



## Source details

### Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

Open Access ⓘ

Scopus coverage years: from 2015 to 2022

Publisher: Elsevier

E-ISSN: 2405-5794

Subject area: [Medicine: Pulmonary and Respiratory Medicine](#) [Medicine: Infectious Diseases](#) [Medicine: Microbiology \(medical\)](#)

Source type: Journal

CiteScore 2021  
**2.5**



SJR 2021  
**0.608**



SNIP 2021  
**0.885**



[View all documents >](#)

[Set document alert](#)

[Save to source list](#) [Source Homepage](#)

[CiteScore](#) [CiteScore rank & trend](#) [Scopus content coverage](#)

#### i Improved CiteScore methodology

CiteScore 2021 counts the citations received in 2018-2021 to articles, reviews, conference papers, book chapters and data papers published in 2018-2021, and divides this by the number of publications published in 2018-2021. [Learn more >](#)



CiteScore 2021 ▾

$$2.5 = \frac{535 \text{ Citations 2018 - 2021}}{211 \text{ Documents 2018 - 2021}}$$

Calculated on 05 May, 2022

CiteScoreTracker 2022 ⓘ

$$3.4 = \frac{800 \text{ Citations to date}}{237 \text{ Documents to date}}$$

Last updated on 05 January, 2023 • Updated monthly

#### CiteScore rank 2021 ⓘ

Category	Rank	Percentile
Medicine		
<a href="#">Pulmonary and Respiratory Medicine</a>	#79/140	43rd
Medicine		
<a href="#">Infectious Diseases</a>	#187/295	36th
Medicine		
<a href="#">Microbiology</a>	#82/118	30th

[View CiteScore methodology >](#) [CiteScore FAQ >](#) [Add CiteScore to your site &](#)

# About Scopus

[What is Scopus](#)

[Content coverage](#)

[Scopus blog](#)

[Scopus API](#)

[Privacy matters](#)

## Language

[日本語版を表示する](#)

[查看简体中文版本](#)

[查看繁體中文版本](#)

[Просмотр версии на русском языке](#)

## Customer Service

[Help](#)

[Tutorials](#)

[Contact us](#)

---

ELSEVIER


[Terms and conditions ↗](#) [Privacy policy ↗](#)

Copyright © Elsevier B.V ↗. All rights reserved. Scopus® is a registered trademark of Elsevier B.V.

We use cookies to help provide and enhance our service and tailor content. By continuing, you agree to the use of cookies ↗.



## Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

COUNTRY	SUBJECT AREA AND CATEGORY	PUBLISHER	H-INDEX
United Kingdom  Universities and research institutions in United Kingdom	Medicine <ul style="list-style-type: none"> <li>Infectious Diseases</li> <li>Microbiology (medical)</li> <li>Pulmonary and Respiratory Medicine</li> </ul>	Elsevier Ltd.	13
PUBLICATION TYPE	ISSN	COVERAGE	INFORMATION
Journals	24055794	2015-2021	<a href="#">Homepage</a> <a href="#">How to publish in this journal</a> <a href="mailto:JCTUBE@elsevier.com">JCTUBE@elsevier.com</a>

### SCOPE

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases aims to provide a forum for clinically relevant articles on all aspects of tuberculosis and other mycobacterial infections, including (but not limited to) epidemiology, clinical investigation, transmission, diagnosis, treatment, drug-resistance and public policy, and encourages the submission of clinical studies, thematic reviews and case reports. Journal of Clinical Tuberculosis and Mycobacterial Diseases is an Open Access publication.

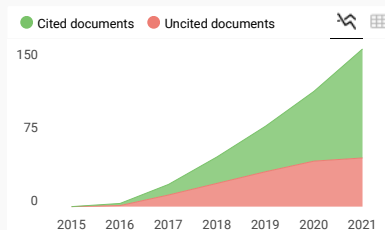
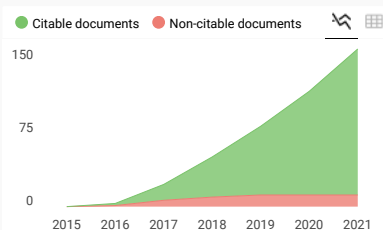
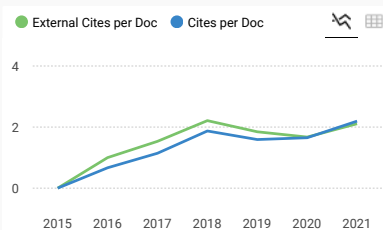
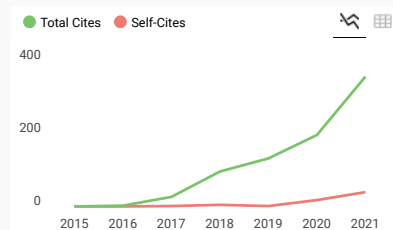
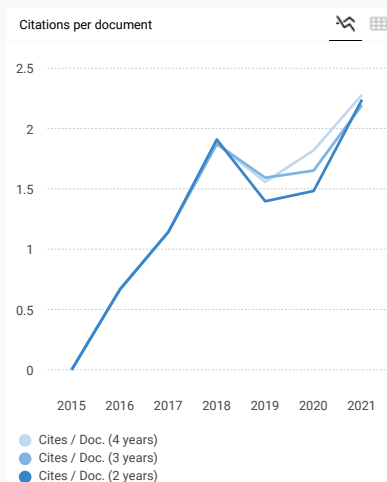
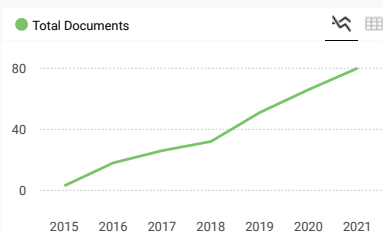
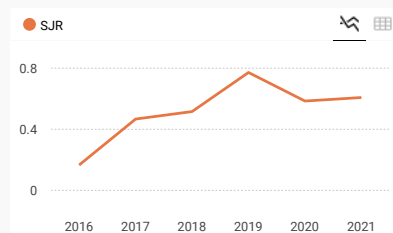


Join the conversation about this journal

# FIND SIMILAR JOURNALS ?

options ⋮

<p>1</p> <p><b>International Journal of Tuberculosis and Lung</b></p> <p>FRA</p> <p><b>87%</b></p> <p>similarity</p>	<p>2</p> <p><b>Indian Journal of Tuberculosis</b></p> <p>IND</p> <p><b>80%</b></p> <p>similarity</p>	<p>3</p> <p><b>International Journal of Mycobacteriology</b></p> <p>IND</p> <p><b>51%</b></p> <p>similarity</p>	<p>4</p> <p><b>BMC Infectious Diseases</b></p> <p>GBR</p> <p><b>48%</b></p> <p>similarity</p>	<p>5</p> <p><b>African Journal of Laboratory Medicine</b></p> <p>ZAF</p> <p><b>46%</b></p> <p>similarity</p>
--	--	---	---	--



Journal of Clinical Tuberculosis and Other...

