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BASIC RESEARCH ARTICLE

Mycobacterium tuberculosis and HIV Co-Infection Among Presumptive Tuberculosis Cases and Asthmatic Patients at University of Gondar Hospital, Northwest Ethiopia

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SUMMARY

Background: **Tuberculosis and Human Immunodeficiency Virus (HIV) have been closely linked since the emergence of Acquired Immunodeficiency Syndrome (AIDS). Several studies have suggested an increased incidence of asthma among HIV positive individuals. This study aimed to determine the prevalence of *Mycobacterium tuberculosis* (MTB) and HIV infection among presumptive tuberculosis cases and asthmatic patients.**

Methods: **A hospital-based, cross-sectional study was conducted on 424 study participants from October 2018 - June 2019. Sociodemographic data and sputum samples were collected and investigated by Ziehl-Neelsen microscopy, Gene Xpert MTB/RIF assay, and culture. The nutritional status of the patients was assessed by body mass index. Finally, data was entered, cleared, and checked using Epi-info version 7 and exported to SPSS version 20 for analysis. Logistic regression was used for statistical association. p-value < 0.05 at 95% CI was considered statistically significant.**

Results: **The overall prevalence of MTB and HIV infection was 3.86% and 5.4%, respectively. The prevalence of MTB infection among presumptive tuberculosis (TB) cases was 4.4%, but none among asthmatic patients. The prevalence of HIV infection among presumptive TB cases and asthmatic patients was 5.2% and 6.6%, respectively. The overall prevalence of malnutrition was 30%. The prevalence of malnutrition among culture-positive TB patients was 31.25% and that of HIV positive cases was 43.5%. The proportion of MTB infection among HIV positive patients was 12.5%. Marital status of the study subjects significantly associated with culture positive MTB infection. Occupation and previous history of tuberculosis infection had a statistically significant association with HIV infection.**

Conclusions: **This study showed a high prevalence of HIV among asthmatic patients compared to presumptive TB cases. So, regular large-scale surveys should be conducted to assess the burden and intervene accordingly.**

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KEY WORDS

Mycobacterium tuberculosis, human immunodeficiency virus, asthma, malnutrition

LIST OF ABBREVIATIONS

AIDS - Acquired Immunodeficiency syndrome
ART - Anti-retroviral therapy
BMI - Body mass index
CD4 - Cluster of differentiation-4
CHF - Congestive Heart Failure
CMHS - College of Medicine and Health Sciences
COPD - Chronic Obstructive Pulmonary disease
DOTS - Directly Observed Short course
HAART - Highly Active Antiretroviral Treatment
HIV - Human Immunodeficiency virus
HTN - Hypertension
IL-1β - Interlaken-one beta
LABA - Long-Acting Beta Agonists
LJ - Löwenstein-Jensen
MDR-TB - Multi-drug resistant tuberculosis
MTB - *Mycobacterium tuberculosis*
NTM - Non-tuberculosis mycobacteria
OIs - Opportunistic infections
RIF - Rifampicin
SABA - Short-Acting Beta Agonists
SPSS - Statistical analysis in Social Sciences
TB - Tuberculosis
TNF-α - Tumor necrosis factor-alpha
UOG - University of Gondar
USA - United States of America
WHO - World Health Organization

INTRODUCTION

Africa is the region with the highest burden of all forms of tuberculosis (TB) cases [1,2], and Ethiopia has a high rate of TB infection. The annual incidence of new TB cases was estimated to be 207/100,000, and the country is one of the 27 high multi-drug resistant tuberculosis (MDR-TB) countries with an estimated 6,200 MDR-TB patients each year [2]. In Gondar, the prevalence of smear-positive and smear-negative tuberculosis infection was reported 16.8% and 54.9%, respectively [3]. Presumptive TB refers to a patient who presents with the symptoms or signs suggestive of TB, whereas a clinically diagnosed TB case is one who has been diagnosed with active TB [4]. Tuberculosis and human immunodeficiency virus (HIV) infection interfere with and impact the pathogenesis of each other. The proposed model of HIV/*Mycobacterium tuberculosis* co-infection is the 'danger-couple' model of disease pathogenesis. *Mycobacterium tuberculosis* and HIV have evolved to favor each other in facilitating the pathogenesis of the disease [5,6].

