Research article

Glycemic status among newly diagnosed tuberculosis patients and their treatment outcomes- A prospective cohort study

Hithaish Kumar R. N.[1], Chythra R. Rao[1], Reshma Kumarchandra[2], Ravindra Maradi[3], Chidananda Sanju S. V.[4]

[1]Department of Community Medicine, [3]Department of Biochemistry, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India
[2]Department of Biochemistry, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India
[4]District Tuberculosis Office, Ajjarkad, Udupi, Karnataka, India

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Corresponding author: **Chythra R. Rao.** Email: chythra.raj@manipal.edu

ABSTRACT

Introduction and Aim: Tuberculosis is a serious systemic infection, which is a serious threat for developing countries including India. To address the disease burden, India has rolled out National Tuberculosis Elimination Program (NTEP) incorporating daily drug regimen with appropriate weight bands for treatment. Monitoring treatment outcomes for daily drug regimen with one-year post-treatment follow-up was the objective of the study.

Materials and Methods: A prospective community-based cohort study was conducted between January 2020 and September 2021, in Udupi district. Patients were recruited from 62 different Primary health centres. Their baseline data was collected, glycaemic status was assessed using glycated hemoglobin. The patients were followed up till their treatment completion and one-year post-treatment follow-up was also done.

Results: One hundred and two patients were diagnosed with tuberculosis during the 1st quarter of 2020 (Jan-Mar 2020) and started on daily drug regimen treatment. Favourable outcomes were noted among 107(95.1%), while unfavourable outcomes were noted among 5(4.9%). Females in younger age group and free from comorbidities had favourable outcomes. Older age groups, prediabetics, patients with lower BMI, and pulmonary tuberculosis had unfavourable outcomes.

Conclusion: The daily drug regimen for tuberculosis was found to be effective in terms of reducing the treatment failure rates. Evaluation of glycaemic status using Glycosylated hemoglobin at the time of diagnosis of tuberculosis is desirable. So that, life style modification could be suggested to avoid progression of prediabetes to diabetes. Screening for diabetes using Glycosylated hemoglobin at treatment initiation is advocated to avoid unfavourable outcomes during TB treatment.

Keywords: Prediabetes; glycosylated hemoglobin; NTEP; tuberculosis; unfavourable outcomes; cohort.

INTRODUCTION

Tuberculosis (TB) is a serious systemic and communicable disease that contributes to increased morbidity and mortality rates around the world. Globally, TB infection remains one of the leading causes of death, with a death rate that appears to be double that of human immunodeficiency virus (HIV) infection. In 2020, nearly 10 million people developed tuberculosis, out of which about 1.3 million deaths and an additional 2.14 lakh deaths due to HIV coinfection have been reported (1). In India, according to the central TB report 2021, the treatment success rate is 82% (2). Diabetes is a chronic, metabolic disorder represented by increased blood glucose levels. By the end of 2030, diabetes is expected to cross 550 million, with 88 million individuals located in the Southeast Asian region (3). Comorbidities like diabetes are known to have a detrimental impact on tuberculosis treatment (4). The association between TB and diabetes is not based on a single mechanism, but immunocompromised individuals are at higher risk for infections such as tuberculosis. This is due to the increased inflammatory response to TB bacilli, and secretion of cytokines that could result in development of insulin resistance (4,5). Increased blood sugar among people with active tuberculosis are linked with increased unfavourable outcomes including leucocytosis and higher bacterial load in the sputum and formation of cavities in lungs (5,6). Phagocytic action is improved when individuals have their glucose levels under control (4). Evidence suggests that optimum glucose levels and management of diabetes decrease the risk of developing tuberculosis and it improves therapeutic outcomes (7). India is facing double burden of tuberculosis and diabetes. Hence the current study was planned to determine the treatment outcomes of patients registered for treatment under National Tuberculosis Elimination Program (NTEP), to determine the glycaemic status of the participants using glycosylated hemoglobin measurement, and to determine the recurrence of

tuberculosis after treatment completion and at one year follow up period.

