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Impact of isoniazid monoresistance on overall and vulnerable patient populations in Taiwan

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ABSTRACT

Isoniazid is an early bactericidal anti-tuberculosis (TB) agent and isoniazid mono-resistance TB is the most prevalent drug-resistant TB worldwide. Concerns exist regarding whether resistance to isoniazid would lead to delayed culture conversion and worst outcomes. From January 2008 to November 2017, adult culture-positive pulmonary TB patients receiving isoniazid, rifampicin, pyrazinamide, and ethambutol were identified through Taiwan Center for Disease Control database and were followed until the end of 2017. Primary outcomes included time to sputum culture conversion (SCC) within two months. Secondary outcomes included death and unfavourable outcomes at the end of 2nd month. A total of 37,193 drug-susceptible and 2,832 isoniazid monoresistant pulmonary TB patients were identified. Compared with no resistance, isoniazid monoresistance was not associated with a delayed SCC (HR: 0.99, 95% Cl: 0.94–1.05, p = 0.8145), a higher risk of 2-month mortality (HR: 1.19, 95% Cl: 0.92–1.53, p = 0.1884), and unfavourable outcomes at 2nd month (OR: 1.05, 95% CI: 0.97–1.14, p = 0.2427). Isoniazid monoresistance was associated with delayed SCC (HR: 0.90, 95% CI: 0.83–0.98, p = 0.0099) and a higher risk of unfavourable outcomes (OR:1.18, 95% CI: 1.05–1.32, p = 0.0053) in patients aged between 20 and 65, and delayed SCC in patients without underlying comorbidities (HR: 0.90, 95% Cl: 0.81-0.98, p = 0.0237). Isoniazid mono-resistant TB had a comparable outcome with drug-susceptible TB at the end of the intensive phase. Healthy, and non-elderly patients were more likely to had culture persistence, raising concerns about disease transmission in these subgroups and warranting early molecular testing for isoniazid resistance.

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KEYWORDS Drug-susceptible; isoniazid resistance; mortality; sputum culture conversion; tuberculosis

Introduction

Tuberculosis (TB) continues to be an important global infectious disease with a substantial disease burden and high mortality rate. According to the World Health Organization (WHO) report, it was estimated that 10.6 million individuals were diagnosed with TB in 2021, representing a 4.5% increase compared to the previous year [1]. This sudden reversal in the declining trend is concerning. Drug-resistant TB (DR-TB) poses a significant challenge to effective treatment, and isoniazid monoresistant TB (HR-TB) is the most common form of DR-TB. It was estimated in a recent meta-analysis that the global prevalence of HR-TB was 7.4% among new TB patients and 11.4% among previously treated TB patients [2]. Addressing the issue of HR-TB is crucial to achieving better global TB control.

HR-TB deserves special attention due to its association with worse treatment outcomes [3]. In a metaanalysis, adverse treatment outcomes including relapse or failure, and acquired drug resistance were 15% and 3.6% for patients with HR-TB, compared with 4% and 0.6% for drug-susceptible TB [3]. Additionally, HR-TB is a precursor to and is associated with emergence of multidrug resistance (MDR). It was estimated that as high as 8% HR-TB patients developed MDR during their treatment [3]. Given these findings, early diagnosis, prompt treatment, and effective measures to prevent the transmission are of great importance in addressing the challenges posed by HR-TB.

While line probe assays such as GenoType MTBDR*plus* (Hain Lifescience, Nehren, Germany) have been endorsed by WHO for detecting isoniazid and rifampicin resistance among smear-positive or culture-

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positive specimens to replace phenotypic testing and in meta-analysis the sensitivity and specificity of detecting isoniazid resistance compared with phenotypic method is high, their use in direct testing among all TB suspects is still not widely adopted due to concerns of sensitivity especially in smear-negative specimens [4,5]. Unlike rifampicin drug resistance, which can be rapidly detected using molecular methods such as the Xpert MTB/RIF Ultra assay, isoniazid resistance is typically unknown until results of conventional culture-based drug susceptibility testing are available. Unfortunately, obtaining these results can take weeks after collecting sputum mycobacterial cultures [6]. This delay in identifying isoniazid resistance can lead to adverse outcomes and TB dissemination, particularly among vulnerable patients.

Currently, there is limited knowledge regarding the specific group of patients who are more likely to experience worse outcomes when facing isoniazid resistance. Considering that isoniazid is an important anti-TB agent known for its early bactericidal effects, it is intriguing to investigate whether resistance to isoniazid prolongs the time required for sputum culture conversion under standard anti-TB treatment [7]. The recommended regimen for treating isoniazid monoresistant TB has changed as evidence showed that the addition of a fluoroquinolone to at least 6 months of daily rifampicin, ethambutol, and pyrazinamide was associated with better outcomes [8]. As a result, the WHO endorsed a regimen of 6 months of fluoroquinolone, rifampicin, ethambutol, and pyrazinamide [9]. It is possible that resistance to isoniazid could hinder the initial bactericidal effects of the treatment, leading to delayed culture conversion. The persistence of mycobacterial culture is a significant factor that influences the transmission and contagiousness of TB. This is because the development of TB disease requires at least one viable Mtb droplet nucleus to reach the lung alveolar macrophage [10]. Therefore, culture persistence plays a crucial role in disease transmission.

The objective of our study is to investigate the impact of isoniazid monoresistance on sputum culture conversion and unfavourable outcomes within the initial twomonth period. Additionally, we aim to identify specific at-risk groups that may experience worse outcomes compared to patients with isoniazid-susceptible TB. By doing so, we hope to identify patients who would benefit from more intensive therapy, close monitoring, and use of rapid molecular testing methods to detect isoniazid resistance. The findings of this study may help develop targeted strategies for managing isoniazid monoresistant TB cases.

Materials and methods

Study design and patients

We recruited adults (age \geq 20) in Taiwan who were culture-positive pulmonary TB patients between January 2008 and November 2017. Eligible participants

were either all susceptible or had isoniazid monoresistant TB and had received at least 14 days of treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol within one month after treatment. Among them, those who exposed to fluoroquinolone, streptomycin, and amikacin within 2 months after treatment were excluded. For the main study, we included patients who survived after the first month of treatment (Figure 1). To recruit this cohort, we utilized the Taiwan Center for Disease Control (CDC) untransitioned TB database, which is an internal database maintained by the Taiwan CDC. It is important to note that this database is distinct from the Taiwan TB transitioned database, which has been previously used in various studies and has provided valuable insights [11,12]. The un-transitioned TB database contains information primarily derived from the clinical practices of the Taiwan's public health and medical systems, focusing on individual TB patients. It includes crucial details such as body weight of the patient, the drug susceptibility of Mycobacterium tuberculosis complex to first-line anti-TB medications (isoniazid, rifampicin, ethambutol), the results of sputum acid-fast smear and mycobacterial cultures before and after TB treatment, and treatment supervision (directly observed therapy, short course [DOTs]). These specific variables were not available in the TB transitioned database or the Taiwan Health Insurance Research Database. By utilizing the un-transitioned TB database, we have access to comprehensive and detailed information that allows for a more in-depth analysis of the impact of isoniazid resistance on treatment outcomes and culture conversion within the initial two-month time frame. Moreover, it is important to note that tuberculosis (TB) is a notifiable disease in Taiwan, meaning that the maintenance of the TB database is mandatory. As a result, the CDC un-transitioned TB database we utilized for this study is comprehensive and includes data from all reported TB cases in Taiwan. To improve the available information for analysis, the CDC linked the un-transitioned TB database to the Taiwan Health Insurance claims database. This linkage allowed us to obtain additional data on the underlying comorbidities of the TB patients. Taiwan has a single payer health insurance system with a coverage rate approaching 100%, providing extensive healthcare coverage for the population (source: https://www.nhi.gov.tw/) [11,13]. Additionally, the mortality data used in our study were obtained from the Department of Statistics in Taiwan. This ensures accurate and reliable information regarding the mortality rates associated with TB cases.

Data collection and definition

In the Taiwan CDC un-transitioned TB database, isoniazid monoresistance was identified and classified based on the level of resistance. First-line anti-TB



Figure 1. Flowchart of case selection HERZ, isoniazid, ethambutol, rifampicin, pyrazinamide; TB, tuberculosis.

drug susceptibility testing (DST) was conducted at quality-assured laboratories that actively participated in a proficiency testing programme organized by the Reference Laboratory of Mycobacteriology at the Taiwan CDC [14]. Briefly, *M. tuberculosis* isolates were subjected to drug susceptibility testing using the proportion method with solid media. Isoniazid monoresistance was defined as resistance to isoniazid and documented susceptibility to rifampicin and ethambutol. Resistance was defined as 1% of the colonies growing in the presence of the following critical concentrations of drugs (low-level isoniazid: 0.2 µg/ml, high-level isoniazid 1 µg/mL) [15]. The Reference Laboratory of Mycobacteriology provides guidance, quality control materials, and training to the participating laboratories, ensuring that standardized protocols and procedures for DST are followed [14].

The definition of urban and non-urban areas in Taiwan followed previous publication [16]. Hospital level was determined based on the hospital's accreditation level with the highest number of visits in the first two months before beginning treatment.

Outcome definition

In this study, there were two primary outcomes and two secondary outcomes. Primary outcomes were time to sputum culture conversion (SCC) and no

