Pulmonology 29 (2023) S92—S95

PULMONOLOGY

www.journalpulmonology.org

LETTER TO THE EDITOR

Back to the roots of medicine: It's severe asthma patient-reported symptoms that matter!

To the Editor,

Severe asthma can be defined as an "asthma which requires treatment with high-dose inhaled corticosteroids (ICS) + LABA to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy".[1] It is an important public health problem strongly associated with a significant health-related quality of life (HRQL) burden [2] and with considerable healthcare costs, almost twice those of non-severe asthmatics.[3]

Several studies have assessed the factors associated with HRQL in severe asthmatics, demonstrating the key role played by asthma control and comorbidities.[2] However, very few studies have assessed the impact of detailed respiratory symptoms on HRQL. A recent study conducted by Louis et al.[4] has demonstrated that dyspnoea was the most impactful symptom on the lives of mild asthmatics. However, to the best of our knowledge, no study has ever assessed the impact of specific respiratory symptoms on HRQL in a population of severe asthmatics. Knowing which symptoms are the most impactful on the lives of severe asthmatics is useful for adopting personalised care strategies.

A cross-sectional study was conducted between 2018 and 2022 on a population of T2 high severe adult asthmatics recruited from the Liege University Hospital Asthma Clinic (Belgium) prior to initiation of biologics (n = 143). All had had at least two exacerbations in the 12 months prior to the visit, with baseline FEV1<80 % predicted. T2 high profile was defined as either one of the following characteristics: (i) blood eosinophil count>300/μl, (ii) FeNO>25 ppb, (iii) IgE>76 KU/l with sensitisation to at least one perennial allergen. Lung function testing was performed by spirometry (Spiro bank; MIR, Rome, Italy) to measure expiratory flow rates. FeNO was measured at a flow rate of 50 ml/s (NIOX; Aerocrine, Solna, Sweden) before spirometry. Asthma control was measured using the Asthma Control Test (ACT).[5] Symptoms were measured by five-point Likert scales ranging from 1 to 5 (5 expressed the highest intensity). HRQL was measured by the mini asthma quality of life questionnaire (AQLQ) composed of 15 items scored on a seven-point Likert scale ranging from 1 to 7 (7 expressed the highest QOL).[6] Median and interquartile range (IQR) were used to describe quantitative variables, while percentages and counts were used for qualitative variables. The associations between symptoms intensity and AQLQ were determined using the Spearman correlation coefficient. Multiple linear regression analyses were performed to identify symptoms independently associated with AQLQ. All statistical analyses were performed using GraphPad Prism software (version 9.4.1) at a significance level of 0.05.

The median age of our patients was 55 (41—65) years and 64 %(92) were female. 61 %(87) were never-smokers, 27 %(39) ex-smokers and 12 %(17) current smokers. The median baseline FEV_1 was 71 %(47 %—82 %) predicted and the FEV_1/FVC was 74 %(61 %—79 %).

The median global mini-AQLQ was 3.9 (3—5.1) and the median ACT was 12 (9—17)(17 % patients with controlled asthma as shown by ACT≥20). The median values of cough, airway secretion, chest tightness, dyspnoea and wheezing intensity scales were 3(2—4), 3(2—4), 3(2—4), 4(3—4) and 3 (2—4), respectively.

For each symptom, a higher intensity score was significantly correlated with low global AQLQ. However, different Spearman correlation coefficients were found depending on the symptoms. Dyspnoea had the strongest correlation with global AQLQ (r_s=—0.66; p<0.0001), while airway secretion displayed the weakest correlation (r_s=—0.26; p = 0.0014) (Fig. 1). After adjusting for age, sex, BMI, FEV_1% predicted, FEV_1/FVC% and asthma control, multiple linear regression analysis (MLRA) showed that only dyspnoea was significantly associated with global AQLQ (Table 1). MLRA also revealed that dyspnoea was independently associated with the activity dimension, while airway secretion and cough were associated with the emotive dimension (Table 1). In addition, cough

Abbreviations: ACT, Asthma control test; AQLQ, Asthma quality of life questionnaire; BMI, Body mass index; FENO, Fraction of exhaled nitric oxide; FEV1, Forced expiratory volume in 1 second; FVC, Forced vital capacity; ICS, Inhaled corticosteroids; LABA, Long-acting beta agonists; OCS, Oral corticosteroids; PROM, Patient-reported outcome measure.

