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Quality of life in allergic rhinitis: relationship with clinical, immunological, and functional aspects

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Clinical and Experimental Allergy

Summary

Background The relationship among nasal obstruction, T-helper type 2-dependent inflammation, nasal airflow limitation, and reversibility to the nasal decongestion test has been evidenced in allergic rhinitis (AR). Moreover, quality of life (QoL) has been widely evaluated in AR and its evaluation is considered in numerous trials.

Objective The aim of this cross-sectional study was to identify the QoL as measured by the Quality of Life Questionnaire in a population of patients with AR and to compare it with clinical, immunological, and functional parameters.

Methods One hundred and twenty-three patients with persistent AR were prospectively and consecutively evaluated. Clinical evaluation, skin prick test, nasal scraping for cytology, rhinomanometry, decongestion test, and QoL questionnaire were performed in all subjects.

Results There was a significant relationship among QoL and functional and immunological parameters. Particularly, the multivariate analysis showed that having more than two sensitivities was a determinant of the QoL. The eosinophil count was significantly associated with QoL as well as the baseline nasal flow (mL/s) with the eye symptoms scale only.

Conclusions This study provides the first evidence that QoL in AR is strictly associated with allergic inflammation and eye symptoms significantly contribute to impairment of QoL.

QoL, moreover, represents an important aspect to consider in managing patients with AR as it has a relationship with clinical, immunological, and functional parameters.

Keywords decongestion test, eosinophils, nasal airflow, persistent allergic rhinitis, quality of life, symptoms

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Introduction

Allergic rhinitis (AR) is the most frequent IgE-mediated disease. Its prevalence is high in the general population and is still progressively increasing [1–3].

AR is classically subdivided into seasonal (SAR) and perennial (PAR), according to the type of allergen and the occurrence of symptoms round the year [4]. SAR is mainly caused by outdoor allergens, such as pollens, whereas PAR is sustained by indoor allergens, including house dust mites (HDMs), pets, and cockroaches. This classification has been recently revised by the Allergic Rhinitis and its Impact on Asthma (ARIA) workshop [5]. The new classification of 'intermittent' (ITR) and 'persistent' (PER) does not consider the type of allergen, but rather the duration of symptoms (days/week and consecutive weeks) and the

impact on QoL. On the basis of these considerations, we have previously performed a study on a large population of subjects perceiving only nasal symptoms, in order to evaluate the clinical and functional aspects in relation to the type of AR and the causal allergen(s) [6]. The large majority of subjects (80%) exhibited a mixed AR (MAR), because they were sensitized both to seasonal and perennial allergens [6]. Moreover, a seasonal variability of the symptom score was detectable both for SAR and PAR patients (SAR patients had more symptoms during spring–summer; PAR patients worsen during autumn–winter), whereas MAR patients did not show seasonal variations [6].

It is well known that allergen exposure activates mast cells with consequent release of preformed mediators, mainly histamine and leukotrienes, and cytokines capable of inducing the recruitment and activation of

inflammatory cells, including eosinophils, neutrophils, and T-helper type 2 (Th2) lymphocytes [7]. These inflammatory events lead to the onset of typical nasal symptoms, including itching, sneezing, rhinorrhoea, and obstruction. Recently, the relationship between nasal obstruction, Th2-dependent inflammation, and nasal airflow limitation has been evidenced both in adults and children having AR [8–10]. In addition, it has been evidenced very recently that the reversibility to the nasal decongestion test is dependent on allergic inflammation [11, 12].

On the other hand, QoL has been widely evaluated in AR and its evaluation is considered in numerous trials [5]. Nevertheless, no study has still globally investigated the impact of nasal symptoms, sensitizations, nasal eosinophils and airflow, and recovery to nasal decongesting on QoL. However, a correlation between RQoL, symptoms, and functional tests (i.e. nasal hyperreactivity) has been published before [13]. Therefore, the purpose of this cross-sectional study was to test the hypothesis that QoL may be related to different clinical, immunological, and functional parameters in a population of patients with PER.