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$ \begin{array}{cccc} {\rm CoPD} & {\rm CoPD} & {\rm S333} (146) & {\rm S422} (14.6) & {\rm 417} (14.7) & {\rm 201} (13.9) & {\rm 216} (15.6) & {\rm 0.4633} & {\rm 0.8313} \\ {\rm Borthinetas} & {\rm 3017} (7.5) & {\rm 2238} (3.0) & {\rm 477} (14.7) & {\rm 201} (13.9) & {\rm 216} (15.6) & {\rm 0.4633} & {\rm 0.3234} \\ {\rm Borthinetas} & {\rm 3017} (7.5) & {\rm 2238} (1.0) & {\rm 457} (1.6) & {\rm 223} (1.6) & {\rm 221} (1.6) & {\rm 0.0224} & {\rm 0.0293} \\ {\rm Stremm contosis} & {\rm 430} (1.1) & {\rm 335} (1.0) & {\rm 45} (1.6) & {\rm 23} (1.6) & {\rm 23} (1.6) & {\rm 0.2244} & {\rm 0.0293} \\ {\rm Stremm contosis} & {\rm 430} (1.1) & {\rm 338} (1.0) & {\rm 45} (1.6) & {\rm 23} (1.6) & {\rm 23} (1.6) & {\rm 0.2244} & {\rm 0.0393} \\ {\rm Stremm contosis} & {\rm 430} (1.1) & {\rm 338} (1.0) & {\rm 93} (1.6) & {\rm 23} (1.6) & {\rm 23} (1.6) & {\rm 0.2244} & {\rm 0.0059} \\ {\rm Disbete melluus} & {\rm 998} (25.0) & {\rm 924} (12.3) & {\rm 936} (26.8) & {\rm 321} (1.2) & {\rm 0.0734} & {\rm 0.0732} & {\rm 0.0931} \\ {\rm Disbetes melluus} & {\rm 9238} (25.0) & {\rm 924} (12.3) & {\rm 336} (1.3) & {\rm 316} (1.3) & {\rm 0.1727} & {\rm 0.0931} \\ {\rm Coronay articlidease} & {\rm 437} (1.0) & {\rm 316} (1.2) & {\rm 148} (0.3) & {\rm 168} (1.3) & {\rm 0.2724} & {\rm 0.0052} \\ {\rm Coronay articlidease} & {\rm 437} (1.0) & {\rm 0.1724} & {\rm 0.0613} & {\rm 0.0724} & {\rm 0.0234} \\ {\rm Coronay articlidease} & {\rm 1412} (2.5) & {\rm 146} (0.5) & {\rm 115} (1.3) & {\rm 0.1724} & {\rm 0.2034} & {\rm 0.2704} & {\rm 0.2704} & {\rm 0.2036} \\ {\rm Coronay articlidease} & {\rm 121} (1.2) & {\rm 220} (1.3) & {\rm 24} (1.0) & {\rm 116} (1.2) & {\rm 116} (1.2) & {\rm 116} (1.2) & {\rm 116} (1.2) & {\rm 100} (1.9) & {\rm 106} (1.0) & {\rm 100} $	833 (146) $5422 (14,6)$ $417 (14.7)$ $201 (13.9)$ $216 (15,6)$ 0.4633 0.8313 $actists$ $1407 (1.7)$ $228 (0.0)$ $177 (13)$ $228 (10)$ 0.2397 0.3397 0.3397 $actists$ $430 (1.1)$ $385 (1.0)$ $45 (1.6)$ $23 (1.6)$ $22 (1.6)$ 0.4633 0.8313 $actists$ $1400 (1.1)$ $385 (1.0)$ $46 (1.6)$ $23 (1.6)$ $22 (1.6)$ 0.0297 0.0931 $actionelss$ $1412 (35.3)$ $924 (2.4)$ $237 (1.2,6)$ $23 (1.6)$ $22 (1.6)$ 0.0297 0.0931 $melltusts$ $2398 (25.0)$ $924 (2.4)$ $237 (2.6,4)$ $386 (2.8)$ $361 (2.6)$ 0.0272 0.0970 0.9931 $melltusts$ $237 (1.3)$ $377 (1.2)$ $237 (1.2)$ $237 (1.2)$ $237 (1.2)$ 0.0072 0.0072 0.0072 $arreid disease437 (1.0)737 (2.4)386 (2.8)74 (2.6)0.66 (2.7)0.00720.0072arreid disease197 (1.2)237 (1.2)237 (1.2)148 (1.2)168 (2.1)0.7720.0072arreid disease197 (1.2)237 (1.2)237 (1.2)126 (0.7)0.07720.0072arreid disease197 (1.2)237 (1.2)126 (0.6)116 (0.7)0.02720.0072arreid disease197 (0.5)127 (2.6)126 (0.7)126 (0.7)0.07720.0072arreid disease197 (1.2)237 (1.6)126 (0.7)126 (0.7)$	Pulmonary disease								
Athma 3017 (75) 279 (75) 226 (8.0) 117 (8.1) 109 (7.9) 0.6637 0.3349 Preuncentists Hard 337 (1) 338 (1) 358 (1) 236 (1) 109 (7) 0.6377 0.3349 Preuncentists Hard 338 (1) 338 (1) 358 (1) 231 (1) 238 (1) 0.0323 0.0323 0.0323 0.0323 System(contos) 430 (11) 338 (1) 358 (1) 23 (1,1) 23 (1,1) 0.0439 0.0323 0.0323 System(contos) 430 (11) 338 (10) 924 (24.9) 747 (26.4) 366 (13) 21 (11) 0.0729 0.0931 System(and straid disease 437 (10) 447 (26.4) 366 (12) 117 (12) 114 (10) 117 (12) 0.0729 0.0672 0.0326 Ornoreix the art failure 216 (5.4) 216 (1.2) 116 (1.2) 116 (1.2) 116 (1.2) 116 (1.2) 0.0729 0.0672 0.0729 0.0576 0.0726 0.0726 0.0726 0.0726 0.0726 0.0721 0.0726	task task 3017 (75) 2291 (75) 226 (8.0) 117 (8.1) 1007 (79) 66297 0.3597 0.3749 task toolosis 430 (17) 380 (17) 180 (17) 166 (12) 213 (10) 213 (10) 213 (10) 0.759 0.779 isease isease 14122 (33.3) 13123 (33.3) 999 (53.3) 510 (35.3) 489 (35.2) 0.9790 0.9931 isease isease 14122 (33.3) 993 (130) 377 (130) 376 (139) 361 (130) 0.7729 0.0932 imelitus 9382 (30) 9241 (24.9) 747 (56.4) 386 (32) 110 (130) 0.7279 0.0932 imelitus 9382 (30) 937 (11) 336 (13) 316 (12.2) 118 (13.1) 0.7271 0.0932 imelitus 2165 (39) 3217 (87) 2167 (30) 316 (12.2) 1168 (12.1) 0.7729 0.0932 imelitus 2165 (39) 3267 (39) 367 (3.2) 1168 (3.1) 0.7729 0.0932 imelitus 2165 (39) 3217 (87) 21576 (30) 1168 (31.2) 0.7729 0.0932 imelitus 2165 (39) 3217 (87) 21676 (30) 1172 (33) 367 (32) 0.0736 imelitus 2165 (31) 3217 (87) 21676 (30) 1172 (33) 0.0672 0.0736 imelitus 2165 (31) 217 (31) 1265 (31) 1266 (31) 1266 (31) 1266 (32) 0.0713 0.0736 imelitus 2265 (31) 127 (32) 3277 (32	COPD	5839 (14.6)	5422 (14.6)	417 (14.7)	201 (13.9)	216 (15.6)	0.4633	0.8313	0.2235
Bronchiectasis 1488 (3.7) 1380 (3.7) 108 (3.8) 5 (3.9) 5 (3.7) 5 (3.9) 5 (3.7) 0.9339 0.7796 Preumconsists 4.30 (1.1) 385 (1.0) 4.5 (1.6) 2.3 (1.6) 2.3 (1.6) 0.0224 0.0939 0.0939 Systemic disease Hypertension 14122 (35.3) 13123 (33.3) 999 (33.3) 510 (33.3) 489 (35.2) 0.9970 0.0931 Hypertension 988 (5.0) 9.241 (2.4) 747 (2.6.4) 386 (2.6.8) 361 (3.0) 0.7727 0.0970 0.0931 Optimize 237 (1.3) 487 (1.2) 747 (2.6.4) 386 (2.6.8) 361 (3.0) 0.7727 0.0970 0.0970 Optimize 237 (1.3) 487 (1.2) 747 (2.6) 174 (1.2) 174 (1.2) 175 (1.2) 0.7727 0.0977 0.0973 Optimize 237 (3.0) 373 (3.1) 373 (3.1) 373 (3.1) 373 (3.1) 386 (2.6.3) 0.7727 0.0973 0.0773 Coronary arterial disease 177 (4.8) 1775 (4.9) 1775 (4.9) 1775	clasis1488 (37)1380 (3.7)108 (3.8)5 (3.9)5 (3.2)0.9330.7796clasis1488 (3.7)1380 (3.1)138 (1.0)45 (1.6)23 (1.6)22 (1.6)0.02240.0033clasies1412 (35.3)1387 (1.3)338 (1.0)45 (1.6)23 (1.6)22 (1.6)0.03240.0033sion1412 (35.3)1313 (35.3)99 (35.3)510 (35.3)489 (35.2)0.99700.9931melltus5216 (3.0)2317 (3.1)338 (1.12)148 (0.3)168 (1.2)0.07770.0973melltus5215 (3.0)4877 (3.0)336 (1.12)148 (0.3)168 (1.2)0.07720.0973melltus5216 (3.0)2000 (3.4)165 (3.6)1017 (2.1)0.77040.06720.0073arterial disease1977 (4.8)1775 (4.8)142 (5.0)67 (4.6)75 (5.4)0.54190.7704we heart failure216 (6.6)110 (6.7)18 (1.3)117 (1.2)0.70040.0513arterial disease420 (1.2)347 (1.1)35 (1.2)18 (1.3)17 (1.2)0.7004arterial disease420 (1.2)347 (1.0)35 (1.2)18 (1.3)17 (1.2)0.7004arterial disease420 (1.2)347 (1.1)35 (1.2)18 (1.3)0.07720.06720.0533arterial disease420 (1.2)347 (1.0)37 (1.2)18 (1.3)17 (1.2)0.70340.5619arterial disease420 (1.2)347 (1.0)37 (1.2)144 (0.6)17 (1.2)0.	Asthma	3017 (7.5)	2791 (7.5)	226 (8.0)	117 (8.1)	109 (7.9)	0.6297	0.3549	0.7980
Preumoconiosis 430 (1.1) 385 (1.0) 45 (1.6) 23 (1.6) 22 (1.6) 0.0224 0.0059 Systemiconiosis Houmoconiosis 430 (1.1) 385 (1.0) 45 (1.6) 23 (1.6) 23 (1.6) 0.0224 0.0059 Systemiconiosis Hyterension 1122 (35.3) 13123 (35.3) 999 (35.3) 510 (35.3) 489 (35.2) 0.9970 0.9931 Diabetes melltus 988 (25.0) 9241 (24.9) 747 (26.4) 386 (26.8) 361 (26.0) 0.1727 0.0070 Dysliptidemia 5275 (13.0) 4837 (13.0) 378 (13.4) 198 (13.1) 0.0727 0.0070 Corronary arterial disease 197 (1.2) 1148 (10.3) 116 (12.1) 107 (12.1) 0.0724 0.0704 Corronary arterial disease 197 (1.2) 215 (1.0) 215 (1.0) 215 (1.0) 0.7375 0.0073 0.0704 Corronary arterial disease 197 (1.2) 148 (10.3) 168 (12.1) 0.2779 0.0675 Corronary arterial disease 197 (12) 173 (12) 173 (12) 0.0734	contosis430 (1.1)385 (1.0)45 (1.6)23 (1.6)23 (1.6)22 (1.6)0.02240.0059 Rease 14122 (35.3)13123 (35.3)939 (35.3)510 (35.3)480 (35.2)0.99700.9971 Rease 14122 (35.3)13123 (35.3)336 (26.8)361 (26.0)0.17270.0695melltus998 (25.0)9241 (24.9)747 (26.4)386 (26.8)361 (26.0)0.17270.0695melltus998 (25.0)934 (3.0)336 (1.12)148 (10.3)168 (12.1)0.272790.0695arterial disease437 (10.9)4663 (10.9)316 (1.12)148 (10.3)168 (12.1)0.272790.0695arterial disease460 (1.2)147 (5.0)0.71 (4.6)75 (5.4)0.272190.0695arterial disease460 (1.2)143 (1.2)29 (1.0)14 (1.0)75 (1.1)0.272190.0695arterial disease460 (1.2)143 (1.2)23 (1.2)17 (1.2)0.06720.05720.0576gis chadred disease460 (1.2)143 (1.2)25 (1.6)77 (4.6)75 (5.4)0.27360.4702gis chadred disease460 (1.2)126 (5.4)17 (1.2)0.06720.05760.0576gis chadred disease460 (1.2)126 (6.6)17 (1.6)75 (4.4)0.73660.4029gis chadred disease460 (1.2)126 (6.6)17 (1.6)77 (1.2)0.73660.4029gis chadred disease130 (0.3)17 (1.6)17 (1.2)0.70360.4029 <t< td=""><td>Bronchiectasis</td><td>1488 (3.7)</td><td>1380 (3.7)</td><td>108 (3.8)</td><td>56 (3.9)</td><td>52 (3.7)</td><td>0.9439</td><td>0.7796</td><td>0.8490</td></t<>	Bronchiectasis	1488 (3.7)	1380 (3.7)	108 (3.8)	56 (3.9)	52 (3.7)	0.9439	0.7796	0.8490
