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Biljana Lazović[1,♣], Nevena Jovičić[2], Vladimir Radlović[2,3], Sanja Šarac[4], Rade Milić[4], Vladimir Žugić[5,3], Ivan Soldatović[6,3]

Electrocardiographic predictors of five years mortality in chronic obstructive pulmonary disease patients

Електрокардиографски предиктори петогодишњег морталитета оболелих од хроничне опструктивне болести плућа

[1]Zemun Clinical Hospital Centre, Department of Pulmonology, Belgrade, Serbia;
[2]University Children's Hospital, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[4]Military Medical Academy, Clinic for Lung Disease, Belgrade, Serbia;
[5]Clinical Centre of Serbia, Clinic for Lung Diseases, Belgrade, Serbia;
[6]Institute of Medical Statistics and Informatics, Belgrade, Serbia;

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♣**Correspondence to:**
Biljana LAZOVIC
Zemun Clinical Hospital Centre, Vukova 9, 11080 Belgrade, Serbia
E-mail: **lazovic.biljana@gmail.com**

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SUMMARY

Introduction/Objective Cardiovascular disease is one of the most common comorbidities among subjects with chronic obstructive pulmonary disease (COPD). The aim of this study is to evaluate ECG parameters and mortality predictors in COPD patients.

Methods A total of 835 consecutive patients were included. Patients were classified to suffer from COPD if in three consecutive postbronhodilatator measurements FEV1/FVC was <70%. Following ECG changes were observed: axis, p wave, low ORS complex, transitional zone, left bundle branch block (LBBB), right bundle branch block (RBBB), incomplete right bundle branch block, S1S2S3 configuration, negative T in V1-V3. Patients were followed up for mortality in a five years period.

Results Both survivors and non-survivors were similar age, gender and COPD status. FVC and FEV1 as well as GOLD stadium are significantly higher in surviving group (p<0.016, p<0.001, p<0.001 respectively). Normal axis was in significantly higher percentage in non-survived patients (p=0.020). Right RBBB and incomplete RBB are more frequent finding in patients who died as (p<0.001, p<0.05, respectively). LBBB, S1S2S3 configuration is in significantly higher percent in non survivors (p<0.016, p<0.001, respectively). In multivariable logistic model, patients with LBBB have two times higher chance of mortality compared to patients without LBBB. Contrary, patients with RBBB have 1.6 times lower chance to have death outcome.

Conclusion Main ECG predictors of COPD patients' five-year mortality are LBBB and RBBB, but according to statistical model, electrocardiogram should be further explored and possibly obligatory involved in a routine clinical practice as an easy and low-cost screening method.

Keywords: chronic obstructive pulmonary disease; electrocardiography; mortality

САЖЕТАК

Увод/циљ Најчешћи коморбидитети међу оболелим од хроничне опструктивне болести плућа (ХОБП) су обољења кардиоваскуларног система.

Циљ ове студије је процена параметара електрокардиографије (ЕКГ) и предиктора смртности код пацијената са ХОБП-ом.

Методе У студију је укључено укупно 835 пацијената. Пацијенти су класификовани да болују од ХОПБ-а ако је у три узастопна мерења постбронходилататора вредност *FEV*1/ *FVC* била < 70%. Праћене су следеће промене у ЕКГ-у: осовина, п талас, комплекс с ниским *ORS*-ом, прелазна зона, блок леве гране Хисовог снопа (*LBBB*), блок десне гране (*RBBB*), непотпуни блок десне гране снопа, конфигурација *S*1*S*2*S*3, негативан *T* у *V*1–*V*3. Праћен је морталитет оболелих у периоду од пет година.

Резултати И преживели и преминули били су сличног узраста, пола и статуса ХОПБ-а. *FVC* и *FEV*1, као и *GOLD stadium*, значајно су већи у групи која је преживела ($p < 0.016$, $p < 0.001$, $p < 0.001$ респективно). Нормална осовина била је у знатно већем проценту код умрлих пацијената ($p = 0{,}020$). Десни *RBBB* и непотпуни *RBBB* су чешћи налаз код болесника који су умрли (p<0,001, p<0.05, респективно). Конфигурација LBBB, S1S2S3 је у знатно вишем проценту код умрлих пацијената (p<0.016, p<0.001, респективно). У мултиваријабилном логистичком моделу, пацијенти са *LBBB* имају двоструко већу шансу за смртност у поређењу са пацијентима без *LBBB*. Супротно, пацијенти са *RBBB* имају 1,6 пута мању шансу да изгубе живот.

