Prevalence And Risk Factors of Electrocardiogram Abnormalities In Patients With Rheumatoid Arthritis: A Machine Learning Study With Follow-Up Data

Zuoyu Hu
The Third Affiliated Hospital of Sun Yat-sen University https://orcid.org/0000-0002-2637-0582
Zhuoran Hu
The Third Affiliated Hospital of Sun Yat-sen University https://orcid.org/0000-0002-6398-9229
Xinghua Guo
The Third Affiliated Hospital of Sun Yat-sen University https://orcid.org/0000-0003-0774-5817
Weizhen Weng
The Third Affiliated Hospital of Sun Yat-sen University https://orcid.org/0000-0002-3846-5925
Ye Chen
The Third Affiliated Hospital of Sun Yat-sen University https://orcid.org/0000-0002-3611-163X
Yunfeng Pan (panyunf@mail.sysu.edu.cn)
The Third Affiliated Hospital of Sun Yat-sen University https://orcid.org/0000-0001-7459-4970

Research Article

Keywords: rheumatoid arthritis, electrocardiogram, risk factors, machine learning, Cox regression

Posted Date: December 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-934178/v2

Abstract

OBJECTIVES: Electrocardiogram (ECG) abnormalities could predict some subsequent cardiovascular events. Cardiac involvement is a major extra-articular manifestation in rheumatoid arthritis (RA). We aimed to determine the prevalence of three major ECG abnormalities in RA patients, discover the associated ECG abnormalities associated with machine learning (ML) approaches, and then examine these preselected factors in the follow-up patients with traditional Cox regression.

METHODS: Consecutive RA patients' records were retrieved from the hospital database; about one-third of patients had follow-up data. Abnormal ECGs with clinical significance were grouped into non-specific ST-segment/T-wave changes, QT interval prolongation, and QRS-T angle increase. Machine learning approaches assessed the associated factors of these abnormalities. The top-important factors selected by the most optimal ML would be used to construct Cox regression models.

RESULTS: Two hundred twenty-six patients were enrolled for the first step cross-sectional study. Non-specific ST-T changes (27%) were the most prevalent abnormalities among patients with abnormal ECGs. Random forest models had the best performance in the discovery of associated factors for three outcomes. Cox regression validated that rheumatoid factor and low-density lipoprotein were common risk factors within those three abnormalities. Hypertension, ESR, and serum immunoglobulin G were influential factors for non-specific ST-T changes, prolonged QT interval, and increased QRS-T angle specifically.

CONCLUSION: Non-specific ST-T changes were the most common abnormalities seen in ECGs of RA patients. Our finding suggests that rheumatoid factor, LDL, hypertension, and inflammatory indicators are important risk factors for these ECG abnormalities.

Significance And Innovations

- RA patients would be vulnerable to cardiovascular diseases. ECG is a feasible method to detect cardiac involvement. Previous studies have reported an association between ECG abnormalities and subsequent cardiovascular events.
- To our knowledge, this is the first endeavor to investigate the prevalence of several common ECG abnormalities in RA patients and the risk factors by machine learning approaches and Cox regression.
- If further studies support our findings, it might be possible to identify those at higher risk of developing ECG abnormalities earlier to take appropriate action to prevent it.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease with synovial inflammation and joint destruction[1], affecting nearly 1% of the world's population[2]. Cardiovascular disease (CVD) is

a major extra-articular manifestation and comorbidity in RA, increasing morbidity and premature CVD-related mortality[3, 4]. Except for the traditional cardiovascular risk factors, like diabetes, hypertension, and hyperlipidemia, the severity of inflammation in RA patients would also increase the risk of CVD[5-8].

Electrocardiogram (ECG) is a routine for detecting and diagnosing abnormalities in the cardiac system. Resting-ECG alterations could help physicians perform a timely intervention on those with high CVD risk. For example, tented T-wave and/or ST-segment changes have been proven to increase the all-cause mortality and be independent risk factors for early CVD events and incident coronary heart disease (CHD) in middle-aged and older individuals [9-12]. Longer heart-rate corrected QT (QTc) intervals have been discovered in RA patients than healthy controls[13]; QTc prolongation was even associated with all-cause death in RA patients [14, 15]. Moreover, QRS -T angle is a predictor of sudden death in a middle-aged general population[16] and could assess the dispersion of myocardial repolarization, a critical factor in arrhythmogenicity[17]. Since QRS-T angle has been established as a repolarization marker[18], there are still limited surveys on this change in RA patients. Therefore, as an affordable and non-invasive examination independent of the operator and the patient's condition, ECG could provide primary but stable evidence for consequent tests or treatments.

Multivariate logistic regression (LR) and Cox proportional hazard (CoxPH) regression are traditional methods for relative factors analysis [19, 20]. However, certain assumptions, such as no multicollinearity among variables, must be satisfied; otherwise, the result would lose robustness. Furthermore, neither LR nor CoxPH regression could not be applied to sparse and high-dimension data directly. Machine learning (ML) has been widely performed for nonlinear prediction tasks in recent years, being more efficient in predictive modeling without the above assumptions[21].

In the present study, we will perform multiple ML methods and conventional LR to screen variables related to three types of ECG abnormalities in a cross-sectional RA population; then validate our findings in the follow-up cohort with conventional CoxPH models.

Methods

Patient selection

RA patients' records were retrieved from the database of the Division of Rheumatology of Third Affiliated Hospital of Sun Yat-sen University from January 2015 to September 2020. Eligible patients were 1) aged >=18, 2) met the 2018 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification criteria[22], and 3) had available ECG records at the time of diagnosis or the follow-up visit. Patients were excluded if they 1) had a CVD event or severe valvular disease; 2) were with hepatic and/or renal failure, and/or abnormal serum electrolytes, 3) were pregnant, 4) were with malignant tumors, 5) were with thyroid disorders (e.g., Grave's disease). All patients provided informed consent for the collection and use of clinical and laboratory data. The procedure complies with the declaration of Helsinki and is approved by the ethics committee The Third Affiliated Hospital of Sun Yat-sen University.