**Q2** Pulmonary and Respiratory Medicine

**SJR 2021** 0.61

best quartile

powered by scimagojr.com

Show this widget in your own website

Just copy the code below and paste within your html code:

`<a href="https://www.scimi`

**SCImago Graphica**

Explore, visually communicate and make sense of data with our **new data visualization tool**.

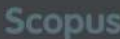


Loading comments...

Developed by:



Powered by:

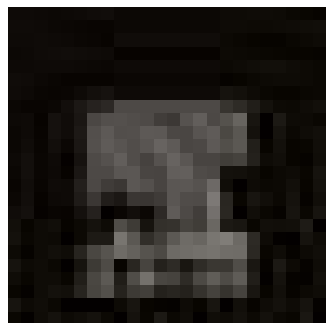


Follow us on @ScimagoJR

Scimago Lab, Copyright 2007-2022. Data Source: Scopus®

EST MODUS IN REBUS  
Horatius (Saturne 7.1.106)

[Edit Cookie Consent](#)



1000  
1000

# CLINICAL TUBERCULOSIS AND OTHER MYCOBACTERIAL DISEASES



## Volume 28

August 2022

[Download full issue](#)

[Previous vol/issue](#)[Next vol/issue](#)

Receive an update when the latest issues in this journal are published

[Sign in to set up alerts](#)

Research article ● Open access

### Emerging threat of drug-resistant tuberculosis and trends in the era of COVID-19: A descriptive study from northwestern Nigeria

Farouq Muhammad Dayyab, Garba Iliyasu, Bashir Garba Ahmad, Ibrahim Aliyu Umar, ... Abdulrazaq Garba Habib

Article 100319

[Download PDF](#) Article preview

Research article ● Open access

### Paediatric progressive primary tuberculosis

Naoki Yogo, Chihiro Furukawa, Satoshi Hayano

Article 100318

[Download PDF](#) Article preview

Research article ● Open access

### Moxifloxacin concentration correlate with QTc interval in rifampicin-resistant tuberculosis patients on shorter treatment regimens

Tutik Kusmiati, Ni Made Mertaniasih, Johanes Nugroho Eko Putranto, Budi Suprpti, ... Aryani Prawita Sari

Article 100320

[Download PDF](#) Article preview

Research article ● Open access

## Health system delay and its associated factors among tuberculosis patients in Gamo Zone public health facilities, Southern Ethiopia: An institution-based cross-sectional study

Asrat Arja, Biruk Bogale, Mesfin Gebremedhin

Article 100325

[Download PDF](#) Article preview

Research article ● Open access

## Health-related quality of life of persons living with tuberculosis: A cross-sectional study

Louisa Quarcoopome, Eric Tornu

Article 100324

[Download PDF](#) Article preview

Research article ● Open access

## An explanation of the 15-year trend and investigation of the tuberculosis cascade in Kurdistan province

Nasrollah Veisi, Hamid Sharifi, Armita Shahesmaeili, Ebrahim Ghaderi, Shoboo Rahmati

Article 100323

[Download PDF](#) Article preview

Research article ● Open access

## Assessing physical and chemical properties of saliva among tuberculosis patients on anti-tuberculosis treatment - An observational study

Vidya Gowdappa Doddawad, S Shivananda, B Madhu, B.M. Gurupadayya, ... BS Jayaraj

Article 100322

[Download PDF](#) Article preview

Research article ● Open access

## Knowledge, attitudes and practices on tuberculosis among screened immigrants in Norway. A cross-sectional study

Ingunn Harstad, Andrea R. Raen, Silje Selseng, Eli Sagvik

Article 100326

[Download PDF](#) Article preview

Research article ● Open access

## Adaptations to the first wave of the COVID-19 pandemic by private sector tuberculosis care providers in India

Shamim Mannan, Charity Oga-Omenka, Akhil Soman ThekkePurakkal, Lavanya Huria, ... Madhukar Pai

Article 100327



Wudalem Amare, Merese Sinaga Tesfome, Gashaw Dessie, Tabarak Malik

Article 100329

[Download PDF](#) [Article preview](#) ✓

Research article • Open access

Evaluation of modified bleach technique for the detection of acid fast bacilli in lymph node aspirate at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia

Firehiwot Mulugeta, Moges Tiruneh, Bewketu Abebe, Gashaw Yitayew, ... Aschalew Gelaw

Article 100328

[Download PDF](#) [Article preview](#) ✓

[Previous vol/issue](#)

[Next vol/issue](#)

ISSN: 2405-5794

Copyright © 2023 Elsevier Ltd.



Copyright © 2023 Elsevier B.V. or its licensors or contributors.  
ScienceDirect® is a registered trademark of Elsevier B.V.

RELX™

[Submit your article](#) ↗

[Guide for authors](#) ↗

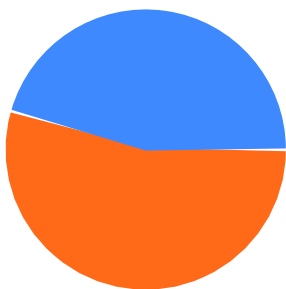
≡ Menu

[Q](#) Search in this journal

- > [Aims and scope](#)
- > **[Editorial board](#)**
- > [Abstracting & indexing](#)
- > [Call for papers](#)
- > [Announcements](#)

## Gender diversity of editors

Based on 73.30% responding editors



- **55%** woman
- **46%** man
- **0%** non-binary or gender diverse
- **0%** prefer not to disclose

> [See more editors by country/region](#)

## Editorial board

### Editor-in-Chief

Dr. Zelalem Temesgen, MD

Mayo Clinic Rochester, Rochester, Minnesota, United States of America

New antimicrobial/antiretroviral/antifungal agents clinical trials, Tuberculosis resistance mechanisms, Treatment of opportunistic infections in immunocompromised hosts, Emerging infections, Medication compliance

### Associate Editors

Professor Shrikala Baliga, MD

Kasturba Medical College, Department of Microbiology, Mangalore, India

Diagnostic Microbiology, Hospital Infections, Quality Assurance, Drug Resistance

Dr. Terence Chorba, MD, DSc

National Center for HIV/AIDS Viral Hepatitis STD and TB Prevention, Atlanta, Georgia, United States of America

Epidemiology, Infectious Diseases, Public Health, Biomedical Ethics, Tuberculosis

Dr. Daniela Cirillo, MD PhD

Submit your article ↗

Guide for authors ↗

Menu



Dr. Degu Dare, MD, PhD

KNCV Tuberculosis Foundation, 's-Gravenhage, Netherlands

Tuberculosis, HIV, ,



Dr. James T. Gaensbauer, MD, MScPH

Mayo Clinic College of Medicine and Science, Rochester, Minnesota, United States of America

Pediatrics, Tuberculosis, Infectious Disease

> View full biography

Assist. Prof. Maryam Mahmood, MBChB

Mayo Clinic Rochester, Rochester, Minnesota, United States of America

Infectious diseases, HIV, mycobacterial infections, cardiovascular infections

Dr. Sundari Mase, MD, MPH

County of Sonoma, Department of Health Services, Santa Rosa, California, United States of America

Tuberculosis



Dr. Pamela J. McShane, MD

The University of Texas Health Science Center at Tyler, Tyler, Texas, United States of America

Bronchiectasis and nontuberculous mycobacteria

> View full biography



Submit your article ↗

Guide for authors ↗

Menu



> view full biography



Dr. Simon Tiberi, MD, FRCP

The Royal London Hospital, London, United Kingdom

Tuberculosis, MDR-TB, XDR-TB, NTM, Therapeutic drug monitoring

> View full biography



Dr. Weibing Wang, PhD

Fudan University, Shanghai, China

Molecular study, epidemiology, tuberculosis, modeling

## Assistant Editors

Dr. Hannah Alsdurf, PhD

University of Ottawa School of Epidemiology and Public Health, Ottawa, Ontario, Canada

Dermatology, Clinical Dermatology, Skin Tuberculosis , Latent Tuberculosis , Cost-Effectiveness Analysis.



