ORIGINAL ARTICLE

Risk of Tuberculosis with the Use of Inhaled Corticosteroids in Delhi/NCR

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Abstract

Background: Tuberculosis (TB) is a global health concern caused by Mycobacterium tuberculosis, primarily affecting the lungs. In addition to TB, chronic respiratory conditions like Chronic Obstructive Pulmonary Disease (COPD) and asthma are becoming more prevalent globally. Inhaled corticosteroids (ICS) are commonly used for COPD and bronchial asthma management, but some recent studies suggest a potential association between ICS usage and an increased risk of TB, raising concerns that they may lower lung immunity and enhance tuberculosis infection.

Aims and objectives: This research study was performed with an aim to investigate whether there is a link between inhaled corticosteroids (ICS) use and the risk of developing tuberculosis (TB) in COPD patients. The primary objective is to study whether the use of inhaled corticosteroids increases the risk of tuberculosis infection. The secondary objective is to compare the risk of TB in vulnerable populations with underlying comorbidities using inhaled corticosteroids.

Materials and methods: This is an observational, analytical study conducted over 2 months in patients with COPD who have been receiving inhaled corticosteroids for more than 2 years.

Results: A total of 97 COPD patients on ICS were recruited and categorized into TB ($n = 4$) and non-TB ($n = 93$) groups based on final outcomes. The mean ICS duration for the non-TB and TB groups was 24.8 and 48.0 months, respectively.

Conclusion: Despite being on ICS for more than 2 years, there was no significant correlation between ICS usage and TB infection. However, the study highlighted the significance of a prior TB history as a risk factor for increased reactivation ($p < 0.001$). Additionally, anemia was observed in reactivated TB cases, suggesting potential implications for identifying underlying chronic diseases in COPD patients.

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Introduction

Tuberculosis (TB) is a global health concern caused by Mycobacterium tuberculosis, primarily affecting the lungs. Despite available drugs and vaccines, TB remains a significant issue in developing countries. The World Health Organization (WHO) aims to end the TB epidemic by 2035 through the "End TB Strategy," emphasizing vaccination, early detection, and timely treatment.[1] India has the highest TB burden, contributing to 26% of global incident cases in 2021.[2] In addition to TB, COPD is one of the top three causes of mortality globally, and 90% of these incidents occur in low and medium-socioeconomic countries. Chronic obstructive pulmonary disease, often referred to as emphysema or chronic bronchitis, is a common lung disease that causes restricted airflow and breathing problems.[3] Patients with COPD exacerbations may develop end-stage COPD if they are not managed promptly with evidence-based therapies. In line with the objectives to address this public health issue, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated in 1998, with the aim of providing guidance, based on the best available scientific evidence, for the management of COPD. Inhaled corticosteroids are commonly used for COPD management, but some recent studies suggest a potential association between ICS usage and an increased risk of TB, raising concerns as they may lower lung immunity and enhance tuberculosis. The present study was carried out with an aim to ascertain an association between ICS use and risk of TB infection, and also to compare the risk of TB in vulnerable populations with underlying comorbidities.

Materials and Methods

The present study is based on data retrieved from the medical records of adult patients who were admitted to the Respiratory and Medicine Department at Sharda Hospital and School of Medical Sciences and Research, Greater Noida, Uttar Pradesh. After the approval of the ethics committee, the data were collected and anonymized. It is an observational analytical study. The study period was 2 months (3rd August 2022–3rd October 2022), and a total of 97 COPD patients were recruited. After a sample size calculation, all patients had been on inhaled corticosteroids for an average of more than 2 years. Study tools included sputum microscopy, chest X-ray, Mantoux test, ESR, and HRCT, if required.

Inclusion Criteria

All individuals above 18 years of age who were prescribed at least one of the following inhalational corticosteroids: beclomethasone, budesonide, triamcinolone, or fluticasone. All patients were prescribed a combination of a short-acting beta-agonist (SABA), salbutamol, and a short-acting muscarinic antagonist (SAMA), ipratropium, or a combination of long-acting beta-2 agonists (LABA)/long-acting muscarinic receptor antagonists (LAMA) and inhalational corticosteroids (ICS) (budesonide/formoterol, fluticasone/salmeterol).

