Disease activity is associated with QTc interval in patients with rheumatoid arthritis: Insights from the KURAMA study

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Abstract

Background: Corrected QT (QTc) prolongation is a frequently observed ECG abnormality in patients with rheumatoid arthritis (RA). **Objectives:** We aimed to investigate the association between disease activity and QTc interval in patients with RA. **Methods:** Data were obtained from the Kyoto University Rheumatoid Arthritis Management Alliance population-based RA cohort. We used a linear model to compare the association between QTc interval and RA-related parameters, including patient characteristics and disease activity assessed using the visual analog scale, C-reactive protein level, erythrocyte sedimentation rate (ESR), disease activity score 28-joint count using erythrocyte sedimentation rate (DAS28-ESR), simplified disease activity index (SDAI), clinical disease activity index (CDAI), and health assessment questionnaire (HAQ) score. We also constructed multivariate linear regression models to adjust for confounding effects. **Results:** The mean QTc interval of 340 patients (mean age: 64.7 ± 12.3 years, female: 289 [85%]) with ECG data was 420.0 ± 18.4, and the mean disease activity indices were: DAS28-ESR, 2.7 ± 1.1 points; CDAI, 5.0 ± 5.2 points; SDAI, 5.4 ± 5.7 points; and HAQ, 0.61 ± 0.71 points. Linear correlations were observed between the QTc interval and all parameters for disease activity in the univariate analysis. The three multivariate linear regression models using age, sex, HAQ score, and disease activity indices (CDAI, SDAI, or DAS28-ESR) were significantly associated with the QTc interval (P = 0.0002, 0.0002, 0.0004, respectively). **Conclusions:** Disease activity is significantly associated with the QTc interval in patients with RA. Attention should be given to ECG abnormalities in patients with RA and progressive disease activity.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation, which mainly affects the peripheral joints with symmetric distribution[1]. Cardiovascular diseases (CVDs) are some of the leading causes of death in patients with RA[2]. In fact, the risk of sudden cardiac death was doubled in patients with RA compared to those without RA[3,4]. Pathological findings in cardiovascular examinations are frequently observed during the course of RA and are important factors that contribute to mortality[2,3]. Several studies have reported that patients with RA have a higher risk of developing atherosclerosis and cardiac arrhythmias[5,6]. RA is not only involved in the development of CVDs but also accelerates disease progression. Clinical and pathological evidence suggest that RA may be associated with chronic inflammation and immune dysregulation during the disease course[7,8].

Electrocardiography (ECG) changes have been reported in patients with RA and other autoimmune diseases. For example, ST-T abnormalities have been observed in patients with systemic lupus erythematosus (SLE), and corrected QT (QTc) prolongation was observed in patients with RA and SLE[9]. Although the mechanisms for such changes have not been elucidated, it is suggested that systemic inflammation may directly result

in electrophysiological changes or indirectly result in structural changes of the heart; these changes are associated with arrhythmias and/or worse cardiovascular outcomes in both the general population and RA patients[5].

In this study, we aimed to investigate the ECG characteristics of patients with RA and the association between QTc interval and disease activity in these patients using a Japanese population-based RA cohort, the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) study.

2. Methods

2.1 Study Population

The design and methods of the KURAMA cohort study have been described previously[10]. Briefly, consecutive patients with RA were recruited from April 1, 2011, and the diagnosis was confirmed using the revised 1987 American College of Rheumatology (ACR) criteria for RA or the 2010 ACR/European League Against Rheumatism classification criteria for RA at the Center for Rheumatic Diseases in Kyoto University Hospital. Among the 545 RA patients included in the KURAMA study from June 2016 to December 2016, 340 consecutive patients who had records of 12-lead ECG were included in the present study. All patients provided informed consent, and procedures were conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Kyoto University Graduate School and the Faculty of Medicine Ethics Committee (R0357).