Dr. Priyanka Anvekar, M.B.B.S

Mayo Clinic Center for Tuberculosis, Rochester, Minnesota, United States of America

FEEDBACK



Dr. Leah Mische, MD

Stanford University, Stanford, California, United States of America

Infectious Diseases, Global Health and Global Medical Education, Vector-Borne Diseases



Dr. Jahanavi M. Ramakrishna, MBBS

Wayne State University School of Medicine, Detroit, Michigan, United States of America

## Advisory Board

Dr. Wondwossen Amogne, MD, PhD

Addis Ababa University, Addis Ababa, Ethiopia

Tuberculosis, HIV, Antiretroviral therapy



Dr. Ritu Banerjee, MD, PhD

Mayo Clinic Rochester, Rochester, Minnesota, United States of America

Antimicrobial stewardship, Novel antimicrobials for drug-resistant organisms, Rapid diagnostics for tuberculosis



Dr. Jeremiah Chakaya, MD

Kenyatta University School of Medicine, Nairobi, Kenya

Tuberculosis, Tuberculosis and HIV

Prof. Dr. Margareth Dalcolmo, MD, PhD

Oswaldo Cruz Foundation, RIO DE JANEIRO, Brazil

Tuberculosis, Other Mycobacteriosis, Pulmonary Infections

Dr. Gerald Friedland, MD

Yale School of Medicine, New Haven, Connecticut, United States of America

Tuberculosis, HIV

Dr. Jennifer Furin, MD, PhD

Case Western Reserve University Division of Infectious Diseases, Cleveland, Ohio, United States of America

Pediatric Drug-Resistant Tuberculosis

Dr. Eric Goosby, MD

University of California San Francisco, San Francisco, California, United States of America

Global Health, International Cooperation, Tuberculosis, Disease Eradication, National Health Programs

Assoc. Professor W. Garrett Hunt, MD, MPH, DTM&H, FAAP

The Ohio State University College of Medicine, Columbus, Ohio, United States of America

Tuberculosis and other mycobacterial diseases, HIV, emerging pathogens, tropical medicine, refugee health, travel medicine, clinical/epidemiologic research, research mentoring, and medical/clinical education of medical students, residents, and fellows in the United States and abroad

Dr. Tereza Kasaeva, PhD

World Health Organization, Genève, Switzerland

Tuberculosis



Dr. William Dwight Miller, MD, MS

University of South Florida, Tampa, Florida, United States of America

Nontuberculous mycobacterial infections, Biomedical Informatics, Pulmonary infections, Sepsis, Health Disparities

Dr. Kogie Naidoo, MD, PhD

Centre for the Aids Programme of Research in South Africa, Durban, South Africa

Tuberculosis, HIV



Dr. Mario Raviglione, MD

University of Milan, Milano, Italy

Tuberculosis, Global Health, Multidrug-resistant tuberculosis, Research

Dr. Christine Sekaggya Wiltshire, MBChB, MMed

Makerere University, Kampala, Uganda

Tuberculosis, HIV

Dr. Surendra Sharma, MD

All India Institute of Medical Sciences, New Delhi, India



Dr. Cesar Ugarte-Gil, MD, PhD

Cayetano Heredia Peruvian University, Institute of Tropical Medicine Alexander von Humboldt, Cercado de Lima, Peru

Tuberculosis, Epidemiology, Clinical research, Systematic reviews, Global Health

Dr. Sandro Vento, MD

University of Botswana, Gaborone, Botswana

Hepatocellular Carcinoma, Hepatitis B, HIV, Tuberculosis, Cirrhosis

Dr. Nancy Wengenack, Ph.D., D(ABMM)

Mayo Clinic Rochester, Rochester, Minnesota, United States of America

Mycobacteria, including Mycobacterium tuberculosis, Fungi, such as Pneumocystis jiroveci, Coccidioides immitis, Histoplasma capsulatum and Blastomyces dermatitidis



Dr. John Zeuli, PharmD

Mayo Clinic, Scottsdale, Arizona, United States of America

Antituberculous drug therapy, NTM infections, Antiretroviral therapy, HIV, Pharmacogenomics, Drug-interaction assessment

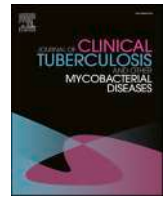
All members of the Editorial Board have identified their affiliated institutions or organizations, along with the corresponding country or geographic region. Elsevier remains neutral with regard to any jurisdictional claims.

Submit your article ↗

Guide for authors ↗

≡ Menu





## Moxifloxacin concentration correlate with QTc interval in rifampicin-resistant tuberculosis patients on shorter treatment regimens

Tutik Kusmiati<sup>a,b,d</sup>, Ni Made Mertaniasih<sup>c,d,\*</sup>, Johanes Nugroho Eko Putranto<sup>e</sup>, Budi Suprapti<sup>f</sup>, Nadya Luthfah<sup>e</sup>, Soedarsono Soedarsono<sup>b,d</sup>, Winariani Koesoemoprodjo<sup>b</sup>, Aryani Prawita Sari<sup>b</sup>

<sup>a</sup> Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Indonesia

<sup>b</sup> Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

<sup>c</sup> Department of Medical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

<sup>d</sup> Laboratory of Tuberculosis, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia

<sup>e</sup> Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

<sup>f</sup> Department of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga, Surabaya, East Java, Indonesia

### ARTICLE INFO

#### Keywords:

Drug-resistant tuberculosis  
Shorter treatment regimen  
Moxifloxacin concentration  
QTc interval

### ABSTRACT

**Background:** Drug-resistant tuberculosis (DR-TB) continues to be a global threat. Moxifloxacin is one of the components of the shorter treatment regimen which is suspected to increase the risk of QT prolongation, although it is also likely to be the most effective against DR-TB. A study to evaluate the correlation between the concentration of moxifloxacin and QTc interval in RR-TB patients who received shorter treatment regimens is needed.

**Methods:** This was an observational study in 2 groups of RR-TB patients on shorter treatment regimens (intensive phase and continuation phase), contain moxifloxacin with body weight-adjusted dose. Blood samples were collected at 2 h after taking the 48th-hour dose and 1 h before taking the 72nd-hour dose.

