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Using C-reactive protein levels as a screening test in early detection of pulmonary tuberculosis in HIV infected individuals and its correlation with CBNAAT

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ABSTRACT

The progression of tuberculosis (TB) is faster in people living with HIV (PLHIV), hence a quicker and efficient method of diagnosis is required. Detection of rise in acute phase protein like CRP is one such method. Studies show that CRP levels can be used as a screening tool for diagnosis of both pulmonary tuberculosis (PTB) and extra pulmonary tuberculosis (ETB). This study aims to determine the efficacy of using blood CRP levels as a screening test alongside CD4 count for early detection of PTB in HIV infected individuals. Relevant clinical history and symptoms of fever, cough, weight loss and night sweats were collected along with Sputum and blood samples all the 104 patients (who were known PLHIV). Sputum samples were processed through CBNAAT and the other for smear and culture. Blood samples were tested for CRP levels and CD4 counts. The baseline CRP found in our study was < 6mg/L. The CRP levels of PTB patients on ART was about 40.2636 mg/L which was significantly higher than PTB patients not on ART (28.5mg/L). CRP showed a negative correlation with CD-4 COUNT (highly significant $p<0.01$) with levels of CRP being about 62 mg/L when CD-4 COUNT was 200. Higher number of TB positives were found with combination of 4 symptoms (WHO screen). Hence CRP should be combined with symptom screen.

Keywords: C-reactive protein, pulmonary tuberculosis, extra pulmonary tuberculosis, PLHIV, CBNAAT.

INTRODUCTION

Tuberculosis in India accounts for about 25% of the global annual incidents. Faster progressing tuberculosis often presents in people living with HIV (PLHIV) as an opportunistic infection, with greater prevalence in resource limited settings (1). Hence a faster and efficient method of diagnosis is of need in such individuals. C-reactive protein is an acute phase protein with levels in the blood found to be high in infections and non infective inflammatory diseases with the levels, significantly high in respiratory tract infections in adults and fever in children (2). It is produced as a result of increase in IL-6 levels in blood, due to inflammation, which results in increase in CRP levels. The normal levels of CRP is < 6 mg/L (the normal range detected varies from lab to lab; the lab diagnostic kit used is qualitative and semi-quantitative rapid latex slide test) The levels are seen in blood as fast as 5- 10 hours after the initiation of inflammation. Thus, it is a very sensitive indicator and we could thus benefit from its use as a screening test.

With this knowledge, it has been proposed as an early diagnostic algorithm of PTB in suspects of possible infection for clinical and radiological referral. There are several tests available and are presently being used for diagnosis of PTB. The time taken for the culture of *Mycobacterium tuberculosis* is also not ideal for diagnosis especially in PLHIV since active tuberculosis infection may boost HIV replication (3). Thus, the sensitivity and specificity of the tests are further decreased in co-infection. Though screening for CRP levels may not be an ideal diagnostic test in terms of specificity, it is an easy, non-invasive, and

patient compliant method of sample collection. It is a simple bed side test for early detection and the results are obtained within a day of collection. Also, according to certain reports, CRP levels are more characteristically higher in bacterial infections (>100 mg/L) than viral infections (< 10 mg/L) (4). Therefore, the presence of a virus (HIV), has little influence on the levels of CRP in TB and HIV co-infection. Although the number of extra pulmonary cases in PLHIV are elevating, PTB cases in PLHIV still maintains a majority in the current scenario. Another parameter that is altered is CD 4 counts. CD-4 cells are a group of T-lymphocytes called T-helper cells whose levels are found to drop in HIV infections as a result of intracellular inhabitation and consequently lysis of these cells. This drop in count can be compounded by the presence of opportunistic infections, one such as Tuberculosis.

