ORIGINAL ARTICLE

Isoniazid resistance profile in rifampicin resistant Mycobacterium tuberculosis

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is a global public health problem. Rifampicin (RIF) resistance has been used as a surrogate marker for MDR-TB but isoniazid (INH) resistance within RIF resistance cases is little known. This study aimed to determine the proportion of INH resistance among RIF-resistant MTB.

Methods: In this cross-sectional study, from March 2021 to February 2022, 53 RIF-resistant MTB isolates in sputum samples detected by Xpert-MTB RIF assay were enrolled. All samples were tested for mutation in katG (codon 315) and inhA promoter (-5, -8, -15 and -16) genes to detect INH resistance by real-time PCR. Statistical analysis was done using IBM SPSS (version 26).

Results: Out of 53 RIF-resistant samples, 15.1% were sensitive to INH, and the rest had concomitant resistance to INH. The proportion of newly diagnosed and previously treated cases was nearly equal, and most of the previously treated cases (92.9%) received treatment regularly. INH-resistant cases were mostly previously treated (55.5%), whereas sensitive cases were mostly newly diagnosed (62.5%). KatG was found to be the prominent mutation, with or without in combination with inhA mutation.

Conclusion: A considerable number of RIF-resistant isolates did not show concomitant resistance to INH. Most of the INH-resistant isolates were associated with katG mutation. Evaluation of INH resistance before using high-dose INH will help to avoid dose-dependent toxicity in MDR-TB patients.

Keywords: MDR-TB, RIF resistance, INH resistance, katG, inhA

INTRODUCTION

Tuberculosis (TB) ranks as the 13th most significant contributor to global mortality and stands as the second most fatal infectious disease, surpassed only by COVID-19.[1] Bangladesh holds the seventh position on a global scale and is placed fourteenth among countries with a high burden of multidrug-resistant TB (MDR-TB).[2] MDR-TB is defined as mycobacterium tuberculosis (MTB) resistant to at least isoniazid (INH) and rifampicin (RIF). It has emerged as a major pitfall of global TB control programs, requiring longer treatment, costly therapies, and higher treatment failure and mortality rates.[3] During 2019, it was approximated that 3.3% of newly reported TB cases and 18% of cases with prior treatment history exhibited MDR-TB or resistance to rifampicin (RR-TB).[2] Prevalence of any resistance to INH, regardless of rifampicin resistance status, is 10.7% among new TB patients and 27.2% among previously treated TB patients.[4] In Bangladesh, resistance to INH in previously treated cases is 49.9% and 10.8% in new patients.[5,6] RIF and INH resistance often occur concurrently as in MDR-TB strains but such resistance arises independently from each other and can occur without resistance to the other as well.[3]

In the molecular assay, more than 95% of RIF resistance is associated with a mutation in 81 base pair rifampin resistance determining region (RRDR) of the bacterial RNA polymerase β subunit (rpoB) gene (codons 507-533), with the most frequent mutation in codon 531. But, INH resistance appears to be more complex and has been associated with multiple genes, most commonly katG and inhA.[7] KatG encodes catalase/peroxidase enzymes, which causes activation of INH, that ultimately disrupts the mycolic acid biosynthesis by inhibiting inhA, which is the NADH-dependent enoyl-ACP reductase enzyme encoded by inhA gene.[8] A mutation in the inhA gene leads to the overexpression of

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HIGHLIGHTS

1. Among RIF-resistant MTB isolates, though the majority showed concomitant resistance to INH, a considerable number were found to be sensitive.
2. INH resistance was mostly associated with katG gene (codon 315) mutation in RIF-resistant cases.

the target this tends to elevate the minimal inhibitory concentration (MIC) of INH.[9] KatG mutation, particularly at codon 315, results in high-level INH resistance, while some katG mutations that retain catalage-peroxidase activity may result in low-level INH resistance.[10] On the other hand, inhA mutation is associated with low-level resistance, and higher doses may overcome this condition and translate into efficacy.[11] In 6.8% INH-resistant isolates, other less common may be responsible.[12] In such situations, INH resistance may potentially be caused by the upregulation of INH inactivators or efflux pumps.[13]