MATERIALS AND METHODS

A prospective community-based cohort study was carried out in Udupi district. Udupi situated in coastal Karnataka is well known for its higher literacy status of 86.3% and good health indices. Udupi district has six TB units with 62 Primary Health Centres (PHC) and 6 Community Health Centres (CHC). One TB unit represents at sub-district level covers 5-lakh population. Institutional ethical committee clearance was obtained (IEC: 622/2019). Official written permission letters were obtained from the District Tuberculosis Control Officer (DTO) and Joint Director for Tuberculosis, Karnataka state. Written informed consent was obtained from all the participants prior to data collection.

Inclusion criteria

Permanent residents of the Udupi district, all the registered patients under the Government sector, both paediatric and adult patients of either gender and patients who were available for the follow-up were included.

Exclusion criteria

The transferred-out, patients who refused to consent for interview and investigations, and patients who were on drug-resistant regimen and outside district patients were not recruited.

Sample size

All tuberculosis patients registered for treatment as new cases during the first quarter of 2020(Jan -March 2020) in Udupi district were enrolled for the study. Diagnosis of pulmonary tuberculosis was microbiologically done by sputum smear or cartridge-based nucleic acid amplification test (CBNAAT) or GeneXpert or by culture, or chest X-ray. Extrapulmonary cases were confirmed via Biopsy or Fine Needle Aspiration Cytology **(**FNAC) or Magnetic resonance imaging (MRI) in addition clinically diagnosed patients for whom treatment was initiated from January 2020 to March 2020 in the government sector were also included in the study and were followed up post completion of their treatment till September 2021.

The study was initiated after obtaining permission from the State Joint Director for Tuberculosis and the District Tuberculosis Control Officer. Details of the patients who were registered for treatment were collected from the District Tuberculosis office, Udupi, following which the patients were contacted and interviewed either in their houses or in nearby Primary Health Centre. Patients were interviewed using a pre-designed questionnaire related to the mode of diagnosis of tuberculosis, history of tuberculosis, or presence of any comorbidities. Blood samples were collected for glycosylated hemoglobin (HbA1c) estimation during their first contact that is within 15 days of treatment initiation and at end of treatment to check their glycaemic status. Smear status was recorded by the end of two months of intensive phase and at treatment completion.

Treatment outcomes were classified as favourable (success) or unfavourable (failure) as per NTEP guidelines. Patients who were either cured or completed their treatment were included for success rate calculation. Loss to follow-up, treatment failure, drug resistance, and death are unfavourable outcomes and were considered as treatment failure. The definitions of the outcome variables are mentioned below (8).

Operational definitions according to National Tuberculosis Elimination Program (NTEP; 8)

New: The patient has never received tuberculosis treatment or been exposed to antituberculosis drugs for less than one month.

Recurrent: Previously declared as cured or treatment completed and subsequently found to be microbiologically or clinically positive for TB.

Treatment after failure: If the biological specimen is positive by smear or culture by the end of the treatment, treatment is considered a failure.

Treatment after loss to follow-up: A person who has been on treatment for one to two months and then missed treatment, declared as loss to follow up and subsequently found to be positive.

Treatment outcome

Cured: Microbiologically confirmed at the beginning of treatment and smear or culture-negative by the end of treatment.

Treatment completed: One who has completed the full course of treatment but has no negative biological sample in last 30 days.

Treatment failure: The biological specimen is positive either by smear or culture at the end of successful completion of treatment.

Loss to follow up: Interruption of the treatment for a month or more.

Not evaluated: Treatment outcome is not assigned due to the transfer out of the patient.

Regimen changed: The patient develops resistance to any first-line drugs during the treatment and put on second line treatment and

Death

Statistical analysis

Data were entered in MS Excel and analysed using Statistical Package for Social Sciences (SPSS) ver.15.

Variables such as age, gender, site of disease, comorbidities, and treatment outcomes are represented as frequencies and percentages. Categorical variables were analysed using chi-square test. P-value ≤ 0.05 was considered to be statistically significant.

RESULTS

A total of 102 patients were diagnosed with tuberculosis were recruited for the study. Among 102 participants 71(69.6%) were diagnosed with pulmonary tuberculosis and the remaining 31(30.4%) were diagnosed with extrapulmonary tuberculosis. Among 31 extrapulmonary cases, pleural effusion was seen in 13(12.7%) patients. Other categories included lymph node involvement 10(9.8%), abdominal tuberculosis 2(2.0%), TB meningitis 1(1.0%) , spinal tuberculosis 2(2.0%), and remaining three were diagnosed with skin, ocular and renal tuberculosis respectively.