Systemic disease 1312 (35.3) 99 (35.3) 510 (35.3) 489 (35.2) 0.9970 0.9931 Hypertension 1412 (35.3) 1312 (35.3) 99 (35.3) 510 (35.3) 489 (35.7) 0.9970 0.9931 Hypertension 088 (25.6) 9241 (24.9) 747 (25.4) 386 (25.6) 0.1727 0.09931 Dyslipidemia 5215 (13.0) 4837 (13.0) 378 (13.4) 198 (13.7) 180 (13.0) 0.7729 0.6019 Dyslipidemia 5215 (10.9) 463 (10.9) 378 (13.4) 198 (13.7) 180 (13.0) 0.7729 0.0672 0.0703 Connective heart failure 2165 (5.4) 1003 1063 (10.9) 168 (12.1) 0.4174 0.3066 Connective heart failure 2165 (5.4) 160 (5.9) 168 (12.1) 0.7153 0.6712 Connective heart failure 2165 (5.4) 163 (6.9) 168 (12.1) 0.3704 0.2165 Chronic kidney disease 430 (1.1) 35 (1.2) 35 (1.0) 17 (1.2) 0.7036 0.2035 Revising prondylits 256 (0.6)<	lisease lisease 489 (35.1) 1312 (35.3) 999 (35.3) 510 (35.3) 689 (35.1) 0.9970 0.9970 0.9971 0.9970 0.99713 0.99713 0.991	Pneumoconiosis	430 (1.1)	385 (1.0)	45 (1.6)	23 (1.6)	22 (1.6)	0.0224	0.0059	0.9830
Hypertension 1412 1312 (35.3) 999 (35.3) 999 (35.3) 999 (35.3) 999 (35.3) 0970 09970 09931 Dyslipideres 231 (32) 231 (32) 336 (32) 01272 00652 00652 Dyslipideres 5216 (32) 337 (33) 316 (112) 188 (32) 0.0779 0.0052 Coronary arterial disease 4379 (109) 4663 (102) 316 (112) 188 (12) 0.0772 0.0772 Coronary arterial disease 4379 (109) 3271 (8.7) 2165 0.0772 0.0727 0.0723 Coronary arterial disease 4379 (12) 4387 (13) 2165 0.779 0.0672 0.0252 Coronary arterial disease 1917 (48) 1726 0.065 100 6.072 0.0727 0.0727 Coronary arterial disease 1917 (48) 1726 0.065 1127 0.0727 0.0727 0.0726 Coronary arterial disease 1917 (48) 1726 0.0672 0.0727 0.0726 Coronary arterial disease 1917 (48) 1726 0.0672 0.0726 0.0726 Coronary arterial disease 1917 (410) 17410 1606 0.077 0.0759 Fuel arteria 1226 0.077 0.0672 0.0779 0.0672 0.0759 Fuel artarioi<	sion $1412 (35.3) 1313 (35.3) 99 (35.3) 510 (35.3) 489 (35.2) 0970 09970 09931 mellitus 5215 (10) 487 (12,9) 747 (36,4) 386 (26,8) 361 (26,0) 01727 00695 arterial disease 4379 (10.9) 4063 (10.9) 378 (13.4) 198 (13.7) 180 (13.0) 07779 0.0079 00556 (12) 175 (5,4) 126 (5,2) 100 (6,9) 115 (8,3) 0.07729 0.0072 00556 (13.6) 100 (6,9) 115 (8,3) 0.07729 0.0072 00556 (13.6) 175 (4.8) 175 (4.8) 142 (5.8) 75 (5,1) 0.25419 0.07729 0.0570 0516 (12) 247 (13.0) 177 (12) 0.0704 0.0726 0.0556 (13.0) 07779 0.0072 0.0556 (13.0) 177 (13.0) 177 (13.0) 07779 0.0570 0516 (13.0) 177 (13.0) 177 (13.0) 177 (13.0) 0704 0.0726 0.0556 (13.0) 177 (13.0) 177 (13.0) 0.0729 0.0516 0.0072 0.0516 0.0001 d.0 arthritis 26 (0.0) 2.00 (0.7) 16 (0.0) 14 (1.0) 15 (1.1) 0.7804 0.5165 0.0022 0.0509 0.0511 0.0736 0.0402 0.0516 0.0011 120 (0.2) 175 (0.3) 17 (12.0) 0.7036 0.0402 0.0509 0.0671 0.0590 0.0511 0.0736 0.0402 0.0516 0.0012 0.0012 0.0012 0.0012 0.0001 0.0012 0.0001 0.0012 0.0001 0.0012 0.0001 0.0012 0.0001 0.0012 0.0001 0.0013 0.0011 0.001 0.0011 0.$	Systemic disease								
	mellitus9988 (25.0)9241 (24.9)747 (26.4)386 (26.8)361 (26.0)0.17270.0695mia5215 (13.0)4337 (13.0)373 (13.4)198 (13.7)198 (13.7)0.06720.0607arterial disease432 (1.0)317 (8.1)112118 (1.1.2)118 (1.2.1)0.72210.0605arterial disease342 (8.6)317 (8.7)215 (7.6)100 (6.9)115 (8.1)0.27210.0607arterial disease466 (1.2)317 (8.1)216 (7.6)100 (6.9)115 (8.1)0.27210.0704dishey disease197 (4.8)1775 (4.8)142 (5.0)67 (4.6)75 (5.4)0.56150.0672oid arthrifs432 (1.1)337 (1.1)357 (1.0)144 (1.0)157 (1.1)0.73640.5615oid arthrifs256 (0.6)240 (0.7)16 (0.6)10 (0.7)6 (0.4)0.70360.4053oid arthrifs256 (0.6)240 (0.7)15 (0.6)10 (0.7)6 (0.4)0.73160.0569oid arthrifs256 (0.6)240 (0.7)16 (0.6)10 (0.7)6 (0.4)0.73160.0569oid arthrifs256 (0.6)240 (0.7)356 (1.0)10 (0.7)6 (0.4)0.73160.0569132 (0.5)130 (0.3)16 (0.6)10 (0.7)6 (0.4)17 (1.2)0.73360.4605132 (0.5)130 (0.3)16 (0.6)10 (0.7)6 (0.4)17 (1.2)0.73640.5516132 (0.5)130 (0.3)121 (0.3)16 (0.6)10 (0.7)6 (0.4) <td>Hypertension</td> <td>14122 (35.3)</td> <td>13123 (35.3)</td> <td>999 (35.3)</td> <td>510 (35.3)</td> <td>489 (35.2)</td> <td>0.9970</td> <td>0.9931</td> <td>0.9388</td>	Hypertension	14122 (35.3)	13123 (35.3)	999 (35.3)	510 (35.3)	489 (35.2)	0.9970	0.9931	0.9388
	mia $5215 (130)$ $4877 (13.0)$ $378 (13.4)$ $198 (13.7)$ $180 (13.0)$ 0.7779 0.6019 arterial disease $3437 (10.9)$ $4053 (10.9)$ $316 (11.2)$ $148 (10.3)$ $168 (12.1)$ 0.2721 0.7004 arterial disease $3427 (8.6)$ $215 (5.6)$ 0.619 $168 (12.1)$ $148 (10.3)$ $168 (12.1)$ 0.2721 0.7004 we heart failure $2165 (5.4)$ $2000 (5.4)$ $1775 (4.8)$ $142 (5.0)$ $67 (4.6)$ $75 (5.4)$ 0.5419 0.5615 e renal disease $1977 (4.8)$ $1775 (4.8)$ $142 (5.0)$ $67 (4.6)$ $75 (5.4)$ 0.5419 0.5615 e renal disease $460 (1.2)$ $437 (1.1)$ $337 (1.1)$ $337 (1.2)$ $18 (1.3)$ $117 (1.0)$ 0.7364 0.5615 g spondylitis $256 (0.6)$ $240 (0.7)$ $16 (0.6)$ $10 (0.7)$ $6 (0.4)$ $117 (1.0)$ 0.7034 0.4072 $120 (0.2)$ $123 (0.5)$ $17 (0.6)$ $16 (0.6)$ $10 (0.7)$ $6 (0.4)$ 0.7503 0.5615 $120 (0.2)$ $123 (0.2)$ $12 (0.3)$ $10 (0.7)$ $6 (0.4)$ $11 (1.0)$ 0.7004 0.5615 $120 (0.2)$ $123 (0.5)$ $177 (0.6)$ $16 (0.6)$ $10 (0.7)$ 0.001 0.0015 0.0059 $100 (0.4)$ $123 (0.3)$ $10 (0.7)$ $10 (0.7)$ $0 (0.4)$ $121 (0.2)$ 0.5416 0.5419 0.5615 $100 (0.4)$ $120 (0.3)$ $10 (0.7)$ $0 (0.4)$ $11 (0.8)$ 0.2203 0.9639 <t< td=""><td>Diabetes mellitus</td><td>9988 (25.0)</td><td>9241 (24.9)</td><td>747 (26.4)</td><td>386 (26.8)</td><td>361 (26.0)</td><td>0.1727</td><td>0.0695</td><td>0.6464</td></t<>	Diabetes mellitus	9988 (25.0)	9241 (24.9)	747 (26.4)	386 (26.8)	361 (26.0)	0.1727	0.0695	0.6464
Coronary arterial disease4379 (10.9)4063 (10.9)316 (11.2)148 (10.3)168 (12.1)0.27210.7004Coronary arterial disease4379 (10.9)4063 (10.9)316 (11.2)148 (10.3)168 (12.1)0.27210.7004Cancer332 (8.6)3217 (8.7)215 (7.6)100 (6.9)115 (8.3)0.06720.06720.3086Congestive heart failure1917 (4.8)177 (4.8)177 (4.6)75 (5.4)0.54190.5615Chore kidney disease1917 (4.8)177 (1.2)29 (1.0)14 (1.0)15 (1.1)0.78040.5615End-stage renal disease460 (1.2)173 (1.2)29 (1.0)14 (1.0)17 (1.2)0.70360.4023Rheumatoid arthritis432 (1.1)397 (1.1)397 (1.1)357 (1.2)18 (1.3)17 (1.2)0.70360.4023Ankylosing spondylitis256 (0.6)240 (0.7)16 (0.6)10 (0.7)6 (0.4)11 (0.8)0.22030.3035Psoriasis110130 (0.3)121 (0.3)17 (1.6)6 (0.4)11 (0.8)0.22030.3056Phum100130 (0.3)121 (0.3)6 (0.4)127 (1.2)0.7030.60440.5168Paoriasis110130 (0.3)130 (0.3)127 (0.6)6 (0.4)13 (1.0)0.703Provinais100130 (0.3)130 (0.3)137 (0.6)141 (1.0)15 (1.1)0.703Provinais100130 (0.3)137 (0.6)130 (0.3)137 (1.2)0.7030.446	arterial disease 4379 (10.9) 4063 (10.9) 316 (11.2) 148 (10.3) 168 (12.1) 0.2721 0.7004 arterial disease 342 (8.6) 2317 (8.7) 215 (7.6) 100 (6.9) 115 (8.3) 0.0672 0.0526 we hart failure 2156 (5.4) 1775 (4.8) 1775 (4.8) 1775 (4.8) 1775 (4.8) 0.7904 0.5165 odiney disease 460 (1.2) 431 (1.2) 297 (1.1) 357 (1.1) 357 (1.1) 0.7804 0.5165 of arthritis 432 (1.1) 337 (1.1) 357 (1.2) 18 (1.3) 177 (1.2) 0.7804 0.5165 of arthritis 432 (1.1) 337 (1.1) 357 (1.2) 187 (1.3) 177 (1.2) 0.7304 0.5055 of arthritis 126 (0.6) 177 (1.2) 0.7036 0.4023 0.6033 of arthritis 126 (0.6) 177 (1.2) 0.7036 0.2203 0.3355 of arthritis 126 (0.6) 177 (1.2) 0.7036 0.2036 0.6033 of arthritis 126 (0.6) 177 (1.2) 0.7036 0.2036 0.6033 of arthritis 126 (0.6) 177 (1.2) 0.7036 0.7936 0.6033 of arthritis 126 (0.6) 177 (1.2) 0.7036 0.7936 0.6033 of arthritis 126 (0.3) 127 (0.3) 0.603 0.6033 0.6033 or arthretic 120 (0.3) 127 (0.3) 0.614 0.7036 0.2036 arthretic 1577 (8.3) 0.3355 <t< td=""><td>Dyslipidemia</td><td>5215 (13.0)</td><td>4837 (13.0)</td><td>378 (13.4)</td><td>198 (13.7)</td><td>180 (13.0)</td><td>0.7279</td><td>0.6019</td><td>0.5509</td></t<>	Dyslipidemia	5215 (13.0)	4837 (13.0)	378 (13.4)	198 (13.7)	180 (13.0)	0.7279	0.6019	0.5509
Cancer3432 (8.6)3217 (8.7)215 (7.6)100 (6.9)115 (8.3)0.06720.0526Congestive heart failure2165 (5.4)2000 (5.4)165 (5.8)79 (5.5)86 (6.2)0.41740.3086Chronic kidney disease1917 (4.8)1775 (4.8)142 (5.0)67 (4.6)75 (5.4)0.54190.5615End-stage renal disease460 (1.2)431 (1.2)29 (1.0)14 (1.0)15 (1.1)0.70360.4029Reumatoid arthritis432 (1.1)397 (1.1)37 (1.2)18 (1.3)17 (1.2)0.70360.4023Reumatoid arthritis243 (0.7)16 (0.6)10 (0.7)6 (0.4)0.59870.5053Ankylosing spondylitis256 (0.6)240 (0.7)16 (0.6)0.4)0.20360.4023No160 (0.4)177 (1.2)0.70360.40230.5053PAOD170 (1.6)6 (0.4)10 (0.7)6 (0.4)0.20360.3053PAOD171 (0.3)9 (0.3)6 (0.4)3 (0.2)0.64460.56870.5053PAOD130 (0.3)121 (0.3)9 (0.3)6 (0.4)3 (0.2)0.64460.90510.0561Medical centre15427 (38.5)173 (13.5)100 (35.6)515 (35.7)493 (35.5)0.00150.00150.0015Regional hospital77576 (43.9)1662 (47.8)66 (47.4)657 (48.4)67 (48.6)0.00150.00150.0015Medical centre1747 (18)740 (11.9)308 (10.9)166 (11.5)176 (12.5)176 (12	we heart failure 3432 (8.6) 3217 (8.7) 215 (7.6) 100 (6.9) 115 (8.3) 0.0672 0.0526 we heart failure 2165 (5.4) 2000 (5.4) 165 (5.8) 79 (5.5) 86 (6.2) 0.4174 0.3086 errore disease 400 (1.2) 4131 (1.2) 291 (1.1) 397 (1.1) 397 (1.1) 357 (1.2) 0.5415 0.5615 errore disease 400 (1.2) 377 (1.1) 397 (1.1) 357 (1.2) 142 (5.0) 174 (1.0) 157 (1.1) 0.7364 0.5615 oid arthritis 2266 (0.6) 240 (0.7) 116 (0.6) 10 (0.7) 0.6 (0.4) 0.7367 0.0539 9 pondylitis 256 (0.6) 240 (0.7) 116 (0.6) 10 (0.7) 0.6 (0.4) 0.7367 0.0537 122 (0.5) 175 (0.5) 176 (0.6) 10 (0.7) 0.6 (0.4) 0.7367 0.0539 9 (0.3) 120 (0.3) 120 (0.3) $9(0.3)$ 0.644 0.2103 0.3353 120 (0.5) 121 (0.3) $9(0.3)$ $6(0.4)$ 17 (1.2) 0.2033 0.3056 130 (0.3) 121 (0.3) $9(0.3)$ $6(0.4)$ 17 (1.2) 0.7304 0.9537 130 (0.3) 121 (0.3) $9(0.3)$ $6(0.4)$ 0.516 0.2033 0.3056 130 (0.3) 121 (0.3) $9(0.3)$ $6(0.4)$ 0.2567 0.9587 0.9587 177 (1.2) 1777 (1.3) 1270 (3.3) 121 (3.4) 0.201 0.7807 0.9587 1777 (1.8)	Coronary arterial disease	4379 (10.9)	4063 (10.9)	316 (11.2)	148 (10.3)	168 (12.1)	0.2721	0.7004	0.1203