https://doi.org/10.1016/j.pulmoe.2023.10.005

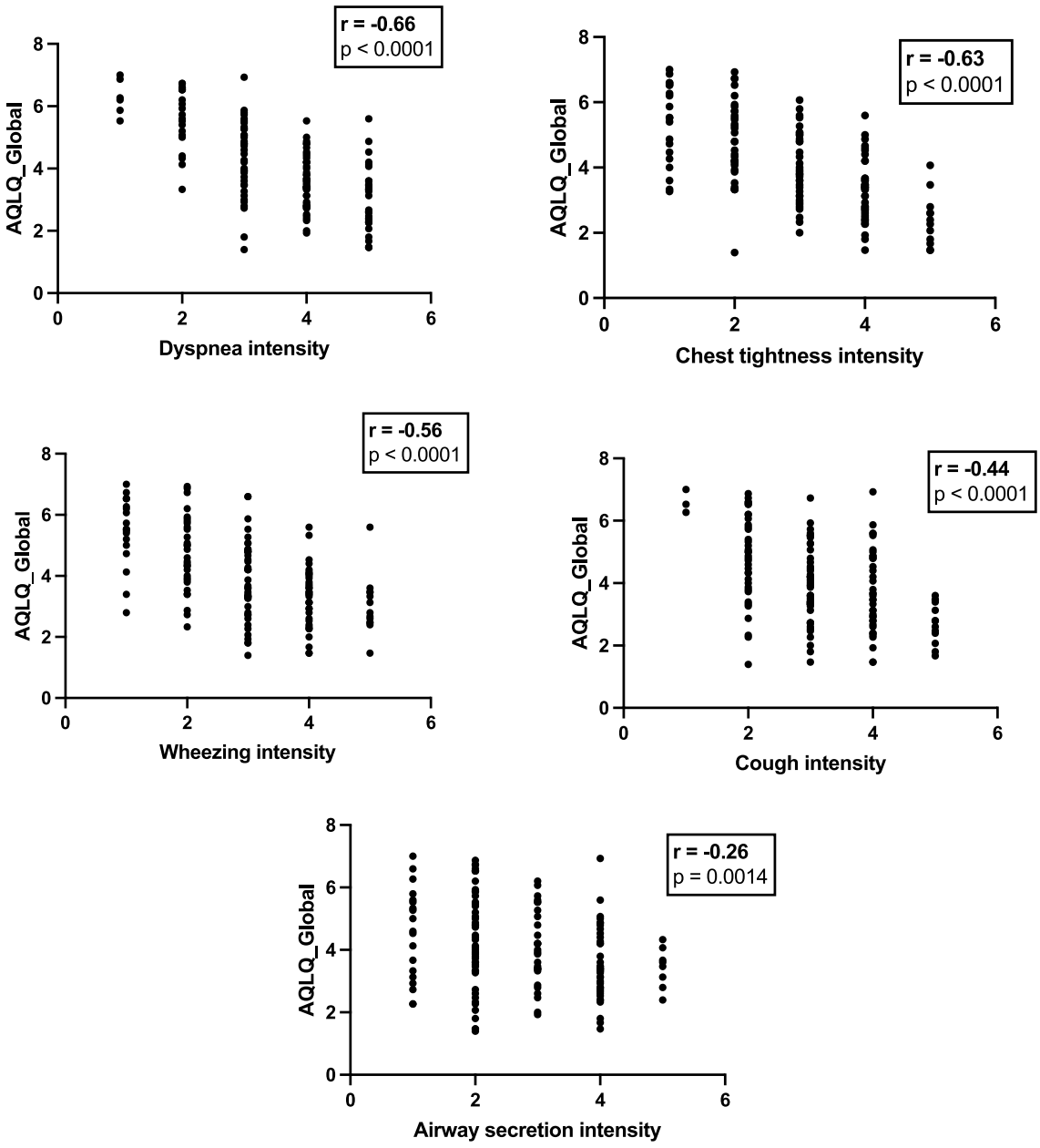

Fig. 1 Correlations between global asthma-related quality of life (AQLQ) score and symptom intensity scores.

emerged as an independent predictor of the environmental dimension (Table 1).

In this study, dyspnoea was the only symptom significantly associated with global AQLQ. It is in line with our recent study[4] focusing on mild asthmatics. Whatever the level of severity of the disease, an increase in dyspnoea is a sign that the patient's quality of life is deteriorating, necessitating appropriate healthcare measures. It would be interesting to follow these same patients longitudinally to determine the effect of biologics treatment on the level of respiratory symptoms' intensity. Even if a recent qualitative study demonstrated the revolutionary effect of biologics on the lives of severe asthmatics,[7] drug impact would be enhanced if part of a global approach based on the patient's needs and expectations, as reported through patient-reported outcome measures (PROMs). It is the combination of a precision medicine based on biologics with a PRO-cision medicine [8] that will undoubtedly contribute to improving the health and quality of life of severe asthmatics, as well as the quality and safety of care.

