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ORIGINAL ARTICLE

Rhinitis, Sinusitis and Upper Airway Disease

Development and validation of combined symptom-medication scores for allergic rhinitis*

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Abstract

Background: Validated combined symptom-medication scores (CSMSs) are needed to investigate the effects of allergic rhinitis treatments. This study aimed to use real-life data from the MASK-air® app to generate and validate hypothesis- and data-driven CSMSs.

Methods: We used MASK-air® data to assess the concurrent validity, test-retest reliability and responsiveness of one hypothesis-driven CSMS (modified CSMS: mCSMS), one mixed hypothesis- and data-driven score (mixed score), and several data-driven CSMSs. The latter were generated with MASK-air® data following cluster analysis and regression models or factor analysis. These CSMSs were compared with scales measuring (i) the impact of rhinitis on work productivity (visual analogue scale [VAS] of work of MASK-air®, and Work Productivity and Activity Impairment: Allergy Specific [WPAI-AS]), (ii) quality-of-life (EQ-5D VAS) and (iii) control of allergic diseases (Control of Allergic Rhinitis and Asthma Test [CARAT]).

Results: We assessed 317,176 days of MASK-air® use from 17,780 users aged 16-90 years, in 25 countries. The mCSMS and the factor analyses-based CSMSs displayed poorer validity and responsiveness compared to the remaining CSMSs. The latter displayed moderate-to-strong correlations with the tested comparators, high test-retest reliability and moderate-to-large responsiveness. Among data-driven CSMSs, a better performance was observed for cluster analyses-based CSMSs. High accuracy (capacity of discriminating different levels of rhinitis control) was observed for the latter (AUC-ROC = 0.904) and for the mixed CSMS (AUC-ROC = 0.820).

Conclusion: The mixed CSMS and the cluster-based CSMSs presented medium-high validity, reliability and accuracy, rendering them as candidates for primary endpoints in future rhinitis trials.

KEYWORDS
medication score, quality-of-life, rhinitis, symptom score, work

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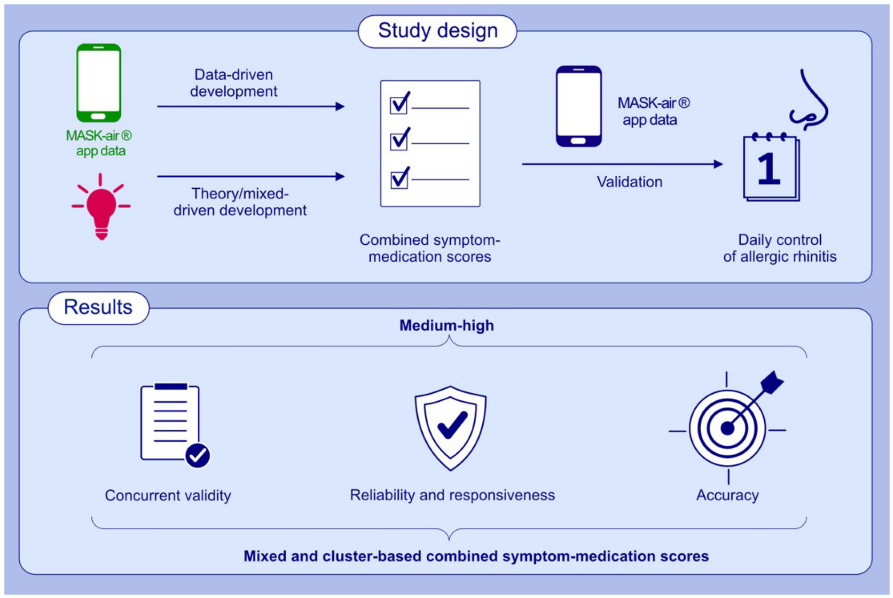

GRAPHICAL ABSTRACT

This study assessed 317,176 days of MASK-air® (Mobile Airways Sentinel NetworK) use from 17,780 users aged 16-90 years, in 25 countries. Real-world data obtained with the MASK-air® app were used to develop combined symptom-medication scores to assess the daily control of allergic rhinitis. These scores had medium-high validity, reliability and accuracy, rendering them as candidates for clinical practice, and for primary endpoints in future rhinitis trials and observational studies.