Methods

Study design

One hundred and twenty-three patients with PER were prospectively and consecutively evaluated (112 males and 11 females, mean age 22.9 ± 5.7 years). Patients reporting concomitant or past asthma symptoms (one or more of: persistent cough, wheezing, dyspnoea, and shortness of breathing, either diurnal or nocturnal) were excluded. Subjects with acute upper respiratory infections, anatomic nasal disorders (i.e. septum deviation), nasal polyps, and patients using nasal or oral corticosteroids or decongestants, antileukotrienes, and antihistamines within the previous 4 weeks were excluded too. Nobody was treated with specific immunotherapy.

The diagnosis of PER was made on the basis of a history of nasal symptoms and positive skin prick test (SPT) according to validated criteria [5].

Clinical evaluation, SPT, nasal scraping, rhinomanometry, and decongestion test were performed in all subjects. The study was approved by the Navy Hospital Institutional Review Board and an informed consent was obtained from the patients.

Skin prick test

It was performed, as stated by the European Society of Allergy and Clinical Immunology [14]. The panel consisted of: HDM (*Dermatophagoides farinae* and *pteronysinus*), cat, dog, grasses mix, Compositae mix, *Parietaria judaica*, birch, hazel, olive tree, *Alternaria Tenuis*, *Cladosporium*,

and *Aspergilli* mix (the concentration of the allergen extracts was 100 IR/mL Stallergenes, Milan, Italy).

Nasal symptoms

The following symptoms were assessed by the patient, answering the questions formulated by the investigator: nasal obstruction, sneezing, rhinorrhoea, and itchy nose. Each symptom was evaluated on the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep) as reported previously. Total symptom score (TSS, range 0–12) being the sum of each individual symptom was considered.

Nasal cytology

Nasal cytologic specimens were obtained by scraping the head of the inferior turbinate with a cotton swab, as described previously [11, 15]. Smears were stained with haematoxylin–eosin and were analysed using an optic microscope (Olympus U-SPT, Olympus Italy, Rome). The number of eosinophils was expressed as a mean of 10 optical fields at $\times 100$ magnification. Mild inflammation is defined by <5 eosinophils, and moderate–severe >5 as defined previously [11, 15].

Rhinomanometry

Nasal airflow was measured by active anterior electronic rhinomanometry (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete GmbH, Mainz, Germany) according to validated criteria [8–10].

Nasal airflow was considered as the sum of recorded airflow through the right and left nostrils, measured in mL/s at a pressure difference of 150 Pa across the nasal passage.

Decongestion test

It was performed as described previously [11, 15]. In brief, after baseline rhinomanometry, two puffs (100 μ L) of naphazoline 0.1% spray were then applied per nostril. Rhinomanometry was performed 5 and 10 min later. The best result was considered. Total nasal airflow volume and percentage of recovery were evaluated.

Quality of life

Health-Related Quality of Life (HRQL) assessment included the above-mentioned Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ); it consists of 28-items distributed into seven dimensions: sleep problems (three

items), non-hayfever symptoms (seven items), practical problems (three items), nasal problems (four items), eye symptoms (four items), activities (three items), and emotions (four items). Responses to the items are scored on a seven-point Likert scale, while dimensions and overall scores are scored on a 0–6 scale; the lower the score, the better the HRQL [16].

Statistical analysis mean and standard deviation (SD) or median and 25th–75th percentiles, and counts and percentages were computed to summarize continuous and categorical variables, respectively.

RQLQ summary scores were computed as the average of the items scores both for the global and for the single dimensions scores. The lower the score, the better the QoL. Decongestion was computed as the absolute difference between the nasal airflow (mL/s) measured before and after the decongestion test. For the purpose of the analysis, decongestion was categorized into two categories (high/medium–low), corresponding to a decongestion $>34\%$ with respect to baseline vs. $\leq 34\%$, respectively. Indeed, the optimal cut-off for defining responder to this test is an increase of 34% of baseline nasal airflow, as defined previously [12].