Effective management of MDR-TB begins with early diagnosis of the cases.[14] DNA probes are used in molecular approaches such as GeneXpert MTB/RIF to identify mutations linked to RIF resistance in the rpoB gene.[15] But, unlike GeneXpert, line probe assay and real -time PCR can detect mutations related to INH resistance, in addition to rpoB gene, completing the detection of MDR-TB. Moreover, when compared to the Xpert assay for smear negative-culture positive specimens, real-time PCR has better sensitivity (75.9%) than Xpert MTB/RIF assay (65.5%) in detecting MTB and drug resistance.[16]

WHO endorsed the use of Xpert MTB/RIF assay for rapid detection of MTB and RIF resistance. RIF resistance is frequently associated with concomitant INH resistance; it is considered to be surrogate marker for multidrug-resistant tuberculosis. For this, when Xpert MTB/RIF detects RIF-resistant MTB, the isolate is considered as MDR-TB without directly testing for isoniazid resistance.[17] Data analysis demonstrates that 33.3% of RIF-resistant isolates from new TB cases and 14.8% of previously treated cases do not display isoniazid resistance.[14] Global project data reports that in low MDR-TB prevalence settings, more than 40% of new cases and even in high MDR-TB burden settings, about 14% of new rifampicin-resistant cases show susceptibility to isoniazid.[18] A study in Bangladesh shows among RIF-resistant MTB, the rate of concomitant resistance to INH is 53.3%.[19] In this condition, methodologies relying on RIF resistance as a marker to detect MDR-TB by GeneXpert assay may not be conclusive.[20]

Moreover, the National Guidelines and for Programmatic Management of Drug Resistant TB recommends the use of shorter all-oral bedaquiline-containing regimen for the treatment of MDR/RR TB since 2020.[6] One of the components of this regimen is high-dose INH. This recommendation is made under the assumption that treatment with high dose of isoniazid may be effective in MTB strains with low-level resistance due to mutation in the inhA promoter region.[21] But, in this high TB burden setting, MDR-TB is mainly diagnosed using RIF resistance as a proxy and genotypic or phenotypic testing for INH resistance is not performed. In this state, if high-level INH resistance is present, a high dose of INH will be unable to overcome a high-level INH resistance and may result in adding toxicity without benefit.[22]

The aim of this study was to determine the extent of INH resistance in RIF-resistant MTB isolates. INH resistance was detected by identifying katG gene (codon 315) and inhA promoter gene (-5, -8, -15 and -16) mutations by real-time PCR.

METHODS

This cross-sectional study was done from March 2021 to February 2022. MTB isolates detected as RIF resistant by Xpert MTB/RIF assay in sputum samples were considered as RIF resistant cases. Samples were collected from five icddr,b TB Screening and Treatment Centers (TBSTC) in Dhaka city and 250 bedded TB Hospital, Shyamoli, Dhaka. We used a convenient sampling technique to collect the desired sample size 85. However, we enrolled 53 due to time and resource constrained. Each participant underwent individual interviews, during which all pertinent information (including the patient's clinical history, specific details about tuberculosis infection history, tuberculosis

TABLE 1 Distribution of RIF-resistant cases according to the treatment history

RIF resistant cases	Number of cases (%)
History of TB (n=53)	
Previously treated cases	28 (52.8)
Newly diagnosed cases	25 (47.2)
Anti-tuberculosis treatment regimen (n=28)	
Category I*	24 (85.7)
MDR-TB treatment	4 (14.3)
Regularity of treatment (n=28)	
Regular	26 (92.9)
Irregular	2 (7.1)

*All drug-sensitive TB patients, whether bacteriologically confirmed or clinically diagnosed, will receive the standard treatment regimen comprising 4 first-line drugs- isoniazid, rifampicin, pyrazinamide, and ethambutol for the initial two months (intensive phase) and 2 drugs-isoniazid and rifampicin for the next 4 months (continuation phase).

