ORIGINAL ARTICLE

Effect of Different Levofloxacin Doses on QTc Interval Prolongation in Multidrug-Resistant Tuberculosis Patients Treated with the 9-Month All-Oral Regimen

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ABSTRACT

Introduction: The World Health Organization (WHO) has recommended the 9-month all-oral regimen for multidrug-resistant tuberculosis (MDR-TB) treatment. This regimen is expected to increase the treatment success rate. Bedaquiline, levofloxacin, and clofazimine are QT-prolonging drugs included in the 9-month all-oral regimen. Bedaquiline and clofazimine are given at the same dose for all patients, while levofloxacine dose is given in 750 mg and 1,000 mg based on the body weight. This study analyzed the correlation between different levofloxacin doses and certain factors on QTc interval prolongation.
Methods: This observational retrospective study used the medical records of MDR-TB patients who underwent the 9-month all-oral regimen. Electrocardiography (ECG) for QTc interval measurement was recorded at the baseline before and 2 weeks after treatment. The measured variables included patient demographic data, body mass index (BMI), electrolyte levels, and comorbidities.
Results: Thirty MDR-TB patients were included in this study. Gender, diabetes mellitus (DM), and levofloxacin dose did not correlate with QTc interval prolongation at 2 weeks after drug administration (p-values of 0.558, 0.197, and 0.134, respectively). Age, potassium level, magnesium level, calcium level, and baseline QTc interval also did not correlate with QTc interval prolongation at 2 weeks after drug administration (p-values of 0.433, 0.479, 0.705, 0.746, and 0.333, respectively). Multivariate analysis showed that the risk factor associated with QTc interval prolongation at 2 weeks after drug administration was a BMI of 0.013.
Conclusion: Different levofloxacin doses did not correlate with QTc interval prolongation in MDR-TB patients treated with the 9-month all-oral regimen. The incidence of QTc interval prolongation was significantly associated with the lower BMI level.

INTRODUCTION

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB) is a global health problem and has caused 10.6 million cases and 1.3 million deaths of TB.[1] The emergence of resistance to anti-TB drugs (ATDs) has become a barrier to global TB elimination efforts.[2,3] Multidrug-resistant TB (MDR-TB) caused by MTB that is resistant to isoniazid (INH) and rifampicin (RIF) (the two most effective first-line ATDs) requires treatment with second-line drugs. Globally, an estimated 410,000 people developed MDR-TB in 2022, with treatment

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success rates for patients with MDR-TB are 63%. Of an estimated 31,000 MDR-TB cases in Indonesia in 2022, the treatment success rate was 52%.[1] The treatment of MDR-TB is challenging as its long duration using different combinations of 2nd-line ATDs has higher cost, more adverse reactions, and more lost-to-follow-up cases.[4,5] It is essential to find a shorter regimen that is more effective and with lower costs for DR-TB treatments.[5]

Many studies have been conducted to find regimens with good efficacy and safety profiles. In 2022, the World Health Organization (WHO) started recommending the 9-month all-oral regimen for MDR-TB treatment.[6] This 9-month all-oral regimen consists of bedaquiline, levofloxacin, ethionamide, ethambutol, INH, pyrazinamide, and clofazimine and is expected to increase the success rate of MDR-TB treatment. However, bedaquiline, levofloxacin, and clofazimine are QT-prolonging drugs. Bedaquiline and clofazimine are given at the same dose, while levofloxacin is given in 750 mg and 1,000 mg based on body weight.[5,6] The different levofloxacin doses raise concern about its adverse effect on QT interval prolongation, especially in MDR-TB patients with higher doses of levofloxacin.

Levofloxacin is a second-generation fluoroquinolone antibiotic with beneficial properties, including high bioavailability and broad-spectrum activity. However, it may also adversely prolong the QTc interval.[7,8] Interval QT prolongation is a serious adverse effect that increases the risk for cardiac arrhythmias such as Torsade de Pointes (TdP) and leads to sudden cardiac death. The adverse impact of QT interval prolongation may cause treatment interruption, reduce treatment adherence, and be associated with morbidity and mortality.[5,9,10] The European Society of Cardiology (ESC) classified a QT interval >500 ms as the mark for the diagnosis of long QT syndrome (LQTS) in asymptomatic patients. Above this level, the risk of arrhythmia and TdP was higher.[11] This interference with cardiac rhythm can be fatal, potentially leading to cardiac arrest, increased hospital length of stay, and mortality.[12]