**Results:** Forty-five RR-TB patients were included in this study. At 2 h after taking the 48th-hour dose, the mean of QTc interval in intensive phase and continuation phase was 444.38 ms vs. 467.94 ms,  $p = 0.026$ , while mean of moxifloxacin concentration in intensive phase and continuation phase was 4.3  $\mu\text{g/mL}$  vs. 4.61  $\mu\text{g/mL}$ ,  $p = 0.686$ . At 1 h before taking the 72nd-hour dose, both moxifloxacin concentration and QTc interval in intensive phase and continuation showed no significant difference with  $p$ -value of 0.610 and 0.325, respectively. At 2 h after taking the 48th-dose, moxifloxacin concentration did not correlate with QTc interval, both in intensive phase ( $p = 0.576$ ) and in continuation phase ( $p = 0.691$ ). At 1 h before taking the 72nd-hour dose, moxifloxacin concentration also did not correlate with QTc interval in intensive phase ( $p = 0.531$ ) and continuation phase ( $p = 0.209$ ).

**Conclusions:** Our study found that moxifloxacin concentration did not correlate with QTc interval, which indicates the safe use of moxifloxacin on QTc interval. In addition to close monitoring of QTc interval, the clinicians should also consider other variables which potentially increase risk for QTc prolongation in DR-TB patients who received shorter treatment regimens.

### 1. Introduction

Drug-resistant tuberculosis (DR-TB) continues to be a threat and the barrier for global TB elimination efforts caused 465,000 cases in 2020. Indonesia is rank 5th for countries with high multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) burden in the world with 24,000 cases. Globally, the latest data show treatment success rates

of 57% for MDR-TB/rifampicin-resistant TB (RR-TB). The success rate for MDR/RR-TB in Indonesia is < 50% due to the high rate of deaths and loss to follow-up [1]. The increase in MDR-TB has further highlighted the need to improve TB treatment [2].

The treatment of MDR/RR TB using a different combination of 2nd line drugs, usually for 18 months is associated with high cost, greater incidence of adverse reactions, and a high rate of loss to follow-up [3]. A

\* Corresponding author at: Jl. Mayjen Prof. Dr. Moestopo No. 47, Surabaya 60131, Indonesia.

E-mail addresses: [tutik.kusmiati93@gmail.com](mailto:tutik.kusmiati93@gmail.com) (T. Kusmiati), [nmademertaniasih@gmail.com](mailto:nmademertaniasih@gmail.com) (N. Made Mertaniasih), [j.nugroho.eko@fk.unair.ac.id](mailto:j.nugroho.eko@fk.unair.ac.id) (J. Nugroho Eko Putranto), [budiprapti@yahoo.co.id](mailto:budiprapti@yahoo.co.id) (B. Suprapti), [nadyalumnir@gmail.com](mailto:nadyalumnir@gmail.com) (N. Luthfah), [ssoedarsono@gmail.com](mailto:ssoedarsono@gmail.com) (S. Soedarsono), [winariani\\_07@yahoo.com](mailto:winariani_07@yahoo.com) (W. Koesoemoprodjo), [aryani\\_sari@yahoo.com](mailto:aryani_sari@yahoo.com) (A. Prawita Sari).

<https://doi.org/10.1016/j.jctube.2022.100320>

shorter MDR/RR-TB regimen for 9–12 months has been promoted by the WHO in 2016 and becomes a priority for certain MDR/RR-TB patients with eligible criteria. This shorter regimen is also expected to increase the success rate of MDR/RR-TB treatment [4]. Despite the shorter duration of this regimen, the adverse effect remains happened and results in treatment interruption, reduce treatment adherence, and associated with morbidity and mortality [4–6].

Interval QT prolongation is one of the most common adverse effects in MDR/RR-TB patients who received the shorter regimens. A fluoroquinolone, moxifloxacin is one of the core components of the shorter MDR/RR-TB treatment regimen which has been known to carry a risk of QT prolongation, although it is also likely to be the most effective against MDR-TB [4,7]. Interval QT prolongation (an abnormality on electrocardiography) is a serious adverse effect that favors the development of cardiac arrhythmias, including Torsade de Pointes (TdP), and leads to sudden cardiac death [7,8].

According to the national program, the use of moxifloxacin in the shorter regimens is based on body weight. Moxifloxacin is given at 400 mg, 600 mg, and 800 mg. However, the safety and efficacy of the recommended dose are still debated. A study reported 7% of MDR/RR-TB patients switched their regimens from shorter regimen to individual regimens due to the presence of prolonged QT. Moxifloxacin was suggested to cause prolonged QT [3]. The QT interval prolongation of moxifloxacin 800 mg was only slightly greater than moxifloxacin 400 mg [9]. A previous study reported the incidence of  $\Delta QT_c > 30$  ms and  $\Delta QT_c > 60$  ms in 21/98 (21.4%) and 10/98 (10.2%) of DR-TB patients who received shorter regimens, respectively. There is no significant difference in the incidence of prolonged  $\Delta QT_c$  in 400, 600, and 800 mg of moxifloxacin dose, and no significant correlation between moxifloxacin dose and  $\Delta QT_c$  [10]. Other studies reported the safety on QT interval of moxifloxacin 400 mg and 600 mg [11,12].

Low concentrations of anti-TB drugs may be associated with poor treatment outcomes as well as high concentrations of these drugs may cause intolerance and toxic effects [13,14]. An appropriate dose of moxifloxacin was important to achieve effective treatment without serious adverse effects. This study was conducted to evaluate the correlation between the concentration of moxifloxacin and  $QT_c$  interval in RR-TB patients who received shorter regimens.

## 2. Methods

### 2.1. Study design and subjects

This was an observational analytic study with a time-series design from September 2019 to February 2020 in Dr. Soetomo Hospital Surabaya, which is the center of East Indonesia TB referral hospital. Consecutive sampling was used in this study. Study subjects were RR pulmonary TB patients based on the GeneXpert examinations who meet inclusion and exclusion criteria. RR-TB patients with age 18 to 65 years old who will start the intensive phase and who are on the continuation phase of shorter treatment regimens were included in this study. RR-TB patients with baseline  $QT_c > 500$  ms, potassium  $< 3.5$  mmol/L, magnesium  $< 1.7$  mmol/L, calcium  $< 8.5$  mmol/L, creatinine clearance  $< 30$  cc/m, aspartate aminotransferase - alanine aminotransferase (AST-ALT)  $> 5$  x upper limit normal (ULN), body mass index (BMI)  $< 18$  kg/m<sup>2</sup>, on anti-arrhythmia therapy, anti-depressant therapy, with bradycardia, anti-fungal treatment (azoles), erythromycin therapy, and phenytoin therapy were excluded from this study. These exclusion criteria are the risk factors of QT interval prolongation [15–17]. Therefore, the results of this study will not be affected by these factors.

