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EVALUATION OF RESISTANCE AND TREATMENT OUTCOMES TO ANTI-TUBERCULAR DRUGS - A RETROSPECTIVE STUDY

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ABSTRACT

Background: Tuberculosis remains a significant global health issue, causing significant mortality, especially in resource-limited settings, particularly in Asia and Africa, with multi-drug-resistant (MDR) and extensively drug-resistant (XDR) variants complicating treatment and control. **Objective:** This study aims to evaluate TB patients' resistance patterns and treatment outcomes at the Nepal Anti Tuberculosis Association (NATA), Biratnagar, Nepal. **Method:** The retrospective, observational study reviewed the medical records of 502 TB patients treated at NATA Biratnagar from June 2012 to July 2014. Data collected included sociodemographic characteristics, types of TB, drug resistance patterns, and treatment outcomes. The study used descriptive statistics to analyse the data. **Results:** 502 tuberculosis patients were included in this study; 357(71%) were male, and 145(29%) were female. People with productive age, 20-40 years of age with a mean age of 35±15.05, were highly susceptible to getting TB infection and drug resistance. Drug-resistant problems occurred in 145 patients, including referred patients. Among drug-resistant tuberculosis patients, 131 patients (90%) with MDR, 6 patients (4%) with pre-XDR, and 9 patients (6%) with XDR-TB. Out of resistant patients, 58 were cured, 8 complete the treatment, 19 failed, 14 died, 15 were treatment defaulters, 6 were transferred out remaining were on treatment among non resistant patients, 130(37%) were cured, 125(35%) complete treatment, 23(6%) failure, 20(6%) died, 12(3%) defaulter, 17(5%) transfer out, 7(2%) diagnosis change and 23(6%) patients were on treatment. **Conclusion:** The study reveals that productive-age individuals are at higher risk of tuberculosis and drug resistance, necessitating awareness programs and improved TB control programs.

KEYWORDS: Mycobacterium tuberculosis, Drug-resistant tuberculosis, Multidrug-resistance, extreme drug resistance treatment outcomes.

IMPACTS ON PRACTICE

- The study's findings indicate that individuals aged 20-40 are at a higher risk for TB infection and drug resistance, suggesting the need for targeted preventive measures and educational campaigns for this demographic.
- Additionally, the high prevalence of drug-resistant TB cases calls for improved diagnostic and treatment strategies. This includes early detection, effective second-line therapies, and robust support systems to enhance treatment adherence and outcomes.

INTRODUCTION

Tuberculosis (TB) remains one of the leading causes of death due to a single pathogen globally. The World Health Organization (WHO) estimates that one-third of the world's population is infected with Mycobacterium tuberculosis. Each year, approximately 9 million people develop active TB, and 1.7 million deaths are reported due to TB.[1,2] Although the global prevalence of TB has shown a decline, with cases dropping from 13 million in 2010 to 12 million in 2011, the disease continues to be a significant health burden, especially in resource-limited settings.[3] Geographical disparities are evident, with America and Europe contributing only 7.3% of the total global TB burden, attributed to substantial investments in control efforts. Conversely, Asia and Africa bear the

brunt, accounting for 59% and 29% of the global burden, respectively, with India and China together comprising 38% of the global TB cases in 2011.[4,5]

Multi-drug resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampicin, has been increasing, posing a significant challenge to TB control programs. In 2012, 3.6% of newly diagnosed cases and 20% of retreatment cases globally were estimated to have MDR-TB, with notable geographical variations in prevalence.[4] Reports from Africa indicate that resistance to one or more anti-TB drugs ranges from 3% to 37.3%, and MDR-TB ranges from 1.4% to 11.6%. Extensively drug-resistant TB (XDR-TB), defined as MDR with additional resistance to fluoroquinolones and at least one second-line injectable drug such as amikacin, has been reported in 92 countries, with approximately 9.6% of MDR-TB patients having XDR-TB globally.[6]

