



## Characteristics and Treatment Outcomes of Isoniazid Mono-Resistant Tuberculosis: A Retrospective Study

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**Purpose:** Isoniazid (INH) mono-resistant tuberculosis (Hr-TB) is a highly prevalent type of drug-resistant TB, possibly associated with unfavorable treatment outcomes. However, definitive guidelines on an optimal treatment regimen and duration for Hr-TB are currently under discussion. We evaluated the characteristics and treatment outcomes of Hr-TB patients.

**Materials and Methods:** We retrospectively reviewed the medical records of Hr-TB patients treated at a South Korean tertiary referral hospital from January 2005 to December 2018.

**Results:** We included 195 Hr-TB patients. 113 (57.9%) were male, and the median age was 56.6 [interquartile range, 40.2–68.6] years. Mutations in *katG* were the most frequent [54 (56.3%)], followed by those in the *inhA* [34 (35.4%)]. Favorable and unfavorable outcomes were noted in 164 (84.1%) and 31 (15.9%) patients, respectively. Smoking history [odds ratio (OR)=5.606, 95% confidence interval (CI): 1.695–18.543,  $p=0.005$ ], low albumin level (OR=0.246, 95% CI: 0.104–0.578,  $p=0.001$ ), and positive acid-fast bacilli culture at 2 months (OR=7.853, 95% CI: 1.246–49.506,  $p=0.028$ ) were associated with unfavorable outcomes.

**Conclusion:** A tailored strategy targeting high-risk patients is imperative for improved treatment outcomes. Further research on the rapid and accurate detection of resistance to INH and other companion drugs is warranted.

**Key Words:** Tuberculosis, isoniazid, treatment outcome

### INTRODUCTION

Isoniazid (INH, H) is a bactericidal first-line drug essential for

**Received:** August 3, 2020 **Revised:** October 22, 2020

**Accepted:** November 11, 2020

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•The authors have no potential conflicts of interest to disclose.

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the treatment of tuberculosis (TB).<sup>1</sup> According to the World Health Organization (WHO), rifampicin (RFP, R)-susceptible, INH-resistant TB (INH mono-resistant TB, Hr-TB) accounts for approximately 8% of all TB cases worldwide.<sup>2</sup> Although some previous studies<sup>3-7</sup> have reported that resistance to INH is not associated with poor outcomes, several recent ones have suggested that patients diagnosed with Hr-TB have worse outcomes than those with drug-susceptible TB<sup>3,8-11</sup> when treated with first-line drugs only. Therefore, early detection and proper management of Hr-TB are of paramount importance.

Currently, there are several diagnostic techniques for detecting drug resistance, including the conventional drug-susceptibility test (DST) and rapid molecular DST that detect specific DNA mutations in the genome of *Mycobacterium tuberculosis*.<sup>12</sup> The optimal use of currently available tests is important

for accurate diagnosis of Hr-TB, especially in high-TB-burden countries where diagnostic testing is limited, and further development of more rapid and accurate testing techniques for detecting INH resistance would be desirable.

WHO guidelines,<sup>2</sup> revised in 2018, recommend treatment with RFP, ethambutol (EMB, E), pyrazinamide (PZA, Z), and levofloxacin (LFX, Q) for a duration of 6 months in patients with Hr-TB. However, high-quality data in support thereof are lacking, and definitive guidelines on an optimal regimen and duration of treatment of Hr-TB have yet to be established. Therefore, we evaluated the clinical characteristics of patients with Hr-TB and explored their treatment outcomes over a 14-year period at a single center in South Korea.

## MATERIALS AND METHODS

### Study population and data collection

In this study, we retrospectively analyzed the records of patients diagnosed with culture-confirmed Hr-TB at a tertiary referral hospital in South Korea from January 2005 to December 2018. Patient data were collected from electronic medical records and included demographic features, as well as results of laboratory, radiographic, and microbiological tests. Patients were considered to be immunocompromised if they were 1) hematopoietic cell transplant recipients, 2) other solid organ transplant recipients, and/or 3) had received any immunosuppressive treatments (e.g., biologic agents targeting inflammatory mediators or corticosteroid therapy).

