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Original Research Article

Correlations between clinical features and CD4 cell count in HIV patients with tuberculosis

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ABSTRACT

Background: The correlation between tuberculosis and HIV is evident from the higher incidents of tuberculosis estimated 5-8% per year among HIV infected person with lesser CD4cell count. The high seroprevalence with tuberculosis in occurrence among AIDS patients.
Methods: 100 HIV positive patients with tuberculosis who were admitted to medicine department and who visited to ARTS center were taken up for study for period of two years from December 2014 to 2016. Type of study is a observational comparative cross sectional study The investigation for HIV and TB were done as per NACO and WHO recommendation ELISA test CD4 cell counts AFB staining chest X-ray FNAC Mountoux test pleural fluid analysis Ascitic fluid analysis CSF fluid analysis USG of thorax CT scan of thorax.
Results: It is seen that the maximum number of patients belong to the age group 31-40 years male 40 (40%) and female 4(4%) the common occupation in the study group was driver 36 (36%) the common constitutional symptom was weight loss physical examination reveal underweight (BMI <16-18.5) 54 (54%) among the study extra-pulmonary TB 63 (63%) X-ray chest finding pleural effusion found in 21% of patients CD4 cell counts 200-500 /µl was seen maximum number of patients.
Conclusions: The CD4cell counts is important investigation in HIV and TB patients it is main investigation to know prognosis of HIV also important for initiation of ARV drugs.it is evident from this study the decrease the CD4cell counts there is increase the incidence of tuberculosis.

Keywords: ARV drugs, CD4cell counts, ELISA test, FNAC, HIV, Mountoux test, TB

INTRODUCTION

The association between tuberculosis and HIV patients is an immediate public health and socioeconomic problem, particularly in the developing world. in early 1992 WHO estimated that approximately 4 million people had been infected with both Mycobacterium tuberculosis and HIV since the beginning of the pandemic, 95% were in developing countries.[1] The association between tuberculosis and HIV is evident from the high incidence of tuberculosis estimated at 5-8% per year among HIV infected persons, the high HIV seroprevalence among patients with tuberculosis, the occurrence of tuberculosis among AIDS patients and the coincidence of increased tuberculosis notifications with the spreading of the HIV epidemic in several African countries.[1]

The WHO Global Tuberculosis Report 2014, shows that 9 million people developed TB in 2013 and l.5 million died including 3,60000 people who were HIV positive.[2] One fifth of the global TB incidence in India with 1.9 million new cases occurring every year and 2.76 lakhs

deaths occur from TB every year, In India it is estimated that 2.31 million individuals are living with HIV infection and 4.9% of new adult TB patients in India are HIV positive.[3] Tuberculosis is the most common opportunistic infection amongst HIV-infected individuals in India.[3] it is a major cause of mortality among patients with HIV and poses a risk throughout the course of HIV even after successful initiation of ART.[4] Patients with HIV infection are more likely to have active TB by many factor when compared with HIV negative population.[5] The risk of developing TB for HIV infected patients in India is estimated to be 7 cases per 100 person per years at risk, compared with a 10% lifetime risk of an immuno competent host.[3] This sets the stage for a deadly synergy between the two infections. HIV targets the CD4 cells by binding to the surface of CD4 cells, entering CD4 cells and becoming a part of them. As CD4 cells multiply to fight infection, they also make more copies of HIV continuing to replicate and leading to gradual decline of CD4 cells. HIV can destroy entire families of CD4 cells.[6]

Pulmonary involvement occurs in about 75% of all HIV infected patients with TB.[7] Unlike other opportunistic infections which have a selective range of CD4 cell in which the disease occurs, TB occurs throughout the course of HIV. The interaction between HIV and TB in persons coinfected with HIV and TB is bidirectional and synergistic. Clinical presentation depends on the level of immuno suppression. Typical manifestations such as upper lobe disease, sputum positivity and cavitation are frequently seen in early HIV when the CD4 + TB cell count >200cells/cumm.[7] Atypical features begin to occur as the immunity declines and the CD4 cell count <200cells/cum with more extrapulmonary manifestations ranging from 46 to 79%.[7] An HIV positive individual with any of the symptoms such as cough of more than 2 weeks duration, fever lasting for more than 2-3 weeks, weight loss, fatigue, unexplained dyspnea, chest pain or haemoptysis should be suspected of having TB and investigated further Extra-pulmonary TB is the commonest cause of pyrexia of unknown origin (PUO) among HIV positive individuals in developing countries.[7] The most frequent extra-pulmonary form of TB is involvement of the lymphnodes with cervical regionbeing the commonest.[7] Lymphnode involvement in HIV is diagnosed by FNAC (done as anoutpatient procedure) or by lymphnode biopsy. The other forms of extrapulmonary TB include pleural effusion, pericardial effusion, abdominal TB, TB meningitis.[7] Intra-cranial space occupying lesions are common in HIV infected individuals, In India the commonest form is cryptococcal meningitis followed by TB meningitis.[7] Mycobacteria is an important cause of PUO particularly among patients with severe immuno suppression but is difficult to diagnose.