Congestive heart failure 2165 (5.4) 2000 (5.4) 165 (5.8) 79 (5.5) 86 (6.2) 0.4174 0.3086 Chronic kidney disease 1917 (4.8) 1775 (4.8) 1775 (4.8) 142 (5.0) 67 (4.6) 75 (5.4) 0.5419 0.5715 End-stage renal disease 1917 (4.8) 1775 (4.8) 142 (5.0) 67 (4.6) 75 (5.4) 0.5719 0.5715 Rheumatoid arthritis 433 (1.1) 397 (1.1) 397 (1.1) 397 (1.1) 357 (1.2) 18 (1.3) 177 (1.2) 0.7704 0.5716 Ankylosing spondylitis 256 (0.6) 240 (0.7) 16 (0.6) 10 (0.7) 6 (0.4) 0.2203 0.3353 Ankylosing spondylitis 122 (0.5) 177 (0.5) 6 (0.4) 11 (0.8) 0.2203 0.3353 PAOD 110 (0.7) 16 (0.6) 10 (0.7) 6 (0.4) 0.2011 0.0511 0.05013 PAOD 110 (0.7) 16 (0.4) 3 (0.2) 6 (0.4) 0.2503 0.3353 PAOD 130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.6446 0.9458 Medical centre 15427 (38.5) 14419 (38.8) 1008 (35.6) 515 (37.7) 493 (35.5) 0.0015 0.0015 0.00015 Regional hospital 1777 (4.3.9) 160 (7.7) 06 (4.7.4) 672 (4.8.4) 0.0015 0.0015 0.00015 Nedical centre 17576 (4.3.9) 160 (7.7) 78 (4.7.4) 672 (4.8.4) 0.0015 0.0015 0.00015	we heart failure $2165 (5,4)$ $2000 (5,4)$ $165 (5,8)$ $79 (5,5)$ $86 (6,2)$ 0.4174 0.3086 didrey disease $1917 (4,8)$ $1775 (4,8)$ $112 (5,0)$ $67 (4,6)$ $75 (5,4)$ 0.5419 0.5615 e renal disease $460 (1,2)$ $431 (1,2)$ $29 (1,0)$ $114 (1,0)$ $15 (1,1)$ 0.7304 0.3615 oid arthritis $432 (1,1)$ $397 (1,1)$ $35 (1,2)$ $114 (1,0)$ $15 (1,1)$ 0.7304 0.3064 $312 (1,1)$ $240 (0,7)$ $16 (0,6)$ $10 (0,7)$ $6 (0,4)$ $11 (0,8)$ 0.5987 0.4023 $312 (0,3)$ $175 (0,5)$ $177 (0,6)$ $6 (0,4)$ $11 (0,8)$ 0.2203 0.3353 $192 (0,5)$ $175 (0,5)$ $177 (0,6)$ $6 (0,4)$ $11 (0,8)$ 0.2203 0.3353 $110 (0,3)$ $121 (0,3)$ $121 (0,3)$ $5 (0,2)$ $5 (0,4)$ $0 (0,0)$ 0.6711 0.5987 0.6509 $120 (3,5)$ $127 (3,5)$ $1419 (3,8)$ $1008 (35.6)$ $515 (35.7)$ $493 (35.5)$ 0.0015 0.0015 0.0005 creditation level $15427 (33.5)$ $14419 (33.8)$ $1008 (35.6)$ $515 (35.7)$ $493 (35.5)$ 0.0015 0.0005 $150 (3,6)$ $2145 (4,3)$ $166 (1,5)$ $122 (48,4)$ 0.2203 0.0015 0.0005 $170 (1,8)$ $2145 (4,8)$ $1008 (35.6)$ $515 (35.7)$ $493 (35.5)$ 0.0015 0.0005 $170 (1,6)$ $120 (1,9)$ $166 (1,5)$ $122 (48,4)$ 0.2203 $0.$	Cancer	3432 (8.6)	3217 (8.7)	215 (7.6)	100 (6.9)	115 (8.3)	0.0672	0.0526	0.1753
Chronic kidney disease197 (4.8)1775 (4.8)1775 (4.8)1775 (4.6)75 (5.4)0.54190.5615End-stage renal disease460 (1.2)431 (1.2)29 (1.0)14 (1.0)15 (1.1)0.78040.5165Rheumatoid arthritis432 (1.1)397 (1.1)397 (1.1)29 (1.0)14 (1.0)15 (1.1)0.70360.4029Rheumatoid arthritis432 (1.1)397 (1.1)35 (1.2)18 (1.3)17 (1.2)0.70360.4023Ankylosing spondylitis256 (0.6)240 (0.7)16 (0.6)10 (0.7)6 (0.4)117 (1.2)0.5033Ankylosing spondylitis155 (0.5)17 (0.6)17 (0.6)6 (0.4)117 (1.2)0.50360.6053Ankylosing spondylitis156 (0.6)17 (0.6)6 (0.4)11 (0.8)0.22030.3353PAOD130 (0.3)17 (1.0)17 (1.0)6 (0.4)11 (0.8)0.22030.3458PAOD130 (0.3)121 (0.3)9 (0.3)6 (0.4)11 (0.8)0.20110.05110.0501PAOD130 (0.3)121 (0.3)121 (0.3)9 (0.3)6 (0.4)3 (0.2)0.64460.9458Medical centre15427 (38.5)14419 (38.8)1008 (35.6)515 (35.7)493 (35.5)0.60150.0002Medical centre15756 (43.9)16220 (43.7)1368 (47.4)6 (2.4)11 (0.2)0.64460.9002Medical centre17756 (43.9)16220 (43.7)1368 (47.4)6 (2.4)124 (47.4)6 (7.4)0.00150.0002 <td>vidue disease1917 (4.8)1775 (4.8)142 (5.0)$67 (4.6)$$75 (5.4)$$0.5419$$0.5615$e rend disease460 (1.2)431 (1.2)29 (1.0)14 (1.0)15 (1.1)$0.7804$$0.5165$oid arthritis432 (1.1)337 (1.1)357 (1.2)17 (1.2)$0.7366$$0.6053$oig archritis256 (0.6)240 (0.7)16 (0.6)10 (0.7)$6 (0.4)$$0.7366$$0.6053$192 (0.5)177 (0.5)6 (0.4)117 (1.2)$0.7366$$0.6053$$0.3353$192 (0.5)177 (0.5)6 (0.4)117 (1.2)$0.7366$$0.6053$130 (0.3)121 (0.3)121 (0.3)9 (0.3)$6 (0.4)$$117 (1.2)$$0.7036$$0.6053$130 (0.3)121 (0.3)121 (0.3)9 (0.3)$6 (0.4)$$117 (1.2)$$0.7036$$0.6053$130 (0.3)121 (0.3)121 (0.3)9 (0.3)$6 (0.4)$$117 (1.2)$$0.7036$$0.6053$entre15427 (38.5)14419 (38.8)1008 (35.6)5 (5.4)$3 (2.2)$$0.6446$$0.9016$hospital17576 (43.9)16220 (43.7)1356 (47.8)$6 (0.4)$$117 (10.2)$$0.0015$$0.0015$hospital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4)$0.6723$$0.0015$$0.0015$spital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4)$0.6723$$0.0015$$0.0015$spital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4)$0.6723$$0.0434$<t< td=""><td>Congestive heart failure</td><td>2165 (5.4)</td><td>2000 (5.4)</td><td>165 (5.8)</td><td>79 (5.5)</td><td>86 (6.2)</td><td>0.4174</td><td>0.3086</td><td>0.4156</td></t<></td>	vidue disease1917 (4.8)1775 (4.8)142 (5.0) $67 (4.6)$ $75 (5.4)$ 0.5419 0.5615 e rend disease460 (1.2)431 (1.2)29 (1.0)14 (1.0)15 (1.1) 0.7804 0.5165 oid arthritis432 (1.1)337 (1.1)357 (1.2)17 (1.2) 0.7366 0.6053 oig archritis256 (0.6)240 (0.7)16 (0.6)10 (0.7) $6 (0.4)$ 0.7366 0.6053 192 (0.5)177 (0.5)6 (0.4)117 (1.2) 0.7366 0.6053 0.3353 192 (0.5)177 (0.5)6 (0.4)117 (1.2) 0.7366 0.6053 130 (0.3)121 (0.3)121 (0.3)9 (0.3) $6 (0.4)$ $117 (1.2)$ 0.7036 0.6053 130 (0.3)121 (0.3)121 (0.3)9 (0.3) $6 (0.4)$ $117 (1.2)$ 0.7036 0.6053 130 (0.3)121 (0.3)121 (0.3)9 (0.3) $6 (0.4)$ $117 (1.2)$ 0.7036 0.6053 entre15427 (38.5)14419 (38.8)1008 (35.6)5 (5.4) $3 (2.2)$ 0.6446 0.9016 hospital17576 (43.9)16220 (43.7)1356 (47.8) $6 (0.4)$ $117 (10.2)$ 0.0015 0.0015 hospital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4) 0.6723 0.0015 0.0015 spital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4) 0.6723 0.0015 0.0015 spital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4) 0.6723 0.0434 <t< td=""><td>Congestive heart failure</td><td>2165 (5.4)</td><td>2000 (5.4)</td><td>165 (5.8)</td><td>79 (5.5)</td><td>86 (6.2)</td><td>0.4174</td><td>0.3086</td><td>0.4156</td></t<>	Congestive heart failure	2165 (5.4)	2000 (5.4)	165 (5.8)	79 (5.5)	86 (6.2)	0.4174	0.3086	0.4156
End-stage renal disease $460(1.2)$ $431(1.2)$ $29(1.0)$ $14(1.0)$ $15(1.1)$ 0.7804 0.5165 Rheumatoid arthritis $432(1.1)$ $397(1.1)$ $397(1.1)$ $397(1.1)$ $397(1.1)$ $397(1.1)$ 0.7036 0.4029 Rheumatoid arthritis $432(1.1)$ $397(1.1)$ $397(1.1)$ $35(1.2)$ $18(1.3)$ $17(1.2)$ 0.7036 0.4029 Ankylosing spondylitis $256(0.6)$ $240(0.7)$ $16(0.6)$ $10(0.7)$ $6(0.4)$ $0.7(12)$ 0.5037 0.6053 Psoriasis $177(0.6)$ $6(0.4)$ $117(0.6)$ $6(0.4)$ $11(0.8)$ 0.2203 0.3353 PAOD $120(0.3)$ $127(0.3)$ $127(0.3)$ $9(0.3)$ $6(0.4)$ 0.001 0.0511 0.0509 PAOD $130(0.3)$ $121(0.3)$ $121(0.3)$ $9(0.3)$ $6(0.4)$ $3(0.2)$ 0.6446 0.9458 PAOD $130(0.3)$ $121(0.3)$ $121(0.3)$ $121(0.3)$ $0.315(0.4)$ $3(0.2)$ 0.0019 0.0011 Pospital accreditation level $1542(38.5)$ $14419(38.8)$ $1008(35.6)$ $515(35.7)$ $493(35.5)$ 0.0015 0.0015 Regional hospital $17576(43.9)$ $1620(47.7)$ $66(4.7)$ $106(1.5)$ $147(4)$ $672(48.4)$ 0.0015 0.0015 Noted 0.0511 $0.035(6)$ $515(35.7)$ $493(35.5)$ 0.0015 0.0015 0.0015 0.0015 Regional hospital $17576(43.9)$ $1620(1.9)$ $166(1.5)$ $166(1.5)$ $162(1.5)$	e rend disease $460 (1.2)$ $431 (1.2)$ $29 (1.0)$ $14 (1.0)$ $15 (1.1)$ 0.7804 0.5165 oid arthritis $432 (1.1)$ $397 (1.1)$ $35 (1.2)$ $18 (1.3)$ $17 (1.2)$ 0.7036 0.4029 oid arthritis $256 (0.6)$ $220 (0.7)$ $16 (0.6)$ $10 (0.7)$ $6 (0.4)$ 0.2033 0.3353 $192 (0.5)$ $175 (0.5)$ $17 (0.6)$ $6 (0.4)$ $11 (0.8)$ 0.2203 0.3353 $192 (0.5)$ $175 (0.5)$ $17 (0.6)$ $6 (0.4)$ $11 (0.8)$ 0.2203 0.3353 $130 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $11 (0.8)$ 0.2203 0.3559 $130 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $11 (0.8)$ 0.2203 0.3559 $130 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $11 (0.8)$ 0.2203 0.3559 $130 (0.3)$ $121 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $0 (0.0)$ 0.0011 $130 (0.3)$ $17576 (43.9)$ $160 (47.4)$ $515 (35.7)$ $493 (35.5)$ 0.0015 0.0015 hospital $1777 (11.8)$ $4409 (11.9)$ $308 (10.9)$ $166 (11.5)$ $142 (10.2)$ 0.0015 0.0015 0.0005 spital $2305 (5.8)$ $2145 (5.8)$ $100 (6.7)$ $78 (5.4)$ $82 (5.9)$ 0.0434 0.5942 $100 (800)$ $31922 (86.0)$ $2425 (85.6)$ $1213 (84.1)$ $1212 (87.3)$ 0.0434 0.5942	Chronic kidney disease	1917 (4.8)	1775 (4.8)	142 (5.0)	67 (4.6)	75 (5.4)	0.5419	0.5615	0.3565