Among 102 patients, 14(13.7%) patients had a history of diabetes and were on treatment. The remaining 88(86.3%) non-diabetic patients were screened for HbA1c levels, 18(17.6%) patients were found to be in the pre-diabetic range and the remaining 70(68.6%) were within normal limits. All the known diabetic patients were on oral hypoglycemic drugs. Baseline socio-demographic details of the study participants are depicted in Table 1. One third of patients had normal BMI.

All the patients were followed up till their treatment completion. Among 102 patients 3(2.9%) developed drug resistance for Isoniazid and isoniazid was replaced by levofloxacin and duration of treatment was extended to nine months and sputum negativity were documented at nine months. Among 71 pulmonary TB patients, 11(15.4%) of patients were found sputum positive by the end of two months of intensive phase treatment. Patients were monitored during their treatment telephonically due to COVID-19 restrictions, and by the end of treatment, HbA1c was estimated again. Patients with diabetes were in optimum glycemic control, and among 18 prediabetic patients, three people had developed diabetes (16.7%). Clinical details and treatment outcomes of the patients are depicted in Table 2. Only a quarter of the patients had pre-existing co-morbidities. Majority of the patients belonged to below poverty line category. Among 102 patients, favorable outcome was noted in 107(95.1%) and unfavorable outcome among 5(4.9%) patients.

Association of treatment outcomes with clinical, sociodemographic, and glycemic status of the patients are depicted in Table 3. Patients were followed up subsequently for another year. Among 102 patients, a 12 years old female pediatric patient without any comorbidities was found to have relapse and was started on Drug sensitive TB regimen.

Table 1: Socio-demographic details of the study participants (n=102)

Characteristics	Frequency (n)	Percentage (%)
Age(years)		
<30	25	24.5
31-45	29	28.4
46-60	26	25.5
>60	22	21.6
Gender		
Male	63	61.8
Female	39	38.2
Socioeconomic status		
Above poverty line (APL)	05	04.9
Above poverty line (BPL)	97	95.1
Body Mass Index (BMI) Kg/m^2		
Underweight (<18.5)	61	59.8
Normal (18.5-24.9)	35	34.3
Overweight or Obese (≥25.0)	06	05.9
Current tobacco use		
Yes	54	52.9
No	48	47.1
Current alcohol use		
Yes	48	47.1
No	54	52.9

Table 2: Clinical characteristics and treatment outcomes of the study participants (n=102)

Characteristics	Frequency (n)	Percentage (%)
Type of tuberculosis		
Pulmonary	71	69.6
Extrapulmonary	31	30.4
Mode of diagnosis		
Microbiology	71	70.5
Pathology	21	20.5
FNAC*	10	9.0
History of TB contact		
Yes	10	9.8
No	92	90.2
Comorbidities		
Present	24	23.5
Absent	78	76.5
Treatment outcomes		
Cured	65	63.7
Treatment Completed	32	31.4
Death	05	4.9
Treatment Failure	-	-

*FNAC- Fine Needle Aspiration Cytology

Table 3: Association of treatment outcomes with demographic, clinical and glycaemic status of the study participants (n=102)

Characteristics		Cured n=65	Treatment completed n=32	Death n=5	P value*
Age group (yrs.)	<30	16(24.6)	08(25.8)	01(20.0)	0.214
	31-45	18(27.7)	11(35.5)	-	
	46-60	20(30.8)	05(12.9)	01(20.0)	
	>60	11(16.9)	08(25.8)	03(60.0)	
Gender	Male	43(66.2)	16(50)	04(80.0)	**<0.001**
	Female	22(33.8)	16(50)	01(20.0)	
Type of TB	Pulmonary	65(100)	01(3.2)	05(100)	**<0.001**
	Extrapulmonary	-	31(96.8)	-	
BMI	Underweight (<18.5)	45(69.2)	16(51.6)	05(100)	**<0.001**
	Normal (18.5-24.9)	18(27.7)	12(35.5)	-	
	Overweight or Obese (≥25.0)	02(3.1)	04(12.9)	-	
Glycosylated hemoglobin	Normal (<5.7%)	43(66.1)	26(81.3)	-	**0.001**
	Pre-diabetic (5.7-6.4%)	09(13.8)	06(18.7)	04(80.0)	
	Diabetic (>6.4%)	13(20.1)	-	01(20.0)	