The association of QoL and continuous variables was measured by means of the Spearman R correlation coefficients; 95% confidence intervals (95% CI) were computed based on the Fisher transformation. The comparison of QoL between strata of a categorical variable was assessed with the Student t test. Differences in QoL scores between groups and 95% CI were computed. The test for trend was used to assess the association of QoL and symptoms score (measured on an ordinal 0–3 scale) [17]. Finally, multivariable regression models were fitted to identify independent determinants of QoL in its different scales. Non-collinear variables with a $P < 0.1$ at the univariable analysis were included in the model. The several models were informally compared by means of the explained variation (R^2 statistic). We verified model adequacy graphically by inspection of the residual.

Stata 9 (Stata Corp., College Station, TX, USA) was used for computation. A two-sided P -value < 0.05 was considered to be statistically significant. Bonferroni correction for multiple end-points was applied when assessing the seven QoL dimensions ($P < 0.0071$).

Results

Patients characteristics

One hundred and twenty-three subjects were included in the study. Their mean age was 23 years (SD 6). Forty were sensitized to pollens alone, 43 to perennial allergens alone, and 40 to both. The majority (90%) had polysensitization and 74 (60%) had sensitization to three or more allergens. The basal nasal airflow was measured to be 471 mL/s (SD 170); after the decongesting test, it was

Table 1. Patients characteristics

Characteristic	Value
Age (years)*	22.9 (5.7)
Basal nasal airflow (mL/s)*	470.9 (169.6)
Post-test nasal airflow (mL/s)*	579.9 (169.6)
Eosinophils (cell number) [†]	9 (6–13)
Number of sensitizations [†]	3 (2–5)
Total symptom score*	8.6 (1.4)
Global score QoL*	4 (0.7)
Activity*	4.3 (0.7)
Sleep*	3.9 (0.7)
General symptoms*	3.8 (0.6)
Practical problems*	4.1 (0.9)
Nasal symptoms*	4.8 (0.8)
Eye symptoms*	3.5 (1.5)
Emotions*	3.9 (0.8)

*Mean (SD).

[†]Median (25th–75th).

QoL, quality of life; SD, standard deviation.

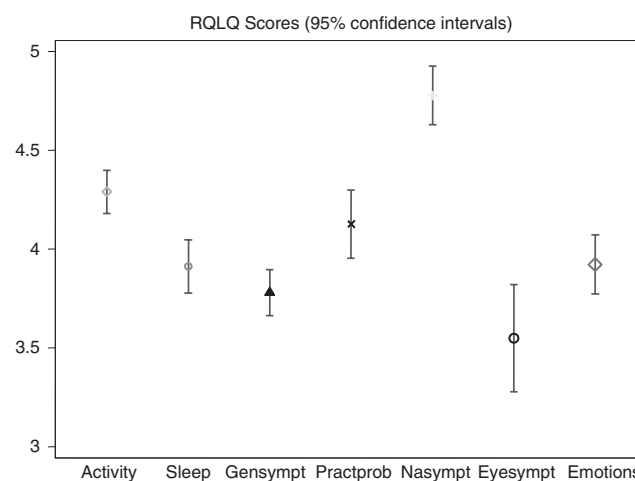


Fig. 1. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores (overall and for each of the seven scales). Mean values and their 95% confidence interval (CI) are reported.

580 mL/s (SD 160). Forty patients were classified as having a high decongestion level ($\geq 34\%$), according to our definition [14], as compared with 83, who were classified into the mid/low decongestion group, such as responders. Other patients characteristics are summarized in Table 1.

Quality of life

The overall RQLQ score was computed to be 4.0 (SD 0.7); scores for the other dimensions ranged from 3.5 to 4.8, as shown in Fig. 1.