### 2.2. Operational definition

Rifampicin-resistant tuberculosis (RR-TB) was defined as the results of *Mycobacterium tuberculosis* detected with rifampicin resistance based on GeneXpert MTB/RIF [18]. RR-TB patients in intensive phase were

defined as RR-TB patients who are eligible to receive shorter regimens and will start intensive phase of treatment. RR-TB patients in continuation phase were defined as RR-TB patients who have completed the intensive phase (4–6 months), i.e. those who have sputum smear conversion after the 4th, 5th, or 6th month. Shorter regimens were as recommended by the WHO in 2016 and the national program in 2019, consisted of 4–6 Km – Mfx – Eto(Pro) – H<sup>High Dose</sup> – Cfz – E – Z / 5 Mfx – Cfz – E – Z for 9–11 months [4,19]. Electrocardiography (ECG) was defined as a 12-lead surface heart recording using an ECG machine. The QT interval is that portion of the ECG that begins at the start of the QRS complex and ends at the termination of the T wave. The  $QT_c$  referred to the corrected QT interval using the Fredericia formula [15]. The changes of  $QT_c$  ( $\Delta QT_c$ ) referred to the difference between the QT interval at baseline and the QT interval at 2 h after taking the 48th-hour dose, and 1 h before taking the 72nd-hour dose.

### 2.3. Concentration of moxifloxacin

All subjects received standardized shorter regimens as recommended by the WHO in 2016 and the national program in 2019, consisted of 4–6 Km – Mfx – Eto(Pro) – H<sup>High Dose</sup> – Cfz – E – Z / 5 Mfx – Cfz – E – Z for 9–11 months [4,19]. Moxifloxacin of 400 mg/tablet (Avelox®, Bayer Health Care) was used and subjects received one of three (400 mg or 600 mg or 800 mg of moxifloxacin). Blood samples were collected at 2 h after taking the 48th-hour dose and 1 h before taking the 72nd-hour dose. Blood samples were taken from RR-TB patients and put into heparin tubes. Blood samples were centrifuged and the plasma was stored in the deep freezer with a temperature of  $-80$  °C). The moxifloxacin concentration was measured by a validated method using High-Performance Liquid Chromatography (HPLC). The separation of moxifloxacin from the plasma matrix using protein precipitation, followed by measurements using the Waters HPLC Alliance e2695 with a detector of Waters 2998 Photodiode Array (PDA). 240  $\mu$ L of acetonitrile solution (100%) was added to the 200  $\mu$ L of plasma sample. The sample was then vortexed for 1 min and centrifuged at a speed of 10,000g for 5 min. A total of 200  $\mu$ L of supernatant was put into the vial and injected into the HPLC with an injection volume of 10  $\mu$ L. Separation using a Sunfire™ C18 column (4.6  $\times$  100 mm, 5  $\mu$ m; Waters, Ireland). The mobile phase consisted of 0.4% TEA in aquabides with a pH of  $\pm 3$  and 100% of acetonitrile (75%:25% (v/v)). The flow rate is 1 mL/min and the PDA detector was set at a wavelength of 296 nm. Accuracy for standard concentration curves is between 95.5% and 103.4%, depends on the standard concentration level. The coefficient of variation for intra- and inter-assay was  $< 7.2\%$  for the range from 0.204 to 10,200  $\mu$ g / mL. The lowest limit value which can be quantified was 0.204  $\mu$ g/mL.

### 2.4. $QT_c$ interval measurement

$QT_c$  interval was measured using ECG machine merc BLT E30 (Guangdong Biolight Meditech, Germany, 2017). A lead of II or V5-V6 on ECG was selected to be read. QT interval from QRS complex up to the end of T-wave was measured. The ECG waves are recorded on special graph paper that is divided into 1 mm<sup>2</sup>, paper speed on ECG was 25 mm/s, therefore each 1 small square corresponds to 0.04 s (40 ms). QT interval was 0.04 s multiplied with the number of small squares of QRS complex up to the end of T-wave. The QT interval of at least three successive beats was measured, and the beat with the maximum interval was taken. If the rhythm is irregular, the average QT interval of 3–5 beats was taken. RR interval (area between two consecutive Rs of the QRS complex in the ECG rhythm strip) was 0.04 s multiplied with the number of small squares of R to R. Heart rate (HR) was 1500 divided by the amount of RR small squares.  $QT_c$  was measured using the Fredericia formula according to the HR of subjects [15].  $QT_c$  interval was measured at 2 h after taking the 48th-hour dose, and 1 h before taking the 72nd-hour dose.

## 2.5. Data analysis and ethical statement

The data obtained in this study were analyzed using Pearson or Spearman-rho method in SPSS 21.0 (IBM Corp., Armonk, NY, USA). Statistical results were considered significant if the p-value was < 0.05. This study was approved by the ethics committee of Dr. Soetomo Hospital with ethical clearance number 1444/KEPK/VIII/2019 August 23rd, 2019.

## 3. Results

A total of 45 RR-TB patients were screened. 29/45 (64%) RR-TB patients are in intensive phase and 16/45 (36%) RR-TB patients are in continuation phase. The administration of moxifloxacin in this study is based on body weight. Subjects in this present study were patients who received moxifloxacin dose 600 mg and 800 mg because patients who received moxifloxacin 400 mg were not found in this study. Table 1 shows the characteristics of RR-TB patients in intensive phase and continuation phase. Potassium, calcium, and magnesium levels decreased significantly in continuation phase with p-value of 0.019, 0.001, and 0.003, respectively.

As shown in Table 1, at 2 h after taking the 48th-hour dose, mean of QTc interval in intensive phase and continuation phase showed a significant difference (444.38 ms vs. 467.94 ms,  $p = 0.026$ ). Mean of moxifloxacin concentration in continuation phase was also higher than intensive phase, although it was not significant (p-value of 0.686). At 1 h before taking the 72nd-hour dose, both moxifloxacin concentration and QTc interval in intensive phase and continuation showed no significant difference with p-value of 0.610 and 0.325, respectively.

Table 2 below showed that there was no correlation between moxifloxacin concentration and QTc interval at 2 h after taking the 48th-hour dose, both in intensive phase and continuation phase with p-value of 0.576 and 0.691, respectively. The change of QTc interval from baseline