### Definition of Hr-TB and treatment outcomes

We conceptualized Hr-TB as TB susceptible to RFP and resistant to INH. An Hr-TB regimen was defined as a set of treatment agents reserved for the second-line treatment of Hr-TB, following detection of Hr-TB by clinicians based on either conventional or rapid molecular DST results. The principles of Hr-TB treatment were based on WHO recommendations.<sup>13-15</sup> When Hr-TB was confirmed without RFP resistance, clinicians continued the Hr-TB regimen with RFP, EMB, and PZA, and they also considered adding fluoroquinolone to the regimen. The regimens could be individually adjusted by the clinicians according to disease severity, adverse events, and/or adherence to the treatment. Treatment extension was considered in the following cases: patients with cavitary forms, those who remained smear-positive at the second month of treatment, those diagnosed with TB spondylitis, and those who were intolerant to first-line TB drugs.

Treatment outcomes were defined according to Korean TB<sup>16</sup> and WHO guidelines.<sup>17</sup> A favorable outcome was defined as a cure and/or treatment completion without relapse, and an unfavorable outcome was defined as treatment failure, death during treatment, lost to follow-up, not evaluated, or relapse after completing the initial treatment.

### Acid-fast bacillus (AFB) cultures and drug-susceptibility testing

Sputum specimens were examined by fluorochrome staining using auramine-rhodamine and were cultured on both solid medium (3% egg-based Ogawa medium) and *Mycobacteria* growth-indicator tube medium (MGIT; Becton Dickson, NJ, USA, since 2008).

Conventional DSTs were conducted at the Korean Institute of Tuberculosis (KIT) until December 2016, after which it continued at Seoul Clinical Laboratories (SCL). DSTs were conducted at KIT using the absolute concentration method with Lowenstein-Jensen medium and were performed at SCL using agar proportion methods with Middlebrook 7H10 medium. Resistance to INH was classified into high-level [minimum inhibitory concentration (MIC)  $\geq 1.0$   $\mu\text{g/mL}$ ] or low-level (MIC 0.1–1.0  $\mu\text{g/mL}$ ) resistance: high-level resistance to INH was defined as resistance to  $\geq 1.0$   $\mu\text{g/mL}$  of INH. Low-level resistance was defined as resistance to lower concentrations (0.1–1.0  $\mu\text{g/mL}$  of INH), but susceptibility to higher concentrations (i.e.,  $\geq 1.0$   $\mu\text{g/mL}$  of INH).

Rapid molecular DSTs were also performed using a line probe assay (AdvanSure™ MDR-TB GenoBlot Assay kit; LG Life Sciences Ltd., Seoul, Korea) to detect genetic mutations of *M. tuberculosis*.

### Statistical analysis

Categorical comparisons were analyzed using the Pearson's chi-squared test or Fisher's exact test. Continuous variables were compared using the Mann-Whitney test or t-test. Multivariate logistic regression analysis was used to identify risk factors associated with unfavorable outcomes. The odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. A  $p$  value  $< 0.05$  was considered significant for all analyses. Data analysis was performed using SPSS version 25 (IBM Corp., released 2017, Armonk, NY, USA).

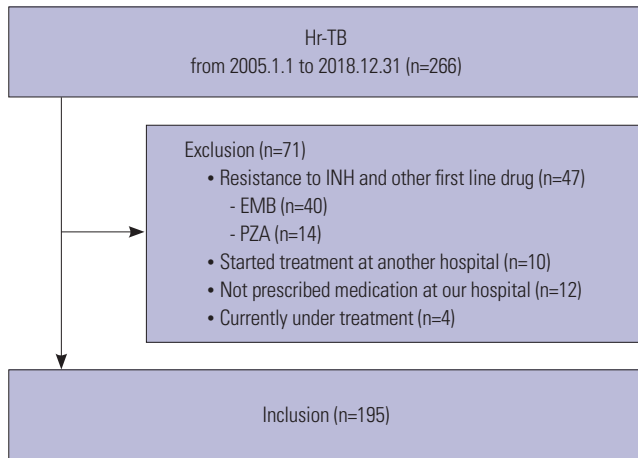
### Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Hospital (IRB No. 4-2020-0324), and the need for informed consent was waived by the committee.

