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COPD and comorbidities in the Republic of Moldova

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Abstract:

BACKGROUND AND AIM: Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide, and the majority of patients have at least one comorbid condition of clinical significance. Therefore, we studied its prevalence and implication based on experience from the Republic of Moldova.

METHODS: The study was a prospective cohort study that included 435 patients with COPD from 2015 to 2017.

RESULTS: We found heart failure in 38.62% of the patients, hypertension in 50.11%, coronary artery disease in 23.45%, diabetes mellitus in 10.11%, renal failure in 1.15%, rheumatoid arthritis in 3.22%, depression in 4.83%, cognitive impairment in 4.37%, obesity in 29.89%, and cachexia in 3.22%. Only 24.65% of patients did not have comorbidities. One comorbidity was found in 23.73%, two in 24.19%, three or more in 27.42%. The Charlson comorbidity index (CCI) had a medium negative correlation with the 6-minute walking test ($r=-0.37$, $p<0.001$) and a weak correlation with the rate of exacerbations ($r=0.17$, $p=0.016$). CCI had a strong correlation with ADO (age, dyspnea and airflow obstruction) ($r=0.75$, $p<0.001$); moderate with BODE (body mass index, airflow obstruction, dyspnea, and exercise) ($r=0.3$, $p<0.001$); and weak with BODEx (body mass index, airflow obstruction, dyspnea, and exacerbations), CODEX (comorbidity, obstruction, dyspnea, and previous severe exacerbations), and DOSE (dyspnea, obstruction, smoking, and exacerbation). CCI had a medium correlation with St. George's Respiratory Questionnaire (SGRQ) activity ($r=0.36$, $p<0.001$), impact ($r=0.34$, $p<0.001$), and total ($r=0.37$, $p<0.001$) scores, and the overall quality of life assessed by SGRQ and Clinical COPD Questionnaire.

CONCLUSIONS: Patients with COPD require a multidisciplinary approach to assess and manage a variety of conditions, which influence the evolution and prognosis of COPD. Patients often have one or two comorbidities of clinical significance, and they are predominantly cardiovascular and metabolic. Patients with comorbidities tend to have a poorer health-related quality of life. Comorbidities can be assessed by multidimensional indexes such as ADO and BODE.

Keywords: Comorbidities, COPD, health-related quality of life, multidimensional indexes

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Introduction

Chronic obstructive pulmonary disease (COPD) is defined as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1] It is also currently the third leading cause of death. From 1990 to 2015, the prevalence of COPD increased by 44.2%, and in 2015, it was the cause of 2.6% of global disability-adjusted life years.[2] Finally, comorbidities increase direct and indirect medical costs of the management of COPD patients.[3,4]

COPD is currently regarded as a systemic condition because it is linked to several comorbidities with major clinical importance including cardiovascular, metabolic, and gastrointestinal comorbidities.[5]

At least one comorbidity of clinical relevance is found in 78.6% of patients, two in 68.8%, and three or more in 47.9% of subjects with cardiovascular being the most predominant comorbidity.[6] This underlines the need for multidimensional assessment and complex management of patients with COPD.[7]

Although the data on COPD comorbidities is widely present in the literature, their prevalence in developing counties is understudied and underreported. There is also limited data on multidimensional indexes and health-related quality of life (HRQL) in COPD patients with comorbidities. Therefore, we studied their prevalence and clinical significance based on experience from the Republic of Moldova.

Materials and Methods

The study was conducted on 435 patients with COPD. The data were acquired prospectively from 2015 to 2017 in a single center of a university hospital. Inclusion criteria for patients with COPD were:

1. Age >50 years;
2. History of COPD over 10 years;
3. $FEV_1/FVC \leq 70\%$;
4. Result of the bronchodilator test with salbutamol (200 μg) ≤15% or 200 ml;
5. Patients with full in-depth anamnesis, completed questionnaires, physical examination, investigations (complete data for analysis); and
6. Written informed consent for inclusion in the study.

Patients were diagnosed and assessed based on the global initiative for chronic obstructive lung disease (GOLD) 2017 positional paper.

