Correlation of inflammaroty cytokines on corrected QT interval in rifampicin-resistant tuberculosis patients

by Tutik Kusmiati

Submission date: 26-Apr-2022 12:11PM (UTC+0800)
Submission ID: 1820553265
File name: ed_QT_interval_in_rifampicin-resistant_tuberculosis_patients.pdf (936.57K)
Word count: 5146
Character count: 27866

Annals of Medicine and Surgery 70 (2021) 102862

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Cross-sectional Study

Correlation of inflammatory cytokines on corrected QT interval in rifampicin-resistant tuberculosis patients

Tutik Kusmiati [a,b,*], Ni Made Mertaniasih [c], Johanes Nugroho Eko Putranto [d], Budi Suprapti [e], Soedarsono [b], Nadya Luthfah [d], Winariani Koesoemoprodjo [b], Aryani Prawita Sari [b]

[a] Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[b] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[c] Department of Clinical Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[d] Department of Vascular and Cardiology Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[e] Faculty of Pharmacy, Universitas Airlangga – Universitas Airlangga Teaching Hospital, Surabaya, Indonesia

ARTICLE INFO

Keywords:
IL-1β
IL-6
RR-TB
TNF-α
QTc prolongation

ABSTRACT

Background: The cases of Rifampicin-Resistant Tuberculosis (RR-TB) in our country have increased every year and RR-TB deaths are thought to be caused by prolongation of the QTc interval due to side effects of anti-tuberculosis drugs. Thus, cytokines are needed to be used as early markers of prolongation of the QTc interval in RR-TB patients.

Objective: This study aims to analyze the correlation of inflammatory cytokines on QTc interval in RR-TB patients who received shorter regimens.

Methods: This study uses a case-control study with a time series conducted in the period September 2019 to February 2020 in one of the referral hospitals for Tuberculosis in Indonesia. Cytokines levels from blood samples were measured using the ELISA method, while QTc intervals were automatically recorded using an electrocardiography machine. The statistical analysis used was the Chi-square test, Man Whitney test, Independence *t*-test, and Spearman-rank test with $p < 0.05$.

Results: There was no significant correlation between inflammatory cytokines and QTc prolongation in intensive phase which TNF-α value (6.8 pg/ml; $r = 0.207$; $p = 0.281$), IL-1β (20.13 pg/ml; $r = 0.128$; $p = 0.509$), and IL-6 (43.17 pg/ml; $r = -0.028$; $p = 0.886$). Meanwhile, in the continuation phase, the values for TNF-α (4.79 pg/ml; $r = 0.046$; $p = 0.865$), IL-1β (7.42 pg/ml; $r = -0.223$; $p = 0.406$), and IL- 6 (40.61 pg/ml; $r = -0.147$; $p = 0.586$).

Conclusion: inflammatory cytokines (TNF-α, IL-1β, and IL-6) cannot be used to identify QTc interval prolongation in RR-TB patients who received shorter regimens.

1. Introduction

The emergence and continuing spread of *Mycobacterium tuberculosis* strains that are resistant to anti-tuberculosis drugs is a worldwide difficult challenge for global tuberculosis (TB) control, despite the availability of therapies to treat TB. The presence of drug resistance is associated with poor treatment management. In 2020, the World Health Organization (WHO) reported 465,000 cases of rifampicin-resistant tuberculosis (RR-TB) with treatment success rates of 57% [1]. The combination of second-line anti-TB drugs to treat drug-resistant tuberculosis (DR-TB) is more toxic and leads to adverse effects. Some adverse effects can be life-threatening. Poor adverse effects management is associated with non-adherence to treatment and result in morbidity and mortality. Baseline evaluation and monitoring during treatment are essential to prevent adverse effects from becoming serious [2].

Multidrug-resistant/rifampicin-resistant (MDR/RR) TB requires treatment with second-line drugs, including several potential QT-prolonging drugs caused by toxic effects [3]. The incidence of QTc

Abbreviations: RR-TB, Rifampicin-Resistant Tuberculosis; TB, tuberculosis; WHO, World Health Organization; MDR, multidrug resistance; BMI, Body mass index; TNF-α, Tumor necrosis factor alpha; IL-1β, interleukin-1β; IL-6, interleukin 6; K, Potassium; Ca, Calcium.

* Corresponding author. Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Jl. Mayjend Prof. Dr. Moetopo No. 6 – 8, Airlangga, Gubeng, Surabaya, East Java, 60286, Indonesia.
E-mail address: tut.kusmiati@gmail.com (T. Kusmiati).

https://doi.org/10.1016/j.amsu.2021.102862
Received 26 July 2021; Received in revised form 12 September 2021; Accepted 13 September 2021
Available online 14 September 2021

interval prolongation has been reported in DR-TB patients who received shorter regimens. The incidence of ΔQTc >30 ms and ΔQTc >60 ms were experienced by 21/98 (21.4%) and 10/98 (10.2%) patients, respectively [4]. A study in 108 DR-TB patients on the shorter treatment regimens reported 20 patients experienced moderate QTc prolongation and 31 patients experienced severe QTc prolongation [5]. Prolongation of heart rate-corrected QT interval (QTc) is a serious adverse effect that potentially increases the risk of torsade de points and independently predicts sudden death in the general population [6].

