Microbiological Pattern of Secondary Infections, Standard Living Index and Pharmacoeconomic Analysis Among Tuberculosis Patients With Comorbidity

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Abstract:Aim: The aim of the present study is to determine the clinical, microbiological pattern of secondary infections and cost of illness for the tuberculosis subjects with and without hypertension. Method: The present study design is a cross-sectional observational prospective during January and December 2018 in a tertiary care teaching hospital located in Uttar Pradesh, India. Totally 68 patients were enrolled in the study. The subjects were divided into 2 groups: group I with TB only and group II with TB and hypertension. The data were collected from prescription and/ or interview with the subjects and Standard of Living Index was also estimated for the subjects. For all the subjects were subjected to either by Mantoux tuberculin skin test or sputum smear or both tests. Results: 27 subjects were having TB and hypertension in stage III (77.42%). 8% and 14% of subjects were having PTB and Extra PTB in group I and II respectively. 36% of subjects having S. aureus as secondary pathogens. 17 isolates carrying pathogens shown resistance to 14 various antibiotics in susceptibility and resistance test. Direct medical costs of group I was INR 5,6668.88 and group II was INR 11,677.08, which was high in both the groups when compared to indirect costs of both the groups; group I was INR 902.41 and in group II was INR 1012.68. Nearly 58.9% and 41.1% of subjects from the group I and group II, respectively, were lost their income during the treatment days. Conclusions: The present study concludes the following based on the findings, prevalence of TB is high in increased age, rural residents and unemployed in lower economic populations. Pulmonary TB cases are more than extrapulmonary TB and S. aureus was the most common secondary infection pathogen in isolates. Total medical cost and direct medical costs were higher in group II, whereas in the group I total medical cost was high. In both groups, a maximum number of subjects were on the medium scale of SLI. Treatment outcome was good in both groups around 70% in group I and 68% in group II among successfully completed subjects, which is as per the WHO standards.

Keywords: Secondary Infection Pathogens, Tuberculosis, Direct Medical Cost, Indirect Medical Cost, Standard Living Index

1. Introduction:

Tuberculosis is an infectious disease, causative organism bacillus Mycobacterium tuberculosis (MTB) which is a part of a complex of organisms including M. bovis (reservoir cattle) and M. africanum (reservoir human). It typically affects the lungs (pulmonary TB) but can also affect other sites (extra pulmonary TB)[1]. MTB is an obligate, pathogenic, rod-shaped and non-motile organism belonging to the family Mycobacteriaceace. It is an aerobic organism; this bacterium requires oxygen to grow and divides every 15-20 hours. It is a treatable, communicable disease has two phases – latent infection and active disease[2]. Tuberculosis is a chronic granulomatous infectious disease. Infection occurs via aerosol, and inhalation of a few droplets containing M. tuberculosis bacilli. After infection, M. tuberculosis pathogenesis occurs in two stages. The first stage is an asymptomatic state that can persist for many years in the host, called latent TB. When the immune system is weak, the bacteria begin replicating and cause characteristic symptoms such as cough, chest pain, fatigue and unexplained weight loss. If left untreated, the disease eventually culminates in death[3,4].

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TB is the 9th leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people[5]. An estimated 10.4 million people fell ill with TB in 2016: 90% were adults, 65% were male, 10% were people living with HIV (74% in Africa) and 56% were in five countries: India, Indonesia, China, the Philippines and Pakistan. Globally, the TB mortality rate is falling at about 3% per year. TB incidence is falling at about 2% per year[6]. According to the recent studies, the WHO TB statistics for India for 2016 give an estimated incidence figure of 2.79 million cases of TB for India. The incidence of TB has reduced from 289 per lakh per year in 2000 to 217 per lakh per year in 2015 and the mortality due to TB has reduced from 56 per lakh per year in 2000 to 36 per lakh per year in 2015. The report highlighted that underreporting and under diagnosis of TB cases continue to be a challenge, especially in countries with large unregulated private sectors and weak health systems, including India. India has highest burden of both TB and MDR TB based on estimates reported in Global TB Report 2016. An estimated 1.3 lakh incident multi-drug resistant TB patients emerge annually in India which includes 79000 MDR-TB Patients estimates among notified pulmonary cases. India bears second highest number of estimated HIV associated TB in the world. An estimated 1.1 lakh HIV associated TB occurred in 2015 and 37,000 estimated number of patients died among them[7,8]. The aim of the present study is to determine the clinical, microbiological characteristics and cost of illness for the tuberculosis patients with and without hypertension in a tertiary care teaching hospital in India.

