases of TB and 417,000 deaths from the disease in the African region. Forty percent of HIV deaths were also due to pulmonary TB.

AIM

To relate the chest radiographic findings of patients with HIV/PTB co-infection to their viral load.

METHODS

The study was a cross-sectional, descriptive plain chest radiographic finding in pulmonary tuberculosis in patients with HIV/AIDS. It was carried out at the Radiology Department of a Tertiary Centre in Nigeria. Institutional consent and authorization for the study were obtained from the various study centers following which ethical clearance was received from the Research and Ethics Committee of the Tertiary Centre with reference number NAUTH/CS/66/VOL.9/2016/123. A detailed explanation of the study was given to each participant and written informed consent was obtained from each patient. All patient information and data obtained were treated with the utmost confidentiality. Patients' names were coded.

The research assistants were healthcare providers in the different hospitals who freely volunteered to assist in the study. The researchers had a detailed and one-on-one explanation of the study with each one of them. They were educated on how to obtain written and informed consent and how to fill out the socio-demographic part of the questionnaire

Using the consecutive sampling method, eligible participants were recruited until the sample size of 112 was reached. Patients were recruited into the study from the PTB/DOTS clinics of the various study centers. The study population were adults of 18 years and above with a laboratory diagnosis of pulmonary tuberculosis and patients with HIV/PTB co-infection who had not started HAART. Subjects less than 18 years old, HIV/PTB patients who had commenced HAART, and any patients who did not give consent were excluded from the study.

The researchers and the research assistants administered the socio-demographic part of the data and obtained the patient's clinical history. The chest radiographs were interpreted under the supervision of a consultant radiologist. Chest radiographic findings and all other information were entered into the study datasheet.

Chest radiographs were taken with the patient standing erect facing the standing bucky of an x-ray machine, arms akimbo or hugging the bucky. The chin was extended and centered on the middle of the top of the cassette. The chest was placed against the cassette. The median sagittal plane was adjusted at right angles to the middle of the cassette. The X-ray beam centered between the 5th & 6th thoracic vertebra passes through the chest in a postero-anterior direction. For an average patient, the manual method used about 60-70kV, and 10-12mAs were used for PA exposure. When the digitizer was used, about 60-70kV and 12-16 mAs were used. A film focus distance of 120cm was used. All exposures were taken at full arrested inspiration.

Laboratory diagnosis of PTB was done using the National TB guidelines.[11] Tests were carried out in the laboratory facilities of the various hospitals. All suspected PTB patients had two sputum samples for Ziehl-Neelson staining and one sample for Gene Xpert analysis done. Samples were collected in sterile dry containers. The first sputum sample was collected on the spot. The second sputum sample was an early morning sputum, which was collected without brushing the mouth or drinking water. Any of these samples were used for the GeneXpert analysis.

A wooden applicator was used to transfer a portion of the smear to the slide. Blood-stained, opaque, greyish, or yellowish sputum was used if present. A thin smear of approximately 2cm x1cm area is made on the slide. The smear was allowed to dry on the slide for about 15 minutes. The slide was then fixed by passing it 3-4 times through gentle flame with the smear uppermost. The slide was stained using the Ziehl-Neelson carbolfuchsin. It was heated slowly until it steamed and maintained for 3-4 minutes by intermittent heating. The slide was then rinsed under gentle running water, decolorized for not more than 3 minutes, rinsed again with water, counter-stained for 60 seconds, and rinsed again with water. The smear was allowed to dry and examined under the microscope.[12] A positive laboratory diagnosis of PTB was made if at least a single smear came out positive.

HIV viral load was assayed using the polymerase chain reaction (PCR) principle. COBAS® AmpliPrep machine was used for the automatic separation and processing of specimens. Cobas TaqMan analyzer was used for in-vitro nucleic acid amplification and detection. This was used for viral detection and quantitative PCR.[13,14] HIV screening was done using a serial algorithm. The first line screening was done using the Determine ELISA kit®. A second-line test using Unigold ELISA kit® when positive was regarded as confirmatory. The ELISA kit® (the start pack) was used as a tiebreaker if there were conflicting results.

The data was entered and cross-checked by two independent persons. The IBM Statistical Package for Social Sciences (SPSS) Statistics version 20.0 (USA; 2015) for Windows software was used for data analysis. Frequency distribution and two-way tables were used to summarize the data. Chi-square(X^2) was used to determine the strength of the association between independent and dependent variables. Using mean and standard deviation, descriptive statistics were done for variables HIV viral load. A test of significance with a p-value of less than 0.05 was considered significant. Logistic regression was also carried out.