Many strategies have been used to monitor the treatment safety and minimize the unfavorable outcomes of MDR/RR-TB treatment, including the implementation of electrocardiography (ECG) to monitor the treatment safety when several QT-prolonging drugs are used [7]. The use of inflammatory cytokines may be useful in the detection or to predict QTc prolongation. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) have been known to induce profound changes in potassium and calcium channels resulting in prolongation of cardiomyocyte action potential duration (APD) [8]. A significant association between inflammation and QTc prolongation has been reported, especially the involvement of TNF-α in the pathology of abnormally prolonged QT-time [9].

The study conducted by Adlan et al. indicates that demonstrated the positive association of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-10) and QT interval in patients with rheumatoid arthritis [6]. A close association between systemic inflammation and QTc interval has been also reported. The use of anti-IL-6 receptor was associated with a rapid and significant reduction of QTc interval, and shortening of QTc interval associated with decreases in circulating level TNF-α in RA patients [8]. Evidence from RA patients suggested that inflammatory cytokines of TNF-α, IL-1β, and IL-6 are associated with QTc interval, but this association is still unknown in DR-TB patients. This study investigated the association between inflammatory cytokines with QTc interval in DR-TB patients who received shorter regimens.

2. Materials and methods

2.1. Participants

Participants in this study were rifampicin-resistant tuberculosis (RR-TB) who were undergoing treatment in a hospital. The inclusion criteria in participants such as patients diagnosed with RR-TB using molecular rapid test using GeneXpert MTB/RIF, aged 18–65 years, and receiving treatment with shorter regimens (intensive or continuation phases). The exclusion criteria in this study are patients who have any risk factors for QTc prolongation such as baseline QTc >500 ms, potassium <3.5 mmol/L, magnesium <1.7 mmol/L, calcium <8 mmol/L, creatinine clearance <30 cc/m, aspartate aminotransferase – alanine aminotransferase (AST-ALT) >5x upper limit normal (ULN), body mass index (BMI) <18 kg/m^2, on anti-arrhythmia therapy, on anti-depressant therapy, with bradycardia, on anti-fungal treatment (azoles), on erythromycin therapy, and phenytoin therapy [3,8,10,11]. Participants or guardians get an explanation regarding the purpose of the research and those who are willing to participate in the research consciously and without coercion fill out the consent form.

2.2. Ethical approval

We have conducted an ethical approval base on the Declaration of Helsinki with registration research at the Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (1444/KEPK/VIII/2019).

2.3. Study design

A case-control study with a time-series design was conducted from September 2019 to February 2020 in one of the referral hospitals for TB in Indonesia. The number of participants in this study was 45 TB patients who were obtained by consecutive sampling method. Participants were divided into 2 groups, such as the intensive phase (n = 29) and the continuation phase (n = 16). This study was reported by the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2019 guideline [12]. RR-TB is defined as TB resistant to rifampicin according to a molecular rapid test using GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) [13,14]. RR-TB patients who are on intensive phase were defined as RR-TB patients who are diagnosed with RR-TB and start intensive phase of treatment with shorter regimens. RR-TB patients on the continuation phase of shorter regimens were defined as RR-TB patients who have culture conversion. Standardized shorter regimens were as recommended by the WHO in 2016 [15,16].

2.4. Measurement of inflammatory cytokines levels

Samples of venous blood were taken from each participant and put into EDTA serum tubes. All samples were stored in a deep freezer with a temperature of −80 °C. After the sample is complete, all samples were put at room temperature for 2 h or at 4 °C for a night. Storage at low temperatures inhibits the process of glycolysis so that the components in the blood do not change during the first 5–6 h of storage [17]. Blood samples of patients were centrifuged at 3000 rpm for 5–10 min in 10 ml sterile tubes to separate the blood plasma and serum. The inflammation cytokines levels were measured using the ELISA kit supplied by Diaclone (Besoncon Cedex, France).

2.5. QTc interval calculation

Twelve-lead electrocardiograms were recorded at a 25 mm/s paper speed using an automated ECG machine merc BLT E30 (Guangdong Biolight Meditech, China). The means of the QT intervals and R-R intervals were obtained by measuring the QT intervals and R-R intervals of three consecutive beats in each lead. The computer program uses successive R-R intervals between all ventricular muscle depolarization (QRS complexes) to calculate the mean heart rate within the recorded period. QTc interval prolonging was calculated using the Fridericia formula [3,11,18].

Fridericia formula is a formula recommended by the U.S. Food and Drug Administration (FDA) for clinical trials on drug safety. Fridericia formula calculation is QTc = QT/[R - R]1/3 [19,20].

2.6. Statistical analysis

Participant characteristics data were analyzed using the chi-square test and the t-independent or Mann-Whitney test based on the distribution of data which was calculated using the Shapiro Wilk test. All obtained data, including the levels of inflammatory cytokines (TNF-α, IL-1β, and IL-6) and QTc interval were analyzed. Statistical analysis was performed with SPSS 21.0 software (IBM Corp., Armonk, NY, USA). The analysis used to find the correlation between inflammatory cytokines and QTc interval in the intensive phase group and continuation phase group is the Spearman rank test. The correlation was considered as significant statistically if p-value < 0.05.

3. Results

3.1. Characteristics of participant

29 RR-TB patients on intensive phase (64%) and 16 RR-TB patients on continuation phase (36%) were included in this study. The average age of the participants was 37.71 ± 13.55 years with a median value of 41.00 (18.00–62.00) years. There was a difference in the mean age in the intensive phase group (37.03 ± 13.76 years) and the continuation phase group (38.94 ± 13.51 years; p = 0.569). Similar conditions were found in the participant's BMI value, which in the intensive phase group was

21.90 ± 3.55 m/kg2 and the group continuation phase was 21.08 ± 3.66 m/kg^2 ($p = 0.530$). Meanwhile, the average BMI of participants was 21.61 ± 3.57 m/kg^2 with a median value of 20.28 (18.03–28.65) m/kg^2 (Table 1).

