Determination of the chronic upper airway inflammatory phenotype using a symptom-score-based algorithm*

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Dear Editor:

Allergic rhinitis (AR), non-allergic rhinitis (NAR), and chronic rhinosinusitis (CRS) are distinct yet prevalent phenotypes of chronic upper airway inflammation [(1)]. The golden standard for diagnosis currently consists of history taking, clinical (endoscopic) examination, skin prick testing, and – if indicated – computed tomography.

Ten percent of primary care consultations is about upper airway symptoms [(2)]. Diagnostic differentiation is important for targeted treatment. However, general practitioners are not trained in performing nasal endoscopy and patients often need referral for specialized investigations. Practical diagnostic tools that can be used in primary care would therefore be useful in daily practice. Patient questionnaires, often used in epidemiologic studies, are useful tools to collect patient data and to assess disease-severity [(3)] and/or quality of life [(4)]. Unfortunately, only few questionnaires, mainly for AR, are developed to assess upper airway pathology [(5–7)]. No diagnostic questionnaires have been developed for NAR or CRS.

In our recently published study on prevalence of nasal hyperreactivity, patients with otorhinolaryngologist-diagnosed chronic upper airway inflammation scored symptom-severity on a 100 mm long visual analogue scale (VAS) [(8)]. Patients were excluded in case of relevant nasal structural abnormalities, such as major septal deviation. AR was diagnosed in case of a positive skin prick test with nasal symptoms compatible with the identified sensitization (284 patients), NAR in case of persistent symptoms in absence of allergy or endoscopic signs of rhinosinusitis (112 patients), and CRS in case of long-lasting nasal obstruction and/or rhinorrhea, with or without facial pain or loss of smell, together with endoscopic signs of sinonasal inflammation (328 patients) (Table S1). Multiple conditions were present simultaneously in 147 patients. In this large cohort, VAS-score profiles were visually distinct across the different phenotypes, with for example more severe itch and sneezing in AR and more olfactory dysfunction and headache/facial pressure in CRS (Figure 1A).

We hypothesized that symptom-specific VAS-scores could be used to predict the chronic upper airway inflammatory phenotype.

The reported VAS-scores and clinical diagnoses – based on history taking, clinical examination, skin prick test, and computed tomography – were used to develop a diagnostic tool. The least absolute shrinkage and selection operator model was used to select the optimal set of VAS-scores for diagnosis classification. Methods are detailed in the online supplement.

Scores for AR, NAR, and CRS were calculated for each patient by the Formulas 1, 2, and 3.

$$\begin{aligned}\text{ARscore} = {} & -0.3369 + 0.0001 * \text{VAS}_{\text{Nasal obstruction}} + 0.0092 * \text{VAS}_{\text{Nasal itch}} + 0.002 \\ & * \text{VAS}_{\text{Sneezing}} + 0.0047 * \text{VAS}_{\text{Itchy eyes}} - 0.0039 \\ & * \text{VAS}_{\text{Headache/facial pressure}}\end{aligned}$$

(Formula 1)

$$\begin{aligned}\text{NARscore} = {} & -1.8797 + 0.023 * \text{VAS}_{\text{Total nasal symptoms}} + 0.0088 \\ & * \text{VAS}_{\text{Nasal obstruction}} + 0.0119 * \text{VAS}_{\text{Rhinorrhea}} - 0.0076 \\ & * \text{VAS}_{\text{Postnasal drip}} - 0.0039 * \text{VAS}_{\text{Nasal itch}} - 0.0113 * \text{VAS}_{\text{Sneezing}} \\ & - 0.0075 * \text{VAS}_{\text{Headache/facial pressure}} - 0.0218 * \text{VAS}_{\text{Loss of smell}}\end{aligned}$$

(Formula 2)

$$\begin{aligned}\text{CRSscore} = {} & 0.0359 + 0.0123 * \text{VAS}_{\text{Postnasal drip}} + 0.0161 * \text{VAS}_{\text{Headache/facial pressure}} \\ & + 0.0258 * \text{VAS}_{\text{Loss of smell}} - 0.005 * \text{VAS}_{\text{Total nasal symptoms}} - 0.0188 \\ & * \text{VAS}_{\text{Nasal obstruction}} - 0.0029 * \text{VAS}_{\text{Rhinorrhea}} - 0.008 * \text{VAS}_{\text{Nasal itch}} \\ & - 0.0017 * \text{VAS}_{\text{Sneezing}} - 0.0131 * \text{VAS}_{\text{Itchy eyes}}\end{aligned}$$

