Resistance to isoniazid (INH) is the most common form of drug resistance in pulmonary tuberculosis (TB). Although fluoroquinolones (FQs) are recommended to strengthen treatment regimens for INH-resistant pulmonary TB, few studies have evaluated the clinical efficacy of FQ-containing regimens in patients with INH-resistant pulmonary TB. A retrospective cohort study of 140 patients with INH-resistant pulmonary TB was performed between 2005 and 2012. We evaluated whether FQ-containing regimens yielded improved treatment outcomes for patients with INH-resistant pulmonary TB. Overall, favorable outcomes were achieved in 128 (91.4%) patients. Unfavorable outcomes occurred in 12 patients (8.6%), including 7 with treatment failure (5.0%), and 5 with relapse after initial treatment completion (3.6%). FQs, such as levofloxacin and moxifloxacin, were given to 75 (53.6%) patients. Favorable treatment outcomes were more frequent for patients who received FQs (97.3% [73/75 patients]) than for those who did not receive FQs (84.6% [55/65 patients]) (P = 0.007). Patients who did not receive FQs were more likely to develop treatment failure (9.2% [6/65 patients] versus 1.3% [1/75 patients]) (P = 0.049) than patients who received FQs. The adjusted proportion of unfavorable outcomes was significantly higher among patients who did not receive FQs (8.8%; 95% confidence interval [CI], 3.3 to 21.5%) than among those who did receive FQs (1.5%; 95% CI, 0.3 to 7.7%) (P = 0.037). These results suggest that the addition of FQs can improve treatment outcomes for patients with INH-resistant pulmonary TB.
TABLE 1 Baseline characteristics of 140 patients with isoniazid-resistant pulmonary tuberculosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Valuea</th>
<th>Patients who received FQs (n = 75)</th>
<th>Patients who did not receive FQs (n = 65)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54 (38–67)</td>
<td>56 (40–67)</td>
<td>46 (33–66)</td>
<td>0.105</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>92 (65.7)</td>
<td>49 (65.3)</td>
<td>43 (66.2)</td>
<td>0.919</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>16 (11.4)</td>
<td>11 (14.7)</td>
<td>5 (7.7)</td>
<td>0.196</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (10.0)</td>
<td>10 (13.3)</td>
<td>4 (6.2)</td>
<td>0.158</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>7 (5.0)</td>
<td>5 (6.7)</td>
<td>2 (3.1)</td>
<td>0.450</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>7 (5.0)</td>
<td>2 (2.7)</td>
<td>5 (7.7)</td>
<td>0.250</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6 (4.3)</td>
<td>3 (4.0)</td>
<td>3 (4.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Previous history of TB treatment</td>
<td>42 (30.0)</td>
<td>20 (26.7)</td>
<td>22 (33.8)</td>
<td>0.355</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive sputum AFB smear</td>
<td>61 (43.6)</td>
<td>32 (42.7)</td>
<td>29 (44.6)</td>
<td>0.817</td>
</tr>
<tr>
<td>Cavitary lesions in chest radiography</td>
<td>33 (23.6)</td>
<td>15 (20.0)</td>
<td>18 (27.7)</td>
<td>0.285</td>
</tr>
</tbody>
</table>

a Data are presented as medians and interquartile ranges or as numbers (%).

Treatment outcomes. Treatment outcomes were defined based on previous studies evaluating the treatment outcomes of INH-resistant TB (10, 12, 14). A patient was considered cured if his/her culture was negative in the last month of treatment and had also been negative at least once in the previous period. Treatment completion was defined as completing treatment without evidence of failure, but without meeting the criteria for being cured. Treatment success in the present study included being cured and completing treatment. Treatment failure was defined as consistently having positive sputum culture results after 4 months of treatment. Relapse was defined as the diagnosis of pulmonary TB in a patient after an initially successful treatment. Treatment success with no evidence of relapse during the follow-up period was defined as a favorable outcome, whereas unfavorable outcomes included treatment failure and relapse after initial treatment success.

Statistical analysis. Data are presented as numbers and percentages for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. Categorical variables were compared using the Pearson χ² test or Fisher’s exact test. Continuous variables were compared using the Mann-Whitney U test. To compare treatment outcomes between patients who received FQs and those who did not receive FQs, adjustments were performed between the two groups for diabetes mellitus status, previous TB treatment history, use of pyrazinamide, and factors with P values of <0.2 by univariate analysis (chronic pulmonary disease, cavitary lesions in chest radiographs, and treatment duration). The adjusted proportion of patients with unfavorable outcomes was calculated by logistic regression analysis. All tests were two-sided, and P values of <0.05 were considered statistically significant. All statistical analyses were performed using SASS 9.4 (SAS Institute, Cary, NC) and R 3.0.3 (Vienna, Austria; http://www.R-project.org/).

