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Original Research Article

Treatment Outcome and Drug Resistant Profile of Isoniazid Monoresistant Pulmonary Tuberculosis Patients in a Tertiary Care Centre: A Prospective Study

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Conflict of interest: Nil

Abstract

Background: Tuberculosis (TB), a communicable disease is a major cause of ill health and one of the leading causes of death worldwide. Global TB report 2022 says an estimated 10.6 million people were infected with TB worldwide in 2021, an increase of 4.5% from 10.1 million in 2020. Isoniazid mono-resistance forms a major part of Drug Resistant Tuberculosis. Resistance to it increases the likelihood of negative treatment outcomes, treatment relapse and death [2,3]. As per National Drug Resistance Survey 2014-2016, Isoniazid resistance is 11.06% and 25.09% and Isoniazid mono-resistance was 3.85% and 7.61% among new and previously treated patients, respectively. Transmission of Isoniazid resistant isolates is possible with mutations, especially katG315T. Hence this study focuses on INH resistance pulmonary Tuberculosis patients, the clinical parameters, genotype profile and their association with the outcome of the disease.

Materials and Methods: A Cohort Study conducted with microbiologically confirmed Isoniazid Mono-resistant Pulmonary Tuberculosis patients diagnosed by First Line Probe Assay registered at a tertiary care hospital over a period of one year were included in the study. Drug sensitive Pulmonary Tuberculosis, Multi drug resistant Tuberculosis, Poly drug resistant pulmonary Tuberculosis, and Extra-pulmonary Tuberculosis were excluded.

All 83 microbiologically confirmed Isoniazid Mono-resistant Pulmonary tuberculosis patients were included in the study. Data was collected with structured questionnaire following informed consent of the participants. Patients were evaluated with Chest X-ray, physical examination, sputum smear, liquid culture & DST, Line Probe Assay and treated as per Guidelines. Data was entered in Microsoft excel and analysis was done in SPSS Software version 21.

Results: Majority of patients belonged to the age group 40-60 (38%). Out of the total 79 patients, 75% were males. About 54% of patients, gained more than 10% of their body weight on completion of treatment. Among patients who gained more than 10% body weight, 53% of patients showed positive outcomes of the treatment. 60.8% patients showed Kat G mutations; 30.2% patients showed Inh A mutations and 5.1% patients showed both. The association between the genetic mutations and outcome of the treatment was not statistically significant. Among all the study participants, 88.6% showed positive outcomes.

Conclusion: Maximum number of patients was in 40 – 60 age group (46%). INH mono-resistant TB was more common in males than females. Diabetic patients were more common than hypertensive patients. Positive outcome with Inh A mutation was more common. Negative outcomes were more common when the pre-treatment weight was less than <10%. Poor weight gain was associated with poor outcomes.

Keywords: Genotype Profile, Isoniazid Mono Resistance, Line Probe Assay.

Introduction

Tuberculosis (TB), a communicable disease is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus (CO VID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1].

Global TB report 2022 says an estimated 10.6 million people were infected with TB worldwide in 2021, an increase of 4.5% from 10.1 million in 2020. The average global burden of disease was around 130 new cases per 100000 population per year. There were an estimated 1.2 million Tuberculosis deaths among HIV-negative people in 2018 and 251000 additional deaths among HIV-positive people. The total number of incident TB patients (new & relapse) notified during 2021 was 19, 33,381 which was 19% higher than that of 2020 [1].

Isoniazid mono-resistance forms a major part of Drug Resistant Tuberculosis with the majority of patients detected with primary mono resistance. Resistance to it increases the likelihood of negative treatment outcomes, treatment relapse and death. The interest in Isoniazid Mono-resistance has lessened as Multi Drug Resistance became more of a concern [2,3].

Isoniazid Mono-resistant pulmonary Tuberculosis is defined as "A Tuberculosis patient, whose biological specimen is resistant to Isoniazid and susceptibility to Rifampicin has been confirmed". In India Isoniazid mono-resistant Tuberculosis was found in 11.4% *of* cases of presumptive Drug resistant Tuberculosis [4]

The global prevalence of Isoniazid Mono-resistant Tuberculosis was 7.4% among new Tuberculosis patients and 11.4% among previously treated Tuberculosis patients1. As per National Drug Resistance Survey 2014-2016, Isoniazid resistance is 11.06% and 25.09% and Isoniazid mono-resistance was 3.85% and 7.61% among new and previously treated patients, respectively. 1 in 8 children with Tuberculosis has Isoniazid resistant Tuberculosis globally [5].