2. Methods

2.1. Study Setting

The study was carried out at the Department of Tuberculosis and Respiratory Diseases in a tertiary care teaching medical college hospital located at Kanpur, Uttar Pradesh. About 320 subjects every month with TB including MDR TB visits the hospital. The present study was conducted under single physician and single centre study. Approximately for every 4 subjects 1 subject was selected for our study. Total sample size was 90 subjects having TB with and without hypertension. The selected subjects were registered between the months of January and December 2017 and successfully completed treatment for TB. The study was designed as cross-sectional observational prospective.

2.2. Ethics

The present study protocol was approved by the institutional ethics committee, Kanpur India. From all the selected study subjects informed consent, in written and oral was obtained.

2.3. Study Population

New and relapsed subjects with TB of both genders, visiting to the hospital for treatment with and without hypertension were considered as an eligible for the study. The study subjects were divided into two groups. The subjects with TB only were designated as Group I and subjects with TB and hypertension were designated as Group II.

2.3.1 Data Collection Tools

A pretested and semi-structured questionnaire was used to collect demographic, laboratory and socioeconomic parameters of patients. In the data collection tool included information on expenditure for the consultation fees, investigations, medicines, travel for escort, and patient before and during treatment. Consecutive all eligible patient was invited to participate in the study. The enrolment rate was 90.67% (68/75). Data collection and interview was conducted in closed room. Since this present study was conducted in the public health facility, subjects have paid registration fee which is considered as physician consultation fee and separately diagnostic fee was collected as laboratory tests and radiography. TB subjects treated with standardised treatment following the RNTCP guideline recommendations for directly observed treatments (DOTs)[9]. All the subjects were on a hospital-based DOT strategy where subjects were observed while taking their pills at the hospital. During the study period, few subjects were treated as out-patient DOT[10]. As per the RNTCP, diagnosis is primarily by sputum test, treatment is DOTs with 3 standardized regimens and recording at uniform interval and system of reporting is used. Diagnosis and treatment are at low cost to the patients.

2.3.2. Selection and Identificationof Isolates

Microorganism isolates were obtained from the TB Patients visited and admitted in hospital for the tuberculosis treatment. The isolates were collected based on their clinical finding and upon recommendation of the physician's. The isolates were collected from the patients with following complaints like fever for 15 days, cough and general body pain. Microorganism isolates were identified by using agar plate diffusion method. Gram positive cocci Staphylococcus aureus used as reference strain and gram negative bacilli Pseudomonas aeruginosa used as control[11].

2.3.3. Cost Calculation

Costs were calculated at two points one was at pre-diagnosis i.e. subjects were affected with TB based on symptoms and second was at post-diagnosis i.e. subjects were affected and confirmed as TB by confirmatory laboratory tests. Direct costs were computed as the sum of the subject perspective costs like physician consultation fee, medicine cost (estimated as an average cost of the medicine which was taken as the median cost to maximum and minimum costs of medicines available in the market) and number of visits to clinic. Indirect costs were computed as the sum of travelling expenditure and loss of salary/ wages. Assuming that an average unskilled labourer in Zambia would work 21 days a month, 8 h per day, we used the monthly incomes re-ported by patients to derive an hourly wage rate.