treatment history, previous treatment regimens, and treatment adherence) was meticulously recorded in a predefined data sheet. Patients who have never been treated for TB or have taken anti-TB drugs for less than one month were defined as new TB patients, whereas patients who had received treatment for more than one month in the past were included as previously treated patients. After collection, the samples were decontaminated using 2% NaOH-NALC solution and phosphate buffer saline following the Mycobacteriology laboratory manual, WHO, 2014.[23] DNA was extracted from the decontaminated sample using GenoType MTBDRplus 2.0 Genolyse kit following user's manual and stored at -20°C. Real-time Quantitative PCR (qPCR) was carried out according to the manufacturer's recommendation in thus extracted DNAs, using a qPCR kit (TRUPCR Rif/INH MTB Drug Resistant Detection Kit, India) in Applied Biosystem 7300 Real-time PCR system. For each sample, a reaction mixture was made where 20µl of PCR master mix was added to 10µl of DNA sample. Then, the plate was sealed and loaded into the instrument. The plate was read at the end of the sixth thermal cycle, and fluorescence was detected. (Fluorescein amidites-FAM for katG and Victoria-VIC for inhA), Mutation caused the katG or inhA probe in the assay to drop out completely, resulting in no detectable cycle threshold due to no amplification. In such cases, where either one of the probes or both the probes that did not show amplification had point mutations in katG gene (codon 315) and/or inhA promoter gene (-5, -8, -15 and -16). Samples that had point mutation in katG gene (codon 315) and/or inhA promoter gene (-5, -8, -15 and -16) by real-time PCR were considered as INH resistant isolates.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) Version 26. Data were normally distributed. Categorical data were expressed in frequency and percentage. The statistical significance was assessed using chi-squared test.

RESULTS

Out of 53 RIF-resistant cases, 15.1% of isolates were INH sensitive, and 84.9% had concomitant resistance to INH by Real-time PCR **(FIGURE 1)**. A total of 28 (52.8%) patients had a previous history of receiving treatment and 25 (47.2%) patients were newly diagnosed cases. Among previously treated cases, 24 (85.7%) patients received Category-I treatment and 4 (14.3%) cases were treated with an MDR-TB treatment

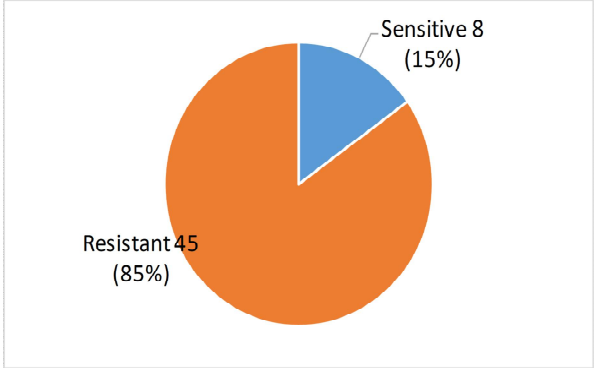
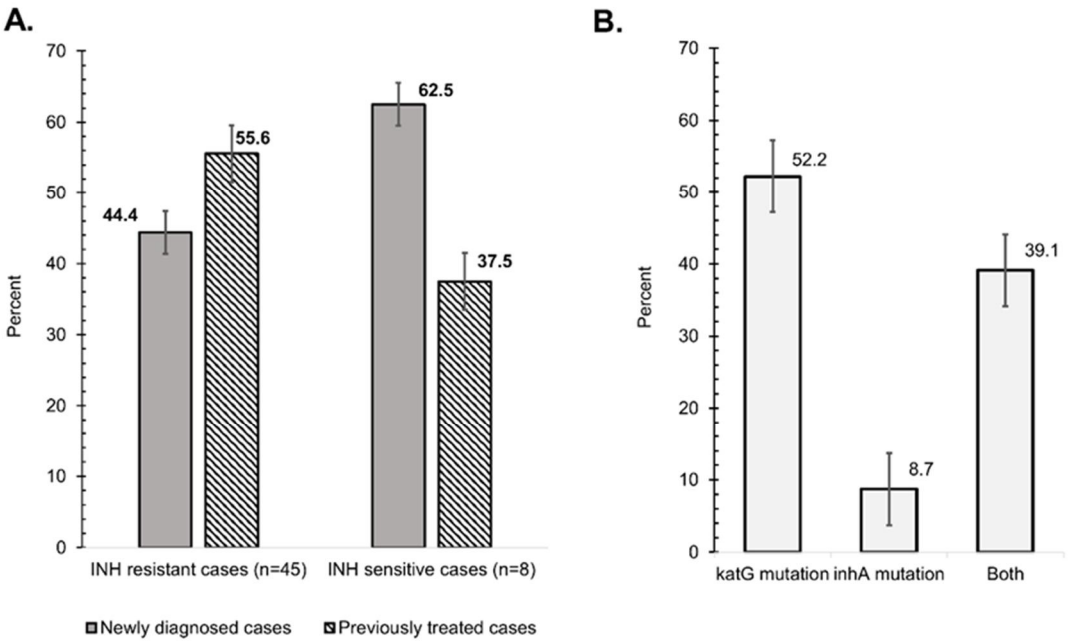