Data collection

For each patient, an in-depth history was obtained. The collected data included information on allergy and atopy, COPD symptoms, smoking status, risk factor analysis, history of acute respiratory events including the number of self-reported COPD exacerbations (during the previous year), and comorbidities.

Pulmonary function data were obtained using standard equipment according to the American Thoracic Society/European Respiratory Society consensus guidelines.[8,9] The HRQL was assessed using St. George's Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT), and Clinical COPD Questionnaire (CCQ). The 6-minute walking distance (6MWD) and the Charlson comorbidity index (CCI) were assessed by the respiratory medicine physician as a standard test.

Several multidimensional indexes were used to assess the patients: BODE (body mass index, airflow obstruction, dyspnea, and exercise),[10] BODEx (body mass index, airflow obstruction, dyspnea, and exacerbations),[11] e-BODE (body mass index, airflow obstruction, dyspnea, exercise, and exacerbation),[11] DOSE (dyspnoea, obstruction, smoking, and exacerbation),[12] ADO (age, dyspnea, and airflow obstruction),[13] and CODEX (comorbidity, obstruction, dyspnea, and previous severe exacerbations).[14]

Statistical analysis

Data analysis was performed using EXCEL and SPSS 16.0 (SPSS, Inc.) programs using the functions and modules of these programs.

The data were presented as a mean value±standard deviation or n (%). The correlation of the parameters was determined by the appreciation of Pearson's (R) correlation coefficient. One-way analysis of variance (ANOVA)

was performed for the comparison of means between the groups with Tukey post hoc analysis. Regression analysis was performed in SPSS using the stepwise linear regression module. A p-value <0.05 was considered statistically significant.

Statement of ethics

This study was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy "Nicolae Testemiţanu," Chisinau, Republic of Moldova (approval number 17/12; dated December 11, 2015).

Results

The descriptive data of the 435 patients are presented in Table 1. The mean age was 62.7±9.8 years, the duration of smoking was 24.3±17.26 years, and the number of exacerbations was 2.78±1.21. According to the global initiative for chronic obstructive lung disease (GOLD) 2011 classification, 70 patients were GOLD B, 87 were GOLD C, and 278 were GOLD D. The mean saturation (SaO_2) at rest was 92.41±6.26, body mass index (BMI) was 27.68±6.99, and 6MWD was 257.45±122.24. The mean number of comorbidities was 1.32±1.24.

Cardiovascular comorbidities (heart failure, hypertension, and coronary artery disease [CAD]) were the most prevalent followed by metabolic comorbidities (diabetes mellitus and obesity). The prevalence of comorbidities is shown in Figure 1. Most frequently, patients had two comorbidities (24.19%) or one comorbidity (23.73%). Of all of the patients, only 24.65% had no associated comorbidities.

As 51.61% of patients had two or more comorbidities, we analyzed their coexistence. The frequency of coexisting comorbidities is shown in Table 2. Cardiovascular diseases (hypertension, CAD, and chronic heart failure) tended to coexist with metabolic diseases (obesity and diabetes mellitus).

There was no statistical difference between the number of comorbidities and GOLD 2001 stages according to classification based on the assessment of lung function (p>0.05) (Table 3).

According to one-way ANOVA, there was no difference in the number of comorbidities or CCI and the GOLD 2001 stages or GOLD 2011 classification (p>0.05) (Table 4).

Table 1: Characteristics of patients with COPD

	Mean±SD
Age (years)	62.70±9.80
Male/female	353/82
Pack/year	31.43±23.54
Duration of smoking (years)	24.30±17.26
Number of exacerbations, n	2.78±1.21
FEV_1 (%)	39.51±15.94
SaO_2 in rest (%)	92.41±6.26
BMI	27.68±6.99
6MWD	257.45±122.24
CAT	25.41±6.97
SGRQ symptom	491.26±96.77
SGRQ symptom (%)	74.95±14.43
SGRQ activity	829.14±231.57
SGRQ activity (%)	68.62±19.01
SGRQ impact	1271.44±350.96
SGRQ impact (%)	60.19±16.62
SGRQ total	2396.70±502.47
SGRQ total (%)	65.11±14.63
CCQ symptom	3.63±0.97
CCQ FUN	2.89±0.96
CCQ MEN	3.99±1.22
CCQ total	3.40±0.90
CCI	2.47±1.35
Number of comorbidities, n	1.32±1.24
Karnofsky	76.33±14.34
BODEx	4.99±1.54
ADO	4.50±1.38
CODEX	4.79±1.43
DOSE	4.32±1.30
BODE	4.53±1.92
GOLD 2011 classification	
GOLD B	70
GOLD C	87
GOLD D	278

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, BMI: Body mass index, 6MWD: 6-minute walking distance, CAT: COPD Assessment Test, SGRQ: St. George's Respiratory Questionnaire, CCQ: Clinical COPD Questionnaire, CCI: Charlson comorbidity index, FUN: Functional state, MEN: Mental state, BODEx: Body mass index, airflow obstruction, dyspnea, and exacerbations, ADO: Age, dyspnea, and airflow obstruction, CODEX: comorbidity, obstruction, dyspnea, and previous severe exacerbations, DOSE: Dyspnea, obstruction, smoking and exacerbation, BODE: Body mass index, airflow obstruction, dyspnea, and exercise

The number of comorbidities correlated positively with CCI (r=0.51, p<0.001) and BMI (r=0.49, p<0.001). Correlation was weak with age (r=0.17, p<0.001) and number of exacerbations (r=0.11, p=0.018) (Table 5). There was a negative correlation with 6MWD (r=–0.26, p<0.001) and SaO_2 (r=–0.17, p=0.001) (Table 5). There was a weak correlation with ADO (0.22, p<0.001), CODEX (r=0.18, p=0.007) and age (r=0.175, p<0.001) (Table 6). The number of comorbidities correlated weak with the quality of life (Table 7).

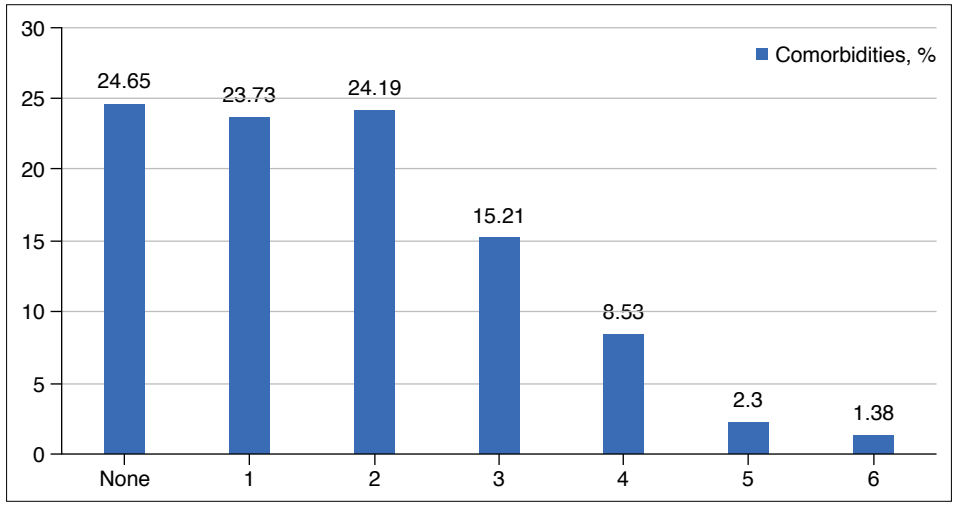

Figure 1: Number of comorbidities in the studied group

In general, it seems that CCI correlated better with the functional state of patients with COPD. CCI had a medium negative correlation with 6MWD (r=–0.37, p<0.001) and a weak correlation with the number of exacerbations (r=0.17, p=0.016) (Table 5). CCI had a strong correlation with ADO (r=0.75, p<0.001), moderate with BODE (r=0.3, p<0.001), weak with BODEx, CODEX, and DOSE (Table 6). CCI had a medium correlation with SGRQ activity (r=0.36, p<0.001), impact (r=0.34, p<0.001), and total (r=0.37, p<0.001) scores and the overall quality of life assessed by SGRQ and CCQ (Table 7). The overall differences in correlation are demonstrated in Tables 5–7.

Linear regression was performed to see if BMI, 6MWD, and age could predict the number of comorbidities.