2.3.4. Assessment of Standard of Living Index (SLI)

SLI was computed as per the definitions provided in the National Family Health Survey (NFHS-I)[12]. The following parameters were taken account into the account while computing the SLI (i) house type, (ii) facility of toilet availability and type, (iii) type of cooking fuel, (iv) drinking water source (v) availability and location of kitchen, (vi) nature house proprietorship, (vii) domestic animal(s) proprietorship and (viii) overall hygiene in the prevailing in the house. Based on the score's subjects were grouped into 3. Group I scored between 0 and 14 and designated as having low SLI; Group II scored between 15 and 24 and designated as having medium SLI and Group III scored between 25 and 67 and designated as having high SLI.

3. Results

3.1. Demographic Studies

Two groups were studied, group I with only tuberculosis subjects and group II with tuberculosis subjects having hypertension. Totally 44 (64.70%) and 24 (35.30%) of males and females, respectively were participated in the present study. 27 (65.85%) of males and 14 (34.15%) of females subjects in group I were having TB only whereas in the group II 17 (62.96%) and 10 (37.04%) males and females were having TB with HTN. The TB was highly prevalent in the age group of 31 – 40 (14; 34.15%) and 41 – 50 (15; 36.59%) were observed in the group I whereas in group II, i.e. subjects with TB and HTN, also observed at same age group between 31 – 40 (7; 25.93%) and 41 – 50 (8: 29.63%). In both the groups the place of residence was majorly from rural place (64.70%) when compared to urban (35.30%).In the present study majority of the subjects were belongs to low income (< INR 10,000) status from both the groups (31; 45.59%). The employment status majority of the subjects in both the groups were from unemployed (25; 36.76%). Most of the subjects were not hospitalized before in both the groups. In the group I 43.85%, 41.57% and 14.58% of subjects were subjected to mantoux tuberculin, sputum smear and both tests respectively whereas mantoux tuberculin, sputum smear and both tests were

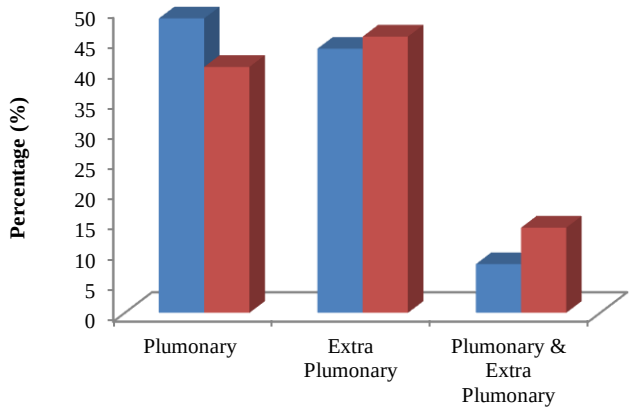
subjected to 33.33%, 44.45% and 22.22% group II respectively. The data are given in the Table No. 1.

