

Socioepidemiological status and clinical outcome of MDR TB patients in a tertiary medical college in Southern Odisha

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Abstract

Introduction: India accounts for one-fourth of the global TB burden. The load of drug-resistant TB is of foremost attention and concern at international, regional, and national levels. As per estimates of TB burden in India in 2018, the MDR/RR-TB incidence was 1.30 lakhs. **Objectives:** Socioepidemiological status and clinical outcome of MDR TB patients in a teaching hospital in tribal area of southern Odisha from 2012-2020. **Material and Methods:** This is a retrospective observational study accepted by the Institutional Ethics Committee of this tertiary medical college & hospital to which the DRTB centre is attached with the agreement of the program administrators. **Inclusion Criteria:** Patients with >15 years of age, those patients with pulmonary and extrapulmonary tuberculosis with normal liver enzymes. **Exclusion Criteria:** Patients having abnormal liver enzymes before treatment, pregnant ladies and children <15 years of age. **Results:** A total of 40 MDR TB patients were included. The patients' mean age was 36.65 ± 11.75 years. 65% of the patients had BMI below 18.5 kg/m². 17.5% of patients had comorbidities. Approximately 45% had successful treatment outcomes. Poor treatment outcome includes loss to follow-up in 22.5% and mortality in 12.5%. We did not find any treatment failure. **Conclusion:** Treatment success outcomes occurred in less than half of the cases. The main predictors of mortality among MDR-TB patients were the presence of comorbidities like anaemia, baseline leucocytosis or lymphopenia, hypoproteinaemia, HIV sero-positivity and smaller baseline BMI.

Keywords: Multidrug-resistant TB, Odisha, treatment outcome, tuberculosis

Introduction

Tuberculosis (TB) remains a foremost cause of health hazard and is one of the top 10 causes of death globally; an estimated one crore of people fell ill with TB in 2019.^[1] India accounts for one-fourth of the global TB burden.^[2] In 2019, India was able to achieve a total notification of 24 lakh TB cases.^[3] Geographically, India ranks one (26%) in the World Health Organization (WHO) regions of South-East Asia (44%), in 2019.^[1]

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Website: www.jfmpc.com DOI: 10.4103/jfmpc.jfmpc 1015 21 About two-third of the TB cases are Males.^[4] In 2019, the highest burden of TB is in adult men, who accounted for 56% of all TB cases followed by adult women (32%) and children (12%).^[1] In India, male, female, and children were 60%, 34%, and 6% of all the TB patients notified, respectively.^[5] 89% of TB patients belong to the age group of 15-69 years.^[4]

Among all TB cases, 8.2% were people living with HIV.^[1] India ranks second in the world and accounts for about 9% of the global burden of HIV-associated TB with an estimated HIV co-infection rate of 3% among TB patients.^[4]

In 2019, there were approximately half a million new cases of rifampicin-resistant TB (of which 78% had multidrug-resistant

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TB, 27% being in India). Globally, 3.3% of new TB cases and 17.7% of previously treated cases had MDR/RRTB.^[1]

As per estimates of TB burden in India in 2018, the MDR/RR-TB incidence was 1.30 lakhs (range 7.7-19.8 lakhs); 4.83% of the total TB incidence.^[5] Globally in 2019, 61% of bacteriologically confirmed pulmonary TB cases were tested for rifampicin resistance with coverage of 59% for new and 81% for previously treated TB patients.^[1] In India, in 2018, 46% for new and 91% for previously treated TB patients of bacteriologically confirmed pulmonary TB cases were tested for rifampicin resistance.^[6] A global total of 206030 cases of multidrug-resistant TB or Rifampicin resistant TB (MDR/RR-TB) were notified in 2019, and 177099 cases were enrolled in treatment.^[1] In India, a total of 58,347 cases (44% of the estimated cases) of multidrug-resistant TB or Rifampicin-resistant TB (MDR/RR-TB) were notified in 2018, and 46,569 (around 35.8% of estimated cases) cases were enrolled in treatment.^[6] The estimated % of new cases and previously treated cases with MDR/RR-TB in 2018 were 2.8% and 14% respectively.^[5] % of those notified tested for rifampicin resistance was 32% of new cases and 82% of previously treated cases.^[7]