Закључак Главни ЕКГ предиктори петогодишњег морталитета код ХОПБ-а су *LBBB* и *RBBB*, али према статистичком моделу, електрокардиограм треба додатно истражити и евентуално обавезно укључити у рутинску клиничку праксу као једноставан и приступачан метод скрининга.

Кључне речи: хронична обструктивна болест плућа; електрокардиограм; морталитет

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a very common, preventable and treatable disease, characterized by respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, caused by significant exposure to noxious particles or gases [1]. It is the fourth leading cause of death worldwide, exceeded by myocardial infarction, malignancy and stroke only [2]. Among chronic high morbidity and mortality diseases throughout the world, many aged people suffer from COPD and die prematurely [2, 3]. COPD complexity and mortality is increased by its exacerbations and co-morbidities [4]. Along with pulmonary involvement, there are significant extra pulmonary effects in COPD [3, 4, 5]. COPD can influence electrocardiographic (ECG) changes variously.

COPD is often associated with cardiovascular diseases, thus representing one of the most frequent and clinically important coexisting condition. An accumulating body of evidence indicates COPD association with coronary artery disease (CAD), chronic heart failure (CHF), hypertension and cardiac arrhythmias, independent of shared risk factors [6, 7]. Apart from the common risk factors presence (age, smoking habit, environmental pollutants, gender and diet), it appears that multiple pathophysiologic abnormalities contribute to both the COPD and CAD development and progression. COPD and CAD association is characterized by specific electrocardiographic (ECG) abnormalities [5, 6, 7].

Changes of Sokolow-Index and clockwise rotation of the horizonal QRS-axis are some of the changes. ECG changes can be found in different stages of COPD and can be associated with the increased death risk. An increased burden of cardiac arrhythmias has also been recognized recently [5]. In COPD, various mechanisms can influence ECG diversely, independent of a possibly CAD [6]. The most consistent patterns reported have been vertical axes for P and QRS and increased P-wave amplitude (P-pulmonale). The QRS amplitudes are often reduced. Previous studies have related ECG findings to obstruction and emphysema and increased pulmonary vascular pressure or right ventricular (RV) hypertrophy. However, none of these studies have linked their findings to the combined effects of obstruction, emphysema and increased afterload [5, 6]. COPD comorbidities have been infrequently studied, mostly in evaluating relationships between COPD and some specific diseases.

The current study was aimed at finding correlationship between electrocardiographic changes and COPD as well as at mortality in relation to ECG [6, 7]. Regular pulmonologist

examination does not include ECG. However, ECG could be the first marker of COPD, approachable, easy to perform and non-expensive, but extremely helpful.

METHODS

A prospective study was conducted from January 2009 to February 2014 in the Clinical Hospital Center Zemun and included 835 COPD patients. COPD cases were diagnosed and selected from patients who were attending Outpatient Department of Respiratory Diseases for treatment of various respiratory problem. Exclusion criteria were any kind of cardiovascular diseases (previous myocardial infarction, arterial hypertension, angina pectoris, congenital cardiovascular disease, heart failure et al.) Also, patients who were not able to adequately perform spirometry were excluded.

Spirometry was performed using the (Turninac, Pneumotah) Pony FX (Cosmed Pulmonary Function Equipment, Rome, Italy), following the ATS/ERS recommendations using postbronhodilatator values in order to overestimate the prevalence of COPD [8]. The ATS/ERS recommendations for chronic obstructive lung disease has defined airflow obstruction if forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) ratio is< 0.70 of predicted. Airflow obstruction severity was graded according to GOLD 2011 as Stage 1-Mild, Stage 2- Moderate, Stage 3-Severe and Stage 4 -Very Severe, characterized by FEV1 is >80% of predicted, 50-80% of predicted, 30-50% and <30% of predicted, respectively [8]. All patients were smokers.

All of the patients have undergone electrocardiography (ECG). A 12-lead ECG (Schiller AT-102), including 3 bipolar limb leads, 3 unipolar limb leads and 6 unipolar precordial leads, was performed. All necessary precautions advised for ECG were followed. ECG was done in supine position. ECG parameters were measured using Minnesota code [9], by two independent persons and their final judge was achieved by consensus in case of disagreement.

The P-value axis and QRS complex were calculated by Cabrera system [9]. The following parameters were followed: high, peaked P wave≥2,5mm height in leads II, III, aVF; right ventricular hypertrophy (RVH)- right axis deviation of +110° or more; dominant R wave in V1 (> 7mm tall or R/S ratio > 1); dominant S wave in V5 or V6 (> 7mm deep or R/S

ratio < 1); QRS duration < 120ms); LBBB (left bundle branch block: the QRS duration ≥ 120 ms, QS or rS complex in lead V1, notched ('M'-shaped) R wave in lead V6), incomplete right bundle branch block (RBBB)(RSR' pattern in V1-3 with QRS duration < 120ms), abnormal transitional zone (poor R-wave progression or "poor anterior R-wave progression"), S1S2S3 pattern (presented with S waves in leads I, II and III and negative T-wave changes in V1-V3). Patients were followed-up for 5 years for the mortality prediction calculations.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade. All procedures were performed in accordance with the Helsinki declaration. All patients have given written informed consent to participate in the study.

Statistical analysis

Results are presented as count (%), mean ± standard deviation or median (25-75th percentile). Group differences were analyzed using parametric (independent samples t test) and non-parametric (Mann-Whitney U test, Pearson chi square test and Fisher's Exact test) tests. Logistic regression analysis was performed to assess independent predictors of mortality. All data were analyzed using SPSS 20.0 (IBM corp.) statistical software. All p values less than 0.05 were considered significant.

RESULTS

Patient were divided in relation to exitus in two groups to one who survived five years period and those who died, as well as on gender. The minimum observed age was 42 years, maximum 84 years and the mean (SD) 63.4 (8.8) years. FVC was statistically higher in non survivors (70.9 ± 14.8) with regard to surviving patients (68.0 ± 15.3). Also, FEV1 was statistically higher in died persons than surviving (44.3 ± 10.7, 41.4 ± 11.7 respectively). FEV1/FVC ratio was statistically higher in non survivors than in survived patients (63.8 ± 60.4-65.8; 63.1 ± 56.9). There was no statistical difference in MEF 25-75 between two groups. GOLD stadium 2, 3, 4 was statistically higher in surviving group. General characteristics and lung function of COPD patients separately for 5-years survivors and non-survivors are presented in Table 1.

As shown, in Table 1, both survivors and non-survivors are similar age, gender and COPD status. Contrary, FVC and FEV1 are significantly higher in survivors group. FEV1/FVC is significantly higher in survivors group, but the difference in medians is small. The most patients were in GOLD stadium 3 where was observed statistical higher mortality than in GOLD 2 and 4.

Normal axis was statistically higher in non-survived patients. Left axis deviation was found in (24.4.9%) non-survivors and 75.6 % in patients who survived 5 years period. Tall, peaked P wave>2.5mm height was described in inferior leads for 30.7% non-survivors and 69.3% survivors. Patient who had no RVH had statistically lower percentage of 5 years of mortality. In contrast, right RBBB was statistically higher finding in patients who died as well as incomplete RBBB. Low QRS was found in 28.0% in non survivors and 72% in survivors, transitional electrocardiographic zone in 29.8 % in non survivors and 70.2% in surviving patients. LBBB was statistically higher in non survivors. Configuration S1S2S3 was statistically higher in non survivors even in small sample; V1-V3 leads negative T wave in 34.3% died and 65.7% survived patients; QRS duration ≤0.12s was found in 33.7% non-survivors and 66.3% surviving. QT<0.12 was found in 29.5% died patients and 70.5% survived. ECG characteristics of COPD patients in relation to five years death outcome are presented in Table 2. Significant correlation with 5-years mortality is observed with normal axis, RVH, incomplete RBBB, LBBB and S1S2S3. Patients with normal axis, incomplete RBBB and LBBB have significantly higher percentage of mortality. Contrary, patients with RVH and RBBB have significantly lower percentage of 5 years mortality. Only six patients have positive S1S2S3 and they will not be included in multivariate model due to small sample size for this analysis.

Logistic regression analysis is performed to assess significant predictors of mortality adjusted for potential confounders. Univariable and multivariable logistic regression analysis results are presented in Table 3. Only variables with p values less than 0.2 are presented in univariate analysis.

Univariable analysis reveals that lung function (FVC, FEV1, FEV1/FVC, GOLD) are significant predictors of mortality. Since all of them are highly multi correlated, FEV1/FVC will be used for multivariable analysis as adjusting variable for ECG parameters. RVH, RBBB, incomplete RBBB, LBBB and S1S2S3 are, also significantly correlated with outcome. Since S1S2S3 is positive in only six patients, due to small sample size, this variable

will not be used in multivariable modeling. Final model is performed using logistic regression backward method. Four steps have been performed to obtain final model. Final model was compared to first model (all variables at the beginning) and results of Hosmer-Lemeshow goodness of fit test and Nagelkerke R squared reveal similar characteristics of both models. We decided to use simple (final, backward model) as model of five years mortality predictors. Final model revealed two significant predictors of five years mortality, RBBB and LBBB. Patients with LBBB have two times higher chance of mortality compared to patients without LBBB. Contrary, RBBB is protective factor and patients with RBBB have 1.6 times lower chance to have death outcome.

DISCUSSION

COPD and cardiovascular diseases have common risk factors, including smoking and ageing. Also, both diseases are presented with pro-inflammatory mechanisms and oxidative stress. Sedentary lifestyle in COPD may contribute to cardiovascular disease developing, as well [3, 4, 10]. A number of studies have reported ECG abnormalities and cardiac arrhythmias in COPD patients [5, 10]. The majority of ECG abnormalities are associated with COPD, which is mostly presented with two factors combination: pulmonary hypertension and anatomic changes. Pulmonary hypertension (PH) however is always the underlying pathologic mechanism for right venrticular hypertrophy in cor pulmonale and altered electrical conduction. Also, hyperinflation causes a thorax heart displacement position. Abnormalities in conduction usually occur late in COPD patients, after the right ventricle hypertrophy has developed to such an extent so that its electrical forces overcome those of the left [11]. In our study, we have found no arrhythmias, despite the fact that almost half of the investigated groups had developed the chronic obstructive pulmonary disease terminal stadium.

We have included 835 cases with stabile phase of chronic obstructive pulmonary disease, evaluated by spirometry and electrocardiography. Some authors have reported higher age in men as a significant risk factor associated with FEV1 declinement with age, so that the advanced disease stage tends to reduce the FEV1/FVC ratio [11, 12]. In our study, both sex were similar age with more female participants, which is contrary to fact that men more frequently suffered from COPD [11, 12, 13]. Some authors have investigated vertical QRS

axis as a single criterion for a COPD disease screening in an adult hospital population, concluding that vertical QRS axis can detect COPD with 89% sensitivity and 96% specifity [10, 11]. In fact, vertical QRS axis is a synonim for COPD and its severity-hanging heart [10, 13]. It is not uncommon, following the reduced Sokolow-Lyon Index for LV mass by obstruction and afterload presumably reflects both increased right-sided and decreased left-sided QRS amplitudes by the combined anatomical and electrical remodelling of the heart [12]. In COPD patients, hyperinflation of the lungs leads to depression of the diaphragm, and this is associated with clockwise rotation of the heart along its longitudinal axis. This clockwise rotation means that the transitional zone (defined as the progression of rS to qR in the chest leads) shifts towards the left with persistence of an rS pattern as far as V5 or even V6. This may give rise to a "pseudoinfarct" pattern, with deep S waves in the right precordial leads simulating the appearance of the QS waves and poor R wave progression seen in anterior myocardial infarction.