## RESULTS

### Study population

From January 2005 to December 2018, 266 adult patients (aged  $\geq 18$  years) with culture-confirmed Hr-TB were enrolled. We excluded patients who were resistant to INH and one other first-line anti-TB drug ( $n=47$ ), who were already under treatment initiated at another hospital ( $n=10$ ), who were not prescribed medication at our hospital ( $n=12$ ), and/or who were currently under treatment ( $n=4$ ). Of the 266 patients, 71 were excluded, and 195 patients met the inclusion criteria (Fig. 1).



**Fig. 1.** Flow chart of the study population. Hr-TB, isoniazid mono-resistant tuberculosis; INH, isoniazid.

**Baseline characteristics**

The baseline characteristics of the study population are shown in Table 1. The median age was 56.6 [interquartile range (IQR), 40.2–68.6] years, and 113 (57.9%) were male. Of the patients under study, 72 (36.9%) had a smoking history, and 54 (27.7%) had received prior TB treatment. AFB smear was positive in 61 (31.3%) patients, and chest radiography detected cavitory lesions in 51 (26.2%). Phenotypic, high-level resistance was found in 138 (70.8%) patients, and low-level resistance was found in 57 (29.2%). Regarding treatment, 123 (63.1%) patients received a regimen of (H)REZ, accounting for the largest proportion, followed by the (H)REZQ regimen. The durations of treatment were approximately 6 months in 67 (34.4%) patients, 7–11 months in 95 (48.7%), and more than 12 months in 33 (16.9%).

**Comparative analysis of conventional and rapid molecular DSTs**

Table 2 shows the concordance between conventional and rapid molecular DSTs for the detection of INH resistance. Among all 195 Hr-TB patients, 145 (74.4%) had both conventional and rapid molecular DST results. Among the latter, 122 (62.6%) patients had specific genetic mutations conferring INH resistance (Table 2A). Table 2B shows the mutation patterns of *katG*, *inhA*, and *ahpC* genes detected by rapid molecular DSTs. Mutations in *katG* were most frequent [54 (56.3%)], followed by *inhA* mutations [34 (35.4%)]. The *katG* mutations were all detected in patients exhibiting phenotypic, high-level INH resistance. In contrast, *inhA* mutations were more frequent in patients with low-level resistance [27 (79.4%)].

**Treatment outcomes**

The clinical treatment outcomes are shown in Table 3. Of the 195 Hr-TB patients, 168 (86.2%) achieved treatment success at the end of treatment, including cure [154 (79.0%)] and completion [14 (7.2%)]. The overall rate of favorable outcomes was

**Table 1.** Baseline Characteristics

Variables	Total (n=195)
Age (yr)	56.6 (40.2–68.6)
Sex, male	113 (57.9)
Body mass index, kg/m <sup>2</sup>	20.8 (19.2–23.1)
Underlying disease	
Hypertension	56 (28.7)
Diabetes mellitus	39 (19.5)
Malignancy	35 (17.9)
Respiratory disease	31 (15.9)
Chronic kidney disease	11 (6.7)
Immunocompromised*	12 (6.2)
Smoking history	72 (36.9)
Prior history of TB treatment	54 (27.7)
Disease site	
Pulmonary	182 (93.3)
Extra-pulmonary	13 (6.7)
Disease severity	
Baseline positive AFB smear	61 (31.3)
Cavitory lesions in chest radiography	51 (26.2)
Phenotypic DST	
High-level resistance	138 (70.8)
Low-level resistance	57 (29.2)
Rapid molecular DST	
Done	145 (74.4)
Mutations	122 (62.6)
Drug regimen composition	
(H)REZ	123 (63.1)
(H)REZQ	46 (23.6)
(H)RZQ	5 (2.6)
(H)REQ	1 (0.5)
(H)RQ	1 (0.5)
Others <sup>†</sup>	19 (9.7)
Treatment duration <sup>‡</sup>	
6 months	67 (34.4)
7–11 months	95 (48.7)
12 months	33 (16.9)