Table 2. Determinants of QoL (univariable analysis)

Variable	Global score		Activity		Sleep		General symptoms	
	Effect (95% CI)	P-value	Effect (95% CI)	P-value	Effect (95% CI)	P-value	Effect (95% CI)	P-value
Baseline airflow*	-11% (-28 to 7)	0.228	-10% (-28 to 7)	0.247	-5% (-22 to 12)	0.558	-9% (-27 to 9)	0.324
Decongestion >34% [†]	0.31 (0.05-0.67)	0.02	0.1 (-0.15 to 0.35)	0.432	0.14 (-0.14 to 0.422)	0.322	-0.05 (-0.28 to 0.19)	0.7
Sensitizations >2*	-0.37 (0.62-0.13)	0.003	-0.15 (-0.38 to 0.07)	0.182	-0.37 (-0.64 to 0.11)	0.005	-0.2 (-0.43 to 0.03)	0.086
Eosinophils* (cell number)	40% (23-53)	<0.001	35% (18-49)	<0.001	11% (-7 to 28)	0.225	16% (-1.5 to 33)	0.072
Total symptom score*	12% (-6 to 29)	0.202	8% (-10 to 25)	0.383	11% (-6 to 29)	0.204	13% (-5 to 30)	0.153
	Practical problems		Nasal symptoms		Eye symptoms		Emotions	
Baseline airflow*	-18% (-35 to 1)	0.042	-12% (-29 to 6)	0.185	-6% (-24 to 11)	0.473	-4% (-21 to 14)	0.665
Decongestion >34% [†]	0.42 (0.05-0.8)	0.027	0.41 (0.1-0.72)	0.009	1.18 (0.63-1.73)	<0.001	0.36 (0.04-0.7)	0.03
Sensitizations >2*	-0.35 (-0.7 to 0.006)	0.054	-0.31 (-0.62 to 0.004)	0.053	-1.07 (-1.63 to -0.51)	<0.001	-0.40 (-0.71 to 0.1)	0.009
Eosinophils* (cell number)	38% (22-52)	<0.001	31% (14-46)	<0.001	51% (37-63)	<0.001	32% (16-47)	<0.001
Total symptom score*	14% (-4 to 31)	0.124	10% (-7 to 28)	0.251	8% (-10 to 25)	0.374	4% (-13 to 22)	0.616

For the seven dimensions of QoL: cut-off for statistical significance, after Bonferroni's correction, $P < 0.0071$ (underlined in the table).

*They are measured by the Spearman correlation coefficient R (95% CI) for continuous variables. A positive R corresponds to a worsening QoL for increases in the measured characteristic; a negative R corresponds to an increasingly better QoL for increases in the measured characteristic.

[†]Effects are measured with the difference in QoL score (95% CI) for categorical variables (based on Student t test). A positive difference corresponds to a better QoL in the presence of the measured characteristic, a negative difference to a worse QoL.

QoL, quality of life; CI, confidence interval.

Table 3. Association of the symptoms score and QoL, globally and for each scale (*P*-values of the test for trend are reported)