Rheumatoid arthritis 432 (1.1) 397 (1.1) 35 (1.2) 18 (1.3) 17 (1.2) 0.7036 0.4029 Ankylosing spondylitis 256 (0.6) 240 (0.7) 16 (0.6) 10 (0.7) 6 (0.4) 0.5987 0.6053 Psoriasis 172 (0.5) 177 (0.6) 6 (0.4) 0.1007 6 (0.4) 0.2003 0.0509 Psoriasis 192 (0.5) 177 (0.5) 6 (0.4) 11 (0.8) 0.2203 0.0509 PAOD 160 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 0 (0.0) 0.0511 0.0509 PAOD 130 (0.3) 121 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.6446 0.9458 Medical centre 15427 (38.5) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0015 0.0015 Medical centre 1572 (43.3) 1620 (1.9) 366 (47.8) 66 (47.4) 67 (47.4) 67 (47.4) 67 (47.4) 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.	oid arthritis $432 (1.1)$ $397 (1.1)$ $35 (1.2)$ $18 (1.3)$ $17 (1.2)$ 0.7036 0.4029 $3 pondylitis$ $256 (0.6)$ $240 (0.7)$ $16 (0.6)$ $10 (0.7)$ $6 (0.4)$ 0.2033 0.6053 $192 (0.5)$ $177 (0.5)$ $16 (0.6)$ $10 (0.7)$ $6 (0.4)$ 0.2203 0.3353 $192 (0.5)$ $175 (0.5)$ $17 (0.6)$ $6 (0.4)$ 0.2203 0.6053 $130 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $0 (0.0)$ 0.0511 0.0509 $130 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $3 (0.2)$ 0.6446 0.9458 creditation level $15427 (385)$ $14419 (388)$ $1008 (35.6)$ $515 (35.7)$ $493 (35.5)$ 0.0015 0.0002 hospital $17576 (43.9)$ $16220 (43.7)$ $1356 (47.8)$ $684 (47.4)$ $672 (48.4)$ 0.0015 0.0002 hospital $17576 (43.9)$ $16220 (43.7)$ $3368 (10.9)$ $166 (11.5)$ $142 (10.2)$ 0.0015 0.0002 spital $2305 (5.8)$ $2145 (5.8)$ $160 (5.7)$ $78 (5.4)$ $82 (5.9)$ 0.0434 0.5942 Specialist $34407 (860)$ $31982 (860)$ 247.8 $121 (84.1)$ $121 (87.3)$ 0.0434 0.5942	End-stage renal disease	460 (1.2)	431 (1.2)	29 (1.0)	14 (1.0)	15 (1.1)	0.7804	0.5165	0.7719
Ankylosing spondylitis 256 (0.6) 240 (0.7) 16 (0.6) 10 (0.7) 6 (0.4) 0.5987 0.6053 Psoriasis 192 (0.5) 175 (0.5) 17 (0.6) 6 (0.4) 11 (0.8) 0.2203 0.3353 HV 160 (0.4) 155 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 11 (0.8) 0.2203 0.3353 HV 160 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 11 (0.8) 0.2203 0.3059 PAOD 130 (0.3) 121 (0.3) 9 (0.3) 121 (0.3) 0.0511 0.0511 0.0509 Modical contre 1542 (38.5) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0015 0.0015 Medical contre 17576 (43.9) 1620 (4.7.8) 684 (47.4) 67 (48.4) 67 (48.4) 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015 0.0015	ng spondylitis $256 (0.6)$ $240 (0.7)$ $16 (0.6)$ $10 (0.7)$ $6 (0.4)$ 0.5987 0.6053 $192 (0.5)$ $177 (0.5)$ $17 (0.6)$ $6 (0.4)$ $11 (0.8)$ 0.2203 0.3353 $160 (0.4)$ $155 (0.4)$ $17 (0.6)$ $6 (0.4)$ $11 (0.8)$ 0.2011 0.0509 $130 (0.3)$ $121 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $11 (0.8)$ 0.2011 0.0509 creditation level $130 (0.3)$ $121 (0.3)$ $9 (0.3)$ $6 (0.4)$ $3 (0.2)$ 0.6446 0.9458 centre $15427 (385)$ $14419 (388)$ $1008 (35.6)$ $515 (35.7)$ $493 (35.5)$ 0.0015 0.0002 hospital $17576 (43.9)$ $16220 (43.7)$ $1356 (47.8)$ $684 (47.4)$ $672 (48.4)$ 0.0015 0.0002 spital $2305 (5.8)$ $2145 (5.8)$ $160 (5.7)$ $78 (5.4)$ $82 (5.9)$ 0.0434 0.5942 specialist $34407 (860)$ $31982 (860)$ $2425 (85.6)$ $1213 (84.1)$ $1212 (87.3)$ 0.0434 0.5942	Rheumatoid arthritis	432 (1.1)	397 (1.1)	35 (1.2)	18 (1.3)	17 (1.2)	0.7036	0.4029	0.9549
Psoriasis 192 (0.5) 175 (0.5) 17 (0.6) 6 (0.4) 11 (0.8) 0.2203 0.3353 HV 160 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 11 (0.8) 0.0511 0.0509 HV 160 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 0 (0.0) 0.0511 0.0509 PAOD 130 (0.3) 121 (0.3) 9 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.0511 0.0509 Mospital accreditation level 130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.0015 0.0458 Medical centre 1542 (38.5) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0015 0.0015 Regional hospital 17576 (43.9) 16220 (43.7) 1356 (47.8) 684 (47.4) 672 (48.4) 0.0015 0.0015 0.0015 0.0015 0.0002 Regional hospital 477 (11.8) 4409 (11.9) 308 (10.9) 166 (11.5) 1447 (40) 672 (48.4) 0.0015 0.0015 0.0015 0.0002 <td>192 (0.5)175 (0.5)17 (0.6)$6 (0.4)$11 (0.8)$0.2203$$0.3353$160 (0.4)155 (0.4)155 (0.4)0 (0.0)0.05110.0509130 (0.3)121 (0.3)9 (0.3)$6 (0.4)$3 (0.2)0.06110.0509creditation level154 (3.5)121 (0.3)9 (0.3)$6 (0.4)$3 (0.2)0.06110.0509centre15427 (38.5)14419 (38.8)1008 (35.6)515 (35.7)493 (35.5)0.00150.0002hospital17576 (43.9)16220 (43.7)336 (10.9)166 (11.5)142 (10.2)0.00150.0002spital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4)82 (5.9)0.04340.59422 specialist3407 (86.0)31982 (86.0)2425 (85.6)1213 (84.1)1212 (87.3)0.04340.5942</td> <td>Ankylosing spondylitis</td> <td>256 (0.6)</td> <td>240 (0.7)</td> <td>16 (0.6)</td> <td>10 (0.7)</td> <td>6 (0.4)</td> <td>0.5987</td> <td>0.6053</td> <td>0.3542</td>	192 (0.5)175 (0.5)17 (0.6) $6 (0.4)$ 11 (0.8) 0.2203 0.3353 160 (0.4)155 (0.4)155 (0.4)0 (0.0)0.05110.0509130 (0.3)121 (0.3)9 (0.3) $6 (0.4)$ 3 (0.2)0.06110.0509creditation level154 (3.5)121 (0.3)9 (0.3) $6 (0.4)$ 3 (0.2)0.06110.0509centre15427 (38.5)14419 (38.8)1008 (35.6)515 (35.7)493 (35.5)0.00150.0002hospital17576 (43.9)16220 (43.7)336 (10.9)166 (11.5)142 (10.2)0.00150.0002spital2305 (5.8)2145 (5.8)160 (5.7)78 (5.4)82 (5.9)0.04340.59422 specialist3407 (86.0)31982 (86.0)2425 (85.6)1213 (84.1)1212 (87.3)0.04340.5942	Ankylosing spondylitis	256 (0.6)	240 (0.7)	16 (0.6)	10 (0.7)	6 (0.4)	0.5987	0.6053	0.3542
HIV 155 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 0 (0.0) 0.0511 0.0509 PAOD 130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0 (0.0) 0.0511 0.0509 Hospital accreditation level 130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.6446 0.9458 Medical centre 15427 (38.5) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0002 Regional hospital 17576 (43.9) 16220 (43.7) 1356 (47.8) 684 (47.4) 672 (48.4) 0.0015 0.0002 Local hospital 277 (5 8) 3467 (1.9) 3467 (1.9) 1456 (11.5) 1457 (42.2) 67.2 (48.4) Other 2356 (47.8) 668 (4.7.4) 67.2 (48.4) 67.6 (12.5) 0.0015 0.0002 Other 2356 (47.8) 166 (11.5) 1456 (11.5) 147.6 (12.5) 147.6 (10.2)	160 (0.4) 155 (0.4) 5 (0.2) 5 (0.4) 0 (0.0) 0.05110.0509130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.0010.05110.0509creditation level1576 (43.9) 121 (0.3) 9 (0.3) 515 (35.7) 493 (35.5) 0.00150.0002hospital17576 (43.9) 16220 (43.7) 1356 (47.8) 684 (47.4) 672 (48.4) 0.00150.0002spital2305 (5.8) 2145 (5.8) 160 (1.9) 308 (10.9) 166 (11.5) 142 (10.2) 0.00150.0002spital2305 (5.8) 2145 (5.8) 160 (5.7) 78 (5.4) 82 (5.9) 0.04340.5942Specialist34407 (860) 31982 (86.0) 2425 (85.6) 1213 (84.1) 1212 (87.3) 0.04340.5942	Psoriasis	192 (0.5)	175 (0.5)	17 (0.6)	6 (0.4)	11 (0.8)	0.2203	0.3353	0.1952
PAOD 130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.6446 0.9458 Hospital accreditation level 15427 (38.5) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0002 Regional hospital 17576 (43.9) 16220 (43.7) 1356 (47.8) 684 (47.4) 672 (48.4) 0.0015 0.0002 0.0002 Regional hospital 17576 (33.9) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0002 0.0002 Regional hospital 17576 (33.9) 16220 (43.7) 1356 (47.8) 684 (47.4) 672 (48.4) 0.0015 0.0002 0.0002 Checal hospital 277 (71.8) 2409 (11.9) 308 (10.9) 166 (17.5) 142 (10.2) 0.014 (12.5) 0.0015 0.0002 Other 2356 (10.3) 160 (57) 78 (5.4) 162 (12.5) 162 (12.5) 162 (12.5) 162 (12.5)	130 (0.3) 121 (0.3) 9 (0.3) 6 (0.4) 3 (0.2) 0.6446 0.9458 ccreditation level 15427 (38.5) 14419 (38.8) 1008 (35.6) 515 (35.7) 493 (35.5) 0.0015 0.0465 0.9458 centre 17576 (43.9) 16220 (43.7) 1356 (47.8) 684 (47.4) 672 (48.4) 0.0015 0.0002 spital 4717 (11.8) 4409 (11.9) 308 (10.9) 166 (11.5) 142 (10.2) 142 (10.2) 142 (10.2) spital 2305 (5.8) 2145 (5.8) 160 (5.7) 78 (5.4) 82 (5.9) 0.0434 0.5942 specialist 34407 (86.0) 31982 (86.0) 2425 (85.6) 1213 (84.1) 1212 (87.3) 0.0434 0.5942	HIV	160 (0.4)	155 (0.4)	5 (0.2)	5 (0.4)	0 (0.0)	0.0511	0.0509	0.0625
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) specialist 34407 (86.0) 31982 (86.0) 2425 (85.6) 1213 (84.1) 1212 (87.3) 0.0434 0.5942	Other	2305 (5.8)	2145 (5.8)	160 (5.7)	78 (5.4)	82 (5.9)			
Chest or ID specialist 34407 (86.0) 31982 (86.0) 2425 (85.6) 1213 (84.1) 1212 (87.3) 0.0434 0.5942		Chest or ID specialist	34407 (86.0)	31982 (86.0)	2425 (85.6)	1213 (84.1)	1212 (87.3)	0.0434	0.5942	0.0154