Sample size

The sample sizes were estimated by PASS 15 software (https://www.ncss.com), with the statistical power (1-β) set 0.90, type I error (α) set 0.05, and assuming that the prevalence of non-specific ST-T changes was about 18% among RA patients[23]. The software calculated that a total sample size of at least 174 would suffice. Finally, we recruited 226 patients for the present study.

Data collection

We used a standard protocol to collect data (characteristics were in table 1), including demographics, disease-related conditions, medication history, laboratory tests, complications, lifestyles, and standard digitally available recorded 12-lead resting ECG reports. Two experienced physicians rechecked computer-assisted reading of ECG reports.

Missing Data

Proportions of missing values were less than 5% across all variables. Multiple imputations were implemented using the 'Multivariate Imputation by Chained Equations' algorithm in R package 'mice' to account for missing data to minimize bias and precision reduction.

Outcome definition

ECGs were categorized into the normal group and the abnormal one. The abnormal ECGs were further defined if patients were a) with non-specific ST-T changes, b) after heart-rate corrected by Bazetts formula ($QTc = QT/\sqrt{RR}$), QTc interval>=430 ms is considered prolonged QTc (since there is no consensus on defining a normal QTc range, with proposed upper limits of normal extending from 430 to 470 ms[24]); c) spatial QRS-T angle is >=90°[25, 26] is defined increased. When more than one abnormality was observed in the same participant, each would be recorded separately.

ML modeling process

To assess the influential factors for three ECG abnormalities, we respectively performed five ML methods, including random forest (RF), stochastic boosting models ('ada'), the latest absolute shrinkage and selection operator (LASSO), extreme Gradient Boosting tree ('xgbtree'), and neural net ('nnet'). Then we used stacking models (using logistic regression as the core algorithm) to ensemble models mentioned above. Therefore, we created six models.

To begin with, we randomly divided samples into the training set and the validation set (ratio 70:30) with the same proportion of positive outcomes by synthetic minority oversampling technique (SMOTE) for reducing the negative effect of the imbalance class of the constructed models[27]. The training set was used to model with 5-fold three times repeated cross-validation.

ML model performance evaluation

Discrimination indicators, including the area under the receiver operating characteristic curve (ROC-AUC), precision, accuracy, recall rate, F1-Measure, and Brier's score for indicating the calibration of 6 models, will be evaluated in the validation set.

Once the most optional models for three outcomes were selected, we screened the top important factors for consequent survival analyses in the follow-up cohort to validate and calculate the hazard ratio (HR) by CoxPH regression. All the analysis was conducted by R 3.6.1 (R Core Team, Vienna, Austria). Package 'caret', 'coxph', 'DwMR' were used for data analysis. The detailed study flow diagram is illustrated in Fig. 1.

Statistical analysis

Statistics were presented as mean±standard error (SD) for continuous variables with normal distribution, median [Interquartile Range, IQR] for those without normal distribution, and percentage for categorical variables. A 2-tailed *p*-value <0.05 was considered to indicate statistical significance.

Results

Characteristics of patients

A total of 226 RA patients participated in the present study. 53.1% of them were female. 96.9% of participants were aged >= 40. Follow-up data were available for 95 patients; the median follow-up interval was 13 months (12 to 22). The baseline characteristics of the patients are presented in Supplementary Table 1, and follow-up information is shown in Supplementary Table 2.

Prevalence of ECG abnormalities

The prevalence of three types of ECG abnormalities is shown in Fig. 2. 7 of 226 patients at baseline and 4 of 95 follow-up patients had more than two ECG abnormalities. All two follow-up patients with increased QRS-T angle had been diagnosed at baseline; on the contrary, follow-up patients with the other two abnormalities were all new-onset in the follow-up.

Models' performance and algorithm selection

RF generated the highest AUCs in predicting non-specific ST-T changes(0.974), QT interval(0.987), and QRS-T angle (0.915), with the lowest Brier's scores in all of these three models. The detailed models' performance is shown in Table 2. Finally, we selected the RF algorithm to construct models.

RF models and variables importance

As shown in Supplementary Fig. 1, we included all variables in the RF models ensuring the lowest error rate. After tuning parameters, we constructed three optimal RF models; parameters of models and the performance of RF models can be seen in Supplementary Table 4.

Fig. 3 showed the top-6 important variables of three RF models. Age and indices of inflammation (CRP, ESR) were in the top rank of the three models. Supplementary Fig.2 showed the top-15 important variables of RF models.

Cox regression for validating factors found associated with ECG abnormalities in RF models

We selected 'stable' factors whose relative importance was >= 5 to perform univariate and multivariate Cox regression. Variables and crude hazard ratio (HR) were shown in Supplementary Table 5; the adjusted ones were compiled in Table 3.

Rheumatoid factor was significant for three kinds of abnormalities; however, its effect was opposite in ST-T changes and the other, except for the very high level (>900 IU/mL, HR[95%CI]=27.78 [25.00, 30.87], p<0.001). The effect of LDL is also different within non-specific ST-T changes and increased QRS-T angle. Slightly increased LDL level (near-optimal) is a protective factor for ST-T changes (HR[95%CI]=0.34 [0.14, 0.82], p=0.017) but a strong risk factor for QRS-T angle increase (HR[95%CI]=2.17 [1.26, 3.73], p=0.005). Underweight patients might have a higher risk for QTc prolongation (HR[95%CI]=1.17 [1.07, 1.28], p=<0.001).

Discussion

In the present retrospective cohort study, we aimed to report the prevalence and associated factors of abnormal ventricular repolarization, which consisted of non-specific ST-T change, prolonged QTc interval, QRS-T angle, etc. The prevalence of newly diagnosed non-specific ST-T changes at baseline and follow-up was higher than reported studies (27% and 20% vs. 17%[23] to 18%[28]). Several factors can explain this difference. Our study population had more moderate and active patients than the previous study cohorts[23] (89.9% vs. 62%, evaluated with DAS28-CRP). When it comes to new-onset prolonged QTc interval at baseline and follow-up, the incidence in our cohort was marked lower than the previous literature (6.2% and 7.4% vs. 30%[28] and cumulative 47.5%[28]), probably because, compared with ours, Chauhan K. et al. had a cohort with a nearly double incidence of hypertension (43% vs. 22.5%) which plays a role in the mechanism of QT interval prolongation[29]. Not yet had published study revealed the occurrence of increased QRS-T angle in RA patients. Our cohort discovered that 5.3% of patients were with increased QRS-T angle.