RESULTS

Baseline characteristics. The baseline characteristics of the 140 patients are summarized in Table 1. Of the 140 patients, 92 (65.7%) were males, and the median age was 54 years (IQR, 38 to 67 years). The most common comorbidity was malignancy (16/140 patients [11.4%]), followed by diabetes mellitus (14/140 patients [10.0%]). None of the patients were positive for human immunodeficiency virus infection. Whereas 98 patients (70.0%) had no previous TB treatment history, 42 (30.0%) had previous TB treatment history. Sputum acid-fast bacillus (AFB) smear tests were positive for 61 patients (43.6%), and cavitary lesions were observed by chest radiography for 33 patients (23.6%). The presence of cavitary lesions in chest radiographs was evaluated based on the formal reports of chest X-rays performed by chest radiologists.

Overall, 75 patients (53.6%) received FQs at the discretion of the attending physician. No statistically significant differences were observed for baseline characteristics, including age, sex, comorbidities, previous TB treatment history, positive AFB smear tests, and cavitary lesions in chest radiographs, between patients who received FQs and those who did not receive FQs. However, there was a significant difference in treatment response between the patients who received FQs at the time of decision-making and those who did not. Compared with patients who received FQs, patients who did not receive FQs were more likely to have improvements in chest X-rays (69.2% [45/65 patients] versus 48.0% [36/75 patients]) (P = 0.011) and negative conversion in sputum AFB smears (59.3% [16/27 patients] versus 31.3% [10/32 patients]) (P = 0.031) at the time that drug susceptibility testing results were provided (see Table S2 in the supplemental material).

Treatment regimens. Sixty-eight patients (48.6%) received a 6-month treatment regimen. The treatment duration was extended to 7 to 12 months and >12 months in 64 (45.7%) and 8 (5.7%) patients, respectively (see Table S3 in the supplemental material). INH was continuously prescribed throughout treatment for 8/140 (5.7%) patients. In contrast, 14/140 (10.0%) patients did not receive INH at the initiation of treatment. These patients included seven with a previous treatment history of INH-resistant TB, five who received anti-TB medication after confirmation of INH-resistant TB, one with a previous INH-induced allergy, and one who had close contact with a patient with INH-resistant TB. INH was discontinued in 118/140 (84.3%) patients a median of 2.1 months (IQR, 1.2 to 2.9 months) after the initiation of anti-TB medication.

As shown in Table 2, no statistically significant differences were observed regarding the use of rifampin, ethambutol, or streptomycin between patients who received FQs and those who did not. While pyrazinamide was used more frequently in patients who did not receive FQs (62/65 patients [95.4%]) than in patients who did not receive FQs (59/75 patients [78.7%]) at the time of decision-making. No statistically significant differences were observed for drug susceptibility testing results between patients who did not receive FQs and those who did not receive FQs. However, there was a significant difference in treatment response between the patients who received FQs at the time of decision-making and those who did not. Compared with patients who received FQs, patients who did not receive FQs were more likely to have improvements in chest X-rays (69.2% [45/65 patients] versus 48.0% [36/75 patients]) (P = 0.011) and negative conversion in sputum AFB smears (59.3% [16/27 patients] versus 31.3% [10/32 patients]) (P = 0.031) at the time that drug susceptibility testing results were provided (see Table S2 in the supplemental material).
TABLE 2 Treatment regimens and clinical outcomes

<table>
<thead>
<tr>
<th>Drug composition</th>
<th>Total (n = 140)</th>
<th>Patients who received FQs (n = 75)</th>
<th>Patients who did not receive FQs (n = 65)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With rifampin</td>
<td>134 (95.7)</td>
<td>71 (94.7)</td>
<td>63 (96.9)</td>
<td>0.686</td>
</tr>
<tr>
<td>With ethambutol</td>
<td>131 (93.6)</td>
<td>68 (90.7)</td>
<td>63 (96.9)</td>
<td>0.176</td>
</tr>
<tr>
<td>With pyrazinamide</td>
<td>124 (88.6)</td>
<td>62 (82.7)</td>
<td>62 (95.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>With streptomycin</td>
<td>2 (1.4)</td>
<td>2 (2.7)</td>
<td>0</td>
<td>0.499</td>
</tr>
<tr>
<td>Duration (mo)</td>
<td>8.3 (6.1–11.6)</td>
<td>9.1 (6.2–12.1)</td>
<td>7.1 (6.1–9.6)</td>
<td>0.026</td>
</tr>
</tbody>
</table>