Exclusion Criteria

Patients below 18 years of age, Patients in any stage of pregnancy, People living with HIV, and people already having chest infections.

Study Design and Conduct

This study focused on patients who had used inhaled corticosteroids (ICSs) or combinations of bronchodilators for at least 3 months. Information on ICS prescription and diagnosed tuberculosis (TB) cases occurring after initiating respiratory medications was collected, utilizing sputum microscopy, chest X-ray, ESR, and Mantoux test results. Covariates such as age, sex, and comorbid conditions known to increase TB risk were considered.

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Statistical Methods

All the data obtained were statistically analyzed in Microsoft Excel using mathematical functions. Means and standard deviations summarized continuous variables, while frequencies and percentages expressed categorical variables. Statistical significance was set at $p < 0.001$.

Results

Table 1 and Figure 1 show that the majority of the study participants (43) were aged 60 years or older, followed by 38 participants aged 41–60 years, and the remaining 16 participants were aged 40 years or younger. As shown in Table 2 and Figure 2, nearly half of the study participants (55) were male, and the remaining 42 were female. The *p*-value for age and gender is > 0.05, which is insignificant. Table 3 and Figure 3 represent comorbidities. The maximum number of participants (89 of 97 recruited) had no prior history of comorbidities. Only eight patients have had comorbidities, out of which five subjects had HTN, two subjects had a history of CAD, and one subject had diabetes mellitus. Covariates, in addition to age and gender, included comorbidities, which were also analyzed. The *p*-value for the above is > 0.05, which is also nonsignificant. Table 4 and Figure 4 display that a large number of study participants (89) have had no history of tuberculosis (TB). Only eight subjects had a history of tuberculosis, of which five subjects were in the non-TB group, and three subjects were in the TB group. However, this difference was statistically significant ($p < 0.001$). This implies that a previous history of tuberculosis can be a risk factor for increased reactivation, which may or may not be associated with ICS use. Table 5 and Figure 5 show that all study participants have used inhaled corticosteroids (ICS). However, 56 subjects had a history of smoking, and 11 subjects had a history of alcohol consumption. There was no significant difference between the Non-TB and TB groups. As shown in Table 6 and Figure 6, all the study participants were normally built with adequate nourishment. However, 12 subjects had pallor, out of which nine were in the non-TB group, and three