Other studies have shown the QRS right axis deviation dominance with clockwise rotation [10, 11, 12, 13]. Unlike Baljepally's study [10] with the vertical QRS axis predominance, the normal axis is more common finding in our study. In fact, it is high statistical important factor in patients who did not survived five years follow up. Also, we have no patient with right axis on electrocardiogram. Our study has shown that vertical axis in COPD patients is not "THE HOLY GRAIL" as it was always connected with COPD. Evaluation of ECG abnormalities significance as COPD prognostic factors has started in 1975, reported by Kok-Jensen that an ECG p-II amplitude of at least 0,20mV is related to poor prognosis [13]. Our study has shown that P wave ≥2,5mm height has no predicted value in mortality of COPD patients. In the present study, peaked P-wave (amplitude more than 2.5 mm), was recorded in 52.33% of the cases with COPD. In Spodicks series, 13.9% of COPD patients had P-wave equal or greater than 2.5mm. Carid and Wilcken found incidence of P-pulmonale in 15.5% of their COPD patients, while some group of authors recorded same incidence of 32.7% in their studies [13, 14]. But, there was no statistical significance between survivors and non-survivors considering p wave height [12, 13, 14] which is not in concordance with previous studies.

Patient who had right ventricular hypetrophy recorded on ECG had lower 5 years percentage of mortality. In our study, most participants belonged to GOLD stadium 3, which is characterized as severe. They had higher mortality percentage in five years period

comparing to GOLD 2 and 4, despite the fact that patient in GOLD 4 stadium had very severe airway obstruction.

Other researchers have found variable COPD pulmonary hypertension and right ventricle remodeling prevalence, increased by disease progression [15, 16], which is in concordance with our results. Although the exact prevalence is unknown, right ventricular hypertrophy appears to be a common complication of chronic lung disease, and more frequently complicates advanced lung disease [14, 16]. Generally, our study has shown earlier electrocardiogram COPD presentation as compared to previous studies, presented already in GOLD 2 stadium, and the most in GOLD 3. In COPD, chronic pulmonary hypertension accompanied with right ventricular work increase results in uniform RV hypertrophy. Several mechanisms including in pathophysiology of pulmonary hypertension, could lead to COPD, chronic cor pulmonale and consecutively to the right heart failure. In patients with COPD, P-pulmonale and the RVH electrocardiographic evidence are not shown unless FEV_1 <45% of predicted is presented (GOLD 2) [12, 13]. This led to conclusion that RVH develops faster than expected [12, 13, 16] which could be applicative to our studies. The appearance of the complete and incomplete RBBB in otherwise healthy individuals is believed to be benign, but several cardiac and pulmonary diseases are known to be associated with RBBB and IRBBB. In our study, there were more frequent in non-survivors and presented mortality risk. It present a challenge for future prospective studies to investigate pathophysiology of this pattern. Investigators from Denmark have explored this issue in the Copenhagen City Heart Study prospective database in almost 19,000 subjects in period from 1976 to 2003. Patients with prior myocardial infarction (MI), heart failure or LBBB were excluded and 18,441 were included to be followed up until 2009. Primary end points were all-cause mortality, major cardiovascular (CV) events and admission for COPD [4]. The original purpose of the study was to focus on prevention of coronary heart disease and stroke but by the time it was expanded. Still, there are no explanations for a lot of questions [4, 16, 17, 18]. Thus, finding of incomplete or complete RBBB in COPD patients should not be neglected and in those cases pulmonologists should ask for more or frequent cardiology examination.

Left bundle branch block (LBBB) has been proposed as a risk factor for cardiovascular morbidity and mortality [16, 17]. LBBB in the absence of a clinically detectable heart disease is associated with new-onset heart failure and death from cardiovascular diseases. Further

study is warranted to determine if additional diagnostic testing or earlier treatment in patients with asymptomatic LBBB can decrease cardiovascular morbidity or mortality [19]. Our study had shown that LBBB is predictor of mortality in COPD patients. There are no facts to suggest a connection between these two things. Possible explanation are age, smoking, hypoxemia atherosclerosis, diabetes.

It is common that patients with chronic obstructive lung disease may show low ORS complex (LQRSV), particularly in the limb leads, because of an increased heart/chest wall distance from the lung hyperinflation, which, if not offset, would be expected to augment QRS potentials by the increased electrical impedance [6, 15, 16]. The amplitude of the QRS complexes may be small in patients with chronic obstructive pulmonary disease as lung hyperinflation lead to poor electrical conductors. Our study had registered low ORS voltage in 69% patients, but it had no influence of outcome in COPD patients.