**Table 1**  
Characteristics of Study Subjects.

Characteristics	RR-TB on Start of Intensive Phase (N = 29)	RR-TB on Start of Continuation Phase (N = 16)	P-value
Age (years)*	37 (18–62)	44 (19–56)	0.569
Sex**			0.673
Women	13	9	
Men	16	7	
BMI (m/kg <sup>2</sup> )*	20.4 (18.03–28.65)	19.06 (18.26–27.68)	0.530
Diabetes mellitus**	14	5	0.429
Albumin***	3.43 ± 0.28	3.65 ± 0.14	0.002
Sodium (mmol/l)	139.06 ± 4.09	140.7 ± 5.87	0.266
Potassium (mmol/l)***	4.3 ± 0.45	3.96 ± 0.4	0.019
Calcium mg/dl***	9.03 ± 0.46	8.67 ± 0.2	0.001
Magnesium (mg/dl)*	2.1 (1.8–2.3)	1.9 (1.8–2.2)	0.003
Moxifloxacin **			0.727
600	17	11	
800	12	5	
QTc Baseline(ms)	417.28 ± 31.2	455.94 ± 16.6	<0.001
Moxy Conc (48 + 2) (µg/mL)***	4.3 ± 2.32	4.61 ± 2.54	0.686
QTc 48 + 2 (ms)***	444.38 ± 31.25	467.94 ± 35.7	0.026
ΔQTc (48 + 2)-Baseline (ms)*	20 ((-17) – (81))	2.5 ((-44) – (115))	0.036
Moxy Conc (72–1) (µg/mL)*	1.01 (0.01 – 3.27)	0.91 (0.01 – 1.61)	0.610
QTc 72–1 (ms)*	448 (386–518)	447 (428–524)	0.325
ΔQTc (48 + 2) - (72–1) (ms)*	0 ((-75) – (60))	7.5 ((-77) – (52))	0.122

\* Median (min–max) using Mann-Whitney Test; \*\* Chi-square; \*\*\*Mean ± Standard Deviation using T-test; BMI = Body Mass Index.

**Table 2**

Correlation Analysis at 2 Hours after the 48th Dose and at 1 Hour before the 72nd- Hour Dose.

			Moxi Conc at 48 + 2				Moxi Conc at 72-1
Intensive phase	QTc at 48 + 2	R	-0.108	QTc at 72-1	R	0.121	
		P	0.576		P	0.531	
	ΔQTc ((48 + 2) - Baseline))	R	-0.157	ΔQTc ((48 + 2) - (72-1))	R	-0.046	
		P	0.415		P	0.813	
Continuation phase	QTc at 48 + 2	R	0.108	QTc at 72-1	R	-0.332	
		P	0.691		P	0.209	
	ΔQTc ((48 + 2) - Baseline))	R	0.249	ΔQTc ((48 + 2) - (72-1))	R	-0.197	
		P	0.353		P	0.464	

Correlation Analysis using Pearson or Spearman-rho Test; R: Correlation Coefficient; P: Sig. (2-tailed).

was also not correlated with moxifloxacin concentration with p-value of 0.415 in intensive phase and 0.353 in continuation phase, respectively. At 1 h before the 72nd-hour dose, moxifloxacin concentration also did not correlate with the QTc interval (p-value of 0.531 in intensive phase and 0.209 in continuation phase), also did not affect the change of QTc interval (p-value of 0.813 in intensive phase and 0.464 in continuation phase).

Our study found that there was no correlation between moxifloxacin concentration and QTc interval. Fig. 1 below showed that moxifloxacin concentration and QTc interval at 2 h after taking the 48th-hour dose and at 1 h before taking the 72nd-hour dose) did not form a specific pattern, indicated that there is no correlation between moxifloxacin concentration and QTc interval.

## 4. Discussion

Moxifloxacin is an 8-methoxyquinolone (fluoroquinolone) antimicrobial drug used for treatment of respiratory infections. It is the most commonly used active control in thorough QT studies (TQTS) because it reliably prolongs the QT interval [20–22]. A single oral dose of 400 mg MX is often used as a positive control in TQT studies [20]. Moxifloxacin is a repurposed drug in DR-TB treatment [22]. Fluoroquinolones, especially moxifloxacin is considered as a QT-prolonging drug and as a component in a shorter regimen to treat eligible RR-TB patients [4]. Chen *et al.* reported a significant prolongation of mean QTc at all time points except 0.5 h post-dose after orally administered moxifloxacin. The peak effect on the *Fridericia* QT correction (QTcf) was 9.35 ms at 3 h post-dose. It was suggested that a 2.084 ms increase in the QTc interval for every 1000 ng/mL increase in plasma concentration of moxifloxacin [8].

The current reference dose of moxifloxacin based on body weight seems to be safe, as moxifloxacin concentration in plasma did not correlate with QTc interval in our study (Table 2). Moxifloxacin is generally well tolerated, although moxifloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients by reversible and dose-dependent but weak blockage of the hERG potassium channels. Higher doses (600–800 mg) suggest that these may be safe when carefully monitored [23]. Kusmiati *et al.* also reported that moxifloxacin at the dosage of 400, 600, or 800 mg does not correlate with the QTc interval (p-value of 0.565) [24]. Hong *et al.* reported that the effect by 800 mg was only slightly greater than that of 400 mg, indicated that the QTc interval prolongation effect of moxifloxacin does not double by doubling the dose from 400 to 800 mg [9]. Although fluoroquinolones are known to prolong the QT interval, however, the prolongation is considered minimal or moderate for moxifloxacin [25].

In this study, we have excluded patients with low levels of potassium and calcium to minimize their effects on QTc interval, therefore, potassium and calcium did not correlate with QTc interval (Table 2). As has