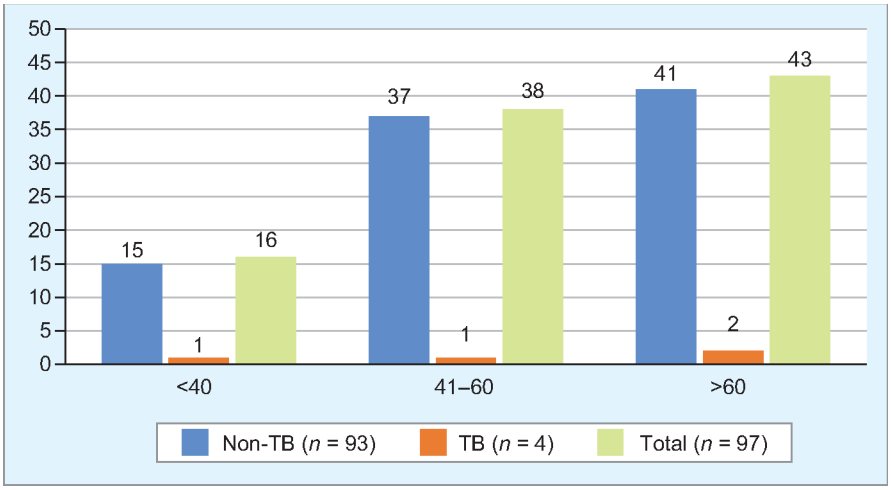

Fig. 1: Study participants according to age

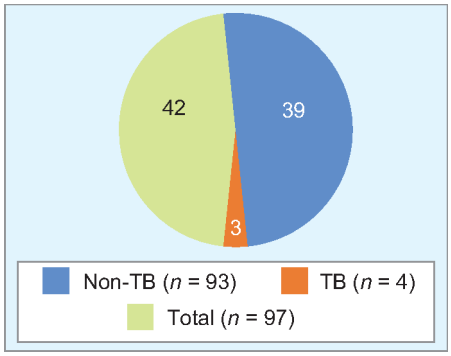

Fig. 2: Study participants according to gender

Table 1: Frequency distribution of study participants according to age

Age (in years)	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value (Chi-square)*
<40	15	1	16	0.808
41–60	37	1	38	
>60	41	2	43	

Table 2: Frequency distribution of study participants according to gender

Gender	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value (Fisher's exact test)*
Female	39	3	42	0.215
Male	54	1	55	

Table 3: Frequency distribution of study participants according to past history of disease

Past history of disease	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
Hypertension	5	0	5	0.806
Coronary artery disease	2	0	2	0.919
Diabetes mellitus	1	0	1	0.959

Table 4: Frequency distribution of study participants according to history of tuberculosis

TB history	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
No	88	1	89	<0.001
Yes	5	3	8	

Table 5: Frequency distribution of study participants according to personal history

Personal history	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
ICS usage	93	4	97	–
No significant family history	93	4	97	–
Smoking				
No	40	1	41	0.434
Yes	53	3	56	
Alcohol				
No	83	3	86	0.387
Yes	10	1	11	

Table 6: Frequency distribution of study participants according to general physical examination

General physical examination	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
Normal built	93	4	97	
Adequate nourishment	93	4	97	
Pallor				
No	84	1	85	0.006
Yes	9	3	12	
Icterus				
No	93	4	97	
Clubbing				
No	92	3	95	0.081
Yes	1	1	2	
Cyanosis				
No	93	4	97	
Lymphadenopathy				
No	93	4	97	
Edema				
No	92	4	96	0.959
Yes	1	0	1	

Table 7: Frequency distribution of study participants according to mean age, ICS duration, and vitals

	Non-TB					*TB*					*Total*					*p-value (Chi-square)*
	Mean	*SD*	*Range*	*Min*	*Max*	*Mean*	*SD*	*Range*	*Min*	*Max*	*Mean*	*SD*	*Range*	*Min*	*Max*	
Age	56.6	14.2	61	20	81	56.3	12.6	28	40	68	56.5	14.1	61	20	81	0.966
ICS duration (in months)	24.8	34.6	179	1	180	48.0	64.2	132	12	144	25.7	36.0	179	1	180	0.208
Pulse rate	84.5	9.1	80	40	120	85.5	3.8	8	80	88	84.5	8.9	80	40	120	0.820
Respiratory rate	20.6	2.6	19	16	35	20.5	1.9	4	18	22	20.6	2.5	19	16	35	0.918
SpO_2	96.5	6.2	59	40	99	97.3	1.5	3	96	99	96.5	6.0	59	40	99	0.811
BP (Sys)	117.5	12.2	69	100	169	120.0	8.2	20	110	130	117.6	12.0	69	100	169	0.685
BP (Dias)	74.9	7.8	40	60	100	72.5	9.6	20	60	80	74.8	7.8	40	60	100	0.549

subjects were in the TB group; this difference was statistically significant ($p < 0.001$). Table 7 delineates that the mean duration for the use of inhalational corticosteroids was 25.72 months. Table 8 and Figure 7 convey that the majority of study participants (93) had no evidence of Tuberculosis (TB) on chest X-ray, and only four subjects had evidence of active tuberculosis. However, this difference was statistically significant ($p < 0.001$). Figure 8 shows that the majority of study participants (96) reported as AFB-negative on sputum microscopy, and only one subject reported as AFB-positive on sputum microscopy. One participant was found to be AFB positive and also showed signs of active tuberculosis (TB) on chest X-ray. ESR was not considered for all the patients; hence, it was analyzed.