RESULTS

There were a total of 112 subjects with 59 females (53.7%) and 53 males (42.3.7%). **Table 1**

The highest age-specific prevalence was seen in those aged 31-40 years and 41-50 years with values of (23.6%) each. The 81-90 years age group had the least number of subjects with 4 patients (1.6%); 1 female (0.4%) and 3 males (1.2%). **Figure 1**

Among the 112 subjects with HIV/PTB co-infection, 79 (70.5%) had viral load > 10,000 copies/ml, of which 41 (36.6%) were females and 38 (33.9%) were males. Twenty-eight (25%) had plasma viral load between 20-10,000 copies/ml, out of which males and females were 14 (12.5%) respectively. Only 5 subjects (4.4%) had plasma viral load < 20 copies/ml, 4 () females and 1 () male. **Table 2**

Subjects with a viral load greater than 10,000 copies/ml showed the highest number of normal radiographs, 13 (11.6%) while none of those with a viral load less than 20 copies/ml had normal radiographs. This distribution was not significant, p-value = 0.489. Opacities were also seen more in those with viral load greater than 10,000 copies/ml, 60 (53.6%) and least in those with viral load less than 20 copies/ml, 4 subjects (3.6%). This was not statistically significant, the p-value was 0.670. There was no significant relationship between the zonal distribution of opacities and the patient viral load categories. **Table 3**

There was no significant relationship between all types of specific chest radiographic findings (bronchopneumonia, lobar pneumonia, nodularity, miliary, cystic changes, fibrosis, lymph nodes, pleural effusion, apical cap, or volume loss) and the viral load categories. **Tables 4**

There was also no significance between the lung cavities and zonal distribution of the chest radiographic findings with the viral load categories of the patients. **Table 5**

The highest number of patients was seen in patients with viral load > 1000 copies/ml, 26 (23.2%) for atypical presentation with a slightly decreased number of patients for typical presentation, 24 (21.4%). There was no significant relationship between the patient viral load category and the presence of typical or atypical post-primary PTB pattern, the p-value = 0.928. **Table 6**

In the logistic regression table, only lymphadenopathy had an Odd's ratio greater than 1, (OR = 3.115) with a p-value of 0.007. The rest of the findings; opacities, bronchopneumonia, cystic change, fibrosis, cavity, thick-walled cavity, thin-walled cavity, and volume loss had OR less than 1 (0.323, 0.550, 0.529, 0.480, 0.267, 0.275, 0.263, 0.308) and p- values of 0.001, 0.028, 0.021, 0.013, 0.001, 0.013, 0.020, < 0.001) respectively. HIV/PTB co-infection is, therefore, a strong risk factor for the development of lymphadenopathy. **Table 7**

Table 1: Showing the gender distribution of the subjects

S/N	**SEX**	**DISTRIBUTION (%)**
1.	MALE	53 (47.3%)
2.	FEMALE	59 (52.7%)
	TOTAL	112 (100%)