1 | INTRODUCTION

Validated symptom-medication scores (SMSs) are needed to investigate the effect of allergic rhinitis (AR) treatments, particularly—but not only—allergen immunotherapy (AIT).[1,2] The European Academy of Allergy and Clinical Immunology (EAACI) defined the Combined Symptom and Medication Score (CSMS) as the harmonized standard for the primary endpoints for AIT trials.[3] However, this endpoint has not been validated prospectively, even if it has been identified as an important unmet need in the EAACI Position Paper for clinical outcomes in AIT trials[3] and in the subsequent collaboration of AIT experts.[4] Mobile health-based approaches may contribute to addressing this problem. MASK-air® (Mobile Airways Sentinel NetworK) is an example of such an approach. This app has a monitoring questionnaire which assesses the daily impact of allergic symptoms (as well as medication use) on the user.[5–7] A recent MASK-air® study has assessed a modified CSMS approach following the approval of new medications (mCSMS).[3,8] While the mCSMS is hypothesis-driven, mobile health data can also be used to generate data-driven SMSs. In the absence of a true gold standard, the creation and validation of a new SMS may involve comparison with scales measuring the impact of AR, particularly through endpoints such as work productivity and quality-of-life.[9,10]

After an automatic search (Antó A, in revision), it was found that a limited number of apps can be used to validate and/or generate a mobile health-based SMS since such apps need to (i) include questions on symptoms and medications, (ii) retrieve data on work productivity, quality-of-life or other impact outcomes, (iii) be multilingual and (iv) have a large number of users to allow analyses in different countries. While three apps were found to fulfil these requirements - Allergymonitor,[11,12] Pollen (Austria)[13] and MASK-air®[5–7] - the latter was the only one (i) with a published thorough methodological evaluation, (ii) which uses a list with all medications customized for each country and (iii) which includes several quality-of-life and work scales that can be used as endpoints to validate SMSs. Furthermore, it has been implemented in over 40,000 users, allowing sensitivity analyses in different countries.

The aim of the study was to assess the validity, test-retest reliability, and responsiveness of two SMSs, as well as to generate and validate data-driven SMSs using the MASK-air® data.

2 | METHODS

2.1 | Study design

We assessed different types of SMSs including one hypothesis-driven score (mCSMS), one mixed hypothesis- and data-driven score (mixed score), and several data-driven SMSs generated with MASK-air® data following different approaches. The data-driven SMSs were developed *de novo* in this study, with different methodological approaches being used given the absence of a single gold standard (i) measure of the daily control of AR and (ii) method of analysis. For each SMS, we assessed concurrent validity, test-retest reliability and responsiveness. We used (i) quality-of-life (EQ-5D visual analogue scale [VAS] and the ninth question of the Work Productivity and Activity Impairment: Allergic Specific [WPAI:AS]—'degree allergy

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affected regular activities'—herein described as 'WPAI:AS activities'), (ii) work (MASK-air® VAS Work, and 'WPAI:AS Work'—that is 'percent overall work impairment due to allergy', as estimated based on three WPAI:AS questions) and (iii) control of allergic diseases (Control of Allergic Rhinitis and Asthma Test—CARAT) as comparators. This study follows the COSMIN standards.[14]

2.2 | Setting and participants

MASK-air® has been available since 2015 and currently exists in 25 countries (www.mask-air.com). We included the daily monitoring data from MASK-air® users aged 16–90 years with a diagnosis of allergic rhinitis. Sensitivity analyses were performed with data from the European and non-European users of the MASK-air® dataset.

2.3 | Data sources and variables

We analysed MASK-air® data from 21 May 2015 to 6 December 2020. MASK-air® comprises six mandatory symptom daily monitoring questions whose responses are provided by means of VASs (0–100 scales, with higher values indicating worse symptoms) on overall, nasal, ocular and asthma symptoms (Table S1). In addition, if users report that they are working, they are asked 'how much allergic symptoms affected work activities on that day' (VAS Work).[8,15,16] Then, users are asked to provide their daily medication using a regularly updated scroll list customized for each country and including all over-the-counter and prescribed AR medications.[17] VAS Work, along with other MASK-air® VASs, has been assessed using MASK-air® data on its validity, reliability and responsiveness.[18]

When responding to the MASK-air® daily monitoring questionnaire, it is not possible to skip any of the questions. The data are saved in the dataset only after the final answer, which precludes missing data.