Discussion

The primary objective of our study is to ascertain the likelihood of developing TB with ICS use in COPD patients. The present study has not proven any such correlation between ICS use and risk of TB development, despite the fact that they were on ICS for approximately 24 months. However, our study demonstrated that a previous history of tuberculosis can be a risk factor for increased reactivation with a statistically significant p-value ($p < 0.001$). Dong et al. conducted randomized controlled trials to assess the impact of ICS on the causation of TB and influenza in COPD patients. The risk of TB and influenza in patients with COPD, from their study the number needed to harm to cause one additional TB event was lower for patients with COPD treated with ICSs in endemic areas than for those in nonendemic areas (909 vs 1,667, respectively); hence, TB risk may not be directly correlated to ICS use as the NNT is not

Table 8: Frequency distribution of study participants according to the investigation

Investigations	*Non-TB (n = 93)*	*TB (n = 4)*	*Total (n = 97)*	*p-value*
Chest X-ray				
Infective etiology, such as tubercular	0	4	4	< 0.001
No evidence of TB	93	0	93	
Sputum microscopy				
AFB negative	93	3	96	0.041
AFB positive	0	1	1	
ESR				
No	93	4	97	

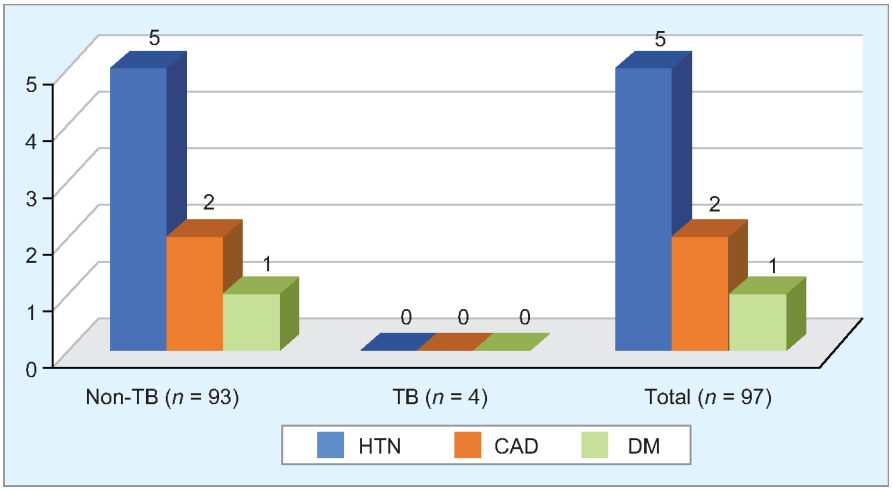

Fig. 3: Study participants according to past history of disease

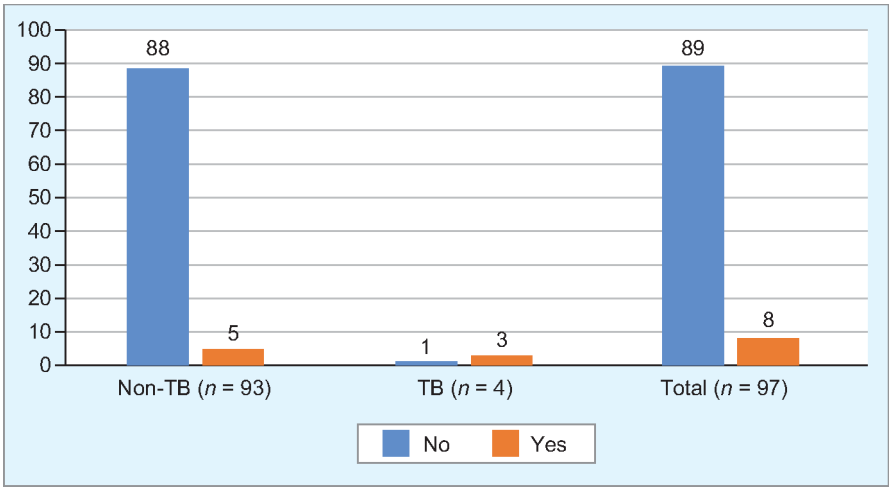

Fig. 4: Study participants according to history of tuberculosis

comparable in both the groups.[4] Castellana et al. conducted a systematic review and meta-analysis in Italy in 2018 to evaluate the effects of inhaled corticosteroids (ICS) on the risk of TB in patients with COPD, which was registered on PROSPERO. Their study demonstrated that ICS use was associated with an increased risk of TB compared with no ICS use (OR = 1.46; 95% CI 1.06–2.01; $p = 0.02$; $I_2 = 96\%$). However, when considering PAF (Population Attributable Fraction), the contribution of ICS to the epidemiology of TB seemed to be limited, leading them to suggest that the risk should be taken into account on an individual basis.