Acquired LQTS is more prevalent and especially caused by QT-prolonging drugs. Certain individual risk factors may also increase this risk.[11] Drug-induced long QT is the most common and preventable cause of QT interval prolongation.[13] Higher doses cause drug-induced QT prolongation, which causes excessive drug concentration in the blood serum. However, the dose or drug concentration is not always the cause. Gender, older age, bradycardia, electrolyte disturbance, heart failure, and so on are risk factors.[14] The evidence showed that drug-induced QTc interval prolongation occurred with at least one risk factor, and there were risk factors in 70% of cases.[15]

QTc interval prolongation in MDR-TB patients on the 9-month all-oral regimen is rarely reported.[4,16] The concentration of quinolone (moxifloxacin) did not correlate with QTc interval in a previous study.[9] A study about QTc interval prolongation in MDR-TB patients on the 9-month all-oral regimen is essential, especially in the concomitant administration of QT-prolonging drugs with different levofloxacin doses as the components in the 9-month all-oral regimen. This is important to prevent adverse effects of QTc interval prolongation, reduce the risk of drug interruption, reduce MDR-TB morbidity and mortality, and also increase the treatment success of MDR-TB. This study evaluated the correlation of different levofloxacin doses and certain factors on QTc interval prolongation in MDR-TB patients treated with the 9-month all-oral regimen.

METHODS

An observational retrospective study was conducted in Dr. Soetomo General Academic Hospital, a tertiary hospital in Indonesia, from January to December 2022 using the data from the medical records. MDR-TB patients who received the 9-month all-oral regimen with complete medical records were included in this study. Patients who were under treatment with additional QT-prolonging drugs and with unregulated DM were excluded from this study. The data from the medical records included patient demographic data (age, sex), body mass index/BMI (weight, height), electrolyte levels (potassium, magnesium, and calcium), and clinical characteristics (comorbidities). The 9-month all-oral regimen consists of bedaquiline (used for six months) in combination with levofloxacin, ethionamide, ethambutol, INH (high-dose), pyrazinamide, and clofazimine for four months, followed by five months of treatment with levofloxacin, clofazimine, ethambutol, and pyrazinamide. Levofloxacin doses were based on body weight: 750 mg for a body weight of 30-45 kg and 1,000 mg for a body weight of over 46 kg.[5,6]

Electrocardiography (ECG) for QTc interval measurement was recorded at the baseline before and two weeks after treatment. Collected data from medical records were entered and analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) for all statistical analysis. Statistical analysis with a p-value <0.05 was considered statistically significant. This study was approved by the ethics committee with ethical clearance number 1795/KEPK/I/2020.

RESULTS

Of the 54 MDR-TB patients who underwent treatment with the 9-month all-oral regimen, 30 MDR-TB patients with a mean age of 46.37 years old were included in this study according to the inclusion and exclusion criteria. These study subjects consisted of eight men and 22 women. Well-controlled diabetes mellitus (DM) was found in 13 (43.3%) patients. Levofloxacine dose, one of the components in the 9-month all-oral regimen for MDR-TB treatment, was given in 750 mg and 1,000 mg based on body weight. In this study, six (20%) patients received levofloxacin 750 mg, and 24 (80%) patients received levofloxacin 1000 mg. This is presented in Table 1.

Table 1. Characteristics of study subjects

	Total (n = 30)
Age (years old)	
Mean ± SD (min-max)	46.37 ± 13.44 (15-69)
Gender	
Men	8 (26.7%)
Women	22 (73.3%)
Diabetes mellitus type 2	13 (43.3%)
Hypertension	3 (10%)
BMI level (kg/m^2)	
Mean ± SD (min-max)	24.64 ± 6.03 (16.2-36.8)
Potassium level	
Mean ± SD (min-max)	4.1 ± 0.54 (3-5.2)
Magnesium (Mg)	
Mean ± SD (min-max)	1.987 ± 0.164 (1.7-2.3)
Calcium (Ca)	
Mean ± SD (min-max)	8.7 ± 0.428 (8-9.6)
Baseline QTc interval (ms)	
Mean ± SD (min-max)	410.93 ± 37.85 (320-467)
Levofloxacin dose	
750 mg	6 (20%)
1,000 mg	24 (80%)
QTc interval at 2 weeks after the drug was administered	
Mean ± SD (min-max)	418 ± 37.8 (334-472)