Significant differences between the intensive and continuation phases were found in potassium (4.30 ± 0.45 vs. 3.97 ± 0.41 mmol/l; CI 0.056–0.606; $p = 0.019$) and calcium levels (9.03 ± 0.46 vs. 8.68 ± 0.20 mg/dl; CI 0.109–0.602; $p = 0.001$). There was a decrease in potassium and calcium levels in the continuation phase (Table 1). The average potassium level of participants was 4.18 ± 0.46 mmol/l with a median value of 4.2 (3.5–5.5) mmol/l and the average value of calcium participants was 8.90 ± 0.42 mg/dl with a median value of 8.90 (8.10–9.80) mg/dl. Most of the participants were male as many as 23 participants (51.10%). In the intensive phase, most of the participants were male (16 participants; 55.20%) and in the continuation phase, the majority were women (9 participants; 56.3%; $p = 0.463$). Some participants have diabetes mellitus as many as 19 participants which in the intensive phase as many as 14 participants (48.30%) and in the continuation phase as many as 5 participants (31.30%; $p = 0.268$).

3.2. Correlation of inflammatory cytokines on QTc interval

The inflammatory cytokines participant values were such us TNF-α was 8.73 ± 9.80 pg/ml, IL-1β was 48.68 ± 109.49 pg/ml, and IL-6 was 125.04 ± 253.80 pg/ml. The significant difference in cytokine values between the intensive phase and continuation phase was found in the IL-1β value (62.78 ± 132.64 vs. 23.14 ± 35.25 pg/ml; $p = 0.040$). Meanwhile, TNF-α (9.05 ± 9.21 vs 8.15 ± 11.09 pg/ml; $p = 0.530$) and IL-6 (166.44 ± 308.99 vs 49.98 ± 37.34 pg/ml; $p = 0.447$). there is no significant difference between the intensive phase and the continuation phase. A significant difference was found in the value of QTc intervals, which in the intensive phase was 417.28 ± 31.22 ms and in the continuation phase was 455.94 ± 16.64 ms (CI -55.648 to −21.675; $p < 0.001$; Table 1). The mean value of QTc intervals prolonging participants was 431.02 ± 32.64 ms with a median value of 433.00 (352.00–476.00) ms.

Our study suggests that levels of TNF-α, IL-1β, and IL-6 have no significant correlation with QTc interval in RR-TB patients, both in the intensive phase and continuation phase. There is no significant correlation between inflammatory cytokines and QTc interval in the intensive phase which statistical analysis results show such us TNF-α ($r = 0.207$; $p = 0.281$), IL-1β ($r = 0.128$; $p = 0.509$), and IL- 6 ($r = -0.028$; $p = 0.886$). Meanwhile, in the continuation phase such us TNF-α ($r = 0.046$; $p = 0.865$), IL-1β ($r = -0.223$; $p = 0.406$), and IL-6 ($r = -0.147$; $p = 0.586$). The same condition was found in the K and Ca analysis of the QTc interval which in the intensive phase the value of K levels ($r = -0.142$; $p = 0.461$) and Ca level ($r = 0.127$; $p = 0.510$) while in the continuation phase the value of K levels was obtained ($r = 0.323$; $p = 0.223$) and Ca levels ($r = 0.312$; $p = 0.239$; Table 2).

There was no significant correlation between levels of inflammatory cytokines (TNF-α, IL-1β, and IL-6) on QTc interval prolonging in the participant. The distribution of levels of inflammatory cytokines and QTc interval prolongation were not found to be correlated between the two variables (Fig. 1).

Table 1
Characteristics of participant.

Characteristics	RR-TB patients		p
	Intensive phase (n = 29)	Continuation phase (n = 16)	
Age (years)	37.03 ± 13.76	38.94 ± 13.51	0.569
BMI (m/kg^2)	21.90 ± 3.55	21.08 ± 3.66	0.530
Potassium (mmol/l)	4.30 ± 0.45	3.97 ± 0.41	0.019*
Calcium (mg/dl)	9.03 ± 0.46	8.68 ± 0.20	0.001*
TNF-α (pg/ml)	9.05 ± 9.21	8.15 ± 11.09	0.530
IL-1β (pg/ml)	62.78 ± 132.64	23.14 ± 35.25	0.040*
IL-6 (pg/ml)	166.44 ± 308.99	49.98 ± 37.34	0.477
QTc interval (ms)	417.28 ± 31.22	455.94 ± 16.64	<0.001**

Note: BMI = Body mass index; TNF-α = Tumor necrosis factor alpha; IL-1β = interleukin-1β; IL-6 = interleukin 6; *significant $p < 0.05$; **significant $p < 0.001$.