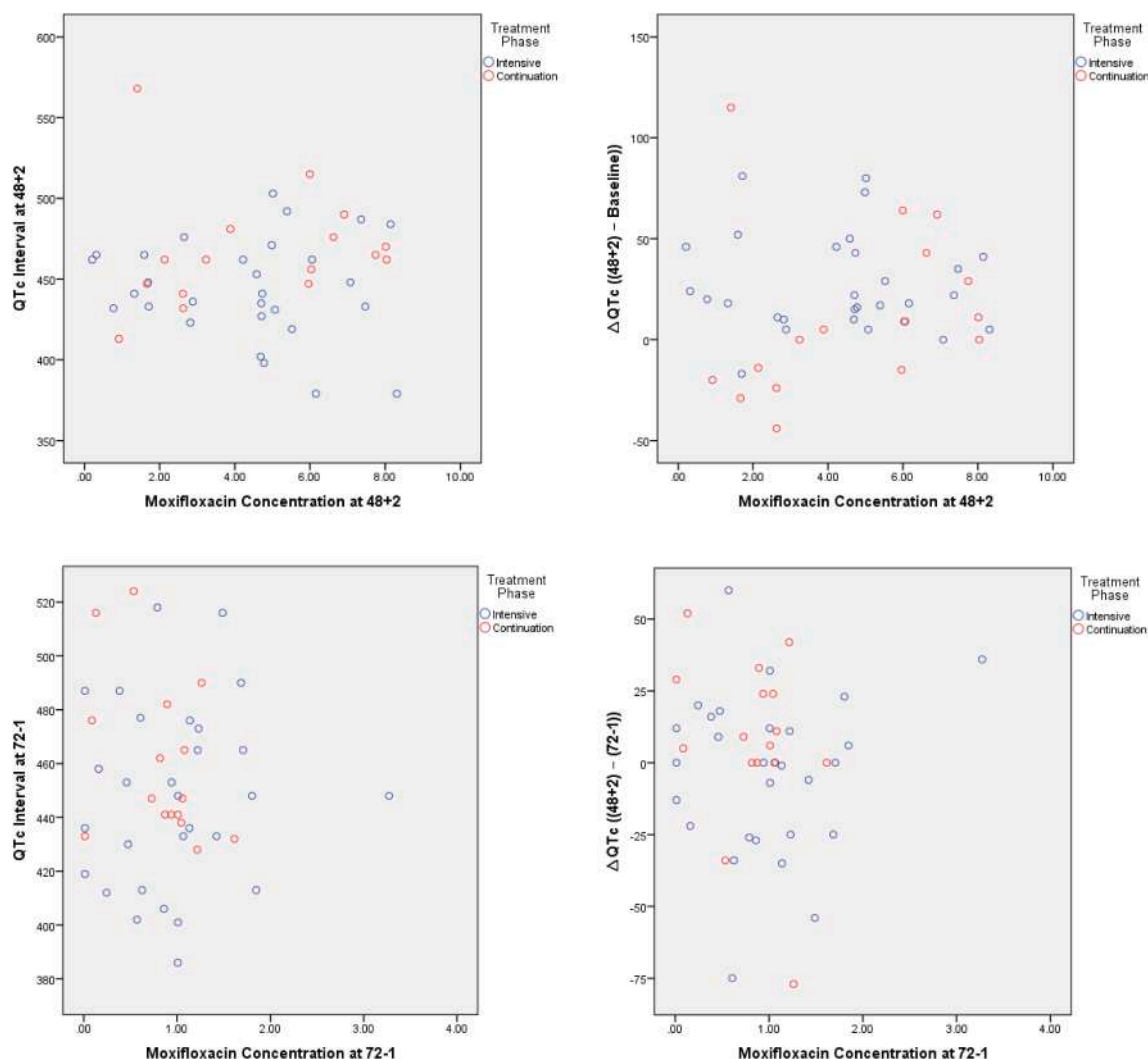


Fig. 1. Scatter Plot of Moxifloxacin Concentration ( $\mu\text{g/mL}$ ) and QTc Interval (ms).  $48 + 2 = 2$  Hours after Taking the 48th Hour Dose;  $72 - 1 = 1$  Hour before Taking the 72nd Hour Dose.

been known that the QT interval indicates the duration of action potential (AP) in ventricles, which represents the sum of ventricular depolarization and repolarization. AP is caused by the transmembrane flow of ions, including inward depolarizing currents mainly through sodium and calcium channels, and outward repolarizing currents mainly through potassium channels. Six sequentially activated currents are fundamentally involved: the sodium current ( $I_{Na}$ ), the transient outward current ( $I_{to}$ ), the L(long-lasting)-type calcium current ( $I_{CaL}$ ), the rapid component of the delayed rectifier potassium current ( $I_{Kr}$ ), the slow component of the delayed rectifier potassium current ( $I_{Ks}$ ), and the inward rectifier potassium current ( $I_{K1}$ ) [16]. The majority of the delayed cardiac repolarisations observed in the clinic are believed to be mediated via inhibition of the cardiac potassium ion channel ( $I_{Kr}$ ) which is encoded by the human ether  $\alpha$ -go-go gene ( $hERG$ ) [26]. Most cases of drug-induced long QT result from an action of the drugs on the ion channel proteins encoded by the  $hERG$  gene that is responsible for the  $I_{Kr}$  repolarizing current. Drug-induced QT prolongation is commonly achieved by directly blocking the  $hERG$  channel. Fluoroquinolones inhibit  $I_{Kr}$  delaying membrane repolarization [27].

Moxifloxacin, a fluoroquinolone antibiotic is known as second-line anti-TB drugs in the medical field, and is critical in DR-TB treatment [11]. Our study indicates that the use of moxifloxacin may be safe, even with 800 mg. A dose of 800 mg per day could result in higher bactericidal activity and an improved outcome [22]. Besides, moxifloxacin is

also likely to be the most effective against MDR-TB [7], as known that the mechanism of fluoroquinolone antibiotics is mainly the inhibition of the activity of DNA gyrase, and thus the destruction of the replication and transcription of DNA in *Mycobacterium tuberculosis*, which further destroys the genetic material in the cells, leading to the death of *Mycobacterium tuberculosis* [11].

According to Table 1, albumin level was found higher in continuation phase. Sanchez *et al.* reported that albumin levels increased quickly by week 4 of treatment [28]. Albumin concentration decreases as increasing disease severity in chronic infection including TB [29]. Wu *et al.* reported that concentrations of serum albumin were significantly lower in patients with an abnormal QTc interval and were associated with QTc prolongation. Hypoalbuminemia may be a marker of comorbidity burden, a low serum albumin level may reflect an inflammatory burden leading to heart failure [30]. A low albumin level is associated with inflammation, and impaired synthetic function of liver and this has been linked to diastolic dysfunction in humans which indicate the association between inflammation and ventricular arrhythmias [31].

Fig. 1 showed that moxifloxacin concentration and QTc interval did not form a certain pattern, strengthen the results in Tables 1 and 2, that there was no correlation between moxifloxacin and QTc interval. The moxifloxacin concentration also did not affect the change of QTc interval ( $\Delta\text{QTc}$ ). An animal study reported different results, moxifloxacin induced a dose-dependent increase in QTc. A maximum increase of 28



ms was observed following the administration of 90 mg/kg moxifloxacin [26].

Our study revealed no correlation between moxifloxacin concentration and QTc interval, suggested the safety use of moxifloxacin, either in 600 or 800 mg. Nachimutu *et al.* stated that the rest of the fluoroquinolones are relatively safe but caution should be applied if there are any underlying risk factors or with co-administration of QT-prolonging drugs [17]. Wang *et al.* also concluded that short-term treatment with a high dose of moxifloxacin (0.6 g/day for 6 months and 0.4 g/day for 9 months) is effective for MDR-TB, and its advantages are a reduction in the incidence of drug-associated adverse reactions and a lack of drug resistance [11]. Kusmiati *et al.* reported that the QTc interval at baseline correlated significantly with the QTc prolongation ( $p < 0.001$ ) [24], while Hong *et al.* stated that Koreans appeared to be more sensitive to moxifloxacin-induced QT prolongation than Caucasians [9]. As fluoroquinolones are known to prolong the QT interval, the WHO guideline recommended cardiac monitoring when using drugs that prolong the QT interval [25].

## 5. Conclusions

Moxifloxacin concentration in plasma (either using the dose of 600 or 800 mg) did not correlate with QTc interval. In addition to close monitoring of QTc interval in DR-TB patients, the clinicians should also consider other variables which potentially increase risk for QTc prolongation in DR-TB patients who received shorter treatment regimens.