**Outcome**

- **Cured**
  - Total: 81 (57.9)
  - FQs: 42 (56.0)
  - No FQ: 39 (60.0)
  - P = 0.633

- **Treatment completed**
  - Total: 52 (37.1)
  - FQs: 32 (42.7)
  - No FQ: 20 (30.8)
  - P = 0.146

- **Treatment failure**
  - Total: 7 (5.0)
  - FQs: 1 (1.3)
  - No FQ: 6 (9.2)
  - P = 0.049

- **Relapse after treatment success**
  - Total: 5/133 (3.8)
  - FQs: 1/74 (1.4)
  - No FQ: 4/59 (6.8)
  - P = 0.170

- **Favorable outcome**
  - Total: 124 (88.6)
  - FQs: 68 (90.7)
  - No FQ: 63 (95.4)
  - P = 0.018

- **Unfavorable outcome**
  - Total: 12 (8.6)
  - FQs: 2 (2.7)
  - No FQ: 10 (15.4)
  - P = 0.007

- **Development of acquired drug resistance**
  - Total: 5 (3.6)
  - FQs: 1 (1.3)
  - No FQ: 4 (6.2)
  - P = 0.183

- **Acquired resistance to rifampin**
  - Total: 3 (2.1)
  - FQs: 1 (1.3)
  - No FQ: 2 (3.1)
  - P = 0.597

---

Patients who received FQs significantly more frequent among patients who did not receive FQs than among those who did receive FQs (9.2% [6/65 patients] versus 1.3% [1/75 patients]) (P = 0.049). Although the rate of relapse after initial treatment success was higher among patients who did not receive FQs (4/59 patients [6.8%]) than among those who did receive FQs (1/74 patients [1.4%]), this difference was not statistically significant (P = 0.170).

Acquired drug resistance developed in 5/140 (3.6%) patients, all of whom had unfavorable outcomes, including four patients who did not receive FQs and one patient who received an FQ. Acquired drug resistance in the four patients who did not receive FQs included acquired resistance to rifampin (n = 2), ethambutol (n = 1), and pyrazinamide (n = 1). For comparison, acquired resistance to rifampin developed in the one patient who received an FQ. Although the development of acquired drug resistance was more frequent among those who did not receive FQs than among those who received FQs, this difference was not statistically significant (6.2% [4/65 patients] versus 1.3% [1/75 patients]) (P = 0.183). Moreover, there was no significant difference in the development of acquired resistance to rifampin between the patients who received FQs and those who did not receive FQs (1.3% [1/75 patients] versus 3.1% [2/65 patients]) (P = 0.597).

Comparison of clinical characteristics between patients with favorable versus unfavorable outcomes. As shown in Table 3, no statistically significant differences were observed between patients with favorable versus unfavorable outcomes regarding comorbidities, previous TB treatment history, positive AFB smears, cavitary lesions in chest radiographs, or the use of rifampin, ethambutol, or pyrazinamide. Compared to patients with unfavorable outcomes (12/140 patients [8.6%]), those with favorable outcomes (128/140 patients [91.4%]) were more likely to have received FQs (57% [73/128 patients] versus 16.7% [21/12 patients]) (P = 0.007) and to have been treated for...
a longer duration (8.8 months [IQR, 6.1 to 11.8 months] versus 6.2 months [IQR, 5.7 to 9.0 months]) \( P = 0.024 \). In contrast, patients with unfavorable outcomes were more likely to have cavities in chest radiographs (6/12 patients [50.0%]) than patients with favorable outcomes (27/128 patients [21.1%]) \( P = 0.035 \).