Non-specific ST-T changes are common findings even in the general population[30]. Previous studies have indicated that these changes significantly correlate with cardiovascular morbidity and mortality[11, 12, 31, 32]. Although the clinical significance of non-specific ST-T changes in patients with RA without CVD is still not certain, it is enticing to speculate that they represent subclinical CVD. QT/QTc interval prolongation is also an independent cardiovascular risk factor [15, 33-35] and is mainly related to cardiac arrest, especially in the RA population. Emerging data have demonstrated the strong relationship between QTc and pro- and anti-inflammatory cytokines[36, 37]. Also, the presence of parasympathetic dysfunction, one of the autonomic dysfunctions in RA patients, could influence the QTc interval[38].

RF models could help primarily discover associated factors. Inflammatory markers, including ESR and CRP, were important for three kinds of ECG abnormalities. When validated in follow-up patients with multivariate CoxPH regression, increased concentration of RF was found a risk factor for three abnormalities, except the concentration was lower than 900 IU/ml for ST-T changes. The impact of CRP and ESR were significantly associated with QRS-T angel increase and QTc prolongation, respectively; however, due to the limited sample size, we did not discover a significant concentration-effect relationship. ESR and CRP are part of extended DAS-28, but their importance varies from different ECG abnormalities.

Age and disease duration is not critical for the higher risk of non-specific ST-T changes, consistent with the previous study[23]. However, another factor, GC usage period, which could partly reflect age, disease duration, and disease activity, influences differently in ST-T changes and QTc prolongation. A regular, adequate GC therapy might be more vital.

A population-based study has shown that LDL levels are independently associated with subclinical atherosclerosis[39], one of the magnifications of non-specific ST-T abnormalities[12], also statistically influencing non-specific ST-T changes in our study, even a near-optimal controlled level of LDL is protective. Nevertheless, when it comes to QRS-T angle increase, LDL should be strictly controlled at or under the optimal level.

Hypertension is a well-documented risk factor for ST-T change[40]; in our cohort, those in graded class-2 or low-risk groups have a higher risk; but hypertensive patients from the high-risk group had a protective effect on ST-T changes. Such difference could be probably because these patients were more cautious and active in controlling blood pressure.

Female has been reported positively related to QTc prolongation in RA[23]. These gender differences appear to correlate with age-dependent changes in serum levels of sex hormones. Androgens would accelerate cardiac repolarization processes and shorten potential action durations by the effect of testosterone on calcium currents[41]. Moreover, low BMI is an independent predictor of QTc interval prolongation in our cohort, similar to a cross-sectional study in women with eating disorders has demonstrated[42]. Therefore, appropriate nutrition enhancement for underweighted RA patients is recommended for lowering the risk of cardiac conduction abnormalities.

sUA level has a positive correlation with prolonged QTc interval, especially in men[43]. Our result also identified that even in those with sUA slightly increased, the risk of QTc prolongation would be twice. QTc intervals were found shortening in female subjects with sickle cell anemia[44]. Those with QTc prolongation in our cohort were mostly women (6 of 7); therefore, mild anemia might have a protective effect on QTc interval.

The impact of immunoglobulin G on QTc prolongation in RA patients is a novel finding in our study. Abnormal levels of serum IgG are one of the early markers of autoimmune diseases[45], especially the

increased ones. Aberrant glycosylated and autoimmunity-triggered IgG[46] could be responsible for inflammation-associated atherosclerosis cardiovascular symptoms[47].

In conclusion, machine-learning analysis can be used when multicollinearity occurs or in a high dimension data warehouse. For instance, the disease duration may depend on age; and preselected the essential variables for the following Cox regression. Another strength of the present study is the comparison between several machine learning approaches since each has its unique pros and cons. As a relatively affordable cardiovascular examination, ECG may be recommended for all the RA patients in their first visit and follow-up visits because such a systemic-involved and chronic disease needs interdisciplinary cooperation to assess the condition holistically and longitudinally. Assisted by the machine-learning method and validated by traditional CoxPH regression, some objective information might be acquired before inviting cardiologist consultations and further expensive or intrusive examinations.

There are several limitations of our study that can impact its generalizability to other populations and the interpretation of its clinical significance. First, the sample size was insufficient, especially the follow-up subjects. Second, we only used resting-12-lead ECGs rather than 24-hour ECG monitoring (Holter), which can measure diurnal variations of ECG intervals. It may cause a higher ‘false-negative rate’ when we diagnosed ECGs. Third, we cannot exclude the possibility of patient selection bias because only a single tertiary referral center participated in this study. Therefore, the prevalence of ECG abnormalities in this study cannot represent the real rate in China. Moreover, although ECG is an affordable, stable, and quick test along with no harm, the information that ECG could offer is limited. Other cardiac imaging examinations, for example, echocardiogram, cardiac magnetic resonance imaging, or radionuclide perfusion, could provide more details about the cardiac lesion. Further longitudinal, prospective studies assessing the role of potential risk factors will help clarify the mechanism of ECG abnormalities among RA patients.

Conclusion

Our data reveals that non-specific ST-T changes were the most common abnormalities seen in RA patients’ ECGs, followed by QTc prolongation and QRS-T angle increase. Inflammatory factors and rheumatoid factors are more important than disease activity for these ECG abnormalities, along with LDL levels. Moreover, relatively strict management of LDL and uric acid may benefit RA patients. Efforts to monitor the ECGs of these key populations need to be instituted.

Declaration

The authors did not have financial support or benefits from commercial sources for the work reported in the manuscript. The authors declare no conflict of interest.

Reference

[1] Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001.

[2] O'Neil LJ, Barrera-Vargas A, Sandoval-Heglund D, Merayo-Chalico J, Aguirre-Aguilar E, Aponte AM, et al. Neutrophil-mediated carbamylation promotes articular damage in rheumatoid arthritis. Sci Adv 2020;6(44).

