

Significance of Total Serum Proteins and Serum Albumin Globulin Ratio in Pulmonary TB with HIV Patients

Kamaldeep Singh¹, Maninder Kaur², Kailash Meena³, Surinder Pal Singh⁴, Karan Sharma⁵, Gurpreet Singh¹

¹Junior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.

²Professor, Department of Biochemistry, Government Medical College, Patiala, Punjab, India.

³Senior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.

⁴Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.

⁵Senior Resident, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.

Abstract

Background: Tuberculosis (TB) is one of the leading causes of morbidity and mortality. In chronic infectious TB disease like TB, the albumin shows a decrease while globulin content shows an increase leading to low albumin to globulin (A/G) ratio and with HIV co-infection there is reversal of A:G ratio. **Aim:** This present study was designed to evaluate the levels of total serum proteins along with serum albumin-globulin ratio in individuals suffering from pulmonary tuberculosis alone and co-infected with HIV. Our study also aimed at correlating these levels with disease severity and whether anti-tubercular therapy has any effect on these biomarkers. **Material and Methods:** This prospective study done at GMC, Patiala included 120 participants (40 of pulmonary TB, 40 pulmonary TB with HIV, 40 healthy individuals). Subjects that met the inclusion criteria based on history, examination and investigation were clinically evaluated and underwent sputum examination, chest x-ray (P-A) view, serum total protein and serum albumin-globulin ratio. Serum total protein and serum albumin-globulin ratio were repeated at end of intensive phase of anti-tubercular treatment. On a routine CXR –PA view by two chest physicians the extent of radiological involvement was estimated. Sputum AFB grading was done according to Zn staining. **Results:** In PTB-HIV and PTB subjects there was a statistically significant (p -value <0.01) increase in mean TSP and A:G ratio from time of diagnosis to end of IP. There was a statistically significant (p -value $=0.01$) increase in mean TSP in all groups of both PTB-HIV and PTB patients from time of diagnosis to end of IP when correlated with the extent of radiological involvement. **Conclusion:** We concluded that TSP and A: G ratios are a good biochemical marker for monitoring of response to anti-tubercular treatment, and disease progression in pulmonary tuberculosis patients alone or co-infected with HIV.

Keywords: Pulmonary tuberculosis with and without HIV co-infection, total serum proteins, serum albumin globulin ratio, sputum AFB, disease severity.

Corresponding Author: Dr. Surinderpal Singh, Professor, Department of Pulmonary Medicine, Government Medical College, Patiala, Punjab, India.

Email: drsurinderpal09@gmail.com

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and is one of the leading causes of morbidity and mortality. Lungs are the most common site for infection with TB. It, however, can also affect other parts of the body. All those who get infected do not necessarily develop TB disease.^[1] Almost 1/3rd of the world population may be infected with tubercle bacillus,^[2] but the vast group of people may only have latent tuberculosis infection. The lifetime risk of progression towards disease among those infected with TB is about 10-15% which gets increased to 10% per year amongst those co-infected with HIV.^[3] Among all incident cases of TB, 8% were people living with HIV. The proportion of TB cases co-infected with HIV was highest in countries in the WHO African Region, exceeding 50% in parts of southern Africa.^[4] Tuberculosis is a major comorbidity in HIV-infected individuals, many of whom suffer from acquired immunodeficiency syndrome (AIDS) 815 000 [729 000–906 000] people living with HIV develop a new TB case.^[5,6] Number of people acquiring HIV are 100 000 [71 000–130 000] and number of people dying from HIV-related causes: 82 000 [55 000–130 000].^[7] In addition, studies have revealed that mycobacteria can more easily infect individuals with HIV infection than those without HIV.^[8] These findings suggest a mutualistic relationship between the two pathogens. It is well established that changes in levels of serum proteins occur in response to both acute and chronic infections. This is especially true for immunoglobulins and acute phase proteins. In an infection like tuberculosis, such changes in serum protein levels are expected. In chronic infectious TB disease, the albumin shows a decrease while globulin content shows an increase leading to low Albumin to Globulin (A/G) ratio and albumin to alpha-2 globulin ratios.^[9] Like all opportunistic illnesses in HIV-infected individuals, TB risk increases at lower CD4 count. Baseline low serum albumin level in cases with CD4 count <200 has been associated with increased mortality. Several studies of HIV-infected individuals have determined that hypoalbuminemia (defined as a serum albumin concentration of <35 g/L) is associated with more rapid progression to AIDS and its associated illness like tuberculosis with accentuated mortality rate.^[10]

Aims and Objectives: -

- To evaluate the levels of total serum proteins and serum albumin-globulin ratio in individuals suffering from pulmonary tuberculosis alone and co-infected with HIV.
- Correlation of levels of total serum proteins along with serum albumin-globulin ratio with disease severity and whether anti-tubercular therapy at end of intensive phase had any effect on these biomarkers.