A recent report shows that 25% of HIV negative patients with TB in the sample of participants, had low CD4 cell count (below 500cells/mm3) (5). Consequently, TB has an impact on CD4 cell levels. CRP and CD 4 counts may thus pose as easier and efficient diagnostic tools to detect PTB in PLHIV. Comparison of the diagnostic value of using CRP levels obtained through immunoassay of blood sample, CD 4 counts obtained through flow cytometry with CBNAAT or Gene Xpert- MTB/RIF (6) (highly sensitive and specific PCR based diagnostic test) having sputum as the source, is the focus of this research paper. The objectives of this study being are to determine the efficacy of using blood CRP levels as a screening test alongside CD4count for early detection of PTB in HIV infected individuals and to demonstrate a significant relationship between CRP levels and CD4 counts in TB and HIV co-infected individuals.

MATERIALS AND METHODS:

Study design: This is a cross sectional study.
Study period: six months
Place of study: Bangalore Medical College and Research Institute, ethical clearance was obtained.
Sample size: 104 samples were taken for the study

Inclusion criteria: All patients between the age groups of 18 and 50 having tested seropositive for HIV and who present with the following symptoms: Cough for more than a week, Fever, Night sweats, Weight loss.

Exclusion criteria: The exclusion criteria are: Patients below 18 years of age, Patients who are on Anti-tubercular therapy(ATT), Patients who have been diagnosed with AIDS.

Sampling and processing: The sample collection was done on the basis of their symptoms. The criteria for sample collection was the 4 symptom screen (cough for a period of a week or more, fever, night sweats, weight loss) as proposed by WHO. The sample collected is of sputum (approx. 1-2 ml) (3), and blood (approx. 3 ml) (7).

Two samples were taken. One early morning sample and the on spot sample was collected in a wide mouthed sterilized glass/plastic container with a screw cap. The sputum samples were processed through CBNAAT, smear and culture.

A venous blood sample for CRP levels and CD 4 counts was obtained from inside the elbow or from the back of the hand using a sterile syringe. The CRP levels were assayed and reported along with an immune status assessment of CD 4 count obtained through flow cytometry. The sensitivity and specificity of using CRP and CD 4 counts is compared with the results obtained through CBNAAT.

RESULTS: Out of a sample size of 104 patients, 60.19% were males. Median age being 38[33-45]. 78 were found to be study relevant cases having presented with clinical symptoms, and were known PLHIV. Of 78 known PLHIV 32 were TB positives. Out of the 32 TB positives, 23 were diagnosed with PTB, and 9 with EPTB. The CRP level of the 32 TB positive HIV patients came up to a mean of 26.0034 mg/L (PTB MEAN CRP = 34.3818 mg/L; EPTB MEAN CRP = 17.625mg/L. Since each of these groups were found to have patients on ART and not on ART, these patients were further broken down into two groups on ART, not on ART. The PTB (on ART) had a mean CRP of 40.2636 mg/L, PTB (not on ART), 28.5mg/L. The EPTB (on ART) had a CRP of 12mg/L and EPTB (not on ART), 23.25mg/L. The CRP levels of the symptomatic but TB negative PLHIV patients was about 12.08- 14 mg /L. The CRP levels of symptomatic TB negative non PLHIV patients was 26 mg/dl with the TB positive patients being 24 mg/dl; which suggests that the symptomatic,

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TB negative group might have another underlying inflammatory condition that could have pushed up the levels higher. Though mentioned, these values do not confer much significance to the report but only for comparison. The mean CRP of the PLHIV, symptomatic, TB positive population has been shown in **TABLE 1**.

Box and whisker plot **[FIGURE 1]** shows two plots with the following values: GROUP 1 shows minimum CRP value to be 6mg/L in TB positive patients having a MEDIAN CRP value of 24. The upper limit (maximum) is 96 mg/L. GROUP 2 shows a mean CRP value of 4.5mg/L (3-6mg/dl taking the baseline CRP value to be 3mg/L; the minimum value is < 6mg/L) and the maximum value of 96mg/L. The MEDIAN CRP value is about 6mg/L. This tells us two things:

1. 1) The upper limit of the two groups are the same (96mg/L) which only means that a few TB NEGATIVE patients have another underlying inflammatory pathology which is the reason for high CRP values.