Table No. 1: *Sociodemographic characteristics of the study subjects (n=68)*

Characteristics	Number of Subjects		Total Number of Subjects (%)
	Group I (N = 41)	Group II (N = 27)	
Gender			
Male	*27 (65.85)*	*17 (62.96)*	*44(64.70)*
Female	*14 (34.15)*	*10 (37.04)*	*24(35.30)*
Age group (Years)			
> 21– 30	*3 (7.32)*	*2 (7.41)*	*5 (7.35)*
31 – 40	*14 (34.15)*	*7 (25.93)*	*21 (30.88)*
41 – 50	*15 (36.59)*	*8 (29.63)*	*23 (33.82)*
51 – 60	*6 (14.63)*	*6 (22.22)*	*12 (17.65)*
Place of residence			
Rural	*24 (58.54)*	*20 (74.07)*	*44(64.70)*
Urban	*17 (41.46)*	*7 (25.93)*	*24(35.30)*
Education Status			
Illiterate	*8 (19.51)*	*4 (14.81)*	*12 (30.88)*
School Level	*21 (51.22)*	*15 (55.56)*	*36 (52.94)*
Graduate and above	*12 (29.27)*	*8 (29.63)*	*20 (29.41)*
Monthly Income (INR)			
< 10,000	*20 (48.78)*	*11 (40.74)*	*31 (45.59)*
10,001 to 25,000	*13 (31.71)*	*9 (33.33)*	*22 (32.35)*
>25,001	*8 (19.51)*	*7 (25.93)*	*15 (22.06)*
Employment Status			
Employed	*10 (24.39)*	*12 (44.44)*	*22 (32.35)*
Unemployed	*16 (34.03)*	*9 (33.33)*	*25 (36.76)*
Retired	*9 (21.95)*	*5 (18.53)*	*14 (20.59)*
Student	*6 (14.63)*	*1 (3.70)*	*7 (10.29)*
History of hospitalization			
Yes	*17 (41.46)*	*16 (59.26)*	*33 (48.53)*
No	*24 (58.54)*	*11 (40.74)*	*35 (51.47)*
Laboratory Tests			
Mantoux tuberculin test	*18 (43.85)*	*9 (33.33)*	*27 (39.70)*
Sputum smear test	*17 (41.57)*	*12 (44.45)*	*29 (42.65)*
Both	*6 (14.58)*	*6 (22.22)*	*12 (17.65)*

48.50%, 43.50 and 8% of subjects were affected with pulmonary, extra pulmonary and both types of TBs were affected in group I while in the group it 40.50%, 45.50% and 14% of subject were observed for pulmonary, extra pulmonary and both type of TBs. The data are represented in the Figure, Fig. No. 1.

Fig. No. 1: Distribution of Type TB Among Study Subjects



3.2. Prevalence of Isolates

Total 90 samples from both the groups with secondary infection were collected. Maximum of the isolates were S. aureus (36%), E. coli (18%), P. aeruginosa (14%), S. epidermidis (10%), M. catarahallis (10%), S. pyogenes (6%), H. influenza (4%) and K. pneumonia (2%) was found to be very minimum. The data are represented in the Table No. 2.

able No. 2:*List and Percentage of Microorganisms Identified in the Both Groups*

Name of Microorganism	Isolate from sample (%)
Staphylococcus aureus	*36*
Escherichia coli	*18*
Pseudomonas aeruginosa	*14*
Staphylococcus epidermidis	*10*
Moraxella catarahallis	*10*
Streptococcus pyogenes	*6*
Hemophilus influenza	*4*

Klebsiella pneumoniae	*2*

Table No. 3: *Susceptibility and Resistance Pattern for Various Microorganisms against Different Antibiotics*

Isolated Micro-organism	Antibiotic used	Susceptible	Resistance
S. aureus	Cefoxitine	S	
	Cefuroxime	S	
	Chloramphenicol	S	
	Co-trimoxazole	S	R (4 isolates)
	Erythromycin	S	
	Linezolid	S	
	Ofloxacin	S	
	Oxacillin	S	
	Vancomycin	S	R (4 isolates)
P. aeruginosa	Amikacin		R
	Ciprofloxacin		R
	Gentamycin	S	
	Imipenem	S	
	Ofloxacin	S	
M. catarahallis E.coli K. pneumonia	Amikacin		R
	Ampicillin		R
	Ceftriaxone	S	
	Cefuroxime	S	
	Ciprofloxacin		R
	Clavulonic acid	S	
	Gentamycin		R
	Imipenem	S	
	Ofloxacin	S	
H. influenza	Ampicillin		R
	Cefuroxime	S	
	Chrolamphenicol		R
	Ciprofloxacin		R
	Co-trimoxazole	S	
	Erythromycin	S	
	Vancomycin	S	
S.pyogenes	Clindamycin	S	
	Co-trimoxazole	S	
	Erythromycin	S	

In the present study susceptibility and resistance profile was studied for various microorganisms against different antibiotics. From the antibiogram profile it was observed that all 5 isolates of M. catarahallis are resistant for ciprofloxacin and 4 isolate among the 21 isolates of S. aureus was resistant against cotrimoxazole and vancomycin. Majority of isolates belong to gram negative were resistant against amikacin, ampicillin and ciprofloxacin. All the isolates of P. aeruginosa were resistant against amikacin andciprofloxacin. The data represented in the Table No. 3.

