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ORIGINAL ARTICLE

TWO-YEAR MORTALITY FOLLOWING A SEVERE COPD EXACERBATION IN BULGARIAN PATIENTS

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Abstract. *Two-year mortality in patients with COPD is expected to be between 10% and 49% depending on the investigated subgroup and specific patients' characteristics.* ***Aim:*** *To assess the two-year mortality in COPD patients following hospitalization for severe exacerbation and to describe the prognostic value of comorbidities and specific patients' characteristics.* ***Materials and methods:*** *We included 152 consecutive patients hospitalized for COPD exacerbation and signing informed consent. The Metabolic syndrome (MS), diabetes mellitus (DM), and hypovitaminosis D were diagnosed according to international guidelines. Demographic parameters (age, sex, smoking status, and the number of pack-years) were recorded. Quality of life was examined using CAT and mMRC questionnaires. The lung function was assessed by spirometry. Two-year mortality was determined according to data extracted from the national death register.* ***Results:*** *Two-year mortality rate was 11.8%. The investigated comorbidities – DM, MS, arterial hypertension (AH) and vitamin D status were no predictors of the two-year mortality. Mortality was increased in patients with mMRC ≥ 2 (17.2 vs. 1.9%, p = 0.005) and CAT score ≥ 10 (14.2 vs. 0%, p = 0.045). Severe exacerbation during the previous year was a risk factor for the registered two-year mortality (17.5% vs 5.6%, p = 0.021). The two-year mortality was increased in the group with FEV1 < 50%, compared to FEV1 > 50% (18.0 vs. 7.7%, p = 0.049). Cox regression analysis showed a 3.0% increase in the mortality rate for each 1% decrease in FEV1, 6.2% for each 1% decrease in PEF, 7.8% for one year of increasing age, 4% for 1% decrease in the FEV1/FVC ratio and 7.1% for each 1 point increase of CAT (all p-values < 0.05).* ***Conclusions:*** *The two-year mortality of COPD patients following a severe exacerbation was relatively low. Chronological age, FEV1, history for severe exacerbation during the previous year, reduced quality of life, and low BMI were all associated with increased mortality. Disease Grade C, mMRC < 2, and CAT score < 10 were associated with a favourable prognosis.*

Key words: *COPD, acute exacerbation, mortality, commorbidity*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities caused usually by significant exposure to noxious particles or gases [1].

Two-year mortality in patients with COPD was described to be between 10 and 49% [2-8]. It depends from the investigated subgroup and specific patients' characteristics (Table 1). Severe exacerbations (hospitalizations), lower FEV1, increased chronological age, lower quality of life, presence of hypoxemia, and comorbidities are well-known risk factors for increased mortality. COPD patients with severe exacerbations are at a particularly high mortality risk. On the other hand, some comorbidities such as vitamin D deficiency and insufficiency, diabetes mellitus (DM), and the metabolic syndrome (MS) were also found to increase mortality [4, 9, 10, 11], but not all studies confirm these results [12, 13, 14].

Table 1. Two-year mortality in COPD according to different publications

Authors, year	Patients	Two-year mortality	Risk factors
Almagro et al. [2], 2002	135 patients after severe exacerbation	35.6%	Age, women, SQRG, previous severe exacerbations, pCO_2
Connors et al. [3], 1996	1016 patients with severe exacerbation	49%	FEV1, BMI, Age, PaO_2
Gudmundsson et al. [4], 2006	416 Patients after severe exacerbation	29.3%	Age, FEV1
Kim et al. [5], 2006	482 patients after ED visit	32%	Age, comorbidities, previous severe exacerbations
Nishimura et al. [6], 2002	183 patients	10%	Dyspnea
Piquet et al. [7], 2013	1824 patients with severe exacerbation	29.4%	Age, lower BMI, lung cancer, cardiovascular comorbidity, previous severe exacerbations, LTOT
Soler-Cataluna et al. [8], 2005	304 patients	25.9%	Severe exacerbations

The aim of the present study was to document the two-year mortality in COPD patients following hospitalization for severe exacerbation and to assess the prognostic value of specific comorbidities and patients' characteristics.