In India, 82% of total TB cases notified in 2018 are pulmonary as compared to 85% globally.^[6] Globally, in 2019, TB case fatality ratio (estimated mortality/estimated incidence) was estimated to be 16% (range, 15-17%).^[1] In India, it was estimated to be 17% (range, 12-24%).^[6]

Without treatment, the mortality rate in patients with TB is high. Treatment for people with rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) is longer, and requires drugs that are more expensive and more toxic.^[8]

The treatment outcome of drug-resistant tuberculosis is extremely variable as reported in different studies with a success rate from 37% to 60%.^[9-12] The Indian studies have also reported variable success rates^[13,14] though WHO has reported a 46% overall success rate in India.^[15] Globally, the latest treatment outcome data show success rates of 57% for MDR/RR-TB.^[1] In India, success rates are 48% for MDR/RR-TB.^[6]

The patients having resistance to both Rifampicin and Isoniazid or having resistance to only Rifampicin are considered as MDRTB (due to high incidence of INH resistance in India.^[2] XDR-TB is defined as resistance to isoniazid and rifampicin, and to any fluoroquinolone, and to any of the 3 second-line injectable medicines (amikacin, capreomycin, and kanamycin).^[16] Multidrug-resistant TB (MDR-TB) is multifactorial and is increased by improper treatment of sensitive TB patients, premature TB treatment interruption, and airborne transmission of resistant bacteria in public places.^[17]

A meta-analysis found significantly higher pulmonary TB prevalence for the tribal population than that estimated for

India.^[18] This study analyses treatment outcomes of MDR-TB patients and determines factors associated with poor treatment outcomes.

Aim of the study

Socioepidemiological status and clinical outcome of MDR TB patients in a teaching hospital in the tribal area of southern Odisha from 2012 to 2020.

Material and Methods

This was a retrospective observational study accepted by the Institutional Ethics Committee of this tertiary medical college & hospital to which the DRTB centre is attached with the agreement of the program administrators.

Inclusion criteria

- Patients with >15 years of age.
- Those patients with pulmonary and extrapulmonary tuberculosis with normal liver enzymes.

Exclusion criteria

- Patients having abnormal liver enzymes before treatment.
- Pregnant ladies and children <15 years of age.

All patients diagnosed with resistant TB during the study period were included. The socio-demographic and clinical data were retrospectively collected from the treatment records: age, gender, height, weight, site of involvement, smear-positive pulmonary tuberculosis (S+) at baseline, MDR TB suspect criteria, seropositivity, TB drug resistance types, comorbidity, haemoglobin, total leukocyte count, differential count, blood sugar, renal function test, liver function test, thyroid function test, and treatment outcomes.

The diagnosis was done by Xpert MTB/RIF and drug susceptibility testing (DST) for first-line anti-TB drugs (rifampicin, isoniazid, streptomycin, and ethambutol) and second-line anti-TB drugs (ofloxacin, kanamycin, and capreomycin).

The MDR-TB regimen consisted of an intensive phase (minimum of 6 months) followed by the continuation phase (18 months) with a total duration of 24 months. Treatment outcomes were defined and classified according to the WHO guidelines.^[19] Successful treatment outcomes include cured patients and those who completed treatment. Poor treatment outcomes include death, TB relapse, loss to follow-up, and failure to complete treatment regimen.

Statistical analysis

The statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 21.0. Discrete variables were presented as frequency and percentages. Continuous variables were presented as means and standard deviation (\pm SD) for unpaired data; Chi-square with Yate's correction test was used to determine the significant associations between categorical variables. A value of $P < 0.05^*$ was considered statistically significant.

Results

In our study that belongs to this geographical area of southern Odisha, from 2012-2020, a total of 40 patients were treated for MDR-TB. Table 1 shows the socio-demographic and clinical characteristics of MDR-TB patients included in our study. The majority of patients were male (n = 30, 75.0%) with M:F ratio of 3:1. The patients' mean age was 36.65 ± 11.75 years, ranging from 16 to 58 years. The mean age of males and females were 37.07 ± 12.46 and 35.4 ± 9.79 years respectively. 72.5% of the MDR TB patients were below 45 years of age with the highest (37.5%) number of patients being in the age group of 31–45 years. 65% of the patients included in this study had BMI below 18.5 Kg/m². We found that 29 (72.5%) of patients were previously treated for TB and 11 (27.5%) were newly diagnosed MDR TB cases.