	Global score	Activity		Sleep		General symptoms		Practical problems		Nasal symptoms		Eye symptoms		Emotions			
		Score	M (SD)	P-value	M (SD)	P-value	M (SD)	P-value	M (SD)	P-value	M (SD)	P-value	M (SD)	P-value			
Sneezing	1	3.72 (0.73)	0.001	3.92 (0.51)	0.001	3.51 (0.73)	0.01	3.48 (0.66)	0.021	3.76 (0.97)	0.003	4.58 (0.8)	0.009	3.27 (1.47)	0.011	3.6 (0.92)	0.016
	2	3.54 (0.86)		4.27 (0.59)		3.89 (0.78)		3.78 (0.67)		3.99 (0.96)		4.61 (0.81)		3.24 (1.58)		3.85 (0.83)	
	3	4.29 (0.62)		4.47 (0.62)		4.10 (0.66)		3.90 (0.6)		4.48 (0.89)		5.1 (0.78)		4.13 (1.29)		4.16 (0.77)	
Itching	1	3.76 (0.67)	0.006	4.05 (0.59)	0.003	3.68 (0.88)	0.032	3.54 (0.63)	0.012	3.76 (0.95)	0.004	4.52 (0.78)	0.027	3.13 (1.27)	0.025	3.69 (0.83)	0.085
	2	4.12 (0.69)		4.38 (0.63)		4 (0.71)		3.87 (0.67)		4.21 (0.99)		4.86 (0.87)		3.64 (1.64)		4.04 (0.85)	
	3	4.25 (0.5)		4.47 (0.42)		4.08 (0.51)		3.93 (0.51)		4.58 (0.66)		5.01 (0.63)		4.06 (1.37)		3.94 (0.76)	
Rhinor.	1	3.88 (0.58)	0.235	4.10 (0.45)	0.114	3.79 (0.66)	0.207	3.73 (0.62)	0.767	3.92 (0.91)	0.281	4.64 (0.66)	0.710	3.27 (1.5)	0.343	3.75 (0.84)	0.279
	2	4.03 (0.6)		4.28 (0.59)		4.05 (0.82)		3.73 (0.61)		4.06 (0.68)		4.68 (0.74)		3.64 (1.3)		3.96 (0.86)	
	3	4.12 (0.75)		4.4 (0.68)		3.92 (0.77)		3.83 (0.68)		4.26 (1.07)		4.89 (0.93)		3.67 (1.6)		4 (0.83)	
Nasal obstruction	1	3.88 (0.64)	0.014	4.14 (0.55)	0.005	3.67 (0.56)	0.334	3.67 (0.6)	0.085	3.96 (0.96)	0.074	4.6 (0.72)	0.017	3.39 (1.43)	0.013	3.74 (0.8)	0.029
	2	4.21 (0.71)		4.48 (0.67)		3.79 (0.74)		3.84 (0.63)		4.21 (0.83)		4.99 (0.92)		3.6 (1.67)		4.06 (0.75)	
	3	4.24 (0.58)		4.5 (0.4)		4.14 (0.75)		3.93 (0.71)		4.36 (0.96)		5.09 (0.91)		4.67 (0.91)		4.17 (0.85)	

For the seven dimensions of QoL: cut-off for statistical significance, after Bonferroni's correction, $P < 0.0071$ (underlined in the table). QoL, quality of life; SD, standard deviation; M, mean.

Determinants of quality of life

The association of patients characteristics and QoL (global QoL and the seven scales) is summarized in Table 2, whereas the association of the symptoms score and QoL is reported in Table 3. A significantly better overall QoL was attained in patients with a decongestion $>34\%$ and in patients with less than; two sensitivities. Conversely, QoL significantly worsened with increasing levels of eosinophils. Higher symptom scores tended to be associated with lower QoL for sneezing, itching, and nasal obstruction.

When considering the single dimensions, patients with decongestion $>34\%$ had a significantly (after Bonferroni correction) higher QoL in the eye symptoms scale and marginally in the nasal symptoms scale. Patients with less than; two sensitivities had better QoL in the sleep and in the eye symptoms scales, and marginally in the emotion scale. Patients with higher eosinophils levels had a worse QoL in the activity, practical problems, nasal symptoms, eye symptoms, and emotion scales. Higher symptoms scores were significantly associated with lower QoL for sneezing in the activity, practical problems and (marginally) the nasal symptoms scales, for itching in the activity and practical problems scales, and for nasal obstruction in the activity scale.