The pathophysiology of asthma is characterized by inflammation and hyper-responsiveness of lung bronchioles. The interrelationship between tuberculosis and bronchial asthma remains controversial. Some authors consider the disease mutually exclusive; others believe that asthma and tuberculosis may occur in the same patient coincidentally, and finally, some think that asthma may predispose to tuberculosis or by contrast, that tuberculosis may favorably increase the course of asthma [7]. Asthma is variously stated to improve or worsen after the development of tuberculosis, or to influence the course of the latter unfavorably. The mechanical sequelae of tuberculosis disease have been blamed for the subsequent development of asthma [8]. Asthma following treatment for tuberculosis appears to be well controlled [9].

There is emerging evidence indicating an association between asthma and HIV infection, but much remains to be learned [10]. The association between asthma and HIV has not been studied as well as the association between HIV and small airway obstruction in general. In the pre-ART era, studies investigated an association between HIV and bronchial hyper-responsiveness, an important feature of the pathophysiology of asthma. A small study of 66 HIV-infected and matched HIV-uninfected controls showed that airway hyper-responsiveness was not more common in HIV-infected subjects compared to HIV-uninfected controls [11]. The overall aim of this study was to determine the prevalence of Mycobacterium tuberculosis and HIV infection among presumptive pulmonary tuberculosis and asthmatic patients.

MATERIALS AND METHODS

Study area

The study was conducted at the University of Gondar comprehensive specialized referral hospital. The hospital provides health care services for more than five million people in Gondar town and the surrounding area. The town has 8 health centers, 21 private clinics, and one referral hospital which has more than 400 beds that provides health services such as surgery, internal medicine, pathology, TB/HIV, dermatology, antenatal care, delivery, postnatal care, laboratory, pharmacy, integrated maternal and neonatal care, and other services for the population of Gondar town and surrounding areas.

Study design, period, and population

A hospital-based cross-sectional study was conducted to determine the prevalence of *Mycobacterium tuberculosis* and HIV infection among presumptive pulmonary tuberculosis and asthmatic patients, from October 2018 - June 2019. Presumptive tuberculosis patients from directly observed short-course (DOTS) TB clinic and asthmatic patients from chronic illness clinic were included in the study during the study period. Study participants who were unable to give socio-demographic information and samples, were currently on antibiotic

treatment, and had a recent history of antibiotic treatment (for TB) in the past two weeks at the time of data collection were excluded.

Study variables

The prevalence of *Mycobacterium tuberculosis* and HIV infection were used as dependent variables whereas, the socio-demographic characteristics were used as independent variables. Risk factors for pulmonary tuberculosis infection such as the previous history of pulmonary tuberculosis infection and close contact with tuberculosis cases was also assessed. Clinical symptoms such as cough for more than 2 weeks, weight loss, and night sweats were also determined. The nutritional status of the study subjects was determined using body mass index (BMI). The history of bronchial asthma, duration of asthma, and asthma treatment history also determined together with the type of asthma medication. Co-morbidity factors such as hypertension, diabetes mellitus, cardiac disease, and congestive heart failure were also assessed.

Sample size determination and sampling technique

Single population proportion formula was used to calculate the sample size. The calculated sample size was 385. After adding a 10% non-response rate, the final calculated sample size was 424. A simple random sampling technique was used and eligible patients during the study period were included in the study until the sample size of 424 was reached. The aims of the study and the benefits of participation were clearly explained to the participants before data collection. Participation was voluntarily and they told them it is their right to withdraw from the study at any time during data collection. A questionnaire, based on known and possible factors, was developed to explore the objectives of the study and pre-tested.

Socio-demographic data collection

A predesigned and structured questionnaire was used for the collection of socio-demographic characteristics (age, gender, level of education, occupation) and clinical characteristics (previous history of pulmonary tuberculosis infection, close contact with tuberculosis cases, cough for more than 2 weeks, weight loss and night sweats) of the patients. A questionnaire was prepared in English and translated into Amharic then translated back into English to check the accuracy of the translation. Data collectors (nurses and laboratory technicians) were recruited and trained on the questionnaire, data collection, and interviewing techniques as well as on specimen collection. Then, the socio-demographic characteristics, clinical information, and specimens were collected.

Specimen collection and laboratory procedures of tuberculosis

Sputum samples from patients presenting symptoms of tuberculosis were collected in plastic, leak-proof, wide-mouthed, sterile containers. A specialist medical doctor and bacteriologist working in the TB clinic performed the necessary clinical and diagnostic workup. Diagnosis of TB was made based on the combined evaluation of clinical, radiological, histopathological, and laboratory features of the patients following the protocol established by the National Tuberculosis and Leprosy Prevention and Control Program [12]. X-ray films were analyzed for the radiological features of TB and were interpreted by a consultant radiologist.