Materials and Methods

The present observational prospective study conducted in Department of Chest And Tuberculosis, Government Medical College, Patiala over a period of 1 year. A total of 120 subjects included in study were divided into three groups as under:-

PTB-HIV group: - 40 cases of pulmonary TB with HIV co-infection, PTB group: - 40 cases of pulmonary TB and Healthy: - 40 healthy controls

Subjects that met the inclusion criteria based on history, examination and investigation were clinically evaluated and underwent sputum examination, chest x-ray (P-A) view, serum total protein and serum albumin-globulin ratio, CD4 count. Serum total protein and serum albumin-globulin ratio were repeated at end of intensive phase of anti-tubercular treatment. Other relevant investigations as per need were done. Institutional ethical committee approval was obtained for this prospective study and written consent taken from all the participants.

Inclusion Criteria

1. Patients who gave consent for study.
2. Patients >18years of age group.
3. Pulmonary TB already diagnosed either microbiologically confirmed or clinic-radiologically diagnosed with or without HIV.

Exclusion Criteria

1. Patients who did not give consent for study.
2. Patient suffering from active liver disease.
3. Patient suffering from severe renal disease, cardiac disease, T2DM.
4. Patient suffering from Extra Pulmonary TB (CNS, Abdominal, Lymph-node, bones, cutaneous etc.)
5. Pregnant and lactating female.

Venous blood samples taken from antecubital fossa by 5ml Syringe after sterilising with spirit swab under strict aseptic conditions. Total serum protein is calculated by Biuret principle. Serum albumin is calculated by Bromo Cresol Green principle. Globulin is calculated by subtracting albumin from total serum protein. A: G ratio is obtained by dividing the albumin by globulin.

HIV diagnosis was confirmed by ELISA➤ **Radiographic involvement^[11]**:-

On a routine CXR –PA view by two chest physicians the extent of disease severity was estimated based on the sum of all areas of abnormality in which a boundary of abnormal opacity could be drawn.

- Minimal lesions were defined as an area less than that above a horizontal line across the 2nd chondro-sternal conjunction of one lung
- Moderately advanced lesions were defined as an area greater in size than the minimal lesions but smaller than that of an entire lung
- Far advanced lesions were defined as an area equivalent to or greater than one lung.

➤ **Sputum AFB grading as per ZN staining^[12]****Statistical Analysis:**

All collected data was entered in the Microsoft excel spread sheet. Data was expressed as mean \pm SD or as appropriate for the parametric data and means were compared using Pearson's chi square test, paired T-test, one way ANOVA. P-value of ≤ 0.05 was taken as statistically significant. All analysis was done in SPSS trial version 26.

Results**Table 1: Mean Serum TSP and A: G Ratio at Time of Diagnosis**

Groups	Mean TSP+SD (g/dL)	P value	Mean A:G	P value
PTB with HIV	6.62+0.32	<0.001	0.73+0.17	<0.001
Healthy	7.23+0.34		1.72+0.19	
PTB	6.94+0.40		0.89+0.22	

In our study, at the time of diagnosis, the mean TSP in the PTB-HIV group was 6.62 ± 0.32 g/dl which was lower than the PTB group had a mean TSP of 6.94 ± 0.4 g/dl and both groups had mean TSP lower than healthy subjects who had mean TSP of 7.235 ± 0.34 g/dl. We found a significant difference in mean TSP levels among cases and controls (p-value<0.001). The mean A: G in the PTB-HIV group was 0.73 ± 0.17 which was

less than the PTB group where the value was 0.89+0.22. Mean A: G in healthy subjects was 1.72+0.19. There was a statistically significant difference in mean A: G ratios among PTB-HIV and PTB groups (p-value<0.001). [Figure1]

Table 2: Mean Serum TSP and A: G Ratio at End of Intensive Phase Treatment

Groups	Mean TSP+SD (g/dL)	P value	Mean A:G+SD	P value
PTB with HIV	7.05+0.32	<0.001	0.86+0.15	<0.001
PTB	7.43+0.43		1.07+0.15	