BMI: body mass index, ms: mili seconds, SD: standard deviation

The results of the correlation analysis in Table 2 show that gender did not correlate with the QTc interval at two weeks after drug administration (p = 0.558). DM, hypertension, and levofloxacin dose also did not correlate with the QTc interval two weeks after drug administration (p-values of 0.197, 0.888, and 0.134, respectively).

Table 2. Correlation of gender, diabetes mellitus, hypertension, and levofloxacin dose on QTc interval at two weeks after drug administration

	QTc Interval at Two Weeks after Drug Administration (ms)	p
Gender*[a]		0.558
Men	416 (334-464)	
Women	438 (358-472)	
Diabetes mellitus**[b]		0.197
Yes	428.31 ± 33.37	
No	410.12 ± 40.03	
Hypertension**[b]		0.888
Yes	415 ± 49.66	
No	418.33 ± 37.45	
Levofloxacin dose**[b]		0.134
750 mg	438.83 ± 29.05	
1000 mg	412.79 ± 38.43	

*: Mann-Whitney test, **: t-test, a: median (min-max), b: mean ± standard deviation

This study found that BMI level significantly correlated with QTc interval two weeks after drug administration (p = 0.021). Age, potassium level, magnesium level, calcium level, and baseline QTc interval did not correlate with QTc interval two weeks after the drug administration with p-values of 0.433, 0.479, 0.705, 0.746, and 0.333, respectively. This is presented in Table 3. The baseline QTc interval for all patients was found to be within the normal range before the initiation of the 9-month all-oral regimen.

Table 3. Correlation of age, body mass index, potassium, magnesium, calcium, and baseline QTc interval on QTc interval at two weeks after drug administration

	QTc Interval at Two Weeks after Drug Administration	
	r	p
Age*	0.149	0.433
BMI level*	-0.418	0.021
Potassium level**	-0.134	0.479
Magnesium level**	-0.072	0.705
Calcium level**	-0.062	0.746
Baseline QTc interval*	-0.183	0.333

BMI: body mass index, r: correlation coefficient, p: sig. (2-tailed), *: Spearman test, **: Pearson test

Multivariate analysis results show that the variable correlated with QTc interval two weeks after drug administration was BMI level p = 0.013. Analysis was performed using multiple linear regression (dependent variable was normal distribution) with the

backward elimination method. The results indicated a negative coefficient of -2.819 (Table 4), which showed a negative relationship between BMI and QTc interval. This means the higher the BMI, the lower the QTc interval two weeks after drug administration, and vice versa. For example, if BMI increases by 1 unit, the QTc interval at two weeks after drug administration is expected to decrease by 2.819 units. The R Square value of 0.203 suggested that approximately 20.3% of the variability in the QTc interval can be explained by the BMI level in this model. The remaining 79.7% of the variability in the QTc interval may be explained by other variables not included in the model.

Table 4. Multivariate of body mass index on QTc interval at two weeks after drug administration

	Unstandardized Coefficients B	Sig	R. Square
BMI level	-2.819	0.013	0.203

BMI: body mass index, B: unstandardized coefficients, p: sig. (2-tailed), R. Square: coefficient of determination

DISCUSSION

This study showed that gender, DM, and hypertension did not correlate with QTc interval two weeks after drug administration (p-values of 0.558, 0.197, and 0.888, respectively). Previous studies reported different results. QT interval prolongation and TdP were more commonly found in women than men.[14,17] Women are one of the risk factors for QTc interval prolongation.[14,17] The factor that might contribute is a difference in sex hormones, which affects cardiac repolarization by regulating ion channels in heart cells. Testosterone in men can shorten the QTc interval, while estrogen is suspected to cause QTc prolongation.[17,18]

In this study, DM was not correlated with QTc interval two weeks after drug administration. This was because all MDR-TB patients with DM were regulated by routine medication to control blood glucose levels. A previous study reported that DM was known to increase the risk of QTc interval prolongation, especially in patients with uncontrolled DM.[19,20] In a previous study, QTc interval prolongation was higher in patients with DM, specifically caused by hyperglycemia and chronic changes in the myocardium.[21]