Transmission of Isoniazid-resistant isolates is possible with mutations, especially katG315T. It is important to diagnose katG315T mutants among Isoniazid-resistant strains as it may be a risk factor for subsequent development of multidrug-resistant Tuberculosis. The genotype profile of Isoniazid resistance shows these mutations: Kat G mutation; Inh A Promoter; Inh A coding region; overexpression of ahpC oxyR; mutations in kasA; Mutation in ndh gene[6].

In a study,72.5% Isoniazid mono-resistant tuberculosis patients had mutations in the katG gene and 27.5% had mutations in the inh A gene [7]. Another study showed 71.0% with mutations in katG315 and 29.0% in the inh A promoter region [8].

Isoniazid mono-resistance pulmonary tuberculosis patients had poor outcome when compared to drug sensitive pulmonary tuberculosis patients. In many countries, high level of isoniazid resistance is seen in new patients, but the lack of drug

susceptibility results for isoniazid by the time of continuation phase leads further to poorer outcome. Of the mutations, katG played a major role in determining of MDR-TB compared to inh A gene. Isoniazid mono-resistance showed positive association with previous history of treatment for TB, MDR-TB contacts, poor treatment compliance [9].

As the End TB strategy envisages reduction of TB incidence by 80% by 2030, it is vital to address Drug resistant TB along with Drug sensitive TB. Studies show Isoniazid Mono resistance far more common than other forms of resistance9. Hence this study focuses on INH resistance pulmonary Tuberculosis patients, the genotype profile and its association with the outcome of the disease.

Objectives

- To estimate the prevalence of clinical parameters among Isoniazid Mono resistant Pulmonary Tuberculosis patients.
- To analyse the association between the clinical parameters and the outcome of the treatment among them.
- To estimate the prevalence of drug resistant mutations among Isoniazid Mono resistant Pulmonary Tuberculosis patients.
- To analyse the association of a drug resistance mutations and the treatment outcome.

Materials and Methods

A Prospective Cohort Study conducted with microbiologically confirmed Isoniazid Mono-resistant Pulmonary Tuberculosis patients diagnosed by First Line Probe Assay registered at Madurai Medical College Hospital over a period of one year from August 2017 to August 2018 were included in the study. Drug sensitive Pulmonary Tuberculosis, Multi drug resistant Tuberculosis, Poly drug resistant pulmonary Tuberculosis, and Extra-pulmonary Tuberculosis were excluded.

"Isoniazid Mono-resistant Tuberculosis" refers to a Tuberculosis patient, whose biological specimen's resistance to Isoniazid and susceptibility to Rifampicin is confirmed. "Microbiologically Confirmed Tuberculosis" refers to a bacteriologically confirmed Tuberculosis case from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF) 13.

All 83 microbiologically confirmed Isoniazid Mono-resistant Pulmonary tuberculosis patients at the Department of Respiratory Medicine of Madurai Medical College Hospital were included in the study. Of all the patients, 4 patients were lost to follow up and 3 patients died during the course of the treatment. Data was collected with structured questionnaire following informed consent of the participants. Data collected included socioeconomic factors, comorbid illness, history of previous treatment, substance use and adverse effects. Patients were evaluated with Chest Xray, physical examination, sputum smear, liquid culture & DST, Line Probe Assay and treated as per Programmatic Management of Drug Resistant Tuberculosis Guidelines. Patients will be followed up periodically as per PMDT Guidelines.

Data was entered in Microsoft excel and analysis was done in SPSS Software version 21. Discrete variables were shown as frequency distributions while continuous variables shown as Mean, Median, Standard deviation. Association between variables was done with Chi-Square test.

Results

Majority of patients belonged to the age group 40-60 (38%). Out of the total 79 patients, 60 (75%) were males and 19 patients were females(Fig 1& 2). Of these patients, 75% were newly diagnosed with Pulmonary tuberculosis while the rest were previously treated (Fig 3). Out of the 79 patients, 30% were known diabetics and

8% were hypertensives. Of all the patients, 51% were smokers and 38% were alcoholics (Table 1). About 54% of patients, gained more than 10% of their body weight on completion of treatment. Of all the patients who gained more than 10% body weight, 53% of patients showed positive outcome of the treatment (Table 2 & 3). On classifying patients based on LPA results, 60.8% patients showed Kat G mutations;30.2% patients showed inh A mutations and 5.1% patients showed both mutations (Fig 4). The association between the genetic mutations and outcome of the treatment was not statistically significant (table 4.1 and 4.2). Among all the study participants, 88.6% showed positive outcome while the rest showed negative outcome (Fig 5).