MATERIALS AND METHODS

We included 152 consecutive COPD patients hospitalized for COPD exacerbation who gave written informed consent. The MS, DM, or hypovitaminosis D were diagnosed according to international guidelines. A cutoff of less than 25 nmol/L 25-hydroxyvitamin D (25(OH)D) was used for vitamin D deficiency, 25-50 nmol/l for insufficiency, and higher than 50 nmol/L for sufficiency [15]. A patient was considered to have DM if at least one of the following was present: 1. fasting blood glucose ≥ 7.0 mmol/L; 2. 2-h plasma glucose ≥ 11.1 mmol/L during a 75 g oral glucose tolerance test (OGTT); 3. HbA1c ≥ 6.5%; 4. Antidiabetic drug treatment [16]. The MS was diagnosed based on ≥ 3 of the following criteria: 1. Waist circumference > 94 cm in males or > 80 cm in females; 2. Triglycerides > 1.7 mmol/L (or under lipid-lowering therapy); 3. High-density lipoprotein (HDL) < 1.0 mmol/L in males or < 1.3 mmol/L in females (or on lipid-lowering therapy); 4. Systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mm Hg (or on antihypertensive therapy); 5. Fasting blood glucose > 6.0 mmol/L (or taking therapy) [17].

Diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1]. Demographic parameters – age, sex, smoking status, and number of pack-years were recorded. Quality of life was assessed using CAT and mMRC questionnaires. The lung function was assessed with use of pre- and post-bronchodilator spirometry, according to ERS/ATS guidelines [18]. A patient was considered as having arterial hypertension if he/she was taking antihypertensive medications. The number of the exacerbations in the previous year was evaluated as follows: severe exacerbation – worsening of the respiratory symptoms, which led to hospitalization; moderate exacerbation – worsening of the respiratory symptoms for which antibiotic or/and systemic steroid treatment was administered, however without hospitalization) [1]. The total number of exacerbations during the previous year was calculated as the sum of the severe and moderate exacerbations. The duration of the current hospital stay was measured in days.

All included patients had FEV1/FVC ratio < 0.70 following administration of a bronchodilator. The patients who did not adhere to the procedures of the study were excluded from further analysis. Informed

consent was signed by all participants prior to any procedures.

Two-year mortality was determined based on the national death register. Statistical analyses were done with the SPSS platform, version 22.0 (SPSS Inc., Chicago, IL, USA). The chi-square test was used for categorical variables. The normal distribution of the continuous variables was assessed by the Shapiro–Wilk test. Normally distributed variables were compared by independent-sample T-tests and analysis of variance (ANOVA) for three or more groups. Abnormally distributed variables were compared by the Mann-Whitney U test for two groups and the Kruskal–Wallis test for three or more groups. We analyzed the mortality according to the Kaplan–Meier method (in weeks). Cox regression was used to determine the significance of important variables affecting survival.

Study methods and sample characteristics, including the prevalence of the comorbidities and their impact on COPD in this group of patients are explained in further detail elsewhere [19, 20]. The results for one-year mortality were published separately [21] as this manuscript is focused on two-year mortality and the comparison between one- and two-year mortality rates.

This study was approved by the Ethical Committee at the Clinical Center for Pulmonary Diseases – 801a/06.03.2017.

RESULTS

152 COPD patients with severe exacerbations were included. Their demographic characteristics are presented in Table 2. Their two-year mortality rate was 11.8% (18/152). Mortality in the second year was 5% only (7/141).

Table 2. Demographic characteristics of the analyzed COPD patients with severe exacerbations

Variable	Value
Mean age, years (± SD)	65.1 (± 9.9) years
Male / Female gender, n	108 (71.1%) / 44 (28.9%)
Mean FEV1, % (± SD)	55.3% (± 19.5%)
Smoking status – Current smoker, n	40 (26.3%)
Smoking status – Former smoker, n	88 (57.9%)
Smoking status – Never-smoker, n	24 (15.8%)
Mean BMI (± SD)	27.3 (± 5.6)
Inhalatory corticosteroids (ICS) treatment, n	127 (83.6%)

The mean age of the patients who died/survived during the follow-up period was 72 years vs. 64 years (p = 0.004). Cox regression showed a 7.4% increase in the two-year mortality for each year of increasing age (p = 0.003). There was a tendency for gender-associated difference in mortality rates (13.9 in males vs. 6.8% in females, p = 0.221), but the sample for this analysis is too small to yield statistical significance (Fig. 1). Ever-smokers (current and former ones) had a two-year mortality of 12.5%, whereas never-smokers – of 8.3% (p = 0.562).