T wave may be inverted in leads V1, V2 or V3 due to RVH, commonly found due to varying effect of lung hyperinflation, axis deviation and enlargement of the right ventricle. Generalized ST depression with T wave inversion may also be seen [17, 18]. In our study, negative T wave had no predictive value in COPD mortality.

The point of our study is to find out which ECG pattern could be predictive model for five years of mortality in COPD patients. We used logistic regression analysis to assess significant predictors of mortality adjusted for potential confounders. Final model had discovered two significant predictors. It turned out that RBBB and LBBB are those ones. In fact, patients who have registered LBBB on ECG have two times higher chance of mortality compared to patients without LBBB. This finding is not surprising considering in mind that LBBB in not ‘naïve’ finding in any patients and disease. Contrary, RBBB is protective factor and patients with RBBB have 1.6 times lower chance to have death outcome. So far, RBBB is not consider as dangerous finding and lot of people have it not knowing for that without any complainments and reveal it accidentally [17, 18]. ‘Silant’ RBBB in COPD patient is very frequent finding. The exact explanation does not exist, but further studies could go further to electrical activity of heart in COPD patients [19, 20].

The ECG findings were found to be 35.7% sensitive and 95.6% specific in diagnosis of COPD among patients having respiratory problems. So, there are chances of false negative but not of false positives in detecting COPD cases by ECG. Based on the findings of the

study, positive predictive value was found to be 71.4% meaning thereby that the chances of COPD among patients having ECG changes are high. Similarly, negative predictive value was 83.0%, meaning thereby that the chances of not having COPD among patients not having ECG changes are also quite high [6, 16, 17, 20].

Improving survival of COPD patients was the central theme over years. Most of the conducted studies put the focus on therapy and rehabilitation, giving no attention to ECG screening for instant. According to our study, electrocardiography screening in COPD patients should be obligatory, followed-up with regulatory ECG monitoring, especially if normal axis, incomplete RBBB and LBBB were found. Those patients should be monitored more frequently by pulmonologist as well as cardiologist.

CONCLUSION

COPD patients with normal axis, incomplete RBBB and LBBB have significantly higher percentage of five years of mortality. Apart that, patient with LBBB have two times higher chance of mortality than those who do not have it. On the other hand, patients with RBBB have lower risk of mortality and this pattern has been supposed as protective in COPD patient according to our study. Main ECG predictors of COPD patients five year mortality are LBBB and RBBB, but according to statistical model, electrocardiogram should be further explored and possibly obligatory involved in a routine clinical practice as an easy and low cost screening method. It is extremely important to emphasize that patients who have both cardiovascular and pulmonary disease are in higher risk of mortality and that both diseases should be treated in parallel and independently as recommended by the GOLD guidelines.

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REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2017 Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD website. http://goldcopd.org/download/326/. doi: 10.1164/rccm.201701-0218PP PMID: 28128970
2. Mejza F, Gnatiuc L, Buist AS, Vollmer WM, Lamprecht B, Obaseki DO, et al. Prevalence and burden of chronic bronchitis symptoms: results from the BOLD study. Eur Respir J. 2017;22;50(5):1700621. DOI: 10.1183/13993003.00621-2017 PMID: 29167298
3. Martinez FJ, Mannino D, Leidy NK, Mannino DM, Han MK, Bacci ED, et al. A new approach for identifying patients with undiagnosed chronic bbstructive pulmonary disease. Am J Respir Crit Care Med. 2017;195:748. DOI: 10.1164/rccm.201603-0622OC PMID: 27783539
4. Rubinsztajn R, Przybyłowski T, Grabicki M, Karwat K, Warzęchowska MM, Batura-Gabryel H, et al. Comorbidities in chronic obstructive pulmonary disease: Results of a national multicenter research project. Adv Clin Exp Med. 2019;28(3):319-324. doi:10.17219/acem/78024 PMID: 30943332
5. Skov MW, Rasmussen PV, Ghouse J, Hansen SM, Graff C, Olesen MS, et al. Electrocardiographic preexcitation and risk of cardiovascular morbidity and mortality: results from the copenhagen ECG Study. Circ Arrhythm Electrophysiol. 2017;10(6):pii: e004778. doi:10.1161/CIRCEP.116.004778. PMID: 28576781
6. Larssen MS, Steine K, Hilde JM, Skjørten I, Hodnesdal C, Liestøl K, Gjesdal K. Mechanisms of ECG signs in chronic obstructive pulmonary disease. Open Heart. 2017; 22:4(1):e000552. doi: 10.1136/openhrt-2016-000552 PMID: 28533915
7. Lazovic B, Mazic S, Stajic Z, Djelic M, Zlatkovic-Svenda M, Putnikovic B. United in prevention-electrocardiographic screening for chronic obstructive pulmonary disease. Acta Informatica Medica. 2013;21(2):127-128. doi: 10.5455/aim.2013.21.127-128 PMID: 24058253
8. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Res Crit Care Med. 2019;200;(8):e70-88 doi.org/10.1164/rccm.201908-1590ST PMID: 31613151
9. Lam A, Wagner GS, Pahlm O. The classical versus the Cabrera presentation system for resting electrocardiography: Impact on recognition and understanding of clinically important electrocardiographic changes. J Electrocardiol. 2015;48(4):476-82. https://doi.org/10.1016/j.jelectrocard.2015.05.011 PMID: 26051487
10. Alter P, Watz H, Kahnert K, Rabe KF, Biertz F, Fischer R, et al. Effects of airway obstruction and hyperinflation on electrocardiographic axes in COPD. Respir Res. 2019;20(1):61. doi: 10.1186/s12931-019-1025-y. PMID: 30917825
11. Kahnert K, Alter P, Young D, Lucke T, Heinrich J, Huber RM, et al. The revised GOLD 2017 COPD categorization in relation to comorbidities. Respir Med. 2018;134:79–85. DOI: 10.1016/j.rmed.2017.12.003 PMID: 29413512
12. Alter P, Watz H, Kahnert K, Pfeifer M, Randerath WJ, Andreas S, et al. Airway obstruction and lung hyperinflation in COPD are linked to an impaired left ventricular diastolic filling. Respir Med. 2018;137:14–22. PMID: 29605197 DOI: 10.1016/j.rmed.2018.02.011
13. Karloh M, Fleig Mayer A, Maurici R, Pizzichini MMM, Jones PW, Pizzichini E. The COPD Assessment Test: What Do We Know So Far?: A systematic review and meta-analysis about clinical outcomes prediction and classification of patients into GOLD stages. Chest. 2016;149(2):413-425. doi: 10.1378/chest.15-1752 PMID: 26513112
14. Brown JP, Martinez CH. Chronic obstructive pulmonary disease comorbidities. Curr Opin Pulm Med. 2016;22(2):113-8. doi:10.1097/MCP.0000000000000241. PMID: 26814720
15. Güder G, Störk S.COPD and heart failure: differential diagnosis and comorbidity. Herz. 2019;44(6):502-508. doi: 10.1007/s00059-019-4814-7. PMID: 31111162
16. Cheng SL, Lin CH, Wang CC, Chan MC, Hsu JY, Hang LW, et al. Comparison between COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores for evaluation of clinical symptoms, comorbidities and medical resources utilization in COPD patients. J Formos Med Assoc. 2019 Jan;118(1 Pt 3):429-435. doi: 10.1016/j.jfma.2018.06.018. PMID: 30150099
17. Mazza A, Bendini MG, Cristofaro RD, Lovecchio M, Valsecchi S, Leggio M, et al. Prevalence and clinical significance of left bundle branch block according to classical or strict definition criteria in permanent pacemaker patients. Clin Cardiol. 2017;40(6): 377–382. doi: 10.1002/clc.22673 PMID: 28294356
18. Pelà G, Calzi LM, Pinelli S, Andreoli R, Sverzellati N, Bertorelli G, et al. Left ventricular structure and remodeling in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11(1):1015-1022 doi.org/10.2147/COPD.S102831 PMID: 27257378

19. Song S, Yang PS, Kim TH, Uhm JS, Pak HN, Lee MH, et al. Relation of chronic obstructive pulmonary disease to cardiovascular disease in the general population. Am J Cardiol. 2017;120:1399–1404. doi: 10.1016/j.amjcard.2017.07.032 PMID: 28826898
20. John J Oppenheimer. What is the role of ECG in the workup of chronic obstructive pulmonary disease (COPD). Update sep 11, 2020. Available from: https://www.medscape.com/answers/297664-7391/what-is-the-role-of-ecg-in-the-workup-of-chronic-obstructive-pulmonary-disease-copd