The aim of the present study was to determine the correlation between clinical manifestations and CD4 cell count level in HIV patients with Tuberculosis and to observe the impact of CD4 count on the severity of manifestations of TB in HIV Patients.

METHODS

100 HIV positive patients with tuberculosis (both pulmonary and extra pulmonary TB) who were admitted to medicine department and who visited the OPD and art centre were taken up for study period of study for two year from December 2014 to November 2016 type of study is an observational comparative cross-sectional study investigation done for HIV. HIV serological status was assessed using three recombinant enzyme link immunoassay (ELISA) method as per NACO guideline Testing positive by all three methods was considered as diagnostic of HIV infection CD4 cell countin HIV positive patients were assessed by CYS FLOW based on flowcytometry technique diagnose of PTB clinical history and examination sputum smear examination for AFB by Ziehl Neelson fluorescent staining method as per RNTCP and chest x ray PA view. diagnosis of extra pulmonary by FNAC or Exicinal biopsy Pleural fluid analysis for AFB cytology Pleural fluid analysis for ADA glucose protein histopathological study culture of specimen for M. tuberculosis Ascitic fluid analysis for ADA cytology CSF analysis lumber puncture CT scan of brain and abdomen other relevant investigation (1) Routine baseline investigation like complete haemogram (2) sputum culture for AFB (3) chest x-ray lateral view (4)USG of thorax abdomen (5) CT scan of thorax (6) Tuberculin test (Mountoux test).

RESULTS

The age and sex distribution among the patients belonged to the age group 31-40 years male 40 (40%) and female 4 (4%) followed by 21-30 years male 16 (16%) and female 6 (6%) maximum number of males belonged to the age 31-41years whereas maximum number of female belonged to age group 21-30 years 40% and 6% respectively the age of study subject ranged from 15-65 years (Figure1).

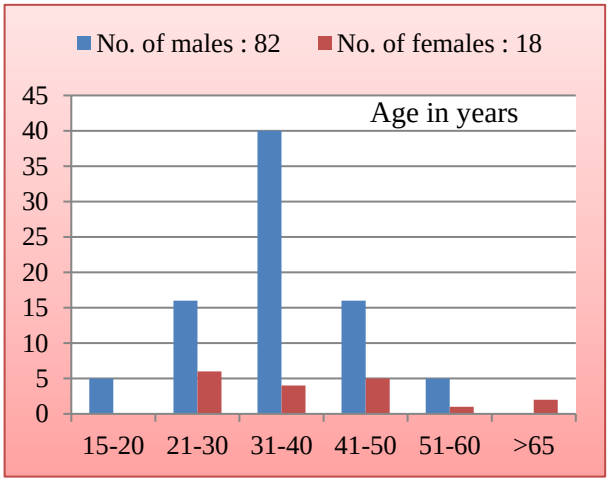

Figure 1: Age and sex distribution.

The common occupations were driver 36(36%) followed by house wives 16(16%), farmer 11(11%), laborer 10(10%), businessmen 8(8%), hotel worker 4(4%), shopkeeper 3(3%), private company worker 3(3%), students 3(3%), weaver 2(2%), mechanics 1(1%) and printing press worker 1(1%) and factory worker 2(2%).

Table 1 shows that commonest constitution symptom was weight loss 69% followed by fever 67% and anorexia 57%, respiratory symptom cough 50% followed by chest pain 29% expectoration 14% closely followed by breathlessness 12% and hemoptysis 2%, gastrointestinal symptom like nausea /vomiting diarrhea constipation jaundice and abdominal distension were with equal frequency at 7% each and neurological symptom like headache and tingling/numbness were 3% each (Figure 2).