Blood collection and screening for HIV

After informed consent and appropriate pretest counseling, about 5 mL of venous blood was collected aseptically from each patient. The screening of HIV antibodies was done using the Enzyme-Linked ImmunoSorbent Assay (ELISA) (HIV1/2: Vironostika HIV Uni-Form II Ag/Ab fourth-generation ELISA, Bio-Merieux, Boxtel, Netherlands. Patients were informed of the results of the HIV test after appropriate post-test counseling.

Data and laboratory quality control

Socio-demographic data quality was maintained using translated questionnaires from English to the Amharic language. Pre-testing of the questionnaire was done before data collection for completeness and appropriateness. The collected data were checked daily for consistency and accuracy. Investigators also followed standard data collection processes. Five percent of the prepared Lowenstein-Jensen (LJ) culture media was randomly selected and incubated aerobically 37°C for 48 hours to check its sterility. In addition, LJ culture media was inoculated with known strains of H37RV *Mycobacterium tuberculosis* and non-tuberculosis mycobacteria (NTM) to check its performance, and reagents for Ziehl-Neelsen microscopy, Gene Xpert MTB/RIF assay, and HIV test were checked. All variables of the study were initially tested for association with MTB and HIV co-infection using the binary logistic regression model. Those which showed statistically significant association with MTB and HIV co-infection were put into the multivariable analysis model to check if the association existed after controlling against all the rest of the variables.

Data entry and analysis

Data was entered into Epidemiological Information (EPI-Info) version-7 to check data completeness and data clearance, then transferred to SPSS version 20 for analysis. The characteristics of the study populations were summarized using frequencies, mean, and standard deviation. Binary logistic regression was used to determine the strength of the association between variables. Moreover, the adjusted odds ratio was computed using multivariate logistic regression for variables with p-value < 0.2 to control the effect of confounding variables. p-value < 0.05 was considered statistically significant at 95% confidence interval.

RESULTS AND DISCUSSION

Socio-demographic characteristics

A total of 424 patients were enrolled in this study. The proportion of the presumptive TB cases was 85.6% (n = 363) and that of asthmatic cases 14.4 % (n = 61). The majority of the cases (55.4%) were male and rural dwellers (53.7%). Data on the age distribution showed that 21.5% of the cases were between 41 - 50 years of age, and 67.7% were married. Farmers accounted for 42.9% by occupation followed by housewives (22.9%) and the majority were illiterate (51.4%) by education followed by primary school (21%) (Table 1).

Pulmonary tuberculosis symptoms and risk factors among study participants

Data of the present study showed that almost 93% of the presumptive TB cases and asthmatic patients had a cough for more than 2 weeks, 82.3% had weight loss, and 83.7% had night sweating. History of the study subjects revealed that 82.1% were new cases, and 17.9% of them were previously treated for TB. The majority of the presumptive TB cases and asthmatic patients (78.8%) had no close contact with TB patients, and two patients were currently smoking.

Prevalence of malnutrition

In this study, the overall prevalence of malnutrition was 30% (Table 2). The proportion of severely malnourished patients was 7.3%. The prevalence of malnutrition among culture-positive TB patients was 26.7%. Malnutrition may predispose people to the development of the clinical disease, and tuberculosis can contribute to malnutrition [13]. In the current study, the prevalence of malnutrition among HIV positive cases was 43.5%. Human immunodeficiency virus infection results in functionally defective metabolic ability at the individual level to absorb, store, and utilize nutrients thus resulting in nutrient deficiencies, compromised immunity, and increased risk of acquiring infectious diseases [14]. The overall prevalence of malnutrition among asthmatic patients was 19.7%, but 9.8% of them were severely malnourished.

Clinical findings of pulmonary tuberculosis and asthmatic patients

Radiological examination of presumptive tuberculosis and asthmatic patients showed that 255 (60.1%) had normal chest X-ray findings. On the other hand, among the presumptive TB cases, chest X-ray suspects of pneumonia and COPD cases were 14.6% and 10.1%, respectively. Moreover, the chest X-ray examination showed that 8.1% of presumptive tuberculosis and asthmatic patients had pulmonary tuberculosis findings. Data on the duration of asthma showed that 26.2% had had the disease for 2 years, 19.7% for 6 - 10 years, and 49.2% for more than 11 years. On the other hand, 41% and 39.4% of the asthmatic patients had mild intermittent and moderate persistent asthma, respectively, but the other 9.8% had severe persistent asthma. The history of tuberculosis treatment among asthmatic patients showed that 34.4% had previously had tuberculosis treatment. Data also showed that 95% of the asthmatic patients took treatment for asthma and the types of asthma medication taken were inhaled SABA (59%), inhaled SABA and LABA (3.3%), inhaled SABA plus LABA plus Prednisolone (13%), and inhaled SABA plus corticosteroid (19.7%) but the other 5% were not on any form of asthmatic medication.