This study found that levofloxacin dose did not correlate with QTc interval two weeks after drug administration (p = 0.134). A previous study also reported no correlation between levofloxacin and QTc interval prolongation.[22] Other risk factors may play a role.[22] Drug-induced QT interval prolongation typically occurred when there was at least one additional risk factor besides drug exposure.[18]

This study found that BMI level was significantly correlated with QTc interval at two weeks after drug administration (p = 0.013) and indicated a negative relationship (B = -2.819). A low BMI level (underweight, BMI <18.5) can cause decreased left ventricular mass, cardiac chamber dimensions, cardiac conduction and repolarization changes, and arrhythmias. Malnourished patients may also experience QTc interval prolongation along with electrolyte disturbances.[23,24] Cardiovascular disorders are often improved when dietary habits are corrected and nutritional status is restored.[25]

In this study, the baseline QTc interval was not correlated with the QTc interval two weeks after drug administration (p = 0.333). The baseline QTc of all participants was within the normal limit. A previous study reported a different correlation between the baseline QTc interval and the start time of QTc prolongation.[16,26] Patients with a longer baseline QTc will significantly likely develop into prolonged QTc. Some studies reported serum electrolyte disturbances as the risk factor for QTc interval prolongation.[27,28] QT interval prolongation is often caused by a disturbance in the various cardiac ion channels, including the potassium, magnesium, and calcium channels.[29–31]

This study found that potassium, magnesium, and calcium levels did not correlate with the QTc interval two weeks after drug administration, with p-values of 0.479, 0.705, and 0.746, respectively. This was insignificant because participants had normal potassium, magnesium, and calcium levels. Other studies showed that QT prolongation is caused by electrolyte disturbances (hypokalemia, hypomagnesemia, and hypocalcemia).[32] In conditions of hypokalemia (potassium levels become lower than 3.5 mmol/L), heart cells experience hyperpolarization with a decrease in muscle contractions, heart rate, and blood pressure.[33] Calcium has diverse roles in neuromuscular mechanisms. In the cardiovascular system, hypocalcemia is known to impair myocardial contractility and prolong the QT interval, predisposing to ventricular arrhythmias.[31] It is important to monitor potassium, magnesium, and calcium concentrations in all patients receiving drugs that can prolong the QT interval.

The QTc interval increases with age, and age-related electrophysiological and structural changes may increase the risk of arrhythmia.[34] Another study in DR-TB patients reported that older age was correlated with QT interval prolongation.[35] This study found that age did not correlate with QTc interval at two weeks after drug administration (p-value = 0.433) because the mean

age of this study subjects was 46.37 years old (<65 years old). A previous study reported that ventricular arrhythmias were found to be higher in the elderly (>65 years old) with the use of QT-prolonging drugs.[36]

The limitations of this study include measuring the QTc interval only at two weeks post-drug administration without evaluating the concentrations of all medications in the 9-month all-oral regimen. Additionally, after two weeks of treatment, electrolytes were not re-measured during the repeat ECG examination. The study also had a limited sample size, which may not represent the entire MDR-TB patient population and could affect the generalizability of the findings.

CONCLUSION

QTc interval prolongation after two weeks of treatment with a 9-month all-oral regimen did not reach the level that causes pathology or LQTS. Different levofloxacin doses did not correlate with QTc interval in MDR-TB patients treated with the 9-month all-oral regimen. Age, normal baseline QT, and participants with normal serum electrolytes (potassium, magnesium, and calcium) did not correlate with QT prolongation in this study. Although not pathological, the occurrence of QTc interval prolongation was significantly associated with lower BMI levels. Close monitoring of the QTc interval is necessary during treatment, especially in MDR-TB patients with lower BMI levels.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Study concept and design: SS, VRCR, and YSC. Collecting data: VRCR and CA. Statistical analysis and interpretation of data: SS. Critical revision of the manuscript for important intellectual content: SS.