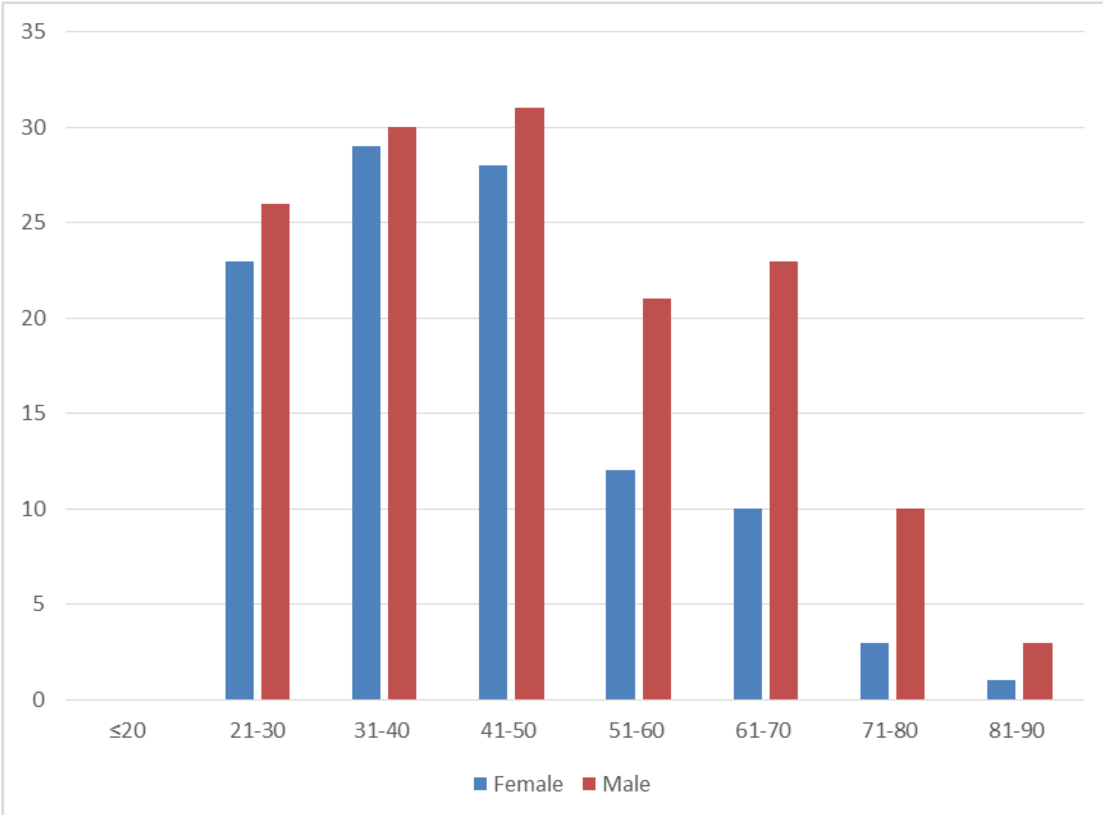

Figure 1: Bar chart showing the distribution of age ranges in males and females in the study population

Table 2: Viral load classification among male and female patients with TB/HIV co-infection (Non-normal distribution)

Viral load classification	**Gender**		**Total**
	Male (N=53)	**Female (N=59)**	
<20 copies/ml	1 (0.9)	4 (3.5)	5 (4.4)
20-10,000 copies/ml	14 (12.5)	14 (12.5)	28 (25)
>10,000 copies/ml	38 (33.9)	41 (36.6)	79 (70.5)
Total	**53 (47.3)**	**59 (52.7)**	**112 (100)**

Table 3: Chi-square analysis showing the relationship between types of pulmonary opacities and their zonal distributions and plasma viral load in patients with HIV/PTB co-infection.

CXR findings	Total Freq (%) (n=112)	Viral load classification			χ^2 value	p-value
		<20 copies/ml	20-10,000 copies/ml	>10,000 copies/ml		
Normal	19 (17.0)	0	6 (5.4)	13 (11.6)	1.432	0.489
Opacities	83 (74.1)	4 (3.6)	19 (17.0)	60 (53.6)	0.800	0.670
Alveolar/Nodular	33 (29.5)	1 (0.9)	6 (5.4)	26 (23.2)		
Interstitial	14 (12.5)	2 (1.8)	1 (0.9)	11 (9.8)	8.071	0.225
Reticulonodular	36 (32.1)	1 (0.9)	12 (10.7)	23 (20.5)		
Right lung						
Lower zone	2 (1.8)	0	2 (1.8)	0		
Mid-zone	5 (4.5)	0	2 (1.8)	3 (2.7)		
Mid + lower zone	7 (6.2)	1 (0.9)	0	6 (5.4)		
Upper zone	15 (13.4)	1 (0.9)	3 (2.7)	11 (9.8)	13.284	0.353
U + L zones	1 (0.9)	0	0	1 (0.9)		
U + M zones	16 (14.3)	1 (0.9)	5 (4.5)	10 (8.9)		
U + M + L zones	25 (22.3)	0	5 (4.5)	20 (17.9)		
Left lung						
Lower zone	3 (2.7)	1 (0.9)	0	2 (1.8)		
Mid-zone	3 (2.7)	0	1 (0.9)	2 (1.8)		
Mid + lower zone	7 (6.3)	0	2 (1.8)	5 (4.5)		
Upper zone	16 (14.3)	1 (0.9)	6 (5.4)	9 (8.0)	12.118	0.629
U + L zones	1 (0.9)	0	0	1 (0.9)		
Upper + mid-zones	7 (6.3)	0	0	7 (6.3)		
U + M + L zones	23 (20.5)	1 (0.9)	5 (4.5)	17 (15.2)		

Table 4: Chi-square analysis showing the relationship between specific chest radiographic findings and plasma viral load classification in patients with HIV/PTB co-infection.