The clinical management of TB involves the use of first and second-line anti-TB drugs. The first-line drugs, such as isoniazid and rifampicin, are potent bactericidal agents that kill dividing bacilli, making patients non-contagious and significantly reducing the treatment duration.[7] The WHO's Directly Observed Treatment-Short Course (DOTS) strategy, recommended globally for National Tuberculosis Control Programs, has been successful in all types of TB. It involves a 6-month regimen with first-line drugs for new patients and an 8-month regimen for retreatment patients.[8] However, the treatment of MDR-TB with this regimen has shown inadequate cure rates, with a retrospective cohort study indicating treatment success rates of 52% in new cases and 29% in previously treated cases.[9]

Treating MDR-TB with second-line drugs can cure over 65% of patients and halt ongoing transmission, yet most evidence of successful MDR-TB management comes from high-income countries.[10] In Nepal, about 45% of the population is infected with TB, with 40,000 new active TB cases annually, leading to 5,000 to 7,000 deaths.[11] The country's National Tuberculosis Program has expanded DOTS to numerous treatments and sub-centers. Yet, challenges persist, especially in the eastern region, where studies have indicated variations in the presence of MDR and XDR-TB cases.[11]

This retrospective study aims to evaluate the resistance and treatment outcomes to anti-tubercular drugs among patients visiting NATA Biratnagar. By analyzing socio-demographic information, co-morbidities, and drug resistance patterns, this research seeks to provide critical data to national regulatory authorities and assist in planning effective control measures to combat microbial drug resistance.

METHODS

Ethics approval

Approval was obtained from the Hospital's committee (Ref no: 56) before conducting the study and collecting data. No information was gathered directly from patients.

Study design

This is a health facility-based retrospective, observational study conducted over a period of 4 months. The study involved collecting patients' medical records available in the hospital's office records.

Study population sample size and sampling method

The National Anti-Tubercular Association (NATA) Hospital in Biratnagar was selected for the study. A sample size of 502 tuberculosis patients was included, consisting of those who initiated treatment at this hospital, as well as those referred from other hospitals and Primary Health Care Centers (PHCCs). Both new and drug-resistant patients were considered in this study. The universal sampling technique was used to collect patients' medical records from the hospital's medical record office for the period from June 2012 to July 2014.

Data collection form design and Validation

The data collection form consists of two main parts. The first part covers the sociodemographic characteristics of the patients, including registration number, place of residence, address, age, sex, marital status, and family history of tuberculosis (TB). The second part collects information related to the disease and treatment outcomes, including types of resistance, smear positivity, culture results, treatment categories, cure rates, treatment failures, and deaths. The data collection form was established based on similar previously published studies.[12,16]

Procedure

Relevant data were extracted from medical records for two consecutive years and recorded in the data collection form. The collected data were then subjected to analysis.

Data analysis

Data were entered into Microsoft Excel and then imported into the Statistical Package for Social Sciences (SPSS) version 16.0. Descriptive statistics were used for the analysis, with results expressed as numbers, percentages, and means.

RESULTS

A total of 502 patients were enrolled in this study, including new smear-positive, smear-negative, and drug-resistant cases. Among these patients, 357 (71%) were male, and 145 (29%) were female. Detailed information is presented in Table 1.

Table 1: Sociodemographics of Patients (N=502).

Variables	Category	Frequency	Percentage (%)
Gender	Male	357	71
	Female	145	29
Age group	0-20	78	15
	20-40	215	43
	40-60	134	27
	60-80	71	14
	>80	4	1
Place of residence	Urban	392	78
	Rural	110	22
Marital Status	Married	386	77
	Single	116	23

Among the study population, 357 (71%) patients were found to be non-resistant to anti-TB drugs, while 145 (29%) were resistant.

Of the 357 non-resistant patients, 327 (92%) had pulmonary tuberculosis, and 30 (8%) had extra-pulmonary tuberculosis. Among these patients, 328 (92%) were treated with category-I drugs (HRZE/S) and 29 (8%) with category-II drugs (HRZES).