REFERENCES

1. World Health Organization (WHO). *Global Tuberculosis Report 2023*. Geneva, https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023 (2023).
2. Soedarsono S, Mertaniasih NM, Kusmiati T, *et al*. Determinant Factors for Loss to Follow-Up in Drug-Resistant Tuberculosis Patients: The Importance of Psycho-Social and Economic Aspects. *BMC Pulm Med* 2021; 21: 360. [PubMed]
3. Tabernero P, Newton PN. Estimating the Prevalence of Poor-Quality Anti-TB Medicines: A Neglected Risk for Global TB Control and Resistance. *BMJ Glob Heal*; 8. Epub ahead of print July 2023. [PubMed]
4. 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 Forensic Med Toxicol* 2020; 15: 1576–1582. [Journal]
5. World Health Organization (WHO). *WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment, 2022 Update*. Geneva, https://www.who.int/publications/i/item/9789240063129 (2022).
6. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit (P2P). *Petunjuk Teknis Penatalaksanaan Tuberkulosis Resistan Obat di Indonesia*. Jakarta, https://tbindonesia.or.id/wp-content/uploads/2021/06/TBRO_Buku-Juknis-Tuberkulosis-2020-Website.pdf (2020).
7. Catelya LG, Tjahjono CT, Hanafi A. Levofloxacin and Drug-Induced Long QT Syndrome (diLQTS): The Incidence and How to Prevent It. *IOP Conf Ser Earth Environ Sci* 2020; 441: 12190. [Journal]
8. Choi E, Beom J, Ahn H, *et al.* Incidence and Risk Factors for QT Prolongation Associated with Fluoroquinolones. *J Korean Soc Heal Pharm* 2023; 40: 195–210. [Journal]
9. Kusmiati T, Mertaniasih NM, Putranto JNE, *et al*. Moxifloxacin Concentration Correlate with QTc Interval in Rifampicin-Resistant Tuberculosis Patients on Shorter Treatment Regimens. *J Clin Tuberc Other Mycobact Dis* 2022; 28: 100320. [PubMed]
10. Kusmiati T, Mertaniasih NM, Putranto JNE, *et al*. Correlation of Moxifloxacin Concentration, C-Reactive Protein, and Inflammatory Cytokines on QTc Interval in Rifampicin-Resistant Tuberculosis Patients Treated with Shorter Regimens. *Acta Med Indones* 2022; 54: 19–27. [PubMed]
11. Parsons G. Mechanisms and Management of Drug-Induced QT Prolongation. *Prescriber* 2022; 33: 19–23. [Journal]
12. Primadana V, Yovi I, Estiningsih DS. Bedaquiline Correlation to QT Interval Prolongation in DR-TB Patients. *J Respirasi* 2022; 8: 140–146. [Journal]