FIGURE 1 INH resistance profile among rifampicin-resistant samples by real-time PCR

regimen. Most previously treated cases (92.9%) received treatment regularly, while 7.1% did not **(TABLE 1)**. Among INH-resistant cases, 55.6% were previously treated, whereas 62.5% of INH-sensitive cases were newly diagnosed **(FIGURE 2)**. Real-time PCR detected katG to be the most dominant mutation (53.3%) responsible for INH resistance, followed by katG mutation in combination with inhA mutation (37.8%) and only inhA mutation was present in a few cases (8.9%) **(FIGURE 2)**.

DISCUSSION

Bangladesh is one of the countries with the highest global MDR-TB burden.[6] Detection of RIF resistance is



FIGRE 2 (A) History of tuberculosis treatment among INH resistant and INH sensitive cases by real-time PCR (B) Mutation profile of INH resistant cases by real-time PCR.

considered a marker for diagnosis of MDR-TB, without directly testing for INH. Despite being a major arm of anti-TB chemotherapy, INH susceptibility remains unevaluated.[14] This study focuses on INH resistance status in RIF-resistant cases.

In this study, among 53 RIF-resistant sputum samples, 15.1% were found to be isoniazid susceptible. Smith et al. found similar findings, where in high MDR-TB burden countries, 14% of RIF-resistant cases were INH susceptible.[18] In 2014, only 1.1% of TB patients worldwide were believed to harbor RIF resistance without concomitant INH resistance.[3] Proportion of RIF -resistant cases that are INH sensitive was detected at 2.8% in some countries of Asia (Bangladesh, Fiji, Indonesia, Papua-new-guinea, Thailand, East-Timor), during 2000-2004.[17] In Bangladesh, a study conducted in 2016 found that among the INH sensitive isolates, only 9.09% were concomitantly resistant to RIF and it was proposed that, nearly 90% RIF resistant strains are also INH resistant.[19] Therefore, this study indicates that the proportion of INH sensitivity among RIF-resistant isolates is increasing. In South Africa, one of the highest drug-resistant TB burden countries, a retrospective data analysis revealed RIF-resistant INH-sensitive cases increased from 15.3% in 2011 to 21.4% in 2014.[24] Increasing rates of RIF monoresistance cases may be responsible for this change.[14] Prevalence of RIF monoresistance was 0.2% and 0.4% in newly diagnosed and previously treated TB patients, respectively, in Bangladesh.[25] In 2020, this prevalence increased to 0.3% and 0.7% accordingly.[5] Similarly, the increasing rate of RIF monoresistance in India (22%), has also raised questions regarding the presence of INH co-resistance in RIF-resistant isolates.[20] So, Xpert MTB/ RIF assay, which is recommended as a first-line test for detection of MDR TB, considering RIF resistance as a 'surrogate marker', may not detect considerable number of INH susceptible, RIF resistant isolates and may need to be complemented by other DST methods.[14]

