Study Code D2287R00112
Edition Number 1.0
Date 28/ 9/ 2017

TITLE: **Evaluation of respiratory symptoms in COPD patients from seven Latin America countries: The LASSYC Study**

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Background: 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 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.

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.

Objective: To investigate the frequency of respiratory symptoms along the 24 hour day, their intensity and related factors in a COPD population from 7 Latin American countries.

Method:

The **L**atin **A**merican **S**tudy of 24-hour **SY**mptoms in **C**hronic Obstructive Pulmonary Disease (LASSYC) was a prospective observational, multicentre, multinational, cross-sectional, non-interventional study (Clinical Trial Registration: NCT02789540), in patients with stable COPD from seven Latin American countries (Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico and Uruguay). The study was approved by the ethics committees for each site and all patients provided written informed consent.

The inclusion criteria were: 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 second/forced vital capacity (FEV_1/FVC) <0.70 criterion, current or ex-smokers with history of ≥10 pack-years and stable disease.

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 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]).

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.

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. The NiSCI included the same three concepts of interest in patients with COPD: 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.

Results:

A total of 795 patients were included in the study. Their characteristics and the differences according to the level of symptoms are presented in Table 1.

Frequency and intensity of early morning and night time symptoms

A total of 147 patients (20%) experienced significant early morning symptoms and 132 experienced night-time symptoms (18%). In general, early morning symptoms were more frequent than night-time symptoms (Fig. 1).

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. (Table 2).

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.

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

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**
Age, years	69.6 (8.7)	70.5 (8.6)	68.9 (8.7)	69.3 (8.8)	0.098
Sex, % male	448 (61.0)	165 (62.7)	172 (63.2)	111 (55.8)	0.203
BMI, kg/m^2	25.7 (5.1)	25.9 (4.9)	25.2 (4.9)	26.3 (5.6)	0.062
Active smokers, %	114 (15.5)	42 (16.0)	39 (14.3)	33 (16.6)	0.778
Pack-years*	42.2 (19.1)	40.7 (18.7)	44.2 (19.7)	41.6 (18.9)	0.724
Physical activity, %					0.050
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
COTE index	1.0 (2.0)	1.0 (2.0)	0.9 (2.0)	1.1 (2.0)	0.605
mMRC	1.8 (1.0)	1.4 (0.9)	1.9 (1.0)	2.4 (1.0)	<0.001
Spirometry					
FVC (% predicted)	73.0 (18.9)	74.4 (19.0)	73.1 (19.1)	71.2 (18.5)	0.197
FEV_1 (% predicted)	49.1 (17.5)	53.6 (17.7)	47.8 (17.8)	45.0 (15.4)	<0.001
FEV_1/FVC	49.1 (11.4)	52.4 (10.9)	47.8 (11.3)	46.5 (11.4)	<0.001
CAT	15.3 (8.1)	9.3 (5.7)	15.5 (5.6)	23.0 (6.9)	<0.001
BODEx	2.9 (1.9)	2.2 (1.7)	3.1 (1.7)	3.8 (1.9)	<0.001
Exacerbations					
Ambulatory	1.1 (1.6)	0.6 (1.0)	1.0 (1.4)	2.0 (2.1)	<0.001
Hospital based	0.4 (1.0)	0.3 (0.9)	0.4 (1.0)	0.6 (1.1)	<0.001
E-RS score					
Total	10.0 (7.0)	3.1 (2.0)	9.9 (2.1)	19.2 (4.4)	<0.001
Breathlessness domain	5.4 (4.2)	1.5 (1.8)	5.6 (2.5)	10.3 (2.7)	<0.001
Cough & sputum domain	2.8 (2.3)	1.3 (1.4)	2.8 (1.8)	4.9 (2.2)	<0.001
Chest symptoms domain	1.8 (2.1)	0.3 (0.6)	1.5 (1.4)	4.0 (2.3)	<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
Night-time symptoms severity score	2.3 (3.7)	0.6 (1.2)	1.6 (2.3)	5.6 (5.0)	<0.001

Night awakenings	0.4 (1.0)	0.1 (0.4)	0.3 (0.9)	1.0 (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 ANOVA for continuous variables and chi-squared for categorical variables.