Table 1. General characteristics of chronic obstructive pulmonary disease patients in relation to exitus

Characteristics	Death in 5 years		p
	No	Yes	
Age (years)	63.3 ± 8.3	63.8 ± 9.1	0.409[a]
Sex			
male	78 (29.5%)	186 (70.5%)	0.918[b]
female	203 (29.2%)	492 (70.8%)	
FVC (%)	70.9 ± 14.8	68.0 ± 15.3	0.007[a]
FEV1 (%)	44.3 ± 10.7	41.4 ± 11.7	< 0.001[a]
FEV1/FVC	63.8 (60.4-65.8)	63.1 (56.9-65.4)	< 0.001[c]
MEF (%)	13.0 (10.5-19.0)	14.6 (11.4-19.0)	0.149[c]
Gold			
2	98 (35.4%)	179 (64.6%)	< 0.001[c]
3	156 (30.1%)	363 (69.9%)	
4	27 (16.6%)	136 (83.4%)	

[a]t test;

[b]Pearson χ^2 test;

[c]Mann–Whitney U-test;

results are presented as count (%), mean ± sd or median (25–75th percentile)

Table 2. Electrocardiographic characteristics of chronic obstructive pulmonary disease patients in relation to 5 years mortality

Characteristics	Death in 5 years		p
	No	Yes	
Axis			
normogram	210 (31.4%)	458 (68.6%)	0.028 [a]
left	71 (24.4%)	220 (75.6%)	
p > 2.5			
no	147 (28.2%)	375 (71.8%)	0.396 [a]
yes	134 (30.7%)	303 (69.3%)	
RVH			
no	269 (28.8%)	664 (71.2%)	0.056 [a]
yes	12 (46.2%)	14 (53.8%)	
RBBB			
no	184 (26.2%)	519 (73.8%)	<0.001 [a]
yes	97 (37.9%)	159 (62.1%)	
Incomplete RBBB			
no	225 (30.9%)	502 (69.1%)	0.047 [a]
yes	56 (24.1%)	176 (75.9%)	
Low QRS			
no	120 (31.3%)	263 (68.7%)	0.260 [a]
yes	161 (28.0%)	415 (72.0%)	
Transitional			
no	58 (27.6%)	152 (72.4%)	0.544 [a]
yes	223 (29.8%)	526 (70.2%)	
LBBB			
no	270 (30.3%)	622 (69.7%)	0.016 [a]
yes	11 (16.4%)	56 (83.6%)	
QRS < 0.12s			
no	252 (28.9%)	621 (71.1%)	0.345 [a]
yes	29 (33.7%)	57 (66.3%)	
S1S2S3			
no	276 (29.0%)	677 (71.0%)	0.010 [b]
yes	5 (83.3%)	1 (16.7%)	
Negative T in V1/V3			
no	269 (29.1%)	655 (70.9%)	0.509 [a]
yes	12 (34.3%)	23 (65.7%)	
QT < 400 ms			
no	2 (16.7%)	10 (83.3%)	0.525 [b]
yes	279 (29.5%)	668 (70.5%)	

[a]Pearson χ^2test;

[b]Fisher's exact test

Table 3. Regression model with exitus as outcome

Characteristics	Univariate		Multivariate (backward method)	
	OR (95% CI)	p	OR (95% CI)	p
FVC	0.988 (0.978–0.997)	0.007		
FEV1	0.978 (0.966–0.990)	< 0.001		
FEV1/FVC	0.949 (0.926–0.973)	< 0.001	0.951 (0.928–0.974)	< 0.001
MEF 25–75	1.005 (0.992–1.018)	0.436		
Gold	1.545 (1.247–1.916)	< 0.001		
Axis	1.421 (1.038–1.944)	0.028		
RVH	0.473 (0.216–1.035)	0.061		
RBBB	0.581 (0.429–0.787)	< 0.001	0.610 (0.448–0.830)	0.002
Incomplete RBBB	1.409 (1.003–1.978)	0.048		
LBBB	2.210 (1.140–4.284)	0.019	2.027 (1.039–3.956)	0.038
S1S2S3	0.082 (0.009–0.701)	0.022		