[3] Figus FA, Piga M, Azzolin I, McConnell R, Iagnocco A. Rheumatoid arthritis: Extra-articular manifestations and comorbidities. Autoimmunity reviews 2021;20(4):102776.

[4] Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Annals of the rheumatic diseases 2005;64(11):1595-601.

[5] Solomon DH, Goodson NJ, Katz JN, Weinblatt ME, Avorn J, Setoguchi S, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Annals of the rheumatic diseases 2006;65(12):1608-12.

[6] Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010;69(11):1920-5.

[7] van Boheemen L, van Beers-Tas MH, Kroese JM, van de Stadt LA, van Schaardenburg D, Nurmohamed MT. Cardiovascular risk in persons at risk of developing rheumatoid arthritis. PLoS One 2020;15(8):e0237072.

[8] Fragoulis GE, Panayotidis I, Nikiphorou E. Cardiovascular Risk in Rheumatoid Arthritis and Mechanistic Links: From Pathophysiology to Treatment. Curr Vasc Pharmacol 2020;18(5):431-46.

[9] Boukens BJ, Sulkin MS, Gloschat CR, Ng FS, Vigmond EJ, Efimov IR. Transmural APD gradient synchronizes repolarization in the human left ventricular wall. Cardiovasc Res 2015;108(1):188-96.

[10] Lehmacher J, Neumann JT, Sörensen NA, Goßling A, Haller PM, Hartikainen TS, et al. Predictive Value of Serial ECGs in Patients with Suspected Myocardial Infarction. Journal of clinical medicine 2020;9(7).

[11] Greenland P, Xie X, Liu K, Colangelo L, Liao Y, Daviglus ML, et al. Impact of minor electrocardiographic ST-segment and/or T-wave abnormalities on cardiovascular mortality during long-term follow-up. Am J Cardiol 2003;91(9):1068-74.

[12] Walsh JA, 3rd, Prineas R, Soliman EZ, Liu K, Ning H, Daviglus ML, et al. Association of isolated minor non-specific ST-segment and T-wave abnormalities with subclinical atherosclerosis in a middle-aged, biracial population: Coronary Artery Risk Development in Young Adults (CARDIA) study. Eur J Prev Cardiol 2013;20(6):1035-41.

[13] Erre GL, Piras A, Piga M, Fedele AL, Mangoni AA, Lazzerini PE, et al. QT and QT dispersion intervals in long-standing and moderately active rheumatoid arthritis: results from a multicentre cross-sectional study. Clinical and experimental rheumatology 2020;38(3):516-22.

[14] 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(1):84-9.

[15] Panoulas VF, Toms TE, Douglas KM, Sandoo A, Metsios GS, Stavropoulos-Kalinoglou A, et al. Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: an association driven by high inflammatory burden. Rheumatology (Oxford) 2014;53(1):131-7.

[16] Aro AL, Huikuri HV, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, et al. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. Europace 2012;14(6):872-6.

[17] Voulgari C, Pagoni S, Tesfaye S, Tentolouris N. The spatial QRS-T angle: implications in clinical practice. Curr Cardiol Rev 2013;9(3):197-210.

[18] Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. Ann Noninvasive Electrocardiol 2014;19(6):534-42.

[19] Biskup M, Biskup W, Majdan M, Targońska-Stępniak B. Cardiovascular system changes in rheumatoid arthritis patients with continued low disease activity. Rheumatology international 2018;38(7):1207-15.

[20] Targońska-Stępniak B, Biskup M, Biskup W, Majdan M. Gender Differences in Cardiovascular Risk Profile in Rheumatoid Arthritis Patients with Low Disease Activity. BioMed research international 2019;2019:3265847.

[21] Pilkington SF, Mahmoud HN. Interpreting the socio-technical interactions within a wind damage-artificial neural network model for community resilience. Royal Society open science 2020;7(11):200922.

[22] Rausch Osthoff AK, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis 2018;77(9):1251-60.

[23] Geraldino-Pardilla L, Gartshteyn Y, Piña P, Cerrone M, Giles JT, Zartoshti A, et al. ECG non-specific ST-T and QTc abnormalities in patients with systemic lupus erythematosus compared with rheumatoid arthritis. Lupus Sci Med 2016;3(1):e000168-e.

[24] Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". J Cardiovasc Electrophysiol 2006;17(3):333-6.

[25] Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, et al. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination

Survey (NHANES III). Am J Cardiol 2012;109(7):981-7.

[26] 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 Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol 2009;53(11):982-91.

[27] Blagus R, Lusa L. Joint use of over- and under-sampling techniques and cross-validation for the development and assessment of prediction models. BMC Bioinformatics 2015;16:363.

[28] Chauhan K, Ackerman MJ, Crowson CS, Matteson EL, Gabriel SE. Population-based study of QT interval prolongation in patients with rheumatoid arthritis. Clinical and experimental rheumatology 2015;33(1):84-9.

[29] Klimas J, Kruzliak P, Rabkin SW. Modulation of the QT interval duration in hypertension with antihypertensive treatment. Hypertens Res 2015;38(7):447-54.

[30] De Bacquer D, De Backer G, Kornitzer M. Prevalences of ECG findings in large population based samples of men and women. Heart 2000;84(6):625-33.

[31] Badheka AO, Rathod A, Marzouka GR, Patel N, Bokhari SS, Moscucci M, et al. Isolated nonspecific ST-segment and T-wave abnormalities in a cross-sectional United States population and Mortality (from NHANES III). Am J Cardiol 2012;110(4):521-5.

[32] Kumar A, Lloyd-Jones DM. Clinical significance of minor nonspecific ST-segment and T-wave abnormalities in asymptomatic subjects: a systematic review. Cardiol Rev 2007;15(3):133-42.

[33] Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. Circulation 1991;83(6):1888-94.

[34] Robbins J, Nelson JC, Rautaharju PM, Gottdiener JS. The association between the length of the QT interval and mortality in the Cardiovascular Health Study. Am J Med 2003;115(9):689-94.

[35] Niemeijer MN, van den Berg ME, Eijgelsheim M, van Herpen G, Stricker BH, Kors JA, et al. Short-term QT variability markers for the prediction of ventricular arrhythmias and sudden cardiac death: a systematic review. Heart 2014;100(23):1831-6.