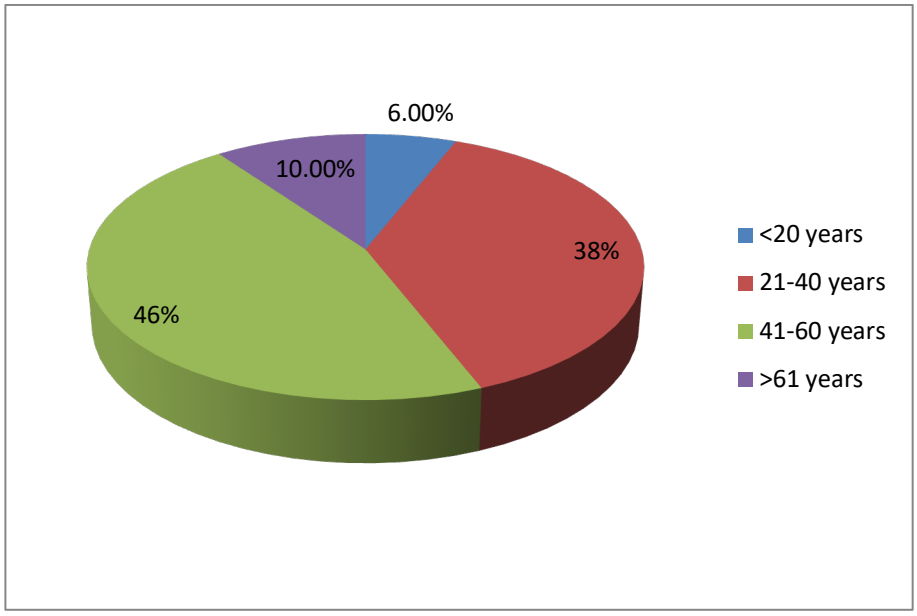

Figure 1: Age distribution among study participants

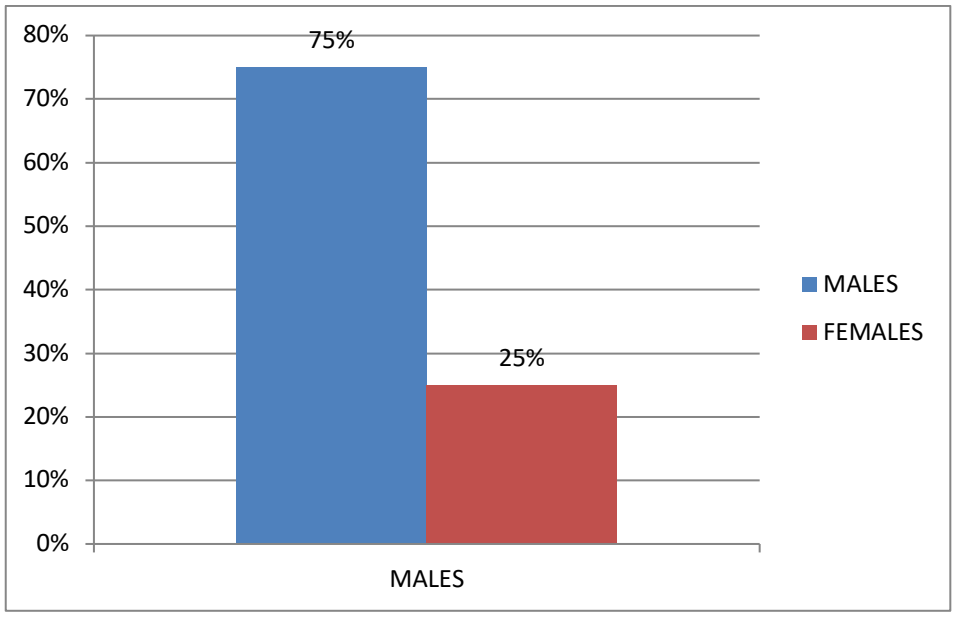

Figure 2: Gender distribution among study participants

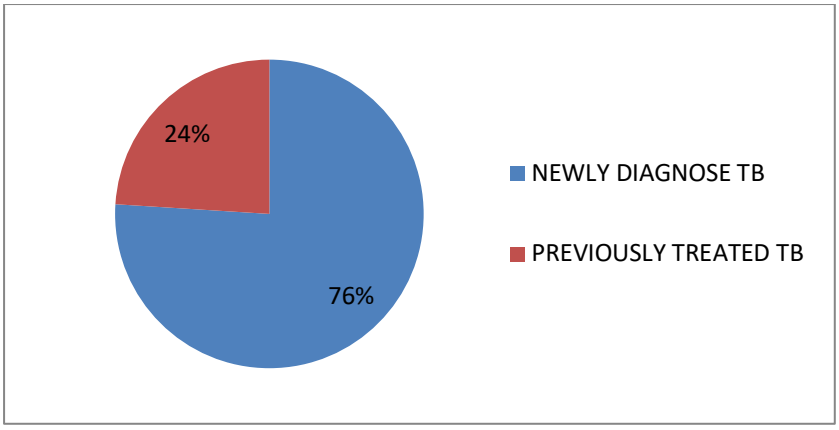

Figure 3: Type of tuberculosis among the study participants

Table 1: Distribution of smoking, alcoholism and comorbid illnesses among the study population

	Frequency (%)
Diabetes Mellitus	24 (30%)
Hypertension	6 (8%)
Smoking	40 (51%)
Alcoholism	30 (38%)

Table 2: Distribution of study participants based on post-treatment weight gain (</>10%)

Weight Gain Percentage	Frequency (%)
>10%	43 (54%)
<10%	36 (46%)
	79