The results of the multivariable analysis are summarized in Figs 2 and 3: having more than two sensitivities was a determinant of the global QoL, and of the sleep, the eye symptoms, and the emotions scales. The eosinophil count was significantly associated with global QoL and with the activity, practical problems, nasal symptoms, eye symptoms, and emotions scales. Finally, the baseline nasal flow (mL/s) was significantly associated with the eye symptoms scale only. No independent predictors of the sleep and of the general symptoms scales were identified. The best predictive model (with the highest explained variation: $R^2 = 0.38$) was obtained when assessing the eye symptoms scale, followed by the model for the global QoL ($R^2 = 0.20$) (see legend of Fig. 2).

Discussion

AR is characterized by an inflammatory response that causes the occurrence of symptoms. Particularly, nasal obstruction constitutes the symptom that expresses allergic inflammation more [8, 9, 14]. Nasal obstruction may be evaluated both subjectively by symptom scoring and objectively by airflow assessing. The limitation of the nasal airflow may be reversible to decongesting and the degree of recovery is associated with inflammatory grade [11, 14]. Moreover, allergic patients frequently present the polysensitization phenomenon that may affect the natural history of allergy. QoL evaluation represents an important step in the study of AR concerning both clinical and therapeutical trials. However, the impact of clinical,

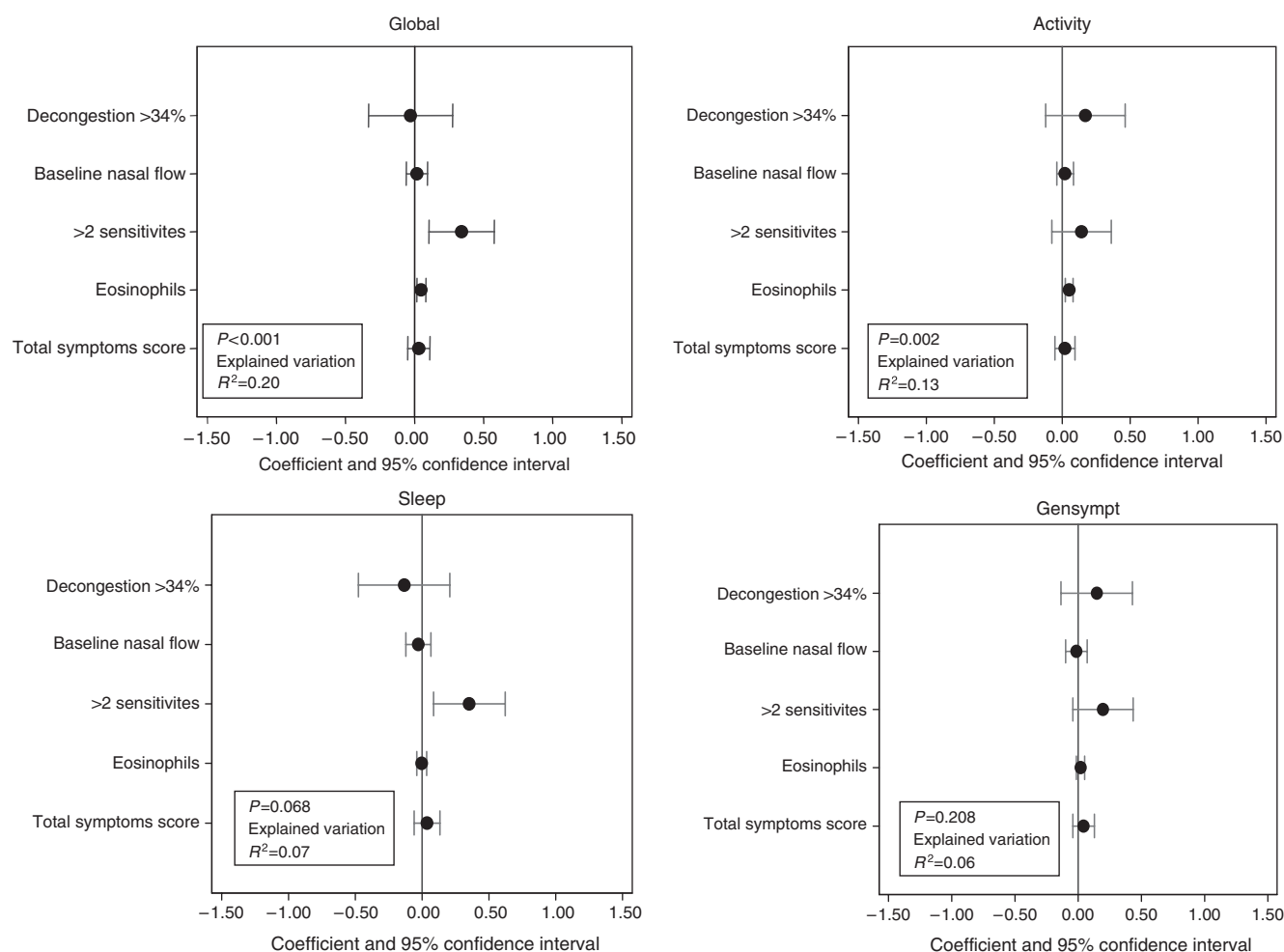


Fig. 2. Multivariable regression models to identify independent determinants of quality of life. Model statistics are summarized below: regression coefficients (dot) and their 95% confidence intervals (CIs) (horizontal segment) are plotted. The vertical line at 0 corresponds to the absence of effect. Ninety-five percent CIs not crossing this line denote independent predictors.