The treatment outcomes for these patients were as follows: 130 (37%) were cured, 125 (35%) completed treatment, 23 (6%) experienced treatment failure, 20 (6%) died, 12 (3%) defaulted, 17 (5%) were transferred out, 6 (2%) had a diagnosis change, and 23 (6%) were continuing treatment and follow-up. Detailed information is presented in Table 2.

Table 2: Other information of Patients non-resistant to anti-TB drugs (N=357).

Variables	Category	Frequency	Percentage (%)
Types of TB	Pulmonary	327	92
	Extra-Pulmonary	30	8
Treatment Category	Cat I	328	92
	Cat II	29	8
Treatment Outcome	Cured	130	37
	Complete	125	35
	Failure	23	6
	Died	20	6
	Defaulter	12	3
	Transfer-Out	17	5
	Diagnosis Change	6	2
	On treatment	23	6

Note; Treatment outcomes
Cured; at the end of treatment at least two sputum smear test negative within one month.
Complete; single test or at the end of treatment no sputum smear test is done.
Failure; Sputum smear positive after continue treatment of 5 months or more.
Died; Death during treatment.
Defaulter; Does not come on treatment 6o days or more. Transfer-out; transfer to another treatment center/district due to some reason

A total of 145 TB patients developed drug resistance, with 68% being male and 32% female. Most of these patients were aged between 0-20 years, with a mean age of 35±15 years. Regarding marital status, 77% were married, while 23% were unmarried. Among these patients, many developed MDR, pre-XDR, and XDR TB.

In terms of treatment outcomes, 12% experienced Category-I failure, 18% experienced Category-II failure, and 35% relapsed. Of these patients, 47% were cured, and 77% completed treatment. Unfortunately, 11% died, 11% were defaulters, and 5% were transferred to higher centres. Additionally, 2% had their diagnosis changed, and 22 patients continued treatment and follow-up. Detailed information is shown in Table 3.

Table 3: Other information on Patients resistant to anti-TB drugs (N=145).

Variables	Category	Frequency	Percentage (%)
Gender	Male	99	68
	Female	46	32
Age Group (Years) (median 35)	0-20	20	14
	20-40	75	52
	40-60	40	27
	60-80	10	7
	>80	0	0
Marital Status	Married	112	77
	Unmarried	33	23
Patient Distribution (District)	Jhapa	71	49
	Morang	43	29
	Sunsari	4	3
	Siraha	6	4
	Udayapur	4	3
	Bhojur	1	1
	Saptari	6	4
	Pachthar	1	1
	Sankhuwasava	1	1
	Ilam	2	1
	Taplejung	3	2
	Terathum	1	1
	Dhankuta	2	1
Resistance Pattern	MDR	131	90
	Pre-XDR	6	4
	XDR	9	6
Types of Patients	Cat I Failure	17	12
	Cat II Failure	26	18
	Relapse	50	35
	New	41	28
	Transfer-in	3	2
	Other MDR	6	4
	Cat I and Cat II failure	2	1
Treatment Outcome	Cure	58	47
	Complete	8	7
	Failure	19	16
	Died	14	11
	Defaulter	15	12
	Transfer-Out	6	5
	Diagnosis Change	3	2

DISCUSSION

In this study, 502 patients, including new and drug-resistant cases, were enrolled and analysed for age, gender, place of residence, marital status, family history of TB, types of TB, treatment initiation, treatment category, category failure, and treatment outcomes.

The findings indicate that tuberculosis was more prevalent in males (71%) than females (29%), with drug resistance also higher in males (68%). These results align with the study by Muhammad Khurram et al. in Pakistan, which reported a male-to-female ratio of 3:2, and with similar research conducted in other countries.[13,14,16,17] This suggests that males are more susceptible to TB, possibly because they spend more time away from home for work or study, increasing their contact with the public.