Co-morbidity factors among presumptive TB cases and asthmatic patients

In this study, a total of 48 (11.3%) study subjects had co-morbidity factors. The major comorbidity factors observed were HIV/AIDS (5.4%) followed by hypertension (3.8%) and diabetes mellitus (0.94%). The major co-morbidity factor among presumptive TB cases was HIV/AIDS (5.5%) followed by hypertension (1.1%), but that of the asthmatic patients was hypertension (19.7%) followed by HIV/AIDS (4.9%) and diabetes mellitus (4.9%) (Table 3).

Prevalence of *Mycobacterium tuberculosis* and HIV infection

The overall prevalence of MTB infection was 3.86%, 4.1% among suspected new tuberculosis cases and 3.95% among retreatment cases. The prevalence of MTB infection among the presumptive TB cases was 4.4%, but the culture result showed none of the asthmatic patients had MTB infection. Previously, a 6% prevalence of culture-confirmed MBT infection, 3.6% among new and 2.4% among retreatment cases were reported in Gondar [15]. The proportion of smear-positive PTB infection was 1.93%, 2.01% and 1.32% among presumptive TB cases, new, and retreatment cases, respectively. Data also showed that the proportion of Gen-Xpert and culture-positive TB cases was 3.58% and 3.86%, respectively, among presumptive TB cases. In this study, only one patient had Isoniazid and Rifampicin resistant MTB isolates and two HIV negative patients had non-tuberculosis mycobacteria.

The overall prevalence of HIV infection was 5.4%; among them, 5.2% were the presumptive TB cases, and 6.6% were asthmatic patients. The proportion of MTB infection among HIV positive patients was 12.5%. In a cross-sectional study, Belay M et al. previously reported a significantly higher proportion (40.4%) of TB-HIV co-infection in the pastoralist area of northeast Ethiopia [16]. On the other hand, Fekadu et al. reported a proportion of 18.2% TB-HIV co-infection in the southern parts of Ethiopia [17]. Recently, a study report based on a systematic review and meta-analysis documented the pooled prevalence of TB-HIV co-infection in Ethiopia as 25.59% [18]. Moreover, studies also suggested an increased incidence of asthma among HIV seropositive individuals receiving treatment with HAART [19,20]. HIV infection alone appears to be related to dyspnea, and a few small studies have tried to explain this asso-

Table 1. Socio-demographic characteristics of presumptive tuberculosis cases and asthmatic patients at the University of Gondar hospital, Northwest Ethiopia, October 2018 - June 2019.

Characteristics of patients		Frequency (No.)	Percent (%)
Gender	male	235	55.4
	female	189	44.6
Residence	urban	196	46.3
	rural	228	53.7
Age	≤ 20	33	7.8
	21 - 30	85	20.0
	31 - 40	84	19.8
	41 - 50	91	21.5
	51 - 60	78	18.4
	+60	53	12.5
Marital status	married	287	67.7
	single	82	19.3
	divorced	23	5.4
	widowed	32	7.5
Occupation	day laborer	32	7.5
	farmer	182	42.9
	government employee	36	8.5
	house wives	97	22.9
	students	23	5.4
	teachers	39	9.2
	others	15	3.5
Educational status	degree	37	8.7
	diploma	26	6.1
	secondary	54	12.7
	primary	89	21.0
	illiterate	218	51.4

Table 2. Prevalence of malnutrition among presumptive tuberculosis cases and asthmatic patients at University of Gondar hospital, Northwest Ethiopia, October 2018 - June 2019.

BMI	All participants n (%)	Presumptive TB cases n (%)	Asthmatic patients n (%)	Culture +ve patients n (%)	HIV +ve patients n (%)
Normal	297 (70.04)	248 (68.3)	49 (80.4)	11 (73.3)	13 (56.5)
Mild malnutrition	65 (15.3)	60 (16.5)	5 (8.2)	---	3 (13.0)
Moderate malnutrition	31 (7.3)	30 (8.3)	1 (1.6)	4 (26.7)	3 (13.0)
Severe malnutrition	31 (7.3)	25 (6.9)	6 (9.8)	---	4 (17.4)
Total	424 (100)	363 (85.6)	61 (14.4)	15 (3.54)	23 (5.4)

ciation [21]. Respiratory co-morbidities are found to be 5 times more prevalent in asthma than in non-asthma patients [22].