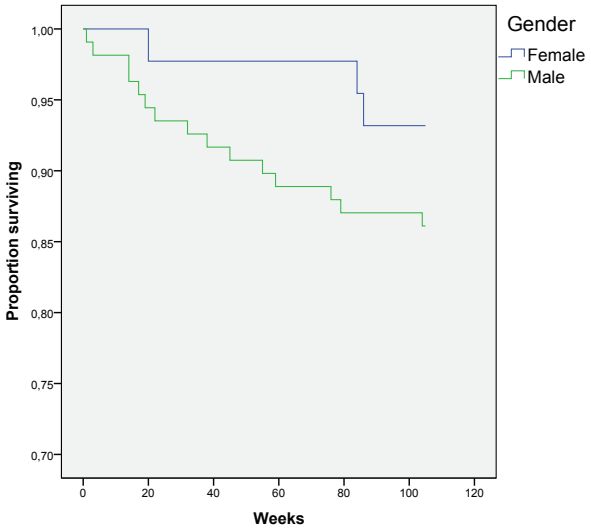


Fig. 1. The Kaplan–Meier curve of two-year survival depending on gender (in weeks)

The presence of severe exacerbation during the previous year was a risk factor for increased two-year mortality (17.5% vs 5.6%, p = 0.021) (Fig. 2). The patients who deceased till the end of the second year had more severe exacerbations in the year previous to the start of the present 2-yr follow-up period (2.11 vs. 1.83). The number of moderate exacerbations did not differ between the groups (0.69 vs. 0.67). The length of hospital stay was not related to mortality (p = 0.930).

MMRC ≥ 2 emerged as a risk factor for increased two-year mortality (17.2 vs 1.9%, p = 0.005) (Fig. 3). CAT score ≥ 10 was also a risk factor for higher two-year mortality (14.2 vs 0%, p = 0.045) (Fig. 4), but not for one-year mortality (8.7 vs 0%, p = 0.133). Cox regression showed a 7.1% increase in two-year mortality for each 1 point CAT increase (p = 0.018).

An absolute but not significant mortality increase was observed in parallel with lower CAT results: 0% mortality in patients with CAT 0-9, 11.1% in patients with CAT 10-19, 16.3% in patients with CAT 20-29, and 25% in patients with CAT > 30 (p = 0.102). The deceased patients had lower results according to the CAT questionnaire with significant differences in total CAT scores (22 vs. 17), as well as when answering

the third (3.44 vs. 2.54), fourth (4.44 vs. 3.46), sixth (2.78 vs. 1.42), and eighth (3.56 vs. 2.63) questions.

There is a trend for increased mortality in patients with GOLD grade D, compared to grade C (13.5% vs 0%, p = 0.088).

Two-year mortality was increased in the group with FEV1 < 50% compared to FEV1 > 50% (18.0 vs. 7.7%, p = 0.049) (Fig. 5). Cox regression showed a 3.0% increase in mortality rate for each 1% decrease in FEV1 (p = 0.027), 6.2% increase for each 1% decrease in PEF (p < 0.0005) and 4% increase for 1% decrease in the FEV1/FVC ratio. FVC was not related to the two-year mortality (p > 0.2).

Increased mortality was related to decreases in FEV1 – 5.9% mortality rate in patients with FEV1 > 80%, 8.2% in patients with FEV1 between 50% and 80%, 17.4% in patients with FEV1 between 30% and 50% and 18.7% in patients with FEV1 < 30%, but this difference was not statistically significant (p = 0.3) (Fig. 6).

The FEV1, PEF, and FEV1/FVC ratios were lower in the patients who died (46 vs. 57%, 37 vs. 58% and 49 vs. 55%, respectively, all p-values < 0.05).

The comorbidities under study – DM, MS, AH, and vitamin D status did not predict the two-year mortality (all p > 0.2). Vitamin D levels and HbA1c did not emerge as risk factors for mortality, according to the Cox regression analysis. Lower HDL showed a trend for increased mortality (20.8 vs. 10.2%, p = 0.121), while, interestingly, increased triglycerides might have protective features – 4.4% vs. 15% (p = 0.069).

Mortality, according to BMI was 42.9%, 14.6%, 12.7% and 2.4% in patients with BMI < 18.5, between 18.5 and 25, between 25 and 30, and >30.0, respectively (p = 0.018) (Fig. 7). The patients with BMI < 30 had

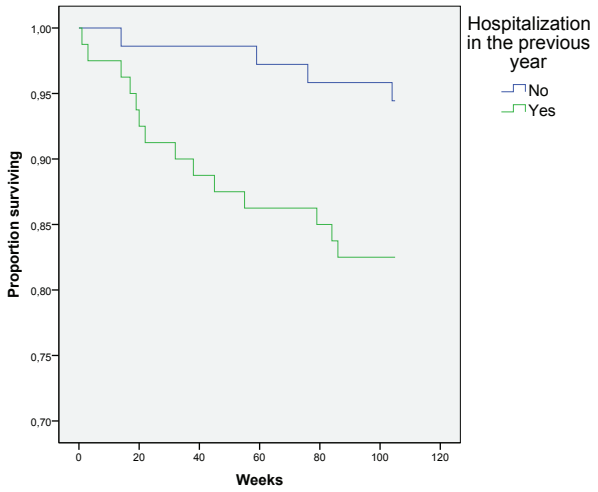


Fig. 2. Kaplan–Meier curve for two-year survival depending on the presence of severe exacerbation in the previous year (in weeks)