[36] Lazzerini PE, Acampa M, Capecchi PL, Fineschi I, Selvi E, Moscadelli V, et al. Antiarrhythmic potential of anticytokine therapy in rheumatoid arthritis: tocilizumab reduces corrected QT interval by controlling systemic inflammation. Arthritis Care Res (Hoboken) 2015;67(3):332-9.

[37] Adlan AM, Panoulas VF, Smith JP, Fisher JP, Kitas GD. Association between corrected QT interval and inflammatory cytokines in rheumatoid arthritis. J Rheumatol 2015;42(3):421-8.

[38] Toussirot E, Serratrice G, Valentin P. Autonomic nervous system involvement in rheumatoid arthritis. 50 cases. J Rheumatol 1993;20(9):1508-14.

[39] Fernández-Friera L, Fuster V, López-Melgar B, Oliva B, García-Ruiz JM, Mendiguren J, et al. Normal LDL-Cholesterol Levels Are Associated With Subclinical Atherosclerosis in the Absence of Risk Factors. J Am Coll Cardiol 2017;70(24):2979-91.

[40] Bao H, Cai H, Zhao Y, Huang X, Fan F, Zhang C, et al. Nonspecific ST-T changes associated with unsatisfactory blood pressure control among adults with hypertension in China: Evidence from the CSPTT study. Medicine (Baltimore) 2017;96(13):e6423-e.

[41] Vicente J, Johannesen L, Galeotti L, Strauss DG. Mechanisms of sex and age differences in ventricular repolarization in humans. Am Heart J 2014;168(5):749-56.

[42] Swenne I, Larsson PT. Heart risk associated with weight loss in anorexia nervosa and eating disorders: risk factors for QTc interval prolongation and dispersion. Acta Paediatr 1999;88(3):304-9.

[43] Guo X, Li Z, Liu Y, Yu S, Yang H, Zheng L, et al. Sex-specific association between serum uric acid and prolonged corrected QT interval: Result from a general rural Chinese population. Medicine (Baltimore) 2016;95(50):e5568.

[44] Ajibare AO, Olabode OP, Fagbemiro EY, Akinlade OM, Akintunde AA, Akinpelu OO, et al. Assessment of Ventricular Repolarization in Sickle Cell Anemia Patients: The Role of QTc Interval, Tp-e Interval and Tp-e/QTc Ratio and Its Gender Implication. Vasc Health Risk Manag 2020;16:525-33.

[45] Aho K, Heliövaara M, Knekt P, Reunanen A, Aromaa A, Leino A, et al. Serum immunoglobulins and the risk of rheumatoid arthritis. Ann Rheum Dis 1997;56(6):351-6.

[46] Su Z, Xie Q, Wang Y, Li Y. Abberant Immunoglobulin G Glycosylation in Rheumatoid Arthritis by LTQ-ESI-MS. Int J Mol Sci 2020;21(6).

[47] Kalinkovich A, Gabdulina G, Livshits G. Autoimmunity, inflammation, and dysbiosis mutually govern the transition from the preclinical to the clinical stage of rheumatoid arthritis. Immunol Res 2018;66(6):696-709.

Tables

Table 1 Candidate variables

Characteristics	Variables (N=82)*
Demographic	(1) age# ; (2) disease duration#; (3) gender; (4) menopausal status for females; (5) BMI#
Disease-related	(6) DAS28-ESR#; (7) DAS28-CRP#; (8) rheumatoid nodules; (9) CRP elevation; (10) CRP#; (11) ESR elevation; (12) ESR#; (13) Baker's cyst; (14) overlap syndrome; (15) vasculitis; (16) RA-ILD; (17) RA-PAH; (18) Felty syndrome
Long-term medication history	(19) initial treatment; (20) regular treatment; (21) period of GC usage#; (22) MTX; (23) LEF; (24) SASP; (25) GTW; (26) HCQ; (27) TGP; (28) Iguratimod; (29) NSAIDs; (30) bDMARDs; (31) types of bDMARDs; (32) Statins; (33) PPI
Laboratorial tests	(34) abnormal WBC#; (35) abnormal PLT #; (36) leukocyturia#; (37) hematuresis#; (38) hypoproteinemia; (39) BUN elevation; (40) sUA elevation; (41) sUA#; (42) CysC elevation; (43) β2MG elevation; (44) hypercholesterolemia #; (45) hypertriglyceridemia; (46) low HDL#; (47) high LDL#; (48) serum IgG#; (49) serum IgA#; (50) serum IgM#; (51) serum C3#; (52) serum C4#; (53) serum total complement#; (54) RF positive; (55) RF#; (56) FER; (57) CEA; (58) AFP; (59) RF-IgA; (60) RF-IgG; (61) RF-IgM; (62) ANA; (63) anti-histone; (64) anti-dsDNA; (65) anti-U1RNP; (66) anti-SSA; (67) anti-scl-70; (68) GPI; (69) AKA; (70) anti-RA33; (71) ACAP
Comorbidity and lifestyle	(72) hypertension; (73) types of hypertension; (74) grades of hypertension#; (75) risk groups of hypertension#; (76) not controlled hypertension; (77) pathoglycemia; (78) types of pathoglycemia; (79) anemia; (80) severities of anemia#; (81) current smoking habits; (82) current drinking habits.

**: all variables were discrete. #: ranked variables.*

RA: rheumatoid arthritis; BMI: body mass index; DAS: disease activity score; ESR: erythrocyte sedimentation rate; CRP:C-reactive protein; ILD: intestinal lung disease; PAH: pulmonary arterial hypertension; GC: glucocorticoid; MTX: methotrexate; LEF: leflunomide; SASP: salicylazosulfapyridine; GTW: tripterygium glycosides; HCQ: hydroxychloroquine; TGP: total glycosides of paeony; NSAIDs: non-steroidal anti-inflammatory drugs; bDMARDs: biological disease modifying antirheumatic drug; PPI: proton pump inhibitor; WBC: white blood cell; PLT: platelets; BUN: blood urea nitrogen; sUA: serum uric acid; CysC: cystatin C; β2MG: β2-microglobulin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; Ig: immunoglobulin; C3&4: complement 3 and 4; RF: rheumatoid factor; FER: ferritin; CEA: carcinoembryonic antigen; AFP: alpha fetoprotein; ANA: anti-nuclear antibody; dsDNA: double-stranded DNA; GPI: glucose-6-phosphate isomerase; AKA: antikeratin antibodies; ACAP: anti-cyclic citrullinated peptide antibody.