Table 1. Demographic data of participants.

positive cultures after 2nd month. Secondary outcomes were death within two months and unfavourable outcomes at 2nd month.

Sputum culture conversion (SCC) is defined as the negativity of three consecutive sputum samples. The date of the first of the three samples being plated is considered as the date of SCC. An unfavourable outcome in the second month assessment point was defined as the occurrence of patient mortality within the initial 2-month treatment period, loss of followup, or failure to achieve SCC. No positive cultures after 2nd month were defined as the absence of any positive TB culture after 2nd month (after 60 days).

Statistical analysis

In this study, we used descriptive statistics to summarize the demographic, clinical, and radiographic characteristics of TB patients. For continuous variables, means were calculated, while proportions were used for categorical variables. To compare differences between groups, we used an independent-sample ttest for continuous variables and a chi-squared test for categorical variables. In the logistic regression analysis, we examined the association between isoniazid resistance and no positive cultures after 2nd month and unfavourable outcomes at the 2nd month. Cox proportional hazard regression models were used to assess the association between isoniazid resistance and time to SCC and survival within 2 months. Additionally, competing risk analysis was also performed for time to SCC using death as the competing risk. Sensitivity analysis was performed by not excluding those who died within one month. For adjustment, we put either isoniazid only (isoniazid mono-resistant vs. all susceptible) or isoniazid low-level and high-level resistance (isoniazid low-level resistant vs. isoniazid high-level resistant vs. all susceptible) in the multivariable models. Subgroup analyses were conducted for different age groups, sex, smear results, body weight, and patients without comorbidities. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A significance level of p <0.05, determined by a two-sided test, was considered statistically significant.

Results

Demographic characteristics

During the study period (2008–2017), there were 144,668 pulmonary TB patients. There were 83,305 (57.6%) patients with culture-positivity and among them, 62915 (75.5%) received at least 14 days of isoniazid, rifampicin, pyrazinamide, and ethambutol. Overall, 49,566 (78.8%) had drug susceptibility results. After excluding resistance to either ethambutol or

rifampicin (n = 162), previous exposure to fluoroquinolone, streptomycin, or amikacin (n = 7241), not categorized within all susceptible, low-dose INH resistance or high-dose resistance (n = 250), aged less than 20 (n = 1213), a total of 40,700 pulmonary TB patients were identified. Among them, 675 died within one month after TB treatment, and the remaining 40,025 pulmonary TB patients were included in the main analysis.

Among them, 92.9% (n = 37,193) had drug-susceptible TB, and 7.1% (n = 2,832) had HR-TB. The median age was 64 years old (mean ± standard deviation [SD], 62.2 ± 18.9) among all susceptible TB and 62 years old (mean ± SD, 61.8 ± 18.1 , p = 0.2618) among HR-TB. There was a male predominance among all susceptible (n = 26645, 71.6%) and HR-TB (n = 2010, 71.0%, p = 0.4492). Among the 2,832 HR-TB patients, 51.0% (n = 1,443) had low-level isoniazid resistance, and 49.0% (n = 1,389) had high-level isoniazid resistance.

Compared to patients with drug-susceptible TB, those with HR-TB were more likely to have cavitary lesions (21.2% vs. 19.5%, p = 0.0291), smear-positive results (56.2% vs. 54.0%, p = 0.0237), and less likely to have extrapulmonary lesions (5.7% vs. 7.2%, p =0.0025). When comparing isoniazid high-level resistance with low-level resistance, patients with low-level resistance tended to be younger $(60.7 \pm 17.9 \text{ vs. } 63.1 \text{ sc})$ ± 18 years old, p = 0.0004), have cavitary lesions (23.5% vs. 18.7%, p = 0.0019), and were less likely to be under the service of a chest/infectious disease subspecialty (84.1% vs. 87.3%, p = 0.0154). There was also a trend towards smear positivity in patients with low-level resistance, although it did not reach statistical significance (57.7% vs. 54.6%, p = 0.0983). The detailed demographic data are described in Table 1.

Within the two months, a total of 854 (2.1%) patients had died. At the 2-month mark, SCC was not achieved in 10,834 (27.1%) of the patients. Therefore, 11,687 patients (29.2%) had an unfavourable outcome at the 2nd month.

Rate and volume of sputum culture examinations

Before treatment, sputum samples were examined in 92.64% of patients. All patients had their sputum samples examined within the first month of treatment. During the first month, a cumulative total of 30,245 patients (75.6%) underwent follow-up sputum cultures, and in the 2nd month, 37,098 patients (92.7%) had follow-up sputum culture performed. By the 6th month, 39,652 patients (99.1%) had undergone follow-up sputum mycobacterial culture (Figure 2).

Furthermore, by the end of the first month of treatment, participants had a median of 3 sputum samples



Figure 2. Proportion of participants who received sputum examinations before and after treatment.

collected (mean \pm SD, 3.2 ± 2.1 samples). At second month, participants had a median of 4 sputum samples collected (mean \pm SD, 4.1 ± 2.7 samples). Figure 2 illustrates the proportion of participants who received sputum examinations before and after treatment.