4. Discussions

Proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 have been well known to have an important role in the host response against *Mycobacterium tuberculosis* infection. TNF-α is an important component of the immune response to TB and is also involved in granuloma formation. IL-1β, which is produced by macrophages and monocytes, has a role in the early stages of antimycobacterial immune response and protects the tissue by activating epithelial antimicrobial peptides [21]. IL-1β does not kill directly *Mycobacterium tuberculosis*, rather IL-1β is induced during infection and is primarily produced by monocytes, macrophages, and dendritic cells. IL-1 signals through the IL-1R1 receptor present on several cells including endothelial cells, monocytes, macrophages, and T lymphocytes. IL-1β is capable of inducing the expression of the neutrophil recruiting cytokine IL-17. Further, the underlying function of IL-1 in *Mycobacterium tuberculosis* appears to be in regulating type I IFN function and helping to maintain the balance between sufficient phagocytes to mediate control of the intracellular pathogen while inhibiting the over recruitment of permissive macrophages mediated by type I IFN [22]. IL-6 is a pleiotropic proinflammatory cytokine. IL-6 is essential for the development of an optimal T-cell response, and a requirement in host resistance to *Mycobacterium tuberculosis* infection [21,22].

In our study, the higher levels of cytokines in the early stage of treatment (intensive phase) are due to a higher inflammation process caused by *Mycobacterium tuberculosis* infection. High levels of IL-6 were observed in TB patients. Infection by *Mycobacterium tuberculosis* also results in the appearance of a strong inflammatory cell-mediated immune response and increased TNF-α levels. Cytokines of TNF-α, IL-1β, and IL-6 are expressed and released at the site of disease after the interaction between T lymphocytes and infected macrophages when *Mycobacterium tuberculosis* invades the lungs [21].

Correlation analysis using Spearman-rho indicates that inflammatory cytokines of TNF-α, IL-1β, and IL-6 did not correlate with QTc interval in RR-TB patients, both in the intensive phase and continuation phase. A previous study in the elderly general population reported a significant correlation of TNF-α and abnormally prolonged QT-time (APTQ) in women, while IL-6 was not significantly related with (APQT) [9]. Another study in patients who experienced TdP reported different results. Systemic inflammation via elevated IL-6 levels was suggested as a novel QT-prolonging risk factor contributing to TdP occurrence, while TNF-α and IL-1 were not correlated with QT prolongation [8].

Potassium and calcium were not correlated with QTc interval,

Table 2
Correlation of inflammatory cytokines on prolonging QTc intervals in RR-TB patients.

QTc Interval	Intensive phase		Continuation phase	
	r	p	r	P
TNF-α (pg/mL)	0.207	0.281	0.046	0.865
IL-1β (pg/mL)	0.128	0.509	−0.223	0.406
IL-6 (pg/mL)	−0.028	0.886	−0.147	0.586
K (mmol/l)	−0.142	0.461	0.323	0.223
Ca (mg/dl)	0.127	0.510	0.312	0.239

Note: TNF-α = Tumor necrosis factor alpha; IL-1β = interleukin-1β; IL-6 = interleukin 6; K = Potassium; Ca = Calcium; *significant $p < 0.05$; **significant $p < 0.001$.