2. 2) The MEDIAN CRP values of the two groups, GROUP 1 and GROUP 2, are 24mg/L and 6mg/L respectively. This tells us that the TB positive patients generally have a higher CRP value than the TB negative group. This indicates the high prevalence of TB in PLHIV.

The CRP values of the TB positive patients are not exceptionally high as mentioned in a few articles. This could be as a result of fewer cases with correct presumptive clinical presentation or indiscriminate self -administration of antibiotics (over the counter). The correlation between CRP values and TB positive results was $r = 0.352$, with a significance of $p < 0.01$.

Relation between CD-4 counts AND CRP: We know that CRP and CD-4 COUNT (Median CD-4 COUNT-206 [IQR: 99 – 389]) have an inverse relationship. It showed a correlation of r= -0.27341 which is highly significant (p<0.01). This can be very depicted in the scattered graph FIGURE 2. This line shows that as the CD- 4 COUNT increases, the CRP levels drop.

The AIDS complex is defined as the stage of HIV infection reaches the final, critical stage which in terms of the CD-4 count translates to a drop in count to < 200 cells/ microliter. The equation of the linear grid line is **y = - 2.617x + 361.5.**

Thus substituting the value of CD-4 COUNT as 200,

200 = -2.617x + 361.5

-161.5 = -2.617x

x =61.712 mg/L

Hence, the CRP level at a CD-4 COUNT of 200 is 61.712 mg/L.

The TB positive patients are grouped onto categories based on their CD-4 COUNTS [**TABLE 2**]. Most of the TB positive patients have CD-4 COUNTS less than a 200 cells/microliter i.e. 59.38% of TB positive patients have counts less than <200 cells/ microliter. If taken below 350 cells/ microliter, the number of TB positive patients reach 84.38%. Guidelines for initiating ART states that ART should be started on patients having counts less than 350. We see that in patients having TB-HIV co-infection, the cells drop further in count resulting in greater number of patients < 100 cells/microliter.

Symptoms and CRP

The efficacy of using CRP is in question since it is not specific. This needs to be combined with another parameter other than the CD-4 COUNT i.e. the symptom screen performed on patients.

1) We found that on using both Asymptomatic and Symptomatic groups of patients, the ROC (Receiver Operating Curve) showed a diagonal relationship. This means that the sensitivity value is approximately equal to the 1- specificity value. That means to say that the number of true positives is the same as the number of false positives [**FIGURE 3**].

2) On plotting the same graph using patients having one symptom or more, we found that the graph line while slightly deviated upwards, still showed a significant diagonal relationship between the two parameters. This might be due to the usage of even one symptom (even one as general as weight loss or fatigue) due to which the sensitivity as shown maintains a diagonal with 1-specificity [**FIGURE 4**].

3) On further narrowing the symptomatic group to patients having more than one symptom (a combination of symptoms) the ROC curve was above the diagonal. Thus, the sensitivity of the test showed promise when a combination of symptoms was taken

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[**FIGURE 5**].

DISCUSSION: The baseline CRP found in our study was < 6 mg/L. This was from a sample of patients with no symptoms and who were PLHIV, not on ART. The Baseline CRP value in the general population as stated by Mahadad Noursadeghi et al. (8) was < 3mg/L. The levels as reported in HIV infected individuals was <6mg/L (about 5.9 mg/L) This shows that HIV infection is not a very high inflammatory disease.