According to TB drug resistance types, 33 (82.5%) patients had rifampicin resistance; 6 (15%) patients had resistance to rifampicin & isoniazid, and 1 (2.5%) patients had other anti-TB drug resistance in addition to rifampicin & isoniazid resistance. With the sites involved in these TB patients, pulmonary TB was found in 38 (95%) patients, extrapulmonary TB was found in 1 (2.5%) patient. In one (2.5%) patient both pulmonary and extrapulmonary (pericardial effusion) sites were involved with tuberculosis. Seven (17.5%) patients had comorbidities with diabetes (4 patients) being found in more than half of those patients with comorbidity.

In our study, we found 38 (95%) patients were sputum positive (S+) at baseline. 3 (7.5%) of patients had contact of known MDR TB [Figure 1].

In our study one (2.5%) patient was transferred in. Treatment outcomes of our study were as follows: 5 (12.5%) patients were transferred out, 18 (45%) had successful treatment, and poor treatment outcome was seen in 14 (35%) patients. During the follow-up period, 8 (20%) patients were cured, 10 (25%) were completed their treatment, 5 (12.5%) died during treatment (4 male and 1 female), 9 (22.5%) defaulted or lost to follow up, and the remaining 3 (7.5%) are on treatment [Figure 2]. Among all the deaths during the study period, 4 (80.0%) patients were Re-treatment cases, S+ at diagnosis. We had not found treatment failure in any case.

Table 2 shows different biochemical parameters of the patients. We found anaemia in 35 (87.5%) patients in our study as per definition by WHO.^[20] 26 male (86.67%) and 9 female (90%) MDR TB patients had anaemia. Only two (5%) patients had thrombocytopenia (total platelet count <1.5 lakhs/uL). Hypoproteinaemia was present in two (5%) MDR TB patients; one of them died during the treatment.

	Ν	%
GENDER		
Male	30	75%
Female	10	25%
AGE GROUP		
15-30 years	14	35%
31-45 years	15	37.5%
46-60 years	11	27.5%
BMI		
<18.5 Kg/m ²	26	65%
>18.5 Kg/m ²	14	35%
Treatment history		
New	11	27.5%
Re- treatment	29	72.5%
Baseline drug resistance		
Only R resistance	33	82.5%
R+H resistance	6 (5 re-treatment	15%
	case, s+ at diagnosis)	
R+H + E resistance	1 (re-treatment case,	2.5%
	s+ at diagnosis)	
Site of tuberculosis		
Pulmonary TB	38	95%
Extra pulmonary TB	1	2.5%
Both pulmonary + Extra pulmonary TB	1	2.5%
COMORBIDITY		
HIV Positive/PLHA	1	2.5%
Diabetes	4	10.0%
Sweet syndrome	1	2.5%
Hepatitis B Positive	1	2.5%

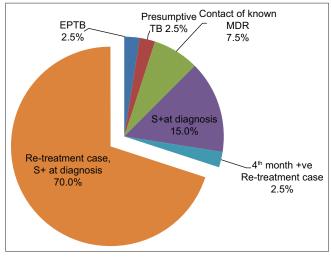


Figure 1: MDR TB suspect criteria at diagnosis

Table 3: shows the total leukocyte count among MDR TB patients. During the course of the study, five (38.46%) persons with leukocytopenia or leucocytosis died.

We found 2 (6.25%) patients had subclinical hypothyroid and 3 (9.37%) had subclinical hyperthyroid among the MDR TB patients studied. 12 (37.5%) patients had sick-euthyroid status [Figure 3].