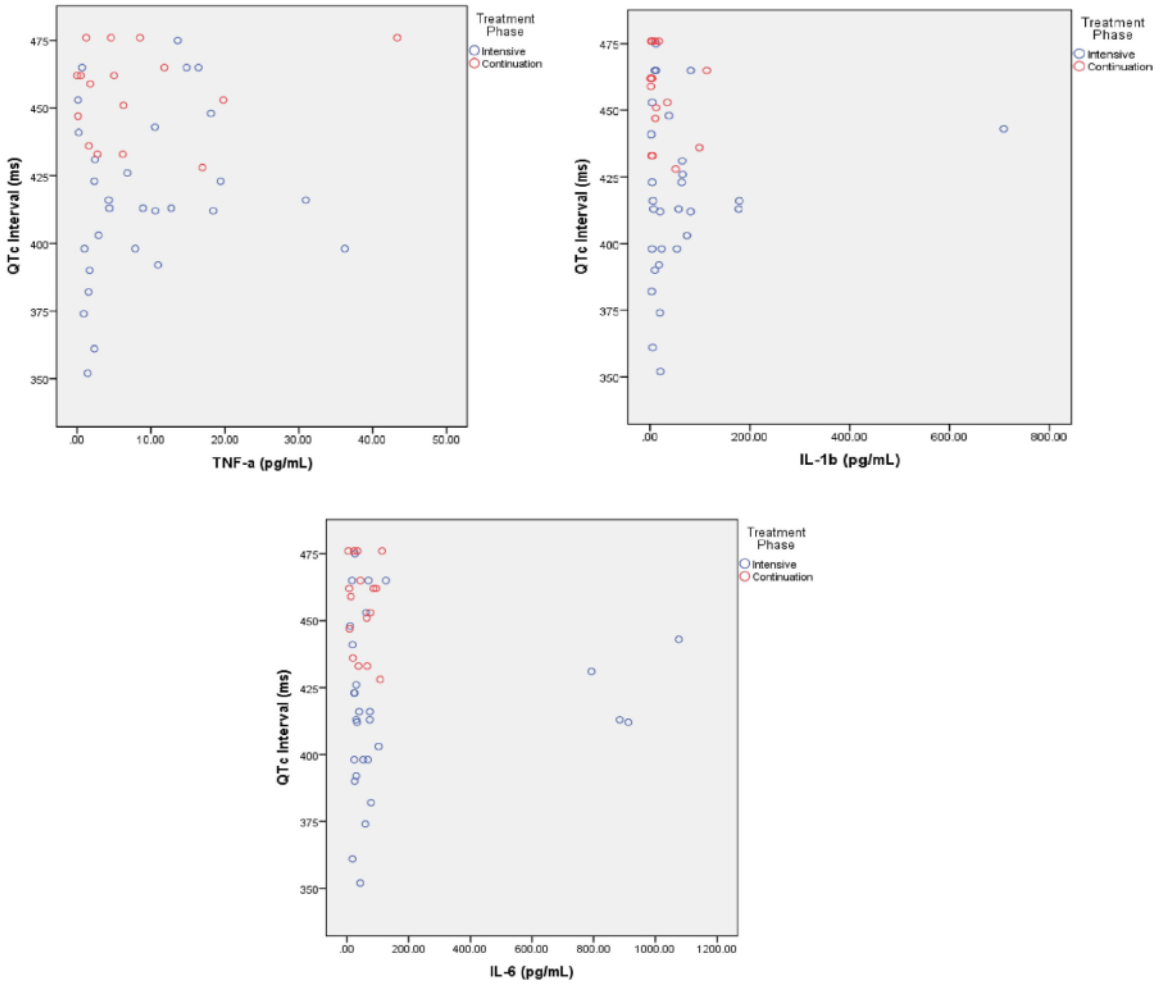

Fig. 1. Scatter plot of inflammatory cytokines (TNF-α, IL-1β, and IL-6) and QTc interval in RR-TB patients.

because RR-TB patients with low potassium and calcium levels have been excluded in this study. This exclusion intends to minimize the influence of other variables on the QTc interval. A previous study stated that inflammatory cytokines (TNF-α, IL-1, IL-6) were considered to correlate with QTc prolongation. Cytokines induced profound changes in potassium and calcium channels resulting in prolongation of cardiomyocyte action potential duration (APD) and increased susceptibility to re-entrant ventricular arrhythmias. TNF-α prolongs APD by reducing potassium currents (the transient outward [Ito], and the rapid [Ikr], and slow [Ikr], components of the delayed rectifier currents), while IL-1 and IL-6 by enhancing the L-type calcium current (ICaL) [8]. TNF-α system was found to influence calcium and potassium channels affecting QT time [9]. Inflammatory activation profoundly impacts the electrophysiological properties of cardiomyocytes via multiple effects, resulting in a prolongation of APD, and thereby of the QTc on ECG. The key mediators seem to be inflammatory cytokines (particularly TNF-α, IL-6, IL-1β), which may affect the myocardium either directly, by modulating specific ion channels critically involved in APD, and indirectly, by increasing central nervous system sympathetic drive on the heart [7,8].

Inflammation plays a central role in many cardiovascular diseases, including heart failure, myocardial infarction, arrhythmias, pericarditis, myocarditis, and sepsis-induced cardiomyopathy [23]. A cohort study of 112 RA patients reported a significant correlation between inflammatory cytokines (TNF-α, IL-1β, IL-6) and QTc interval [6]. Patients with connective tissue diseases, positive anti-RO/SSA, and long QTc intervals were found to have significantly higher levels of IL-1β [24]. Increased proinflammatory interleukin-6 (IL-6) levels are associated with acquired long QT syndrome (LQTS) in patients with systemic inflammation. A previous study demonstrated that IL-6 inhibition of IKr and the resulting prolongation of APD has mediated via IL-6R and Janus kinase (JAK) pathway activation and forms the basis for the observed clinical QT interval prolongation [25].

The distribution of cytokines (TNF-α, IL-1β, and IL-6) and QTc intervals prolonging were no correlation. Cytokine levels decreased in the continuation phase (although only IL-1β indicates significance). Conversely, the QTc interval increased significantly in the continuation phase. These results suggested that inflammatory cytokines did not play any role on QTc intervals in RR-TB patients. This was different from a cohort study in the UK, which suggested a lower inflammatory burden may protect against QTc prolongation in patients with rheumatoid arthritis (RA) [6]. Another study also reported the possible contribution of IL-1β in modulating susceptibility to QTc prolongation after cardiac surgery [26].

Other factors such as medication possibly contribute to QTc interval

in our study. RR-TB in continuous phase patients taking moxifloxacin is suspected of having a prolonged QTc interval. Serums of QT-prolonging drugs may accumulate more and longer in the continuation phase could increase QTc interval. A study of the linear pharmacokinetic-pharmacodynamic model reported a 1.5 ms increase in QTc was observed for every 1 μM increase in free systemic exposure of moxifloxacin [27]. Another study stated that QT prolongation correlates with increases in TNF-α, IL-1β, and IL-6. Pro-inflammatory cytokines cause QT prolongation by acting through stimulation of reactive oxygen species (ROS), and then ceramides, while QT-prolonging agents were considered to bypass the initial steps of this pathway and directly affect ceramides [28].

Tuberculosis is a very common problem in developing countries, and treatment-related complications are common and sometimes underrated and this study will aid the physicians to be aware of common and uncommon but life-threatening side effects of anti-tuberculosis treatment So well written and nicely organized.

5. Conclusion

Our study suggested that inflammatory cytokines (TNF-α, IL-1β, and IL-6) do not correlate with QTc intervals, and could not be used to identify QTc prolongation in RR-TB patients who received shorter regimens. Other markers other than TNF-α, IL-1β, and IL-6 may need to be explored for early detection of the risk of QTc prolongation in RR-TB patients.

Ethical approval

We have conducted an ethical approval base on Declaration of Helsinki at Ethical Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Sources of funding

None.

Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Registration of research studies

1.Name of the registry: Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
2.Unique identifying number or registration ID: 1444/KEPK/VIII/2019.
3.Hyperlink to your specific registration (must be publicly accessible and will be checked): .