In addition to symptom daily monitoring, MASK-air® users may respond (albeit in a non-mandatory way) to the other questionnaires that were used in this study as SMS comparators:

- *EQ-5D-5L* assesses the respondents' health status through five dimensions/questions (each with five levels) followed by a VAS assessing the general health status on that day.[19] The EQ-5D-5L has been widely assessed (in different populations) on its validity, reliability, discriminatory power and feasibility, displaying a better performance than previous health status questionnaires, particularly regarding mild health problems.[19,20] In this study, we only used the EQ-5D-VAS as a comparator.
- *CARAT* is a ten-item questionnaire, resulting in a score assessing the control of allergic rhinitis and asthma in the previous four weeks.[21] CARAT has demonstrated that it displays a high internal consistency, concurrent validity, test-retest reliability and responsiveness.[21,22] While initially developed and tested on Portuguese patients with AR and asthma, CARAT has been translated and validated in several other populations.[23,24]

Research in context

Evidence before this study: Validated combined symptom-medication scores (CSMSs) are needed to investigate the effects of allergic rhinitis treatments and are requested by the European Medicines Agency. However, existent CSMSs are poorly validated. In fact, based on a MEDLINE search in April 2021, we found that a hypothesis-driven CSMS has been developed with the goal of being a standard endpoint for immunotherapy trials in patients with allergic rhinitis. This CSMS has not yet been fully validated, only correlated with the impact of allergic rhinitis on work productivity, with moderate results. A modified version of the CSMS has also been proposed, following the approval of new medications, but the correlations with patient-reported outcomes were moderate. None of these existing CSMSs were generated through a data-driven approach. In fact, both the original and modified versions were computed by the average of a symptom score (assessing the severity of allergic rhinitis symptoms) and a medication score (considering the medication classes used by the patient). Valid and reliable scores are therefore needed to combine patients' symptoms and medications, and to be used as endpoints.

Added value of this study: In this study, we used real-world data (obtained with an app) from patients with allergic rhinitis to generate data-driven CSMSs as well as to assess their validity, test-retest reliability and responsiveness. Such properties were also assessed for a hypothesis-driven CSMS and for a mixed hypothesis- and data-driven CSMS (mixed CSMS). We assessed data corresponding to 317,176 days of MASK-air® use from 17,780 users in 25 countries. The mixed CSMS and most of the data-driven CSMSs were found to have moderate-to-strong validity, high test-retest reliability and moderate-to-large responsiveness. The best-performing data-driven CSMS was also found to have high accuracy (AUC-ROC = 0.904), with values<15.8 (on a 0–100 scale) indicating good AR control, and values >35.3 indicating worse AR control.

Implications of all the available evidence: The developed and assessed CSMSs form a bridge between clinical practice (namely patient-centred care and shared decision-making), randomized control trials, and real-life observational studies for medications and allergen immunotherapy. For example, CSMSs can be used to stratify patients for allergen immunotherapy and to follow them during the course of their treatment. This has the potential for improving the efficacy of allergen immunotherapy (as well as of other allergic rhinitis treatments) and can even have a relevant impact on reimbursement strategies.

- *WPAI:AS* is a 9-item questionnaire assessing the impact of allergies on work and academic productivity over the last week.[25,26] This questionnaire has been assessed on its validity, reproducibility

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and responsiveness in AR patients participating in a clinical trial.[27] Both 'WPAI:AS Work' and 'WPAI:AS activities' have been used as comparators in this study.

2.4 | Symptom-medication scores

2.4.1 | mCSMS

The mCSMS was computed as previously published[8] (Table S2).

2.4.2 | Mixed CSMS

The mixed CSMS is a mixed hypothesis- and data-driven score, which is calculated by multiplying VAS Global allergy symptoms by a medication factor. The rationale of the data-driven score follows real-life data obtained in MASK-air®[28,29]: (i) medications have a variable effect, (ii) there is a reduction in the efficacy of medications when VAS Global allergy symptoms increases and (iii) co-medication is surprisingly not very effective.[17,28,29] Thus, it was proposed that when VAS Global allergy symptoms were under 50/100, H1-antihistamines (by any route) increased the score by 10%, intranasal corticosteroids by 25%, azelastine-fluticasone intranasal formulation by 50%, systemic corticosteroids by 70% and other medications by 10%. Co-medication increased the score by an added 10%. For VAS ranging from 50 to 75/100, the increment was divided by two; while for VAS over 75/100, the increment was divided by four. An example is given in Table S3.