TB, tuberculosis; AFB, acid-fast bacillus; DST, drug-susceptibility test; H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; Q, fluoroquinolone.

Data are presented as numbers (%) or medians (IQRs).

\*Immunocompromised patients: 1) hematopoietic cell transplant recipients, 2) other solid organ transplant recipients, and 3) patients who received any immunosuppressive treatments (e.g., biologic agents targeting inflammatory mediators, or corticosteroid therapy). <sup>†</sup>Others: includes multi-drug-resistant TB regimens. <sup>‡</sup>Treatment duration: time from the initiation to the completion of TB treatment.

84.1%. Unfavorable outcomes occurred in 31 (15.9%) patients: treatment failure [1 (0.5%)], death during treatment [5 (2.6%)], loss to follow-up [5 (2.6%)], not evaluated [16 (8.2%)], and relapse after successful initial treatment [4 (2.1%)]. The duration from the end of treatment to diagnosis of relapse was 461.0 days (IQR 124.3–1001.3). The characteristics of these relapsed patients are shown in Supplementary Table 1 (only online).

### Risk factors for unfavorable outcomes

To identify risk factors associated with unfavorable outcomes, we performed an analysis based on baseline characteristics, on-treatment culture status, and treatment regimens. Compared to patients with favorable outcomes, those with unfavor-

able outcomes had greater frequencies of co-morbidity with malignancy (35.5% vs. 14.6%,  $p=0.010$ ), chronic kidney disease (16.1% vs. 4.9%,  $p=0.037$ ), and smoking history (67.7% vs. 31.1%,  $p<0.001$ ), as well as lower levels of protein (6.7 g/dL vs. 7.1 g/dL,  $p=0.018$ ) and albumin (3.2 g/dL vs. 4.0 g/dL,  $p<0.001$ ) (Supplementary Table 2, only online). Positive AFB culture at 2 months after treatment initiation (16.1% vs. 2.4%,  $p=0.006$ ) and drug-induced hepatitis (25.8% vs. 9.1%,  $p=0.015$ ) were

**Table 2.** Conventional and Rapid Molecular DSTs for INH

A. Comparative analysis of conventional and rapid molecular DSTs for INH			
	Total (n=195)	Conventional DST	
		R	
Rapid molecular DST	Done	145 (74.4)	
	R	122 (62.6)	
	S	23 (11.8)	
	Not done	50 (25.6)	
B. Phenotypic resistance according to specific mutations			
Mutated genes	Total (n=96*)	Phenotypic resistance	
		High level (n=69)	Low level (n=27)
<i>katG</i>	54 (56.3)	54 (100.0)	0
<i>inhA</i>	34 (35.4)	7 (20.6)	27 (79.4)
<i>ahpC</i>	2 (2.1)	2 (100.0)	0
<i>katG</i> & <i>inhA</i>	6 (6.3)	6 (100.0)	0

DST, drug-susceptibility test; INH, isoniazid; R, resistant; S, susceptible. Data are presented as numbers (%).

\*Twenty-six patients did not have their mutation sites reported.

**Table 3.** Clinical Treatment Outcomes

Treatment outcomes	Total (n=195)
Treatment success at end of treatment	168 (86.2)
Treatment failure	1 (0.5)
Death during treatment	5 (2.6)
Loss to follow up*	5 (2.6)
Not evaluated	16 (8.2)
Relapse	4 (2.1)
Primary study outcomes	
Favorable outcomes <sup>†</sup>	164 (84.1)
Unfavorable outcomes <sup>‡</sup>	31 (15.9)

Data are presented as numbers (%).