**Effects of FQs on treatment outcomes of INH-resistant pulmonary TB.** The crude proportions, adjusted proportions, and odds ratios for unfavorable outcomes for patients with INH-resistant pulmonary TB are shown in [Table 4](#), presented according to FQ status. The crude proportion of unfavorable outcomes was higher for patients who did not receive FQs (15.4%; 95% confidence interval [CI], 8.5 to 26.3%) than for those who did receive FQs (2.7%; 95% CI, 0.7 to 10.0%), and the difference was statistically significant (12.7%; 95% CI, 3.2 to 22.2%) \( P = 0.017 \). Moreover, the adjusted proportion of unfavorable outcomes was higher for patients who did not receive FQs (8.8%; 95% CI, 3.3 to 21.5%) than for those who did receive FQs (1.5%; 95% CI, 0.3 to 4.5%)

### TABLE 3 Comparison of clinical characteristics of patients with favorable versus unfavorable outcomes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 140)</th>
<th>Favorable outcomes (n = 128)</th>
<th>Unfavorable outcomes (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54 (38–67)</td>
<td>54 (37–67)</td>
<td>51 (41–72)</td>
<td>0.650</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>92 (65.7)</td>
<td>83 (64.8)</td>
<td>9 (75.0)</td>
<td>0.751</td>
</tr>
</tbody>
</table>

Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Total (n = 140)</th>
<th>Favorable outcomes (n = 128)</th>
<th>Unfavorable outcomes (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy</td>
<td>16 (11.4)</td>
<td>15 (11.7)</td>
<td>1 (8.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (10.0)</td>
<td>12 (9.4)</td>
<td>2 (16.7)</td>
<td>0.343</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>7 (5.0)</td>
<td>7 (5.5)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>7 (5.0)</td>
<td>5 (3.9)</td>
<td>2 (16.7)</td>
<td>0.111</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>6 (4.3)</td>
<td>6 (4.7)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Previous history of TB treatment

<table>
<thead>
<tr>
<th>Previous history of TB treatment</th>
<th>Total (n = 140)</th>
<th>Favorable outcomes (n = 128)</th>
<th>Unfavorable outcomes (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive sputum AFB smear</td>
<td>61 (43.6)</td>
<td>54 (42.2)</td>
<td>7 (58.3)</td>
<td>0.281</td>
</tr>
<tr>
<td>Cavitory lesions in chest radiographs</td>
<td>33 (23.6)</td>
<td>27 (21.1)</td>
<td>6 (50.0)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

Drug regimen composition

<table>
<thead>
<tr>
<th>Drug regimen composition</th>
<th>Total (n = 140)</th>
<th>Favorable outcomes (n = 128)</th>
<th>Unfavorable outcomes (n = 12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With rifampin</td>
<td>134 (95.7)</td>
<td>122 (95.3)</td>
<td>12 (100)</td>
<td>1.000</td>
</tr>
<tr>
<td>With ethambutol</td>
<td>131 (93.6)</td>
<td>119 (93.0)</td>
<td>12 (100)</td>
<td>1.000</td>
</tr>
<tr>
<td>With pyrazinamide</td>
<td>124 (88.6)</td>
<td>113 (88.3)</td>
<td>11 (91.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>With FQ</td>
<td>75 (53.6)</td>
<td>73 (57.0)</td>
<td>2 (16.7)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

| Treatment duration (mo)     | 8.3 (6.1–11.6) | 8.8 (6.1–11.8)              | 6.2 (5.7–9.0)               | 0.024   |

\( ^a \) Data are presented as medians and interquartile ranges or as numbers (%).
7.7%), and the difference was statistically significant (7.4%; 95% CI, 0.2 to 15.5%) \( (P = 0.037) \). The crude and adjusted odds ratios for unfavorable outcomes for patients who did not receive FQs versus patients who did receive FQs were 6.636 (95% CI, 1.397 to 31.518) \( (P = 0.017) \) and 6.840 (95% CI, 1.122 to 41.704) \( (P = 0.037) \), respectively.

### DISCUSSION

In the present study, we evaluated the clinical usefulness of FQ-containing regimens in the treatment of INH-resistant pulmonary TB. Our study included 140 patients with INH-resistant pulmonary TB, approximately half of whom received FQ-containing regimens. The present study showed that patients who received FQs were more likely to have favorable treatment outcomes (treatment success without relapse).

Attempts to treat INH-resistant TB have yielded unsatisfactory outcomes. Although early studies found that treatment failure was low with a standard 6-month regimen \( (2, 24) \), the relapse rate was about twice as high for patients with INH-resistant TB than for patients with drug-susceptible TB \( (2) \). Furthermore, a large-scale retrospective cohort study showed that INH resistance of any type was associated with treatment failure in both new and retreatment cases \( (3) \). Another study also found that INH resistance (resistance to INH or INH plus streptomycin) was associated with treatment failure, which resulted in acquired drug resistance in a considerable proportion of cases, including multidrug-resistant TB cases \( (4) \).