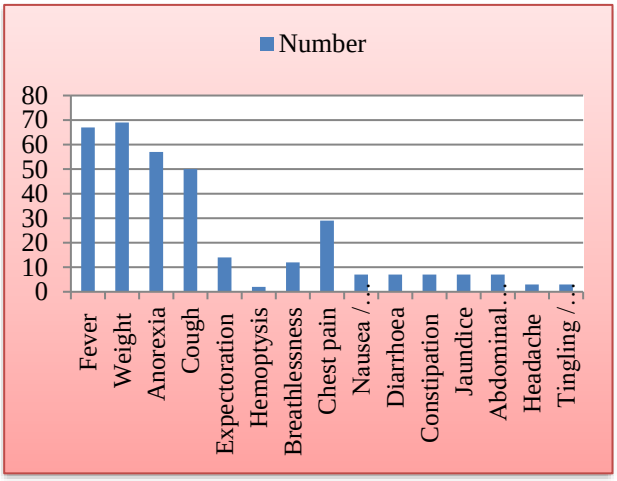

Figure 2: Symptoms of patients.

Table 1: Physical sign.

Sign	Number of patients	percent
Body weight as per BMI	7	7
Very severely underweight (BMI:<15)	12	12
Severely underweight (BMI:<15:16)	23	23
Underweight (BMI:<16-18.5)	54	54
Normal (BMI: 18.5-25	2	2
Overweight (BMI: 25-30)	2	2
Moderately obese (BMI:<30:35)	0	0
Severe obese (BMI:<35:40)	0	0
very severe obese (BMI:> 40)	51	51
Pallor	4	4
Icterus	29	29
Lymphadenopathy	3	3
Respiratory rate >20/MIN	13	13
Oral candidiasis	19	19

Physical examination reveal BMI <18.5 kg/mm2 in 42% pallor 51% lymphadenopathy 29% oral candidiasis 19% tachypnea13% ictrus 4% pedal oedema 3% of patients (Table 1).

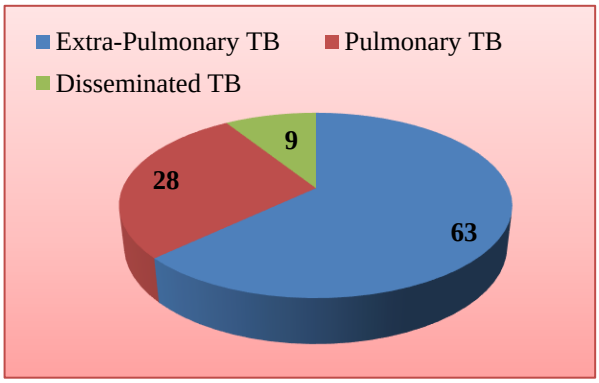

Figure 3: Distribution of types of tuberculosis.

Among 100 patients 33% had tuberculin negativity i.e. induration <5mm and tuberculin positivity i.e. in duration >5mm.

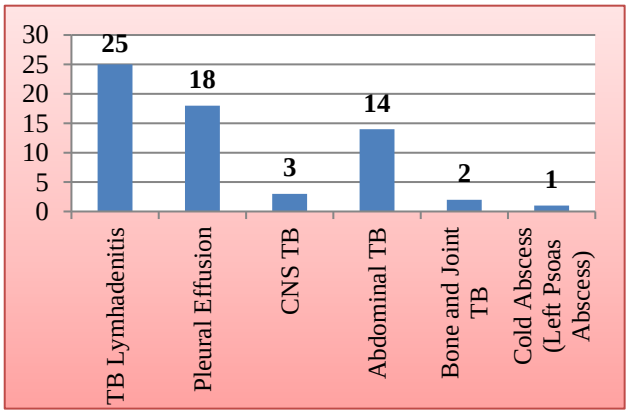

Figure 4: Distribution of extra - pulmonary tuberculosis.

Table 2: Correlation of CD4 count and type of tuberculosis.

CD4	PTB		Disseminated (%)	EPTB (%)	Total
	+ve PTB (%)	+ve PTB (%)			
>200	2 (18.2)	4 (23.5)	3 (33.3)	28 (44.4)	37
200-500	5 (45.5)	7 (41.2)	6 (66.7)	32 (50.8)	50
>500	4 (36.4)	6 (35.3)	0	3 (4.8)	13
Total	11	17	9	63	100

The mean CD4 count was 289±177.49 mean CD4 count in male was 280.90±174.35 and mean CD4 count in female was 331.22±190.84 (Table 2).