2.2 ECG Analysis

A 12-lead electrocardiogram was recorded at a paper speed of 25 mm/s and an amplification of 10 mm/mV. For each ECG, the following parameters were recorded: heart rate, rhythm, RR interval, PR interval, QRS duration, QT interval, QTc interval, presence of QTc prolongation (QTc interval [?]450 ms for men and [?]460 ms for women)[11], premature atrial/ventricular contraction, atrial fibrillation, bradycardia, conduction disorder, and left ventricular hypertrophy. QT interval was defined as the beginning of the QRS to the end of the T wave, and QTc interval was calculated using Bazett's formula[12]. Left ventricular hypertrophy was assessed using the Socolow–Lyon criteria[13]. All electrocardiograms were examined by two cardiologists (T.A. and X.S.) who were blinded to all other clinical data.

2.3 Assessment of Clinical Data

The patients' baseline characteristics were assessed by physicians and recorded by clinical research assistants. Hypertension was diagnosed if patients had a blood pressure of >140/90 mmHg on [?]2 occasions or were already on antihypertensive therapy. Diabetes was diagnosed based on the classification of diabetes mellitus by an expert committee. Dyslipidemia was diagnosed in patients with a history of total cholesterol >240 mg/dL or those who received lipid-lowering medication.

Parameters related to RA disease activity were also collected, including swollen joint count based on the assessment of 28 joints (SJC28), tender joint count based on assessment of 28 joints (TJC28), the presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA), C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), Health Assessment Questionnaire (HAQ) disability index score, and the patient's assessment of pain measured using a 100-mm visual analog scale (VAS).

Disease activity of RA was evaluated with the disease activity score 28-joint count using erythrocyte sedimentation rate (DAS28-ESR), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and physical disability by the HAQ index. SDAI, CDAI, and DAS28-ESR were calculated using the following formulas: SDAI = SJC28 + TJC28 + (VAS by patient) + (VAS by clinician) + CRP; CDAI = SJC28 + TJC28 + (VAS by patient) + (VAS by clinician); DAS28-ESR = 0.56 × [?](TJC) + 0.28 x [?](SJC) + 0.7 x ln(ESR) + 0.014 x (VAS)[14].

The DAS28-ESR disease activity of RA was defined as DAS28-ESR <2.6 for remission, <3.2 for low disease activity, [?]5.1 for moderate disease activity, and >5.1 for high disease activity. SDAI disease activity was defined as SDAI <3.3 for remission, <11 for low disease activity, [?]26 for moderate disease activity, and >26

for high disease activity. CDAI disease activity was defined as CDAI <2.8 for remission, <10 for low disease activity, [?]22 for moderate disease activity, and >22 for high disease activity. With regard to treatment, the use of prednisolone, disease-modifying anti-rheumatic drugs (DMARDs), methotrexate, and biologic agents were collected.

2.4 Statistical Analysis

Continuous data are expressed as mean +- SD, and categorical data are expressed as numbers and percentages. We examined the relationship between QTc interval and patient characteristics and RA disease activity using Student's t-test for normally distributed data or Wilcoxon rank-sum test for non-normally distributed data. In addition, we assessed the association between QTc interval and RA medication using the Wilcoxon rank-sum test to investigate the effects of medications on the QTc interval.

Univariate associations between the QTc interval and clinical variables were assessed using Pearson or Spearman correlations based on the distribution of variables. Multigroup comparisons were performed using the analysis of variance, and further between-group comparisons were performed using Tukey's test.

Variables significantly associated with the QTc interval were used as potential independent variables in a multivariate linear regression model. We also included each patient's age and sex because these parameters were reported to be associated with the QT interval[11,12]. We developed multivariate linear regression models using these potential and predetermined covariates. In this study, statistical significance was determined by $p < 0.05$. Data were analyzed using JMP 15.0 (Statistical Analysis System, Institute Inc., NC, USA).