3.3. Cost of Treatment

The total cost for group I subjects was calculated as 6569.28 ($94) ± 5047.52 INR and for group II subjects was about 12689.76 ($182) ± 4335 INR. The total cost includes direct medical as well direct non – medical and indirect costs. Direct medical costs was found to be higher in both the groups (Group I: 5342.16 ($76) ± 5276.64 INR; Group II 10939.32 ($157) ± 3437.76 INR) when compared to direct non-medical and indirect costs among both the groups. The data are expressed as Mean ± SD and represented in the Table No. 4. All the direct and indirect costs were high for group II compared with group I. Lab and X-ray examinations costs were high in group II than group I. The data are provided in the Table No. 5.

Table No. 4: Direct medical, indirect medical and total costs incurred by the subjects

Groups	Direct Cost INR ($)		Indirect Cost INR ($)	Total Cost INR ($)
	Medical	Non-Medical		
I	5342.16 ($ 76) ±5276.64	324.72 ($ 5) ±307.88	902.41 ($ 13) ±1945.92	6569.29 ($ 94) ±5087.52
II	10939.32 ($ 157) ±3437.76	737.76 ($ 11) ±1862.76	1012.68 ($ 15) ±2325.12	12689.76 ($ 182) ±4335

Values are expressed in Mean ± SD

Table No. 5: Direct and indirect costs incurred by the subjects

	INR ($)		
Types of Costs	Group I	Group II	Total

Direct Costs			
a) Medicalcost			
Hospital visit and stay	2587.56 (36.23)	6572.16 (92.01)	9159.72 (128.24)
Consultation costs and registrationfees	168.48 (2.36)	206.16 (2.89)	374.64 (5.24)
Laboratory charges for diagnosis& treatment	2077.8 (29.09)	3692.4 (51.69)	5770.2 (80.78)
Cost of medication other than TB drugs	431.28 (6.04)	545.64 (7.64)	976.92 (13.68)
Total	5265.12 (73.72)	11016.36 (154.23)	16281.48 (227.94)
b) Non-medicalcost			
Expenditure incurred for travelling	81.00 (1.13)	101.52 (1.42)	182.52 (2.56)
Expenditure incurred for food	243.72 (3.41)	636.24 (8.91)	879.96 (12.32)
Total	324.72 (4.54)	737.76 (10.33)	1062.48 (14.88)
Indirect Costs			
Income loss to the subjects	341.28 (4.78)	392.04 (5.49)	733.32 (10.27)
income loss to thecare taker(s)	561.12 (7.86)	620.64 (8.69)	1181.76 (16.54)
Total	902.40 (12.64)	1012.68 (14.18)	1915.08 (26.81)

Values are expressed in Mean

Subjects in both the groups suffered with loss of working days during the study period, the group II (61.20%) had more loss when compared with the group I (58.90%). The data are represented in the Fig. No. 2. The group II 25%, 17%, 15% and 12% subjects spent for < 500 INR, 501 to 1000 INR, 1001 to 1500 INR and > 500 INR respectively, which is higher costs incurred for the treatment when compared with the group I. The data are represented in the Fig. No. 3.When computing the standards of living index (SLI) it was observed that the both groups were maximum in the medium scale of SLI, while comparing both the groups at medium scale of SLI, subjects with group I were more when compared with the group II.The data are represented in the Fig. No. 4. The treatment outcome was also measured in the present study and found to be significantly high, nearly 70% and 68% of subjects were successfully completed the treatment in the group I and II respectively. Around an average of 11% defaulters were observed in the treatment schedule in both the groups and remaining an average of 20% of subjects met failure in the treatment in both the groups. The data are represented in the Fig. No. 5.