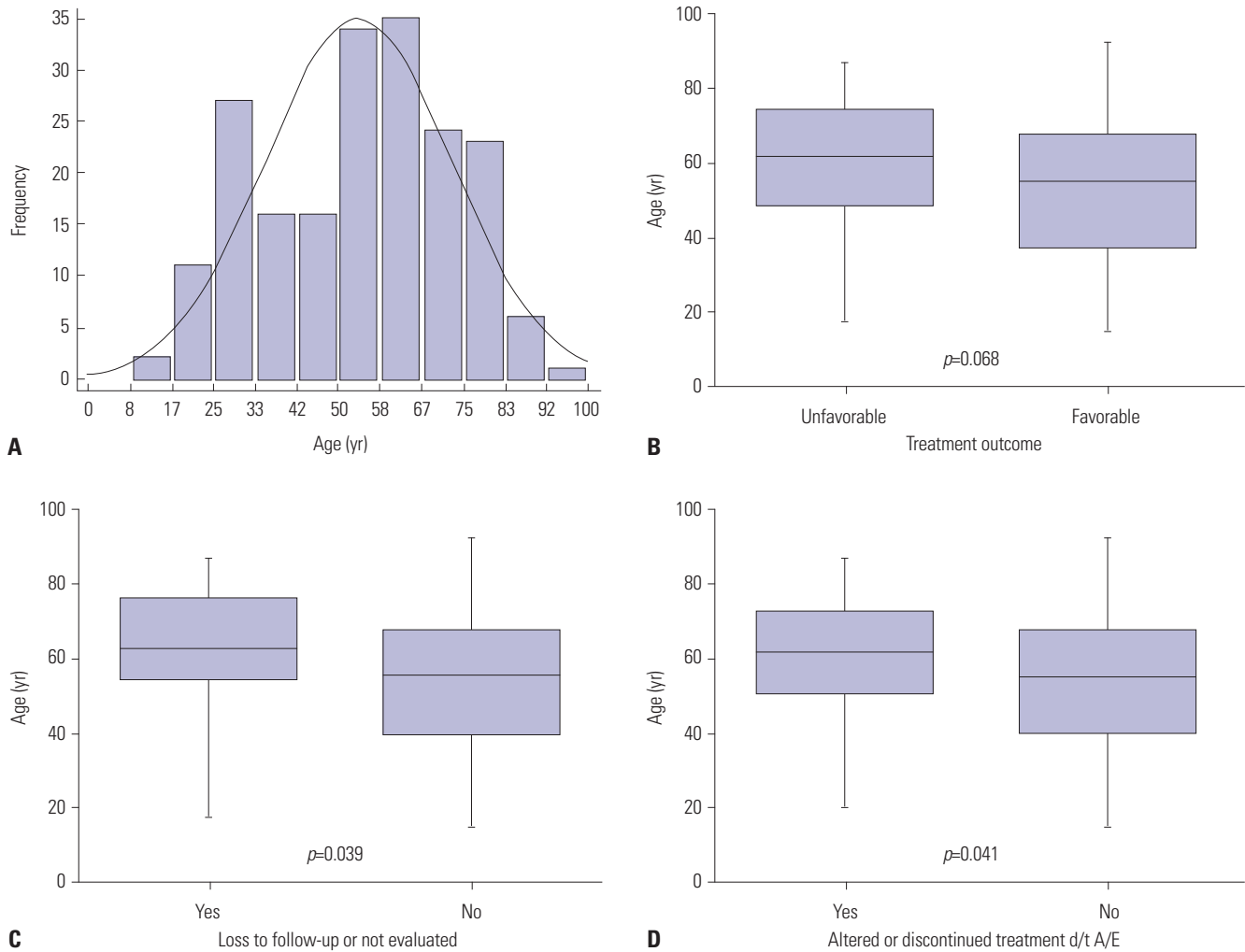
\*Loss to follow-up: treatment was interrupted for  $\geq 2$  months, <sup>†</sup>Favorable outcomes: cure and/or treatment completion without relapse, <sup>‡</sup>Unfavorable outcomes: treatment failure, death, lost to follow-up, not evaluated, or relapse after completing the initial treatment.