3. Results

The clinical and ECG characteristics of the patients with RA are summarized in Table 1. The mean age of the patients was 64.7 +- 12.3, and the majority were female (289 patients, 85.0%). The mean body mass index (BMI) was 22.4 +- 3.8 kg/m^2. Hypertension, diabetes, dyslipidemia, and current smokers were found in 126 (37.1%), 32 (9.4%), 133 (39.1%), and 116 (34.1%) patients, respectively.

The median duration of RA was 3,563 days (25th to 75th percentile: 1,733–7,547 days). The majority of patients with RA were RF-positive (75.0%) and ACPA-positive (77.9%). The VAS, CDAI, SDAI, DAS28-ESR, DAS28-CRP, and HAQ scores are provided in Table 1. Patient VAS scores were significantly higher than clinician VAS scores (24.5 +- 23.4 vs. 8.7 +- 11.5, $p < 0.0001$). In the laboratory data, the mean ESR and CRP level of the included patients were 20.6 +- 17.2 mm/h and 0.44 +- 1.06 mg/L, respectively. DMARDs were used by 90.0% of the patients, while 68.2% received methotrexate (MTX), 54.7% received biologic agents, 26.1% received prednisolone treatment, and 36.2% received more than two types of RA drugs (Table 1). Patients receiving prednisolone treatment showed a longer QTc interval than that of patients not receiving prednisolone treatment (424.2 +- 20.4 ms vs. 418.5 +- 17.4 ms, $p = 0.014$). No difference in the QTc interval was observed between those with and without MTX or biologic agent treatments (Supplementary material).

3.1 ECG Characteristics

Through direct ECG review, the mean heart rate was 68.0 +- 10.9 bpm, and the QTc interval was 420.0 +- 18.4 ms. There were 14 patients (4.1%) with QT prolongation (Table 1). Sinus tachycardia was found in 4 of the 340 patients with RA (1.1%), and sinus bradycardia was found in 80 patients (23.5%). At baseline, 31 patients (9.1%) had conduction disorders. Arrhythmia was found in 63 patients (18.5%), with 37 having premature atrial contractions, 19 having premature ventricular contractions, 5 having both, and 2 having atrial fibrillation.

3.2 Factors Associated with QTc Interval

Results showed significantly different QTc intervals between patients with and without hypertension (423.7 +- 20.3 ms vs. 418.0 +- 16.8 ms, $p = 0.011$, respectively). No significant difference was observed between the QTc intervals between patients with and without diabetes, or male and female (Fig. 1). In addition,

significantly longer QTc intervals were observed in patients with higher disease activity scores as assessed by SDAI, CDAI, DAS28-ESR, and DAS28-CRP (all p values <0.001, compared by ANOVA, see Fig. 2).

In the univariate linear correlation analysis, age, heart rate, VAS score, CDAI, SDAI, HAQ, DAS28-ESR, and DAS28-CRP were positively associated with QTc interval (Table 2). A significant association was identified between the QTc interval and ESR ($p < 0.0001$) and CRP ($p = 0.001$). Differences in QTc interval were also observed between patients with an ESR of [?]30 and <30 (418.1 +- 17.2 ms vs. 426.7 +- 21.4 ms, $p = 0.004$), as shown in Fig. 1.

In the multivariate linear regression analysis, age, sex, HAQ, and CRP levels were included in Model 1; SDAI and DAS28-ESR were included in Models 2 and 3, respectively (Table.2). As a result, age, male sex, and CDAI were independently associated with the QTc interval in Model 1. In Model 2, age, male sex, and SDAI were independently associated with the QTc interval, and an independent association was observed between the DAS28-ESR and QTc interval in Model 3 ($p = 0.0004$).

4. Discussion

To the best of our knowledge, this is the first study to investigate and observe a significant association between the QTc interval and symptomatic indices of RA. Specifically, CDAI, SDAI, and DAS28-ESR were independently associated with the QTc interval, in addition to the associations with ESR and CRP.