Due to the unfavorable outcomes with standard 6-month treatment regimens, the current guidelines recommend either using pyrazinamide continuously throughout the 6 months or prolonging the treatment duration. The U.S. \( (7) \) and British \( (8) \) guidelines recommend using a 6-month regimen with rifampin, ethambutol, and pyrazinamide and a 12-month regimen (2 months of rifampin, ethambutol, and pyrazinamide followed by 10 months of rifampin and ethambutol), respectively. However, few clinical data have been obtained to support these recommendations. One retrospective study involving 39 patients with INH-resistant pulmonary TB observed two relapses but no treatment failures when patients were treated with a 6-month regimen of INH, rifampin, ethambutol, and pyrazinamide \( (25) \). In contrast, other studies have reported poor treatment outcomes, with treatment success rates of 71% and 65% for a 9-month regimen of rifampin, ethambutol, and pyrazinamide \( (16) \) and 12-month regimen of INH, rifampin, ethambutol, and pyrazinamide (and streptomycin, only for retreatment cases) \( (15) \), respectively. The latter study \( (15) \) also found that 61% of all patients with poor treatment outcomes developed multidrug-resistant TB. However, most studies have found that the treatment regimens prescribed to patients with INH-resistant TB in clinical practice vary considerably \( (10, 12, 13, 17, 19) \). The favorable treatment outcomes in these studies ranged from approximately 80% to 98% \( (10, 12, 13, 17, 19) \).

The overall rate of favorable outcomes in the present study was 91.4%; interestingly, this rate was significantly higher for patients who received FQs than for patients who did not receive FQs \( (97.3% \text{ versus } 84.6%) \). Although few studies have evaluated the treatment outcomes with FQ-containing regimens for the treatment of INH-resistant TB, two recent studies suggested that FQs might be helpful for the treatment of INH-resistant TB \( (13, 20) \). Bang and colleagues evaluated 110 patients with some type of INH resistance and found that only 80% were treated successfully \( (13) \). However, the outcome success rate reached 90% for the 40 patients who received an FQ in addition to their treatment regimen, although the statistical significance of this finding was not determined \( (13) \). More recently, Chien and colleagues found that the addition of FQs to the regimens of patients for whom rifampin had been discontinued improved treatment outcomes for INH-resistant TB, although this finding was not statistically significant in the overall study population \( (20) \). However, some aspects of this study limit the conclusions that can be drawn regarding the role of FQs in the treatment of INH-resistant pulmonary TB. First, the study was not designed to evaluate the role of FQs in the treatment of INH-resistant TB. Second, the study included deaths not caused by TB as unfavorable outcomes; the authors acknowledged that patients receiving FQs in the continuation phase probably had a higher death rate due to more severe disease conditions or random errors \( (20) \).

A recent large-scale meta-analysis evaluating 33 trials with 1,907 patients found that patients with favorable outcomes, including lower failure, relapse, and acquired drug resistance rates, were more likely to have received (i) rifampin for longer durations, (ii) streptomycin, and (iii) treatment with a larger number of effective drugs \( (6) \). Specifically, the use of streptomycin resulted in fewer treatment failures and less acquired drug resistance \( (6) \). In our study, only two patients received streptomycin. This small number is probably due to its inconvenient administration routes, i.e., intravenous or intramuscular injection. Instead, about half of

### TABLE 4

<table>
<thead>
<tr>
<th>State of the data</th>
<th>Proportion of unfavorable outcomes (%)</th>
<th>Difference in proportion</th>
<th>OR ( a )</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>Patients who received FQs: 2.7 (0.7–10.0)</td>
<td>Patients who did not receive FQs: 15.4 (8.5–26.3)</td>
<td>12.7 (3.2–22.2)</td>
<td>6.636</td>
<td>1.397–31.518</td>
</tr>
<tr>
<td>Adjusted ( b )</td>
<td>Patients who received FQs: 1.5 (0.3–7.7)</td>
<td>Patients who did not receive FQs: 8.8 (3.3–21.5)</td>
<td>7.4 (0.2–15.5)</td>
<td>6.840</td>
<td>1.122–41.704</td>
</tr>
</tbody>
</table>

\( a \) Data are percentages and 95% CI.

\( b \) Adjusted for diabetes mellitus status, previous tuberculosis treatment history, use of pyrazinamide, and factors with \( P \) values of <0.2 according to univariate analysis (chronic pulmonary disease, cavitary lesions in a chest radiograph, and treatment duration).