A study by Sten Skogmar et al. (5) showed that the levels of CRP in patients with HIV (pre-ART) and TB was about 36 mg/L. In our study we found HIV positive, TB positive patients had a CRP of 25.88 mg/L which comprised of 12 PTB and 9 EPTB patients. The CRP levels of PTB patients not on ART was 28.5 mg/L and EPTB was 23.25 mg/L. The levels of CRP were higher in PTB patients by a difference of 5.25 mg/L which though not significant goes along with the results in the study by Nathella Pavan Kumar et al. (9). They found that the patients had a CRP of 30.11 ng/ml (PTB), and 26.71 ng/ml(EPTB). The CRP levels of PTB patients on ART was about 40.2636 mg/L which was significantly higher than PTB patients not on ART (28.5mg/L). We know that CRP is an inflammatory biomarker which, when its levels increase in blood is a sign of inflammation (in this case by infection, more so by bacterial than viral). This biomarker as we know is produced by inflammatory cells. With PLHIV (not on ART) having very low immune cell count, the production of this biomarker is bound to be less almost mimicking the the state of normal individual. This could be the reason the levels of baseline CRP fall within the normal range of levels in HIV infected individuals. Thus we can look at the increase in the levels of CRP in PTB patients on ART from a similar angle which is that with the decreased destruction of immune cells (mainly T- Helper cells)., the levels of CRP increase in response to the opportunistic infection while still maintaining a low response to viral infections i.e. by treating HIV infection, the immune cells can respond better to the opportunistic infection (TB). Hence with PTB patients not on ART, the immune cells being very low, rise in CRP to the underlying inflammatory condition (PTB) is relatively low.

There is a negative correlation between CD-4 count and CRP with a significance of $p<0.01$. This is also shown in the research paper by Nagesh Y Wadgera et al. (10) This just means that with a decrease in CD-4 count, the levels of CRP increase. We found that the median CD-4 count of the PLHIV group was found to be 206 (IQR: 99-389). Most of the TB positive HIV patients had their CD-4 COUNTS less than a 200 cells / microliter as mentioned in the table earlier. This is indicative of TB's influence on CD4 cells.

Many research papers published by Christina Yoon et al (2013) (11), Cain KP et al (2013) (12) et al stated the importance of using symptom screen to diagnose TB in HIV individuals. Their studies showed that symptom screen combined with CRP, upped the specificity. We also learnt that the WHO screen is not the ultimate primary screen to be used, as a few research papers like the one by Christian Yoon et al (11). They emphasize the need to use CRP as a method to rule out the cases without symptoms of active TB.

In our Research study we found that high and equal number of PTB positives were seen with a combination of cough and fever with night sweats and weight loss or just cough and fever. The CRP levels were 32.3 mg/Land 21.9 mg/L respectively. We also stated earlier on that all the asymptomatic people were negative for CRP (<6 mg/L). But the levels of CRP were higher with levels being as high as 53.8 mg/L in case of the combination of cough, fever and weight loss and another case of a patient having cough, night sweats and weight loss with CRP of 48mg/L. These groups had a generally high CRP due to the common symptom of weight loss which is a factor that increases CRP.

There was no correlation between symptoms and CRP. Both these diagnostic facilities had their share of false positives. The lower predictive value of CRP as impressed upon us by Lawn et al could be a huge disadvantage in its usage as it could lead to delays in management (13). The false positives using the combination C, F, W, N was 36%(64% patients were found to be PTB positive in this group) which is better than the false positives in any other category. This also goes along with the fact that this group had a highest number of positives than any other group. The CRP levels of patients with this combination was about 32.3mg/L which comes close to the MEAN

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CRP of PTB positives i.e. 34mg/L. Hence we can come to a conclusion that the greater the number of symptoms in a combination, compatible with TB, the greater are the number positives. Other than this, the correlation between symptoms and CRP is not highly significant. We found that both the groups had their share of false positives. The sensitivity of CRP also increased when a combination of symptoms was used as a primary screen.

Lawn et al. (13) found that the values of CRP rang from an insignificant 1.5 mg/L to 400 mg/L in the TB positives. The positive predictive value ranged from 17.9% to 100 %. Their study highlighted the need to use CRP as a prognostic indicator rather than a diagnostic indicator with values of 50mg/L associated with poor prognosis. They stated that CRP was not associated with radiological extent of the disease or the mycobacterial load in patients with advanced AIDS.