Systemic inflammation is one of the important features of RA; meanwhile, inflammatory parameters are also risk factors contributing to QTc interval prolongation. Prolongation of the QTc interval is an important finding because it has been reported to be associated with cardiovascular death as a result of fatal ventricular tachycardia[15]. As demonstrated in this study, CRP and ESR levels were significantly associated with the duration of the QTc interval. Additionally, our results aligned with those of existing studies. In the cohort study by Lazzerini et al.[7], in which a significant correlation was observed between high sensitivity CRP (hsCRP) and the QTc interval, patients whose high-sensitivity CRP levels were higher than 0.5 mg/dL had a significantly prolonged QTc interval than those with lower hsCRP levels (424.3 +- 21.7 ms vs. 409.6 +- 19.9 ms, $p < 0.005$).

Our data demonstrated significant and independent associations between the symptomatic indices of RA and QTc intervals. SDAI constitutes counting of SJC28 and TJC28, VAS by patient, VAS by clinician, and CRP value. CDAI was developed to provide a simplified and comprehensive means of assessing RA activity[14,16]. The CRP level was not included in the CDAI; unlike SDAI, however, it can be calculated immediately in the absence of laboratory tests, allowing for simple and rapid disease activity assessment of RA patients during follow-up[14,17]. The association between CVDs and CDAI has also been reported previously. Cui et al. found that the presence of [?]1 CVD risk factor was independently associated with higher CDAI[18]; Fabio et al. used the Expanded Risk Score in patients with RA to evaluate the cardiovascular risks among those who underwent biological treatment[16]. As a result, they observed a significant decrease of estimated CVD risk in those with persistent CDAI [?]10. Our results indicate that RA-associated symptoms may be used as a predictor of QTc interval, which further support previous findings.

In a cohort study by Chauhan et al.[5], the incidence of QTc prolongation (defined as QTc [?]500 ms) during follow-up was significantly higher in patients with RA than in patients without RA. It has been reported that RA can directly affect cardiac electrophysiology by inflammatory cytokines during myocardial electrical instability[19,20]. Autonomic nervous system dysfunction was more prevalent in patients with RA, thus inducing sympathetic overactivation of stimulated β1-adrenergic receptors, increasing heart rate, and affecting calcium and potassium conductance. Consequently, the action potential duration and QTc interval were affected[21]. Chronic inflammation in RA can indirectly cause a series of structural changes, such as atherosclerosis, hypertrophy, necrosis, or fibrosis, and also increase the risk of coronary heart disease and heart failure[19,22,23]. Coronary atherosclerotic burden significantly increased in RA patients, and as Karpouzas et al. reported[24], more coronary plaques were found in RA patients than in matched controls. In addition, RA patients had a higher score for segment stenosis and plaque size, and the trend was independent of cardiovascular risk factors[24]. Puntmann et al.[25]compared the magnetic resonance data of RA patients

and healthy individuals and found that the RA group showed significantly increased end-diastolic volumes and reduced ejection fraction, indicating myocardial alterations in RA patients.

In terms of the medications used for RA patients in this study, prednisolone treatment was associated with a prolonged QTc interval compared with other medications; however, no difference was observed in the comparison of MTX or biologic agents. As prednisolone treatment was likely to be selected for patients with more severe systemic inflammation, it might reflect higher disease activity. As mentioned above, inflammation plays an important role in an abnormal QTc interval. Thus, medications that modulate systemic inflammation may lead to such changes[1]. In a cohort evaluated by Kobayashi et al.[6], patients receiving the IL-6 inhibitor tocilizumab showed a significant reduction in QTc interval. They also found that the CRP level was independently associated with the QTc interval.