Association between isoniazid resistance and outcomes

Cox regression model for time to SCC

In multivariable Cox regression analysis, neither isoniazid resistance nor the level of isoniazid resistance was found to be associated with the time to SCC within 2 months (1. Adjusted with isoniazid resistance only, isoniazid resistance, adjusted hazard ratio [aHR]: 0.99, 95% CI: 0.94–1.05, p = 0.8145; 2. Adjusted for isoniazid low-level resistance and high-level resistance, isoniazid low-level resistance, aHR: 1.02, 95% CI: 0.95–1.10, p = 0.5898; isoniazid high-level resistance, aHR: 0.97, 95% CI: 0.89–1.04, p = 0.3811, Table 2). The factors associated with the time to SCC in primary analysis and sensitivity analysis, with or without competing risk analysis are illustrated in Supplementary Table 1. The Kaplan-Meier curve of time-to-culture conversion in the overall cohort is illustrated in Figure 3A.

Logistic regression model for no positive cultures after 2nd month

In multivariable logistic regression analysis for no positive cultures after 2nd month, neither isoniazid resistance nor the level of isoniazid resistance was found to be associated with no positive cultures after 2nd month (1. Adjusted with isoniazid only, isoniazid resistance, adjusted odds ratio [aOR]: 0.96, 95% CI: 0.88–1.05, p = 0.3398; 2. adjusted with low- and high-level isoniazid resistance, isoniazid low-level resistance, aOR: 1.00, 95% CI: 0.88–1.12, p = 0.9468; isoniazid high-level resistance, aOR: 0.92, 95% CI:

Table 2. Association between isoniazid resistance and different clinical outcomes.

							lsoniazid	resistand	ce	
		l	soniazid resist	ance		low-level		high-level		
Outcome	Model	ES*	95% Cl	p value	ES*	95% Cl	p value	ES*	95% CI	p value
Time to Sputum culture Conversion	CR	0.99	0.94—1.05	0.8145	1.02	0.95—1.10	0.5898	0.97	0.89—1.04	0.3811
No positive cultures after 2nd month	LR	0.96	0.88-1.05	0.3398	1.00	0.88-1.12	0.9468	0.92	0.82-1.04	0.1858
2-month survival	CR	1.19	0.92-1.53	0.1884	1.36	0.97—1.90	0.0731	1.02	0.70-1.49	0.9114
Unfavorable Outcome at 2nd Month	LR	1.05	0.97—1.14	0.2427	1.03	0.92—1.16	0.6017	1.07	0.95—1.21	0.2428

Models were adjusted for isoniazid resistance, age, sex, body weight, cavitation, smear positivity, extrapulmonary tuberculosis, income, marriage status, urbanization, comorbidities, hospital accreditation level and doctor specialty.

Abbreviation: CI, confidence interval; CR, cox regression; ES, effect size; LR, logistic regression

* ES (effect size) represents hazard ratio in cox regression and odds ratio in logistic regression.



Figure 3. Kaplan-Meier curves of time to sputum culture conversion among all cohort (A), participants aged between 20 and 65 (B) and healthy participants (C).

0.82-1.04, p = 0.1858, Table 2). Factors associated with no positive cultures after 2nd month in the primary analysis and sensitivity analysis are illustrated in Supplementary Table 2.

Cox regression model for mortality within two months

In multivariable Cox regression analysis, isoniazid resistance was not found to be associated with the worst survival within two months (adjusted for isoniazid only, isoniazid resistance, aHR: 1.19, 95% CI: 0.92-1.53, p = 0.1884). However, isoniazid low-level resistance showed a borderline association with a higher risk of death within two months (adjusted for isoniazid low-level resistance and high-level resistance, isoniazid low-level resistance, aHR: 1.36, 95% CI: 0.97-1.90, p = 0.0731; isoniazid high-level resistance, aHR: 1.02, 95% CI:0.70-1.49, p = 0.9114, Table 2). Factors associated with mortality within two months in primary analysis and sensitivity analysis are illustrated in Supplementary Table 3.

Logistic regression model for unfavourable outcomes at 2nd month

In multivariable logistic regression analysis for unfavourable outcomes in the 2nd month, neither isoniazid resistance nor the level of isoniazid resistance was found to be associated with unfavourable outcomes (isoniazid resistance, aOR: 1.05, 95% CI: 0.97-1.14, p = 0.2427; isoniazid low-level resistance, aOR: 1.03, 95% CI: 0.92-1.16, p = 0.6017; isoniazid high-level resistance, aOR: 1.07, 95% CI: 0.95-1.21, p = 0.2428). Factors that were identified to be associated with unfavourable outcomes in the 2nd month in the analysis and sensitivity analysis are summarized in Supplementary Table 4.

Subgroup analysis

Subgroup analysis adjusted isoniazid resistance for SCC

The Kaplan-Meier curves of time to SCC among individuals aged between 20 and 65 years and healthy patients are illustrated in Figure 3. In the Cox regression analysis, isoniazid resistance was associated with a longer time to SCC among individuals aged between 20 and 65 years old (aHR: 0.90, 95% CI: 0.83–0.98, p = 0.0099) and healthy patients (without comorbidities) (aHR: 0.90, 95% CI: 0.81–0.98, p = 0.0237) (Figure 4A, left panel). Among individuals aged 20-65, isoniazid resistance was less likely to achieve sputum culture conversion in 2nd month (aOR: 0.86, 95% CI: 0.76–0.96, p = 0.0088) (Figure 4A, right panel).

Subgroup analysis adjusted isoniazid resistance for survival and unfavourable outcome

Isoniazid resistance was not associated with the worst 2-month survival among the abovementioned 4 subgroups (Figure 4B, left panel), but was associated with a higher risk of unfavourable outcome in 2nd month in patients aged between 20 and 65 (aOR: 1.18, 95% CI: 1.05–1.32, p = 0.0053) (Figure 4B, right panel).

Subgroup analysis adjusted isoniazid low- and high-level resistance for SCC

Isoniazid low-level resistance was associated with a longer time to SCC among individuals aged between 20 and 65 years old (aHR: 0.88, 95% CI: 0.79–0.98, p = 0.0197), whereas isoniazid high-level resistance was associated with a longer time to SCC among healthy patients (without comorbidities) (aHR: 0.83, 95% CI: 0.73–0.96, p = 0.0097) (Supplementary Figure 1). Also, individuals aged 20–65 with low-level isoniazid resistance were less likely to achieve SCC within 2 months (aOR: 0.82, 95% CI: 0.70–0.95, p = 0.0105) (Supplementary Figure 1).

Subgroup analysis adjusted isoniazid low- and high-level resistance for survival and unfavourable outcome

Isoniazid low-level resistance was associated with a worse 2-month survival in smear-positive patients (aHR: 1.60, 95% CI:1.06–2.40, p = 0.0235) and a higher likelihood of unfavourable outcomes at the 2nd month in patients aged between 20 and 65

(A)		Tim	e to spu	itum cult	ure conv	ersion			No po	ositive	cultures	after 2nd	month	
Group	Ν	Event	(%)		HR	95% CI	p value	N	Event	(%)		OR	95% CI	p value
All cohort All susceptible INH	37193 2832	18217 1364	(49.0) (48.2)	н	1.00 0.99	(0.94,1.05) 0.8145	37193 2832	27150 2041	(73.0) (72.1)	H	1.00 0.96	(0.88,1.04)	0.3398
Age between 20 and 65 All susceptible INH	18976 1521	9278 683	(48.9) (44.9)	H	1.00 0.90	(0.83,0.98) 0.0099	18976 1521	14035 1073	(74.0) (70.5)	H	1.00 0.86	(0.76,0.96)	0.0088
Pulmonary cavitation All susceptible INH	7239 599	2857 231	(39.5) (38.6)	H	1.00 1.01	(0.88,1.15) 0.9305	7239 599	4915 394	(67.9) (65.8)	⊢ ∎-1	1.00 0.91	(0.76,1.09)	0.3158
Smear-positive All susceptible INH	20091 1592	8539 640	(42.5) (40.2)	H=1	1.00 0.94	(0.87,1.02) 0.1311	20091 1592	13842 1071	(68.9) (67.3)	H=1	1.00 0.92	(0.83,1.03)	0.1601
Healthy All susceptible INH	13909 1015	6836 458	(49.1) (45.1)	Herl	1.00	(0.81,0.98) 0.0237	13909 1015	10327 753	(74.2) (74.2)	H	1.00	(0.85,1.15)	0.9051
			0 Delaye	1 d	2 Quickene	d				0 Wor	1 se	2 Better		
(В)			2-n	nonth su	rvival			U	Infav	orable	outcome	e at secon	d month	
(B) Group	N	Even	2-n	nonth su	rvival _{HR}	95% CI	p value	U N	Event	orable	outcome	e at secon OR	d month 95% Cl	p value
(B) Group All cohort All susceptible INH	N 37193 2832	Even 3 790 64	2-n (%) (2.1) (2.3)	nonth su	rvival HR 1.00 1.19	95% CI (0.92,1.53)	p value 0.1884	N 37193 2832	Event 8 10832 855	(%) (2 (29.1) (30.2)	e outcome	e at secon OR 1.00 1.05	d month 95% Cl (0.97,1.14)	p value 0.2427
(B) Group All cohort All susceptible INH Age between 20 and 65 All susceptible INH	N 37193 2832 18976 1521	Even 3 790 64 98 12	2-n (%) (2.1) (2.3) (0.5) (0.8)	nonth su	rvival HR 1.00 1.19 	95% CI (0.92,1.53) (0.80,2.65)	p value 0.1884 0.2249	U N 37190 2832 18976 1521	Event 3 10832 855 6 5039 460	(%) (%) (2(29.1) (30.2) (26.6) (30.2)	e outcome	e at secon OR 1.00 1.05 H 1.00	d month 95% Cl (0.97,1.14) (1.05,1.32)	p value 0.2427 0.0053
(B) Group All cohort All susceptible INH Age between 20 and 65 All susceptible INH Pulmonary cavitation All susceptible INH	N 37193 2832 18976 1521 7239 599	Even 3 790 64 6 98 12 89 9	2-n (%) (2.1) (2.3) (0.5) (0.8) (1.2) (1.5)	nonth su	rvival HR 1.00 1.19 → 1.00 1.45 → 1.00 → 1.17	95% Cl (0.92,1.53) (0.80,2.65) (0.59,2.35)	p value 0.1884 0.2249 0.6507	N 37193 2832 18976 1521 7239 599	Event 8 10832 855 6 5039 460 2413 214	(%) (%) (2(29.1) (30.2) (26.6) (30.2) (33.3) (35.7)	e outcome	e at secon OR 1.00 1.05 H 1.00 H 1.18 H 1.00 H 1.11	d month 95% Cl (0.97,1.14) (1.05,1.32) (0.93,1.32)	p value 0.2427 0.0053 0.2607
(B) Group All cohort All susceptible INH Age between 20 and 65 All susceptible INH Pulmonary cavitation All susceptible INH Smear-positive All susceptible INH	N 37193 2832 18976 1521 7239 599 2009 1592	Even 3 790 64 5 98 12 89 9 1 448 43	2-n (%) (2.1) (2.3) (0.5) (0.8) (1.2) (1.5) (2.2) (2.7)	nonth su	HR 1.00 1.19 1.45 1.00 1.45 1.45 1.00 1.17 1.00 1.13	95% Cl (0.92,1.53) (0.80,2.65) (0.59,2.35) (1.00,1.87)	p value 0.1884 0.2249 0.6507	U N 37193 2832 18976 1521 7239 599 20091 1592	Event 3 10832 855 3 5039 460 2413 214 1 6696 564	(%) (%) (2 (29.1) (30.2) (26.6) (30.2) (33.3) (35.7) (33.3) (35.4)	e outcome	e at secon OR 1.00 1.05 H 1.10 H 1.11 H 1.00 H 1.11	d month 95% Cl (0.97,1.14) (1.05,1.32) (0.93,1.32) (0.99,1.23)	p value 0.2427 0.0053 0.2607 0.0646
(B) Group All cohort All susceptible INH Age between 20 and 65 All susceptible INH Pulmonary cavitation All susceptible INH Smear-positive All susceptible INH Healthy All susceptible INH	N 37192 2832 18976 1521 7239 599 2009 ⁻¹ 1592 13903 1015	Even 3 790 64 3 98 12 89 9 1 448 43 9 116 13	2-n (2.1) (2.3) (0.5) (0.8) (1.2) (1.5) (2.2) (2.7) (0.8) (1.3)	nonth su	HR 1.00 1.19 1.00 1.45 1.00 1.45 1.00 1.17 1.00 1.36 1.00 1.50	95% Cl (0.92,1.53) (0.80,2.65) (0.59,2.35) (1.00,1.87) (0.85,2.67)	 p value 0.1884 0.2249 0.6507 0.0531 0.1632 	N 37193 2832 18976 1521 7239 599 20091 1592 13903 1015	Event 3 10832 855 3 5039 460 2413 214 1 6696 564 9 3698 275	(26.6) (33.3) (35.7) (26.6) (33.3) (35.7) (33.3) (35.4) (26.6) (27.1)	e outcome	e at secon OR 1.00 1.05 H 1.10 H 1.18 H 1.00 H 1.11 1.00 1.11 1.00 1.03	d month 95% Cl (0.97,1.14) (1.05,1.32) (0.93,1.32) (0.99,1.23) (0.89,1.19)	p value 0.2427 0.0053 0.2607 0.0646 0.6787