Table 3: Association between weight gain and outcome of the treatment

Weight gain	Outcome of the treatment		P value
	Positive	Negative	
>10 %	30	6	0.03
<10 %	42	1	
	72	7	

*Mid-P exact test.

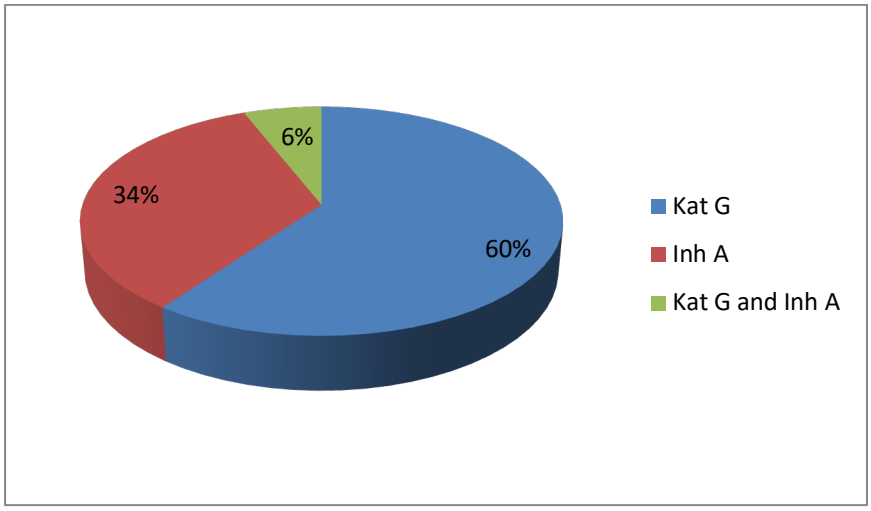

Figure 4: Distribution based on genetic mutations among study participants

Table 4.1: Association between genetic mutations and treatment outcome of patients

Genetic mutation	Treatment outcome		P value
Kat G	Positive	Negative	0.4
Present	42 (87.5%)	6 (12.5%)	
Absent	28 (90%)	3 (10%)	
	70	9	

*Fisher exact test

Table 4.2

Genetic Mutation	Treatment Outcome		P value
Inh A	Positive	Negative	0.6
Present	25 (92.6%)	2 (7.4%)	
Absent	45 (86.5%)	7 (13.5%)	
	70	9	