4.1 Limitations

This study had several important limitations. First, we did not have data on additional medications unrelated to RA treatment in the study patients. Drugs not intended for RA, such as amiodarone, quinidine, and isoprenaline, may also influence the QTc interval[1,12,26], but we failed to analyze the potential influence of these drugs. In addition, all data were only obtained at baseline; therefore, we were not able to analyze the follow-up changes of medications and treatment effects due to the cross-sectional design of this study. Second, potassium and calcium channels are associated with the action potential duration, leading to changes in the QT interval[1]. However, patient laboratory data on electrolytes were not investigated in this study despite the observation of treatment effects on both systemic inflammation and QT interval. Finally, we could not analyze adverse cardiac events in the study patients. As the QTc interval has been reported to be associated with cardiovascular events, future large-scale studies are necessary to examine the relationship between the QTc interval and patient prognosis.

5. Conclusion

The disease activity indices CDAI, SDAI, and DAS-ESR28 were significantly associated with the QTc interval in patients with RA. Clinicians should pay attention to ECG findings in patients with worsening RA symptoms. Future studies are needed to examine the association between sequential changes in RA symptoms and the QTc interval.

References

[1] Lazzerini PE, Capecchi PL, Laghi-Pasini F. Systemic inflammation and arrhythmic risk: Lessons from rheumatoid arthritis. Eur Heart J 2017;38:1717-1727. https://doi.org/10.1093/eurheartj/ehw208.

[2] Shoenfeld Y, Gerli R, Doria A, Matsuura E, Cerinic MM, Ronda N, et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. Circulation 2005;112:3337-3347. https://doi.org/10.1161/CIRCULATIONAHA.104.507996.

[3] Lazzerini PE, Acampa M, Capecchi PL, Hammoud M, Maffei S, Bisogno S, et al, Association between high sensitivity C-reactive protein, heart rate variability and corrected QT interval in patients with chronic inflammatory arthritis. Eur J Intern Med 2013;24:368-374. http://doi.org/10.1016/j.ejim.2013.02.009.

[4] Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, Gabriel SE. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: A population-based cohort study. Arthritis Rheum 2005;52:402-411. https://doi.org/10.1002/art.20853.

[5] Chauhan K, Ackerman MJ, Crowson CS, Matteson EL, Gabriel SE. Population-based study of QT interval prolongation in patients with rheumatoid arthritis. Clin Exp Rheumatol 2015;33:84.

[6] Kobayashi H, Kobayashi Y, Yokoe I, Kitamura N, Nishiwaki A, Takei M, Giles JT. Heart rate–corrected qt interval duration in rheumatoid arthritis and its reduction with treatment with the interleukin 6 inhibitor tocilizumab. J Rheumatol 2018;45:1620-1627. https://doi.org/10.3899/jrheum.180065.

[7] Lazzerini PE, Capecchi PL, Laghi-Pasini F. Long QT syndrome: An emerging role for inflammation and immunity. Front Cardiovasc Med 2015;2:26. https://doi.org/10.3389/fcvm.2015.00026.

[8] Panoulas VF, Toms TE, Douglas KMJ, Sandoo A, Metsios GS, Stavropoulos-Kalinoglou A, Kitas GD. Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: An association driven by high inflammatory burden. Rheumatology (Oxford) 2014;53:131-137. https://doi.org/10.1093/rheumatology/ket338.

[9] Seferović PM, Ristić AD, Maksimović R, Simeunović DS, Ristić GG, Radovanović G, et al. Cardiac arrhythmias and conduction disturbances in autoimmune rheumatic diseases. Rheumatology (Oxford) 2006;45(suppl. 4):iv39-iv42. https://doi.org/10.1093/rheumatology/kel315.

[10] Terao C, Hashimoto M, Yamamoto K, Murakami K, Ohmura K, Nakashima R, et al. Three groups in the 28 joints for rheumatoid arthritis synovitis - Analysis using more than 17,000 assessments in the KURAMA database. PLOS ONE 2013;8:e59341. https://doi.org/10.1371/journal.pone.0059341.

[11] Rautaharju PM, Surawicz B, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. Part IV: The ST Segment, T and U waves, and the QT interval A scientific statement from the American Heart Association electrocardiography and Arrhythmias Co. J Am Coll Cardiol 2009;53:982-991. http://doi.org/10.1016/j.jacc.2008.12.014.