The proportion of previously treated and newly diagnosed tuberculosis patients had a small difference (52.8% versus 47.2%) in this study. However, the prevalence of RIF-resistant TB is higher among previously treated patients than newly diagnosed cases (18% compared to 3.8%) globally.[1] Though newly diagnosed patients are also at risk of RIF-resistant TB

due to either spontaneous mutations or transmission of drug-resistant strains, different findings in this study may occur due to a smaller number of samples, which may not represent the population.[26] Among previously treated patients, a majority (92.9%) of the patients received treatment regularly. A study conducted among pulmonary MDR-TB patients in Bangladesh also found that most of the previously treated cases (63.6%) had a history of taking regular treatment.[27] Though traditionally, the etiopathogenesis of MDR-TB is attributed to poor compliance and programmatic failure, in a study conducted in South India, previous TB treatment did not show a significant positive association with MDR (AOR 1.1 95% CI: 0.8–1.5, *P* 0.52). This result supports the observation found in a survey conducted in the Asian and African region by Dheda et al. claiming that factors other than poor compliance and program failure are strongly implicated in the prevalence of MDR-TB, and they need to be identified.[28]

This study revealed that a majority (62.5%) of INH-sensitive cases had no previous history of treatment. This finding aligns with another study, where 33.3% of RIF-resistant INH-sensitive patients were new cases and retreatment cases were 14.8%.[14] On the other hand, most of the INH-resistant cases (55.6%) in this study had a previous history of receiving treatment. A study among re-treatment cases in Bangladesh found 89.3% cases to be INH resistant.[29] An underlying factor contributing to this observation might stem from the prolonged previous TB therapy in cases requiring retreatment, potentially elevating the susceptibility to drug resistance. The likelihood of having drug-resistant tuberculosis was found to be directly related to the total time (measured in months) of prior anti-tuberculosis treatment.[30]

In the present study, the predominant (53.3%) mutation responsible for INH-resistance was in katG (codon 315), followed by mutation in both katG and inhA gene (37.8%) and mutation in inhA gene alone (8.9%). Similar distributions were observed in laboratory-based surveillance in Pakistan, where any katG mutation was present in 76.1% and inhA mutation was present in 7.6% in RIF-resistant isolates, but the proportion of double mutation found was 3.1%.[31] Globally, with a wide variation, katG mutations tend to be more frequent (42–95% of isolates), while inhA mutations occur in 6–43% of isolates; around 10% of M. tuberculosis isolates have both mutations.[11] Though the findings of this study are consistent with these ranges regarding the katG and inhA mutation, the proportion of isolates conferring double mutations was much higher. This phenomenon could arise due to the considerable variation in the prevalence of mutations in the katG and inhA genes across different geographical regions.[32] Moreover, isoniazid-resistant M. tuberculosis isolates with katG gene (codon-315) mutation are found to be strongly associated with high-level drug resistance due to extensive loss of enzymatic activity.[33] In these conditions, isoniazid will not be effective even when administered in higher dose, resulting in high-level INH resistance.[34] WHO has recommended for short-course MDR-TB treatment regimen containing high-dose INH in MDR-TB patients since 2016, which is also included in the National Guideline and Operational Manual for Drug-resistant TB of Bangladesh in 2020.[6] Results of this study suggest that patients should be evaluated for isoniazid sensitivity before starting standardized short-course treatment regimen for MDR-TB, containing high dose INH to avoid dose-related toxicity.

One limitation of this study was that the sample size was relatively low. However, the strength of the study lies in the fact that, samples had been collected from the screening and referral centres for tuberculosis. Additionally, for INH resistance, the two most common responsible gene mutations (katG and inhA) were detected. Moreover, though several studies demonstrated RIF and INH-monoresistance status, no other recent study has revealed INH resistance in RIF-resistant cases in our country.

Conclusion

A considerable proportion of samples were susceptible to INH among RIF resistance isolates. Most of the isoniazid-resistant isolates were associated with mutation in katG followed by mutation in inhA.

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Author Contributions

Conception and design: NS. Acquisition, analysis, and interpretation of data: NS. Manuscript drafting and revising it critically: NS, AAS, ANIS, SA. Approval of the final version of manuscript: NS, AAS, ANIS, SA. Guarantor accuracy and integrity of the work: AAS, ANIS, SA.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

The protocol was approved with ethical clearance by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh (BSMMU/ 2021/6521, date-17/07/2021). Minor changes in the title was approved later bearing the same number and date (Registration no- 3552).

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