In our study we found that the range of CRP in positives was from 6 mg/L to 96 mg/L. This was a relatively better result as the range is smaller than given by Lawn et al (13).

CBNAAT was the confirmatory diagnostic method used to diagnose possible TB patients. This test however, as reported by Y Hanifa et al (2013) (14) was not very sensitive in detection of TB due to its decreased sensitivity in smear negative cases (15). The sensitivity came down to 43- 73%. This report stated that the while the specificity is high, sensitivity is alarmingly low in this research paper. The bacterial load in smear negative cases being in insignificant amounts, requires a highly sensitive diagnostic equipment or method for diagnosis where sensitivity should not change based on the patient population. This however was not reported in all research papers but a few like this one paper. The sensitivity of this equipment could thus depends on the prevalence setting.

CONCLUSION: The study showed that the CRP levels were negative (< 6mg/L) in HIV infected subjects who were not on ART. This shows that in a viral infection like HIV where there is decrease in immune cell count, there is no rise in CRP to levels indicative of inflammation. The study showed a mean CRP of about 34 mg/L in the PTB positive group. The levels in PTB patients on ART was about 40 mg/L and in PTB patients not on ART, CRP was 28.5 mg/L. CRP showed a negative correlation with CD-4 count (highly significant $p<0.01$) with levels of CRP being about 62 mg/L when CD-4 count was 200. CRP showed a positive correlation with CBNAAT (highly significant $p<0.01$). CRP showed a positive correlation with combination of symptoms. This was almost nil when asymptomatic or symptomatic group with only one symptom was considered. Higher number of TB positives were found with combination of 4 symptoms (WHO screen). Hence CRP should be combined with symptom screen.

SUGGESTIONS: CRP with symptom based screen should be evaluated with other parameters or tried in different settings. The study should include other parameters like procalcitonin and any other acute phase proteins. It should also be compared with interleukins or interferons like the Quantiferon Assay which can detect latent infections (16). This increases the significance of the study. More research should be done on ART patients. ART drugs may bring up the levels of CD 4 counts and help in fighting off not only HIV but also TB because of their immune response is magnified. Hence symptoms which appear in the first few months of initiating ART should be carefully watched for. Clinical pattern and CRP levels or any acute inflammatory proteins should be assessed to detect any lapses in the symptom appearance in PLHIV on ART for any subclinical infection. Another factor that continues to plague newer diagnostic approaches, is the economic affordability. But it remains that the efficacy of using CRP as a screening test cannot be determined with just one overview, especially in a country where TB is still on a high. The diagnostic approach should be assessed in primary and tertiary care hospitals where there is a difference in the type of equipment available. We should continue studies to break down any barriers in this difficult task of diagnosis of Tuberculosis.