Dash and Behera: Clinical outcome of MDR TB patients

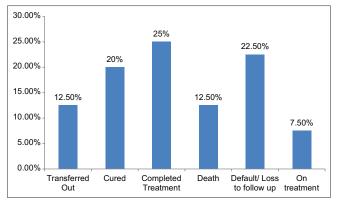


Figure 2: Treatment outcomes of MDR TB patients

Table 2: Biochemical Parameters In MDR TB Patients			
PARAMETERS	MEAN±SD		
Height	1.57±0.09		
Weight	44.53±9.19		
BMI (Kg/m ²)	18.14 ± 4.01		
Total leukocyte count ($n=37$)	9482.16±3236.83		
Hemoglobin (n=37)	10.22 ± 1.98		
Total platelet count $(n=37)$	3.10±1.51		
Serum urea	23.31±8.65		
Serum creatinine	0.89 ± 0.27		
Total bilirubin (mg/dl)	0.65 ± 0.36		
Direct bilirubin (mg/dl)	0.25 ± 0.14		
SGOT	31.76±26.62		
SGPT	36.61±19.54		
ALP	264.13±188.14		
Serum protein	7.10±1.27		
Serum T3 (n=32)	1.49±0.68		
Serum T4 (<i>n</i> =32)	83.03±36.25		
TSH (n=32)	1.48±1.19		

Table 3: Total leukocyte count in MDR TB patients (n=37)					
Total leucocyte count	Ν	%			
<4000	1	2.70%			
4000 - ≤ 11000	24	64.87%			
>11000	12	32.43%			

All 5 MDR TB patients who died during the course of the treatment had BMI <18.5 kg/m² and anaemia with 2 (40%) having severe anaemia. Six (85.71%) out of 7 MDR TB patients with comorbid conditions had anaemia. Four (80%) of the death were re-treatment cases. Table 4 shows none of the variables are associated statistically significant with the treatment outcomes. The impact of HIV and diabetes mellitus on the outcomes of treatment could not be compared as these comorbidities were present in very few cases.

Discussion

In our study, the majority of patients were male. El Hamdouni *et al.*,^[21] Bastos *et al.*,^[22] Patel *et al.*^[23] found male predominance

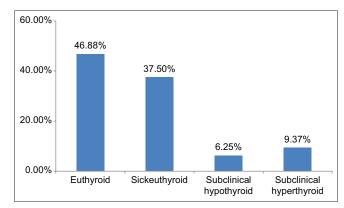


Figure 3: Thyroid profile in MDR TB patients

among MDR-TB patients. Most of the patients are young with a mean age of 36.65 ± 11.75 years, ranging from 16 to 58 years, in agreement with El Hamdouni *et al.*^[21] who found the mean age of 35.5 ± 13.3 years. Our study revealed 65.0% of the MDR TB patients were in the age group of 31-60 years. 89% of TB cases come from the age group of 15-69 years, with the majority among the working-age group.^[4] 80% of female patients were of reproductive age (15-45 years); Patel *et al.*^[23] found 92.5% of female patients in the same age group.

65% of the patients included in this study had BMI below 18.5 Kg/m², comparable to Agarwalla *et al.* study (73%).^[24] All the patients died in our study had BMI <18.5 kg/m². The success rate was lower in patients having BMI <18.5 kg/m² in comparison to patients having BMI greater >18.5 kg/m².^[24] Meressa D. *et al.*^[25] reported BMI had a significant association with MDR-TB treatment outcome.

According to TB drug resistance types, our study is comparable to Girum *et al.*^[26] study who found resistance to rifampicin in 89% (vs 82.5%), resistance to rifampicin & isoniazid in 9.7% (vs 15%), and resistance to more than two drugs in only 1.3% (vs 2.5%) of patients, respectively.

Approximately 72.5% of patients were previously treated for TB in our study. 83.2%, 98.5% and 90.3% of patients had prior TB treatment in El Hamdouni *et al.*^[21] Meressa D. *et al.*^[25] and Girum *et al.*^[26] studies respectively. 95% of patients were sputum positive (S+) at baseline in our study which was higher than El Hamdouni *et al.*^[21] study (81.2%). In our study, we found 27.5% were newly diagnosed MDR TB cases, which is a worrisome factor. With the sites involved in these TB patients, pulmonary TB and extrapulmonary TB were found in 95% and 2.5% of patients respectively. In 2.5% of patients, both pulmonary and extrapulmonary (pericardial effusion) sites were involved with tuberculosis. Similar results are found in Girum *et al.*^[26] study with 93.5%, 3.25%, 3.25% in pulmonary, extrapulmonary, and both respectively.