(Formula 3)

The predicted probability (P) of a specific patient having a particular diagnosis was calculated by Formula 4.

$$\text{P} = \frac{\exp(\text{score})}{1 + \exp(\text{score})}$$

(Formula 4)

In our cohort, the diagnosis (AR/NAR/CRS) with the highest predicted probability correlated with the clinical diagnosis in 69.6% of the cases. In patients with a mixed phenotype, the diagnosed phenotypes had the highest and second highest predicted probability in 83.7% of the cases (Figure 1B). Nasal hyperreactivity did not aid differentiation between AR, NAR, and CRS.

Although it was no objective of the initial study and patients with (anatomical) pathologies contributing to nasal symptoms were excluded, the interesting observation that a model could be created based on just 9 VAS-scores illustrates the power of well-targeted questions. This observation opens doors for future studies where models with an even higher predictive accuracy could be obtained by carefully selecting and attributing weight to the correct questions. Indeed, our questionnaire did not include questions on, for example, the seasonal variation, previous personal or familial diagnosis of atopy, or the effect of medications already used.

Such practical tools could facilitate diagnosing patients when clinical/technical examination of the patient is limited, such as in tele-consultation. Additionally, they could be used by non-ENT clinicians, who often are not trained in performing a rhinological examination or lack access to required tools (e.g. endoscopy/skin prick test). To this end, the currently presented model illustrates the concept of symptom-score-based algorithmic differentiation of disease phenotypes yet requires further validation. Production of a clear-cut, validated, and ready-for-use algorithm was beyond the scope of our report. Rather, we here present

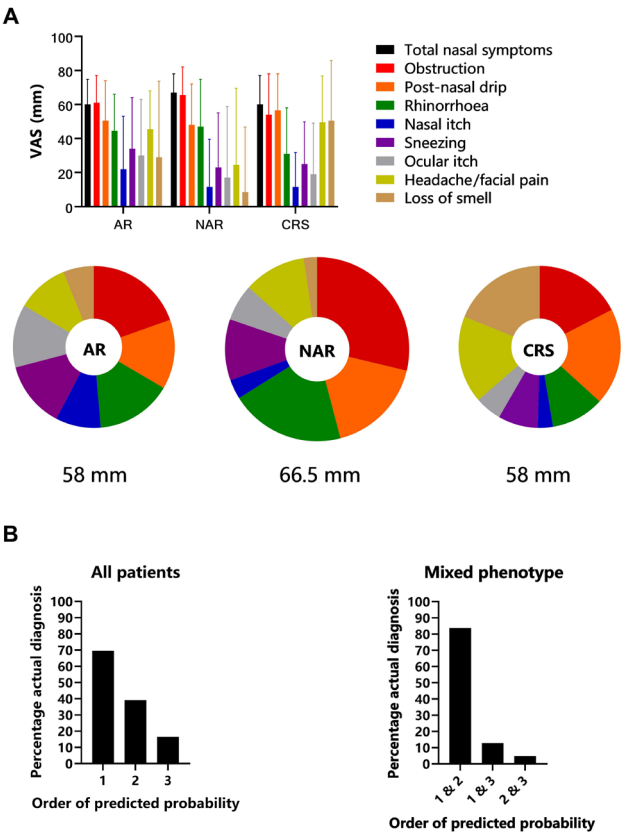

Figure 1. Weight of each symptom in different phenotypic patient groups and diagnostic accuracy of the model. A) Bar chart (median and interquartile range) and pie charts of the VAS scores across different phenotypic groups. The pie charts are built up from the median VAS-scores for every symptom. One hundred percent of the pie equals the sum of the symptom-specific medians. Or, 100 % of the pie = median($\text{VAS}_{\text{obstruction}}$) + median($\text{VAS}_{\text{post-nasal drip}}$) + median($\text{VAS}_{\text{rhinorrhoea}}$) + median($\text{VAS}_{\text{nasal itch}}$) + median($\text{VAS}_{\text{sneezing}}$) + median($\text{VAS}_{\text{ocular itch}}$) + median($\text{VAS}_{\text{headache/facial pain}}$) + median($\text{VAS}_{\text{loss of smell}}$). The median VAS-score for total nasal symptoms is indicated below each pie chart. B) The percentage of cases where the actual clinical diagnosis had the highest, middle, or lowest predicted probability in all patients and specifically in patients with mixed phenotype. AR: allergic rhinitis, NAR: non-allergic rhinitis, CRS: chronic rhinosinusitis.

a new concept as illustration and inspiration for future studies where such use of statistics and automated computation is the primary goal (Figure S1). Lastly, implementation of such questionnaires in mobile e-health applications could generate large data sets, serving to develop more potent algorithms based on machine learning [9].