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FIGURE LEGENDS

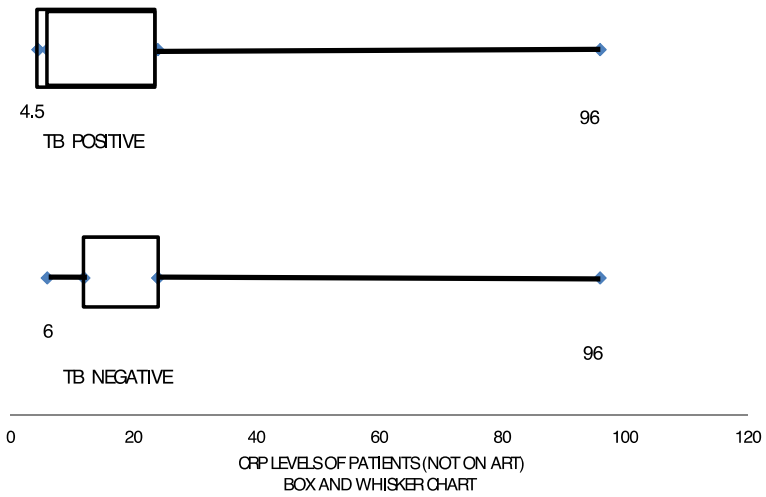

FIGURE 1: Box and whisker plot

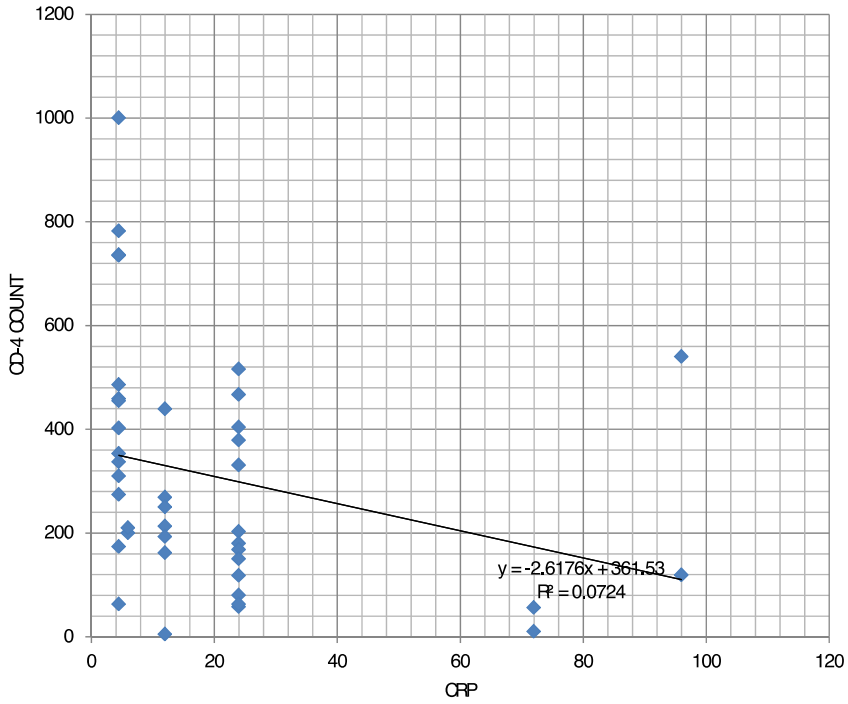

FIGURE 2: scattered plot with slope showing the relation between CRP and CD-4 COUNT

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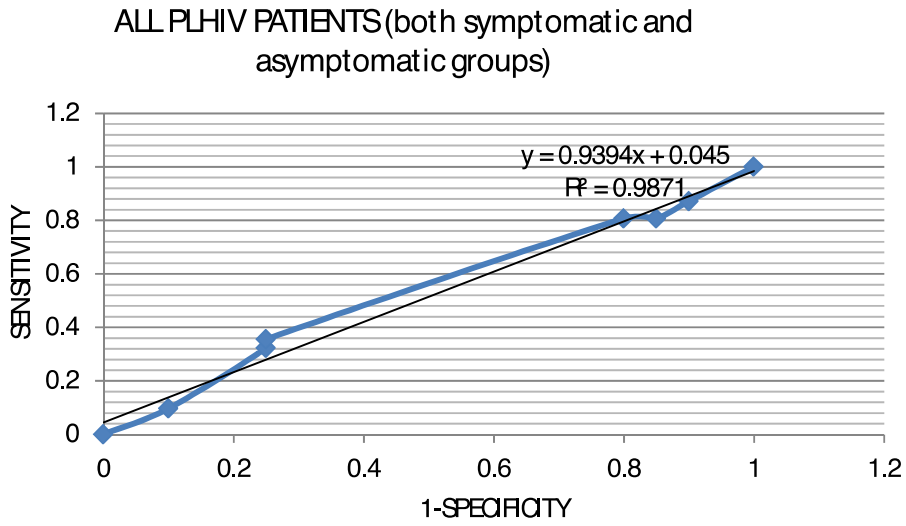

FIGURE 3: sensitivity and specificity of CRP in symptomatic and asymptomatic group