**Table 4.** Univariate and Multivariate Logistic Regression Analyses for Unfavorable Outcomes

Variables	Unadjusted			Adjusted		
	OR	95% CI	p value	OR	95% CI	p value
Age (yr)	1.022	0.999–1.045	0.057	1.001	0.971–1.032	0.951
Sex, male	1.961	0.851–4.517	0.114	0.443	0.124–1.580	0.210
Body mass index, kg/m <sup>2</sup>	1.012	0.885–1.159	0.858	0.999	0.841–1.186	0.989
Hypertension	2.032	0.919–4.495	0.080			
Diabetes mellitus	1.251	0.495–3.166	0.636			
Malignancy	3.208	1.366–7.534	0.007	2.389	0.799–7.146	0.119
Respiratory disease	0.321	0.073–1.422	0.135			
Chronic kidney disease	3.750	1.139–12.351	0.030	2.474	0.550–11.133	0.238
Immunocompromised*	1.845	0.470–7.242	0.380			
Smoking history	4.653	2.044–10.590	<0.001	5.606	1.695–18.543	0.005
Prior history of TB treatment	1.835	0.822–4.096	0.139			
Total protein level, g/dL	1.054	0.965–1.153	0.243			
Albumin level, g/dL	0.220	0.117–0.415	<0.001	0.246	0.104–0.578	0.001
Baseline positive AFB smear	1.482	0.668–3.287	0.333			
Cavitary lesions in chest radiography	1.722	0.755–3.928	0.196			
High-level resistance	1.225	0.513–2.927	0.648			
Fluoroquinolone use	0.847	0.374–1.920	0.692			
Injectable agents use	0.464	0.058–3.727	0.470			
Positive AFB culture at 1 month	2.226	0.845–5.861	0.105			
Positive AFB culture at 2 months	7.692	1.938–30.532	0.004	7.853	1.246–49.506	0.028
Drug induced hepatitis	3.455	1.318–9.059	0.012	1.156	0.321–4.153	0.825

OR, odds ratio; CI, confidence interval; TB, tuberculosis; AFB, acid-fast bacillus.

\*Immunocompromised patients: 1) hematopoietic cell transplant recipients, 2) other solid organ transplant recipients, and 3) patients who received any immunosuppressive treatments (e.g., biologic agents targeting inflammatory mediators or corticosteroid therapy).



**Fig. 2** The age distribution of the study patients. (A) Histogram showing the age distribution of the study patients. (B) Box plot of the age distribution according to treatment outcomes. (C) Box plot of the age distribution according to loss to follow-up or not evaluated. (D) Box plot of the age distribution according to adverse events. d/t, due to; A/E, adverse events.

more frequent in patients with unfavorable outcomes than in those with favorable outcomes. Patients received Hr-TB treatment for a median of 211.0 (IQR 124.0–273.0) days and treatment as a whole for a median of 273.0 (IQR 187.0–342.0) days.

Based on a multivariate analysis performed on baseline characteristics, as well as on-treatment culture status and regimens, smoking history (OR=5.606, 95% CI: 1.695–18.543,  $p=0.005$ ), low albumin level (OR=0.246, 95% CI: 0.104–0.578,  $p=0.001$ ), and positive AFB culture at 2 months (OR=7.853, 95% CI: 1.246–49.506,  $p=0.028$ ) were associated with unfavorable treatment outcomes (Table 4).