Using the stepwise method it was found that BMI, 6MWD, and age could explain a modest amount of the variance in the number of comorbidities [F(1, 329)=110.158, p<0.001, R^2=0.365, adjusted R^2=0.359].

In this model, the analysis shows that BMI significantly predicted the number of comorbidities [β=0.104, t(329)=11.89, p<0.001] and age also contributed to this model [β=0.027, t(329)=4.11, p=0.006], whereas 6MWD had a small protective effect [β=0.003, t(329)=4.11, p<0.001].

A separate analysis was performed to assess whether ADO could predict CCI. Using the enter method, it was found that ADO could explain a significant amount of the variance in the CCI [F(1, 329)=236.16, p<0.001, R^2=0.602, adjusted R^2=0.600; β=0.776, t(329)=15.367, p<0.001).

Table 2: Frequency of coexisting comorbidities

Commorbidities	HF,		DM,		RF,		HT,		CAD,		RA,		DP,		EN,		OB,		CH,	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
HF		–	27	16.07	4	2.38	112	66.67	74	44.05	7	4.17	6	3.57	14	8.33	52	30.95	7	4.17
DM	27	61.36		–	2	4.65	36	83.72	20	46.51	1	2.33	3	6.98	2	4.65	21	48.84	0	0.00
RF	4	80.00	2	40.00		–	3	60.00	3	60.00	0	0.00	1	20.00	1	20.00	3	60.00	0	0.00
HT	112	51.38	36	16.51	3	1.38		–	76	34.86	10	4.59	17	7.80	10	4.59	104	47.71	2	0.92
CAD	74	72.55	20	19.61	3	2.94	76	74.51		–	4	3.92	12	11.76	5	4,90	41	40.20	4	3.92
RA	7	50.00	1	7.14	0	0.00	10	71.43	4	28.57		–	5	35.71	1	7.14	9	64.29	0	0.00
DP	6	28.57	3	14.29	1	4.76	17	80.95	12	57.14	5	23.81		–	4	19.05	11	52.38	0	0.00
EN	14	73.68	2	1053	1	5.26	10	52.63	5	26.32	1	5.26	4	21.05		–	9	47.37	1	5.26
OB	52	40.00	21	15.67	3	2.24	104	77.61	41	30.60	9	6.72	11	8.21	9	6.72		–	0	0.00
CH	7	50.00	0	0.00	0	0.00	2	14.29	4	28.57	0	0.00	0	0.00	1	7.14	0	0.00		–

HF: Heart failure, DM: Diabetes mellitus, RF: Renal failure, HT: Hypertension, CAD: Coronary artery disease, RA: Rheumatoid arthritis, DP: Depression, EN: Encephalopathy, OB: Obesity, CH: Cachexia

Table 3: Distribution of comorbidities according to GOLD 2001 classification

GOLD stages	n	HF,		DM,		RF,		HT,		CAD,		AR,		DP,		EN,		OB,		CH,		Mean
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Stage 2	95	25	36.23	9	13.04	1	1.45	51	73.91	22	31.88	8	11.59	9	13.04	1	1.45	42	60.87	1	1.45	1.78
Stage 3	167	67	77.01	25	28.74	2	2.30	82	94.25	38	43.68	3	3.45	7	8.05	7	8.05	45	51.72	4	4.60	1.68
Stage 4	173	76	27.34	10	3.60	2	0.72	85	30.58	42	15.11	3	1.08	5	1.80	11	3.96	43	15.47	9	3.24	1.68
Total	435	168		44		5		218		102		14		21		19		130		14		1.70

HF: Heart failure, DM: Diabetes mellitus, RF: Renal failure, HT: Hypertension, CAD: Coronary artery disease, AR: Arthritis, DP: Depression, EN: Encephalopathy, OB: Obesity, CH: Cachexia