[12] Al-Khatib SM, LaPointe NMA, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA 2003;289:2120-2127. https://doi.org/10.1001/jama.289.16.2120.

[13] Antikainen RL, Grodzicki T, Palmer AJ, Beevers DG, Webster J, Bulpitt CJ. Department of Health and Social Security Hypertension Care Computer Project (DHCCP). Left ventricular hypertrophy determined by Sokolow–Lyon criteria: A different predictor in women than in men? J Hum Hypertens 2006;20:451-459. https://doi.org/10.1038/sj.jhh.1002006.

[14] Aletaha D, Smolen J. The simplified disease activity index (SDAI) and the clinical disease activity index (CDAI): A review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol 2005;23(suppl. 39):S100-S108.

[15] Sordillo PP, Sordillo DC, Helson L. Review: The prolonged QT interval: Role of pro-inflammatory cytokines, reactive oxygen species and the ceramide and sphingosine-1 phosphate pathways. In Vivo 2015;29:619-636.

[16] Cacciapaglia F, Fornaro M, Venerito V, Perniola S, Urso L, Iannone F. Cardiovascular risk estimation with 5 different algorithms before and after 5 years of bDMARD treatment in rheumatoid arthritis. Eur J Clin Investig 2020;50:1-8.

[17] da Mota LMH, Laurindo IMM, de Carvalho JF, dos Santos-Neto LL. Prognostic evaluation of early rheumatoid arthritis. Swiss Med Wkly 2010;140:w13100. https://doi.org/10.4414/smw.2010.13100.

[18] Cui K, Movahedi M, Bombardier C, Kuriya B. Cardiovascular risk factors are negatively associated with rheumatoid arthritis disease outcomes. Ther Adv Musculoskelet Dis 2021;13:X20981217. http://www.ncbi.nlm.nih.gov/pubmed/1759720.

[19] Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: State of the art and future perspectives. Ann Rheum Dis 2011;708-14. https://doi.org/10.1136/ard.2010.142133.

[20] Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: Mechanisms underlying premature cardiovascular events in rheumatologic conditions. Eur Heart J 2015;36:482-49c. https://doi.org/10.1093/eurheartj/ehu403.

[21] Dekkers JC, Geenen R, Godaert GL, Bijlsma JW, van Doornen LJ. Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease. Clin Exp Rheumatol 2004;22:63-70.

[22] Murphy SP, Kakkar R, McCarthy CP, Januzzi JL. Inflammation in heart failure: JACC state-of-the-art review. J Am Coll Cardiol 2020;75:1324-1340. https://doi.org/10.1016/j.jacc.2020.01.014.

[23] Tomaselli GF, Zipes DP. What causes sudden death in heart failure? Circ Res 2004;95:754-763. https://doi.org/10.1161/01.RES.0000145047.14691.db.

[24] Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis 2014;73:1797-1804. https://doi.org/10.1136/annrheumdis-2013-203617.

[25] Puntmann VO, Taylor PC, Barr A, Schnackenburg B, Jahnke C, Paetsch I. Towards understanding the phenotypes of myocardial involvement in the presence of self-limiting and sustained systemic inflammation: A magnetic resonance imaging study. Rheumatology 2009;49:528-535. https://doi.org/10.1093/rheumatology/kep426.

[26] Hii JT, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Precordial QT interval dispersion as a marker of torsade de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 1992;86:1376-1382. https://doi.org/10.1161/01.cir.86.5.1376.

