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The prevalence of prolonged QTc increases by GOLD stage, and is associated with worse survival among subjects with COPD

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ABSTRACT

Background: The role of QTc-prolongation, in relation to the increased mortality in COPD, is unclear.
Objectives: To estimate the prevalence and prognostic impact, assessed as mortality, of QTc-prolongation in COPD, restrictive spirometric pattern (RSP), and normal lung function (NLF), respectively.
Methods: All individuals ($n = 993$) with COPD and age- and sex-matched non-obstructive referents were identified from well-defined population-based cohorts examined in Northern Sweden in 2002–04. In 2005, the study-sample was invited to re-examination including ECG; QTc was calculated and mortality data collected until 31st December 2010.
Results: The prevalence of QTc-prolongation was higher among people with RSP than among those with NLF and, although similar in NLF and COPD, the prevalence increased by COPD-severity. Among participants with COPD, those with QTc prolongation had higher mortality than those with normal QTc, while no such differences were found among participants with NLF or RSP.
Conclusion: Among participants with COPD, the prevalence of QTc-prolongation increased by disease-severity and was associated with mortality.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major public health problem, though greatly under-diagnosed.[1,2] The burden of symptoms is high,[3] comorbidities are common,[4] and cardiovascular comorbidities contribute to the increased mortality among subjects with COPD.[5,6]

Prolonged QTc on electrocardiogram (ECG), i.e. heart rate corrected QT-interval, is a risk marker of arrhythmic episodes and sudden cardiac death.[7-9] There are rare hereditary forms of prolonged QTc, but the acquired form, due to advancing age, electrolyte abnormalities, structural heart disease, and specific drugs, is more common.[10]

A few studies on small and highly selected populations of COPD have suggested that individuals with COPD have an increased prevalence of prolonged QTc.[11] In a population of moderate to severe COPD, the development of ventricular arrhythmias was associated with prolonged QTc,[12] and people with COPD had an increased risk of sudden cardiac death,[13] which may be related to ventricular arrhythmias.

There are different spirometric criteria for COPD which partially overlap. In most clinical guidelines, as well as the Global Initiative for Obstructive Lung Disease (GOLD) document, airway obstruction in COPD is defined by a post-bronchodilator fixed ratio, $FEV_1/FVC < 0.70$,[14,15] while the lower limit of normal, LLN, is recommended in epidemiological studies.[16] Besides COPD, restrictive spirometric pattern, RSP, on dynamic spirometry, is also associated with an increased mortality in cardiovascular disease.[17] RSP is more common than previously realized,[18] and QTc prolongation may contribute to the observed increased cardiovascular mortality. However, there is a lack of population-based studies comparing the prevalence of QTc prolongation among individuals with and without COPD and the possible impact of QTc prolongation on mortality in these groups. Furthermore, to our knowledge, there are no studies addressing these questions among individuals with RSP.

The aim of this population-based study was to estimate the prevalence of prolonged QTc among adults with chronic airway obstruction (COPD) and restrictive pattern respectively, in comparison with normal lung function. In addition, the study aimed to evaluate if prolonged QTc was associated with mortality over a five-year period. A sensitivity analysis was also performed by applying the LLN-COPD spirometric criterion in the GOLD-COPD population.

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Methods

Study population and sample

In 2002–04, four population-based adult cohorts within the epidemiological research program the Obstructive Lung Disease in Northern Sweden (OLIN) studies were invited to re-examination. The recruitment of these cohorts has been described previously.[19] All participants with obstructive lung function impairment (COPD, $n = 993$) were identified by lung function testing together with age- and sex-matched referents without airway obstruction (non-COPD) and recruited to a longitudinal population-based observational study, the OLIN COPD study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Ethics Committee at Umeå University, Umeå, Sweden. Written informed consent was obtained from all participants. Since 2005, the study sample ($n = 1986$) has been invited to annual examinations with a basic program including dynamic spirometry and a structured interview. The study design was previously described in detail.[19] The current study is based on data obtained in 2005, when ECG recordings were also performed.[20] In total 1625 subjects, of which 634 with COPD, had complete data on ECG, spirometry and structured interview. The structured interview collected data on respiratory symptoms, smoking habits and co-morbid conditions. The original age- and sex-matching was removed after recruitment to the study. Mortality data were collected from the national population register during the observation time; from date of examination in 2005 until 31st December 2010.

Electrocardiography

ECG was performed before spirometry, after sufficient rest, and recorded as a standard resting 12-lead ECG in the supine position. All ECGs were classified according to the Minnesota Code (MC).[20,21] Subjects were excluded if they had ECG-abnormalities which could interfere with measurements of the QT interval ($n = 145$, Fig. 1). QT-measurements were performed manually with a calliper of a 0.01 mm resolution by a qualified observer blinded to clinical data. A second qualified observer measured a random sample of the ECGs and the observers' measurements were compared employing correlation analyses of maximum QT-distance and mean RR-interval ($r = 0.94$, $p < 0.001$ and $r = 0.89$, $p < 0.001$ respectively). The QT was measured in three consecutive ECG complexes in lead II, V5 and V6. The mean QT-interval of each lead was calculated and the R-R interval was measured in the lead with the longest mean QT interval. To identify the end of the T-wave, the "tangent method" was used.[22] Corrected QT intervals (QTc) were derived using the Bazett formula[23] for heart rates < 90 bpm and the Fridericia formula for heart rates ≥ 90 bpm.[24] A threshold of 450 ms for men and 460 ms for women was used to define prolonged QTc intervals.[25] Borderline QTc was defined as 430–449 ms for men and 440–459 ms for women.

Lung function

Lung function test was performed using a dry volume spirometer, the Vicatest 5 (Gebr. Mijnhardt B.V. Odijk, Netherlands). Vital capacity (VC) was defined as the highest value of forced vital capacity (FVC) and slow vital capacity (SVC). The reversibility test was performed with Ventoline® 4 × 0.2 mg if $FEV_1/VC < 0.70$ or $FEV_1 < 80\%$ of predicted value. Based on the best values of VC and FEV_1 pre- or post-reversibility test, COPD was defined as $FEV_1/VC < 0.70$ (GOLD-COPD) and by the LLN criterion, FEV_1/VC below the fifth percentile of the reference value (LLN-COPD). Disease severity among subjects with COPD was based on $FEV_1\%$ predicted, further classified according to GOLD into GOLD 1-4.[14] Non-COPD, defined as $FEV_1/VC \geq 0.70$, was further divided into normal lung function (NLF), $FEV_1/VC \geq 0.70$ and $VC \geq 80\%$, and restrictive spirometric pattern (RSP), $FEV_1/VC \geq 0.70$ and $VC < 80\%$. Local reference values based on respiratory healthy non-smokers were used.[26]

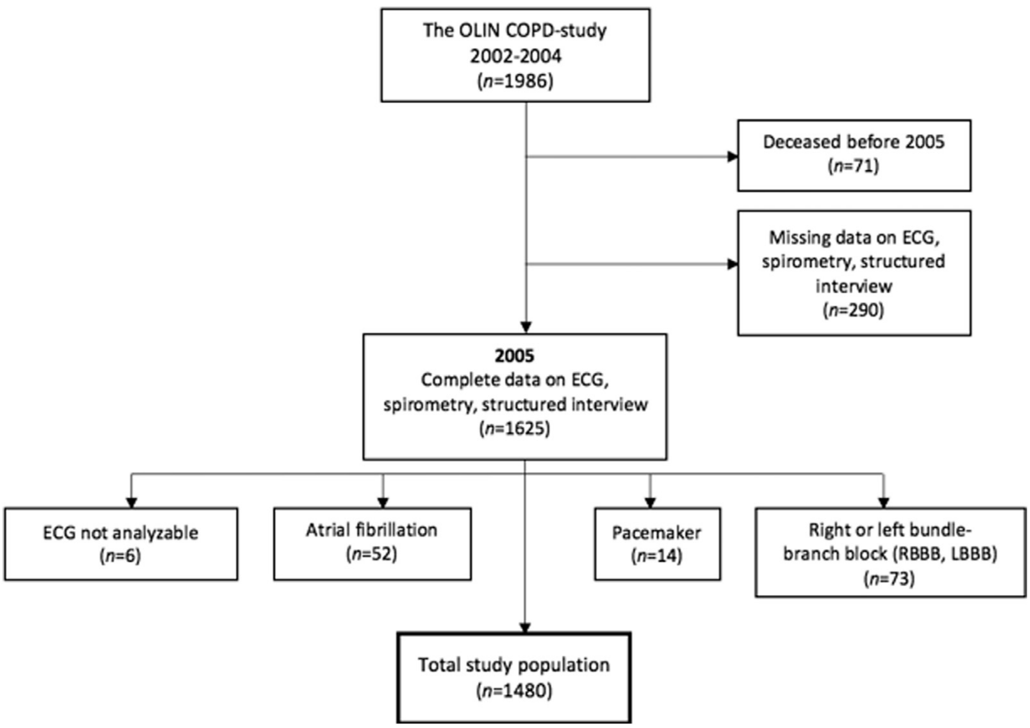

Fig. 1. Recruitment of the study population.

Statistical analysis

Statistical analyses were performed with the program SPSS version 22.0 (IBM, Armonk, NY, USA). Categorical variables were compared using the chi-square test and one sample chi-square. Fischer's exact test was used when appropriate. Continuous data was analyzed with histograms and P-P plots, and followed a Gaussian distribution. Independent sample *t*-test and ANOVA were used to compare means. Pearsons correlation was used for inter-rater reliability test comparing ECG-readers QT measurements. All tests were two tailed, and p values of < 0.05 were considered statistically significant. Survival by normal, borderline and prolonged QTc interval was illustrated by Kaplan-Meier curves separately for subjects with NLF, RSP, GOLD-COPD and LLN-COPD, respectively.

Results

A flowchart of the study sample, recruitment, inclusions and exclusions is shown as Fig. 1. The study sample included 1480 adults with complete data on spirometry, interview and ECG with QTc measurements (Fig. 1), whereof 571 GOLD-COPD and 909 non-COPD, the latter further divided into NLF ($n = 734$) and RSP ($n = 175$). The distribution of disease severity in GOLD-COPD was 41.0% GOLD 1 ($n = 234$), 51.7% GOLD 2 ($n = 295$) and 7.4% GOLD 3–4 ($n = 42$). The clinical and demographic characteristics of the study population are presented in Table 1.

Subjects with RSP had a higher mean age, mean BMI and a higher prevalence of diabetes, hypertension, angina, AMI and the compound measure ischemic heart disease (IHD) than subjects with NLF (Table 1). Mean QTc was longer, and the prevalence of prolonged QTc was higher in RSP than NLF ($p = 0.012$ and 0.027), significantly so also among men, but not among women. The prevalence of borderline QTc was non-significantly higher in RSP than in NLF ($p = 0.208$) (Table 2).

Subjects with GOLD-COPD had a higher mean age and burden of tobacco smoking, but lower mean BMI, than those with NLF. The prevalence of acute myocardial infarction (AMI) was higher in GOLD-COPD than NLF, while the prevalence of the compound measure IHD was similar (Table 1). Mean QTc and prevalence of prolonged QTc were similar in NLF and GOLD-COPD, while the prevalence of borderline QTc was higher in GOLD-COPD than in NLF ($p < 0.001$). Among men, the mean QTc and the prevalence of borderline QTc were higher in GOLD-COPD than NLF, while among females, similar comparisons were non-significant (Table 2).

Mean QTc was higher in GOLD 2 and GOLD 3-4 than in GOLD 1, with a similar pattern in both sexes. The prevalence of borderline and prolonged QTc was higher in GOLD 2 and GOLD 3-4 than in GOLD 1, with a similar pattern among men for prolonged QTc, and among women for borderline QTc (Table 3). The prevalence of borderline as well as prolonged QTc increased by GOLD grade (test for trend $p = 0.002$ for both groups).

Among those with GOLD-COPD, 299 subjects, 52%, fulfilled the spirometric criteria for LLN-COPD. Supplemental Table 1 show basic characteristics comparing NLF and LLN-COPD. The proportion of women was lower in LLN-COPD than NLF, while the mean age was similar. Otherwise the pattern was similar as when comparing NLF and GOLD-COPD.

When comparing mean QTc and prevalence of borderline and prolonged QTc between NLF and LLN-COPD (supplemental Table 2), the pattern was similar as between NLF and GOLD-COPD; the prevalence of borderline QTc was higher in LLN-COPD than NLF, significantly so also among men ($p = 0.005$) (supplemental Table 2). QTc variables by GOLD grade had a similar pattern in LLN-COPD as in GOLD-COPD. Mean QTc was longer in GOLD 3-4 than GOLD 1, and non-significantly so also when comparing GOLD 2 and GOLD 1. The prevalence of prolonged QTc was higher in GOLD 2 and GOLD 3-4 than in GOLD 1. Corresponding analyses showed a similar pattern among men, but not among women, with the reservation for few cases in the sex-stratified analyses (supplemental Table 3). The prevalence of prolonged but not borderline QTc increased by GOLD grade (test for trend $p = 0.043$ and 0.187, respectively).

The cumulative overall mortality was 7.1% ($n = 52$) in NLF, 12.6% ($n = 22$) in RSP, 11.6% ($n = 66$) in GOLD-COPD and 12.4% ($n = 37$) in LLN-COPD. In Table 4, the mortality is presented by normal, borderline and prolonged QTc in each group respectively. There were no significant findings in the NLF and RSP groups. The mortality was higher among those with borderline QTc than those with normal QTc in GOLD-COPD and LLN-COPD, and prolonged QTc was associated with a higher mortality than normal QTc in GOLD-COPD, and non-significantly so also in LLN-COPD. Test for trend was positive in both GOLD-COPD and LLN-COPD ($p = 0.005$ and 0.012). The mortality was similar in borderline and prolonged QTc in both GOLD-COPD ($p = 0.665$) and LLN-COPD ($p = 0.845$). Survival by normal, borderline and prolonged QTc interval is illustrated by Kaplan-Meier curves by group in Fig. 2A) NLF, B) RSP, C) GOLD-COPD, and D) LLN-COPD, and the corresponding

Table 1
Clinical and demographic characteristics of the sample at baseline, comparing subjects with normal lung function (NLF) with restrictive spirometric pattern (RSP) and GOLD-COPD, respectively. Significant values in bold. *N* (%), unless otherwise stated

Category	Variable	NLF $n = 734$	RSP $n = 175$	P[b]	GOLD-COPD $n = 571$	P[c]
Sex	Women	363 (49.5)	78 (44.6)	0.245	260 (45.5)	0.159
Age	Age, mean (SD)	64.1(11.2)	67.7 (9.8)	**<0.001**[d]	66.1 (10.3)	**0.001**[d]
BMI	BMI, mean (SD)	27.0 (4.1)	29.0 (4.9)	**<0.001**[d]	26.3	**0.002**[d]
Smoking habits	Pack-years, mean (SD)	6.9 (10.6)	8.3 (12.6)	0.117	16.4 (16.2)	**<0.001**[d]
	Non-smoker	349 (47.5)	82 (46.9)	0.869	141 (24.7)	**<0.001**[d]
	Ex-smoker	289 (39.4)	74 (42.3)	0.480	228 (39.9)	0.838
	Current smoker	96 (13.1)	19 (10.9)	0.427	202 (35.4)	**<0.001**[d]
Comorbidities	Diabetes	58 (7.9)	37 (21.1)	**<0.001**[d]	48 (8.4)	0.741
	Hypertension	230 (31.3)	90 (51.4)	**<0.001**[d]	197 (34.5)	0.227
	Angina pectoris	74 (10.1)	28 (16.0)	**0.026**	63 (11.0)	0.578
	AMI	17 (2.3)	11 (6.3)	**0.006**[d]	28 (4.9)	**0.011**[d]
	CABG	22 (3.0)	8 (4.6)	0.295	9 (1.6)	0.094
	PCI	12 (1.6)	5 (2.9)	0.346	9 (1.6)	0.933
	IHD[a]	87 (11.9)	35 (20.0)	**0.004**[d]	84 (14.7)	0.129

[a] Ischemic Heart Disease (IHD), includes any of angina pectoris, myocardial infarction (AMI), Coronary artery Bypass Graft (CABG) and Percutaneous Coronary Intervention (PCI).
[b] Comparison between NLF and RSP.
[c] Comparison between NLF and COPD.
[d] Significant also after Bonferroni correction for multiple testing.

Table 2
Comparing mean QTc values, the prevalence of prolonged QTc and borderline QTc in subjects with normal lung function (NLF) to those with restrictive spirometric pattern (RSP) and GOLD-COPD, respectively. Analyses are also stratified for sex. Significant values in bold

Variables	Sex	NLF $n = 734$	RSP $n = 175$	P[c]	COPD $n = 571$	P[d]
QTc ms, mean (SD) (range)	All	414.3 (25.3) (343.0–509.3)	419.8 (27.6) (357.5–501.28)	**0.012**[e]	416.1 (25.8) (344.7–501.4)	0.208
	Men	409.7 (25.5) (343.0–503.2)	417.3 (30.6) (357.5–501.3)	**0.026**	413.9 (26.6) (344.7–498.7)	**0.034**
	Women	419.1 (24.1) (345.3–509.3)	422.9 (23.2) (363.0–486.9)	0.633	418.8 (24.5) (356.6–501.4)	0.870
Heart rate, mean (SD)	All	68.9 (11.3)	68.9 (12.4)	0.986	71.1 (12.3)	**0.001**[e]
	Men	66.7 ± 11.4	66.6 ± 12.5	0.963	70.0 ± 12.3	<**0.001**[e]
	Women	71.2 ± 10.8	71.8 ± 11.7	0.691	72.4 ± 12.2	0.227
Prolonged QTc n(%)[a]	All	48 (6.5)	20 (11.4)	**0.027**	39 (6.8)	0.835
	Men	26 (7.0)	15 (15.5)	**0.009**[e]	27 (8.7)	0.416
	Women	22 (6.1)	5 (6.4)	0.907	12 (4.6)	0.434
Borderline QTc, n(%)[b]	All	80 (10.8)	25 (14.3)	0.208	98 (17.2)	**0.001**[e]
	Men	45 (12.1)	11 (11.3)	0.831	62 (19.9)	**0.005**[e]
	Women	35 (9.6)	14 (17.9)	**0.034**	36 (13.8)	0.103

[a] Prolonged QTc is defined as ≥ 450 ms for men and ≥ 460 ms for women.
[b] Borderline QTc is defined as ≥ 430 ms for men and ≥ 440 ms for women.
[c] Comparison between NLF and RSP.
[d] Comparison between NLF and COPD.
[e] Significant also after Bonferroni correction for multiple testing.

log rank test indicated different survival when comparing normal, borderline and prolonged QTc in GOLD-COPD and LLN-COPD ($p = 0.016$ and $p = 0.019$), but not in NLF and RSP.

Discussion

In this population-based study the prevalence of borderline QTc was higher in both groups with airway obstruction, GOLD-COPD and LLN-COPD, when compared with NLF. The prevalence of prolonged QTc did not differ between groups. Mean QTc increased by GOLD stage regardless of COPD definition, and so did the prevalence of borderline and prolonged QTc. In general, the observed differences were more pronounced among men than among women. Both borderline and prolonged QTc were associated with increased mortality when compared with normal QTc among subjects with GOLD-COPD and LLN-COPD. Although individuals with restrictive spirometric pattern (RSP) had more diabetes, cardiovascular disease, longer mean QTc interval, and higher prevalence of prolonged QTc compared to subjects with NLF, neither borderline nor prolonged QTc was associated with increased mortality among them.

Acquired prolonged QTc is more common among adults and is associated with advanced age, electrolyte abnormalities, structural heart disease and specific drugs.[27,28] There is also evidence that prolonged QTc is associated with an increased risk for death.[29,30] There was no association between QT interval and overall or cardiovascular mortality in a follow-up of the original community-based cohort of the Framingham Heart Study.[31] However, the QT interval was associated with increased all-cause mortality as well as cardiovascular and sudden cardiac death in a later follow up of the Framingham Heart study, which also included a second cohort. However, the risk was attenuated after adjustment for heart rate.[3] In a large US population-based study including > 15,000 subjects there was an increased risk for cardiovascular death associated with prolonged QTc among both men and women.[32] In the large Rotterdam study, prolonged QTc, defined as > 440 ms, was associated with an increased risk for death among subjects without signs of cardiac dysfunction, independent of age, sex, medication and previous myocardial infarction.[1]

Even though the pathophysiological relationship between COPD and prolonged QTc is not clear, subjects with COPD and hypoxemia may have autonomic neuropathy associated with prolonged QTc interval and an increased risk for death.[33] The assumption of a relationship between autonomic neuropathy associated with chronic lung disease, prolonged QTc, and mortality is also supported by a study of 3000 elderly Japanese-American men on Hawaii.[34] There are a few studies on highly selected COPD-populations focusing on the prevalence and prognostic impact of prolonged QTc; longer mean QTc was associated with mortality in a follow up of subjects with COPD without known cardiovascular disease hospitalized due to exacerbation.[35] In a

Table 3
The QTc interval among subjects with GOLD-COPD by GOLD-grade. Comparing mean QTc values, prevalence of prolonged QTc and borderline QTc in GOLD 1 with GOLD 2 and GOLD 3-4, respectively. Analyses are also stratified for sex. Significant values in bold

Variable	Sex	GOLD 1 $n = 234$	GOLD 2 $n = 295$	P[c]	GOLD 3–4 $n = 42$	P[d]
Sex n (%)	Women	115 (49.1)	131 (44.4)		14 (33.3)	
QTc ms, mean (SD)	All	411.7 (23.3)	418.9 (27.3)	**0.001**[e]	421.2 (25.2)	**0.017**[e]
	Men	409.0 (23.9)	415.9 (28.3)	**0.032**	423.0 (24.1)	**0.006**[e]
	Women	414.4 (22.4)	422.7 (25.5)	**0.008**[e]	417.6 (27.9)	0.628
Heart rate, mean (SD)	All	70.1 (12.3)	70.8 (11.7)	0.550	78.4 (14.4)	<**0.001**[e]
	Men	67.9 (11.6)	70.4 (11.8)	0.639	78.4 (15.1)	**0.001**[e]
	Women	72.4 (12.6)	71.7 (11.6)	0.659	78.2 (15.3)	0.110
Prolonged QTc, n (%)[a]	All	8 (3.4)	26 (8.8)	**0.012**[e]	5 (11.9)	**0.017**[e]
	Men	4 (3.4)	18 (11.0)	**0.018**[e]	5 (17.9)	**0.004**[e]
	Women	4 (3.5)	8 (6.1)	0.340	0 (0)	0.478
Borderline QTc, n (%)[b]	All	27 (11.5)	62 (21.0)	**0.004**[e]	9 (21.4)	0.080
	Men	19 (16.0)	37 (22.6)	0.169	6 (21.4)	0.489
	Women	8 (7.0)	25 (19.1)	**0.005**[e]	3 (21.4)	0.067

[a] Prolonged QTc is defined as ≥ 450 ms for men and ≥ 460 ms for women.
[b] Borderline QTc is defined as ≥ 430 ms for men and ≥ 440 ms for women.
[c] Comparison between GOLD 1 and GOLD 2.
[d] Comparison between GOLD 1 and GOLD 3-4.
[e] Significant also after Bonferroni correction for multiple testing.

Table 4
Comparing cumulative mortality across 5 years among subjects with normal QTc, borderline QTc and prolonged QTc by group; normal lung function (NLF), restrictive spirometric pattern (RSP), GOLD-COPD and LLN—COPD. Data are presented as n (%). Significant values in bold

	Normal	Borderline	P[a]	Prolonged	P[b]	P[c]
NLF	39 (6.4)	8 (10.0)	0.236	5 (10.4)	0.289	0.155
RSP	17 (13.1)	3 (12.0)	0.883	2 (10.0)	0.700	0.695
GOLD-COPD	41 (9.4)	17 (17.3)	**0.023**[d]	8 (20.5)	**0.030**	**0.005**
LLN-COPD	20 (9.1)	12 (21.8)	**0.009**[d]	5 (20.0)	0.090	**0.012**

[a] Comparing normal QTc and borderline QTc.
[b] Comparing normal QTc and prolonged QTc.
[c] Mantel Haenzel test for trend.
[d] Significant also after Bonferroni correction for multiple testing.

population of 91 subjects with more severe COPD, close to every third had a prolonged QTc interval defined as > 450 ms, which was significantly more common than among controls.[5] In 246 patients above the age of 65, with a COPD diagnosis from general practice confirmed by post-bronchodilator $FEV_1/FVC < 0.70$, 9% had prolonged and 16% borderline QTc, and the prevalence of prolonged- but not borderline QTc increased by GOLD stage; in GOLD 1, 2 and 3, 6%, 8% and 13% respectively.[36] Also in this study, the Bazett formula was used for correction of heart rate, but the cut-off for borderline and prolonged QTc was slightly higher for women than in our study; 450–470 ms and > 470 ms, respectively. In another study, where 281 out of 2585 participants fulfilled the spirometric COPD criteria, COPD was associated with prolonged QTc, using similar cut-offs as in our study, but employing the Framingham formula for heart rate correction.[37] While the studies referenced above indicate that the prevalence of prolonged QTc interval may be increased and have an impact on prognosis in COPD, there is a lack of population-based studies including subjects with COPD confirmed by generally accepted spirometric criteria.

To the best of our knowledge, this is the first population-based study to show that not only the prevalence of ischemic ECG abnormalities,[20] but also borderline and prolonged QTc, increased by disease severity among subjects with COPD, confirmed by post-bronchodilator spirometric criteria. Furthermore, regardless of whether COPD was defined by the post-bronchodilator fixed-ratio criteria (GOLD-COPD) or the lower limit of normal criteria (LLN-COPD), both borderline and prolonged QTc were associated with worse survival than normal QTc among subjects with COPD, but not among subjects with NLF or RSP. RSP is associated with an increased cardiovascular burden,[17,38] also confirmed by our study. Still, despite a higher burden of CVD, longer mean QTc and higher prevalence of prolonged QTc in RSP than in NLF, we found no increased mortality related to QTc prolongation in RSP, nor in NLF.

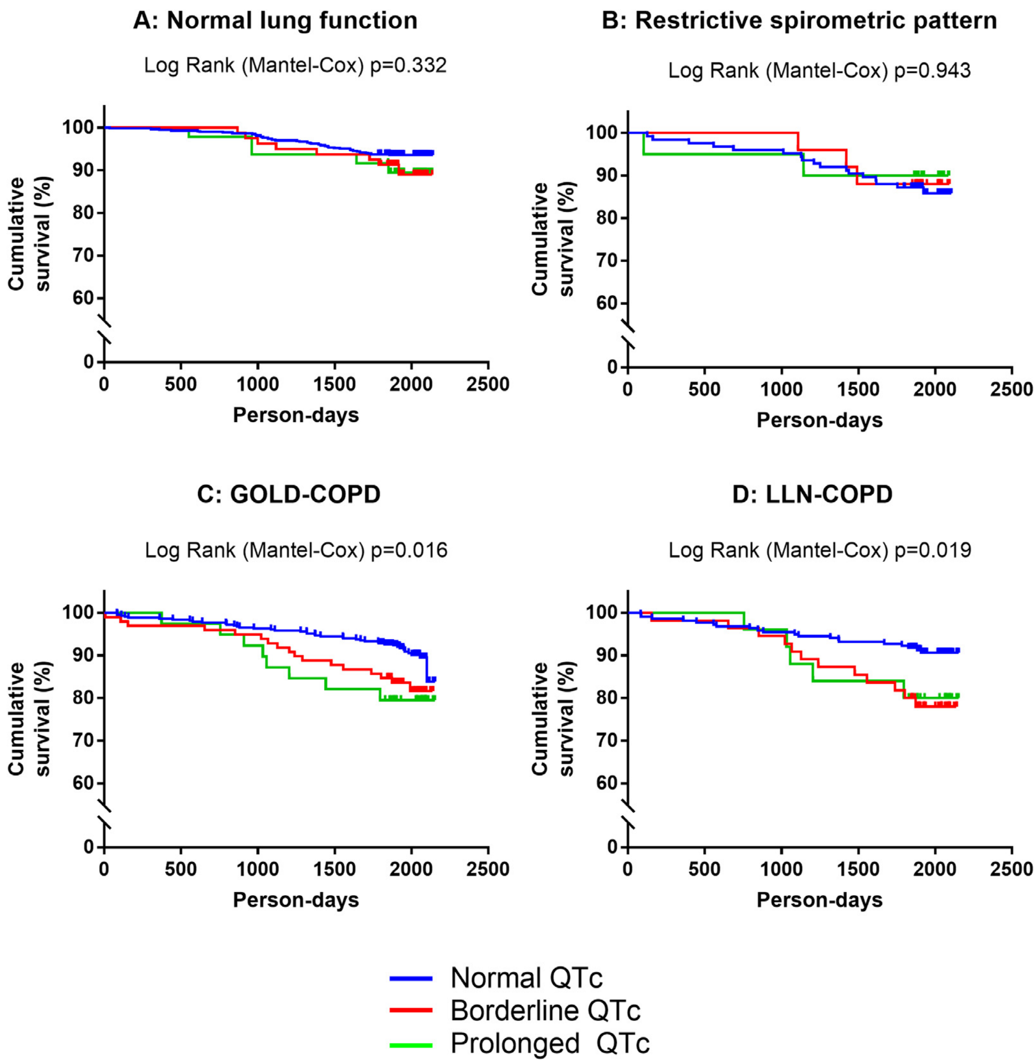

Fig. 2. Kaplan–Meier curves illustrating survival among subjects with normal, borderline and prolonged QTc respectively within the groups (A) Normal lung function, (B) Restrictive spirometric pattern, (C) GOLD-COPD, and (D) LLN—COPD.

The current study has some limitations, for example, lack of information about medications. It is known that different drugs may affect the QT-interval and induce Torsades de Pointes.[39] B-agonists, a commonly used drug in COPD, has been associated with increased all-cause mortality,[40] but there is no clear evidence that b-agonists have a significant clinical effect on the QTc. However, caution regarding medication that may interact and be harmful to subjects with prolonged QTc is warranted. Furthermore, the study population was not large enough to allow analyses of subpopulations or multivariate risk factor analyses. Thus, the results of the sex-stratified analyses have to be interpreted with caution, due to a low number of cases in some groups.

An additional limitation is the challenge of recognizing the end of the T-wave when measuring the QT interval on the ECG. We used the "tangent method" to identify the end of the T-wave,[22] a commonly used method with a high reproducibility, but considered to give systematically shorter QT measurement compared to other methods.[41] We used the cut-off for prolonged QTc according to the American Heart Association,[25] while the cut-off for borderline QTc is debatable, as there is no generally accepted gold standard.[44] The methods for heart rate adjustment are also not well established. The Bazett formula is one of the most commonly used[1,5,39,42] and was used in this study for heart rates up to 90 bpm, while the Fridericia formula was used for heart rates above that. However, the Bazett formula may overestimate the risk for death associated with QTc[43] and, according to a recently published paper, the Fredericia, Hodges and Framingham formulas were better than the Bazett formula to remove the effect of heart rate on the QT interval.[44] On the other hand, the method for heart rate adjustment does not affect the association between death and QTc.[35] Similar adjustments for heart rate were used in all groups, and the chosen formulas likely do not explain the observed differences between them. Furthermore, our results are based on ECG registration at one occasion; QTc interval may change over time and others have shown that consistent, but not inconsistent, QTc-prolongation is associated with increased risk for death.[45]

Most previous studies of QTc in COPD have been performed in highly selected populations, including subjects with more severe COPD, and the results of these studies may also be affected by the under-diagnosis of COPD.[1] In contrast, our cohort includes mostly people with mild to moderate COPD, corresponding to the known distribution of disease severity in population-based studies.[46] Our results are thus not affected by the known under-diagnosis[1,47] and are expected to be generalizable to COPD in the population. While the current study has some limitations, the increased cumulative mortality illustrated by the Kaplan-Meier curves associated with borderline and prolonged QTc in COPD, but not RSP and NLF, is clearly hypothesis generating. Important future research questions will be to evaluate the possible impact of medication on QTc among individuals with COPD, and to enlarge the study sample to allow multivariate risk factor analyses and analyses of subpopulations.

Conclusion

In this population-based study, diabetes, cardiovascular disease and QTc prolongation were more common among subjects with restrictive spirometric pattern than normal lung function. However, neither the borderline or prolonged QTc were associated with increased mortality among those with restrictive spirometric pattern or normal lung function. Among subjects with obstructive lung function impairment, regardless if defined by the post-bronchodilator fixed ratio or the LLN-criteria, the prevalence of QTc prolongation increased by GOLD stage, and both borderline and prolonged QTc intervals were associated with worse survival when compared with normal QTc. Thus, a simple 12-lead ECG including assessment of QTc may be of prognostic value in COPD. Further studies of factors associated with prolonged QTc intervals in COPD and, thereby possible means of intervention, should be considered.

Conflict of interest

None of the authors have any conflict of interest to report towards this manuscript.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hrtlng.2018.09.015.

References

1. Lamprecht B, Soriano BJ, Studnicka M, et al. Determinants of underdiagnosis of COPD in national and international surveys. *Chest*. 2015;148(4):971–985. Oct.
2. Akamatsu K, Yamagata T, Kida Y, Tanaka H, Ueda H, Ichinose M. Poor sensitivity of symptoms in early detection of COPD. *COPD*. 2008;5(5):269–273.
3. Eckerblad J, Tödt K, Jakobsson P, et al. Symptom burden in stable COPD patients with moderate or severe airflow limitation. *Heart Lung*. 2014;43(4):351–357. Jul-Aug.
4. Anecchino C, Rossi E, Fanizza C, De Rosa M, Tognoni G, Romero M. Prevalence of chronic obstructive pulmonary disease and pattern of comorbidities in a general population. *Int J Chron Obstruct Pulmon Dis*. 2007;2(4):567–574.
5. Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res*. 2014;15:89.
6. Berry CE, Wise RA. Mortality in COPD: causes, risk factors, and prevention. *COPD*. 2010;7(5):375–382.
7. 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):1888–1894.
8. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis*. 2001;43(5 Suppl 1):1–45.
9. Noseworthy PA, Peloso GM, Hwang SJ, et al. QT interval and long-term mortality risk in the Framingham Heart Study. *Ann Noninvasive Electrocardiol*. 2012;17(4):340–348.
10. Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. *ScientificWorldJournal*. 2012;2012 212178.
11. Sievi NA, Clarenbach CF, Camen G, Rossi VA, van Gestel AJ, Kohler M. High prevalence of altered cardiac repolarization in patients with COPD. *BMC Pulm Med*. 2014;14:55.
12. Yildiz P, Tukek T, Akkaya V, et al. Ventricular arrhythmias in patients with COPD are associated with QT dispersion. *Chest*. 2002;122(6):2055–2061.
13. Lahousse L, Niemeijer MN, van den Berg ME, et al. Chronic obstructive pulmonary disease and sudden cardiac death: the Rotterdam study. *Eur Heart J*. 2015;36(27):1754–1761.
14. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med*. 2017;195(5):557–582. Mar 1.
15. Miravitlles M, Vogelmeier C, Roche N, et al. A review of national guidelines for management of COPD in Europe. *Eur Respir J*. 2016;47(2):625–637.
16. Bakke PS, Ronmark E, Eagan T, et al. Recommendations for epidemiological studies on COPD. *Eur Respir J*. 2011;38(6):1261–1277.
17. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax*. 2010;65(6):499–504.
18. Mannino DM, McBurnie MA, Tan W, et al. Restricted spirometry in the Burden of Lung Disease Study. *Int J Tuberc Lung Dis*. 2012;16(10):1405–1411.
19. Lindberg A, Lundbäck B. The Obstructive Lung Disease in Northern Sweden Chronic Obstructive Pulmonary Disease Study: design, the first year participation and mortality. *Clin Respir J*. 2008;2(Suppl 1):64–71.
20. Nilsson U, Johansson B, Eriksson B, Blomberg A, Lundback B, Lindberg A. Ischemic heart disease among subjects with and without chronic obstructive pulmonary

disease–ECG-findings in a population-based cohort study. *BMC Pulm Med*. 2015;15:156.
21. Prineas RJ, Crow RS, Blackburn HW. *The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification*. Boston, Mass.: J. Wright; 1982.
22. Postema PG, De Jong JS, Van der Bilt IA, Wilde AA. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm*. 2008;5(7): 1015–1018.
23. Bazett HC. An analysis of time relations of the electrocardiogram. *Heart*. 1920;7:353–370.
24. Fridericia LS. The duration of systole in an electrocardiogram in normal humans and in patients with heart disease. 1920. *Ann Noninvasive Electrocardiol*. 2003;8 (4):343–351.
25. Rautaharju PM, Surawicz B, Gettes LS, 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):982–991.
26. Backman H, Lindberg A, Odén A, et al. Reference values for spirometry - report from the Obstructive Lung Disease in Northern Sweden studies. *Eur Clin Respir J*. 2015;2:26375.
27. Moreno-Gutierrez PA, Gaviria-Mendoza A, Canon MM, Machado-Alba JE. High prevalence of risk factors in elderly patients using drugs associated with acquired torsades de pointes chronically in Colombia. *Br J Clin Pharmacol*. 2016;82(2): 504–511.
28. Vandael E, Vandenberk B, Vandenberghe J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. *Int J Clin Pharm*. 2017;39 (1):16–25.
29. Chugh SS, Reinier K, Singh T, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: the Oregon Sudden Unexpected Death Study. *Circulation*. 2009;119(5):663–670.
30. Kozik TM, Wung SF. Cardiac arrest from acquired long QT syndrome: a case report. *Heart Lung*. 2009;38(3):238–242. May-Jun.
31. Goldberg RJ, Bengtson J, Chen ZY, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study experience). *Am J Cardiol*. 1991;67(1):55–58.
32. Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR, Study A. Heart rate-corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC study. *J Am Coll Cardiol*. 2004;43 (4):565–571.
33. Stewart AG, Waterhouse JC, Howard P. The QTc interval, autonomic neuropathy and mortality in hypoxaemic COPD. *Respir Med*. 1995;89(2):79–84.
34. Sharp DS, Masaki K, Burchfiel CM, Yano K, Schatz IJ. Prolonged QTc interval, impaired pulmonary function, and a very lean body mass jointly predict all-cause mortality in elderly men. *Ann Epidemiol*. 1998;8(2):99–106.
35. Zulli R, Donati P, Nicosia F, et al. Increased QT dispersion: a negative prognostic finding in chronic obstructive pulmonary disease. *Intern Emerg Med*. 2006;1 (4):279–286.
36. Warnier MJ, Rutten FH, Numans ME, et al. Electrocardiographic characteristics of patients with chronic obstructive pulmonary disease. *COPD*. 2013;10(1): 62–71.
37. Armstrong HF, Lovasi GS, Soliman EZ, et al. Lung function, percent emphysema, and QT duration: The Multi-Ethnic Study of Atherosclerosis (MESA) lung study. *Respir Med*. 2017;123:1–7.
38. Eriksson B, Lindberg A, Mullerova H, Ronmark E, Lundback B. Association of heart diseases with COPD and restrictive lung function–results from a population survey. *Respir Med*. 2013;107(1):98–106.
39. Woosley RL, Heise CW, Romero KA. www.Crediblemeds.org. QTdrugs List, Accession Date 6/15/18, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755.
40. Salpeter SR. Bronchodilators in COPD: impact of beta agonists and anticholinergics on severe exacerbations and mortality. *Int J Chron Obstr Pulm Dis*. 2007;2(1):11–18. Mar.
41. Kasamaki Y, Ozawa Y, Ohta M, et al. Automated versus manual measurement of the QT interval and corrected QT interval. *Ann Noninvasive Electrocardiol*. 2011;16 (2):156–164.
42. Johnson JN, Ackerman MJ. QTc: how long is too long? *Br J Sports Med*. 2009;43 (9):657–662.
43. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc*. 2016;5(6):1–10.
44. Mohebi R, Jehan A, Grober A, Froelicher V. Percentile categorization of QT interval as an approach for identifying adult patients at risk for cardiovascular death. *Heart Rhythm*. 2017;14(8):1210–1216.
45. Niemeijer MN, van den Berg ME, Deckers JW, et al. Consistency of heart rate-QTc prolongation consistency and sudden cardiac death: the Rotterdam Study. *Heart Rhythm*. 2015;12(10):2078–2085.
46. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007;370(9589):741–750. Sep 1.
47. Lindberg A, Bjerg A, Bjerg-Bäcklund A, Rönmark E, Larsson LG, Lundbäck B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med*. 2006;100(2):264–272.