Fig. No. 2: Loss of working days during study period

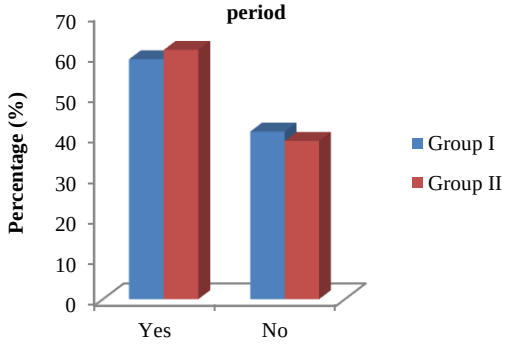


Fig. No. 3: Proportion of cost of treatment to monthly income

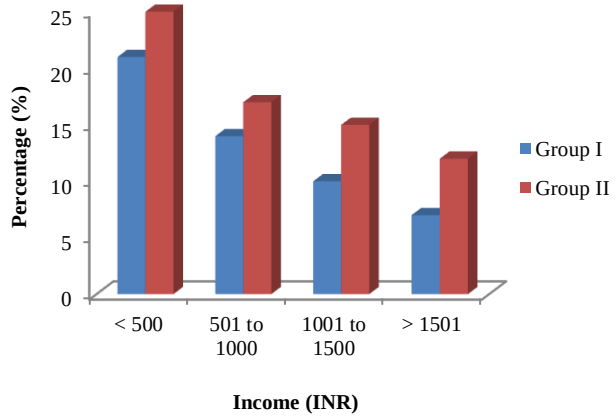


Fig. No. 4: Standard of Living Index Among the Study Subjects

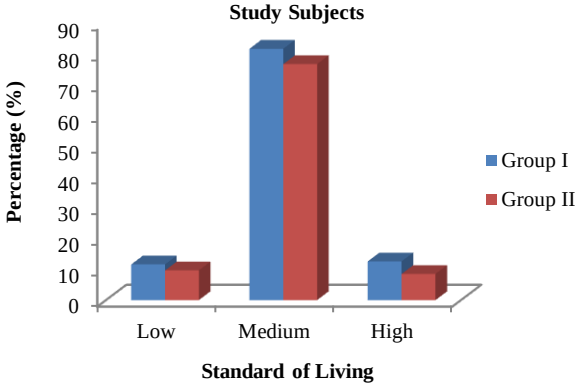
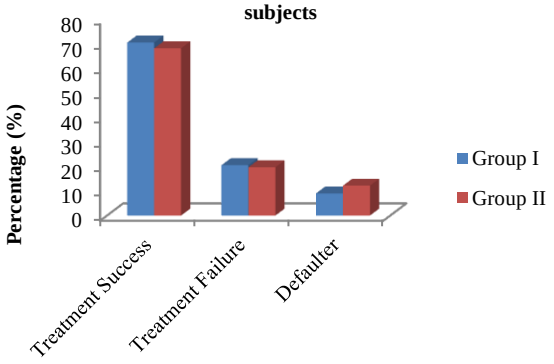