immunological, and functional aspects on QoL has been never investigated. Therefore, the aim of this study was to consider this issue in a cohort of patients with PER. However, the wash-out for medication might have led to exclusion of patients with severe rhinitis, not able to stop their medication. Thus, this cohort might be considered representative for moderate rhinitis.

The first finding confirms that RQLQ scores ranged between 3.5 and 4.8: values super-imposable to data in the literature.

Univariable determinants of QoL (globally and for some of the seven scales) were: decongestion (no response or response, such as change $<34\%$ or $\geq 34\%$ of baseline), number of sensitivities (less than 2 or more than 2), and eosinophil level, and among symptoms, sneezing itching, and nasal obstruction symptoms scores. These data underline the fact that QoL values are associated with many aspects of AR, mainly concerning allergic inflammation (eosinophils and recovery to decongesting), immune re-

sponse to allergens (sensitizations), and individual clinical status (symptoms severity).

Differences in QoL or strength of the association between patients characteristic and QoL are generally the most for the eye symptoms scale. This aspect highlights the importance of eye symptoms associated with AR as they are frequently very annoying and bothersome.

Moreover, multivariable analysis identifies the number of sensitivities and eosinophils count as independent determinants of QoL (globally and for some scales) and baseline nasal flow as an independent determinant of the eye symptoms scale. Therefore, QoL appears to be dependent on the degree of immune response to allergens.

Limits of the study

Although a significant association has been shown between a series of objective measurements and some QoL scales, the size of these associations was generally small to