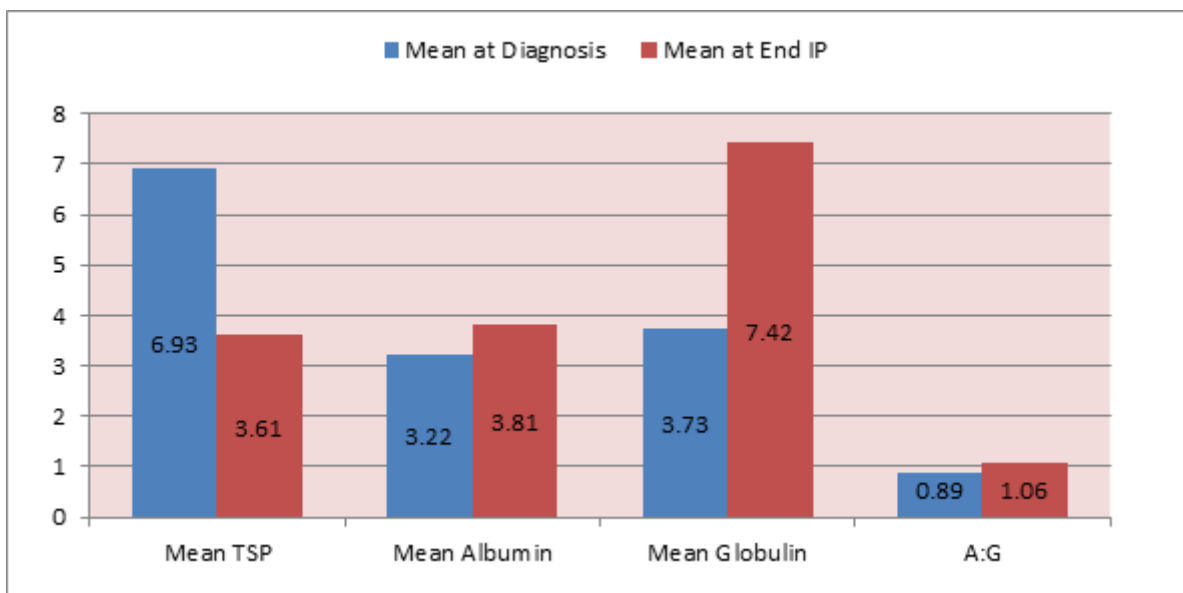


Figure 1:

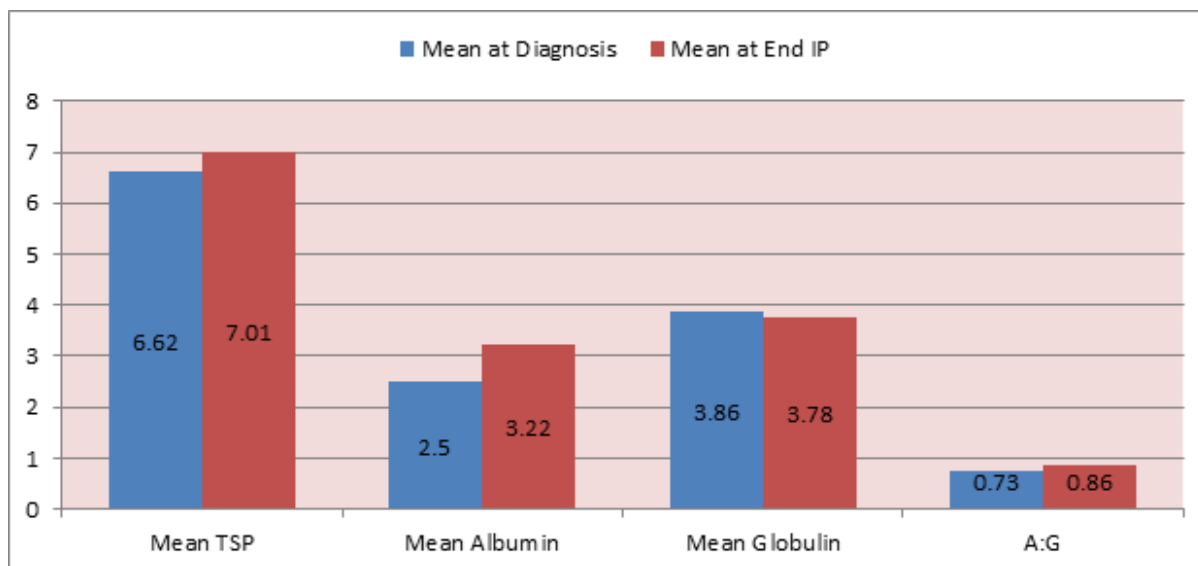


Figure 2:

Table 3: Changes in Mean TSP, Albumin and A:G Ratio from Time of Diagnosis to End of IP in PTB with HIV Group

Groups	Mean at Diagnosis	Mean at End IP	Difference between mean at diagnosis and End IP	Std. error	P value
TSP	6.62+0.32 g/dL	7.05+0.32 g/dL	-0.384	0.441	<0.001

Albumin	2.5 g/dL	3.22 g/dL	-0.476	0.509	<0.001
Globulin	3.86 g/dL	3.783 g/dL	.092	0.586	0.325
A:G	0.73 g/dL	.86 g/dL	-0.135	0.225	<0.001

When comparing the difference between mean (TSP and A: G) from diagnosis to end of an intensive phase in PTB-HIV patients the mean increase in TSP was 0.384 ± 0.441 g/dL which was statistically significant (p-value <0.001).

The difference in mean A: G ratio was 0.135 ± 0.225 which was statistically significant (p-value < 0.001). [Figure3]

Table 4: Correlation of Changes in Mean TSP, Albumin and A:G with Radiographic Involvement in PTB with HIV Group

Radiographic involvement	Mean TSP+SD (g/dL)	P value	Mean albumin+SD	P value	Mean A:G+SD	P value
Far advance lesions	0.607+0.43 g/dL	0.001	0.464+0.45 g/dL	0.932	0.083+0.19	0.379
Moderate advance lesions	0.378+3.89 g/dL		0.53+0.64 g/dL		0.180+0.29	
Minimal advance lesions	0.036+0.21 g/dL		0.452+0.52 g/dL		0.186+0.22	

In PTB-HIV subjects there was a statistically significant (p-value=0.01) increase in mean TSP in all groups from time of diagnosis to end of IP when correlated with the extent of radiological involvement in patients having far advanced lesions, the mean increase in TSP was $0.607+0.43$ g/dL, in moderate advanced was $0.378+3.89$ g/dL and minimal advanced was $0.036+0.21$ g/dL respectively. [Figure4]

It was not a statistically significant (p-value=0.379) increase in mean A: G ratios in any of the patients at end of IP in the PTB-HIV group.

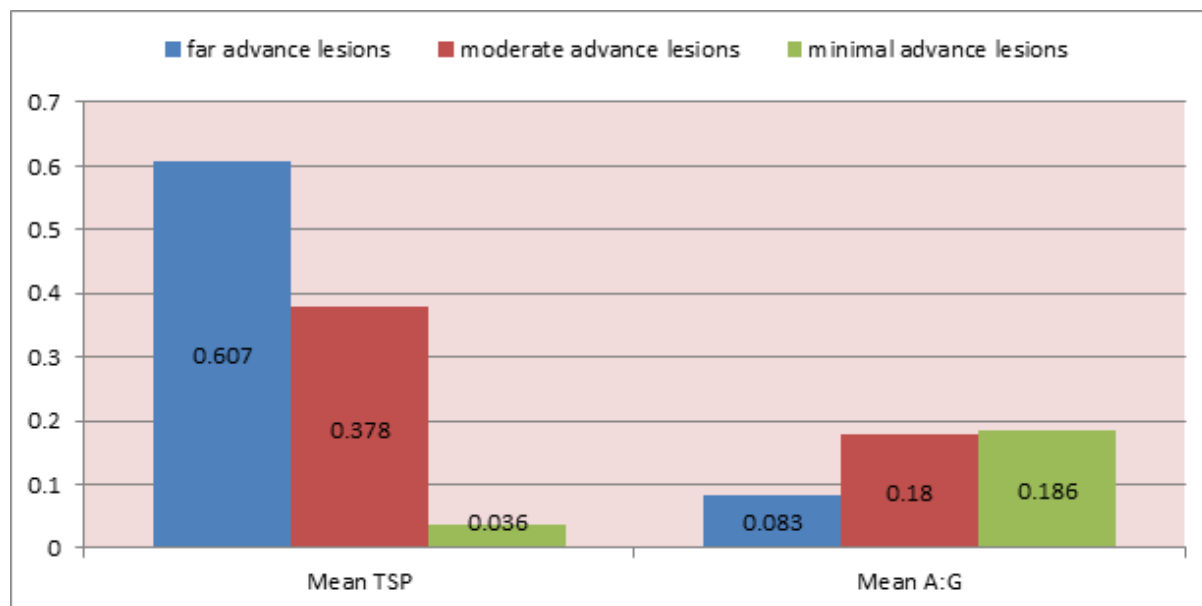


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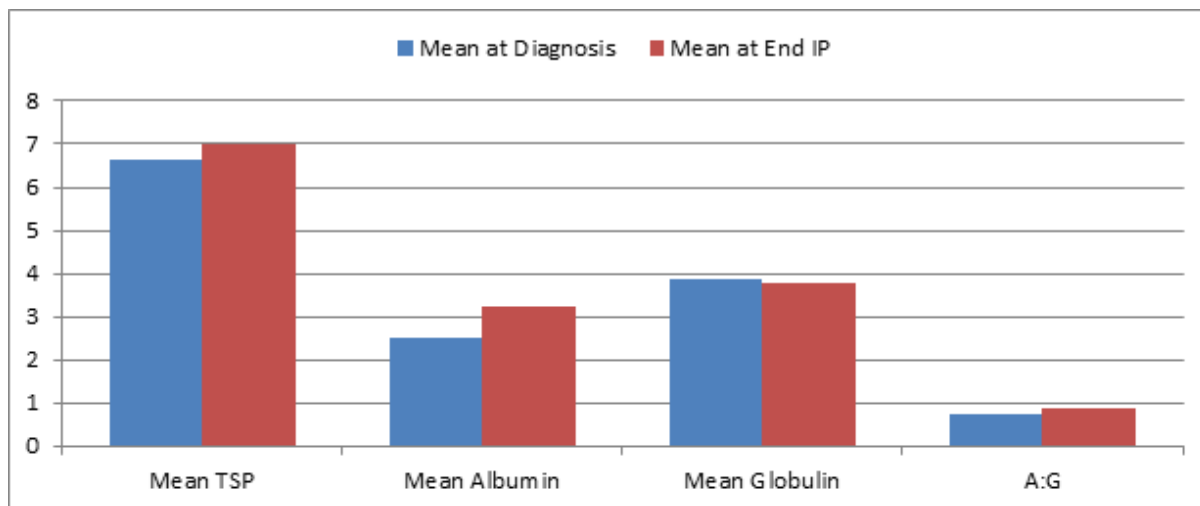


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Table 5: Changes in Mean TSP, Albumin and A:G Ratio from Time of Diagnosis to end of IP in PTB Group

Groups	Mean at Diagnosis	Mean at End IP	Difference between mean at diagnosis and End IP	Std Error	P value
TSP	6.938 g/dL	3.613 g/dL	-0.487	0.495	<0.001
Albumin	3.225 g/dL	3.813 g/dL	-0.586	0.458	<0.001
Globulin	3.738 g/dL	7.425 g/dL	0.126	0.644	0.225
A:G	.89	1.067	-0.17	0.278	<0.001

When comparing the difference between mean (TSP and A: G) from diagnosis to end of an intensive phase in PTB patients the mean increase in TSP was 0.487 ± 0.495 g/dL which was statistically significant (p-value<0.001).The increase in mean A: G ratio was 0.17 ± 0.278 which was statistically significant (p-value<0.001). [Figure5]

Table 6: Correlation of Changes in Mean TSP, Albumin and A:G with Radiographic Involvement in PTB Group

Radiographic involvement	Mean TSP+SD (g/dL)	P value	Mean albumin+SD (g/dL)	P value	Mean A:G+SD	P value
Far advance lesions	0.741+0.74 g/dL	0.02	0.6+0.54 g/dL	0.914	0.12+0.32	0.311
Moderate advance lesions	0.383+0.38 g/dL		0.52+0.42 g/dL		0.15+0.30	
Minimal advance lesions	0.45+0.45 g/dL		0.61+0.36 g/dL		0.27+0.17	

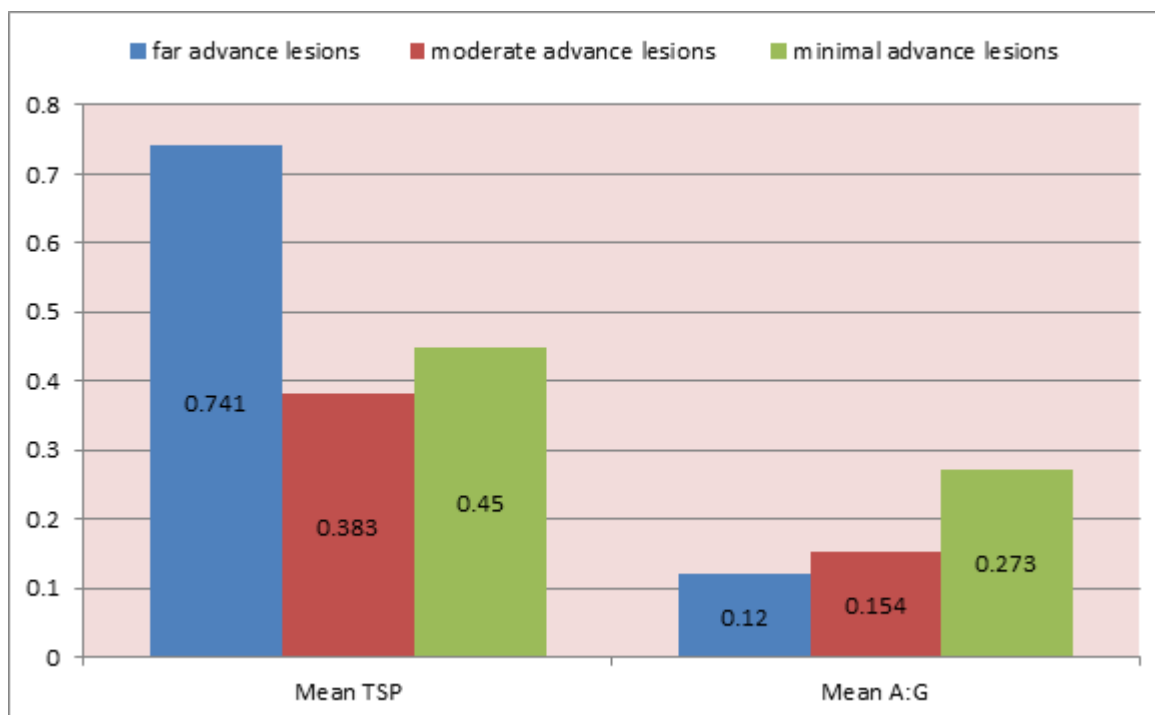


Figure 5: ?

Discussion

In our study, of the total subjects (n=120) included in the study, 74 (61.66%) were Males and 46 (38.33%) were females. In the PTB-HIV group, 34 patients (85%) were males and only 6 (15%) were females. This can be due to the more prevalence of HIV in males as compared to females. The distribution in the PTB group was 16 males (40%) and 24 females (60%). There is a greater preponderance of males in PTB in all other studies but in contrast, our PTB group shows the more female patient that may be because at that particular time number of female patients attending the clinic were more and females also have increased prevalence of smoking which increases the risk of tuberculosis.^[13] The mean age of the patients in PTB-HIV was 36.03 years, 33.38 years in PTB, and 38.03 years in healthy controls. Majority of the subjects belonged to the 21-30 age group (n=44) followed by 31-40(n=27), 41-50 age group(n=23). This also agrees with previous reports from developing countries where most of the TB-affected individuals were below 30 years.

In our study, at the time of diagnosis, the mean TSP in the PTB-HIV group was 6.62 ± 0.32 g/dl which was lower than the PTB group had a mean TSP of 6.94 ± 0.4 g/dl and both groups had mean TSP lower than healthy subjects who had mean TSP of 7.235 ± 0.34 g/dl. We found a significant difference in mean TSP levels among cases and controls (p-value<0.001). Mean TSP values were comparable and in concordance with, Adedapo et al,^[14] but Shingdang et al,^[15] Sasaki et al,^[16] and Yamanaka et al.^[17] The loss of appetite in TB patients is due to endotoxins produced by mycobacteria which results in low intake of proper diet thus leading to malnutrition and in chronic diseases like tuberculosis and HIV it results in impaired intestinal absorption of nutrients, decreasing the levels of TSP, albumin.^[18,19] In the current study, at diagnosis, the mean A: G in the PTB-HIV group was 0.73 ± 0.17 which was less than the PTB group where the value was 0.89 ± 0.22 . Mean A: G in healthy subjects was 1.72 ± 0.19 . There was a statistically significant difference in mean A: G ratios among PTB-HIV and PTB groups (p-value<0.001). There was the reversal of A: G ratios in both the groups, however it was more in the PTB-HIV group as compared to the PTB group because in HIV there is hyperglobulinemia. In HIV there is a chronic inflammation that could be because of decreased albumin levels.^[20,21]