**Age distribution of the study patients**

Fig. 2 shows the age distribution of the study patients. The median age was 56.6 (IQR, 40.2–68.6) years (Fig. 2A). There were no significant age differences between the unfavorable and favorable treatment outcome groups (62.0 years vs. 56.0 years,  $p=0.068$ ) (Fig. 2B). However, we discovered that older age was

associated with “loss to follow-up” or “not evaluated” as treatment outcomes ( $p=0.039$ ) (Fig. 2C). Furthermore, patients whose treatment regimens were altered or those who discontinued treatment earlier than scheduled due to adverse events were older than those who maintained the same treatment regimen (62.8 years vs. 54.6 years,  $p=0.041$ ) (Fig. 2D).

**DISCUSSION**

In this study, we evaluated the clinical characteristics and treatment outcomes of patients with Hr-TB. The overall favorable outcome rate was 84.1%, which was not inferior to those reported in recent meta-analyses of Hr-TB.<sup>9,11,18</sup> The favorable treatment outcome rate in the current study was also higher than that in patients with multidrug-resistant TB (76.6%) from 2005–2017 at our institution.<sup>19</sup> The results for Hr-TB were, however, inferior to those for drug-susceptible TB in Korea.<sup>20</sup> In addition, we dis-

covered that several factors were associated with unfavorable outcomes, including smoking, low level of albumin at diagnosis, and positive culture at 2 months of treatment.

One of the explanations for the relatively poor treatment outcomes in our study might be the older age of the participants. They had a median age of 56.6 (IQR 40.2–68.6), which was higher than that of patients from the aforementioned studies,<sup>19–21</sup> possibly leading to suppressed treatment success. Treatment outcomes in older adult patients are known to be worse than those in their younger counterparts, mainly because of delayed diagnosis, frequent co-morbidities, and increased rates of adverse events.<sup>22</sup> Among our participants, patients whose treatment regimens were altered or those who discontinued treatment earlier than scheduled due to adverse events were older than those who maintained the same treatment regimen. We further discovered that older age was associated with loss to follow-up or not undergoing evaluation, which were major forms of unfavorable outcomes in the current study. Thus, to improve the treatment outcomes for Hr-TB, regular monitoring, supportive intervention to maintain strict adherence to the recommended TB treatment, and effective management of adverse reactions are needed for older patients.

The WHO guidelines, revised in 2018, suggested that treatment success rate was higher when fluoroquinolone was added to the (H)REZ regimens;<sup>2</sup> thus, they recommended Hr-TB treatment with RFP, EMB, PZA, and LFX for 6 months. However, in our study, we did not find significant differences in favorable outcomes between patients receiving fluoroquinolones and those who did not. In this study, only 36.3% of patients received fluoroquinolones as a therapeutic agent, probably because this study utilized data from as far back as 2005, before the guidelines were revised. Thus, fluoroquinolones might have been administered to patients who had extensive disease or experienced adverse drug reactions. It was not possible to control for all the possible confounding in this study.

For the diagnosis and treatment of Hr-TB, an empirical approach is generally not advised.<sup>23</sup> Thus, rapid detection of Hr-TB with laboratory confirmation plays an important role in accurate treatment. However, a conventional DST is time consuming; therefore, Hr-TB may be undetected and mistaken for pan-susceptible TB, which may lead to insufficient treatment and the spread of Hr-TB.<sup>9</sup> In addition, conventional DSTs may yet be unavailable in resource-limited, high-TB-burden countries.<sup>24</sup> Although line probe assay is also used as a rapid molecular test to identify INH and RFP resistance through gene mutations,<sup>25</sup> the sensitivity of INH resistance detection by this method is lower than that of RFP resistance detection.<sup>26</sup> The sensitivity of rapid molecular DSTs in the current study was 84.1%, a finding consistent with the results of a meta-analysis.<sup>27</sup> As other genetic mutations associated with INH resistance have yet to be discovered, further development of rapid and accurate testing techniques for the detection of INH resistance is needed. To this end, the use of whole-genome sequencing,

which uses the complete DNA sequence of an organism's genome,<sup>28</sup> may prove beneficial: according to findings from a prospective study,<sup>29</sup> whole-genome sequencing predicted drug-susceptibility with an accuracy of 93%.