In conclusion, dyspnoea is the most impactful symptom on the lives of severe asthmatics, even if other symptoms - airway hypersecretion and cough - appear to influence independently some of the dimensions of quality of life.

Table 1 Multiple linear regression for the relationship between symptom intensity scales and global AQLQ and its 4 dimensions (n = 143).

	Global AQLQ		Symptoms dimension		Activity dimension		Emotive dimension		Environmental dimension	
	Regression coefficient	p-value	Regression coefficient	p-value	Regression coefficient	p-value	Regression coefficient	p-value	Regression coefficient	p-value
Age (years)	−0.009077 *	0.0320	−0.007345	0.0617	−0.01287 **	0.0084	−0.004239	0.5861	−0.01297	0.1318
Gender (male)	0.04046	0.7725	−0.1170	0.3701	0.1227	0.4462	0.1413	0.5870	0.1084	0.7050
BMI (kg/m2)	0.009459	0.4580	0.02395 *	0.0453	−0.02744	0.0626	0.02251	0.3421	0.02304	0.3767
FEV_1% predicted	0.001612	0.7504	0.0008127	0.8632	0.007564	0.1954	−0.003597	0.7024	0.0008082	0.9378
FEV_1/FVC%	−0.004356	0.5856	−0.01111	0.1371	−0.005342	0.9970	0.01074	0.4694	−0.01424	0.3839
FeNO (ppb)	−0.001160	0.5254	0.001071	0.5289	−0.002160	0.3041	−0.002429	0.4741	−0.002546	0.4954
wheezing intensity score	−0.02593	0.7308	−0.2557 ***	0.0004	0.1140	0.1895	0.06463	0.6443	0.1105	0.4735
dyspnoea intensity score	−0.1970 *	0.0401	−0.01431	0.8716	−0.5580 ****	<0.0001	−0.2696	0.1287	0.02778	0.8863
Chest tightness intensity score	−0.1074	0.1649	−0.08728	0.2252	−0.009077	0.9183	−0.1956	0.1733	−0.2348	0.1379
Airway secretion intensity score	−0.02706	0.6879	0.005607	0.9288	0.03156	0.6834	−0.2934 *	0.0205	0.06485	0.6377
Cough intensity score	0.1530	0.1196	−0.1309	0.1525	0.06571	0.5589	0.4599 *	0.0125	0.4722 *	0.0196
ACT	0.1852 ****	<0.0001	0.1792 ****	<0.0001	0.1725 ****	<0.0001	0.1942 ****	<0.0001	0.1917 ****	<0.0001

Abbreviations: AQLQ, asthma quality of life questionnaire; ACT, asthma control test; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.;
*$p<0.05$; ** $p<0.01$; *** $p<0.001$; **** $p<0.0001$.

Conflicts of interest

Outside of this submitted work, RL received unrestricted research grants from GSK, AstraZeneca, Novartis and Chiesi and lecture or adboard fees from GSK, AZ, Novartis and Sonafi. Outside of this submitted work, FS received lecture or adboard fees from Chiesi, AZ, GSK, and Novartis. Outside this submitted work, JB reports personal fees (member of advisory boards, consultations, honoraria for meeting lectures) from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi—Aventis, Teva, Uriach. Shareholder of KYomed Innov and MASQUE-air-SAS. The rest of the authors declare that they have no relevant conflicts of interest.

Ethics approval and consent to participate

The Study was approved by the CHU Liège ethics committee. Signed informed consent was obtained from patients as soon as they entered the asthma clinic of the CHU Liège. They agreed that their clinical data and the health outcomes they reported in the routine setting would be used for the purposes of research.

Funding

The study received support from a federal grant of the Belgian Government (EOS 0013618F and EOS O.001422).

Authors' contributions

GL, BP, RL & JB contributed to the conception of the study. FS, & RL contributed to data acquisition. GL performed statistical analysis. GL, BP, FS, RL, MG, BSP, EVG & JB drafted and critically revised the work. All authors gave final approval of the manuscript.

Acknowledgements

We would like to thank Anna Bedbrook for reviewing the English version of the manuscript.

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Received 14 September 2023; Accepted 5 October 2023
Available online 11 November 2023