Guarantor

Tutik Kusmiati.

Consent

Written informed consent was obtained from the patient.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgment

The authors thank Fis Citra Ariyanto for editing and proofing assistance.

References

[1] M.B. Souleymane, A. Piubello, I.M. Lawan, S. Hassane-Harouna, M.M. Assao-Neino, A. Soumana, et al., High rifampicin-resistant TB cure rates and prevention of severe ototoxicity after replacing the injectable by linezolid in early stage of hearing loss, Eur. Respir. J. 57 (1) (2021), https://doi.org/10.1183/13993003.02250-2020.
[2] G. Ramachandran, S. Swaminathan, Safety and tolerability profile of second-line anti-tuberculosis medications, Drug Saf. 38 (3) (2015) 253–269, https://doi.org/10.1007/s40264-015-0267-y.
[3] I. Monedero-Recuero, L. Hernando-Marrupe, A. Sánchez-Montalvá, V. Cox, M. Tommasi, J. Furin, et al., QTc and anti-tuberculosis drugs: a perfect storm or a tempest in a teacup? Review of evidence and a risk assessment, Int. J. Tubercul. Lung Dis. : Off. Int. Union Against Tubercul. Lung Dis. (2018), https://doi.org/10.5588/ijtld.18.0423.
[4] T. Kusmiati, N.M. Mertaniasih, J.N.E. Putranto, B. Suprapti, D.P.A. Krisdanti, Y.D. S. Kusumastrini, et al., Factors that contribute to the QTc interval prolongation in DR-TB patients on STR regimen, Indian J. Foren. Med. Toxicol. 15 (1) (2021), https://doi.org/10.37506/ijfmt.v15i1.13641, 1605-12.
[5] T. Kusmiati, Y.D. Suci, K.P. Dewi, Soedarsono, QTc interval prolongation in drug resistant-tuberculosis patients treated with shorter treatment regimen, Med. Leg. Update 21 (2) (2021) 1208–1215, https://doi.org/10.37506/mlu.v21i2.2855.
[6] A.M. Adlan, Inflammation and heart rate-corrected QT interval: evidence for a potentially reversible cause of sudden death in patients with rheumatoid arthritis? J. Rheumatol. 45 (12) (2018) 1609–1610, https://doi.org/10.3899/jrheum.180921.
[7] S. Katrak, P. Lowenthal, R. Shen, L. True, L. Henry, P. Barry, Bedaquiline for multidrug-resistant tuberculosis and QTc prolongation in California, J. Clin. Tubercul. other Mycobacterial Dis. 23 (2021), 100216, https://doi.org/10.1016/j.jctube.2021.100216.
[8] P.E. Lazzerini, F. Laghi-Pasini, I. Bertolozzi, G. Morozzi, S. Lorenzini, A. Simpatico, et al., Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes, Heart (Br. Cardiac Soc.) 103 (22) (2017) 1821–1829, https://doi.org/10.1136/heartjnl-2016-311079.
[9] D. Medenwald, J.A. Kors, H. Loppnow, J. Thiery, A. Kluttig, S. Nuding, et al., Inflammation and prolonged QT time: results from the cardiovascular disease, living and ageing in halle (CARLA) study, PloS One 9 (4) (2014), e95994, https://doi.org/10.1371/journal.pone.0095994.
[10] S. Nachimuthu, M.D. Assar, J.M. Schussler, Drug-induced QT interval prolongation: mechanisms and clinical management, Therapeut. Adv. Drug Saf. 3 (5) (2012) 241–253, https://doi.org/10.1177/2042098612454283.
[11] E. Harausz, H. Cox, M. Rich, C.D. Mitnick, P. Zimetbaum, J. Furin, QTc prolongation and treatment of multidrug-resistant tuberculosis, Int. J. Tubercul. Lung Dis. : Off. Int. Union Against Tubercul. Lung Dis. 19 (4) (2015) 385–391, https://doi.org/10.5588/ijtld.14.0335.
[12] R. Agha, A. Abdall-Razak, E. Crossley, N. Dowlut, C. Iosifidis, G. Mathew, STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery, Int. J. Surg. 72 (2019) 156–165, https://doi.org/10.1016/j.ijsu.2019.11.002.
[13] S.C. van Kampen, N.H. Susanto, S. Simon, S.D. Astiti, R. Chandra, E. Burhan, et al., Effects of introducing xpert MTB/RIF on diagnosis and treatment of drug-resistant tuberculosis patients in Indonesia: a pre-post intervention study, PloS One 10 (6) (2015), e0123536, https://doi.org/10.1371/journal.pone.0123536.
[14] P.M. Christopher, A. Widysanto, GeneXpert Mycobacterium tuberculosis/rifampicin assay for molecular epidemiology of rifampicin-Resistant Mycobacterium tuberculosis in an Urban Setting of Banten province, Indonesia, Int. J. Mycobacteriol. 8 (4) (2019) 351–358, https://doi.org/10.4103/ijmy.ijmy_138_19.
[15] WHO Guidelines Approved by the Guidelines Review Committee, WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment, World Health Organization, Geneva, 2019.
[16] WHO Guidelines Approved by the Guidelines Review Committee, WHO Consolidated Guidelines on Tuberculosis: Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, World Health Organization, Geneva, 2020.
[17] A. Dorhoi, S.H. Kaufmann, Tumor necrosis factor alpha in mycobacterial infection, Semin. Immunol. 26 (3) (2014) 203–209, https://doi.org/10.1016/j.smim.2014.04.003.
[18] T. Kazumi, A. Kawaguchi, T. Hirano, G. Yoshino, C-reactive protein in young, apparently healthy men: associations with serum leptin, QTc interval, and high-density lipoprotein-cholesterol, Metab. Clin. Exp. 52 (9) (2003) 1113–1116, https://doi.org/10.1016/s0026-0495(03)00184-7.
[19] D.Q. Phan, M.J. Silka, Y.T. Lan, R.K. Chang, Comparison of formulas for calculation of the corrected QT interval in infants and young children, J. Pediatr. 166 (4) (2015) 960–964, https://doi.org/10.1016/j.jpeds.2014.12.037, e1-2.