Multivariate regression analysis

Multivariate logistic regression analysis showed a statistically significant association between culture-positive MTB infection with that of the marital status of the

Table 3. Co-morbidity factors among presumptive TB cases (n = 363) and asthmatic patients (n = 61) at the University of Gondar Hospital, Northwest Ethiopia; October 2018 - June 2019.

Co-morbidity factor	Presumptive TB cases n (%)	Asthmatic patients n (%)	Total n (%)
HIV/AIDS	20 (5.5)	3 (4.9)	23 (47.9)
Hypertension	4 (1.1)	12 (19.7)	16 (33.3)
Diabetes mellitus	1 (0.27)	3 (4.9)	4 (8.3)
RA	1 (0.27)	--	1 (2.1)
Cardiac disease	--	2 (3.3)	2 (4.2)
COPD	--	1 (1.6)	1 (2.1)
LDS	--	1 (1.6)	1 (2.1)
Total	26 (7.2)	22 (36.1)	48 (11.3)

HIV - human immunodeficiency virus, AIDS - acquired immunodeficiency syndrome, RA - Rheumatoid Arthritis, COPD - Chronic Obstructive Pulmonary disease, LDS - Lumbar Degenerative Spondylosis.

study subjects (p = 0.001). Married patients had an almost 3-times higher risk (95% CI = 1.46 - 9.94) to acquire MTB infection than either single or divorced ones. However, no statistically significant association between culture-positive MTB infection with the nutritional status, HIV status, previous history of tuberculosis infection, tuberculosis close contact, and clinical symptoms such as cough, weight loss, night sweats, and bronchial asthma. Pulmonary tuberculosis distribution by marital status was previously reported in Denmark indicating that married patients had the lowest incidence for all age groups. The rates were twice as high among single and widowed men, and four times higher among divorced men [23]. In South Africa, Herrera Rodriguez FA and Agbo SO reported that single marital status was strongly associated with an increased risk of PTB among HIV positive patients [24].

Multivariate logistic regression analysis was also computed by taking the HIV status of the study subjects as a dependent variable but all the socio-demographic characteristics, clinical parameters, co-morbidity factors, asthma, and culture-positive MTB infection as independent variables. Data showed a statistically significant association between HIV infection with that of occupation (p = 0.001) and previous history of tuberculosis infection (p = 000). In a study conducted in India, socio-demographic variables significantly associated with having HIV among women were marital status and certain occupations [25]. Also reported was that women with less economic opportunities are more vulnerable to HIV [26].

CONCLUSION

The overall prevalence of MTB infection was 3.86%, and that of TB-HIV co-infection was 12.5%. The prevalence of HIV among asthmatic patients was higher than the presumptive TB cases. Marital status of the study subjects significantly associated with culture-positive MTB infection. Occupation and previous history of tuberculosis infection had a statistically significant association with HIV infection.

Limitations

The limitation of this study was the number of asthmatic cases was smaller than the presumptive TB cases. Moreover, because of budget and lack of facility, we were unable to perform molecular analysis for further investigation of results.

Ethics Approval and Consent to Participate:

Ethical approval was obtained from the University of Gondar ethical review board through a letter numbered O/V/P/RCS/05/477/2016. Permission and support letters were obtained from the College of Medicine and Health Sciences hospital director's office and then permission was also obtained from each participant. The purpose and importance of the study were explained to each study participant. To ensure confidentiality, participant's information, anonymous typing was applied whereby the name of the participant and any identifier of participants were not written on the questionnaire, and during the interview to keep the privacy, they were interviewed alone. All data was collected after full verbal consent was obtained from study participates. The study participants were informed of any positive findings. Positive patients for TB and/or HIV were treated by the Hospital at the DOTS clinic. A chest X-ray examination was done as part of the clinical investigation for the patient but not for the research purposes.

Availability of Data and Materials:

Data were registered on Microsoft excel spreadsheet and the datasets are available from the corresponding

author but will not be shared to ensure patient's confidentiality.

Declaration of Interest:
We declare that we have no competing interests.

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Funding is not applicable because we have not received any funds for this study.

Authors' Contributions:
BG: Designed the study, involved in data collection, data analysis, and interpretations. He also was involved in the draft preparation and write-up of the manuscript. AT: Data analysis, interpretation, manuscript write-up and review. TT and ZT: involved in the proposal writing and examined radiological images. WH: also involved in the proposal writing and designed the investigations among the asthmatic patients. EM: involved in proposal design, and data analysis. TS: participated in patient recruitment, laboratory investigation, and data analysis. WS: participated in data analysis and interpretation of results. All authors commented and approved the final manuscript prior to submission for publication.

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