[5] Global Initiative for Chronic Obstructive Lung Diseases (GOLD) 2022[6] discusses the benefit of triple therapy with a long-acting beta 2-agonist (LABA)/long-acting muscarinic antagonist (LAMA)/inhaled corticosteroid (ICS). This combination is associated with reduced mortality compared with LABA/LAMA therapy in symptomatic patients with a history of frequent and/or severe exacerbations. Chang-Hoon-Lee et al. conducted a case-control study in 2013 to establish the relationship between inhaled corticosteroids and TB, in which they concluded that the use of ICS increases the risk of TB with an adjusted OR (aOR) of 1.20; 95% CI 1.08 to 1.34. The association was dose-dependent (p for trend < 0.001). However, they noted a limitation in their study of recruiting heterogeneous patients with various respiratory diseases, which could have led to the obfuscation of the actual effects of the drugs on the risk of TB.[7] Notably, their results are in contrast to our study results, emphasizing the need for an individualized approach to assess the risk associated with ICS use.

The secondary objective of our study is to compare the risk of TB in vulnerable populations with underlying comorbidities who are also on ICS for a long duration. Since our study is based on a simple random sampling, the majority of our patients, almost 92%, are found to have no underlying comorbidities. Hence, we could not establish the relationship between TB and comorbidities. However, our study has proven that a previous history of tuberculosis can be a risk factor for increased reactivation ($p < 0.001$). Moreover, study results showed that people with reactivated TB were noted to be anemic, and this difference was statistically significant ($p < 0.001$) when compared to the non-TB group. The current study implies that a previous history of tuberculosis can be a risk factor for increased reactivation, and also screening of the comorbidities should be an important component in the management of a COPD patient, as anemia may have been caused by the underlying chronic disease apart from COPD.

According to a study conducted by Chung et al. in Taiwan titled "Use of inhaled corticosteroids and the risk of tuberculosis. A countrywide study of 8091 TB patients and 32,364 non-TB patients denoted that long-term use of ICS is associated with a 2.04-fold