Figure 4. Forest plot of subgroup analysis on time to sputum culture conversion within two months and no positive cultures after 2nd month (A) and on 2-month survival and unfavourable outcome at 2nd month (B).

(aOR: 1.24, 95% CI: 1.06–1.44, p = 0.0066) (Supplementary Figure 2).

Discussion

Our large-scale population-based cohort demonstrated that isoniazid monoresistance was not associated with sputum culture conversion or unfavourable outcomes at the 2-month after treatment, as compared to fully susceptible tuberculosis. However, upon closer examination of subgroups, we discovered a greater likelihood of delayed culture conversion among younger patients and those without comorbidities. Moreover, when comparing low-level and high-level isoniazid resistance, we found that low-level resistance was more commonly associated with adverse outcomes across various metrics.

Our study has several strengths. Its populationbased design resulted in a large number of patients, making it one of the largest cohorts ever described in the literature. Additionally, the database for untransitioned TB contains detailed information on sputum mycobacterial examinations, results, and drug susceptibility. In Taiwan, the diagnosis and treatment of TB are fully funded by the National Health Insurance programme, supplemented further by additional contributions from the Taiwan CDC [14]. Taiwan has achieved excellent performance in TB control. Taiwan's impressive success in TB control is evidenced by the notification rate of all TB forms, which dropped from 67.4 per 100,000 populations in 2006 to 30.1 per 100,000 populations in 2022 (https://monitor. cdc.gov.tw/). The cooperation between the public health system and the medical system provided a solid background for our studies.

In a previous study that looked at household contacts with different drug susceptibility patterns of the index case, it was discovered that household contacts of index cases with isoniazid monoresistance were at a higher risk of TB infection compared to cases of drug-susceptible TB [17]. Additionally, genetic variations such as the *katG* S315 T or *inhA* promoter mutation have been linked to TB transmission. Strains carrying these mutations are more likely to spread [18]. In our study, we failed to detect a difference in sputum conversion between isoniazid monoresistant TB and drug-susceptible TB. This may be due to the fact that common mutations in isoniazid resistance are not associated with an increase in virulence or reproductive ability [19,20]. We, however, observed that isoniazid monoresistance was associated with delayed culture conversion in specific patient groups.

Furthermore, we found that low-level isoniazid resistance was associated with a higher risk of delayed culture conversion and adverse outcomes. Interestingly, low-level isoniazid-resistant-TB cases were more likely to exhibit cavitation and have positive sputum smears. Additionally, previous studies have suggested that specific gene mutations (e.g. KatG and/or inhA) in isoniazid resistance can have different impacts on patient outcomes [21,22]. The higher virulence of isoniazid low-level resistance compared to high-level resistance may also be due to the genetic mutations involved. Importantly, while some may assume that low-level isoniazid resistance indicates lower virulence due to the low MIC level, our findings suggest that low-level isoniazid resistance should still be given special attention.

The findings that younger patients and those without comorbidities with isoniazid monoresistant TB tend to have delayed culture conversion compared with drug-susceptible TB are interesting. While comparing the impact of isoniazid resistance on outcomes between isoniazid monoresistant TB and drug-susceptible TB, a possible explanation is that among patients with more intact immune status, drug resistance is more likely to contribute to a significant difference in culture conversion time than among patients with impaired immune status. This aligns with the aim of this study, which calls for more rapid molecular testing to detect isoniazid resistance to facilitate early and more effective treatment regimens. Interestingly, in multidrug-resistant TB patients, delayed culture conversion has also been observed among human immunodeficiency virus (HIV)-negative patients compared with HIV-positive patients [23,24]. The interaction between the immune system and drugresistant TB may be complex and somewhat counterintuitive.

The findings indicating that middle-aged and young adults were associated with delayed culture conversion are of particular significance and warrant special attention. Previous research, including a systematic review and meta-analysis, has indicated that a considerable proportion of TB transmission occurs at the community level rather than within households [25]. Additionally, several studies have demonstrated that young adults are more likely to experience loss to follow-up in TB treatment [26]. Because, middleaged individuals and young adults are often actively working and socially engaged, they may have a higher potential for community-level TB transmission. The results of our study, which indicate that this population is at higher risk for delayed culture conversion, suggest that testing for isoniazid resistance may be beneficial in preventing TB transmission among middle-aged and young adults.

In a study conducted in the United Kingdom, whole genome sequencing (WGS) showed faster results for drug susceptibility testing compared to traditional phenotypic tests [27]. This approach was particularly effective in identifying isoniazid resistance. Most treatment modifications resulting from WGS were related to isoniazid resistance [27]. In another retrospective cohort study in France, molecular detection of isoniazid resistance on an initial sample was independently associated with a shorter time to adequate treatment [28]. Additionally, risk factors associated with isoniazid-resistant TB are not efficient in effectively screening isoniazid-resistant TB [29]. The systematic implementation of rapid molecular testing on clinical samples remains the only effective way to make early diagnoses of HR-TB [29].

At present, there is no point-of-care test commercially available that is specifically designed to detect isoniazid resistance. Some line probe assays, such as MTBDRplus (Hain Lifescience, Nehren, Germany) were designed to detect isoniazid resistance, but were limited by their requirement for specialized facilities and exhibited low sensitivity in smear-negative specimens [4]. Widely used tests, such as Xpert MTB/RIF and Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, USA), can detect rifampicin resistance by targeting the *rpoB* gene mutation [30]. However, these tests do not directly detect isoniazid resistance, which is an important aspect of TB management. Our study emphasizes the significance of rapid molecular methods for detecting isoniazid resistance. The recently introduced Xpert MTB/XDR (Cepheid, Sunnyvale, USA) assay may offer a potential solution to this issue. According to a recent systematic review and meta-analysis, the Xpert MTB/XDR assay has shown a pooled sensitivity of 94.2% and a specificity of 98.5% for detecting isoniazid resistance [31]. Although caution is still warranted due to the limited number of detected resistance variants in specific genes, [31] early diagnosis of isoniazid-resistant TB using the Xpert MTB/XDR assay could be beneficial in implementing more intensive and targeted management strategies for patients with isoniazid-resistant TB.

While our study focused on the short-term (twomonth) outcome of isoniazid monoresistance, the long-term treatment outcome is equally important. A meta-analysis comparing isoniazid monoresistant TB to drug-susceptible TB (the same comparator used in our study) found that isoniazid monoresistance was associated with a higher risk of treatment failure and acquired drug resistance when using firstline drugs [3]. More recent studies largely support the conclusion that isoniazid monoresistant TB carries a higher risk of unfavourable outcomes compared to drug-susceptible TB [32,33]. However, a recent casecontrol study conducted in France presented contrasting results. This study found no significant difference in treatment success rates between isoniazid monoresistant and drug-susceptible TB. Notably, in this French study, fluoroquinolone was added among a majority of isoniazid monoresistant TB patients (56 out of 99, or 56.6%) [29] This aligns with the aim of our study, which emphasizes the importance of early identification of drug resistance and the implementation of optimal treatment regimens.

Although our study provides valuable insights, it is important to acknowledge certain limitations. The study design was retrospective, which could introduce biases and limitations. The follow-up of sputum mycobacterial culture was not standardized, and there may be variations in the timing and frequency of culture collection among participants. However, it is important to note that a substantial proportion of patients (75.6% within one month and 92.7% within two months) underwent follow-up sputum culture, and the participants had a median of four sputum specimens by the end of the second month. This high rate and volume of follow-up sputum cultures help mitigate the potential weaknesses associated with the retrospective design. Secondly, our study did not consider the specific impact of anti-TB treatment on the outcomes observed. During the study period, the recommended treatment for isoniazidresistant TB in Taiwan followed certain guidelines, including the use of rifampicin, pyrazinamide, and ethambutol, with or without isoniazid, while fluoroquinolones were not suggested during that time. Therefore, the potential impact of these drugs on treatment outcomes was of less concern in our study. Additionally, we did not assess long-term follow-up data to evaluate the impact of isoniazid resistance on the long-term prognosis of patients. Instead, we evaluated the outcome at the 2nd month, which may better reflect the impact of rapid bactericidal effect of isoniazid. Lastly, we did not have information on pyrazinamide resistance in our databases, as drug susceptibility testing for pyrazinamide is not routinely performed in clinical practice.

Conclusions

In conclusion, our study findings suggest that there is no significant correlation between isoniazid monoresistance and unfavourable outcomes two months after treatment. However, we have identified specific patient groups who are at a higher risk for delayed culture conversion and adverse outcomes compared to those with drug-susceptible tuberculosis. These highrisk groups include younger patients and those being previously healthy. These findings emphasize the importance of targeted interventions and close monitoring for these at-risk individuals to ensure timely culture conversion and improved treatment outcomes. Additionally, the development and implementation of rapid molecular testing methods for isoniazid resistance can help identify patients who may need more intensive therapy and closer follow-up.

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No potential conflict of interest was reported by the author(s).

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Author contributions

M.-R. L., J.-Y. W. and L.-T. K. conceptualized the study. M.-R. L., L.-T. K., J.-H. C.,C.-H.L. and J.-Y. W. was responsible for the data curation. M.-R. L. M.-C. L and L.-T. K. analyzed the data. L.-T. K. was responsible for funding acquisition. M.-R. L., L.-T. K. and J.-Y. W. investigated and collected the data. J.-Y. W., L.-T. K., M.-R. L and J.-H. C. designed the study. J.-Y. W., M.-C. L. and C.-H. L. supervised the study processing. M.-R. L., L.-T. K., J.-H. C., C.-H.L., M.-C. L. and J.-Y. W. wrote the original draft. M.-R. L., J.-Y. W. and L.-T. K. wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics statement

The study received approval from the Institutional Review Board (IRB) of National Taiwan University Hospital Hsin-Chu Branch (IRB number: 108-058-E). Informed consent was waived because the study utilized an encrypted database and did not pose any additional risk to participants.

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