*Fisher exact test

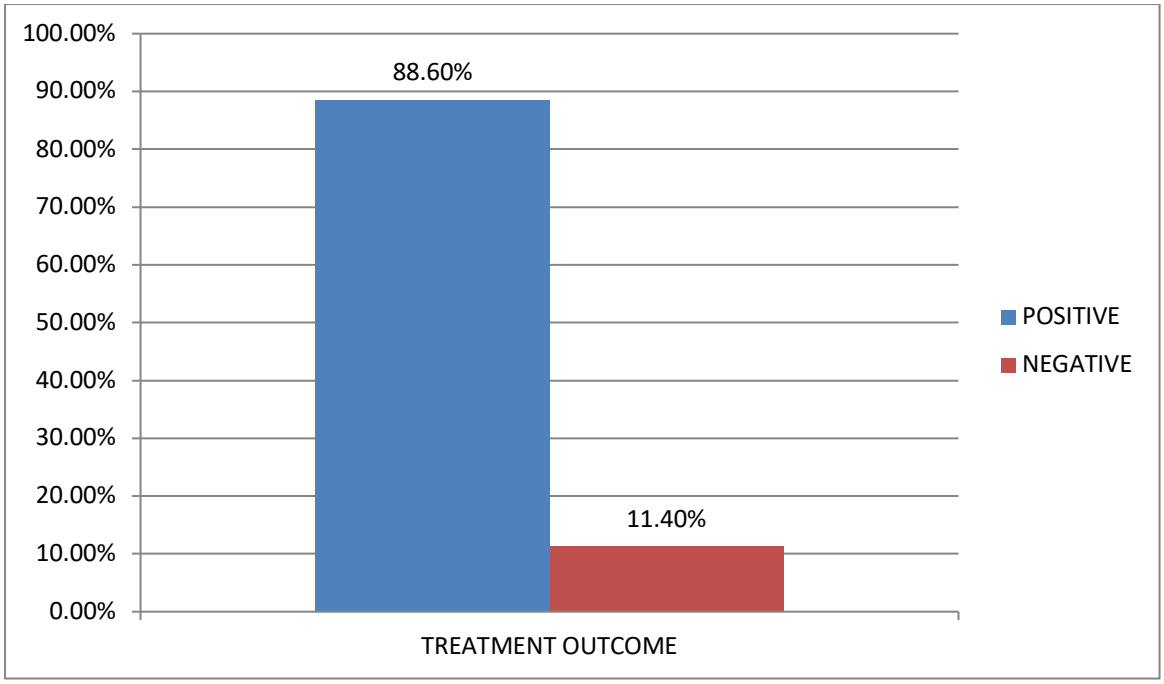

Figure 5: Treatment outcome of study participants

Discussion

Of the total 79 patients included in our study, patients are grouped into three age groups. The percentage of patients in each age groups <20, 20-40, 40-60, and >60 are as follows 6.32% (5), 37.97% (30), 45.56% (36), 10.12% (8).

Mean age was 43 years, In a study by Karo *et al*, similar observation was made where median age was 41. Males accounted for 75.95% of our study population, while females accounted for 24% of sample size.

60 (76%) of the patients were newly diagnosed Tuberculosis patients with primary Isoniazid monoresistance whereas 19 (24%) patients were previously treated for Tuberculosis. Similar observation was seen in many studies [10]. 24 (30%) patients were diabetic and the rest were non-diabetic at the onset of treatment similar to the study by kranti *et al*. 51% (40) patients were smokers. Similar observations were seen in other studies.

8% of the study sample was known hypertensive patients. 30 (38%) of the 79 patients were alcoholics. 36 (46%) patients had percentage weight gain less than 10%. 43(54%) patients had weight gain more than 10% at the end of the treatment similar to many other studies. Inh A was seen in 27(34.2%) patients. Of which 92.6% had positive outcome and 7.4% had negative outcome. KatG was seen in 48(60.8%) patients. Of these, 87.5% had positive outcomes and 12.5% had negative outcome. KatG and Inh A mutation was seen in 4 (5.1%) patients of which 25% had negative outcome. There was no difference in outcome between various types of mutations. This observation is in line with various other studies which have noted no difference in outcome between mutations [2].

In a study by Charan *et al*, the most common mutation in Isoniazid mono-resistance was kat G (65.1%), followed by inh A (28.1%) and both inh A and katG (6.7%). Similar observations were made in other studies [15,16]. Treatment completed and Cured were considered together as Positive outcome and Failure and Death was considered as Negative outcome. Final outcome of H mono-poly regimen is as follows Treatment completed – 29(36.7%), Cured – 41(51.9%), Death – 3(3.8%), Failure – 6(7.6%). The success rate of INH Mono/Poly DRTB registered in 2019 under NTEP is 78%. In a study by Gegia *et al,* the failure of INH Mono-resistant TB was at 11% [11].

Conclusion

Maximum number of patients was in the 40 – 60 age group (46%). INH mono-resistant TB was more common in males than females (76% vs 24%). Diabetic patients were more common than hypertensive patients. Positive outcome with Inh A mutation was more common than Kat G mutations. Negative outcomes were more common when the pre-treatment weight was less than <10% (statistically significant p-value <0.05). Poor weight gain was associated with poor outcomes (46% vs 10%, P value – 0.046).

Limitations

This study is an Observational study – RCTs are needed for better comparison of various regimens used for INH Mono-resistant Tuberculosis.

Sample size – due to COVID-19 leading to disruption of medical services the sample size is small. Large sample would be better in measuring the significance between various variables.

Statistical matching was not done adequately.

Missing parameters like severity of disease, BMI, CXR at end of treatment would make this study even more complete.

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