In our study, at end of the Intensive phase, the mean TSP in PTB-HIV patients was lower as compared to the PTB group. This was found to be statistically significant (p -value <0.001) However, lower TSP in the PTB-HIV group as compared to the PTB group could be due to the synergistic effect of both TB and HIV diseases in the PTB-HIV group as both of these are chronic diseases and causes malnourishment, further compromising the immune system The increase in mean TSP in both groups could be due to the effect of ATT. Our findings are in concordance with Harries et al and Khan et al.^[22,23]

In the present study, at the end of IP, the mean A: G ratio in PTB with HIV was less than PTB. The p -value was <0.001 . There was a correction of reversal of A: G ratios in cases of the PTB group however it was not true for the PTB-HIV group because of persistent hyperglobulinemia. Our findings are in concordance with Patil et al,^[24] which showed the same results.

When comparing the difference between mean (TSP and A: G) from diagnosis to end of an intensive phase in PTB-HIV patients the mean increase in TSP was 0.384 ± 0.441 g/dL which was statistically significant (p -value <0.001). It shows that there was an improvement in the TSP levels from the time of diagnosis to the end of IP. It could be due to the effect of ATT. The difference in mean A: G ratio was 0.135 ± 0.225 which was statistically significant (p -value < 0.001). Rise in mean A: G ratios could be due to an increase in albumin levels but the decrease in globulin levels which could be due to the effect of ATT. When comparing the difference between mean (TSP and A: G) from diagnosis to end of an intensive phase in PTB patients the mean increase in TSP was 0.487 ± 0.495 g/dL which was statistically significant (p -value <0.001).The increase in mean A: G ratio was 0.17 ± 0.278 which was statistically significant (p -value <0.001). It shows that at end IP there is an increase in the TSP and A: G ratio from diagnosis which could be due to anti-tubercular treatment of 8 weeks. Our findings were comparable to available literature Adedapo et al.^[13] Our study results suggested that TSP and A: G can be used for the monitoring of treatment response.

In PTB-HIV subjects there was a statistically significant (p -value=0.01) increase in mean TSP in all groups from time of diagnosis to end of IP when correlated with the extent of radiological involvement in patients having far advanced lesions, the mean increase in TSP was 0.607 ± 0.43 g/dL, in moderate advanced was 0.378 ± 3.89 g/dL and minimal advanced was 0.036 ± 0.21 g/dL respectively. It could be due to the effect of ATT that there was an increase in mean TSP in all the groups at end of IP because ATT decreases the disease activity leading to improvement in malnutrition leading to improvement in malabsorption which was impaired in PTB-HIV infected patients. However, it was not a statistically significant (p -value=0.379) increase in mean A: G ratios in any of the patients at end of IP in the PTB-HIV group. In PTB subjects there was a statistically significant (p -value=0.02) increase in mean TSP in all groups of the extent of radiological involvement from time of diagnosis to end of IP. Patients having far advanced lesions mean increase in TSP was 0.741 ± 0.74 g/dL, in moderate advanced was 0.383 ± 0.38 g/dL and in minimal advanced was 0.45 ± 0.45 g/dL respectively. An increase in mean TSP levels in patients having far advanced lesions is more than minimal and moderate advance because of low levels of TSP at diagnosis. An increase in mean TSP could be due to the effect of anti-tubercular therapy. However, there was no statistically significant (p -value=0.311) increase in mean A: G ratios in any of the three groups of radiological involvement at end of IP.

Conclusion

In our study, TSP levels and A: G ratio were low in cases as compared to controls at the time of diagnosis. There was a statistically significant (p -value= <0.001) increase in mean TSP and A: G ratio from time of diagnosis to end of Intensive phase in all the patients irrespective of sputum AFB grading. There was a statistically significant correlation found between the

TSP levels and the extent of radiological involvement in all the patients. However, it was not true for the A: G ratio. We concluded that TSP and A: G ratios are a good biochemical marker for monitoring of response to anti-tubercular treatment, and disease progression in pulmonary tuberculosis patients alone or co-infected with HIV.

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