\( c \) Calculated as follows: \( \frac{\text{proportion of unfavorable outcomes for patients who did not receive FQs}}{\text{proportion of unfavorable outcomes for patients who did receive FQs}} \). Therefore, positive values signify that the patients who did not receive FQs had worse outcomes than the patients who did receive FQs, whereas negative values would signify the opposite.

\( d \) OR, odds ratio. The OR was calculated using the ratio of the odds of unfavorable outcomes for patients who did not receive FQs to the odds of unfavorable outcomes for patients who did receive FQs. Therefore, values of >1 signify that the patients who did not receive FQs had worse outcomes than the patients who did receive FQs, whereas values of <1 would signify the opposite.
the patients received FQs. Consistent with the effect of streptomycin observed in previous studies (6), the use of FQs reduced treatment failure, suggesting that FQs might be able to substitute for streptomycin in the treatment of INH-resistant pulmonary TB. However, in contrast to the preventive effect of streptomycin on the acquired drug resistance observed in previous studies (6), the use of FQs did not prevent acquired drug resistance in this study. Moreover, adding FQs was not associated with acquired resistance to rifampin.

Two opposing positions have been articulated regarding the use of FQs in the treatment of INH-resistant TB. Some experts insist that FQs need to be saved for patients with multidrug-resistant TB (9). On the other hand, others recommend broadly using FQs because the treatment outcomes for INH-resistant TB are not satisfactory and treatment failure is known to be associated with the development of acquired drug resistance, including multidrug resistance (26). In support of the latter position, the present study found that the treatment outcomes for INH-resistant pulmonary TB were not satisfactory, especially for patients who did not receive FQs, whose rate of favorable outcomes was approximately 85%. Moreover, 25% (3/12 patients) of all patients with unfavorable outcomes developed multidrug-resistant TB. In contrast, additional FQ use improved treatment outcomes. The use of FQs was associated with a lower rate of treatment failure. These results effectively support the use of strong regimens for the treatment of INH-resistant pulmonary TB.

The present study did have several limitations. First, although we showed that additional FQ use can be helpful in the treatment of INH-resistant pulmonary TB, the optimal treatment regimen cannot be deduced from our study because the number of various treatment regimens used was not sufficient for comparison. Second, treatment durations were longer for the patients who received FQs than for patients who did not receive FQs. Since we had already considered the association between longer durations of treatment and favorable outcomes, we performed a multivariate logistic regression analysis with adjustment for treatment duration. As shown in Table S4 in the supplemental material, treatment duration showed a tendency associated with favorable outcomes; however, this was not statistically significant. In comparison, the use of FQs was significantly associated with favorable outcomes. We further performed a univariate analysis with stratification of treatment duration to evaluate the effect of adding an FQ on favorable outcomes according to treatment duration. As shown in Table S5 in the supplemental material, the use of FQs was significantly associated with a favorable treatment outcome for patients who were treated for a longer duration and showed a tendency for a favorable outcome for patients who were treated for a short duration. These additional results provide more evidence that adding an FQ to the treatment regimen for INH-resistant pulmonary TB is associated with favorable outcomes regardless of treatment duration. Third, INH was discontinued in most patients (about 95%) after confirmation of INH resistance in this study. However, since the serum concentration of INH is usually higher than the threshold concentration of INH resistance (0.2 µg/ml) with an usual adult dose (27), INH may still contribute to favorable treatment outcomes for INH-resistant TB. Therefore, if treatment was prolonged with continuation of INH, the proportion of unfavorable outcomes might be lower and the effect of FQ might not be significant. Fourth, considering the retrospective nature of this study, there is still a possibility that the favorable treatment outcomes for patients who received FQs might have been affected by the longer treatment duration even though we adjusted for various baseline demographic data and clinical factors, including treatment duration. Further studies are needed to confirm the role of FQs in the treatment of INH-resistant pulmonary TB. Lastly, since drug susceptibility tests with ethambutol and pyrazinamide might not be reproducible, the association between acquired resistance to ethambutol and pyrazinamide and unfavorable outcomes in this study needs to be interpreted with caution (28).

In conclusion, INH-resistant pulmonary TB is associated with improved outcomes when FQs are added to standard treatment regimens. Therefore, the addition of FQs to treatment regimens should be considered for the treatment of INH-resistant pulmonary TB.

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