Table 1. Patient characteristics

General information	
Age, yrs	64.7 ± 12.3
Females, n (%)	289 (85%)
BMI, kg/m^2	22.4 ± 3.8
Hypertension, n (%)	126 (37.1%)
Diabetes mellitus, n (%)	32 (9.4%)
Dyslipidemia, n (%)	133 (39.1%)
Smoking, n (%)	116 (34.1%)
Inflammatory markers	
ESR, mm/h	20.6 ± 17.2
CRP, mg/dL	0.44 ± 1.06
RA characteristics	
Duration of RA, days	3,563 [1,733–7,547]
RF-positive, n (%)	255 (75.0%)
ACPA-positive, n (%)	265 (77.9%)
Patient VAS	24.5 ± 23.4
Clinician VAS	8.7 ± 11.5
SJC-28	0.71 ± 1.42
TJC-28	0.93 ± 1.96
DAS28-ESR	2.7 ± 1.1
DAS28-CRP	2.3 ± 0.9
CDAI	5.0 ± 5.2
SDAI	5.4 ± 5.7
HAQ	0.61 ± 0.71
Medication use, n (%)	
DMARDs	306 (90.0%)
Biologic agents	186 (54.7%)
Prednisolone	89 (26.1%)
Methotrexate	232 (68.2%)
RA drugs [?]2	123 (36.2%)
ECG characteristics	
HR, bpm	68.0 ± 10.9
RR interval, ms	896.7 ± 136.3

General information	
PR interval, ms	161.4 ± 25.2
QRS interval, ms	88.4 ± 12.1
QT interval, ms	396.0 ± 26.7
QTc interval, ms	420.0 ± 18.4
PAC, n (%)	42 (12.3%)
PVC, n (%)	24 (7.1%)
AF, n (%)	2 (0.6%)
Bradycardia, n (%)	80 (23.5%)
Conduction disorder, n (%)	31 (9.1%)
RBBB, n (%)	15 (4.4%)
LVH, n (%)	26 (7.6%)
QT prolongation, n (%)	14 (4.1%)

RA, rheumatoid arthritis; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; APCA, anti-citrullinated protein antibodies; VAS, visual analog scale; SJC, swollen joint count; TJC, tender joint count; DAS28, 28-joint count Disease Activity Score; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying antirheumatic drug; HR, heart rate; PAC, premature atrial contraction; PVC, premature ventricular contraction; AF, atrial fibrillation.

Table 2. Linear correlation and multivariate linear regression analysis of QTc interval and RA parameters

	Linear correlation		Multivariate model 1		Multivariate model 2	
	Estimated parameter	**P value**	**Estimated parameter**	**P value**	**Estimated parameter**	**P va**
Age	0.39	<0.0001	0.36	<0.0001	0.36	<0.0
Male	-	-	-0.48	0.73	-0.48	0.73
CRP	3.14	0.0010	1.26	0.21	0.42	0.69
HAQ	4.91	0.0005	-1.59	0.38	-1.59	0.38
CDAI	0.92	<0.0001	0.84	0.0002		
SDAI	0.89	<0.0001			0.84	0.000
DAS28-ESR	4.94	<0.0001				

Model1: QTc interval = 393.3 + 0.36 × Age + (-0.48) x Male + 1.26 x CRP + (-1.59) x HAQ + 0.84 x CDAI; **Model2:** QTc interval = 393.3 + 0.36 x Age + (-0.48) x Male + 0.42 x CRP + (-1.59) x HAQ + 0.84 x SDAI; **Model3:** QTc interval = 390.4 + 0.30 x Age + (-1.47) x Male + 0.60 x CRP + (-0.80) x HAQ + 4.18 x DAS28-ESR

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, visual analog scale; DAS28, 28-joint count Disease Activity Score; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; HAQ, Health Assessment Questionnaire

Figure Legends

Fig. 1 Comparison of corrected QT (QTc) interval by rheumatoid arthritis-related parameters. No association is observed between the QTc interval and sex, diabetes, or the presence of rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) (1A, 1B, 1D, and 1E); Patients with hypertension or an erythrocyte sedimentation rate (ESR) higher than 30 mm/h have longer QTc intervals (1C and 1F).

Fig. 2 Comparison of corrected QT (QTc) interval by disease activity indices. The analysis of variance

indicated that patients with elevated disease activity show significantly longer QTc intervals ($p < 0.0001$).