The study also revealed that individuals in the productive age group of 20-40 years were more commonly infected with TB, with drug resistance prevalent in 52% of this age group. These findings are consistent with the study by Fivy Kurniawati et al. in Malaysia.[18] People in this age group often leave home for opportunities to study or work, leading to increased exposure to TB in crowded areas.[6]

Tuberculosis was more prevalent in urban areas (96%) compared to rural areas (4%), indicating a higher risk of transmission in crowded urban environments such as refugee camps, prisons, nursing homes, and among

migrant workers. This observation is similar to findings in other countries.[13,17] Additionally, TB and drug resistance were more prevalent among married individuals (77%), a finding that aligns with research conducted in Delhi.[17]

Among the 502 patients, 357 (71%) were sensitive to all anti-TB drugs and considered non-resistant, while 145 (29%) were resistant to one or more anti-TB drugs. These results are consistent with studies in other countries.[6,15,19,20] The high incidence of drug resistance may be attributed to factors such as medication interruption, side effects, lack of access to healthcare, and poor awareness of drug resistance.

Pulmonary tuberculosis was more significant among non-resistant patients (92%), with only 8% having extra-pulmonary tuberculosis. This finding is consistent with research in other countries, indicating that pulmonary TB is more easily transmitted through the respiratory tract.[20]

Most new patients were treated with category-I (HRZE/S) drugs (92%), and 8% with category-II drugs (HRZES), suggesting that pulmonary tuberculosis was more common. These findings were similar to research in Turkey by Suheyla Surucuoglu et al.[20] Treatment outcomes showed that 37% were cured, 35% completed treatment (success rate of 72%), 6% experienced treatment failure, 6% died, 3% defaulted, and 8% were still undergoing treatment and follow-up. These results align with studies conducted in other countries but differ from the study by Muhammad Khurram et al. in Pakistan, which included only drug-resistant patients.[13]

In the context of eastern Nepal, this hospital is a leading centre for treating TB patients, including drug-resistant cases. The study found higher drug resistance in Jhapa and Morang districts, possibly due to the living conditions of Bhutanese refugees in camps, facilitating TB transmission.

Among the 145 drug-resistant patients, 90% were MDR, 4% were pre-XDR, and 6% were extreme drug-resistant (XDR). MDR patients are resistant to Rifampicin and Isoniazid, pre-XDR to Isoniazid, Rifampicin, and Fluoroquinolone, and XDR to Isoniazid, Rifampicin, Fluoroquinolone, and Kanamycin. These findings are consistent with studies by Nizar Ahmed Rao et al. in Pakistan and Suzanne M. Marks et al. in the US.[19,21]

Of the drug-resistant patients, 67% were previously treated elsewhere and referred to this centre, indicating higher treatment failure in those previously treated elsewhere. The study also found that 12% of patients undergoing treatment were category-I failures, 18% were category-II failures, 35% relapsed, 28% were new cases, 2% transferred, 4% had other MDR forms, and 1% were category-I and II failures. These findings suggest that relapse patients are more likely to develop drug resistance, although this does not match other research findings.

Among the drug-resistant patients treated at this centre, treatment outcomes were: 47% cured, 7% completed treatment, 16% experienced treatment failure, 11% died, 12% defaulted, 5% transferred out, 2% had a diagnosis change, and 22 patients were still undergoing treatment and follow-up. The high cure rate for MDR patients but low for XDR patients aligns with research in other countries.[12,13,15,17]

Limitations

This study on TB has limitations, including the inability to assess risk factors or patient socio-economic status, not evaluating drug resistance for all first and second-line drugs, and a lack of treatment outcomes of some patients because of missing records. The high drug resistance observed may be due to the inclusion of patients from other hospitals and PHCCs, potentially not representing the entire Nepali TB population.

CONCLUSION

Our study revealed that individuals in the productive age group of 20-40 years are at a higher risk of contracting tuberculosis and developing drug resistance. Therefore, awareness programs on preventing tuberculosis, drug resistance, and its consequences are essential. The study also highlighted that patients often interrupt their anti-tubercular therapy. In this region, the high resistance rate indicates a need for improvement in the TB control program.

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