* Maximum number of missing (n=124, pack-years smoked)

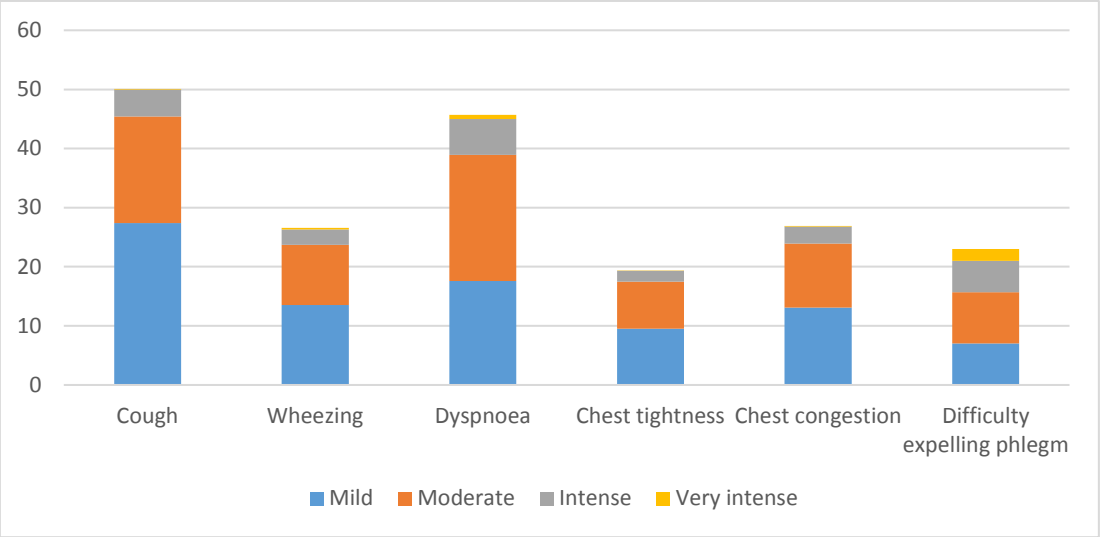
Table 2. Demographic and clinical characteristics of COPD patients according to the presence of early morning and night-time symptoms.

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*	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*	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.

* Maximum number of missing (n=123, variable pack-years)

A) Early morning



B) Night-time

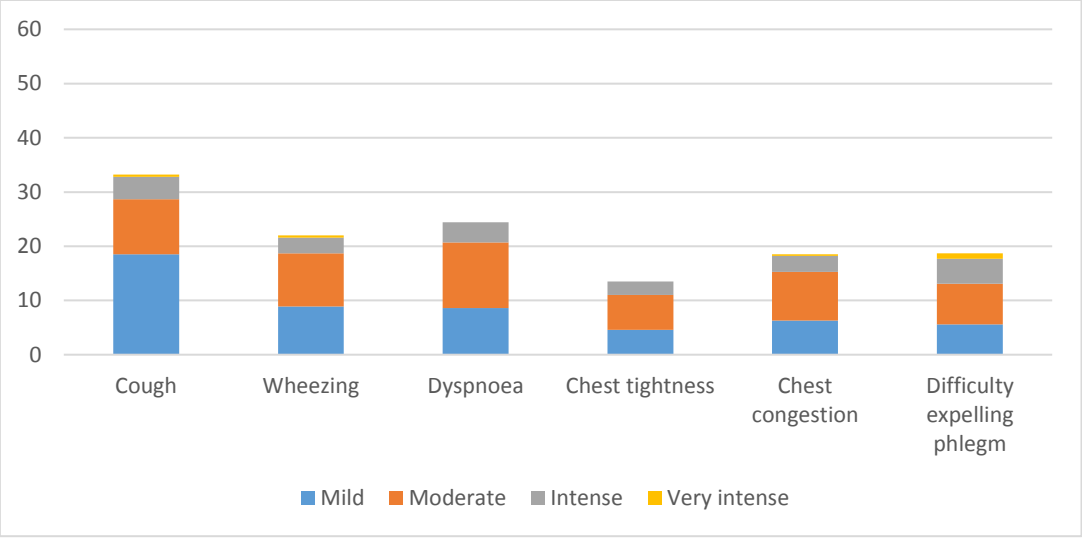


Figure 1. Prevalence of the most frequent (A) early morning and (B) night-time symptoms, including their severities.