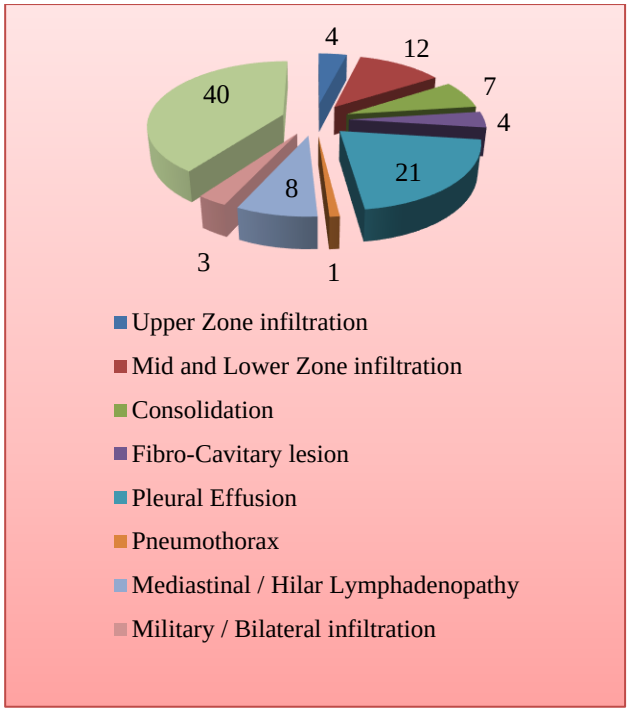

Figure 5: Chest X-ray findings.

Among 100 patients upper zone infiltration were seen in 4% mid and lower zone infiltration in 12% consolidation in 7% fibro cavitory lesion in 4% bilateral infiltration and milliary lesion in 3% among the extra pulmonary lesion pleural effusion in 21% pneumothorax in 1% mediastinal and hilar lymphadenopathy in8% chest x-ray normal in 40% (Figure 5).

CD4 count 200-500 cells was seen in 53% patients followed by 100-200 cells 22%.14% patients were in >500 cell count 8% patients in 50-100 cell count and 3% patients were found in <50 cell count (Figure 6).

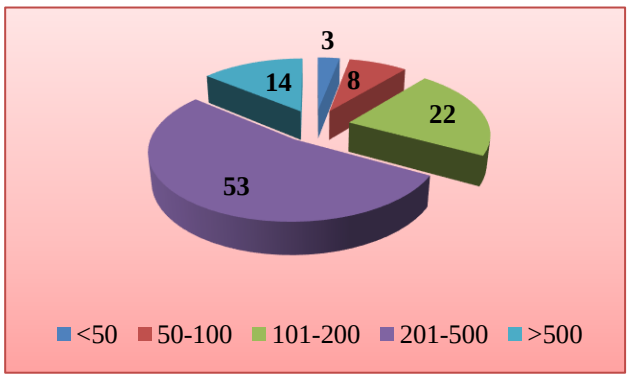

Figure 6: Correlation of CD4 Count and Number of patients.

18.2% of sputum +ve PTB, 23.5% of sputum negative PTB, 44.4% of EPTB and 33.3% of disseminated TB had CD4 count <200, 45.5% of sputum +ve PTB, 41.2% sputum -ve PTB, 50.8% of EPTB and 66.7% of Disseminated TB had CD4 count between 200-500, 81.9% of sputum negative PTB had CD4 count >200 which is highly significant (Table 3).

Table 3: Correlation distribution of different types of tuberculosis in relation to CD4 count.

	No.	Mean CD4 count	Standard deviation
Septum positive PTB	11	444.09	144.57
Sputum negative PTB	17	399.44	234.07
EPTB	63	245.36	149.41
disseminated	09	240.00	79.24
total	100	289.96	177.49

P>0.001 (HS)

Mean CD4 count in patient with sputum +ve PTB was 444.09±144.57 and in sputum -ve PTB was 399.44±234.07. Mean CD4 count in EPTB was 245.36±149.41 and Disseminated TB was 240.0±79.24. it was seen that the mean CD4 count was significantly high in sputum +ve PTB followed by sputum -ve PTB, then by EPTB and was significantly low in disseminated TB. This was found to be statically significant with P<0.001.