Table 2 Models' performance

Nonspecific ST-T changes					
Models	AUC	Brier's score	Precision	Recall rate	F1-measure
RF	0.974	0.416	0.711	0.969	0.821
ADA	0.947	0.574	0.778	0.933	0.848
LASSO	0.942	0.577	0.789	0.922	0.850
NNET	0.886	0.712	0.756	0.907	0.824
Stacking model (LR)	0.970	0.668	0.811	0.961	0.879
Prolonged QTc interval					
RF	0.987	0.398	0.857	0.996	0.923
LASSO	0.979	0.586	0.994	0.913	0.955
NNET	0.982	0.745	0.993	0.913	0.955
Stacking model (LR)	0.962	0.593	0.952	0.833	0.889
Increased QRS-T angle					
RF	0.915	0.314	0.611	0.997	0.758
ADA	0.873	0.516	0.667	0.857	0.750
LASSO	0.857	0.459	0.667	0.823	0.774
xGBTree	0.886	0.567	0.661	0.786	0.688
Stacking model (LR)	0.891	0.478	0.778	0.778	0.778

RF: random forest; ADA: stochastic boosting models;xGBTree: eXtreme gradient boosting; NNET: neural net; LASSO: least absolute shrinkage and selection operator. AUC: area under the receiver operating characteristic curve.

Table 3 Adjusted hazard ratios of three outcomes

	Nonspecific ST-T changes		**Prolonged QTc interval**		**Increased QRS-T angle**	
	AIC=203.6		AIC=627.7		AIC=699.7	
	HR [95%CI]	*p*	*HR [95%CI]*	*p*	*HR [95%CI]*	*p*
Rheumatoid factor, IU/mL*						
Normal (<16)	Ref.		Ref.		Ref.	
~100	0.83 [0.80, 0.85]	<0.001	1.22 [0.43, 3.47]	0.706	1.23 [0.79, 1.90]	0.355
~300	0.84 [0.81, 0.87]	<0.001	9.69 [6.12, 15.33]	<0.001	1.72 [1.13, 2.62]	0.011
~600	1.02 [0.97, 1.07]	0.463	4.75 [2.33, 9.71]	<0.001	2.91 [1.54, 5.50]	0.001
~900	0.91 [0.84, 0.98]	0.017	12.20 [6.29, 23.67]	<0.001	4.86 [1.34, 17.61]	0.016
>900	27.78 [25.00, 30.87]	<0.001	9.52 [1.32, 68.51]	0.025	Inf [0.00, Inf]	0.992
Period of GC usage, months*						
No	Ref.		Ref.			
~6	0.96 [0.90, 1.02]	0.209	0.95 [0.86, 1.04]	0.283		
~12	1.18 [1.13, 1.24]	<0.001	0.84 [0.77, 0.91]	<0.001		
~24	1.39 [1.32, 1.45]	<0.001	1.00 [0.91, 1.09]	0.923		
>24	0.31 [0.25, 0.38]	<0.001	0.97 [0.88, 1.08]	0.605		
Grades of hypertension						
No	Ref.					
1	0.99 [0.33, 3.02]	0.988				
2	0.15 [0.05, 0.53]	0.003				

3	0.14 [0.03, 0.65]	0.012				
High low-density lipoprotein (LDL), mmol/L						
optimal (~2.59 mmol/L)	Ref.		Ref.		Ref.	
near optimal (-3.37)	0.34 [0.14, 0.82]	0.017	0.47 [0.01, 15.78]	0.675	2.17 [1.26, 3.73]	0.005
borderline high (~4.12)	1.37 [0.24, 7.89]	0.723	0.01 [0.00, 8213.42]	0.475	13.43 [7.69, 23.44]	<0.001
high (~4.90)	0.00 [0.00, Inf]	0.556	0.55 [0.07, 4.49]	0.574	0.00 [0.00, 0.00]	<0.001
very high (>4.90)	1051.55 [0.00, Inf]	0.776	1.54 [0.25, 9.54]	0.64	0.00 [0.00, Inf]	0.926
Gender						
Female			Ref.			
Male			0.21 [0.10, 0.47]	<0.001		
BMI, kg/㎡, n (%)*						
normal (18.5~23.9)			Ref.			
underweight (<18.5)			1.17 [1.07, 1.28]	<0.001		
overweight (24~27.9)			0.88 [0.75, 1.03]	0.099		
obese (>=28)			1.29 [0.07, 22.60]	0.86		
ESR						
~15(male) or ~20(female)			Ref.			
~30			1.52 [0.58, 3.99]	0.39		
~50			6.38 [4.03, 10.09]	<0.001		
~70			5.80 [3.63, 9.26]	<0.001		

~90	1.61 [0.72, 3.63]	0.248		
>90	0.57 [0.13, 2.54]	0.46		
sUA, μmol/L*				
<420	Ref.			
~500	2.01 [1.20, 3.35]	0.008		
~600	1.58 [0.70, 3.58]	0.273		
~700	0.00 [0.00, Inf]	0.937		
Hypoalbumin*				
No	Ref.			
Yes	0.97 [0.90, 1.05]	0.42		
Anemia				
No	Ref.			
Mild	0.26 [0.14, 0.47]	<0.001		
Moderate	2.65 [0.86, 8.14]	0.09		
Severe	Inf [0.00, Inf]	0.868		
CRP, mg/L, n (%)				
<=6			Ref.	
~10			1.70 [1.07, 2.71]	0.025
~20			0.62 [0.35, 1.08]	0.09
~30			0.00 [0.00, Inf]	0.701
~50			0.00 [0.00, Inf]	0.85