17.5% of patients with MDR TB had comorbidities; comparable to El Hamdouni *et al.*^[21] study (19.8%) and Girum *et al.*

Independent variables	Treatment outcomes n (%)		Р
	Poor treatment n (%)	Successful treatment n (%)	
AGE GROUP			
15-30 years	2 (6.25%)	7 (21.875%)	$\chi^2 = 4.6426$, DF=2,
31-45 years	5 (15.625%)	8 (25.0%)	P=0.0981
46-60 years	7 (21.875%)	3 (9.375%)	
Gender			
Male	11 (34.375%)	14 (43.75%)	$\chi^2 = 0.003$, DF=1,
Female	3 (9.375%)	4 (12.5%)	P=0.9570
BMI			
$<18.5 \text{ Kg/m}^{2}$	10 (31.25%)	11 (34.375%)	$\chi^2 = 0.055$, DF=1,
$>18.5 \text{ Kg/m}^2$	4 (12.5%)	7 (21.875%)	P=0.8146
Sputum +ve			
Yes	13 (40.625%)	17 (53.125%)	$\chi^2 = 0.034$, DF=1,
No	1 (3.125%)	1 (3.125%)	P=0.8540
Re- treatment case			
Yes	8 (21.875%)	15 (46.875%)	$\chi^2 = 1.534$, DF=1,
No	6 (9.375%)	3 (9.375%)	P=0.2156
Drug resistant			
Only R resistance	13 (40.625%)	14 (43.75%)	$\chi^2 = 0.455$, DF=1,
R+H resistance	1 (3.125%)	4 (12.5%)	P=0.4998
Anemia			
Mild anemia	5 (15.625%)	4 (12.5%)	$\chi^2 = 3.2407$, DF=2,
Moderate anemia	6 (9.375%)	13 (40.6255%)	P=0.1978
Severe anemia	3 (9.375%)	1 (3.125%)	
Leucopenia & Leucocytosis			$\chi^2 = 1.603$, DF=1,
Yes	7 (21.875%)	4 (12.5%)	P=0.2055
No	7 (21.875%)	14 (43.75%)	1 012000
Comorbidity			
Yes	4 (12.5%)	2 (6.25%)	$\gamma^2 = 0.638$, DF=1,
No	10 (31.25%)	16 (50.0%)	$\chi = 0.030, D1 = 1,$ P=0.4244
Thyroid dysfunction (n=28)	10 (01.2070)	10 (00.070)	1 0.1211
Euthyroid	5 (17.86%)	7 (25.0%)	$\gamma^2 = 0.3993$, DF=2,
Sickeuthyroid	4 (14.28%)	8 (28.58%)	$\chi = 0.5995, D1 = 2,$ P = 0.9190
Subclinical hypothyroid/Subclinical hyperthyroid	2 (7.14%)	2 (7.14%)	1-0.7170

study (15%).^[26] Diabetes was the most common comorbidity found in 10% of patients with MDR TB; similar to Agarwalla *et al.* study.^[24] HIV was found in 2.5% of patients with MDR TB; comparable to India TB report 2019, Agarwalla *et al.* study,^[24] and Girum *et al.* study.^[4,26]

We found anaemia in 87.5% of patients in our study. Gil-Santana L. et al.[27] found anaemia in 88.9% of patients. All MDR TB patients who died during the course of the study period had anaemia. 85.71% of MDR TB patients with comorbid conditions had anaemia. We found leukocytopenia and leucocytosis in 35.13% of patients; all the patients who died during the course of the treatment had either leucocytosis or leukopenia. 80% of them also have lymphopenia at baseline. Carole Chedid et al.[28] study found high WBC counts and low lymphocyte proportions at baseline are significantly associated with the risk of poor treatment outcome. 50% of MDR TB patients with hypoproteinaemia died during the treatment. Among the deaths, 80.0% of MDR TB patients were Re-treatment cases, S+ at diagnosis. We found 37.50% of patients had sick euthyroid syndrome, 6.25% of patients had subclinical hypothyroid and 9.37% had subclinical hyperthyroid among the MDR TB patients studied. One of the two subclinical hypothyroid patients with MDR TB was HIV +ve and defaulter. Ige OM *et al.*^[29] study found 4.35%, 7.83%, and 1.74% of patients had sick euthyroid syndrome, subclinical hypothyroidism, and subclinical hyperthyroidism respectively. Dash M *et al.*^[30] found sick euthyroid syndrome in 35.82% of TB patients. Subclinical hypothyroidism increases the risk of depression and reduces adherence to MDR-TB and HIV treatment.^[31]