CXR findings	Total Freq(%) (n=112)	Viral load classification			χ^2 value	p-value
		<20 copies/ml	20-10,000 copies/ml	>10,000 copies/ml		
Bronchopneumonia	66 (58.9)	2 (1.8)	14 (12.5)	50 (44.6)	2.283	0.319
Lobar pneumonia	17 (15.2)	2 (1.8)	5 (4.5)	10 (8.9)	2.938	0.176
Nodularity	55 (49.1)	1 (0.9)	12 (10.7)	42 (37.5)	2.441	0.328
Miliary	11 (9.8)	0	2 (1.8)	9 (8.0)	0.991	0.609
Cystic change	30 (26.8)	3 (2.7)	6 (5.4)	21 (18.8)	3.224	0.216
Fibrosis	23 (20.5)	3 (2.7)	5 (4.5)	15 (13.4)	4.872	0.123
Lymph Node	20 (17.9)	0	5 (4.5)	15 (13.4)	1.155	0.822
Pleural Effusion (PE)	37 (33.0)	2 (1.8)	10 (8.9)	25 (22.3)	0.269	0.818
Right PE	18 (16.1)	2 (1.8)	4 (3.6)	12 (10.7)	2.234	0.335
Left PE	22 (19.6)	0	8 (7.1)	14 (12.5)	2.821	0.262
Apical Cap	13 (11.6)	0	2 (1.8)	11 (9.8)	1.613	0.737
Volume loss	22 (19.6)	1 (0.9)	6 (5.4)	15 (13.4)	0.078	0.910

Table 5: Chi-square analysis showing the relationship of lung cavities and their zonal distribution with plasma viral load classification in patients with HIV/PTB co-infection.

CXR findings	Total Freq (%)(n=112)	Viral load classification			χ^2 value	p-value
		<20 copies/ml	20-10,000 copies/ml	>10,000 copies/ml		

Cavities	10 (8.9)	1 (0.9)	0	9 (8.0)	4.088	0.090
Thick-walled	5 (4.5)	1 (0.9)	0	4 (3.6)	4.204	0.138
Thin-walled	4 (3.6)	0	0	4 (3.6)	1.732	0.643
Right Lung						
Mid-zone	1 (0.9)	0	0	1 (0.9)	4.291	0.258
Upper zone	6 (5.4)	1 (0.9)	0	5 (4.5)		
Left Lung						
Mid-zone	1 (0.9)	0	0	1 (0.9)	1.732	0.733
Upper zone	3 (2.7)	0	0	3 (2.7)		
Number of Cavities						
One	6 (5.4)	1 (0.9)	0	5 (4.5)		
Two	2 (1.8)	0	0	2 (1.8)	0.562	1.000
Three	1 (0.9)	0	0	1 (0.9)		

Table 6: Chi-square analysis showing the relationship between post-primary PTB pattern and plasma viral load in HIV/PTB co-infected patients.

Post-primary TB pattern	**Total Frequency (%) (n=112)**	**Plasma Viral load (% Frequency)**			**χ^2value**	**p-value**
		<20 copies/ml	**20-10,000 copies/ml**	**>10,000 copies/ml**		
Atypical	37 (33.0)	2 (1.78)	9 (8.0)	26 (23.2)		
Typical	36 (32.1)	2 (1.78)	10 (8.9)	24 (21.4)	0.818	0.928

Table 7: Bivariate Logistic regression analysis showing an association between patients with HIV/PTB co-infection and the development of significant abnormal chest radiographic findings.

Findings	**(HIV/PTB co-infection)** ***(n=112)***				
	OR	**Std. Error**	***P-value***	**(95% CI)**	
				Lower	Upper
Opacities	0.323	0.114	0.001*	0.161	0.647
Bronchopneumonia	0.550	0.149	0.028*	0.323	0.936
Cystic change	0.529	0.145	0.021*	0.308	0.907
Fibrosis	0.480	0.141	0.013*	0.269	0.854
Cavities	0.267	0.102	0.001*	0.126	0.566
Thick-walled	0.275	0.142	0.013*	0.099	0.760
Thin-walled	0.263	0.150	0.020*	0.086	0.807
Lymph Node	3.115	1.321	0.007*	1.357	7.152
Volume loss	0.308	0.090	<0.001*	0.173	0.548

Note:

For Outcome variables, absent = reference recoded as 0

For predictor variables, PTB patients only = reference, recoded as 1

OR = Odds ratio, * = significant p-value

DISCUSSION

The highest age-specific prevalences were in the age groups 31-40 years and 41-50 years age brackets and they were affected equally, 59 subjects (23.6%) respectively. This is in concordance with studies by Ojiezeh et al[15] and Adetunji et al[16] with PTB being most prevalent in those aged between 25 and 40 years and 31-40 years respectively. It is contrary to that reported by Ogbo et al[17] (National study) with the highest PTB burden seen in those aged 50-69 years. In the present study, the high disease burden seen in young adults could be due to improvement in case reporting, unemployment, and migration of young adults to overcrowded urban areas, which is a known risk factor for PTB. The variance between the lower age-specific prevalence of PTB in this study compared to the higher prevalence in the aforementioned by Ogbo et al,[17] may be indicative of the rising disease prevalence in young adults over decades.

Patients' viral load (PVL) values were skewed to the right. Since a majority of patients were young adults, the PVL skewed to the right could be an indication of prompt diagnosis among the young adults with an obvious high level of infectiousness in the youths.[18] A slightly higher number of females 41 (36.6%) had PVL >10,000 than males 38 (33.9%) while both sexes had equal numbers 14 (12.5%) with PVL 20-10,000 copies/ml. More patients 79 (70.5%) had PVL > 10,000 copies/ml while only 28 (25%) and 5 (4.4%) had 20-10,000 and < 20 copies/ml respectively.

There was also a significant weak negative correlation between $CD4^+$ count values and viral load, (coefficient of correlation, $r = -0.3271$, p-value < 0.001). These findings agree with reports by Govender et al[19] (mean PVL higher in males than females unlike in the present study) and Haokip et al[20] where 187 patients (54%) and 48 patients (58.5%) had viral load > 10,000 copies/ml respectively with negative correlations between $CD4^+$ count and viral load. A negative correlation between $CD4^+$ and PVL may not always be the case since some patients with high

$CD4^+$ count may have high PVL and vice versa.[21] Ballah et al[22] also concur with the findings of a negative correlation between CD4+ count and PVL as noted in the index study.

Among those with atypical patterns, 26 patients (23.2%) had viral load > 10,000 copies/ml, 9 (8.0%) had 20-10,000 copies/ml while only 2 (1.78%) had < 20 copies/ml. The typical pattern was also more in those with viral load > 10,000 copies/ml and least in those with viral load < 20 copies/ml. This was not statistically significant with a p-value of 0.928). The findings of more typical and atypical post-primary PTB patterns at high PVL values further buttress the aforementioned weak negative correlation between $CD4^+$ and PVL.

Ballah et al[22] however reported a statistically significant relationship between radiographic pattern and PVL. In their study, patients with PVL ≥ 10,000 copies/ml had fewer nodular lesions (p-value = 0.038), lower zone involvement (p-value = 0.008) as well as more hilar and mediastinal lymphadenopathy (p-value = 0.012). This is contrary to that seen in this study with the highest nodularity seen in patients with viral load > 10,000 copies/ml (41= 37.5%), with a p-value of 0.328.

The presence of normal radiographs, all the specific radiographic findings, and their zonal distribution across the lung were predominantly more frequent in the PVL group > 10,000 copies/ml. None of these radiographic findings showed any significant relationship with the PVL category. This is due to the aforementioned non-normal or skewed distribution of plasma viral load.

The Odd ratio (OR) of the development of lung cavity and volume loss in HIV/PTB co-infection were the least compared with the rest of the other findings. The matrix metalloproteases (MMP) expression is a family of zinc-dependent proteases expressed in diseased tissues that are undergoing repair and remodeling.[23] This process leads ultimately to cavity formation, alveolar destruction, and volume loss. This is because tuberculosis-induced MMP concentrations are suppressed by HIV infection.[24] **Limitation**: There is a possibility of an occult immunodeficiency state which could have altered the exact radiographic pattern of PTB infection. In the apparently normal radiographs, very small abnormalities could have been missed in the hidden areas of the lung. The time interval before the conversion of the sputum to negative against the viral load was not done which would have been an indicator of the response to therapy.

CONCLUSION

There was no significant relationship between chest radiographic findings and patients' plasma viral load. The study showed that patients with HIV/PTB co-infection had very high chances of developing only lymphadenopathy unlike the rest of the other chest finding like cavities, volume loss, or effusion.

RECOMMENDATION: The high age-specific prevalence of pulmonary tuberculosis in the young adults in this study shows that the disease is yet to abate. This necessitates further actions on PTB prevention and control across all levels of health care, health agencies, and governments.

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