Pleural effusion was the most common x ray finding with 31.8% at CD4 count <200 cells 68.2% at CD4 count >200. Infiltration were the next most common x-ray finding with 25% at CD4<200 31.35%at CD4 cell count between 200-500 43.75% at CD4 cell count >500 followed by consolidation at 57.1% at CD4 between 200-500 and 42.9% at CD4 <200 the milliary lesion were seen at CD4 level between 200-500 maximum number of hilar/mediastinal lymphadenopathy cases at CD4 count of <200 out of 4 fibro cavitary lesion 3 were seen at CD4 count >500 one with CD4 count 200-5002 cases of exudate one CD4 count <200 one CD4 count between 200-500.

60% of the patients with upper zone lesion had sputum +ve PTB and 40% had sputum -ve PTB 78.8% of the mid/lower zone lesion had sputum -ve PTB and 21.1% had sputum +ve lesion 84.6% of the multiple zone lesion 84.6% of the multiple zone lesion had sputum -ve PTB15.4%had sputum +ve PTB (Table 4).

Table 4: Correlation of CD4 count and zonal distribution of lesions in chest X-ray.

CD4 count				
	Upper zone	Mid / lower zones	Multiple zones	Total
<100	0	3 (10%)	3(18.8%)	6
101-200	1(16.7%)	6 (20%)	3(18.8%)	10
>200	5(83.3%)	21(70%)	10(62.5%)	36
Total	6	30	16	52

The lesion in patients with CD4 count >200 is the highest in upper zone (83.3%) followed by mid/lower zone (70%) and multiple zone (62.5%). the percentage of lesions in patients with CD4 count <200 is highest in multiple zones (37.6), followed by mid/lower zones (30%) and least in the upper zones with just 16.7%. No of lesions in the upper zone in patients with CD4 count <100. This is found to be statically significant with p-value <0.001 (HS).

A single hemithorax was most commonly affected in cases with CD4 count >200 (61.5%), while in cases with CD4 count less than 200 single hemithorax involvement was seen in 58.8% and bilateral involvement was seen in 29.45% of cases with CD4 count <200 and 28.2% of cases with CD4 count >200. Hilar lymphadenopathy was the only radiological finding in 11.8% of the cases with CD4 count <200 and in 10.3% of cases with CD4 count >200.

Correlation of CD4 count with sputum positivity that of the sputum positive cases i.e. 9 out of 12 cases have a CD4 count above 200 and only 3 sputum positive cases gave CD4 count below 200.

DISCUSSION

In this study 100 HIV seropositive patients with tuberculosis were studied. out of 100 patients 82% were males and 18% were females. This is comparable to the study in which 68.9%were males and 31% were females.[8] NACO also report 61% males and39% females.[9] This is similar to the study.[10]

Most of the patients in the study group were in the age group 21 - 50 years (87%) the mean age of males being 35.83 years and of females being 38.56 years. This is comparable to the study in which 84.6% of patients belonged to the age group 21 - 40 years and study shows about 83 % patients in the age group 15-49 years.[9,10] This reflects the sexually active age group which is commonly affected by the disease.

Most common occupation was drivers (36%), followed by housewives (16%), farmers (11%), labourers (10%), businessmen (8%), hotel workers (4%) students(3%), shopkeepers (3%), private company workers (3%), factory workers (2%), weavers (2%), mechanics (1%) and printing press workers (1%) which indicates the coinfection affected people across varied occupational groups This is similar to the studies Piramanayagam et al and Mohanty et al in which the most common occupation observed was truck drivers report states that long distance truck drivers and single migrant labourers constitute a significant proportion of HIV patients, Zuber et al study reported 36.8% patients working as manual labourers were found a similar occupation profile.[11-14] In this study l6 out of 18 females were house wives, 2 were daily labourers and 1 out of them was unmarried. In all of the married women, both the husband and wife were affected except in one who had a history of blood transfusion during previous pregnancy. This finding is consistent with the study Deivanayagam et al study.[15] The Most common constitutional symptom in the study group was weight loss (69%), followed by fever (67%) and anorexia (57%).

This is comparable with the study done by National AIDS Control organization Report (2012) wherein, anorexia 100%, weight loss 100%.[8] Fever was comparable with studies Jaryal et al and Kumar et al. [16,17] Most common respiratory symptom in this study was cough but the percentage (50%) was much less in comparison to studies (85.4%) in Jaryal et al, (97%) in Deivanayagam et al and (100%) of NACO report.[8,15,16] The other respiratory symptoms of chest pain (29%), expectoration (14%), breathlessness (12%) hemoptysis (2%) were less in comparison to other studies. This could be due to the less number of HIV sero positive patients with pulmonary tuberculosis and more number of extra - pulmonary tuberculosis in this study. Hemoptysis (2%) was less in this study as compared to that (48.3%) in NACO report, (18%) Deivanayagam et al and (11.5%) in Jaryal et al. [8,15,16] This could be due to the paucity of fibro cavitary lesions among the already lesser number of pulmonary tuberculosis.

Pallor (51%) was the most common sign reported in this study 42% of the cases in this study patients were underweight as evidenced by BMI <18.5 kg/m^2 which is comparable with that of (47%) Deivanayagam et al study.[15] Respiratory distress was seen in13 % cases which is less in comparison with that of (42.94%) Jaryal et al study due to lesser number of pulmonary tuberculosis cases in this study Lymphadenopathy was seen in 29% cases which is comparable and the same with that of (29%).[15,16] This is due to the fact that extra -pulmonary tuberculosis was in higher proportion in this study and amongst them TB Lymphadenitis was the commonest.

Extra - pulmonary tuberculosis was the most common type of tuberculosis 63%. 28% of the cases in the study pulmonary tuberculosis and disseminated tuberculosis was in 9 % of the cases. This is comparable to study in whose extra-pulmonary tuberculosis was 54.6%, pulmonary tuberculosis was 28% and disseminated tuberculosis 17.4%.[17] Other studies had a significantly higher proportion of pulmonary tuberculosis other studies across the globe also reported higher proportion of extra - pulmonary tuberculosis (53 - 63%) of total TB patients in HIV infected and was more common in severely immuno-compromised.[16,1819]

Sputum positivity (12%) in the study was comparable with studies of Jaryal et al (15%) and study of Jones et al (21.4%).[16,18] But it was lower in comparison to studies Deivanayagam et al (72%) and Swaminathan et al (49.33%).[14,15] ln these two-studies sputum culture was also done The low sputum positivity in the study could be

attributable to lesser number of pulmonary tuberculosis cases and the paucity of cavitary lesions.

Among X-ray findings, pleural effusions were most common (21%) followed by infiltrative lesions (16%), mediastinal /hilar lymph adenpathy was seen in 8% of the cases.

As regards infiltrations, upper zone infiltrations were seen in 4% of the patients, mid and lower zone infiltrations were seen in 12% of the cases and miliary/extensive infiltrations in 3%. Similar pattern and frequency of distribution zone - wise was reported.[16]

Fibro-cavitary lesions were seen in 4% of cases, consolidation in 7% in 40% of the patients the chest X - ray was normal. As is obvious the radiological manifestations in the study are mixed and varied This is due to the fact that majority of the patients had extra - pulmonary tuberculosis and the X-ray findings of Tuberculosis will depend on the level of immune suppression.

Among the isolated extra-pulmonary tuberculosis, TB lymphadenitis was seen in 40%of the cases, followed by pleural effusion in 29%, abdominal tuberculosis in 22%, CNS TB in 5%, bone and joint TB in 3% and cold abscess left psoas abscess in 1%. Lymphadenopathy and pleural effusion are the most common forms of extra-pulmonary tuberculosis seen in the study. These findings are in sync with other studies like Jaryal et al and Swaminathan et al.[16,18]

ln the study tuberculin positivity (>5mm induration) was in 67% of the patients out of which 25 % had induration in the range of 5-9 mm 20 patients in the range of 10 - 15 mm and 22 patients had in duration >15mm. Tuberculin negativity was seen in 32% of the patients. This finding is not in consortium and is in sharp contrast to study done by Sharma et al where there was tuberculin negativity in 85.7% patients.[19] This could be attributed to the lesser degree of immune suppression in this study and the mean CD4 count being higher than in other studies.

The mean CD4 count in this study was 289.96±177.49 The mean CD4 count among males was 280.9±174.35 and the mean CD4 count among females was 331-.22 ±190.84. The degree of immunosuppression was less in females than in males. This could be attributed to the lesser number of female patients in this study.

ln this study CD4 count >200 cells/µl was seen in 67% of the patients and CD4 count< 200 cells/µl was seen in 33% of patients. Study reported CD4 < 200cells/µl in 82.6%(20). Higher CD4 count in this study could be attributed to a high index of suspicion prompt diagnosis and early initiation of therapy. The mean CD4 count in patients with sputum +ve PTB is 444.09 ±144.57, and in sputum -ve PTB it was found 399.44 ±234.07. In EPTB the mean CD4 count was 245.36±149.41 and in disseminated TB it was found 240±79.24. This difference is found statistically significant with a p value <0.001 and it reflects the higher incidence of disseminated TB and EPTB in patients with lower CD4 counts.

Correlation between zonal distribution and CD4 count revealed that in patients with CD4 count <200, the upper zone affection was nil. Multiple zone affection was highest at 18.8% followed by mid zone affection at 10% which was found to be statistically significant. The reverse was seen in patients with CD4 count >200, where the percentage of upper zone affection was highest at 83.3%, followed by mid zone affection at 70% and multiple zone affection at 62.5%. It is seen in this study that the typical manifestations of upper zone affection occurs at lesser levels of immune suppression at higher CD4 counts and as the level of immune-suppression increases and the CD4 count decreases the frequency of mid/lower zones and multiple zones affection increases These findings can be corroborated with study upper zone infiltrates typical of PTB reactivation was found and lower and middle zone infiltrates occurred overa wide intermediate range with lower mean CD4 counts.[20]

Correlation between sputum positivity and CD4 count revealed that the percentage of sputum positivity with typical upper zone affection increased in the same direction as CD4 count with 18.2% at CD4 count < 200 increasing to 45.5% CD4 between 200 - 500 and 36.4% CD4 count >500 cells/µl out of the sputum positive PTB cases, the percentage of upper zone affection was the highest at 60% mid/lower zone affection 21% and multiple zone affection 15.4% Correlation between CD4 count and hemithoraces affection revealed. The mid thorax affection was higher at 61.5% in patients with CD4 count >200 than in patients with CD4 count <200 58.8%. The predilection for bilateral affection was almost comparable in patients with CD4 <200 (29.45%) and in those with CD4> 200 (28.2%). However, the percentage of isolated hilar lymphadenopathy was higher at 11.8% in patients with CD4 <200 as compared in patients with CD4 >200 at 10.3%. It is thus seen that the radiological manifestations of PTB depend largely on the degree of immuno suppression. At higher levels of CD4 counts when the immune system is relatively intact, reactivation of disease process manifests in the forms of typical presentations of upper zone affection.

Tuberculosis is the most important opportunistic infection in HIV infected patients as well as the leading cause of death conversely HIV is the most important risk factor that promotes progression to active TB in people with Mycobacterium tuberculosis infection without treatment HIV and TB can work synergistically to shorten lifespan. This study strives to identify and determine the latest trends in HIV TB coinfection with its correlation to CD+ count level which may prove to be crucialin limiting the infection and ensuring longevity and better quality of life amongst the infected sero positive. The maximum number of patients were in the productive age between 20

-50 years, the mean age and CD4 count in females is higher than that of males in this study. This could be attributed to the lesser number of females in the study.

As regards to occupation, although the maximum number of patients were drivers, there were also quite a number of businessmen, company and factory workers amongst the study population which highlights the fact that the infection is prevalent in all sections of the society, no occupation or class being absolutely immune. Considering symptoms, in this study, fever was found to be more prevalent than cough, which depicts a salient point that Mycobacteria is an important cause of PUO particularly among patients with severe immuno suppression and lower CD+ counts, hence a patient presenting with isolated fever not responding to empirical treatment should raise a high level of suspicion and alert the physician towards subjecting the patient for both HIV and tuberculosis screening. Similarly, pallor being the most commonly found sign, unlike others studies.

True to its title, this study has also determined a significant correlation of CD4 cell count with the clinical profile of tuberculosis. Unlike other studies a large majority of patients in this study had extrapulmonary tuberculosis whose mean CD4 cell count was lesser than that of PTB. However, a relatively higher mean CD4 cell count in this study in comparison to previous studies states a salient fact that manifestations of tuberculosis can occur at any level of CD4 cell count and not just at counts <200, for which a high degree of clinical precision is a prerequisite for diagnosis.

CONCLUSION

Thus, overall the significant correlation of CD4 count with clinical and radiological manifestations unveiled in this study resurrects and re-establishes CD4 count assay as an useful diagnostic tool, prognostic indicator and a guide to assessment of response to therapy of enormous and unequivocal importance. The TB and HIV act synergistically to short enthe lifespan of patients higher incidence of EPTB in patients with less CD4 cell counts and were more immuno compromise state.

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