

QTc Interval is Associated with Atrial Fibrillation in Individuals with Metabolic Syndrome Phenotype

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Purpose: Manifestations of metabolic syndrome (MetS) carry risks for atrial fibrillation (AF). The study determined whether any electrocardiographic parameter can reflect increased AF risk in individuals with MetS.

Patients and Methods: From our University Hospital database, we examined the presence of AF and its correlation with MetS manifestations, renal function, lipid profiles, and electrocardiographic parameters (P wave duration, PR interval, QRS width, and QTc intervals). Between January 2008 and December 2015, data from 4479 adults (women 41.6% vs men 58.4%) were identified.

Results: The overall prevalence of AF was 12.4%, without sex differences (women, 12.8% vs men, 12.1%). Patients with AF were older (age 73.9 ± 11.8 vs non-AF 67 ± 13.5 years), with lower lipid levels (TG, total cholesterol, and LDL-cholesterol, all $p < 0.0001$), and at lower eGFR level (64.1 ± 30.9 vs non-AF 68.8 ± 41.4 mL/min/1.73m², $p < 0.0001$). Besides, sex differences were present in all electrocardiographic parameters (all $p < 0.05$). Hypertension had the highest odds ratio (1.33; $p = 0.026$) for AF. Comparing AF to non-AF, the QTc of quartiles was significantly different ($p < 0.0089$). The shortest and longest QTc quartiles had an increased incidence of AF.

Conclusion: AF risk in patients with MetS phenotypes can be reflected by QTc quartiles.

Keywords: atrial fibrillation, electrocardiography, metabolic syndrome, lipid, QTc interval

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and increases the risk of ischemic stroke, heart failure and systemic thromboembolism.¹⁻³ The prevalence of AF and AF-related stroke has increased significantly in recent years, and the trend of increase is estimated to continue in the near future.⁴ Patients with metabolic syndrome (MetS), which manifests with hypertension, insulin resistance, diabetes mellitus (DM), hypertriglyceridemia, and central obesity, have an increased risk of AF.^{2,5,6} Moreover, each manifestation of the MetS is correlated with the development of AF.⁷⁻⁹

Despite advancements in pharmaceutical control for hypertension, DM, and hyperlipidemia, the prevalence of AF is still growing.¹ One possible reason is the aging of population and the increased prevalence of MetS.¹⁰ For instance, over 20% of general population in the United States has MetS.¹¹ In fact, long-term rhythm control of AF is challenging, particularly for individuals with MetS.^{12,13} This could be another reason for the growing number of patients with AF. On the other hand, thrombotic events (on higher CHA2DS2-Vasc score; prediction for thromboembolism) are caused by the coexistence of MetS for AF patients.¹⁴ The health burden related to AF and related complications is estimated to be five times that of non-AF illness.¹⁵ To reduce the burden of AF, it is crucial to identify the risks of AF in daily practice and to intervene in a prevention strategy.

Standard electrocardiography (ECG) is commonly used in clinical settings. This study was aimed to investigate whether any ECG parameters can predict the risk of AF in a common patient population that manifested with MetS phenotypes. The study was performed by analyzing a single-center medical database to calculate the predictive value of variable clinical manifestations and ECG parameters for the occurrence of AF.

Materials and Methods

Study Design

This was a retrospective, cross-sectional, observational, and single-center database study (Figure 1). Patients attending the outpatient department during 2008–2015 were eligible for this study if they had any diagnosis code matching MetS manifestations (including hypertension, hyperlipidemia, and DM). The exclusion criteria included a lack of complete ECG within 6 months, lack of laboratory tests within 6 months, any thyroid disorders, any diagnosis of heart valve diseases, pulmonary hypertension, congenital heart diseases, pacemaker rhythm, second- and third-degree AV block. The data of all study subjects were delinked to any private and/or personal information, including their chart number. A waiver of documentation of informed consent was given and all protocols were approved by the Division of Medical Statistics and Bioinformatics, Department of Medical Research, and the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E(II)-20170077). Estimate Glomerular Filtration Rate (eGFR) was calculated by clinical laboratories serum creatinine (Scr) value with the equation as follows: eGFR (mL/min/

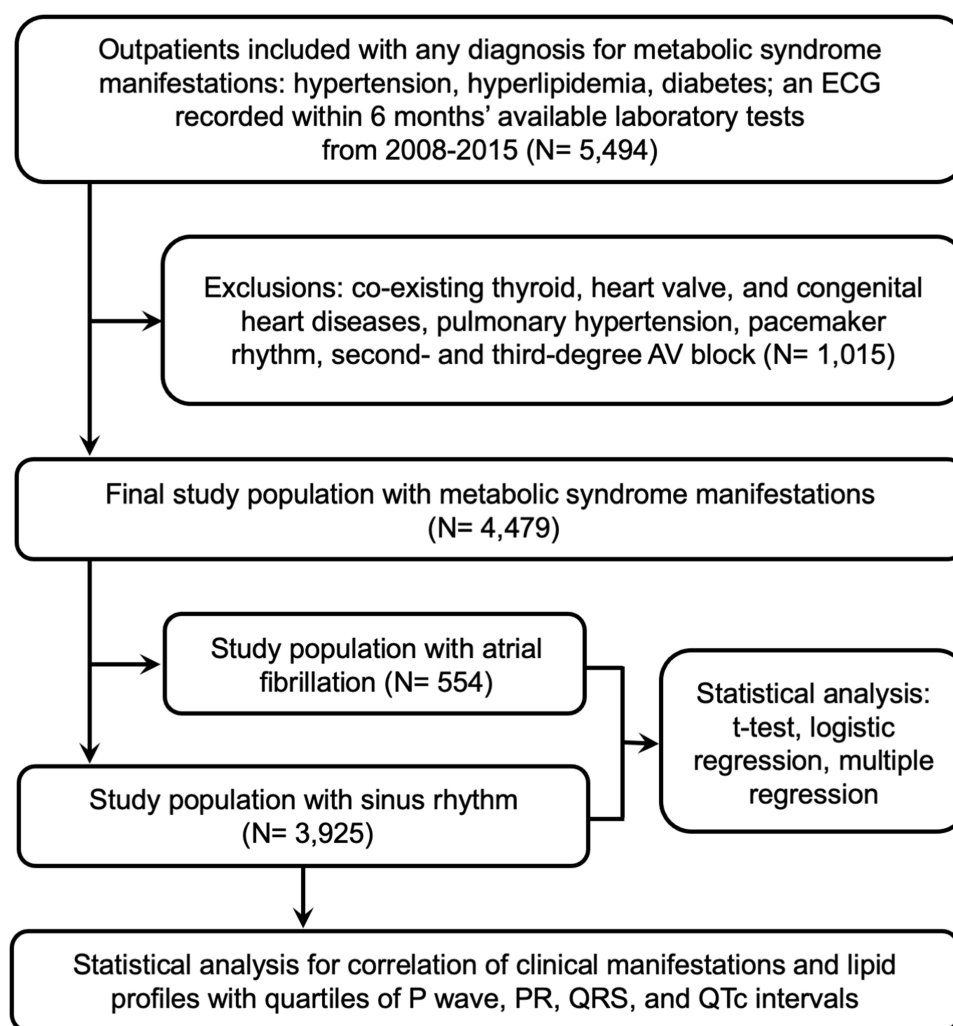


Figure 1 Flow diagram for patient inclusion in the analysis.

$1.73 \text{ m}^2) = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$. Very low-density lipoprotein (VLDL)-cholesterol (C) (VLDL-C) was calculated by the equation as follows: $\text{VLDL-C} = \text{total cholesterol} - \text{low-density lipoprotein-cholesterol (LDL-C)} - \text{high-density lipoprotein-cholesterol (HDL-C)}$.

Definitions for Clinical Diagnosis

Clinical diagnoses were defined by the out-patient diagnosis ICD9 code numbers as follows: hypertension (4011, 4019, 40,210, and 40,290), DM (7902, 25,000, and 25,002), dyslipidemia (2720, 2721, 2722, 2724, 2728, and 2729), thyroid disorders (240, 241, 242, 243, 245, and 246), heart valve diseases (35, 396.9, 424.0, 424.1, 424.2, and 424.3), pulmonary hypertension (416.0), and congenital heart diseases (745, 746, and 747).¹⁶

Electrocardiographic Parameters

The parameters measured in the standard 12-lead ECG included P wave duration, PR interval, QRS width, QTc interval, and cardiac rhythm (sinus rhythm, AF and/or flutter, pacemaker rhythm, ventricular tachycardia, supraventricular tachycardia, and second- or third-degree atrial-ventricular block). QT interval was corrected using Bazett's formula and generated automatically by a Fukuda ECG machine.

The measurements were performed by a medical technician who was blinded to any clinical information, according to the AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram.¹⁷

Statistical Analyses

All continuous variables are presented as the mean \pm standard deviation. The QQtc are divided into quartile by three cut points, 25% percentile, median and 75% percentile. To compare the differences between the non-AF and AF groups, Student's *t* test was used for continuous data, and a chi-square test or Fisher's exact test was used for binary data. To compare differences among QQtc divisions, analysis of variance (ANOVA) was conducted to compare numerical data. To evaluate the determinant factor for AF, univariate logistic regression was used, and the odds ratios (ORs) and 95% confidence intervals (CIs) for the presence of AF were calculated. The resulting significant variables were included for multivariate logistic regression. Statistical significance was set at $P < 0.05$. All analyses were performed using SAS software (version 9.3; SAS Institute, Cary, NC, USA).

Results

Demographic and Baseline Characteristics of the Study Population

Between 2008 and 2015, a total of 5494 patients with diagnoses related to MetS and with available laboratory data within 6 months of a complete 12-lead ECG were eligible for this study. After exclusion criteria, data from the final population of 4479 (58.4% male) were collected for statistical analysis. Based on reviewing ECG, 3925 (87.6%) patients had sinus rhythm, and 554 (12.4%) patients had AF (Figure 1). Demographic and baseline characteristics are presented in [Supplementary Table 1](#). Overall, women (71.8 ± 12.2 years) were older than men (65.1 ± 13.7 years; $P < 0.0001$) and had a higher prevalence of DM and hypertension, but lower prevalence of gout (all $P < 0.01$). In lipid profiles, women had higher levels of total cholesterol, HDL-cholesterol, and VLDL-cholesterol (all $P < 0.05$). Regarding ECG parameters, women had shorter duration of P waves, shorter PR intervals, shorter duration of QRS complexes, and longer QTc intervals (all $P < 0.01$).

Comparison Between Individuals with and without AF

The clinical characteristics of individuals¹⁸ with and without AF are shown in [Table 1](#). Compared with individuals without AF, those with AF were older (73.9 ± 11.8 years vs 67 ± 13.5 years, $P < 0.0001$), more likely to have hypertension (85.6% vs 81.7%, $P = 0.0256$), and less diagnosed with DM (60.1% vs 65.7%, $P = 0.0094$). In biochemistry, AF patients had lower levels of alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR),¹⁸ glucose, LDL-cholesterol, VLDL-cholesterol, non-HDL cholesterol, triglyceride, and higher levels of HDL-cholesterol (all $P < 0.05$). Regarding the ECG parameters, the duration of the QRS complex and QT interval did not differ between

Table I Comparisons Between Individuals with and without AF

Variables	AF Absent n = 3925	AF Present n = 554	P-value
Age (years)	67 ± 13.5	73.9 ± 11.8	<0.001
Male, n (%)	2300 (58.6)	316 (57)	0.485
DM, n (%)	2580 (65.7)	333 (60.1)	0.009
Hypertension, n (%)	3206 (81.7)	474 (85.6)	0.025
Gout, n (%)	300 (7.6)	51 (9.2)	0.200
Hyperlipidemia, n (%)	2340 (57.6)	272 (49.1)	<0.001
Biochemistry			
ALT, IU/L	30.1 ± 43.3	26.4 ± 19.9	0.003
Creatinine, mg/dL	1.8 ± 2.1	1.5 ± 1.3	<0.001
eGFR, mL/min	68.8 ± 41.4	64.1 ± 30.9	0.004
Glucose, mg/dL	126.2 ± 51.8	121.3 ± 41.8	0.024
Total cholesterol, mg/dL	172.2 ± 48.3	155.8 ± 42.5	<0.001
HDL-C, mg/dL	40.1 ± 13.2	41.4 ± 13.7	0.037
LDL-C, mg/dL	103.4 ± 39.4	91.6 ± 35.0	<0.001
VLDL-C, mg/dL	28.8 ± 18.2	22.8 ± 13.3	<0.001
non-HDL-C, mg/dL	132.1 ± 46.0	114.5 ± 40.5	<0.001
Triglyceride, mg/dL	138 ± 97.3	107 ± 65.8	<0.001
Medications			
β-blockers, n (%)	300 (7.6)	52 (9.4)	0.153
Lipid-lowering, n (%)	92 (2.3)	15 (2.7)	0.599
Antiarrhythmics, n (%)	13 (0.3)	19 (3.4)	<0.001
Anti-coagulants, n (%)	129 (3.3)	20 (3.6)	0.691
Electrocardiographic parameters			
QRS, ms	94.5 ± 24.1	95.7 ± 23.7	0.262
QTc, ms	426.1 ± 35.4	427.9 ± 48.1	0.392
QQRS, ms			
Q1 (< 82), n (%)	1081 (27.5)	154 (27.8)	0.524
Q2 (82–90), n (%)	1019 (26.0)	137 (24.7)	
Q3 (90–100), n (%)	879 (22.4)	115 (20.8)	
Q4 (> 100), n (%)	946 (24.1)	148 (26.7)	

(Continued)

Table 1 (Continued).

Variables	AF Absent n = 3925	AF Present n = 554	P-value
QQTc, ms			
Q1 (< 404), n (%)	972 (24.8)	158 (28.5)*	0.008
Q2 (404–424), n (%)	1033 (26.3)	115 (20.8)	
Q3 (424–444), n (%)	981 (25.0)	129 (23.3)	
Q4 (> 444), n (%)	939 (23.9)	152 (27.4)*	

Notes: Values are given as mean \pm SD or number, or percentage in the specific group. Chi-square is used for category variable. *Indicates P value < 0.05.

Abbreviations: DM, diabetes mellitus; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; P, P wave duration; PR, PR interval; QRS, QRS width; QTc, corrected QT interval; QQRS, quartiles of the QRS width; QQTc, quartiles of the QTc interval.

individuals with and without AF. Nevertheless, the quartile analysis of QTc interval showed more distribution over short (QTc < 404 ms) and long QTc interval quartiles (QTc > 444 ms) in patients with AF. To determine the sex differences, separate analyses were performed for male and female individuals ([Supplementary Table 2](#)). In females, some clinical variables, such as DM, ALT, eGFR, and HDL-C, lost significant correlations, but hyperlipidemia and cholesterol remain significant markers.

The Correlation of Clinical Characteristics with Quartiles of QTc

The analysis for evaluating the correlation between clinical characteristics and ECG parameters is shown in [Table 2](#). Overall, the quartiles of QTc were positively correlated with age, creatinine and eGFR levels, and the presence of gout (all $P < 0.05$). On the other hand, the quartiles of QTc were negatively correlated with male sex and VLDL-C levels (both $P < 0.05$). For the ECG parameters, the QTc was positively correlated with PR interval and QRS duration (both $P < 0.0001$) but was not correlated with P wave duration.

The upper normal limits of QTc in males and females are different. For this reason, separate analyses of AF and QT quartiles in men and women were performed ([Supplementary Tables 3 and 4](#)). Significance correlated variables with QTc quartiles were mostly unchanged for men and women in separately analyses. Interestingly, the diagnoses of DM and TG, which were not shown to be significant in [Table 2](#), were significantly correlated with QTc quartiles for both men and women ([Supplementary Tables 3 and 4](#)). In addition, only in women, P wave duration was significantly correlated with QTc quartiles ([Supplementary Table 4](#)).

The Clinical Characteristics Correlated with AF

The results of the univariate and multivariate analyses are shown in [Table 3](#). In univariate analysis, older age, lower levels of VLDL-C, triglyceride, total cholesterol, LDL-C, and eGFR, and the shortest and longest quartiles of QTc were significantly correlated with the presence of AF (all $P < 0.01$). After a multivariate analysis, only age was significantly correlated with the presence of AF ($P < 0.0001$).

Discussion

The main findings of this study that analyzed the patient population with manifestations of MetS included (1) the shortest and longest quartile of QTc intervals reflect increased incidence for AF; (2) QTc interval was significantly correlated with age, sex, VLDL-C, eGFR, and gout; (3) older age was independently associated with the presence of AF; (4) hypertension had the highest odds ratio for AF; (5) individuals with AF had lower levels of total cholesterol, LDL-C, VLDL-C, and triglycerides compared to those without AF; and (6) sex differences were recognized in clinical

Table 2 Correlations of Clinical Characteristics and Other Electrocardiographic Parameters in the Quartiles of QTc

Variables	QQTc1 (< 404 ms) n = 972	QQTc2 (404–424 ms) n = 1033	QQTc3 (424–444 ms) n = 981	QQTc4 (>444 ms) n = 939	P-value
Age	66.3 ± 13.6	66.3 ± 13.1	67.1 ± 13.3	68.4 ± 13.9	0.001
Male, n (%)	604 (62.1)	631 (61.1)	571 (58.2)	494 (52.6)	<0.001
VLDL-C, mg/dL	27.4 ± 15.9	29.6 ± 18.8	28.7 ± 19	29.3 ± 19.1	0.034
Triglyceride, mg/dL	132.3 ± 86.8	143.8 ± 106.8	138.6 ± 100.4	136.9 ± 93.1	0.068
Cholesterol, mg/dL	170.4 ± 48.9	174.7 ± 46.9	173.5 ± 48.8	170 ± 48.6	0.081
HDL-C, mg/dL	40 ± 13.2	40.1 ± 13	40.5 ± 12.8	39.7 ± 13.9	0.634
LDL-C, mg/dL	103.1 ± 41	105 ± 38.2	104.3 ± 38.6	101 ± 39.8	0.132
ALT, IU/L	32 ± 37.6	28.8 ± 20.3	30 ± 57.9	29.7 ± 49.4	0.510
Creatinine, mg/dL	1.4 ± 1.5	1.5 ± 1.7	1.9 ± 2.2	2.3 ± 2.8	<0.001
eGFR, mL/min	77.8 ± 46.5	71.9 ± 36.5	64.9 ± 40.3	59.9 ± 39.5	<0.001
Glucose, mg/dL	124 ± 45.4	125.8 ± 53.5	125.7 ± 50.2	129.4 ± 57.6	0.213
DM, n (%)	630 (64.8)	670 (64.9)	634 (64.6)	646 (68.8)	0.160
Hypertension, n (%)	777 (79.9)	829 (80.3)	822 (83.8)	778 (82.9)	0.066
Hyperlipidemia, n (%)	595 (61.2)	626 (60.6)	594 (60.6)	526 (55.9)	0.067
B-blocker, n (%)	76 (7.8)	68 (6.6)	70 (7.1)	86 (9.2)	0.164
Lipid-lowering, n (%)	19 (2)	24 (2.3)	23 (2.3)	26 (2.8)	0.708
Anti-arrhythmias, n (%)	4 (0.4)	≤2 (0)	4 (0.4)	3 (0.3)	0.810
Anti-coagulants, n (%)	18 (1.9)	47 (4.5)	32 (3.3)	32 (3.4)	0.009
Gout, n (%)	55 (5.7)	88 (8.5)	73 (7.4)	84 (9)	0.031
Sleep apnea, n (%)	≤2 (0)	≤2 (0)	≤2 (0)	≤2 (0)	0.799
PR (msec)	167.6 ± 29.9	170.3 ± 30.7	173.9 ± 33.6	175.6 ± 36.5	<0.001
QRS (msec)	87 ± 11.8	90.5 ± 19.4	95.3 ± 30.2	105.7 ± 26.8	<0.001
P (msec)	109 ± 17.8	109.8 ± 17.3	110.7 ± 17.5	110.2 ± 19.2	0.191
Non-HDL (msec)	130.4 ± 46.4	134.6 ± 44.1	133 ± 46.8	130.3 ± 46.9	0.108

characteristics and ECG parameters. Nevertheless, there was no sex difference in the incidence of AF in the study population.

The average age was 67.9 years for the study population, and the prevalence of AF was 12.4%. In a Japanese population with an average age of 63 years, the prevalence of AF was 9.4%⁵. The incidence rate of AF was higher in men than in women.¹⁹ We suggest that the lack of sex difference in AF incidence may have resulted from the older age of the female population ([Supplementary Table 1](#)).

Hypertension was the most important risk factor for AF in this study. Poor control of blood pressure in elderly patients is associated with a higher incidence of new-onset AF and poorer cardiovascular outcomes of AF compared with normotensive or well-controlled hypertensive patients.²⁰ The awareness of hypertension and good control of blood pressure should be emphasized for individuals with MetS phenotypes.

Table 3 Univariate and Multivariate Analysis for the Presence of AF

Variables	Univariate			Multivariate		
	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Age	1.04	1.04–1.05	<0.001	1.036	1.025–1.046	<0.001
Male	0.94	0.78–1.12	0.485	1.177	0.936–1.481	0.163
VLDL-C	0.97	0.96–0.98	<0.001			
Triglyceride	0.99	0.99–1	<0.001	0.999	0.996–1.002	0.588
Cholesterol	0.99	0.99–0.99	<0.001	0.986	0.972–1.000	0.050
HDL-C	1.01	1–1.01	0.037	1.015	0.998–1.032	0.080
LDL-C	0.99	0.99–0.99	<0.001	1.008	0.994–1.024	0.266
ALT	1	0.99–1	0.049	0.998	0.994–1.003	0.499
eGFR	1	0.99–1	0.019	1	0.997–1.003	0.987
AC glucose	1	1–1	0.056			
DM	0.79	0.66–0.94	0.009	0.84	0.672–1.061	0.147
Hypertension	1.33	1.03–1.71	0.026	1.1	0.8–1.52	0.561
Hyperlipidemia	0.65	0.55–0.78	<0.001	0.886	0.706–1.112	0.295
B-blocker	1.25	0.92–1.71	0.154			
Lipid-lowering	1.16	0.67–2.02	0.600			
Anti-arrhythmias	10.68	5.24–21.75	<0.001	12.129	5.004–29.398	<0.001
Anti-coagulants	1.10	0.68–1.78	0.691	0.545	0.273–1.089	0.086
Gout	1.23	0.9–1.67	0.201			
QRS (ms)	1	1–1.01	0.264			
QTc (ms)	1	1–1	0.283			
non-HDL	0.99	0.99–0.99	<0.001			
QQRS (ms)						
Q1	1.06	0.83–1.36	0.644			
Q2 (Ref)	-	-	-			
Q3	0.97	0.75–1.49	0.839			
Q4	1.16	0.91–0	0.232			
QQTc (ms)						
Q1	1.46	1.13–1.89	0.003	1.147	0.843–1.559	0.382
Q2 (Ref)	Ref	-	-	Ref	-	-
Q3	1.18	0.91–1.54	0.220	1.134	0.832–1.547	0.426
Q4	1.45	1.12–1.88	0.004	1.099	0.804–1.502	0.552

Abbreviations: DM, diabetes mellitus; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very-low-density lipoprotein cholesterol; P, P wave duration; PR, PR interval; QRS, QRS width; QTc, corrected QT interval; QQRS, quartiles of the QRS width; QQTc, quartiles of the QTc interval; Ref, reference.

Clinical studies have shown interesting but contradictory results regarding the correlation between dyslipidemia and AF. Large-population case-control studies and meta-analyses have shown that statins can prevent AF in long-term use.^{21,22} Statin use was shown to reduce the postoperative AF by 50%.²³ On the other hand, similar to the findings from our study, the inverse association between LDL-C and the presence of AF was shown in a prospective cohort of a population of apparently healthy female healthcare professionals aged over 45 years.²⁴ One possible cause is that the association between dyslipidemia and AF is mediated by non-cholesterol components of lipoproteins, instead of direct cholesterol effects.²⁵ This postulation is partially supported by another sub-analysis of the Framingham heart study, in which high triglyceride levels were associated with a higher risk of AF.²⁶ Another possible cause is that during the postprandial period, the plasma concentration of TG-rich lipoproteins such as chylomicron and VLDL changes largely.²⁷ Most clinical studies, as well as the present study, applied 8 to 12 hours of fasting as a standard for blood sampling. As a result, the importance of postprandial lipids and AF risk is masked in most clinical observations. One of our clinical studies demonstrated the significant correlation of postprandial VLDL with atrial remodeling in MetS.²⁸

From our results, patients with the shortest and longest QTc quartiles had a higher incidence of AF. This finding was in line with a published meta-analysis, in which every 10-ms prolongation in QTc had a significantly increased risk for AF with a hazard ratio of 1.17²⁹ and another study that reported young-onset AF with a short QT interval.^{30,31} In contrast, obesity-related cardiac ion channel regulation and QT prolongation have been suggested to contribute to the pathogenesis of AF in MetS.⁹ It is possible that short and long QTc values correlate with different types of AF. This hypothesis requires a large population study to be conducted. Short QTc may be related to a smaller degree of LVH, or a subset of patients with some genetic variants relevant to cardiac channel function. Loss of significant correlation between QTc quartiles and incidence of AF suggests that QTc quartiles are at least partially attributed to co-existing clinical manifestations.

From our analyses, the electrocardiographic parameters, PR, QRS, and QTc interval were significantly correlated with renal function (Table 2). The lower the eGFR, the longer the PR interval, QRS width, and QTc interval. Prolonged QTc in patients with chronic kidney disease has been recognized, and the causes are complex, including co-existing DM, hypertension, heart failure, uremic toxins, electrolyte disturbances, and autonomic dysfunction.³² The coincidence of PR and QRS prolongation indicates that global intracardiac conduction delay, which is associated with gap junction dysfunction, also brings increased risk for AF.^{33,34}

There are several limitations to this study that should be mentioned. First, this retrospective study did not include central obesity as an important inclusion parameter, which was not recorded in a routine outpatient-based chart review. Unmeasured confounders were possible. Second, a routine 12-lead ECG might have missed cases of paroxysmal AF so that listing of the type of AF (paroxysmal / persistent/ chronic) was not possible. Lastly, the results were derived from our medical center and might not be applicable to the general population.

Conclusion

The incidence of non-valvular AF in this single-center outpatient population with MetS phenotypes was high. Sex differences in clinical and electrocardiographic parameters should be considered. The QTc in quartiles were significantly correlated with multiple factors including age, sex, VLDL/TG, renal function, gout, and DM, and most of those are correlated with metabolic syndrome. Short and long QTc were correlated with increased incidence of AF. AF risk in patients with MetS phenotypes can be reflected by QTc quartiles.

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Disclosure

The authors report no conflicts of interest in this work.

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