[20] M. Çap, Bilge Ö, F. Işık, C. Burak, A. Karagöz, İnci Ü, et al., The effect of favipiravir on QTc interval in patients hospitalized with coronavirus disease 2019, J. Electrocardiol. 63 (2020) 115–119, https://doi.org/10.1016/j.jelectrocard.2020.10.015.

[21] S. Wu, Y. Wang, M. Zhang, S.S. Shrestha, M. Wang, J.Q. He, Genetic polymorphisms of IL1B, IL6, and TNFα in a Chinese han population with pulmonary, Tubercul. BioMed Res. Int. 2018 (2018), 3010898, https://doi.org/10.1155/2018/3010898.

[22] R. Domingo-Gonzalez, O. Prince, A. Cooper, S.A. Khader, Cytokines and chemokines in Mycobacterium tuberculosis infection, Microbiol. Spectr. 4 (5) (2016), https://doi.org/10.1128/microbiolspec.TBTB2-0018-2016.

[23] Y. Szekely, Y. Arbel, A review of interleukin-1 in heart disease: where do we stand today? Cardiol. Ther. 7 (1) (2018) 25–44, https://doi.org/10.1007/s40119-018-0104-3.

[24] C.N. Pisoni, S. Reina, D. Arakaki, A. Eimon, C. Carrizo, E. Borda, Elevated IL-1β levels in anti-Ro/SSA connective tissue diseases patients with prolonged corrected QTc interval, Clin. Exp. Rheumatol. 33 (5) (2015) 715–720.

[25] A.S. Aromolaran, U. Srivastava, A. Alí, M. Chahine, D. Lazaro, N. El-Sherif, et al., Interleukin-6 inhibition of hERG underlies risk for acquired long QT in cardiac and systemic inflammation, PloS One 13 (12) (2018), e0208321, https://doi.org/10.1371/journal.pone.0208321.

[26] M.D. Kertai, Y. Ji, Y.J. Li, J.P. Mathew, J.P. Daubert, M.V. Podgoreanu, Interleukin-1β gene variants are associated with QTc interval prolongation following cardiac surgery: a prospective observational study, Canadian journal of anaesthesia = J. Canadien d'anesthesie. 63 (4) (2016) 397–410, https://doi.org/10.1007/s12630-015-0576-8.

[27] K.J. Watson, W.P. Gorczyca, J. Umland, Y. Zhang, X. Chen, S.Z. Sun, et al., Pharmacokinetic-pharmacodynamic modelling of the effect of Moxifloxacin on QTc prolongation in telemetered cynomolgus monkeys, J. Pharmacol. Toxicol. Methods 63 (3) (2011) 304–313, https://doi.org/10.1016/j.vascn.2011.03.002.

[28] P.P. Sordillo, D.C. Sordillo, L. Helson, Review: the prolonged QT interval: role of pro-inflammatory cytokines, reactive oxygen species and the ceramide and sphingosine-1 phosphate pathways, In vivo (Athens, Greece) 29 (6) (2015) 619–636.

Correlation of inflammaroty cytokines on corrected QT interval in rifampicin-resistant tuberculosis patients

ORIGINALITY REPORT

19%	14%	14%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Aysim Gunes, Laurent Bilodeau, Catherine Huet, Assia Belblidia et al. "Plasma sgp130 is an independent predictor of non-alcoholic fatty liver disease severity", Cold Spring Harbor Laboratory, 2022 Publication	1%
2	Kazumi, T.. "C-reactive protein in young, apparently healthy men: associations with serum leptin, QTc interval, and high-density lipoprotein-cholesterol", Metabolism, 200309 Publication	1%
3	Mastoureh Naddafi, Abbasali Abouei Mehrizi, Mohammad Ali Eghbal, Mahmoud Ghazi Khansari et al. "Reducing the risk of death induced by aluminum phosphide poisoning: The new therapies", Chemosphere, 2022 Publication	1%
4	PATTANSHETTY, Deepak J, GAJUAPALLI, Rama Dilip, ANNA, Kiran and SAPPATI BIYYANI, Raja Shekhar. "Prevalence of QT interval	1%

prolongation in inflammatory bowel disease", Türk Gastroenteroloji Vakfı, 2016.
Publication

5	synapse.koreamed.org Internet Source	1 %
6	Ginenus Fekadu, Legese Chelkeba, Tsegaye Melaku, Elsah Tegene, Ayantu Kebede. "30-day and 60-day rates and predictors of mortality among adult stroke patients: Prospective cohort study", Annals of Medicine and Surgery, 2020 Publication	1 %
7	Pietro Enea Lazzerini, Franco Laghi-Pasini, Pier Leopoldo Capecchi, Mohamed Boutjdir. "Emerging risk factors for QT interval prolongation and torsades de pointes", Elsevier BV, 2022 Publication	1 %
8	Geetha Ramachandran, Soumya Swaminathan. "Safety and Tolerability Profile of Second-Line Anti-Tuberculosis Medications", Drug Safety, 2015 Publication	1 %
9	Dspace.Stir.Ac.Uk Internet Source	<1 %
10	bmcpublichealth.biomedcentral.com Internet Source	<1 %