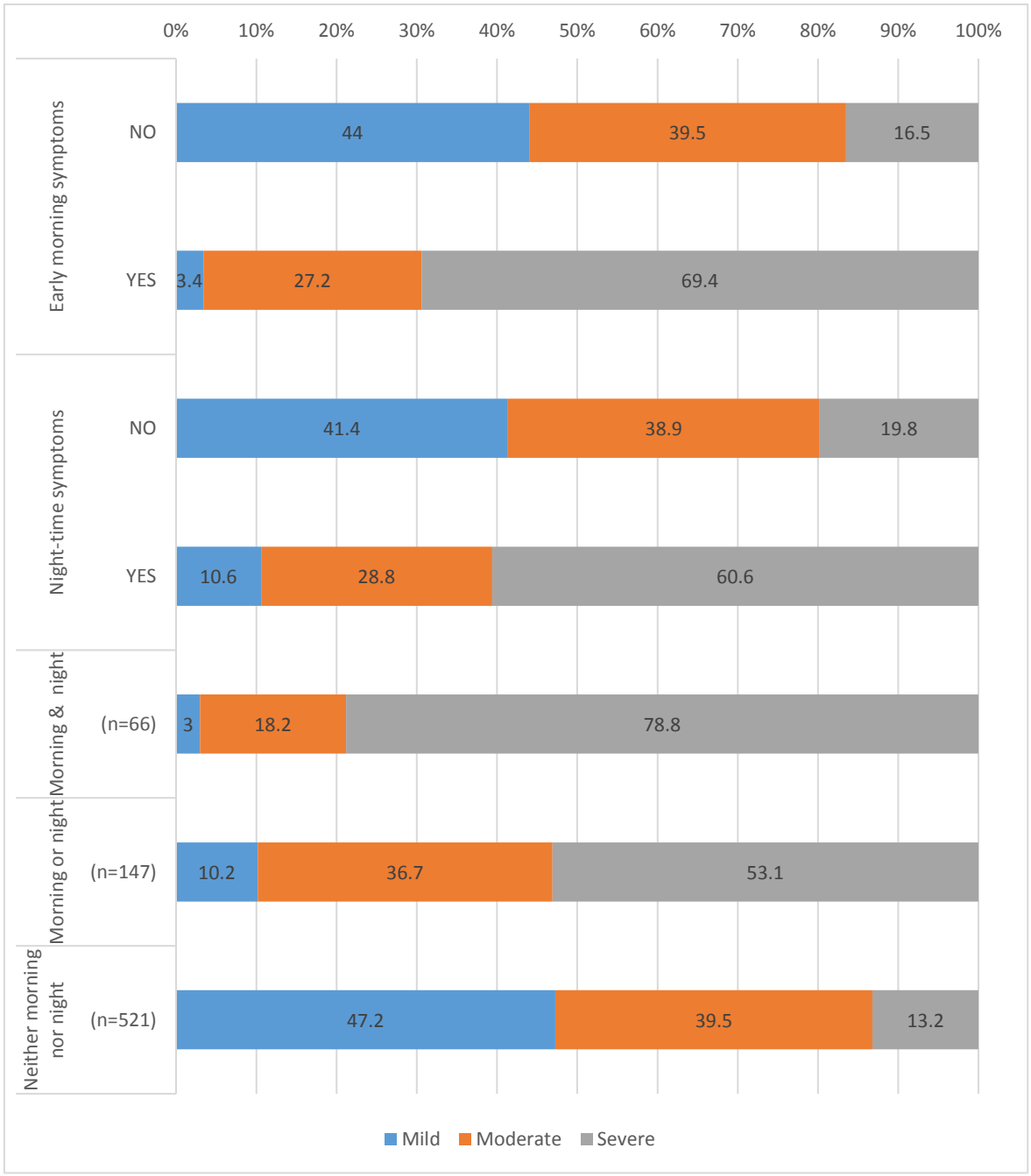


Figure 2. Relationship between severity of daytime symptoms and prevalence of morning and night-time symptoms.