Table 4: Comorbidities and GOLD classification 2011

GOLD 2011	n	HF,		DM,		RF,		HT,		CAD,		RA,		DP,		EN,		OB,		CH,		Mean
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
GOLD B	70	21	30.43	7	10.14	0	0.00	37	53.62	14	20.29	2	2.90	4	5.80	0	0.00	27	39.13	1	1.45	1.65
GOLD C	87	29	33.33	14	16.09	2	2.30	42	48.28	20	22.99	3	3.45	5	5.75	2	2.30	28	32.18	2	2.30	1.68
GOLD D	278	118	42.45	23	8.27	3	1.08	139	50.00	68	24.46	9	3.24	12	4.32	17	6.12	75	26.98	11	3.96	1.71
Total	435	168		44		5		218		102		14		21		19		130		14		1.69

HF: Heart failure, DM: Diabetes mellitus, RF: Renal failure, HT: Hypertension, CAD: Coronary artery disease, RA: Rheumatoid arthritis, DP: Depression, EN: Encephalopathy, OB: Obesity, CH: Cachexia

Table 5: Correlation between functional state, the number of comorbidities, and CCI

Parameter	Number of comorbidities		CCI	
	r	p	r	p
Age	0.175	<0.001	0.836	<0.001
SaO_2	–0.170	0.001	–0.113	0.159
Number of exacerbations	0.115	0.018	0.172	0.016
BMI	0.496	<0.001	–0.038	0.599
6MWD	–0.266	<0.001	–0.377	<0.001
CCI	0.511	<0.001	–	–
Karnovsky	–0.119	0.121	–0.205	0.010
Pack/year	–0.005	0.928	0.028	0.694
Duration of smoking	0.026	0.743	–0.053	0.397

CCI: Charlson comorbidity index, BMI: Body mass index, 6MWD: 6-minute walking distance

Table 6: Correlation between multidimensional indexes, the number of comorbidities, and CCI

Parameter	Number of comorbidities		CCI	
	r	p	r	p
BODE	0.104	0077	0.303	<0.001
BODEx	0.052	0.349	0.244	0.001
ADO	0.229	<0.001	0.752	<0.001
CODEX	0.182	0.007	0.260	<0.001
DOSE	0.117	0.030	0.220	0.002
e-BODE	0.040	0.471	0.118	0.081

CCI: Charlson comorbidity index, BODE: Body mass index, airflow obstruction, dyspnea, and exercise, BODEx: Body mass index, airflow obstruction, dyspnea, and exacerbations, ADO: Age, dyspnea and airflow obstruction, CODEX: Comorbidity, obstruction, dyspnea, and previous severe exacerbations, DOSE: Dyspnea, obstruction, smoking, and exacerbation, e-BODE: Body mass index, airflow obstruction, dyspnea, exercise, and exacerbation

Table 7: Correlation between quality of life, the number of comorbidities, and CCI

Parameter	Number of comorbidities		CCI	
	r	p	r	p
CAT	0.183	0.003	0.107	0.517
SGRQ symptom	0.117	0.016	0.152	0.034
SGRQ symptom (%)	0.108	0.027	0.152	0.034
SGRQ activity	0.177	<0.001	0.364	<0.001
SGRQ activity (%)	0.177	<0.001	0.364	<0.001
SGRQ impact	0.227	<0.001	0.346	<0.001
SGRQ impact (%)	0.230	<0.001	0.347	<0.001
SGRQ total	0.221	<0.001	0.377	<0.001
SGRQ total (%)	0.221	<0.001	0.377	<0.001
CCQ symptom	0.100	0.050	0.176	0.027
CCQ FUN	0.118	0.021	0.293	<0.001
CCQ MEN	0.088	0.083	0.457	<0.001
CCQ total	0.115	0.024	0.324	<0.001

CCI: Charlson comorbidity index, CAT: COPD Assessment Test, SGRQ: St. George's Respiratory Questionnaire, CCQ: Clinical COPD Questionnaire, FUN: Functional state, MEN: Mental state

Discussion

COPD is currently regarded as a systemic condition as it is linked to several comorbidities with major clinical importance.[5,15,16] Aging and smoking status might also be responsible for the prevalence of comorbidities in COPD.[17,18] It is important to assess and manage comorbidities in COPD, but currently there is no worldwide-established holistic approach.[19]