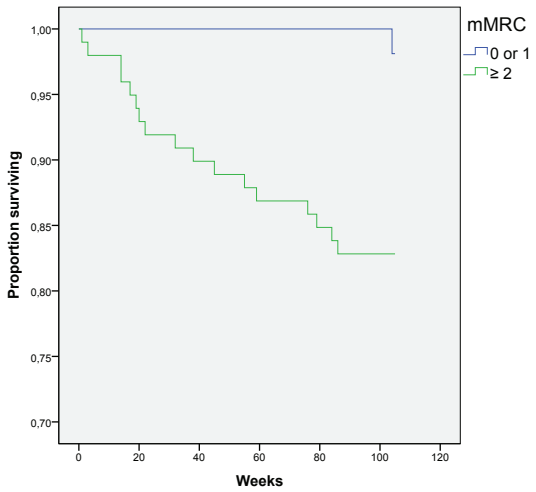


Fig. 3. Kaplan–Meier curve for two-year survival according to mMRC results (in weeks)

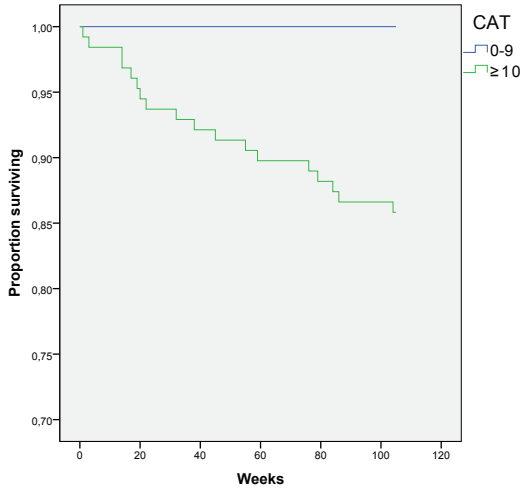


Fig. 4. Kaplan–Meier curve for two-year survival according to CAT results (in weeks)

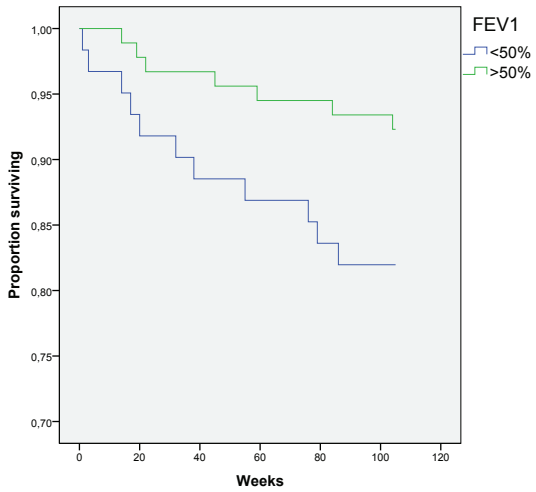


Fig. 5. Kaplan–Meier curve for two-year survival according to FEV1 (in weeks)

increased two-year mortality, compared to those with BMI > 30 (15.5 vs 2.4%, p = 0.03). A more profound difference in mortality was observed between patients with BMI < 18.5 vs. patients with BMI >18.5 (10.3 vs. 42.9%, p = 0.009). The Cox regression showed a 13.4% mortality decrease for each 1 unit increase in BMI (p = 0.008).

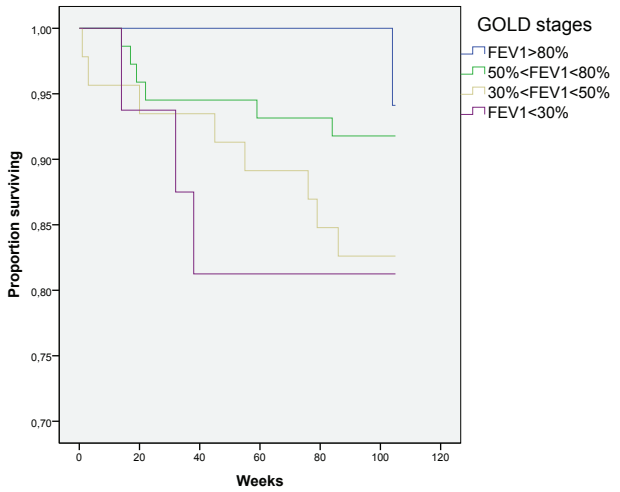


Fig. 6. Kaplan–Meier curve for two-year survival according to GOLD stages (in weeks)

