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Extra-respiratory symptoms in patients hospitalized for a COPD exacerbation: Prevalence, clinical burden and their impact on functional status

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Abstract

Introduction: In COPD management, the improvement of the health status by alleviating respiratory symptoms is among the main aims. However, little is known on the prevalence and burden of extra-respiratory symptoms which can also be distressing especially during a COPD exacerbation.

Objectives: To evaluate the prevalence of extra-respiratory symptoms and their impact on health and functional statuses in patients hospitalized for a COPD exacerbation.

Methods: Health status was evaluated with the COPD Assessment Test (CAT), functional status with Karnofsky index, and presence and severity of respiratory symptoms were evaluated with Edmonton Symptom Assessment Scale (ESAS).

Results: In a sample of 47 patients, fatigue was found to be the most prevalent 95.7% followed by pain 74.5%, lack of appetite 72.3%, depression and anxiety (each in 63.8%), drowsiness 59.6% and nausea 31.9%. The concomitant presence of an increasing number of symptoms (three, four, five, six or seven) was individually associated with worse health status or of functional status (eg, CAT score in patients with three most prevalent symptoms, fatigue, pain and lack of appetite 29.6 vs 25.1, $P = .006$ in patients without them; Karnofsky index scores in patients with the four most prevalent symptoms 52 vs 65.6, $P = .001$). Linear regressions confirmed that the increase in the number of concomitant extra-respiratory symptoms significantly correlated with the worsening of health/functional status. In conclusion, the burden of extra-respiratory symptoms in patients with hospitalized for a COPD exacerbation is significant and impact significantly on health/functional status.

KEYWORDS

chronic obstructive pulmonary disease, ESAS scale, extra-respiratory symptoms, functional status, health status

1 | INTRODUCTION

In chronic obstructive pulmonary disease (COPD), it was demonstrated that the impairment of health status and that of the functional status are mainly because of the presence, and to the progressive pattern of respiratory symptoms such as dyspnea or cough with sputum production.[1] Consequently, the aim of most therapeutic interventions has been to improve such symptoms, expecting a parallel increase in health status.[2] However, not always a decrease in the severity of respiratory symptoms is associated with a significant amelioration of the health status. This might be explained by the fact that

other factors such as extra-respiratory symptoms might be significant determinants of health status worsening. For example, fatigue, which is the main extra-respiratory symptom found in COPD was demonstrated to be associated with an impaired health status.[3]

During exacerbated COPD health and functional statuses are also deeply altered. However, little is known on this matter probably because of the reticence in measuring these outcome measures especially as far as the health status was concerned, during exacerbations. Existing questionnaires such as Clinical COPD Questionnaire or COPD Assessment Test were demonstrated to be reliable tools to measure health status during COPD exacerbations.[4,5]

In COPD exacerbations, extra-respiratory symptoms can be bothersome, can negatively impact both health and functional statuses, and can contribute significantly to the clinical burden of (exacerbated) illness. However, little is known on this topic especially because the available studies rather focused on the relationship between respiratory symptoms and health status and because the interest in measuring functional status during an exacerbation was limited. The analysis presented below tries to fill this gap by evaluating the prevalence of extra-respiratory symptoms as well as their clinical burden and their impact on functional status in patients with severe COPD exacerbations (hospitalizations).

TABLE 1 Characteristics of the analyzed sample

Variable/parameter	Number of patients observed	Value
Age (years) mean (SD)	47	68.4 (5.6)
Gender		
Female	47	9
Male		38
Smoking status		
Ex-smokers	44	31
Current smokers		7
Non-smokers		6
FEV1%pred (mean,SD)	46	34% (14.3)
ESAS-PAIN (mean, SD)	47	4.7 (2.28)
ESAS-FATIGUE (mean, SD)	47	7.23 (1.78)
ESAS-BREATHLESNESS (mean, SD)	47	6.4 (1.96)
ESAS-LACK OF APETITE (mean, SD)	47	4.95 (2.17)
ESAS-DEPRESSION (mean, SD)	47	4.98 (2.2)
ESAS-ANXIETY (mean, SD)	47	4.87 (2.21)
ESAS-DROWSINESS (mean, SD)	47	4.13 (2.24)
ESAS-NAUSEA (mean, SD)	47	2.12 (2.32)
CAT score (mean, SD)	47	27.5 (5.6)
KPSS score (mean, SD)	47	61.3 (13.7)

2 | MATERIALS AND METHODS

The analysis described below was performed in patients hospitalized for a COPD exacerbation between February and July 2017 and who agreed to participate in this study after signing the informed consent. Included were subjects with known COPD diagnosis**.** Excluded were subjects hospitalized for other conditions, patients unable to understand the questions related to data collection, patients with cognitive deficits, patients who were too ill or who did not agree to participate to this study.