The prevalence of comorbidities in COPD can be up to 81.2–94.1%.[20] In our study, 75.35% of patients had comorbidities, which is a smaller percentage but nevertheless demonstrates a high burden of comorbidities. COPD patients have hypertension in 28.5–64.7%,[21–23] heart failure in 12.3–28.3%,[21,24,25] diabetes mellitus in 6.3–18.7%,[26,27] obesity in 17.9–35%,[28,29] renal failure in 20.8–31%,[30,31] depression in 21.4–32.2%,[32,33] and encephalopathy in 27–42%.[34,35] In our study, renal failure, depression, encephalopathy, and rheumatoid arthritis are reported less frequently. Partially this can be due to the fact that these conditions are less frequently evaluated and screened in COPD patients. Overall comorbidities in COPD are undertreated, and there is limited awareness about them in the COPD population.[36] The prevalence of cardiovascular and metabolic diseases is similar to the reported studies.

At least one comorbidity of clinical relevance is found in 25.2–78.6% of patients, two in 28.3–68.8%, and three or more in 46.5–47.9% of subjects.[6,37] In our study, one comorbidity was found in 23.73%, two in 24.19%, and three or more in 27.42%. Most frequently, patients have one or two comorbid conditions of clinical significance. Three or more comorbidities are less frequently encountered in our group.

The reported overall prevalence of comorbidities is 2.6–6 per patient,[6,38,39] whereas in our study, it is lower (1.3 per patient). There are different opinions on whether comorbidities are determined by GOLD stages or GOLD 2011 classification. There are data that comorbidities increase their prevalence progressively up to the last stage of COPD severity, except the cardiovascular and the metabolic ones which drop in the IV GOLD stage.[6] We found that comorbidities tended to increase with the GOLD 2011 classification, although we did not find it statistically significant. Cardiovascular comorbidities did increase according to GOLD stages although this finding was not statistically significant. Other comorbidities showed variable distribution according to GOLD stages except obesity, which was frequent in all stages. Several comorbidities are associated with having frequent exacerbations and increased exacerbation risk such as heart failure, pulmonary cancer, depression, and osteoporosis.[40]

The overall number of comorbidities seems not to be related to airflow obstruction and age, but to acute exacerbation of COPD, dyspnea measured with Medical Research Council (MRC) scale, and male gender.[20] Park and coworkers demonstrated that some comorbidities

are lower in the obstructive lung function group, especially in the severe airway obstruction groups.[23] Others report that the severity of airflow limitations is not linked to comorbidities.[41] The strong correlation with ADO demonstrates otherwise. This may be particular to the studied group because the study included only patients with moderate, severe, and very severe disease.

CAT can be for instance indicate comorbidities such as gastroesophageal reflux disease and depression, which may coexist unrecognized.[42] This underlines several important points. First, comorbidities can be assessed by multidimensional indexes such as ADO and BODE. Second, these indexes might be specific to different comorbidities.

Comorbidities are also tightly linked with the quality of life and should be taken into consideration in the clinical management of patients with severe COPD.[43] Higher SGRQ scores can be seen in mild-to-moderate COPD patients with extrapulmonary comorbidities.[44] CCI is one of the major determinants of HRQL in COPD patients.[45] It seems that both CCI and the number of comorbidities significantly affect the HRQL in patients with COPD when assessed by CCQ and SGRQ.

The key limitations include the relatively small number of patients, and comorbidities were analyzed on the basis of self-reporting; probably some of the comorbidities were underestimated. In addition, CCI can underestimate the burden of comorbidities. The sex was not taken into consideration and comorbidities tend to differ between males and females. We also did not take into consideration the differences between the rural and urban populations.

Conclusion

Several important points should be taken into consideration for the clinical practice: patient with COPD requires a multidisciplinary approach to assess and manage a variety of conditions, which influence the evolution of the disease and prognosis. COPD patients often have one or two comorbidities of clinical significance, and they are predominantly cardiovascular and/or metabolic. These two groups of diseases tend to coexist together and probably share common pathophysiological bases. Comorbidities can be assessed by multidimensional indexes such as ADO and BODE. Patients with comorbidities tend to have a poorer HRQL.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the State University of Medicine and Pharmacy "Nicolae Testemiţanu," Chisinau, Republic of Moldova Ethics Committee (No: 17/12, Date: 11/12/2015).

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