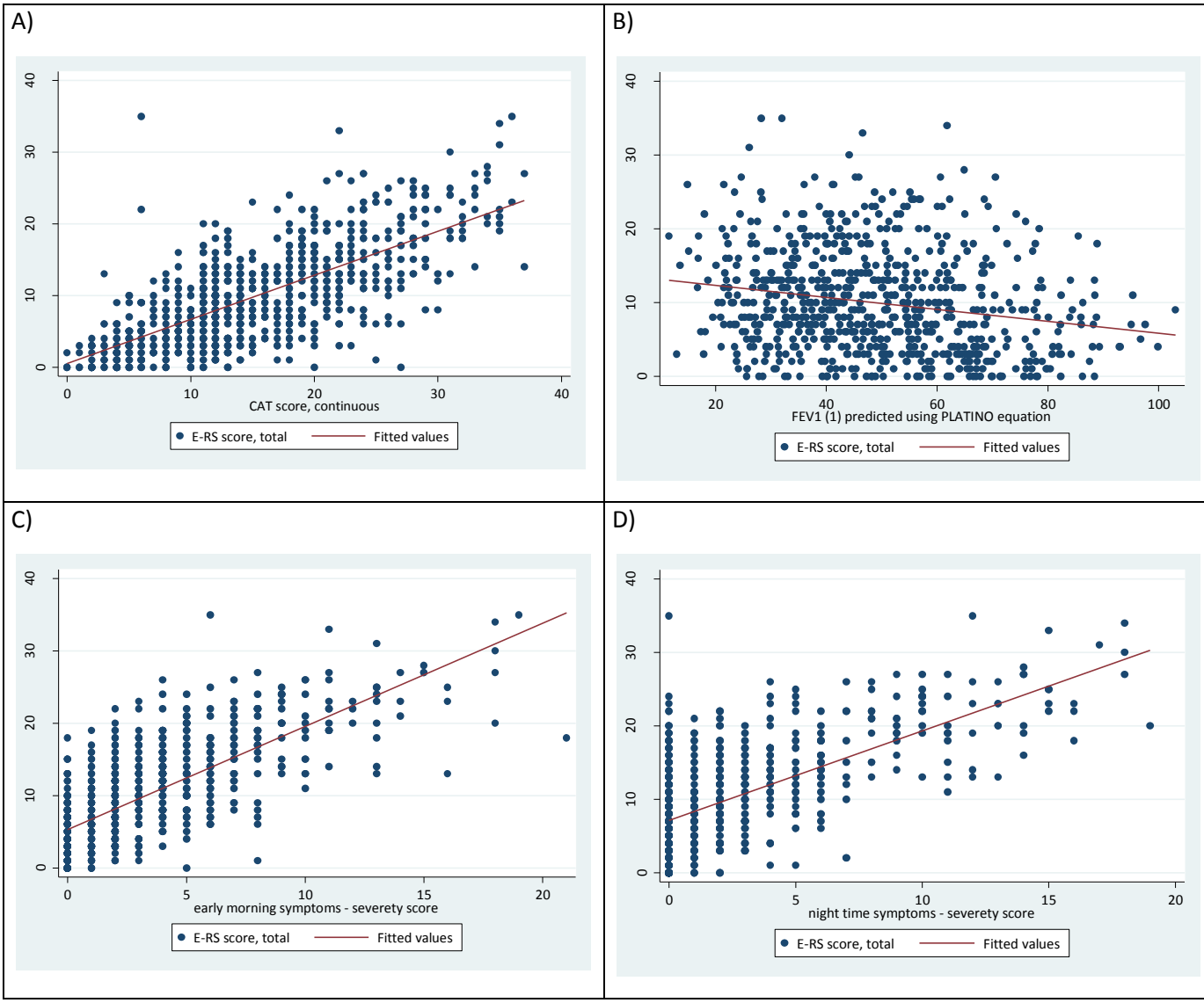


Figure 3. Scatter plot showing the correlation between E-RS global score and: A) CAT score; B) FEV_1 (% predicted); C) early morning symptom score; and D) night-time symptom score.

Conclusions:

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. Tailored therapy according to symptom pattern could provide increased benefit in the management of COPD patients.