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Prevalence and impact of respiratory symptoms in a population of patients with COPD in Latin America: The LASSYC observational study

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ABSTRACT

Background: To analyse the relationship between symptoms at different times during the 24-hour day and outcomes in COPD.
Methods: Observational cross-sectional study in a patients from 7 Latin American countries. The frequency of symptoms in the morning, at night and during the day was explored by means of standardised and validated questionnaires, and the relationship between symptoms and exacerbations and quality of life were investigated.
Results: 734 patients (59.6% male, mean age 69.5 years, mean FEV_1 50% predicted normal) were recruited. The most frequent symptoms during the day were dyspnea (75% of patients, of which 94% mild-moderate) and cough (72.2%, of which 93.4% mild-moderate). Highly symptomatic patients had a greater impairment in FEV_1, more exacerbations and worse scores in COPD assessment test (CAT) and Body Mass Index, Obstruction, Dyspnoea and Exacerbations (BODEx) index (all $p < 0.001$). Morning symptoms were more frequent than night-time symptoms, particularly cough and dyspnoea (morning: 50.1% and 45.7%; night-time: 33.2% and 24.4%, respectively), and mostly rated as mild or moderate. Patients with morning or night-time symptoms presented with worse severity of daytime symptoms. There was a strong correlation between intensity of daytime with morning or night-time symptoms, as well as with CAT score ($r = 0.715$; $p < 0.001$), but a weak correlation with FEV_1 ($r = -0.205$; $p < 0.001$).
Conclusion: Morning symptoms were more frequent than night-time symptoms, and having either morning and/or night-time symptoms was associated with worse severity of daytime symptoms. Increased symptoms were strongly associated with worse quality of life and more frequent exacerbations, but weakly associated with airflow limitation.
Clinical trial registration: NCT02789540.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the world and its prevalence is projected to increase in the coming years [1]. In Latin America, two large epidemiological studies have provided information on the prevalence of COPD in this region; PLATINO was performed across five Latin American cities and found an overall prevalence of COPD of 14.3% [2] and PREPOCOL reported an overall prevalence of 8.9% across five cities in Colombia [3].

Symptoms of COPD – including progressive dyspnoea, chronic cough, excessive sputum production and decreased exercise tolerance – can impact considerably on patients' daily activities and quality of life

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Table 1
Demographic and clinical characteristics of COPD patients according to the intensity of daytime symptoms.

Characteristics	All patients (n = 734)	Mild symptoms (n = 263)	Moderate symptoms (n = 272)	Severe symptoms (n = 199)	P value[b]			
					All	Mild x Moderate	Mild x Severe	Moderate x Severe
Age, years	69.6 (8.7)	70.5 (8.6)	68.9 (8.7)	69.3 (8.8)	0.098	0.104	0.510	1.000
Sex, % male	448 (61.0)	165 (62.7)	172 (63.2)	111 (55.8)	0.203	0.905	0.131	0.103
BMI, kg/m^2	25.7 (5.1)	25.9 (4.9)	25.2 (4.9)	26.3 (5.6)	0.062	0.464	1.000	0.094
Active smokers, %	114 (15.5)	42 (16.0)	39 (14.3)	33 (16.6)	0.778	0.599	0.854	0.504
Pack-years[a]	42.2 (19.1)	40.7 (18.7)	44.2 (19.7)	41.6 (18.9)	0.724	0.161	1.000	0.556
Physical activity, %					0.050	0.195	0.033	0.097
Low	278 (37.9)	86 (32.7)	104 (38.2)	88 (44.2)				
Moderate	169 (23.0)	68 (25.9)	54 (19.9)	47 (23.6)				
High	287 (39.1)	109 (41.4)	114 (41.9)	64 (21.2)				
Comorbid asthma	33 (4.5)	15 (5.7)	8 (2.9)	10 (5.0)	0.279	0.155	0.750	0.244
COTE index	1.0 (2.0)	1.0 (2.0)	0.9 (2.0)	1.1 (2.0)	0.605	1.000	1.000	0.951
mMRC	1.8 (1.0)	1.4 (0.9)	1.9 (1.0)	2.4 (1.0)	< 0.001	< 0.001	< 0.001	< 0.001
Spirometry								
FVC (% predicted)	73.0 (18.9)	74.4 (19.0)	73.1 (19.1)	71.2 (18.5)	0.197	1.000	0.215	0.873
FEV_1 (% predicted)	49.1 (17.5)	53.6 (17.7)	47.8 (17.8)	45.0 (15.4)	< 0.001	< 0.001	< 0.001	0.239
FEV_1/FVC	49.1 (11.4)	52.4 (10.9)	47.8 (11.3)	46.5 (11.4)	< 0.001	< 0.001	< 0.001	0.589
CAT	15.3 (8.1)	9.3 (5.7)	15.5 (5.6)	23.0 (6.9)	< 0.001	< 0.001	< 0.001	< 0.001
BODEx	2.9 (1.9)	2.2 (1.7)	3.1 (1.7)	3.8 (1.9)	< 0.001	< 0.001	< 0.001	< 0.001
Exacerbations								
Ambulatory	1.1 (1.6)	0.6 (1.0)	1.0 (1.4)	2.0 (2.1)	< 0.001	0.001	< 0.001	< 0.001
Hospital based	0.4 (1.0)	0.3 (0.9)	0.4 (1.0)	0.6 (1.1)	< 0.001	0.355	< 0.001	0.020
E-RS score								
Total	10.0 (7.0)	3.1 (2.0)	9.9 (2.1)	19.2 (4.4)	< 0.001	< 0.001	< 0.001	< 0.001
Breathlessness domain	5.4 (4.2)	1.5 (1.8)	5.6 (2.5)	10.3 (2.7)	< 0.001	< 0.001	< 0.001	< 0.001
Cough & sputum domain	2.8 (2.3)	1.3 (1.4)	2.8 (1.8)	4.9 (2.2)	< 0.001	< 0.001	< 0.001	< 0.001
Chest symptoms domain	1.8 (2.1)	0.3 (0.6)	1.5 (1.4)	4.0 (2.3)	< 0.001	< 0.001	< 0.001	< 0.001
Early morning symptoms severity score	3.3 (3.6)	1.0 (1.4)	2.9 (2.4)	6.8 (4.2)	< 0.001	< 0.001	< 0.001	< 0.001
Night-time symptoms severity score	2.3 (3.7)	0.6 (1.2)	1.6 (2.3)	5.6 (5.0)	< 0.001	< 0.001	< 0.001	< 0.001
Night awakenings	0.4 (1.0)	0.1 (0.4)	0.3 (0.9)	1.0 (1.6)	< 0.001	0.070	< 0.001	< 0.001

Note: all values are presented as mean (SD). For the cases of sex, active smokers and physical activity, values are presented as N (%). *P*-value is for ANOVA for continuous variables and chi-squared for categorical variables.

[a] Maximum number of missing (n = 124, pack-years smoked).

[b] Pairwise comparison was made through Bonferroni multiple testing for continuous variable and simple chi-square test for categorical ones.

and present with considerable variation for the same degree of airflow limitation. COPD symptoms have been reported to be worse at night and in the early morning, which may be reflected in disturbed sleep and limitations on morning activities [4].

Moreover, the health-related quality of life (HRQoL) is being increasingly recognised as an important outcome when evaluating patients with COPD and diverse studies have demonstrated that although more severe patients presented with poorer HRQoL, there was considerable variation within each stage of disease severity [5].

In an European observational study, it was shown that more than half of patients experienced COPD symptoms throughout the whole 24-hour day and there was a significant relationship between symptoms throughout the 24-hour day and worse patient-reported outcomes, suggesting that improving 24-hour symptoms should be an important consideration in the management of COPD [6]. The present study investigated the prevalence of respiratory symptoms in a population of COPD patients from Latin America and evaluated their relationship with COPD severity, exacerbations and patient-reported outcomes.

2. Method

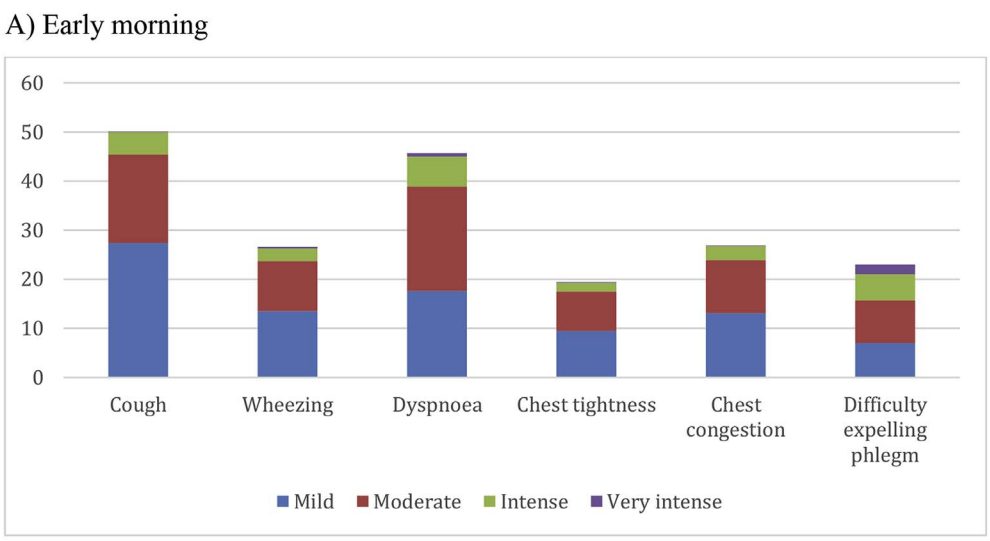
The **L**atin **A**merican **S**tudy of 24-hour **SY**mptoms in **C**hronic Obstructive Pulmonary Disease (LASSYC) was an observational, multicentre, multinational, cross-sectional, non-interventional study (Clinical Trial Registration: NCT02789540), the objective of which was to describe prevalence, severity and inter-relationship of early morning, day and night-time symptoms with COPD severity, exacerbations and patient reported outcomes (PROs) in patients with stable COPD from seven Latin American countries (Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico and Uruguay) [7]. The study was approved by the ethics committees for each site and all patients provided written informed consent.

Patients fulfilling the following inclusion criteria were consecutively recruited from outpatient clinics: age ≥40 years, diagnosis of COPD at least for 1 year, spirometry with a COPD diagnosis using the post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.70 criterion, current or ex-smokers with history of ≥10 pack-years and stable disease (without exacerbation treatment at study visit and in the previous 2 months, without changes in current treatment during the same period). The exclusion criteria were: diagnosis of sleep apnoea, other chronic respiratory diseases (bronchiectasis, lung cancer, cystic fibrosis) or any acute or chronic condition that would limit the patient's ability to participate in the study.

For each patient, the following information was collected: social demographics, smoking history, exacerbation history and healthcare resource utilization during last 12 months. The level of dyspnoea was measured using the modified scale of the Medical Research Council (mMRC) [8]. The COPD severity level was measured using the Body Mass Index, Airflow Obstruction, Dyspnoea and Exacerbations (BODEx) index [9]. Comorbidities were assessed by a COPD comorbidity index (COPD specific comorbidity test, COTE) [10]. The COPD Assessment Test (CAT) was used to evaluate the impact of the disease [11].

2.1. Assessment of early morning, daytime and night-time symptoms

The Evaluating Respiratory Symptoms (E-RS) in COPD questionnaire was used to evaluate daytime symptoms (E-RS™: COPD; formerly



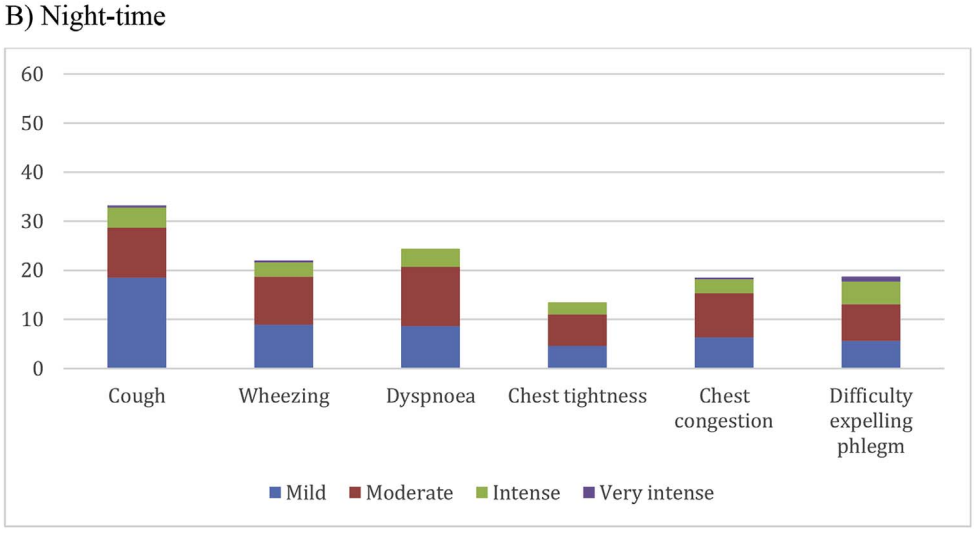


Fig. 1. Prevalence of the most frequent (A) early morning and (B) night-time symptoms, including their severities.

EXAcerbations of Chronic pulmonary disease Tool [EXACT™] – Respiratory Symptoms) (The EXACT and E-RS are owned by Evidera. Permission to use these instruments was obtained from Evidera [exactpro@evidera.com]). The E-RS is a derivative of EXACT and was developed to assess the efficacy of treatment on symptoms in clinical trials [12,13]. The E-RS, which uses the eleven respiratory symptom items from the 14-item EXACT daily diary, provides a more comprehensive assessment of the burden of respiratory symptoms in COPD than standard PROs and has shown consistency with the classification of less symptomatic and more symptomatic patients by GOLD groups [14,15]. The E-RS provides a total score ranging from 0 to 40 and three subscales: RS-Breathlessness (scale range 0–17), RS-Cough and sputum (scale range 0–11) and RS-Chest symptoms (scale range 0–12), where higher scores represent greater severity of symptoms. The E-RS assesses symptoms occurring from the start of regular daytime activities to the moment that patient goes to sleep of previous day of the study visit day [12].

Morning symptoms were assessed with the Early Morning Symptoms of COPD Instrument (EMSCI), which assesses symptoms that occur during the time from when patients get out of bed to start their daily living activities through to the moment that they are ready for activities of the day at study visit [16]. The EMSCI was designed to measure three concepts of interest in patients with COPD: 1. occurrence and severity of six morning symptoms ("Did you experience any of the following in the morning: cough, wheezing, shortness of breath, tightness in the chest, chest congestion, and difficulty bringing up phlegm?") and overall severity of symptoms ("Overall, how severe were your COPD symptoms this morning?"); 2. the impact of these symptoms in terms of limitation of morning activities ("To which extend were your morning activities limited due to your COPD symptoms?"); 3. rescue medication use ("How many puffs of your rescue medication did you take this morning?"). If patients experienced a specific symptom in the morning, they were asked to indicate the severity of the individual symptom (e.g., "How severe was your cough?") from mild to very severe on a four-point scale (i.e., mild = 1, moderate = 2, severe = 3, very severe = 4).

The night-time symptoms were assessed with the Night-time Symptoms of COPD Instrument (NiSCI). The NiSCI assesses symptoms that occur from the time from when patients go to bed the previous night until they wake up and get out of bed to start their daily living activities of the day of study visit [16–18]. Similar to the EMSCI, the NiSCI included the same three concepts of interest in patients with COPD: 1. occurrence and severity of the same six night-time symptoms and overall severity of symptoms ("Overall, how severe were your COPD symptoms last night?"); 2. the impact of these symptoms in terms of night-time awakenings ("Last night, did you wake up because of your COPD symptoms?"; "How many times did you wake up because of your COPD symptoms?"); 3. rescue

Table 2
Demographic and clinical characteristics of COPD patients according to the presence of early morning and night-time symptoms.

Characteristics	Early morning symptoms			Night-time symptoms		
	No (n = 587)	Yes (n = 147)	P value	No (n = 602)	Yes (n = 132)	P value
Age, years	69.7 (8.7)	70.0 (8.8)	0.368	69.8 (8.7)	68.5 (8.4)	0.110
Sex, % male	377 (64.2)	71 (48.3)	< 0.001	367 (61.0)	81 (61.4)	0.932
BMI, kg/m^2	25.8 (4.9)	25.5 (5.8)	0.626	25.8 (5.1)	25.6 (5.0)	0.662
Active smokers, %	88 (15.0)	26 (17.7)	0.420	95 (15.8)	19 (14.4)	0.690
Pack-years[a]	42.7 (19.0)	40.5 (19.5)	0.261	42.9 (19.5)	39.4 (1.6)	0.073
Physical activity, %			0.017			0.733
Low	210 (35.8)	68 (46.3)		227 (37.7)	51 (38.6)	
Moderate	133 (22.7)	36 (24.5)		142 (23.6)	27 (20.5)	
High	244 (41.6)	43 (29.3)		233 (38.7)	54 (40.9)	
Comorbid asthma	25 (4.3)	8 (5.4)	0.536	25 (4.2)	8 (6.1)	0.338
COTE index	1.0 (2.0)	1.1 (2.1)	0.658	1.1 (2.1)	0.7 (1.5)	0.029
mMRC	1.7 (1.0)	2.4 (1.1)	< 0.001	1.8 (1.0)	2.2 (1.0)	< 0.001
Spirometry						
FVC (% predicted)	73.2 (18.8)	72.3 (19.3)	0.617	73.5 (18.8)	71.0 (19.6)	0.180
FEV_1 (% predicted)	50.1 (17.8)	44.9 (15.6)	0.001	49.7 (17.7)	46.5 (16.2)	0.064
FEV_1/FVC	49.9 (11.4)	45.9 (11.1)	< 0.001	49.2 (11.5)	48.5 (11.4)	0.519
CAT	13.2 (7.0)	23.6 (6.9)	< 0.001	13.8 (7.3)	22.5 (7.7)	< 0.001
BODEx	2.7 (1.8)	3.9 (2.0)	< 0.001	2.8 (1.8)	3.6 (2.0)	< 0.001
Exacerbations						
Ambulatory	0.9 (1.3)	1.9 (2.3)	< 0.001	1.0 (1.4)	1.8 (2.2)	< 0.001
Hospital based[a]	0.3 (0.9)	0.6 (1.1)	0.002	0.3 (0.9)	0.7 (1.2)	< 0.001
E-RS score						
Total	8.0 (5.7)	17.6 (6.3)	< 0.001	8.6 (6.1)	16.1 (7.3)	< 0.001
Breathlessness domain	4.3 (3.6)	9.6 (3.4)	< 0.001	4.8 (4.0)	8.1 (4.1)	< 0.001
Cough & sputum domain	2.4 (2.1)	4.3 (2.5)	< 0.001	2.4 (2.1)	4.5 (2.3)	< 0.001
Chest symptoms domain	1.3 (1.6)	3.7 (2.6)	< 0.001	1.4 (1.8)	3.5 (2.6)	< 0.001
Early morning symptoms severity score	2.0 (2.0)	8.4 (3.7)	< 0.001	2.5 (2.8)	6.7 (4.5)	< 0.001
Night-time symptoms severity score	1.4 (2.4)	6.1 (5.1)	< 0.001	1.3 (2.4)	7.1 (4.6)	< 0.001
Night awakenings	0.2 (0.8)	1.2 (1.8)	< 0.001	0	2.3 (1.6)	< 0.001

Note: all values are presented as mean (SD). For the cases of sex, active smokers and physical activity, values are presented as N (%). *P*-value is for *t*-test for continuous variables and chi-squared for categorical ones.

[a] Maximum number of missing (n = 123, variable pack-years).

medication use ("How many puffs of your rescue medication did you take last night?"). If patients experienced a specific symptom in the previous night, they were asked to indicate the severity of the individual symptom (e.g., "How severe was your cough?") from mild to very severe on a four-point scale (i.e., mild = 1, moderate = 2, severe = 3, very severe = 4). If patients indicated that they had woken up due to COPD symptoms, they were asked to note the number of times that they had woken up due to these symptoms.

The severity of daytime symptoms was classified as mild, moderate or severe according to the distribution of scores of the E-RS in tertiles. The presence of significant early morning symptoms was considered when dyspnoea in the morning was rated as moderate or higher, plus other symptoms, classified as moderate or more severe; for night-time symptoms, we considered significant those patients who woke up at least once at night due to COPD symptoms.

2.2. Statistical analysis

A sample size of 860 patients offers a maximum margin of error (minimum precision) of 4% for estimating the percentage of patients within each category of the primary endpoint (frequency of early morning, day and night-time COPD symptoms), considering maximum indetermination (p = 40%) and a confidence level of 95%. Considering that approximately 5% of patients will not be evaluable (missing data or major protocol violation), the final sample size will be 900 patients.

Descriptive statistics included the absolute and relative frequencies for categorical variables and mean and standard deviation for numerical ones. For comparison between groups, Pearson chi-square tests and Student t-tests (dichotomous exposure) and analysis of variance (ANOVA, three or more categories in exposure variable) were performed for categorical and numerical outcomes, respectively. Subjects with different symptom severity were compared in terms of age (complete years), sex, BMI (kg/m^2), smoking status, pack-years smoked in life, physical activity levels (low, moderate and high), presence of asthma, COTE index, dyspnoea (mMRC scale), lung function parameters (FVC and FEV_1 as % predicted according to the PLATINO equations [19], and FEV_1/FVC ratio), CAT score, BODEx index, ambulatory and hospital-based exacerbations.

Pearson's correlation was used to determine the relationship between E-RS score and CAT score, FEV_1 (% predicted) and early morning and night-time symptoms scores. We also performed unadjusted and adjusted linear regression models with the E-RS total score as the outcome and age, sex, physical activity, FEV_1 and exacerbations (both ambulatory and hospital based) as independent variables. The adjusted regression considers the inclusion of all variables simultaneously in the model. All analyses were performed using Stata 13.1 (StatCorp LP, 2013. Stata Statistical Software: Release 13. College Station, TX, USA).

3. Results

3.1. Patient population

A total of 795 patients were included in the study, of whom 59.6% were male with a mean age of 69.5 years (standard deviation [SD] 8.7 years) and mean post-bronchodilator FEV_1 of 50.0% (SD 18.6%) of predicted. Complete information about symptoms derived from the questionnaires was obtained from 734 patients (92.3%).

3.2. Characteristics of patients according to the severity of daytime symptoms

Patients with more severe symptoms during the daytime had a

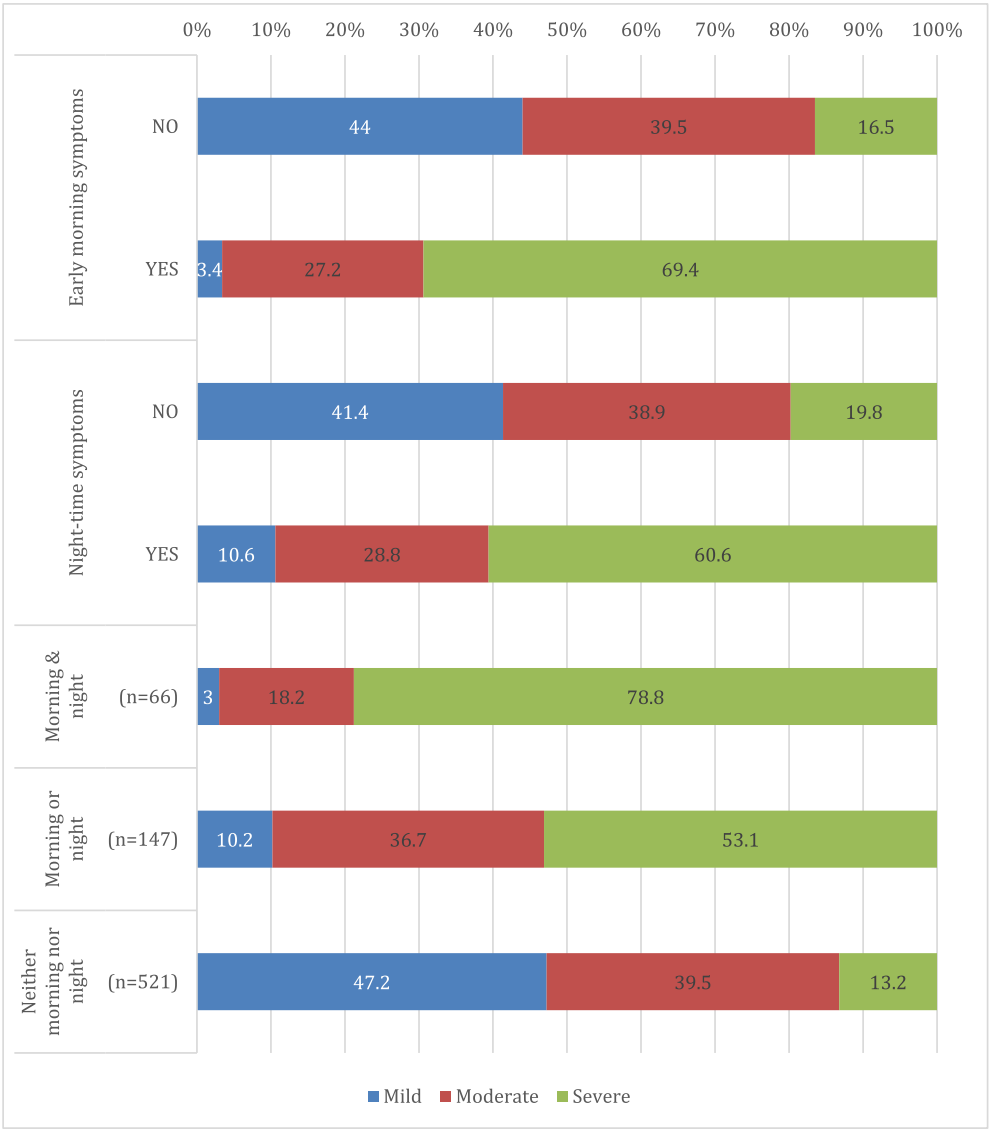


Fig. 2. Relationship between severity of daytime symptoms and prevalence of morning and night-time symptoms.

higher impairment in lung function and more exacerbations, both ambulatory and hospital-based. These patients also scored significantly worse in the mMRC dyspnoea score, the CAT questionnaire and BODEx index (all $p < 0.001$) and had a reduced physical activity that approached significance ($p = 0.050$) (Table 1).

3.3. Frequency and intensity of early morning and night time symptoms

In general, early morning symptoms were more frequent than night-time symptoms (Fig. 1). Cough was the most frequent symptom (50.1% in the morning and 33.2% at night), followed by dyspnoea (45.7% in the morning and 24.4% at night). The majority of symptoms were rated as mild or moderate in severity (Fig. 1). A total of 147 patients (20%) fulfilled our criteria for significant early morning symptoms and 132 for night-time symptoms (18%).

3.4. Characteristics of patients with early morning or night-time symptoms

Patients with early morning symptoms were more frequently women, had worse lung function and were less physically active compared with patients without morning symptoms. However, these differences were not observed when comparing patients with or without night-time symptoms. Both groups of symptomatic patients, in the morning or at night, showed worse mMRC, CAT and BODEx scores and reported more exacerbations in the year prior to the study (Table 2).

3.5. Relationship between severity of daytime symptoms and morning and night-time symptoms

There was a strong relationship between the presence of morning or night-time symptoms and the severity of daytime symptoms measured by the E-RS (Fig. 2). Up to 69.4% of patients with morning symptoms had severe daytime symptoms compared with only 16.5% of those without morning symptoms. Similarly, 60.6% of patients with night-time symptoms had severe daytime symptoms compared with 19.8% of those without night-time symptoms. Among patients with morning and night-time symptoms, 78.8% had severe daytime symptoms compared with only 13.2% of those with neither morning nor night-time symptoms.

3.6. Correlations of severity of daytime symptoms with morning and night-time symptoms and characteristics of COPD

There was a strong correlation between E-RS and CAT scores (r: 0.715; $p < 0.001$; Fig. 3A), but a weak correlation with FEV_1% predicted ($r = -0.205$; $p < 0.001$; Fig. 3B). There were also strong correlations between E-RS scores and EMSCI and NiSCI scores (r: 0.732

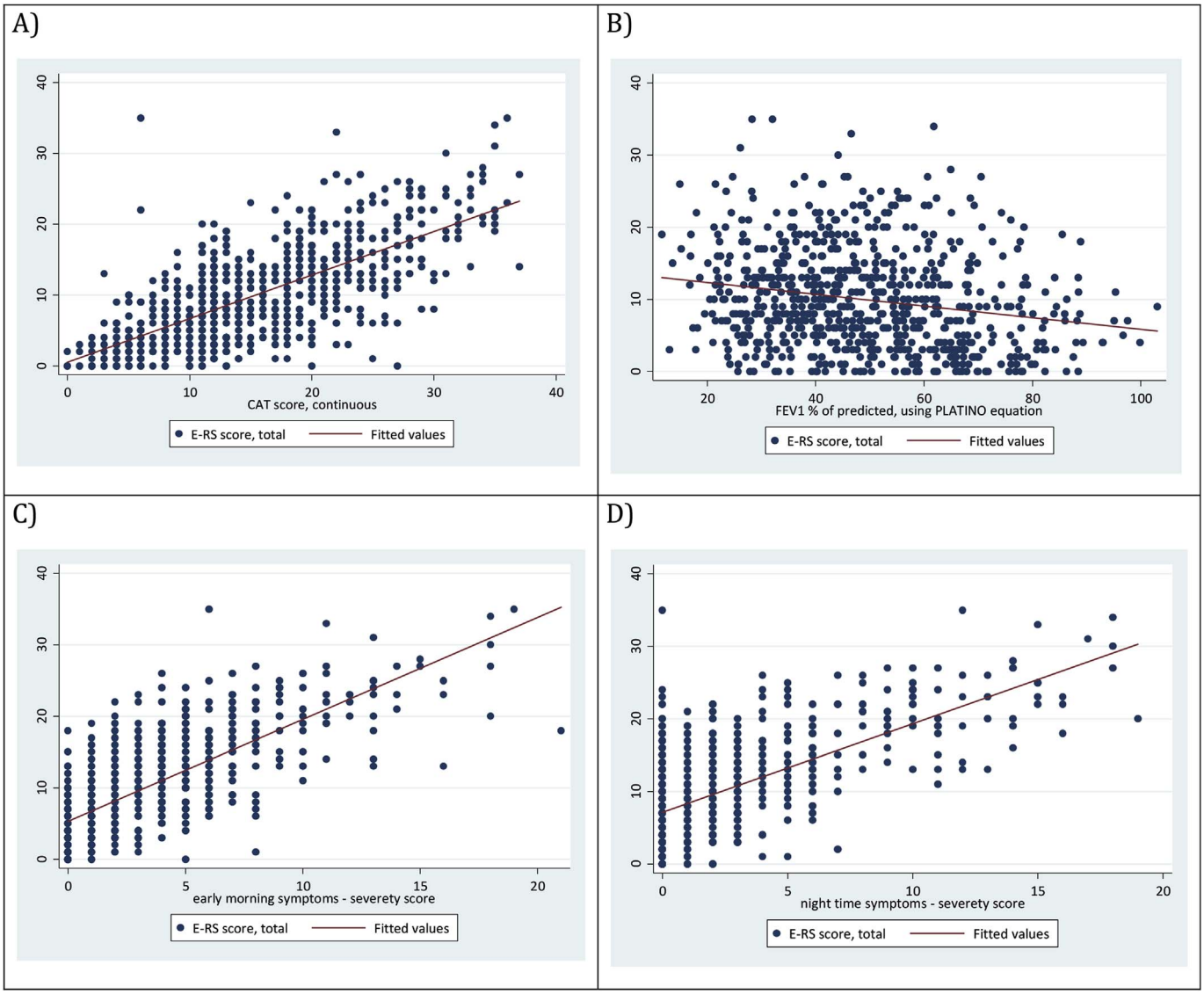


Fig. 3. Scatter plot showing the correlation between E-RS global score and: A) CAT score; B) FEV_1 (% predicted); C) early morning symptom score; and D) night-time symptom score.

and r: 0.644, respectively; both $p < 0.001$; Fig. 3C and D).

3.7. Linear regression modelling

Table 3 presents the results for the unadjusted and adjusted linear regression analyses. After the full adjustment, age ($\beta = -0.08$; 95% CI -0.14; -0.03; $p = 0.004$), FEV_1 ($\beta = -0.05$; 95% CI -0.07; -0.02; $p = 0.001$) and physical activity ($p = 0.042$) were significantly associated with the E-RS score. Among exacerbations, only ambulatory based exacerbations were associated with the outcome ($p < 0.001$).

4. Discussion

The results of this study have shown a high frequency of respiratory symptoms in a population of COPD patients in Latin America. However, the frequency of significant early morning and night-time symptoms (20% and 18%) was lower than in previous studies, basically because of the more restrictive definition of "significant" symptoms used in the current study. A close relationship between the presence of morning and night-time symptoms and the severity of daytime symptoms was observed, and a strong correlation between the severity of daytime symptoms (E-RS scores) and the severity of both early morning and night-time symptoms (EMSCI and NiSCI scores). However, the correlation between severity of symptoms and degree of airflow limitation was weak.

Daytime symptoms in our study were measured using the E-RS, which is a sensitive and validated tool to investigate and quantify symptoms of COPD in a clinical trial setting [12,13]. Furthermore, symptomatic patients are usually defined as those patients with an E-RS score of at least 10 units. This threshold was selected based on evidence suggesting that 10 units could distinguish between less symptomatic (GOLD groups A and C) and more symptomatic (GOLD groups B and D) patients [14,15]. Consistent with this definition, 10 units was the mean score of our patients classified as moderately symptomatic, whereas those classified as highly symptomatic had an E-RS mean score of 19.2 units.

As expected for a symptoms questionnaire, the E-RS scores correlated strongly with the mMRC and CAT scores; however, although severely symptomatic patients had worse FEV_1 (% predicted) compared with those who were less symptomatic, the correlation of E-RS scores with FEV_1 was poor, as has been observed with the correlations between lung function and other symptom questionnaires. This poor correlation indicates that lung function and symptoms are two dimensions of the disease relatively independent and justifies the evaluation of symptoms in the therapeutic decision-making for patients with COPD, as suggested by GOLD [20] and COPD guidelines [21,22]. Older age, more impaired FEV1, low level of

Table 3
Unadjusted and adjusted linear regression analysis for the ERS score and selected variables.

Variable	Unadjusted	Adjusted[a]
	β (95% CI)	β (95% CI)
Age	*P = 0.033*	*P = 0.004*
	−0.06 (−0.12; −0.01)	−0.08 (−0.14; −0.03)
Sex	*P = 0.037*	*P = 0.267*
Female	0.00 (reference)	0.00 (reference)
Male	−1.08 (−2.09; −0.06)	−0.55 (−1.53; 0.43)
Physical activity	*P = 0.010*	*P = 0.042*
Low	0.00 (reference)	0.00 (reference)
Moderate	−1.18 (−2.49; 0.13)	−1.12 (−2.37; 0.13)
High	−1.77 (−2.89; −0.63)	−1.35 (−2.50; −0.24)
FEV_1 (% predicted)	*P < 0.001*	*P = 0.001*
	−0.07 (−0.10; −0.05)	−0.05 (−0.07; −0.02)
Number of ambulatory based exacerbations	*P < 0.001*	*P < 0.001*
	1.58 (1.28; 1.87)	1.43 (1.11; 1.76)
Number of hospital based exacerbations	*P < 0.001*	*P = 0.587*
	1.25 (0.72; 1.77)	0.15 (−0.39; 0.70)

[a] The adjusted analysis included all variables presented in the table simultaneously in the model. *P*-value was obtained using the Wald test.

physical activity, and more frequent ambulatory exacerbations were the variables significantly and independently associated with increased intensity of respiratory symptoms.

There has been an increased interest in describing the patterns of symptoms throughout the 24-hour day in patients with COPD. Large studies have identified subgroups of patients that experienced symptoms predominantly in the morning, during the day or at night [6,23], and they suggested that tailored therapy according to the pattern of symptoms could provide increased benefits in the management of these patients [24]. Partridge et al. [25] identified, for the first time, mornings as the most symptomatic period of the day for COPD patients. Their results were confirmed in a large European survey which showed that all respiratory symptoms, and in particular cough and phlegm, were more severe on waking and these morning symptoms restricted patients' ability to perform morning routines [26]. Cough and sputum, followed by dyspnoea, were also the most frequent morning symptoms in a more recent international study, with 88% of patients reporting these symptoms being of mild or moderate severity [6]. The prevalence of morning symptoms in COPD ranges from 37% to 94% across different studies, depending on the severity of the patients studied and the definition used [4,27,28]. We used a very restrictive definition of “significant” morning symptoms that required at least moderate dyspnoea plus another moderate symptom. This definition was arbitrary but identified a subgroup of patients that, besides having more severe COPD in terms of lung function and BODEx, were more frequently women, more inactive and suffered more exacerbations, suggesting that this definition identified individuals that required more intensive or focused treatment to alleviate these morning symptoms.

Similarly, our frequency of 18% for night-time symptoms was lower that the reported frequencies of between 25% and 88% [4]’ which is again because of our more restrictive definition of requiring at least one awakening due to respiratory symptoms. Interestingly, our definition of significant night-time symptoms did not identify any particular subgroup of patients and was only associated with more severe COPD and more frequent exacerbations. In a European retrospective analysis of real-world data describing 2807 patients with COPD, 78% of patients experienced physician-reported night-time disturbances due to symptoms and these patients experienced a higher incidence of daytime breathlessness and more frequent exacerbations within the previous 12 months compared with patients who had no night-time symptoms [29]. Furthermore, the presence of night-time symptoms was associated with a greater likelihood of experiencing COPD morning symptoms, disturbed sleep and poorer quality of life [29]. These findings were consistent with other reports which demonstrated that night-time symptoms impaired sleep quality and morning routine, which combine to compromise overall health status [26,30–32]. In addition to the prevalence of significant morning and night-time symptoms, it is important to emphasise that approximately half of patients suffered from dyspnoea and/or cough in the morning and between one-quarter and one-third suffered from dyspnoea and/or cough in the night.

The association between symptoms at different periods of the 24-hour day has already been observed in a European study where up to 56.7% of patients presented with symptoms during the three parts of the day (morning, daytime and night), whereas only 10.6% of patients presented with symptoms during only one part of the day [6]. We extended this observation by demonstrating that patients that had significant morning and/or night symptoms also had a higher severity of daytime symptoms. In fact, up to 78.8% of patients with both morning and night-time symptoms also had severe daytime symptoms. This finding suggests that there is a subgroup of very symptomatic patients with COPD that may require a more focused therapy orientated to the relief of symptoms [15,24,28,33].

A relevant observation in our study was the relationship between the severity of daytime symptoms and/or the presence of significant morning or night-time symptoms and the frequency of exacerbations. Exacerbations have been reported to be associated with an impairment in HRQoL [34], a decline in lung function [35] and increased mortality [36]; therefore, strategies directed to prevent exacerbations are of utmost importance in the management of COPD [37]. Previous studies have suggested that symptomatic patients are more likely to experience exacerbations [26,29,38]; therefore, there is the possibility that in highly symptomatic patients, a targeted therapy directed to improve symptom control could also contribute to reduce exacerbation risk [24]. In addition, the relationship between psychological profiles or increased anxiety and depression and intensity of symptoms also deserves further investigation.

Our study has several limitations; despite the inclusion of a large number of patients from seven countries, we cannot conclude that our sample is representative of the COPD patient population in Latin America; however, the sample included patients with different degrees of severity treated in different settings and may provide a valid estimate of the characteristics of these patients in the area. In order to avoid misdiagnosis with other respiratory diseases, never smokers were not included; therefore results cannot be extrapolated to this population of patients with COPD. The definitions of severity of daytime symptoms and of “significant” morning and night-time symptoms are arbitrary as no universally accepted definitions exist. In any case, the proposed definitions identified patients with different degrees of impairment and different outcomes. Although the use of questionnaires is the only way to investigate the frequency and severity of symptoms, their interpretation may be subjected to bias. Finally, since this was a cross-sectional study we could not prospectively analyse the impact of symptoms on outcomes such as quality of life or exacerbations. We could only investigate the relationship with previous history of exacerbations and the presence and severity of symptoms.

The LASSYC study has provided for the first time a description of the frequency, intensity and distribution of respiratory symptoms through the 24-hour day in a large population of COPD patients in Latin America. It has demonstrated the large burden of symptoms and the relationship between symptoms and poor outcomes in COPD.

Author contribution

MM, AM, MVLV, AC, LU, ARV, LM, AL, FCW, FS and MMO contributed substantially to the study design, data collection, interpretation, and reviewed the manuscript. AM and FCW performed the data analysis while all authors were involved with data interpretation. MM wrote the manuscript. All authors approved the final version of the

manuscript and agreed to its submission to Respiratory Medicine.

Conflicts of interest

Ana Menezes has been paid for her work as a statistician for the LASSYC study by AstraZeneca. Filip Surmont is an Employee of AstraZeneca. The remaining authors have no real or perceived conflicts of interest in relation to this work.

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