11	Kenny J. Watson, William P. Gorczyca, John Umland, Ying Zhang et al. "Pharmacokinetic–pharmacodynamic modelling of the effect of Moxifloxacin on QTc prolongation in telemetered cynomolgus monkeys", Journal of Pharmacological and Toxicological Methods, 2011 Publication	<1 %
12	bmcpediatr.biomedcentral.com Internet Source	<1 %
13	jphres.org Internet Source	<1 %
14	www.nature.com Internet Source	<1 %
15	e-journal.unair.ac.id Internet Source	<1 %
16	insights.ovid.com Internet Source	<1 %
17	www.jofamericanscience.org Internet Source	<1 %
18	hdl.handle.net Internet Source	<1 %
19	pergamos.lib.uoa.gr Internet Source	<1 %
20	aging-us.com	

	Internet Source	<1%
21	www.um-surabaya.ac.id Internet Source	<1%
22	T Kamisako. "Serum platelet-activating factor acetylhydrolase (PAF-AH) activity in patients with hyperbilirubinemic hepatobiliary disease", Hepatology Research, 2003 Publication	<1%
23	ogma.newcastle.edu.au Internet Source	<1%
24	www.ashdin.com Internet Source	<1%
25	www.slideshare.net Internet Source	<1%
26	Pietro Enea Lazzerini, Maurizio Acampa, Pier Leopoldo Capecchi, Irene Fineschi et al. "Antiarrhythmic Potential of Anticytokine Therapy in Rheumatoid Arthritis: Tocilizumab Reduces Corrected QT Interval by Controlling Systemic Inflammation", Arthritis Care & Research, 2015 Publication	<1%
27	d-nb.info Internet Source	<1%

28	Majid Bani-Ata, Abdelwahab Aleshawi, Muayyad Ahmad, Omar Saleh et al. "Endoscopic Dacryocystorhinostomy: A comparison of Double-flap and Single-flap Techniques", Annals of Medicine and Surgery, 2020 Publication	<1 %
29	eprints.lancs.ac.uk Internet Source	<1 %
30	mdpi-res.com Internet Source	<1 %
31	mgend.med.kyoto-u.ac.jp Internet Source	<1 %
32	research.vu.nl Internet Source	<1 %
33	www.science.gov Internet Source	<1 %
34	Raffaella Mormile. "Obstructive sleep apnea and susceptibility to sudden cardiac death: A single player for both conditions?", Cardiovascular Pathology, 2020 Publication	<1 %
35	Submitted to Universitas Airlangga Student Paper	<1 %
36	ccforum.biomedcentral.com Internet Source	<1 %

37	coek.info Internet Source	<1 %
38	journals.biologists.com Internet Source	<1 %
39	link.springer.com Internet Source	<1 %
40	mafiadoc.com Internet Source	<1 %
41	"Essential Tuberculosis", Springer Science and Business Media LLC, 2021 Publication	<1 %
42	G. B. Migliori, C. Lange, R. Centis, G. Sotgiu et al. "Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases", European Respiratory Journal, 2008 Publication	<1 %
43	Kerry Atkinson, David Mabey. "Revolutionizing Tropical Medicine", Wiley, 2019 Publication	<1 %
44	Linda Ferrante, Siri H. Opdal, Ståle Nygård, Åshild Vege, Torleiv O. Rognum. "Gene expression profile in cases of infectious death in infancy", Pediatric Research, 2020 Publication	<1 %

45	Sally Mahdiani, Lina Lasminingrum, Bambang Purwanto, Riri Handayani. "Canal wall down in tuberculosis matoiditis: 4 case series", International Journal of Surgery Case Reports, 2021 Publication	<1 %
46	Www.rcpe.ac.uk Internet Source	<1 %
47	bmcinfectdis.biomedcentral.com Internet Source	<1 %
48	clinicaltrial.gov Internet Source	<1 %
49	jonuns.com Internet Source	<1 %
50	profiles.uonbi.ac.ke Internet Source	<1 %
51	researchspace.ukzn.ac.za Internet Source	<1 %
52	tohoku.repo.nii.ac.jp Internet Source	<1 %
53	www.aidsdatahub.org Internet Source	<1 %
54	www.ashp.org Internet Source	<1 %

55	www.frontiersin.org Internet Source	<1%
56	Priyanka Anand, Jacob J. Mayfield, Beixin He, Kavita B. Khaira. "Unusual T-wave Changes and Extreme QTc Prolongation in a 71-year-old man with Asymptomatic COVID Infection", HeartRhythm Case Reports, 2021 Publication	<1%
57	Sandip V. Barvaliya, Mira K. Desai, Jigar R. Panchal, Rajesh N. Solanki. "Early treatment outcome of bedaquiline plus optimised background regimen in drug resistant tuberculosis patients", Indian Journal of Tuberculosis, 2020 Publication	<1%
58	doi.org Internet Source	<1%
59	dspace5.zcu.cz Internet Source	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

Correlation of inflammaroty cytokines on corrected QT interval in rifampicin-resistant tuberculosis patients

GRADEMARK REPORT

FINAL GRADE

/100

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6