>50	0.00 [0.00, Inf]	0.89
Serum immunoglobulin G (IgG)		
normal	Ref.	
decreased	6.33 [4.17, 9.62]	<0.001
increased	3.54 [1.92, 6.53]	<0.001
**: After entering variables into the Cox regression equations, the proportional hazards (PH) assumption would be checked using statistical tests based on the scaled Schoenfeld residuals. R function 'cox.zph' was used. P<0.05 is deemed violating the PH assumption so that we created an time-variable interaction item (time-dependent variables), then replace the original variables with these items.*		

Figures

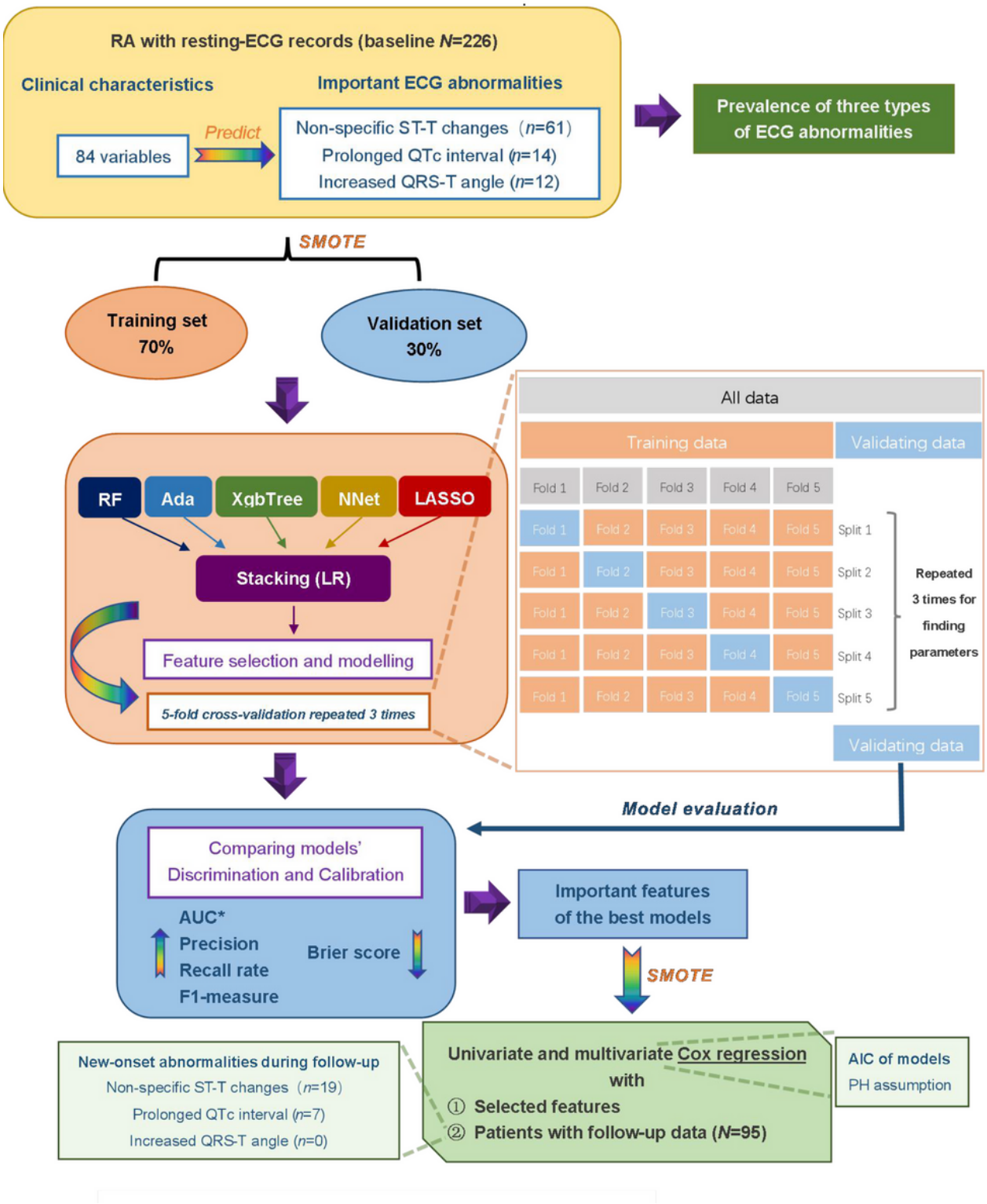

Figure 1

The Study flow diagram

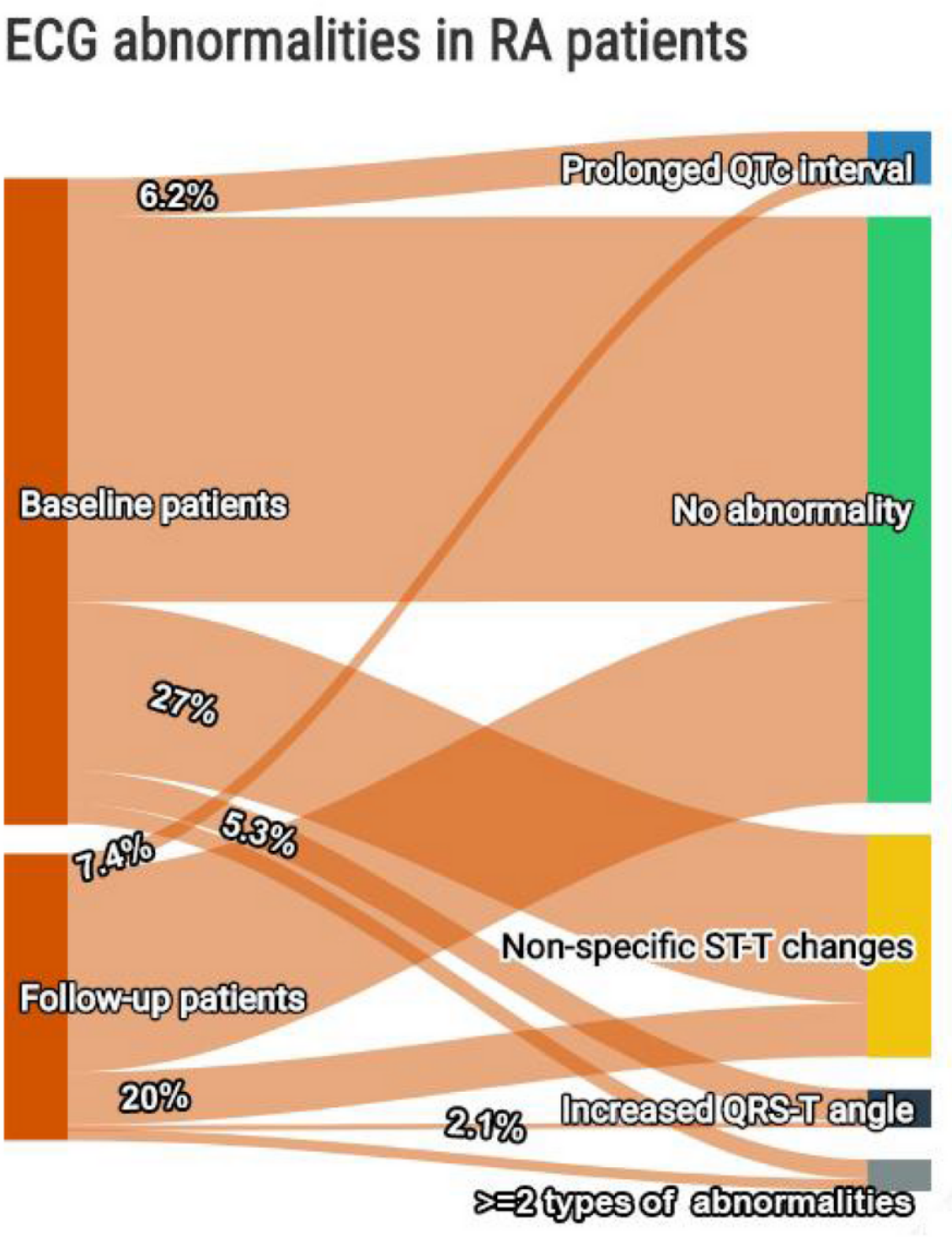

Figure 2

The prevalence of ECG abnormalities

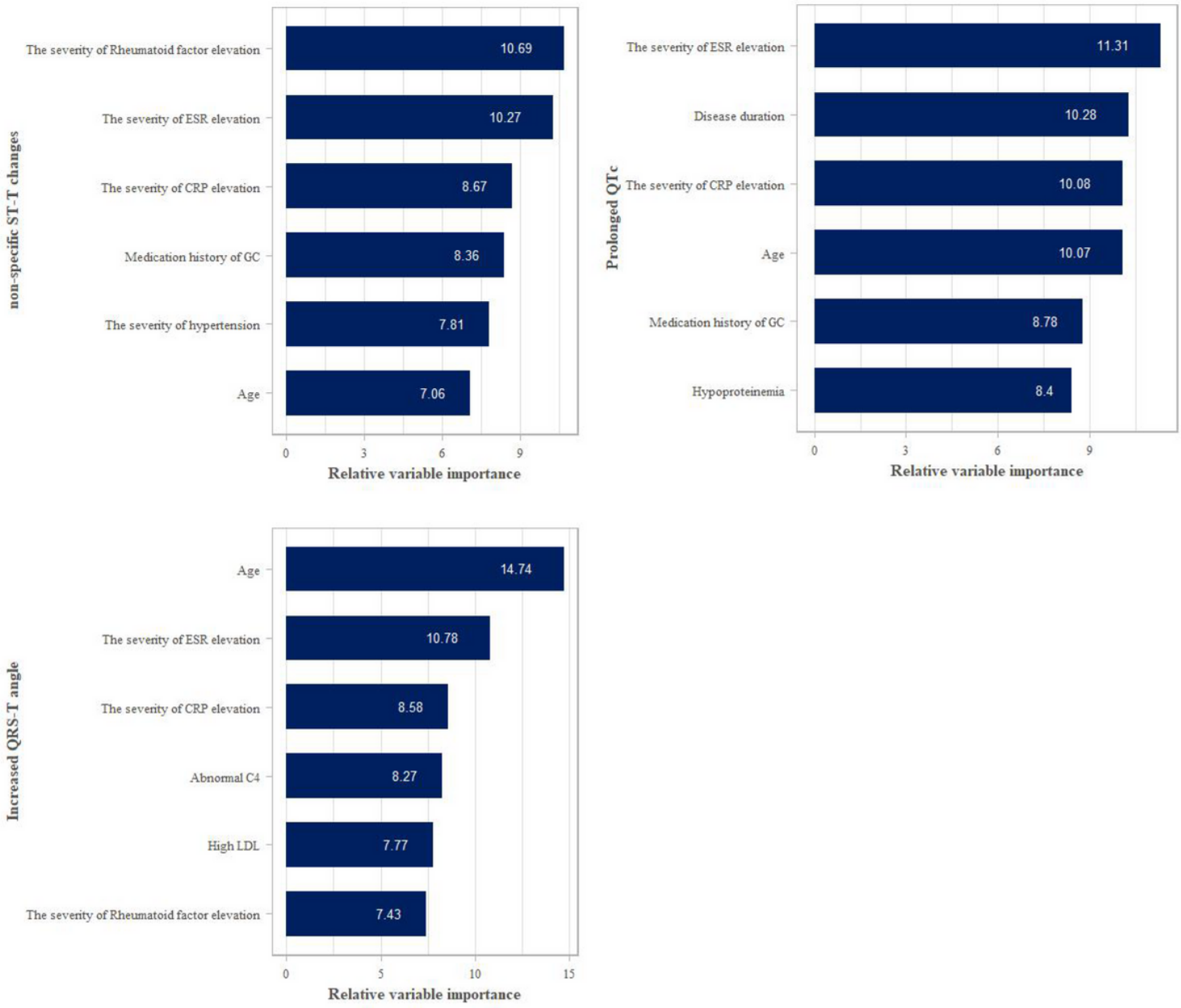

Figure 3

The top-6 important variables selected by three RF models. a. nonspecific ST-T changes; b. prolonged QTc interval; c. increased QRS-T angle.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf