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A normal electrocardiogram indicates a better prognosis in patients with moderate to very severe chronic obstructive pulmonary disease

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The role of electrocardiography (ECG) in predicting mortality in patients with chronic obstructive pulmonary disease (COPD) has not been sufficiently established. Research question: Is a normal ECG associated with a better prognosis than an abnormal ECG in patients with COPD? ECG parameters were assessed in patients enrolled in the Czech Multicenter Research Database of COPD. We assessed ECGs from baseline (August 2013) until December 31, 2019, or until death. The primary endpoint was 5-year overall survival depending on the ECG findings. A total of 300 subjects were enrolled in the study and 143 died during follow-up. This multicenter noninterventional observational prospective study revealed a significant difference in 5-year overall survival between COPD patients with normal ECGs and those with prognostically significant or other ECG abnormalities (76.8%, 38.2%, and 63.4%, respectively; P < 0.001). Patients with prognostically significant ECG abnormalities had a 2.537-fold greater mortality risk at 5 years than those with normal ECGs. In the COPD setting, patients with normal ECGs had a better prognosis than those with prognostically significant abnormalities suggesting that ECG may be a valuable tool for predicting mortality risk in these patients.

Keywords Chronic obstructive pulmonary disease, Electrocardiography, Mortality, Prognosis

Abbreviations

BMI	body mass index
BODE	Body mass index, bronchial obstruction, dyspnea, exercise
CAT	COPD assessment test
COPD	chronic obstructive pulmonary disease
ECG	electrocardiography/electrocardiogram
FEV_1	forced expiratory volume in one second
LAH	left anterior hemiblock
LBBB	left bundle branch block
LPH	left posterior hemiblock
mMRC	modified Medical Research Council
RBBB	right bundle branch block

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6MWD   six-minute walk distance

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease characterised by chronic respiratory symptoms conditioned by airway (bronchitis, bronchiolitis) and/or alveolar (emphysema) abnormalities that cause persistent, often progressive, airflow obstruction[1]. COPD is the third leading cause of mortality worldwide. It was reported to account for 3.23 million deaths in 2019[2]. Mortality in patients with COPD increases with disease severity and the presence of various comorbidities[3–5]. In particular, COPD often coexists with cardiovascular disease, and cardiovascular comorbidities in patients with COPD contribute to increased mortality[6,7].

Electrocardiography (ECG) is an inexpensive and widely available test. COPD-related ECG abnormalities are common, and their prevalence increases with disease severity[8,9]. Typical ECG abnormalities in COPD patients include patterns of right atrial enlargement (P pulmonale), right ventricular hypertrophy (the sum of the R wave in lead V_1 and the S wave in lead V_5 or V_6 greater than 1.05 mV), right bundle branch block, poor R-wave progression, low QRS voltage in the limb leads, right or left axis deviation, sinus tachycardia, and supraventricular arrhythmias[9–15]. Patients with COPD are a heterogeneous group with different clinical phenotypes. Therefore, individual ECG abnormalities are influenced by several pathophysiological factors, such as the presence of emphysema, increased pulmonary vascular pressure, and right ventricular hypertrophy[8–10,13–18].

Several studies have shown that selected ECG abnormalities are associated with worse survival in patients with COPD. For example, resting heart rate[19] and ischaemic abnormalities on ECG were reported to be more common in patients with more severe COPD and to be associated with increased mortality[20–22]. In addition, prolonged QTc was shown to be associated with increased mortality risk in patients with COPD because these patients are at increased risk for ventricular arrhythmias and sudden cardiac death[23,24].

Despite the availability of the above data, the overall prognostic value of normal vs. abnormal ECG findings in predicting mortality in patients with COPD has not been sufficiently established. The novelty of our study lies in the fact that it is primarily a mortality prospective study focusing on the overall analysis of the ECG recording, not on the monitoring of a specific parameter (resting heart rate, ischemic changes and/or QTc interval etc.) only[19–24].

Our study also focused on ECG findings associated with right-sided cardiac overload and their impact on the prognosis of patients with COPD without the use of echocardiography. This may be beneficial in routine clinical practice because ECG is an inexpensive and widely available test that can provide a rapid prediction of patient prognosis without the need to refer patients for much more expensive and less accessible echocardiography.

Therefore, we aimed to assess the significance of normal ECGs in patients with COPD for predicting mortality. The primary endpoint was 5-year overall survival in COPD patients with normal ECGs compared with those with abnormal ECGs.

Methods

Population

The study included participants enrolled in the Czech Multicenter Research Database of COPD, a noninterventional multicenter observational prospective database collecting and analysing data on real-world mortality and morbidity in an unselected population of patients with moderate to very severe COPD (registered at ClinicalTrials.gov, NCT01923051 Registration Date 2013-08-13)[25]. Participants were aged 18 years or older and included both men and women. The main inclusion criterion was a diagnosis of stable COPD (no acute exacerbation for at least 8 weeks prior to study enrollment) with a postbronchodilator forced expiratory volume in one second (FEV_1) of 60% or less and an ECG performed at the baseline visit (not all centers participating in the registry performed ECG). Each participant signed a written informed consent form to participate in the study. Detailed information on the inclusion and exclusion criteria in the Czech Multicenter Research Database of COPD was published previously[25].

Study Design

The ECG parameters of patients enrolled in the Czech Multicenter Research Database of COPD were assessed[25]. Only centers performing ECGs participated in the study. These included University Hospital Hradec Kralove, University Hospital Brno, University Hospital Motol in Prague, Bulovka University Hospital in Prague, Regional Hospital Jihlava, Regional Hospital Ceske Budejovice, University Hospital Plzen, Klaudian Hospital in Mlada Boleslav and Masaryk Hospital in Usti nad Labem.

Patient recruitment started in August 2013, and data were collected on December 31, 2019. Follow-up visits were scheduled every 6 months, and ECG was performed once a year. The main statistical analysis was based on the ECGs recorded at baseline (initial ECG). We also evaluated the last ECG obtained before December 31, 2019, or before the patient's death and compared changes in the ECG over time. These second ECGs were only used to assess the stability of the ECG findings over time, and were not used to calculate prognosis (unpublished data; some insights are presented in the Discussion section). Data on patient characteristics, including age, sex, body mass index (BMI), smoking status, comorbidities, lung function, 6-minute walk test, symptoms (according to the COPD Assessment Test [CAT] score and modified Medical Research Council [mMRC] Dyspnea Scale), and the use of specific medications, were obtained from electronic case reports. BMI, bronchial obstruction (postbronchodilator FEV_1%), dyspnoea (mMRC) and exercise capacity (Six Minute Walk Distance) were used to calculate the BODE index[1].

Standard 12-lead ECG was performed in the supine position after a 10-minute rest. At the time of ECG recording, the patient was clinically stable, with no exacerbation of COPD and no worsening of any comorbidity. ECG was always performed in the morning after the use of regular long-term inhaled medication and after the administration of over-the-counter medications. ECG results were interpreted independently by 2 pneumologists who were well trained in clinical ECG analysis; in cases of disagreement, the ECG was reevaluated by a cardiologist. Any disagreement in the ECG readings was resolved by consensus. The following ECG parameters were assessed: heart rate, PQ interval, QRS interval, corrected QT interval (Bazett's formula), P-wave abnormalities (P pulmonale as a sign of right atrial enlargement: P-wave amplitude in leads II, III, or aVF of > 2.5 mm; P mitrale as a sign of left atrial enlargement: P-wave duration > 0.11 s), PQ interval abnormalities (presence of atrioventricular blocks, supraventricular arrhythmias), QRS abnormalities (presence of left bundle branch block, right bundle branch block, left anterior fascicular block, left posterior fascicular block, nonspecific ventricular conduction abnormalities, or pacemaker rhythm), right ventricular hypertrophy (R in lead V_1 + S in leads V_5 or V_6 > 1.05 mV), low QRS amplitude in limb leads (QRS [R + S]: <5 mm in leads I, II, III, and aVF), right axis deviation (> 90°), and left axis deviation (< −30° to −90°). Ischemic changes (Q/QS wave and ST/T abnormalities) were evaluated according to the Minnesota Code classification system for electrocardiographic findings[26]. A normal ECG was defined as follows: heart rate ≤ 90 bpm; no P wave, PQ interval, QRS, or QTc abnormalities; and no ischaemic changes, axis deviations, nor extrasystoles. The division of ECG pathologies between prognostically significant and non-significant was made on the basis of an initial analysis of all-cause mortality in our cohort (Tables 1 and 2). ECG abnormalities associated with an increased risk of all-cause mortality were categorised as prognostically significant, and other ECG abnormalities were included in the category of prognostically non-significant abnormalities. A prognostically significantly abnormal ECG was defined as follows: a heart rate > 90 bpm, QRS interval ≥ 120 ms, P-wave abnormalities, right ventricular hypertrophy, and signs of cor pulmonale. Prognostically non-significant abnormal ECG was defined as follows: non-sinus rhythm; supraventricular arrhythmia (atrial fibrillation); PQ interval ≥ 200 ms; atrioventricular blocks of 1st degree; intraventricular conduction blocks (if it was not part of cor pulmonale) or pacemaker rhythm; supraventricular and ventricular extrasystoles; low QRS voltage; poor R-wave progression; left ventricular hypertrophy; ischaemic changes; right, left and extreme axis deviation; and QTc > 450 ms for male and > 460 ms for women. Lung function tests were performed according to the European Respiratory Society/American Thoracic Society guidelines[27], and COPD was defined as a postbronchodilator FEV_1 to forced vital capacity ratio of less than 0.70 in the absence of any other explanation for bronchial obstruction[1].

The study was conducted in accordance with the laws of the Czech Republic and the ethical principles of the Declaration of Helsinki. Institutional Multicenter Ethic Committee of University Hospital Hradec Kralove (Charles University, Czechia, EU) approved study protocol with informed consent on 12 February 2013; approval number 201,303 501P. More information can be found at http://chopn.registry.cz/index-en.phpand was published previously[25].

Outcomes
The primary endpoint was 5-year overall survival, which was dependent on the ECG findings.

Statistical analysis
Standard descriptive statistics were used in the analyses. Descriptive statistics of the baseline characteristics were obtained for the 2 groups (participants who died during follow-up and survivors on December 31, 2019). The quantitative data are presented as the means (standard deviations) and medians (minima and maxima). Categorical parameters were described by absolute and relative frequencies (percentages). Differences in quantitative data between survivors and non-survivors were tested via the Mann−Whitney test. The dependence of 2 categorical parameters was tested by Pearson's χ^2 test or Fisher's exact test, as appropriate. Survival analysis was used to analyse the time to death. Associations between ECG parameters and mortality were assessed via Kaplan−Meier curves (p values comparing survival curves corresponding to the log-rank test) and a multivariate regression model with covariates such as age, sex, FEV_1, BMI, smoking status, and comorbidities (ischemic heart disease, congestive heart failure, atrial fibrillation, type 2 diabetes, malignancies, depression, and anaemia). The Cox proportional hazards model was used to examine the associations between patient survival and one or more predictor variables. Time was calculated from the date of the baseline visit. Patients who did not die were censored (their survival time was calculated as of December 31, 2019). Patients with more than 60 months of follow-up were censored at 60 months to calculate the difference in 5-year survival. A CART (classification and regression tree) was used for classifying patients into living and dead groups according to the BODE index and ECG categories. Two new binary parameters were developed. A comparison of these parameters (classification ability of BODE/ECG) was performed via receiver operating characteristic (ROC) curve analysis and area under the curve (AUC). Statistically significant results were considered at $p < 0.05$, and receiver operating characteristic curve analysis was used to determine the area under the curve.

Results
A total of 300 patients with moderate to very severe COPD were enrolled, 143 of whom died during follow-up. The baseline demographic and clinical characteristics of the survivors and non-survivors are shown in Table 1. Patients who died during follow-up were significantly older, had a lower BMI, and had more comorbidities than survivors did. In addition, deceased patients had a lower FEV_1, a shorter 6-minute walk distance, greater minimum oxygen saturation and a greater decrease in oxygen saturation in the 6-minute walk test. They also had more symptoms (according to the CAT and mMRC) and were more likely to receive diuretics and theophylline. A total of 80 patients died from respiratory causes, 25 patients died from cardiovascular causes, 12 patients died

Parameter	Survivors $n = 157$	Non-survivors $n = 143$	p value
Men, n (%)	120 (76.4)	105 (73.4)	0.548
Women, n (%)	37 (23.6)	38 (26.6)	
Age (y)	69.2 ± 9.2	73.1 ± 7.3	< 0.001
BMI (kg/m^2)	28.6 ± 5.7	26.6 ± 6.6	0.004
Smoking status			
Current smoker, n (%)	13 (8.3)	18 (12.6)	0.472
Former smoker, n (%)	124 (79.0)	108 (75.5)	
Nonsmoker, n (%)	20 (12.7)	17 (11.9)	
Pack-years	31.4 ± 20.4 30 (0.0; 106.0)	34.7 ± 28 34 (0.0; 190.0)	0.416
Comorbidities, n (%)			
Ischemic heart disease	33 (21)	48 (33.6)	0.014
Congestive heart failure	22 (14)	47 (32.9)	< 0.001
Atrial fibrillation (including paroxysmal events in the past)	16 (10.2)	33 (23.1)	0.003
Arterial hypertension	91 (58)	105 (73.4)	0.005
Malignant tumor	8 (5.1%)	17 (11.9%)	0.033
Type 2 diabetes	32 (20.4)	45 (31.5)	0.028
Depression	16 (10.2)	33 (23.1)	0.003
Anemia	2 (1.3)	12 (8.4)	0.004
Lung functions and GOLD stage			
FEV$_1$ (% of predicted normal value)	44.5 ± 10.7	39.7 ± 11.8	< 0.001
FVC (%)	67.1 ± 6.1	62.1 ± 17.5	0.008
FEV$_1$/FVC (%)	48.7 ± 11.8	47.5 ± 11.6	0.279
GOLD stage[1], n (%)			
2	61 (38.9)	33 (23.1)	0.016
3	78 (49.7)	76 (53.2)	
4	18 (11.4)	34 (23.8)	
6-minute walk test			
Distance (m)	337.5 ± 116.4 360 (80.0; 540)	230 ± 112.2 180 (40.0; 480)	< 0.001
Minimum oxygen saturation during or after the test (%)	89.2 ± 6.3 90.0 (58.0; 98.0)	84.9 ± 8.7 87 (54.0; 97.0)	< 0.001
Largest drop in oxygen saturation during the test (%)	5.1 ± 4.4 4.0 (−1.0; 24.0)	7.3 ± 5.6 6.0 (−1.0; 28.0)	0.001
> 1 acute exacerbation/12 months	32 (20.4)	47 (32.9)	0.014
Symptoms			
CAT score (0–40)	13.6 ± 7.4 14 (1;36)	16.4 ± 7.9 17 (0;39)	0.003
mMRC Dyspnea Scale, n (%)			
0	7 (4.5)	7 (4.9)	0.009
1	31 (19.7)	17 (11.9)	
2	74 (47.1)	51 (35.7)	
3	20 (12.7)	23 (16.1)	
4	25 (15.9)	45 (31.5)	
Medication, n (%)			
LAMAs	125 (79.6)	112 (78.3)	0.783
LABAs	96 (61.1)	94 (65.7)	0.410
LAMAs + LABAs (fixed in single inhaler)	7 (4.5)	6 (4.2)	0.911
Continued			

Parameter	Survivors $n = 157$	Non-survivors $n = 143$	p value
ICS + LABA (fixed in single inhaler)	47 (30.1)	34 (24.1)	0.297
ICS + LABA (fixed and non-fixed combination)	89 (56.7)	76 (53.1)	0.563
Theophylline	66 (42)	85 (59.4)	0.003
Beta-blockers	46 (29.3)	48 (33.6)	0.426
Diuretics	54 (34.4)	80 (55.9)	< 0.001

Table 1. Baseline demographic and clinical characteristics of the Study Population. Continuous variables are expressed as the means ± SDs, and categorical variables are expressed as numbers (%). The median is presented for values with a large SD. [1] Only patients with GOLD stages 2–4 were included in the study. Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; CAT, COPD Assessment Test; GOLD, Global Initiative for Obstructive Lung Disease; mMRC, Modified Medical Research Council Dyspnea Scale; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroid.

from cancer, and 8 patients died from a combination of respiratory and cardiovascular causes. See supplementary table S1 for details.

A comparison of the ECG parameters between survivors and non-survivors is shown in Table 2. Heart rate > 90 bpm, QRS ≥ 120 ms, P-wave abnormalities, right ventricular hypertrophy, and signs of cor pulmonale on ECG were significantly more common in deceased patients. A normal ECG curve was more common in survivors. On the basis of these data, patients were divided into 3 groups for further analyses: group 1, which included patients with normal ECGs; group 2, which included patients with one or more ECG abnormalities classified as prognostically significant; and group 3, which included patients with other ECG abnormalities classified as prognostically nonsignificant.

Data on the primary endpoint in the 3 groups are presented in Table 3; Fig. 1. A heart rate > 90 bpm, QRS interval ≥ 120 ms, P-wave abnormalities, right ventricular hypertrophy, and signs of cor pulmonale were associated with a significantly lower 5-year overall survival rate. In patients with normal ECGs, the 5-year overall survival rate was 76.8% (95% CI 0.647–0.889; $p = 0.001$), whereas it was 38.2% (95% CI 0.297–0.467; $p < 0.001$) in patients with prognostically significant ECG abnormalities and 63.4% (95% CI 0.546–0.721; $p = 0.071$) in patients with prognostically nonsignificant ECG abnormalities.

The results of the analysis of ECG parameters as predictors of mortality are presented in Table 4. The results of the univariate and multivariate analyses for the 3 groups based on ECG abnormalities are shown in Table 5. Patients with prognostically significant ECG abnormalities had a 3.747-fold greater mortality risk at 5 years than patients with normal ECGs did (95% CI 1.993–7.046; $p < 0.001$) and a 2.537-fold greater risk (95% CI 1.331–4.836; $p = 0.005$) after adjustment for age, sex, BMI, FEV_1, smoking status, and comorbidities. There was no significant difference in 5-year mortality risk between patients with normal ECGs and those with prognostically nonsignificant ECG abnormalities (hazard ratio [HR] 1.471; 95% CI 0.751–2.882; $p = 0.261$). A normal ECG was associated with a 63% reduction in mortality risk (HR 0.369, $p = 0.002$).

There was no difference between the classification ability of the BODE (AUC with 95% CI: 0.625 (0.553–0.697); $p = 0.001$) and ECG categories (AUC with 95% CI: 0.642 (0.572–0.713); $p < 0.001$). A comparison of the AUCs is shown in Fig. 2. The P value of the DeLong test for the comparison of two AUCs was 0.646.

Discussion

In this multicenter prospective observational study, a normal ECG in patients with moderate to very severe COPD was associated with increased 5-year overall survival compared with patients with prognostically significant ECG abnormalities. The mortality risk at 5 years was greater in patients with prognostically significant ECG abnormalities even after adjustment for age, sex, BMI, FEV_1, smoking status, and selected comorbidities. Thus, the risk of death was greater even after excluding factors known to be associated with a worse prognosis in patients with COPD. The prognostically significant ECG abnormalities that were shown to be independent predictors of death, on the basis of baseline data, included heart rate > 90 bpm, QRS ≥ 120 ms, P-wave abnormalities, right ventricular hypertrophy, signs of cor pulmonale, or a combination thereof.

The association of a higher heart rate with a worse prognosis in patients with COPD is consistent with previous data reported by Jensen et al.[19] In an analysis of the Copenhagen City Heart Study, Jensen et al.[19] reported that the resting heart rate was associated with both cardiovascular mortality and all-cause mortality across all stages of COPD. In patients with moderate COPD, the resting heart rate predicted a 10-year difference in median life expectancy between patients with a resting heart rate of less than 65 bpm and those with a resting heart rate of 85 bpm or higher.

A wide QRS interval is common in patients with ischaemic heart disease or chronic heart failure. In our study, ischaemic ECG changes were not associated with worse 5-year overall survival, which contrasts with the results of the obstructive lung disease in northern Sweden (OLIN) COPD study by Nilsson et al.[22] This discrepancy may have been caused by the differences in the study population, as patients in their study were younger and had less severe COPD. In addition, the authors compared COPD patients with non-COPD individuals with normal lung function, whereas we studied only patients with moderate to very severe COPD. Nilsson et al.[22] reported

ECG parameter		Survivors n = 157	Non-survivors n = 143	p value
Sinus rhythm, n (%)		149 (94.9)	130 (90.9)	0.176
Heart rate (bpm)		79.0 ± 14.6 78.0 (52.0; 129.0)	85.0 ± 17.7 83.0 (50.0; 136.0)	0.003
Heart rate	≤ 90 bpm	130 (82.8)	96 (67.1)	0.002
	> 90 bpm	27 (17.2)	47 (32.9)	
PQ interval (ms)		157.6 ± 26.4 160.0 (110.0; 260.0)	155.2 ± 32.5 150.0 (100.0; 260.0)	0.252
QRS interval (ms)		92.5 ± 17.4 90.0 (70.0; 180.0)	96.7 ± 20.0 90.0 (70.0; 160.0)	0.088
QRS interval, n (%)	QRS < 120 ms	148 (94.3)	122 (85.3)	0.010
	QRS ≥ 120 ms	9 (5.7)	21 (14.7)	
QTc (ms)		412.6 ± 30.2 410.0 (340.0; 480.0)	419.2 ± 30.1 420.0 (320.0; 500.0)	0.075
Any abnormality of P-wave/PQ interval[1], n (%)		27 (17.2)	56 (39.2)	< 0,001
Atrial fibrillation, n (%)		5 (3.2)	12 (8.3)	0.078
P-wave abnormality, n (%)	P mitrale	2 (1.3)	10 (7.0)	0,012
	P pulmonale	11 (7.0)	32 (22.4)	< 0.001
Any QRS abnormality[2], n (%)		47 (29.9)	66 (46.2)	0.004
QRS abnormality, n (%)	LBBB	2 (1.3)	8 (5.6)	0.052
	RBBB	4 (2.5)	9 (6.3)	0.111
	LAH	17 (10.8)	8 (5.6)	0.101
	LPH	1 (0.6)	1 (0.7)	0.999
	Incomplete RBBB	16 (10.2)	25 (17.5)	0,066
LVH, n (%)		14 (8.9)	10 (7.0)	0.539
RVH, n (%)		7 (4.5)	22 (15.4)	0.001
Signs of cor pulmonale[3], n (%)		2 (1.3)	15 (10.5)	0.001
Poor R wave progression, n (%)		60 (38.7)	71 (49.7)	0.057
Ischemic changes, n (%)		27 (17.2)	34 (23.8)	0.157
Heart axis (°)		34.2 ± 52.1 45.0 (−120.0; 150.0)	31.2 (53.4) 45.0 (−120.0; 120.0)	0.642
Heart axis, n (%)	< − 90°	2 (1.3)	2 (1.4)	0.966
	−90°; −31°	18 (11.5)	17 (11.9)	
	−30°; 90°	125 (79.6)	111 (77.6)	
	> 90°	12 (7.6)	13 (9.1)	
Extrasystoles[4], n (%)		3 (1.9)	6 (4.2)	0.318
Low QRS voltage in limb leads, n (%)		11 (7.0)	12 (8.4)	0.652
Normal ECG, n (%)		39 (24.8)	11 (7.7)	< 0.001

Table 2. ECG parameters of the study population at the baseline visit. Continuous variables are expressed as the means ± SDs, and categorical variables are expressed as numbers (%). The median is presented for values with a large SD. 1 Including P pulmonale, P mitral, 1st degree atrioventricular blocks and atrial fibrillation. 2 Including bundle branch blocks, hemiblocks, pacemaker rhythm, and a nonspecific disorder of intraventricular conduction. [3]Signs of cor pulmonale included both P pulmonale + RBBB and P pulmonale + RVH. [4]Both supraventricular and ventricular. Abbreviations: ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; LAH, left anterior hemiblock; LPH, left posterior hemiblock; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

that ischaemic ECG abnormalities were associated with increased mortality in both patients with and without COPD. In the COPD cohort, the association was still observed after adjustment for confounders.

P-wave abnormalities and ECG signs of right ventricular hypertrophy or cor pulmonale are the classic markers of right-sided cardiac overload[11,12]. In some cases, COPD can lead to pulmonary hypertension, which may cause right ventricular hypertrophy and cor pulmonale, which are well-known markers of more advanced disease and are predictors of a worse prognosis[28]. Incalzi et al.[28]. reported significantly shorter survival in patients with ECG evidence of chronic cor pulmonale than in those without such evidence on ECG (2.5 vs. 3.5 years). Our observations confirmed this finding; signs of P pulmonale and right bundle branch block or P pulmonale and right ventricular hypertrophy were noted in 1.3% of the survivors and in 10.5% of the non-survivors.

In our cohort, prolonged QTc was not associated with a worse prognosis, which contrasts with the findings of previous studies by Van Oekelen et al.[22]. and Nillson et al.[24]. Van Oekelen et al.[22]. included older patients and performed ECG in hospitalized patients without stable disease (during acute exacerbation), which may explain

ECG parameter	24 months		36 months		60 months		p value
	Number at risk	OS (95% CI)	Number at risk	OS (95% CI)	Number at risk	OS (95% CI)	
HR							
≤ 90 bpm	n = 187	0.827 (0.778–0.877)	n = 167	0.739 (0.682–0.796)	n = 97	0.582 (0.517–0.648)	0.014
> 90 bpm	n = 52	0.703 (0.599–0.807)	n = 43	0.581 (0.469–0.693)	n = 26	0.436 (0.321–0.551)	
QRS interval							
< 120 ms	n = 218	0.807 (0.760–0.854)	n = 194	0.719 (0.665–0.772)	n = 117	0.575 (0.515–0.635)	0.003
≥ 120 ms	n = 21	0.700 (0.536–0.864)	n = 16	0.533 (0.355–0.712)	n = 6	0.277 (0.109–0.445)	
HR > 90 bpm + QRS ≥ 120 ms							
No	n = 235	0.802 (0.756–0.848)	n = 207	0.706 (0.654–0.759)	n = 123	0.556 (0.497–0.614)	0.012
Yes	n = 4	0.571 (0.205–0.938)	n = 3	0.429 (0.062–0.795)	n = 0	-	
Sinus rhythm							
No	n = 13	0.619 (0.411–0.827)	n = 11	0.524 (0.310–0.737)	n = 6	0.413 (0.195–0.630)	0.084
Yes	n = 226	0.810 (0.764–0.856)	n = 199	0.713 (0.660–0.766)	n = 117	0.555 (0.496–0.615)	
P mitrale							
No	n = 231	0.802 (0.756–0.848)	n = 205	0.712 (0.659–0.764)	n = 121	0.561 (0.502–0.620)	0.002
Yes	n = 8	0.667 (0.400–0.933)	n = 5	0.417 (0.138–0.696)	n = 2	0.167 (0.000–0.378)	
P pulmonale							
No	n = 210	0.817 (0.770–0.864)	n = 189	0.735 (0.681–0.789)	n = 113	0.589 (0.528–0.650)	< 0.001
Yes	n = 29	0.674 (0.534–0.814)	n = 21	0.488 (0.339–0.638)	n = 10	0.286 (0.146–0.425)	
LBBB							
No	n = 232	0.800 (0.754–0.846)	n = 204	0.703 (0.651–0.756)	n = 121	0.558 (0.499–0.616)	0.025
Yes	n = 7	0.700 (0.416–0.984)	n = 6	0.600 (0.296–0.904)	n = 2	0.200 (0.000–0.448)	
RBBB							
No	n = 229	0.798 (0.751–0.844)	n = 202	0.704 (0.651–0.757)	n = 120	0.557 (0.498–0.616)	0.130
Yes	n = 10	0.769 (0.540–0.998)	n = 8	0.615 (0.351–0.880)	n = 3	0.288 (0.032–0.545)	
LAH							
No	n = 217	0.789 (0.741–0.837)	n = 189	0.687 (0.632–0.742)	n = 110	0.534 (0.473–0.594)	0.179
Yes	n = 22	0.880 (0.753–1.000)	n = 21	0.840 (0.696–0.984)	n = 13	0.668 (0.478–0.858)	
Incomplete RBBB							
No	n = 207	0.799 (0.750–0.848)	n = 185	0.714 (0.659–0.769)	n = 106	0.556 (0.494–0.618)	0.336
Yes	n = 32	0.780 (0.654–0.907)	n = 25	0.610 (0.460–0.759)	n = 17	0.478 (0.322–0.634)	
Poor R-wave progression							
No	n = 135	0.808 (0.749–0.868)	n = 124	0.743 (0.676–0.809)	n = 65	0.569 (0.491–0.647)	0.183
Yes	n = 102	0.779 (0.708–0.850)	n = 84	0.641 (0.559–0.723)	n = 56	0.507 (0.420–0.593)	
LVH							
No	n = 220	0.797 (0.750–0.845)	n = 192	0.696 (0.641–0.750)	n = 111	0.542 (0.481–0.602)	0.727
Yes	n = 19	0.792 (0.629–0.954)	n = 18	0.750 (0.577–0.923)	n = 12	0.580 (0.382–0.779)	
RVH							
Continued							

| ECG parameter	24 months		36 months		60 months		p value
	Number at risk	OS (95% CI)	Number at risk	OS (95% CI)	Number at risk	OS (95% CI)	
No	$n = 219$	0.808 (0.761–0.855)	$n = 191$	0.705 (0.650–0.759)	$n = 118$	0.578 (0.518–0.638)	0.002
Yes	$n = 20$	0.690 (0.521–0.858)	$n = 19$	0.655 (0.482–0.828)	$n = 5$	0.235 (0.070–0.401)	
Signs of cor pulmonale							
No	$n = 227$	0.802 (0.756–0.849)	$n = 200$	0.707 (0.654–0.760)	$n = 121$	0.570 (0.511–0.629)	0.001
Yes	$n = 12$	0.706 (0.489–0.922)	$n = 10$	0.588 (0.354–0.822)	$n = 2$	0.132 (0.000–0.302)	
Ischemic changes							
No	$n = 192$	0.803 (0.753–0.854)	$n = 175$	0.732 (0.676–0.788)	$n = 100$	0.567 (0.503–0.632)	0.068
Yes	$n = 47$	0.770 (0.665–0.876)	$n = 35$	0.574 (0.450–0.698)	$n = 23$	0.455 (0.330–0.581)	
Heart axis							
< −90°	$n = 2$	0.500 (0.010–0.990)	$n = 2$	0.500 (0.010–0.990)	$n = 2$	0.500 (0.010–0.990)	0.640
−90°; −31°	$n = 29$	0.829 (0.704–0.953)	$n = 25$	0.714 (0.565–0.864)	$n = 13$	0.494 (0.323–0.666)	
−30°; 90°	$n = 191$	0.809 (0.759–0.859)	$n = 168$	0.712 (0.654–0.770)	$n = 99$	0.562 (0.498–0.627)	
> 90°	$n = 17$	0.680 (0.497–0.863)	$n = 15$	0.600 (0.408–0.792)	$n = 9$	0.460 (0.256–0.663)	
≤ 90°	$n = 222$	0.807 (0.761–0.854)	$n = 195$	0.709 (0.655–0.763)	$n = 114$	0.553 (0.493–0.613)	0.299
> 90°	$n = 17$	0.680 (0.497–0.863)	$n = 15$	0.600 (0.408–0.792)	$n = 9$	0.460 (0.256–0.663)	
Extrasystoles							
No	$n = 232$	0.797 (0.751–0.843)	$n = 204$	0.701 (0.648–0.754)	$n = 120$	0.552 (0.493–0.610)	0.150
Yes	$n = 7$	0.778 (0.506–1.000)	$n = 6$	0.667 (0.359–0.975)	$n = 3$	0.333 (0.025–0.641)	
Low QRS amplitude in limb leads							
No	$n = 221$	0.798 (0.751–0.845)	$n = 195$	0.704 (0.650–0.758)	$n = 113$	0.544 (0.484–0.604)	0.918
Yes	$n = 18$	0.783 (0.614–0.951)	$n = 15$	0.652 (0.458–0.847)	$n = 10$	0.565 (0.363–0.768)	
Normal ECG							
No	$n = 193$	0.772 (0.720–0.824)	$n = 164$	0.656 (0.597–0.715)	$n = 101$	0.502 (0.439–0.565)	0.001
Yes	$n = 46$	0.920 (0.845–0.995)	$n = 46$	0.920 (0.845–0.995)	$n = 22$	0.768 (0.647–0.889)	
Comparison of groups based on ECG abnormalities							
Group 1 (normal ECG)	$n = 46$	0.920 (0.845–0.995)	$n = 46$	0.920 (0.845–0.995)	$n = 22$	0.768 (0.647–0.889)	< 0.001
Group 2 (prognostically significant ECG abnormalities)	$n = 92$	0.708 (0.630–0.786)	$n = 72$	0.554 (0.468–0.639)	$n = 40$	0.382 (0.297–0.467)	
Group 3 (prognostically nonsignificant ECG abnormalities)	$n = 101$	0.842 (0.776–0.907)	$n = 92$	0.767 (0.691–0.842)	$n = 61$	0.634 (0.546–0.721)	

**Table 3**. Overall survival during follow-up on the basis of ECG abnormalities. [1]Signs of cor pulmonale included both P pulmonale + RBBB and P pulmonale + RVH. Abbreviations: ECG, electrocardiogram; HR, heart rate; LBBB, left bundle branch block; RBBB, right bundle branch block; LAH, left anterior hemiblock; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

the discrepancy. In addition, the prediction of mortality risk was no longer significant after adjustment for age and FEV_1[22]. As for the study by Nillson et al.[24]. , the discrepancy may have been caused by the differences in the study population in terms of patient age, COPD stage, and sample size[24].

In our study, the multicomponent BODE index was also calculated to determine survival. A subsequent comparison of the ability to predict survival revealed comparable sensitivity and specificity. Certainly, this comparison with the gold standard for determining survival, the BODE index, is only an indicative unvalidated comparison.

The strengths of our study include its multicenter and prospective design and the inclusion of an unselected population of patients with moderate to very severe COPD, which is consistent with real-world clinical practice.
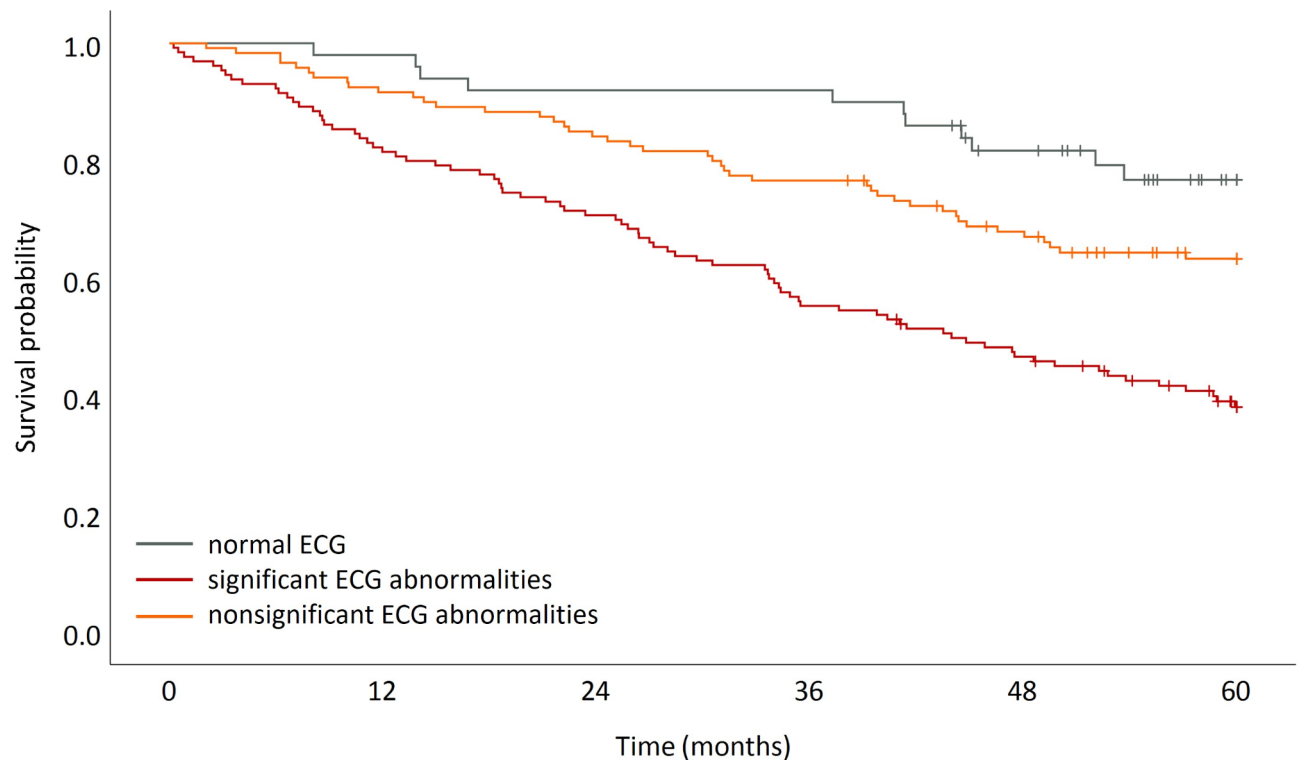
Fig. 1. Overall survival of patients with COPD depending on the presence of electrocardiographic (ECG) abnormalities. ECG, electrocardiogram.

ECG parameter		HR (95% CI)	P value
Heart rate	< 70 bpm	Reference parameter	
	70–90 bpm	1.182 (0.746–1.871)	0.476
	> 90 bpm	1.577 (1.091–2.279)	0.015
QRS	≥ 120 ms	2.014 (1.263–3.213)	0.003
HR > 90 bpm + QRS ≥ 120 ms		2.743 (1.208–6.226)	0.016
Sinus rhythm		0.596 (0.329–1.079)	0.088
P-wave abnormalities[1]		2.089 (1.473–2.963)	< 0.001
QRS abnormality[2]		1.571 (1.117–2.209)	0.009
Poor R-wave progression		1.259 (0.896–1.770)	0.184
LVH		0.892 (0.468–1.699)	0.728
RVH		2.029 (1.272–3.236)	0.003
Signs of cor pulmonale[3]		2.423 (1.391–4.221)	0.002
Ischemic changes		1.439 (0.971–2.135)	0.070
Heart axis > 90°		1.353 (0.763–2.398)	0.301
Extrasystoles		1.809 (0.798–4.105)	0.156
Low QRS amplitude in limb leads		1.035 (0.543–1.971)	0.918
Normal ECG		0.369 (0.199–0.684)	0.002

Table 4. Analysis of ECG parameters as predictors of mortality. [1]Including P. pulmonale, P. mitrale. [2]Including bundle branch blocks and hemiblocks. nonspecific ventricular conductance abnormalities. [3]Signs of cor pulmonale included both P pulmonale + RBBB and P pulmonale + RVH. Abbreviations: ECG, electrocardiogram; HR, heart rate; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy.

Another strength is the use of an inexpensive, easily accessible and reproducible test that has long been available in routine clinical practice, including for general practitioners.

Our study has several limitations. First, the project used ECG recordings from routine practice and not ECG recordings on a device designed for scientific purposes, which would allow the most accurate ECG analysis. Second, we also examined the last ECG performed before December 31, 2019, or before the patient's death, and

Study group depending on ECG abnormalities	Univariate analysis		Multivariate analysis[1]	
	HR (95% CI)	p value	HR (95% CI)	p value
Normal ECG	Reference parameter		Reference parameter	
Prognostically significant ECG abnormalities	3.747 (1.993–7.046)	< 0.001	2.537 (1.331–4.836)	0.005
Prognostically nonsignificant ECG abnormalities	1.805 (0.931–3.500)	0.081	1.471 (0.751–2.882)	0.261

Table 5. Univariate and multivariate analyses of mortality risk according to ECG abnormalities. [1] Adjusted for age, sex, BMI, FEV_1, smoking status, and comorbidities. BMI, body mass index; ECG, electrocardiogram; FEV1, forced expiratory volume in one second.
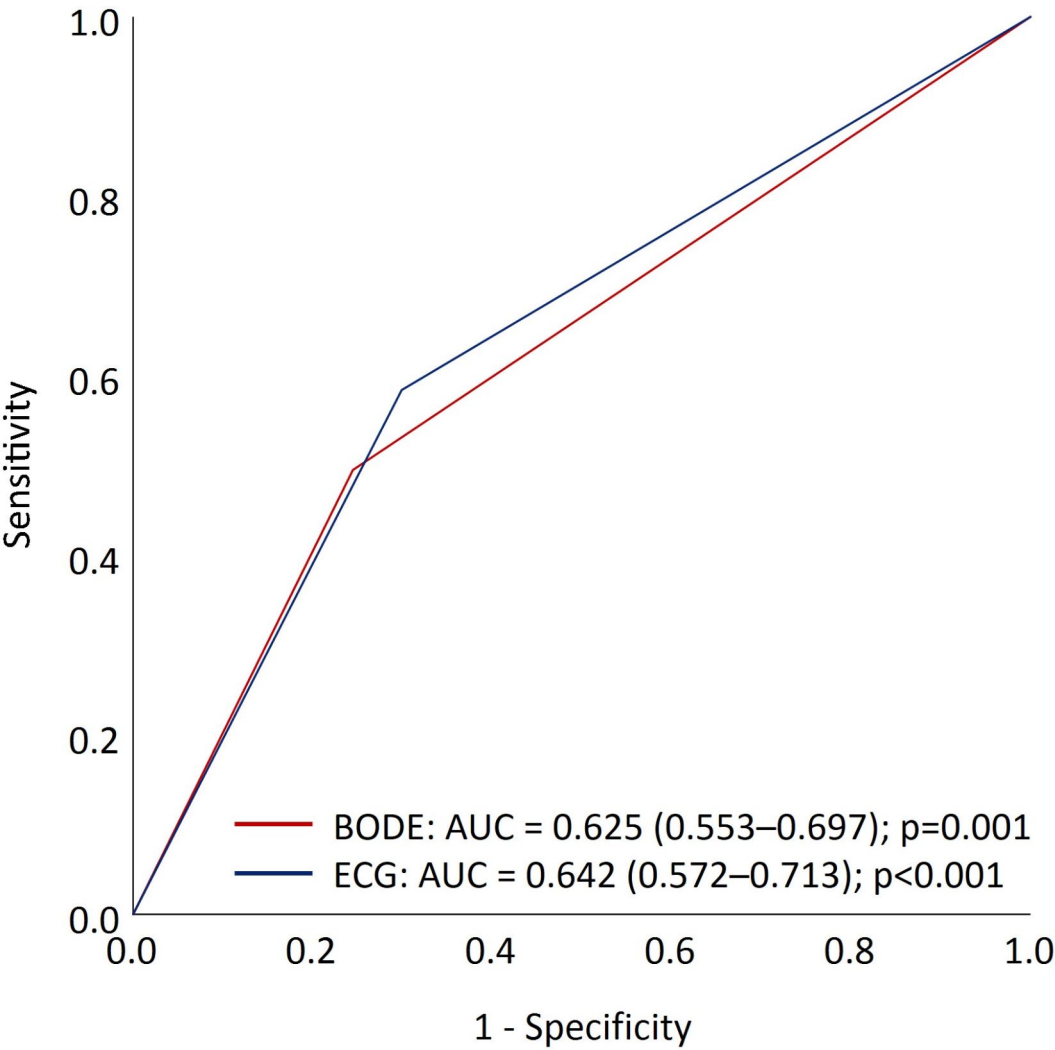
Fig. 2. Comparison of the BODE index and ECG to predict the survival of patients with COPD. AUC, area under the curve; BODE index, body mass index; bronchial obstruction, dyspnea, exercise; ECG, electrocardiogram.

stability in individual ECG parameters were monitored over time. Overall, 62% of COPD patients had the last available ECG stable, i.e. the same as the initial one. More than 80% of patients with an initially significantly abnormal ECG had the same ECG appearance on the last known ECG recording. Two third of patients with a nonsignificant abnormality remain stable over time. The least ECG stability is seen in the initially normal ECG, this tends to change more over time (to both nonsignificantly and significantly abnormal recordings). However, in those patients where the initial normal ECG is stable (i.e. still normal on the last ECG recording) there is a 93% chance of being in the survivors group. In our opinion, the above underlines the prognostic importance of a normal ECG recording for COPD patients. Finally, our results are influenced by the fact that we did not have

COPD patients with second/third degree AV block or atrial flutter in the study population. Therefore, these ECG pathologies are not included in either of the abnormal ECG categories.

Conclusions

This multicentre, non-interventional, observational, prospective study showed a significantly higher 5-year overall survival rate in stable COPD patients with FEV1 ≤ 60% and normal ECGs than in those with prognostically significant ECG abnormalities. Therefore, ECG can serve as a simple, inexpensive and widely available tool in the overall assessment and management of patients with COPD, guiding treatment decisions and prognostication. However, although an ECG provides valuable information, it should only be used as one part of a clinical evaluation. The prognosis of COPD patients is multifactorial and should include assessments of lung function, exercise capacity, comorbidities, and other factors in addition to ECG.

Data availability

The data that supported the findings of this study are available from [Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic], but restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of [Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic]. Raw data for dataset are not publicly available to preserve individuals' privacy under the European General Data Protection Regulation. If somebody wants to request the data from this study, please contact Katerina Kusalova (kusalova@biostatistika.cz) from Institute of Biostatistics and analyses. The institute will share the required dataset with her/his.

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Author contributions

MKu takes full responsibility for the content of the manuscript including the data and analyses. MKu, MKo, MSo, analyzed ECG. MKu, MSo, BN, MSv, and VK contributed to data curation and methodology. MSv contributed to statistical analysis. VK, and BN performed conception/design of the Czech Multicenter Research Database of COPD. MKu, MKo, BN, MP, KB, LF, PV, PM, TD, PS, and VK contributed to acquisition, and interpretation of data for the work. VK and MSv contributed to research/manuscript supervision. MKu, MS, KB, and VK contributed to writing the original draft. MS prepared all tables and Figs. 1 and 2. All authors reviewed critically manuscript content, gave the final approval of the version to be submitted.

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Declarations

Competing interests

The authors declare no competing interests

Ethics approval and consent to participate

The study was conducted in accordance with the laws of the Czech Republic and the ethical principles of the Declaration of Helsinki. Institutional Multicenter Ethic Committee of University Hospital Hradec Kralove (Charles University, Czechia, EU) approved study protocol with informed consent on 12 February 2013; approval number 201303 501P.

Additional information

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