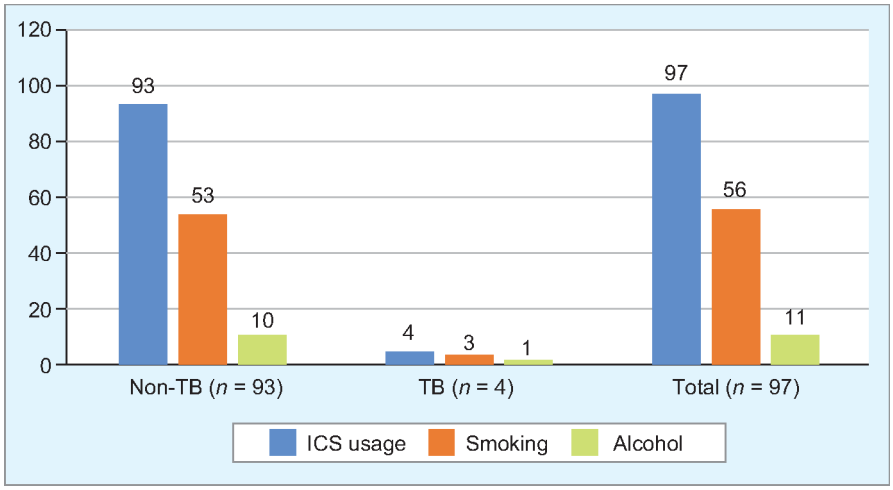

Fig. 5: Study participants according to personal history

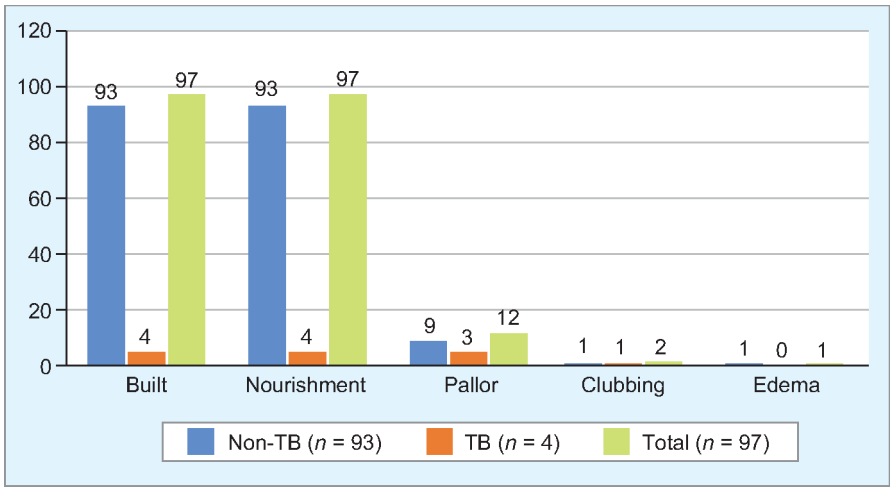

Fig. 6: Study participants according to general physical examination

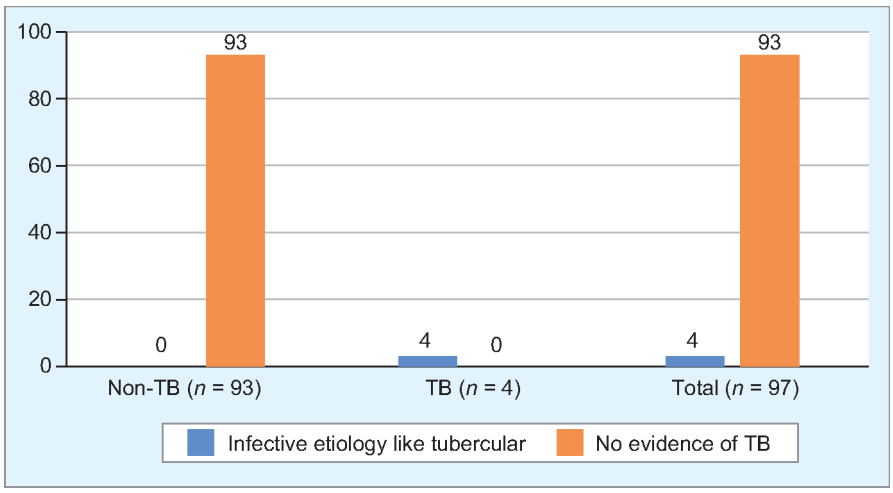

Fig. 7: Study participants according to chest X-ray

increased risk of developing TB (adjusted OR (aOR), 1.20; 95% CI 1.08 to 1.34). In a country with an intermediate TB burden, it was determined that using ICS raises the risk of developing TB. Their results are contrary to ours. However, the majority of their patients were known to have diabetes mellitus, liver cirrhosis, cancer, and end-stage renal failure, and were already on oral steroids and DMARDS (disease-modifying agents), which may explain the underlying immunodeficiency. However, they have also demonstrated that study participants with pre-existing TB history have displayed an 8.5-fold increased risk of TB development compared with other participant who has no prior TB history; these results are similar to our study.[8] The other study conducted by "Venkitakrishnan et al. in South India shows a slightly increased risk of TB reactivation, with only one additional TB reactivation occurring out of 909 COPD patients receiving ICS in endemic locations, which demonstrates the low size of this risk with a population attributable percentage of 0.49%, in a high burden country for tuberculosis."[9]