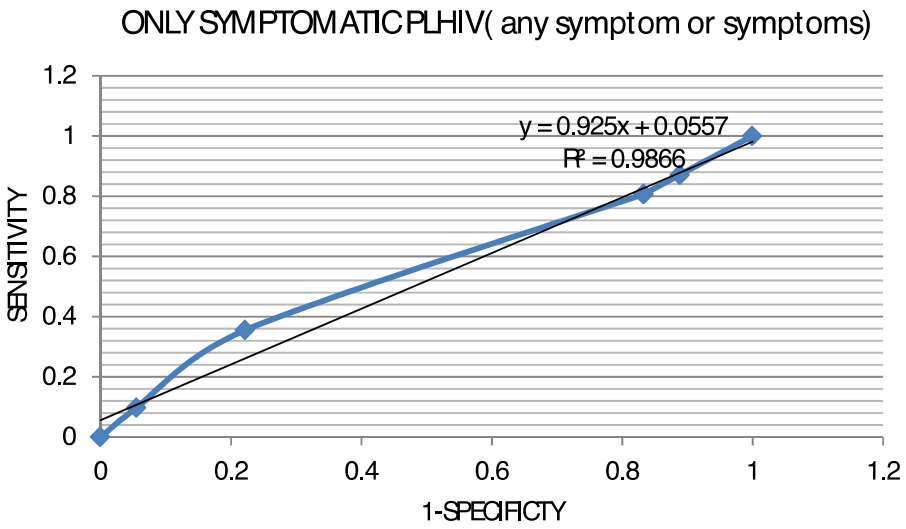

FIGURE 4: sensitivity and specificity of CRP in symptomatic group

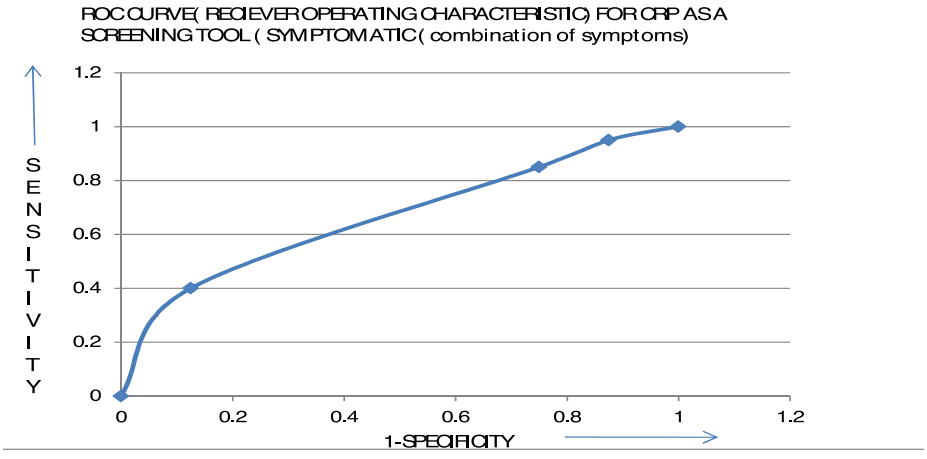

FIGURE 5: sensitivity and specificity of CRP in symptomatic group (only combination of symptoms)

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TABLES

GROUPED PATIENT DATA	No: of Patients	MEAN CRP(mg/L)
Asymptomatic PLHIV, not on ART (baseline CRP)	5	<6
Symptomatic PLHIV ,TB positive, not on ART	20	26.4
Symptomatic PLHIV ,TB negative, not on ART	20	17.55-18.6
Symptomatic non-PLHIV, TB positive	2	24

TABLE 1: shows the mean CRP of patient groups

CD4 counts (cells/ microliter)	PTB patients	ETB patients	TOTAL
< OR=100	6	4	10
>100-200	7	2	9
>200-350	6	2	8
>350-500	4	1	5
>500	0	0	0
TOTAL	23	9	32

TABLE 2: CD-4 counts and the number of TB positives

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