## Ethical Statement

The authors attest that this clinical investigation was determined to the Institutional Review Board/Ethics Committee review, and the corresponding protocol/approval number is 1444/KEPK/VIII/2019 and has been approved on August 23rd, 2019. We also certify that we have not plagiarized the contents in this submission and have done a Plagiarism Check. Written informed consent was obtained from all participants.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- [1] World Health Organization. Global Tuberculosis Report. Geneva: World Health Organization, 2020.
- [2] Niward K, Davies Forsman L, Bruchfeld J, Chrysanthou E, Carlström O, Alomari T, *et al.* Distribution of plasma concentrations of first-line anti-TB drugs and individual MICs: a prospective cohort study in a low endemic setting. *J Antimicrob Chemother* 2018;73(10):2838–45.
- [3] Soedarsono S, Kusmiati T, Wulaningrum PA, *et al.* Factors Cause of Switching Shorter Regimen to Longer Regimen in Multidrug-Resistant/ Rifampicin-Resistant Tuberculosis Treated Patients in Dr. Soetomo Hospital Surabaya, Indonesia. *Indian J Med Forensic Med Toxicol* 2020;15:1589–95.
- [4] World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis: 2016 Update. Geneva: World Health Organization, 2016.
- [5] Atif M, Bashir A, Ahmad N, Fatima RK, Saba S, Scallion S. Predictors of unsuccessful interim treatment outcomes of multidrug resistant tuberculosis patients. *BMC Infect Dis* 2017;17(1). <https://doi.org/10.1186/s12879-017-2746-5>.
- [6] Tag El Din MA, El Maraghy AA, Abdel Hay AHR. Adverse reactions among patients being treated for multidrug resistant tuberculosis at Abbassia Chest Hospital. *Egypt J Chest Dis Tuberc* 2015;64(4):939–52.
- [7] Harausz E, Cox H, Rich M, Mitnick CD, Zimetbaum P, Furin J. QTc prolongation and treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2015;19(4):385–91.
- [8] Chen Q, Liu Y-M, Liu Y, Mendzelevski B, Chanter D, Pu H-H, *et al.* Orally administered moxifloxacin prolongs QTc in healthy Chinese volunteers: a randomized, single-blind, crossover study. *Acta Pharmacol Sin* 2015;36(4):448–53.
- [9] Hong T, Han S, Lee J, *et al.* Pharmacokinetic-pharmacodynamic analysis to evaluate the effect of moxifloxacin on QT interval prolongation in healthy Korean male subjects. *Drug Des Dev Ther* 2015;9:1233–45.
- [10] Kusmiati T, Mertaniasih NM, Putranto JN, *et al.* Factors that Contribute to the QTc Interval Prolongation in DR-TB Patients on STR Regimen. *Indian J Med Forensic Med Toxicol* 2020;15:1618–25.
- [11] Wang Q, Zhang C, Guo J, *et al.* Super-compact treatment with a high dose of moxifloxacin in patients with drug-resistant tuberculosis and its resistance mechanisms. *Exp Ther Med* 2015;9(4):1314–8.
- [12] Nair D, Velayutham B, Marimuthu M, *et al.* Effect of moxifloxacin on QTc interval in adults with pulmonary tuberculosis. *Natl Med J India* 2018;31(1):58.
- [13] Kayhan S, Akgunes A. Therapeutic monitoring of isoniazid, rifampicin, ethambutol and pyrazinamide serum levels in the treatment of active pulmonary tuberculosis and determinants of their serum concentrations. *Afr J Pharm Pharmacol* 2011;5: 2035–41.
- [14] Park JS, Lee J-Y, Lee YJ, Kim SJ, Cho Y-J, Yoon HI, *et al.* Serum levels of antituberculosis drugs and their effect on tuberculosis treatment outcome. *Antimicrob Agents Chemother* 2016;60(1):92–8.
- [15] United States Agency for International Development. Guide for QTc monitoring and management of drug-resistant TB patients with QT-prolonging agents. New York: USAID, 2018.
- [16] Lazzerini PE, Capecchi PL, Pasini FL. Long QT syndrome: an emerging role for inflammation and immunity. *Front Cardiovasc Med* 2015;2. <https://doi.org/10.3389/fcvm.2015.00026>.
- [17] Nachimuthu S, Assar MD, Schussler JM. Drug-Induced QT interval prolongation: mechanisms and clinical management. *Ther Adv Drug Saf* 2012;3(5):241–53.
- [18] Indonesian Ministry of Health. Technical Guideline for Programmatic Management of Drug Resistant Tuberculosis. Jakarta: Indonesian Ministry of Health, 2014.
- [19] Indonesian Ministry of Health. Guidelines for Drug-Resistant Tuberculosis Management in Health Care Facility. Jakarta: Indonesian Ministry of Health, 2019.
- [20] Xu F-Y, Huang J-H, He Y-C, Liang L-Y, Li L-J, Yang J, *et al.* Population pharmacokinetics of moxifloxacin and its concentration-QT interval relationship modeling in Chinese healthy volunteers. *Acta Pharmacol Sin* 2017;38(11):1580–8.
- [21] Mason JW, Florian JA, Garnett CE, Moon TE, Selness DS, Spaulding RR. Pharmacokinetics and pharmacodynamics of three moxifloxacin dosage forms: implications for blinding in active-controlled cardiac repolarization studies. *J Clin Pharmacol* 2010;50(11):1249–59.
- [22] Gillespie SH. The role of moxifloxacin in tuberculosis therapy. *Eur Resp Rev* 2016;1(25):19–28.
- [23] Naidoo A, Naidoo K, McIlerron H, Essack S, Padayatchi N. A review of moxifloxacin for the treatment of drug-susceptible tuberculosis. *J Clin Pharmacol* 2017;57(11): 1369–86.
- [24] Kusmiati T, Suci YD, Dewi KP, *et al.* QTc interval prolongation in drug resistant tuberculosis patients treated with shorter treatment regimens. *Med Leg J Update* 2021;21:1208–15.
- [25] World Health Organization. WHO Operational Handbook on Tuberculosis: Drug-Resistant Tuberculosis Treatment. Geneva: WHO, 2020.
- [26] Watson KJ, Gorczyca WP, Umland J, Zhang Y, Chen X, Sun SZ, *et al.* Pharmacokinetic-pharmacodynamic modelling of the effect of Moxifloxacin on QTc prolongation in telemetered cynomolgus monkeys. *J Pharmacol Toxicol Methods* 2011;63(3):304–13.
- [27] Cubeddu L. Drug-induced Inhibition and Trafficking Disruption of ion Channels: Pathogenesis of QT Abnormalities and Drug-induced Fatal Arrhythmias. *Curr Cardiol Rev* 2016;12:141–54.
- [28] Sanchez A, Azen C, Jones B, Louie S, Sattler F. Relationship of acute phase reactants and fat accumulation during treatment for tuberculosis. *Tuberc Res Treat* 2011;2011:1–7.
- [29] Bisaso KR, Owen JS, Ojara FW, Namuwenge PM, Mugisha A, Mbuagbaw L, *et al.* Characterizing plasma albumin concentration changes in TB/HIV patients on anti retroviral and anti-tuberculosis therapy. In *Silico Pharmacol* 2014;2(1).
- [30] Wu C-C, Lu Y-C, Yu T-H, Wang C-P, Hung W-C, Tang W-H, *et al.* Serum albumin level and abnormal corrected QT interval in patients with coronary artery disease and chronic kidney disease. *Intern Med J* 2018;48(10):1242–51.
- [31] Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, *et al.* Novel metabolic risk factors for incident heart failure and their relationship with obesity. *J Am Coll Cardiol* 2008;51(18):1775–83.