Severity of the extra-respiratory symptoms was measured with the Edmonton Symptom Assessment Scale (ESAS). ESAS is a tool developed in order to document in a rapid and reliable manner the symptom burden in patients requiring palliative care. It is a numerical multisymptom scale evaluating the severity of various symptoms such as pain, fatigue, breathlessness, lack of appetite, anxiety, depression, drowsiness, nausea on a scale ranging from 0 (no symptom) to 10 (maximum severity symptom).[6] Extra-respiratory symptoms were considered as clinically significant (bothersome for the patient if scored at least 4).[7] The use of ESAS in COPD is of more recent date and in studies evaluating rather a cluster of chronic diseases than a specific condition.[8] ESAS gains more terrain in COPD as a reliable symptom tool, and we report in this study its use in patients with exacerbated COPD.

Health status was evaluated with COPD Assessment Test (CAT) test which is an 8-item disease-specific questionnaire which measures the impact of the disease on various routine activities of daily living: scores range from 0 to 40 with higher scores corresponding to a more impaired health status.[9]

Functional status was assessed with Karnofsky Performance Status Scale (KPSS) named briefly Karnofsky index. This is a tool initially developed to predict survival in cancer patients undergoing chemotherapy.[10] KPSS measures functional status corresponding to various health states ranging from 100% "no evidence of disease" to 0 death. Currently KPSS is a recognized measure of functional status outside oncology setting, being extensively used in various chronic conditions such as COPD.[11]

Clinical burden of (clinically significant) extra-respiratory symptoms was evaluated with two indexes, a quantitative more objective index consisting of the number of clinically significant symptoms in the same patient, and a more subjective index measuring the degree of impaired health status associated with concomitant presence of various such symptoms in an individual.

Airways obstruction was measured with post-bronchodilator FEV1% predicted, this outcome measure being only used to characterize the analyzed sample from the perspective of the severity of lung function impairment.[12]

Statistical analysis was performed with the IBM SPSS version 18 and with MedCalc version 15 software. Between-group comparisons were made with student *t* test. To describe the association between score data, the Spearman correlation was performed. To find the linear dependency, the Pearson correlation was computed. Linear regression was also performed if both correlation coefficients were comparable, in order to further study the effect of the increase in the number of extra-respiratory symptoms on the outcome (health, respectively, functional status). The decision on the significance of the statistical hypothesis was according to standard significance of .05.

3 | RESULTS

Population characteristics are featured with relevant variables and parameters in Table 1. A total number of 47 COPD was included in the analysis.

3.1 | Prevalence of extra-respiratory symptoms

The most prevalent clinically significant extra-respiratory symptom was found to be fatigue which was detected in 45 (95.7%). The next prevalent clinically symptom was represented by pain which was detected in 35 (74.5%) of patients severe pain (ESAS score of pain at least 7) in particular being found in 11 (23.4%) patients. Figure 1 presents the prevalence of all extra-respiratory symptoms measured.

3.2 | Burden of extra-respiratory symptoms

The first three most prevalent clinically significant symptoms were detected concomitantly in 25 (53.2%) patients, the first four /five each in 15 (31.9%), the first six in 15 (31.9%) and all seven symptoms were present in 7 (14.9%) COPD patients.

The concomitant presence of the first three most prevalent symptoms, that is, fatigue, pain and lack of appetite, was associated with a significantly worse mean CAT score compared with that of patients without them, 29.6 versus 25.1, $P = .006$. When clinically significant depression was present concomitantly with the first three most prevalent symptoms, mean CAT score was more impaired 31.6 versus 25.5, $P < .001$. Addition of anxiety to the first four most prevalent symptoms was associated with a persistent and comparable worsening of CAT score 31.4 versus 25.8, $P = .001$ and an identical effect was detected in patients exhibiting also drowsiness. Finally in patients with all seven clinically significantly extra-respiratory symptoms CAT score was still worse than in patients without all these symptoms 31.3 versus 26.8 $P = .05$.

The increase in the number of concomitant clinically significant extra-respiratory symptoms was associated with a directly proportional significant increase in CAT scores (ie, worsening of health status), Spearman's rho 0.49, $P < .001$. Pearson's correlation coefficient was 0.46 ($P = .001$), demonstrating a linear (proportional) relationship between the number of symptoms and the increase in CAT score. A linear regression was further applied in order to compute to further analyze the effect of progressive increase in number and the "increase per symptom" added in CAT score: we found that for each extra-respiratory symptom the increase in CAT score was 1.7 ($P = .001$, Figure 2).

3.3 | Impact of the number of clinically significant extra-respiratory symptoms on functional status

The concomitant presence of the first three extra-respiratory symptoms did not have a significant impact on functional status. However, the presence of the first four most prevalent symptoms was associated with a significantly worse functional status, KPSS 52 versus 65.6, $P = .001$. Presence of first five symptoms, respectively, first six

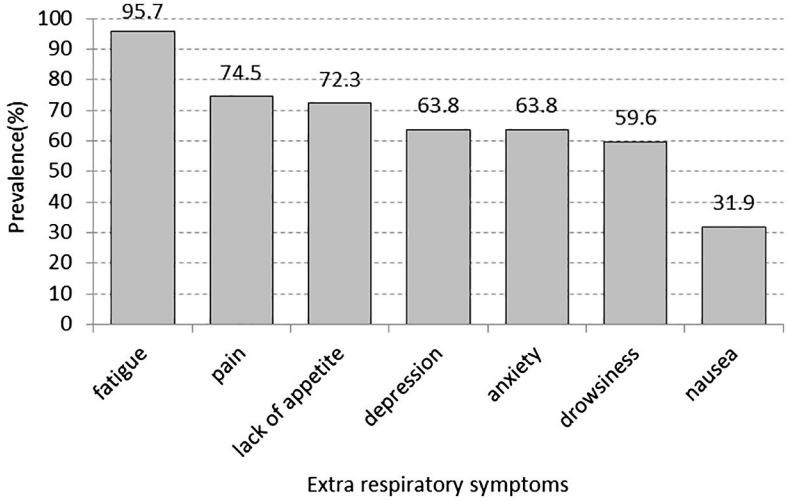

FIGURE 1 Prevalence of the extra-respiratory symptoms

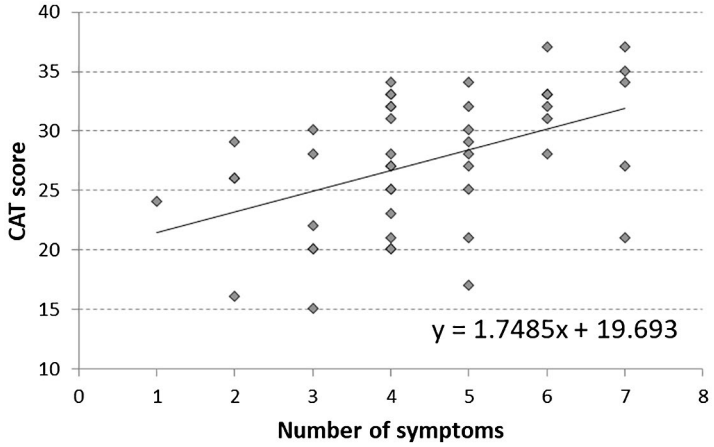

FIGURE 2 Linear regression of the CAT scores versus the increase in the number of clinically significant extra-respiratory symptoms

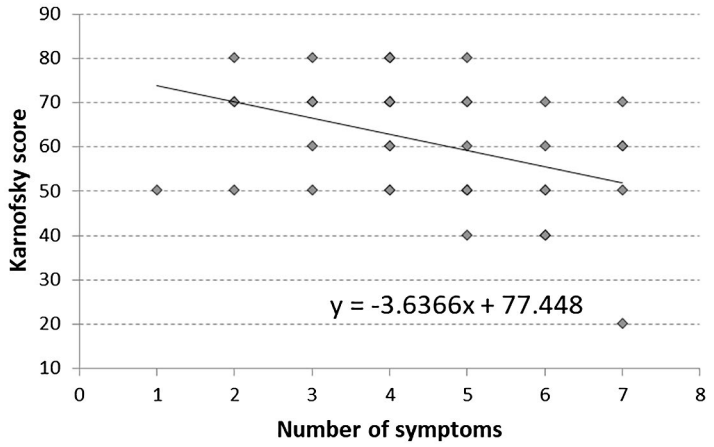

FIGURE 3 Linear regression of the KPSS scores versus the increase in the number of clinically significant extra-respiratory symptoms

had a similar effect KPSS 52.1 versus 65.1, $P = .002$. Surprisingly, patients with all seven symptoms, even if exhibiting worse functional status, did not differ significantly as far as this was concerned, when compared to patients without all these symptoms (52.8 vs 62.8, $P = .07$). Correlation analyses were carried out in a similar manner with that of CAT scores, and again, significant (inversely proportional) correlations between the increase in the number of symptoms and worsening (decrease) of KPSS were found: Spearman's $\rho = -0.39$, $P = .006$, Pearson's coefficient $= -.41$, $P = .004$). Linear regression yielded a decrease in KPSS of 3.63 units of score (%) for each added symptom ($P = .006$, Figure 3).

Both health status and functional status significantly correlated, a worsening of the former (ie, increase in CAT score) being associated with a worsening of the latter (ie, decrease in KPSS): Spearman's $\rho = -0.57$, $P < .001$, Pearson's coefficient $= -.58$, $P < .001$.

3.4 | Impact of symptoms clustering on length of hospital stay

Length of hospital stay (LoS) is known to be a marker of exacerbation severity respectively disease morbidity. LoS was compared in patients with highest extra-respiratory symptom burden in terms of number, that is, in those having all seven extra-respiratory symptoms with that in those not having them and it was found that the former category tended to have larger LoS than the latter although probably because of the limited sample size this difference was not statistically significant (11 vs 10.3 days, $P = .7$).

4 | DISCUSSION

In COPD patients hospitalized for an exacerbation, extra-respiratory symptoms were prevalent, and the higher their number the worse the respiratory health status and functional disability were.

Most of the existing studies focused on fatigue and more recently on pain. In these studies, fatigue was demonstrated to individually impact on health status, and to be a marker of disease severity, mortality and morbidity but in patients with stable disease.[3,13,14] However, none of the existing studies examined the prognostic value of other individual or clusters of extra-respiratory symptoms on these outcome measures in both stable or exacerbated COPD.

Pain was also investigated in patients with COPD in terms of site involved, severity and its impact on health status, and

compared to that found in matched normal controls: it was found that impairment of health status (Physical Functioning domain of the SF-36) as a result of pain was more consistent in patients with COPD than in controls.[15] The same team also demonstrated that in COPD pain severity was inversely correlated with exercise capacity and with health status scores (SF-36).[16] A prognostic value of chronic pain in COPD patients was not yet demonstrated.

The evaluation of extra-respiratory symptoms in COPD beyond fatigue and pain is still not considered as worthwhile because little is known on the effects of such symptoms on relevant outcome measures such as health status. A further barrier against an approach might be represented by the difficulty in finding appropriate tools to simultaneously assess such symptoms. ESAS scale address this limitation, being demonstrated as an easy and reliable tool to rapidly gather a comprehensive picture regarding the symptom burden in each patient across various chronic conditions including COPD.[17]

Health status is well known as prognostic factor for COPD mortality and morbidity in stable state and in light of this evidence can be assimilated as a measure of clinical burden of the disease.[18] It might be expected that the impairment of the health status can be due exclusively to the severity of respiratory symptoms and to their impact on the individual ability to perform daily routine activities. In fact, several studies focused on the outcome measures related to the respiratory disability such as breathlessness, impaired exercise capacity and found them to be significant determinants of the health status along with the illness perception, depression or disease coping.[19,20] However, our data demonstrate that other determinants such as the number and the severity of extra-respiratory symptoms can also contribute to the worsening of the health status and that the same clinical burden of extra-respiratory symptoms can also explain the worsening of functional status. It would be interesting to find out how this happens for each of these two patient reported outcomes. A clinical explanation of these results would be the fact that, for example, extra-respiratory symptoms such as fatigue or pain can further limit the performance of daily activities. Another explanation would be the self-perceived severity of respiratory symptoms such as dyspnea might be accentuated by the association of these extra-respiratory symptoms leading to a worsening of the health status.

Previous studies outlined the fact that a poor functional status was an independent risk factor for the subsequent disease morbidity (COPD exacerbations) but it was the respiratory disability mainly producing this worsening.[21,22] Our study demonstrates that extra-respiratory symptoms can also contribute to an impaired functional status during a severe COPD exacerbations and therefore their burden (the concomitant occurrence of several such symptoms, their severity) might also indirectly predict the impaired functional status.

Therefore, occurrence of extra-respiratory symptoms in severe COPD exacerbations could not only explain the worse health and functional status in patients with comparably severe respiratory symptoms but might also be the reason for their slower or their lack of full recovery after exacerbation. As functional status is the main element in establishing disease trajectory, the issue of the prognostic value of such extra-respiratory symptoms starts to take shape and investigative value.

In our study, we evaluated the extra-respiratory symptoms in patients with severe COPD exacerbation and found that their clustering might be associated with prolonged length of stay. This particular aspect needs however further studies in larger cohorts in order to better ascertain this relationship and in order to find out if this clustering might not also be a predictor of in hospital or short-term (post discharge) mortality.

In this study, the health status and the severity of the symptoms were not assessed for their dynamics during hospitalization for COPD exacerbation. This would be an interesting issue beyond our analysis because it may offer information on the potential role of such symptoms as "unexpected" factors of severity for a particular hospitalization episode.

To conclude the data presented in this paper demonstrate the importance of extra-respiratory symptoms in patients with severe COPD exacerbations and offers preliminary evidence on the rationale to evaluate them in this clinical setting.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest with the conducts of this article.

AUTHOR CONTRIBUTIONS

Designed the study and performed some of the statistics: Antoniu, Boiculese
Interviewed the patients and collected the data: Apostol
Performed statistics: Boiculese

ETHICS

The study received approval of the institutional ethics committee.

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