In our data, more than half of the attending physicians altered the treatment regimen for Hr-TB after obtaining results from full phenotypic DSTs, including PZA and LFX. This took over 1 month, which is longer than the turn-around time of a rapid molecular test for INH. The exclusion of RFP resistance is essential before commencing Hr-TB treatment, and exclusion of resistance to fluoroquinolones and PZA before Hr-TB treatment with a fluoroquinolone-containing regimen is ideal to reduce the acquisition of additional drug resistance.<sup>23</sup>

Updated WHO guidelines recommended, as a minimum, rapid molecular testing for RFP resistance before commencing treatment with an Hr-TB regimen. However, we found 47 patients (among 266 INH resistance-confirmed patients) with resistance to INH and EMB or PZA simultaneously during the study period, though we excluded them from the final study population. We also discovered eight cases of Hr-TB isolates resistant to fluoroquinolone (among 266 INH resistance-confirmed patients). Even though drug-resistant TB surveillance has indicated that fluoroquinolone resistance among RFP-susceptible TB patients is generally low,<sup>30</sup> reliable and rapid molecular methods for the exclusion of fluoroquinolone and PZA (possibly) before administering a Hr-TB regimen are urgently necessary.

There were a few limitations to our study. First, we did not compare Hr-TB to drug-susceptible TB. Second, our study was a single-center trial, and the results may not be applicable in other settings. The retrospective design of this study was limited to the review of medical records; therefore, our data may not be as accurate as data collected within the context of a prospective study. Third, since pre-revised guidelines recommended the addition of fluoroquinolone only for extensive disease burden, fewer cases involving its administration were reported in this study, which includes data from 2005. Due to the small sample size, analysis of the association between treatment regimens and treatment outcomes was limited. Fourth, our data includes 16 cases of patients with “not evaluated” outcomes, including 14 cases of domestic transfer out, and two cases of international transfer out. Although the final treatment outcome for patients with “not evaluated” outcomes is unknown, this study classified these cases as unfavorable outcomes. It is important to systematically operate national databases to ensure that the treatment of transferred-out patients is consistent and complete.

In conclusion, 84% of Hr-TB patients achieved favorable outcomes with guideline-based treatment, and previous smoking history, low levels of albumin, positive AFB culture at 2 months of treatment, and development of drug-induced hepatitis during treatment were associated with unfavorable treatment outcomes of Hr-TB. A tailored strategy targeting high-risk patients

is required to improve treatment outcomes. Furthermore, though the line probe assay helps in the detection of Hr-TB, further research into more rapid and accurate techniques for detecting resistance to INH and other Hr-TB treatment drugs is warranted.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Se Hyun Kwak and Young Ae Kang. **Data curation:** Se Hyun Kwak. **Formal analysis:** Se Hyun Kwak. **Investigation:** Se Hyun Kwak. **Methodology:** Se Hyun Kwak, Ji Soo Choi, and Eun Hye Lee. **Project administration:** Se Hyun Kwak and Young Ae Kang. **Resources:** Young Ae Kang. **Software:** Se Hyun Kwak and Young Ae Kang. **Supervision:** Eun Young Kim, Ji Ye Jung, Moo Suk Park, Young Sam Kim, Joon Chang, and Young Ae Kang. **Validation:** Su Hwan Lee, Ah Young Leem, Sang Hoon Lee, Song Yee Kim, Kyung Soo Chung, and Young Ae Kang. **Visualization:** Se Hyun Kwak. **Writing—original draft:** Se Hyun Kwak. **Writing—review & editing:** Se Hyun Kwak and Young Ae Kang. **Approval of final manuscript:** all authors.

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