In our study; 45% had successful treatment with 20% cured and 25% completed treatment. Comparable to our study, Chaves-Torres NM *et al.*^[32] study in Colombia found successful treatment in 49.9% MDR/RR-TB cohort. El Hamdouni *et al.*^[21] study found successful treatment outcomes in 53.5% of MDR TB cases with a higher cure rate of 44.5% but with a lower completed treatment rate of 8.9%. Leimane *et al.*^[33] in Latvia also reported a higher cure rate of 67.6% and a treatment completion rate of 1.6% only with successful treatment of 69.2%; similar to Datta *et al.*^[34] study in India (71.2%) and Oliveira O *et al.*^[35] study in Portugal (70.2%). The success rate in our study was higher than the ones found by Elmi *et al.*,^[36] Agarwalla *et al.*,^[24] 38%, 39%, and 39% respectively. Girum *et al.*^[26] study found a successful treatment rate in 42.2% MDR TB cases with 25.3% patients cured and 16.9% completed their treatment which is comparable to our study.

In our study, we found poor treatment in 35% of patients. El Hamdouni et al.^[21] and Patel et al.^[23] study found higher poor treatment outcome in 46.5% and 57% of patients respectively. Girum et al.^[26] study found poor treatment outcome in only 22.4% of patients with a probable cause of 33.1% of patients being on treatment. Our poor treatment outcome is due to high default or lost to follow up which is 22.5% in our study. El Hamdouni et al.^[21] and Agarwalla et al.^[24] had higher lost to follow-up in 34.6% and 28% of patients respectively. Patel et al.[23] study had default cases in 21% which is similar to our study. Girum et al.^[26] and Leimane et al. found much lower defaulted or lost to follow-up in 13% and 14.5% of patients respectively.[33] One reason for the lower success rate is due to higher loss to follow-up rate. In our study, a long duration of treatment and an improvement in symptoms were among possible reasons for loss to follow-up or discontinuation of therapy. The study of Holtz et al.[38] observed lack of patient-provider interaction, drug use, and socioeconomic characteristics as the major factors associated with loss to follow-up.

The mortality rate is 12.5% in our study; higher than El Hamdouni *et al.*,^[21] Girum *et al.*,^[26] and Leimane *et al.*,^[33] studies who found mortality rates of 4.9%, 8.4%, and 5.7% respectively. Patel *et al.*,^[23] and Datta *et al.*,^[34] found much higher mortality rates of 29.7% and 21.1% respectively. We had not found treatment failure in any case. Girum *et al.*,^[26] study also found no treatment failure. El Hamdouni *et al.*,^[21] Patel *et al.*,^[23] and Leimane *et al.*,^[33] had treatment failure in 6.9%, 6.2%, and 10.3% patients respectively.

Our study found a lower success rate which may be observed in the early months of the commencement of the program. At the beginning of the DOTS—Plus program under RNTCP, Thomas *et al.*^[11] study in 2007, showed a success rate of 38% with a high default rate of 24%. But with patients treated under the programmatic conditions with the standardized regimens, more current studies have evidence of a better success rate ranging from 54 to 63% and a lower default rate ranging from 9.2% to 23%.^[13,39] A meta-analysis of several studies by Ahuja *et al.*^[40] revealed that the success rate was variable with a success rate of 54% and a default rate of 23% in general.

Conclusion

The present study, in Koraput, shows a below average success rate with high prevalence of lost to follow-up among MDR TB patients. Treatment success outcomes occurred in less than half of the cases; lesser than the target to be achieved which is set by WHO. The main predictors of mortality among MDR-TB patients were presence of comorbidities like anaemia, baseline leucocytosis or lymphopenia, hypoproteinaemia, HIV sero-positivity and smaller baseline BMI. The increase in the proportion of new cases among the MDR-TB indicates an urgent need for a better strategy for early detection and containment of MDR-TB. Interventions to improve patient nutrition as well as measures to ensure treatment adherence through strengthening the health care system and patient education might help to improve the performance of the program and treatment success rates.

Ethical approval

The study was approved by Institutional Ethics Committee.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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