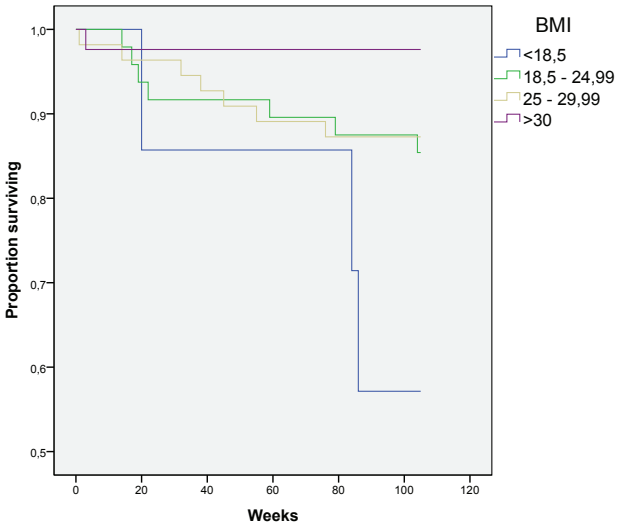


Fig. 7. Kaplan–Meier curve for two-year survival stratified to BMI (in weeks)

DISCUSSION

This study reported a two-year mortality of 11.8% in COPD patients with severe exacerbation, a rate that was relatively low, compared to other studies (Table 1). The reasons for this observation could be explained by the younger age of the participants (a mean of 65 years), a longer mean duration of hospital stay of 7.5 days with later patient's discharge, and higher FEV1 (mean was 55%). Second, in-hospital mortality was not relevant to this analysis, as all patients were studied before discharge and in a stable condition for more precise assessment of comorbidities. Nevertheless, this low mortality could be explained by an improved care in the last years, particularly affecting cardiovascular comorbidities and risks.

Chronological age was a risk factor for two-year mortality in this study as shown by other authors also [2, 3, 4, 5, 7]. However, mortality was not related to gender, although some authors had found increased mortality in females [2].

Severe exacerbations during the previous year (prior to baseline) were a risk factor for increased mortality as stated by other investigators [2, 5, 7, 8]. Literature data, as did our study, suggested an association between the two-year mortality rates and the patients' characteristics such as age and FEV1. The correlation to FEV1 is inverse and more apparent than the association with age, which is direct and less clear in origin.

The number of moderate exacerbations, the total number of exacerbations, and the duration of the hospital stay were not related to one-year and two-year mortality rates.

Reduced quality of life emerged as a risk factor for two-year mortality, a finding not explicitly stated by the aforementioned studies (see Table 1). Both CAT < 10 and mMRC < 2 are associated with a favourable prognosis, but there is 0% mortality in patients with fewer symptoms (CAT score < 10).

Reduced FEV1, FVC/FEV1 ratio, and PEF, but not FVC are risk factors for increased two-year mortality, in line with other studies [3, 4]. We observed increasing mortality in higher GOLD stages, although not reaching statistical significance. However, patients with FEV1 < 50% had a significantly higher two-year mortality, compared to patients with FEV1 > 50%.

This study confirmed the role of lower BMI as a risk factor for mortality, as stated by other authors also [3, 7]. However, all of the investigated comorbidities – hypovitaminosis D, DM, MS, and AH were not predictors of the two-year mortality. This is an interesting finding, especially in the modern concept of comorbidities and their impact on COPD. Nonetheless, our findings need additional evaluation to determine if they are applicable only for this subgroup of COPD patients with severe exacerbation – the 'severe exacerbator' phenotype.

The precise registration and documentation of outcomes such as demographic parameters, exacerbations in the previous year, hospital stay, pulmonary function, and quality of life represent an important strength of this study. Second, the examined comor-

bidities - vitamin D, DM, AH, and MS are diagnosed according to the international guidelines with minimum risk of bias.

This study had a relatively small sample size which may have led to a lack of power for some of the outcomes. However, it shapes well enough the risk factor profile for two-year mortality in these patients. And at last but not at least, some of the aforementioned similar studies have had a comparable number of participants.

CONCLUSIONS

In this study the two-year mortality in COPD patients surviving a severe exacerbation was relatively low. Age, FEV1 value, the presence of severe exacerbation during the previous year, reduced quality of life and low BMI were all associated with increased mortality. Grade C, mMRC < 2 and CAT score < 10 were associated with a favorable prognosis.

Disclosure Summary: *The authors have nothing to disclose.*

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