*****Chi-square test

DISCUSSION

The effective management of tuberculosis along with associated comorbidities is essential for the National Program (NTEP) to achieve stated goal of treatment success rate and move towards elimination of tuberculosis by declining the burden of tuberculosis mortality and morbidity. Diabetes is one of the second leading causes of tuberculosis treatment failure, relapse, and death (5). Although the bidirectional screening for TB and diabetes has been recommended, it is being done by random blood sugar estimation only. The World Diabetes Foundation (WDF) and The International Union Against Tuberculosis and Lung Disease (Union) insisted on the dual management of TB and DM (9,10).

The majority of the diagnosed tuberculosis cases in the present study were males, this finding was consistent with the findings of studies by Vijay *et al.,* in Bangalore (11), Chennaveerappa *et al.,* in Hassan (12), Laux *et al.,* in Chhattisgarh (13), Tola *et al.,* in eastern Ethiopia (14), and Abebe *et al.,* in Ethiopia (15). The reason for the higher TB incidence in males may be due to increased exposure to infections in comparison to females and better health seeking behaviour among males.

Patients diagnosed with TB ranged in age from 10-90 years, with most patients being in the age group of 20-60 years. These findings were consistent with those of Bisoi *et al.,* (16), and Gurupreet *et al.,* (17). Tuberculosis disease affects all ages, but it is more prevalent in the economically productive age group in developing countries, affecting the country's socioeconomic growth (1,2).

There were 31(30.4%) extrapulmonary cases, which accounted for more than one-third of the cases reported for treatment. These findings were similar to those of Tola *et al.,* in Ethiopia (14). In the current study diabetes mellitus among the diagnosed TB patients was 14 (13.7%). Proportion was lower than earlier studies which ranged from 18% and 38.5% (17-21), it could be attributed to study settings and smaller sample size. Desai *et al.,* included the patients who were hospitalized for TB treatment with known history of diabetes (18).

The overall favourable treatment outcome of the registered TB patients in the current study was 107(95.1%), which is higher than the studies reported from Bangalore by Vijay *et al.,* (65.7%)(11), Tamilnadu by Thomas *et al.,* (75%)(22). In contrast, results are lower in comparison to the study by Desai A et al (96.3%)(18), which was a hospital-based study. The higher favourable outcome in the current study can be attributed to the regular follow up of the patients by health care workers and Accredited Social Health Activist (ASHA) workers who worked as Directly Observed Treatment Short-course (DOTS) providers.

Deaths due to Tuberculosis in the current study was 5(4.9%), which was lower than the study findings by Parida *et al.,* (10.7%) (23), which was a retrospective record-based study. The results of studies conducted in Ethiopia by Tola *et al.,* (3.9 %) (14), Abebe *et al.,* reported (4.8%) (15), and Desai *et al.,* (3.4%) (18)

which were also significantly lower. Two studies which reported lower death rates are retrospective studies (14,15).

Association between gender, type of tuberculosis, Body Mass Index (BMI), and optimum glycaemic control were identified as factors associated with unfavourable outcome among diagnosed tuberculosis cases. Studies by Kornfeld *et al.,* (24), and Bhargava *et al.,* (25) also reported that low BMI was associated with unfavourable treatment outcomes. Study by Mukhtar *et al.,* (21) glycaemic control was associated with unfavourable treatment outcomes. Tola *et al.*, (14) reported that gender, and pre-treatment weight gain was significantly associated with treatment outcomes.

Inability to contact patients initiated on treatment in private hospitals was a major limitation of the study. Due to COVID-19 restrictions for travel, personal visits for follow up could not be done, but telephonic contact was done and necessary details were obtained.

CONCLUSION

The newer daily drug regimen for tuberculosis is effective in terms of reducing the treatment failure rates. Screening for pre-diabetes among tuberculosis patient needs to be initiated at time of tuberculosis diagnosis. Counselling needs to be offered for life style modifications to avoid progression to diabetes among these individuals. Screening for diabetes using glycosylated hemoglobin in the community setting at tuberculosis treatment initiation is ideal for early detection and appropriate management.

CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

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