The most recent (2023) GOLD Report states that a single COPD exacerbation can triple the lung function decline in mild COPD patients. It also emphasizes the use of blood eosinophils in deciding whether to initiate ICS. The current GOLD report strongly favors ICS use if history of hospitalizations for exacerbations of COPD, and if ≥ 2 moderate exacerbations of COPD per year, or history of concomitant asthma, and also if eosinophils ≥ 300/µL. This study also proposes to de-escalate ICS if patients develop frequent episodes of pneumonia or if they have preexisting tuberculosis, and if the blood eosinophil count is <100/ µL.[10] Malerba et al. conducted research in Italy to review the rationale for the single-inhaler LABA/LAMA for COPD. The study concluded to consider LAMA/LABA combinations rather than monotherapy, and their study also highlighted the consideration of ICS use in COPD patients if their sputum shows an elevated eosinophil count.[11]

To acknowledge our results, the strengths and limitations of our study must be elucidated. All the covariates in our study had *p*-values > 0.05, indicating they were not significant, and none were on any immunosuppressive medications. One of the main strengths of this study is having fewer confounding variables. Hence, this study infers the effect of ICS in quantifying the risk of future TB development in COPD patients.

Limitations

Since the present research is an observational analytical study with a small sample size, it limits the generalizability. Hence, more randomized controlled trials with large sample sizes are required to ensure the external validity in a diverse socio-economic population.

Conclusion

In conclusion, the current research has not shown any evidence of new TB risk in COPD patients who are on ICS for approximately 2 years. However, our study demonstrates

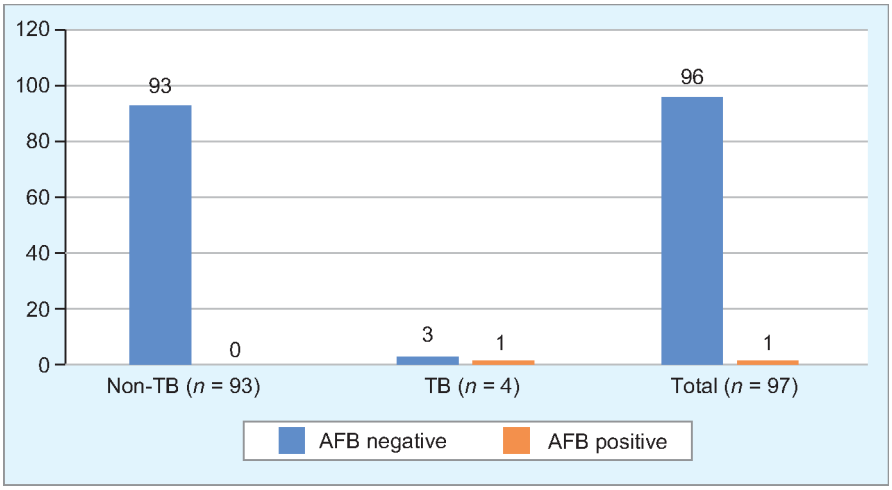

Fig. 8: Study participants according to sputum microscopy

that a previous history of tuberculosis can be a risk factor for increased reactivation, which is worth highlighting. Anemia of chronic disease is probably the most common type of anemia associated with COPD. Even so, anemia may not always be attributed to an untreated or progressive COPD, but may also be caused by any other underlying chronic diseases, such as tuberculosis, especially in countries with a high prevalence of TB. We propose a future scope for new research to decide whether concomitant comorbidities have any added role in the causation of TB in COPD patients who are on ICS. Frequent exacerbations of COPD accelerate disease progression and may contribute to premature mortality outcomes. Therefore, our study suggests that prescribing inhaled corticosteroids, especially during COPD exacerbations, is justified, as the benefits outweigh the risks.

Acknowledgments

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