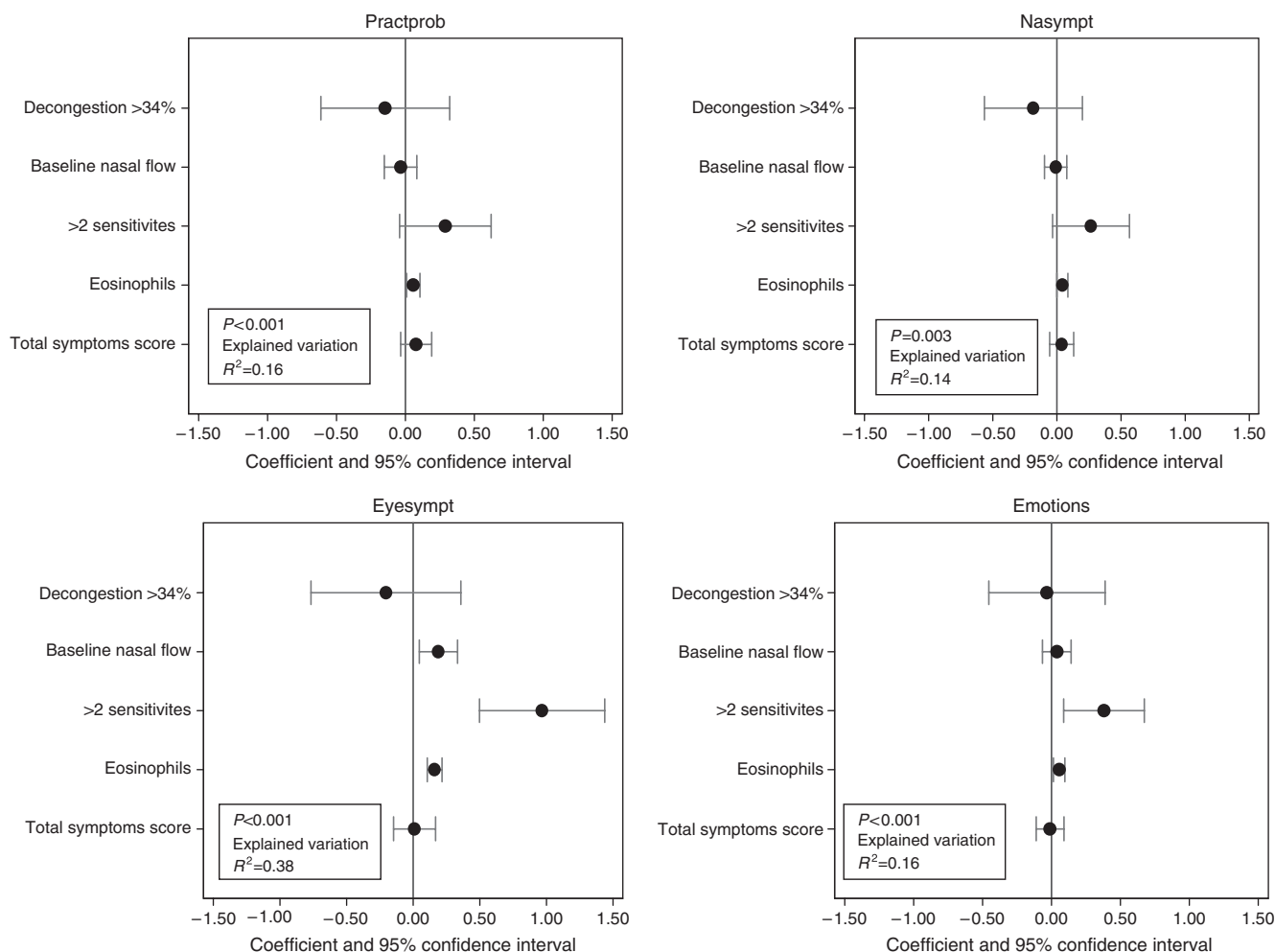


Fig. 3. Multivariable regression models to identify independent determinants of quality of life. Model statistics are summarized below: regression coefficients (dot) and their 95% confidence intervals (CIs) (horizontal segment) are plotted. The vertical line at 0 corresponds to the absence of effect. Ninety-five percent CIs not crossing this line denote independent predictors.

moderate (1 unit in the QoL 0–6 scale being the largest difference for categorical variables, 50% the strongest correlation for continuous variables, and 34% the explained variation at the multivariable analysis in the eye symptoms scale). However, this is not surprising, because QoL measurements have been put forward as a tool to cover other aspects of disease than conventional or biological tests do.

In conclusion, this study provides the first evidence that QoL in AR is strictly associated with allergic inflammation and eye symptoms significantly contribute towards impairing QoL.

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