In conclusion, based on symptom-specific VAS-scores and clinical diagnosis by thorough clinical and technical examination, we developed an illustrative diagnostic algorithm which helps to differentiate patients with chronic upper airway inflammation in

various phenotypic subgroups.

Abbreviations

AR: allergic rhinitis; NAR: non-allergic rhinitis; CRS: chronic rhinosinusitis; VAS: visual analogue scale.

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Authorship contribution

WB, PH, LVG: study design and conception, data collection, data interpretation, drafting the article, and revising the article for important intellectual content. MJ: Data collection and revising the article for important intellectual content. IG: Statistical analysis and revising the article for important intellectual content. RS: Initial study proposal, data interpretation and revising the article for important intellectual content. BS, KT: Data interpretation, drafting the article, and revising the article for important intellectual content.

Conflict of interest

The authors declare no conflict of interest.

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This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

Supplement methods

Study design, participants, and outcome parameters

Six hundred and five otorhinolaryngologist-diagnosed patients filled-out a questionnaire encompassing questions on symptom severity. The study was approved by the Ethical Committee Research of University Hospitals Leuven (S62213) and registered on clinicaltrials.gov (NCT03893227).

Patients with chronic upper airway inflammation were defined as having upper airway symptoms persisting for at least 1 hour per day for 12 weeks or longer in absence of anatomical causes. Patients were aged 18-65 years old and were diagnosed with allergic rhinitis (in case of a positive skin prick test and a pattern of nasal symptoms compatible with the atopic sensitizations identified), non-allergic rhinitis (in case of persistent symptoms of upper airway inflammation and inflammation limited to the nasal cavity and negative skin prick tests or symptoms not compatible with the atopic sensitization), or chronic rhinosinusitis according to the EPOS-guidelines (inflammation of the nose and paranasal sinuses characterized by two or more symptoms of which at least one is nasal obstruction or rhinorrhea, with or without facial pain or loss of smell, together with endoscopic signs of sinonasal inflammation and/or mucosal changes within the ostiomeatal complex or sinuses) [1].

The severity of various rhinological symptoms were indicated on a 100 mm long line, resulting in a visual analogue scale (VAS)-score ranging from 0 to 100. Twenty-nine patients of whom one or more VAS-scores were missing were excluded from analysis.

Statistical methods

To describe and compare patient characteristics, continuous variables were tested with Kruskal-Wallis test with post-hoc Dunn's multiple comparisons test and proportions were compared with a chi-square test. P-values were considered significant if $p < 0.05$.

The least absolute shrinkage and selection (LASSO) models were used to select the optimal set of VAS scores for diagnosis classification. The LASSO model is a shrinkage method which minimizes the regression coefficients to avoid overfitting, forcing the coefficients towards 0 and select the non-zero variables as the optimal predictors. In this way, the potential multicollinearity is avoided, and a variable selection is performed including the more relevant predictors.

The LASSO models were performed for each diagnosis including all VAS scores by using GLMNET package in R version 4.0.2 (R-Studio, Boston, MA) [2]. We used 10-fold cross-validation step for hyper-parameter tuning for the shrinkage parameter for LASSO model. Subsequently, the logistic LASSO regression coefficients of selected covariates were used to calculate the risk score as a measure of the probability of having diagnosis for each patient. Twenty-six percent of the patients exhibited a mixed phenotype, restricting to fit a multinomial model with three diagnoses.

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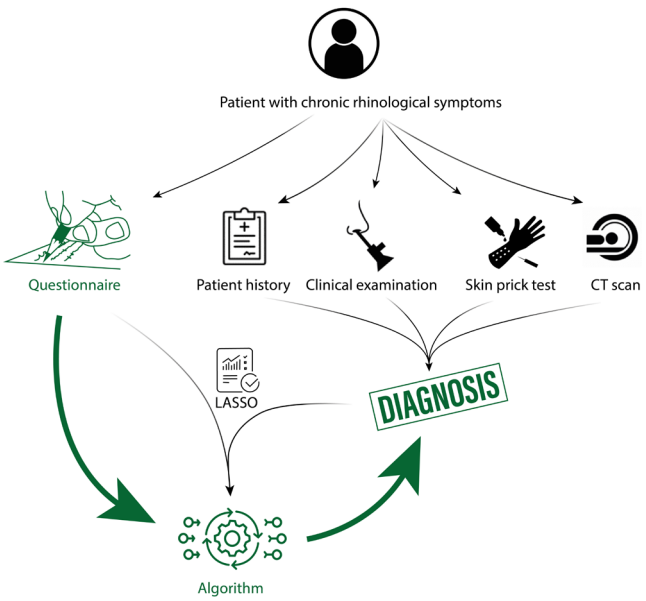