13. Tiver KD, Dharmaprani D, Quah JX, *et al*. Vomiting, Electrolyte Disturbance, and Medications; The Perfect Storm for Acquired Long QT Syndrome and Cardiac Arrest: A Case Report. *J Med Case Rep* 2022; 16: 9. [PubMed]
14. Uchikawa M, Hashiguchi M, Shiga T. Drug-Induced QT Prolongation and Torsade de Pointes in Spontaneous Adverse Event Reporting: A Retrospective Analysis Using the Japanese Adverse Drug Event Report Database (2004-2021). *Drugs - Real World Outcomes* 2022; 9: 551–559. [PubMed]
15. United States Agency for International Development (USAID). *Guide for QTc Monitoring and Management of Drug-Resistant TB Patients with QT-Prolonging Agents*. Washington, D.C., https://www.tbdiah.org/wp-content/uploads/2020/07/Guidance_on_ECG_monitoring_in_NDR_v2-1.pdf (2018).
16. Kusmiati T, Suci YD, Soedarsono. QTc Interval Prolongation in Drug Resistant-Tuberculosis Patients Treated with Shorter Treatment Regimen. *Med Leg Updat* 2021; 21: 1208–1215. [Journal]
17. Prajapati C, Koivumäki J, Pekkanen-Mattila M, *et al*. Sex Differences in Heart: From Basics to Clinics. *Eur J Med Res* 2022; 27: 241. [PubMed]
18. Akturk G, Kalkan S. Drug-Induced QT Interval Prolongation: Mechanisms, Risk Factors, Genetics and Clinical Management. *J Basic Clin Heal Sci*. Epub ahead of print 1 September 2019. [Journal]
19. Lin N, Zhang H, Li X, *et al*. The Influence of Different Glucose Tolerance on QTc Interval: A Population-Based Study. *BMC Cardiovasc Disord* 2023; 23: 47. [PubMed]
20. Taubel J, Pimenta D, Cole ST, *et al*. Effect of Hyperglycaemia in Combination with Moxifloxacin on Cardiac Repolarization in Male and Female Patients with Type I Diabetes. *Clin Res Cardiol* 2022; 111: 1147–1160. [PubMed]
21. Aburisheh K, AlKheraiji MF, Alwalan SI, *et al*. Prevalence of QT Prolongation and Its Risk Factors in Patients with Type 2 Diabetes. *BMC Endocr Disord* 2023; 23: 50. [PubMed]
22. Isralls S, Baisley K, Ngam E, *et al*. QT Interval Prolongation in People Treated with Bedaquiline for Drug-Resistant Tuberculosis under Programmatic Conditions: A Retrospective Cohort Study. *Open Forum Infect Dis* 2021; 8: ofab413. [PubMed]
23. Kusmiati T, Mertaniasih NM, Putranto JNE, *et al*. Factors that Contribute to the QTc Interval Prolongation in DR-TB Patients on STR Regimen. *Indian J Forensic Med Toxicol* 2020; 15: 1605–1612. [Journal]
24. Pueringer J, Cinderella J, Treuth MG. A Case of Profound Bradycardia in Endurance Athlete with Severe Anorexia Nervosa. *Case Reports in Cardiology* 2022; 2022: 6589758. [PubMed]
25. Friars D, Walsh O, McNicholas F. Assessment and Management of Cardiovascular Complications in Eating Disorders. *J Eat Disord* 2023; 11: 13. [PubMed]
26. Khan F, Ismail M, Khan Q, *et al*. Moxifloxacin-Induced QT Interval Prolongation and Torsades de Pointes: A Narrative Review. *Expert Opin Drug Saf* 2018; 17: 1029–1039. [PubMed]
27. TeBay C, Hill AP, Windley MJ. Metabolic and Electrolyte Abnormalities as Risk Factors in Drug-Induced Long QT Syndrome. *Biophys Rev* 2022; 14: 353–367. [PubMed]
28. Li J, Yang G, Cai Q, *et al*. Safety, Efficacy, and Serum Concentration Monitoring of Bedaquiline in Chinese Patients with Multidrug-Resistant Tuberculosis. *Int J Infect Dis* 2021; 110: 179–186. [PubMed]
29. Yao Y, Xue J, Li B. Obesity and Sudden Cardiac Death: Prevalence, Pathogenesis, Prevention and Intervention. *Front Cell Dev Biol* 2022; 10: 1044923. [PubMed]
30. Kumar M, Perucki W, Hiendlmayr B, *et al*. The Association of Serum Magnesium Levels and QT Interval with Neurological Outcomes after Targeted Temperature Management. *Ther Hypothermia Temp Manag* 2022; 12: 210–214. [PubMed]
31. Avci BS, Avci A, Aksu A, *et al*. QTc, Tp-e Interval and Tp-e/QTc Ratio in Patients with Hypocalcemia-Case Control Study. *Int J Cardiovasc Sci* 2021; 34: 87–94. [Journal]
32. Al-Akchar M, Siddique MS. Long QT Syndrome. Treasure Island (FL), 2024. [PubMed]
33. Teymouri N, Mesbah S, Navabian SMH, *et al*. ECG Frequency Changes in Potassium Disorders: A Narrative Review. *Am J Cardiovasc Dis* 2022; 12: 112–124. [PubMed]
34. Guettler N, Rajappan K, Nicol E. The Impact of Age on Long QT Syndrome. *Aging* 2019; 11: 11795–11796. [PubMed]
35. Brust J, Gandhi N, Wasserman S, *et al*. Effectiveness and Cardiac Safety of Bedaquiline-Based Therapy for Drug-Resistant Tuberculosis: A Prospective Cohort Study. *Clin Infect Dis*; 73. Epub ahead of print 21 April 2021. [PubMed]
36. Khatib R, Sabir FRN, Omari C, *et al*. Managing Drug-Induced QT Prolongation in Clinical Practice. *Postgrad Med J* 2021; 97: 452–458. [PubMed]