Fig. No. 5: Treatment outcome among the study subjects



4. Discussion:

Most of the males were affected then females, as smoking may be trigger factor in males. Higher the age group higher the prevalence of occurring TB and mostly affected with pulmonary TB. Many people were unemployed and were having low income economic status living in rural area, which shows low awareness of TB to the people as the cause factor for TB. Out of 90 collected sputum samples, 65 (72.22%) of subjects have shown the presence of secondary bacterial infection whereas 25 (27.78%) did not have secondary bacterial infection in both groups. The present study also revealed that 49 (75.38%) of new subjects were having secondary bacterial infection and 16 (24.62%) of subjects were belongs to the category of treatment failure and shown for the presence of secondary bacterial infection. 38 (58.465) and 27 (41.54%) of males and females respectively, were having secondary bacterial infections in pulmonary and extra pulmonary tuberculosis. From the results we observed that wereisolationfive types of secondary bacterial infectionsamong 65 patients like(i) 32 (49.23%) subjects with S. pneumoniae; (ii) 12 (18.46%) with S. pyogens; (iii) 7(10.78%) with S. aureus; (iv)7 (10.78%) with K. pneumoniaeand (v) 7 (10.78%) with E. coli.In the present study it was observed that all micro-organisms under study have shown resistance to the antibiotics like amikacin, ampicillin, co-trimoxazole, ciprofloxacin, chrolamphenicol, gentamycin[11]. The present study has computed the economic burden of TB treatment to subjects. The total cost for the subjects was INR 6569 ($94) and 12689 (182$) for the group I and II respectively in DOTS programme. The difference was found to be double in the group II subjects with hypertension. The main objective of the RNTCP is that subjects treated may lead to minimize wages losses or travel cost due to disease.Government is taking steps to set up DOTs centre in highly populated and easy accessible places and affordable to the antituberculosis agents[13]. In the present study subjects were spent travel for treatment incurred more than the medical costs. There is similar finding reported by Zwarenstein et al in 1998[14]. But Muniyandi et al in 2005 reported that the travel cost incurred for the treatment was lower when compared to other costs[15]. All the subjects were received the antituberculosis agents without any hindrances during the study and beyond the study period. Apart from the availability, in the DOTs programme subjects were provided the treatment under direct supervision of healthcare workers, which led to the achievement of more than 87% of subjects, were cured from tuberculosis[16]. In both the groups subjects were treated with DOTs, which have shown significant less indirect costs for the group I when compared to group II was around INR902 (13$) vs INR 1013 (14.18$). The absenteeism for the work was around 59% and 61% was observed among 15% of subjects and this result isnot similar to that observed in Zambia (31%)[17]. This might be possibly because of decentralized treatment services. The present confirms the treatment success rates were as mentioned by the WHO. This present study confirms that the subjects can able to attend for their work with a minimum loss on working days or wages.In this study, around 81%and 77% of the subjects participated in this study found to have medium SLI scores in the group I and II respectively. In the present study, more than one third of the monthly income was spent to treat the disease by subjects, in the low income level.Our study results are similar to the findings of M. Muniyandi et al 2005 and Kamolratanakul P et al 1999[18]. The results from the present study showed that the TB programme and measures to control the TB were effective in minimizing expenditures incurred for the treatment especially spent for travel cost met by the low income group of subjects. The SLI scores were calculated commonly for both the groups[19,20]. Limitations of the present study are the that excluded subjects who had unsuccessfully completed treatment or death due to any cause, treatment failures and subjects who are missed to follow up. In this study subjects were selected who regularly visits to single physician and no comparison group also.The present findings have shown that TB with hypertension (group II) is comparatively low, but the treatment costs and duration were more than the other group i.e. group I.The TB prevalence pattern and ratios of SLI might vary from different regions of the country and same cannot be generalized cross the country.

Conclusion

From the present study, we can conclude that, as the age increases the prevalence of TB also high. The prevalence of TB was high in unemployed with low economic populations living in rural areas. Pulmonary TB has highly occurred than extra pulmonary TB. Staphylococcus aureus was the most common secondary infection pathogen observed from isolates. Total medical cost was high for group II than group I. Direct medical cost was higher than indirect cost in both the groups. Both groups maximum number of subjects were in medium scale of SLI when

compared to low and high SLI. Treatment outcome was high in both groups around 70% and 68% of subjects successfully completed the treatment in group I and group II respectively, which is as per the WHO standards.

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