Figure S1. Overview of the methodological principle. From each patient, we collected the symptom-specific VAS-scores by means of a questionnaire. Clinical diagnosis was made by an otorhinolaryngologist based on patient history, clinical examination including nasal endoscopy, skin prick testing, and computed tomography. We then developed a diagnostic algorithm based on symptom-specific VAS-scores only, bypassing the need for full clinical work-up.

Table S1. Patient characteristics.

	AR (N=141)	NAR (N=93)	CRS (N=195)	Mixed phenotype (N=147)				P-value
				AR+NAR (N=14)	AR+CRS (N=128)	NAR+CRS (N=4)	AR+NAR+CRS (N=1)	
Age (years) (IQR)	32 (25-44)	43 (31-55)	51 (36-59)	51 (36-58)	41 (33-52)	44 (26-59)	49	<0.0001†
Male/female	76/65	43/50	130/65	7/7	78/50	0/4	0/1	0.0028 ‡
Smokers (%)	23 (16.3)	11 (11.8)	35 (17.9)	0 (0)	17 (13.3)	1 (25.0)	0 (0)	NS ‡
Allergy (%)								
House dust mite	92 (65.2)	0 (0)	0 (0)	6 (42.9)	88 (68.8)	0 (0)	0 (0)	<0.0001‡
Tree-/grass pollen	103 (73.0)	0 (0)	0 (0)	9 (64.3)	92 (71.9)	0 (0)	1 (100)	<0.0001‡
Animals	56 (39.7)	0 (0)	0 (0)	4 (28.6)	42 (32.8)	0 (0)	0 (0)	<0.0001‡
Fungi	11 (7.8)	0 (0)	0 (0)	5 (35.7)	10 (7.8)	0 (0)	0 (0)	<0.0001‡
Nasal polyps (%)	0 (0)	0 (0)	107 (54.9)	0 (0)	81 (63.3)	0 (0)	0 (0)	<0.0001‡
VAS total nasal symptoms (mm) (IQR)	58 (42-74)	65 (48-78)	59 (30-77)	70 (46-77)	62 (42-78)	73 (67-79)	93	NS†
Medication use last 3 months (%)	131 (92.9)	80 (86.0)	184 (94.4)	14 (100)	124 (96.9)	4 (100)	1 (100)	NS‡
History of rhinological surgery or trauma	35 (24.8)	38 (40.9)	106 (54.4)	5 (35.7)	66 (51.6)	1 (25.0)	0 (0)	<0.0001‡

† Mann-Whitney test, ‡ Chi square test. AR: allergic rhinitis; NAR: non-allergic rhinitis; CRS: chronic rhinosinusitis; IQR: interquartile range; VAS: visual analogue scale.

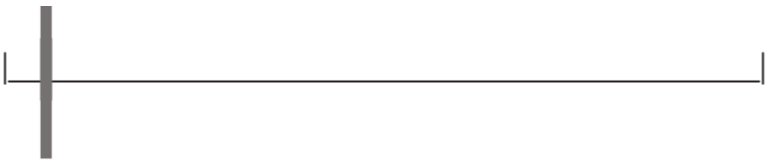
Symptom severity scales

Please indicate with a vertical line on the scale to which degree you suffered from the following symptoms in the past three months:

Example: If you did not suffer a lot from a blocked nose, your score could look like this:

Blocked nose:

No *Very severe*



- Severity of the total nasal symptoms:

No *Very severe*

- Blocked nose:

No *Very severe*

- Phlegm at the back of the throat:

No *Very severe*

- Runny nose:

No *Very severe*

|_____|

- Itchy nose:

No *Very severe*

|_____|

- Sneezing:

No *Very severe*

|_____|

- Itchy eyes:

No *Very severe*

|_____|

- Headache or facial pressure:

No *Very severe*

|_____|

- Loss of smell:

No *Very severe*

|_____|