2.4.3 | Cluster-based scores

K-means cluster analysis was performed to automatically identify groups of observations with different levels of AR control/impact. Therefore, clusters were defined according to (i) VAS Work and EQ-5D-VAS values simultaneously (ie comparators assessing a single day) and (ii) CARAT and 'WPAI:AS activities' values simultaneously (ie comparators assessing a period longer than a single day). For each analysis, an optimal number of five clusters were identified (Figure S1).

Computation of the SMSs was then accomplished using multivariable regression models. The regression coefficients obtained with each model were those used in each respective SMS (Table 1). For the multivariable regression models, the dependent variable was based on the results of the k-means cluster analysis, and the covariates—including the daily monitoring VASs and medication variables—were selected according to statistical and clinical criteria. We built three different SMSs for each cluster-based approach:

- *Worst-controlled versus remainder*: This score was developed by applying multivariable logistic regression models with the dependent variable consisting of a binary variable differentiating the worst-controlled cases (as identified by k-means cluster analysis) *versus* the remainder.
- *Best-controlled versus remainder*: This score was developed by applying multivariable logistic regression models with the dependent variable consisting of a binary variable differentiating the best-controlled cases *versus* the remainder.
- *Three/five control classes*: This score was developed by applying ordinal logistic regression models with the dependent variable consisting of differentiating between three levels of control (clusters defined based on VAS Work and EQ-5D-VAS) or five levels (clusters defined based on CARAT and 'WPAI:AS activities').

2.4.4 | Linear regression-based scores

We built multiple linear regression models. The dependent variable corresponded to the average of VAS Work and EQ-5D VAS, and the independent variables corresponded to VAS Global allergy symptoms along with the medication classes used (grouped as in the mixed CSMS). The regression coefficients obtained with each multiple linear model were those used in each respective SMS (Table 1).

In accordance with the rationale underlying the mixed CSMS, an additional linear regression-based score was computed, following an alternative approach. We started by identifying cut-off points for VAS Global allergy symptoms based on their association with AR control (as defined by the average of VAS Work and EQ-5D VAS), using k-means cluster analysis methods. We automatically identified three VAS Global allergy symptom intervals: VAS<25; 25≤VAS<60; VAS≥60. For each interval, we computed a multiple linear regression model, with the dependent variable corresponding to the average of VAS Work and EQ-5D VAS, and the independent variables corresponding to VAS Global allergy symptoms and all medication classes (as grouped in the mixed CSMS). The regression coefficients obtained with each multiple linear model were those used in each respective SMS (Table 1).

2.4.5 | Factor analysis-based scores

A first factor analysis was performed with all symptoms and medication variables. Four factors were identified with eigenvalues >1. Each variable with a loading >0.25 was subsequently weighted by its loading on the respective factor, with the creation of four new variables (each representing one factor). These new variables were subject to a second-level factor analysis, with definition of a single factor. Therefore, for the computation of the SMS coefficients, each variable was weighted by its loading on the respective factor times the loading that the factor had on the second-level factor analysis (Table 1).

2.5 | Biases

Potential information biases were addressed by restricting our analyses to data from users with self-reported AR. We addressed

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TABLE 1 Formulae for computation of data-driven symptoms and medication scores

Cluster-based scores (clusters defined based on VAS Work and EQ−5D VAS)
Worst-controlled versus remainder [(0.059 × VAS Global Symptoms) + (0.006 × VAS Eyes) + (0.018 × VAS Asthma) + (−1.662 if ocular antihistamines are used) + (−0.055 if MPAzeFlu is used) + (−0.297 if oral antihistamines are used)] ×12.048
Best-controlled versus remainder [(0.037 × VAS Global Symptoms) + (0.033 × VAS Eyes) + (0.020 × VAS Nose) + (0.027 × VAS Asthma) + (0.450 if MPAzeFlu is used) + (0.424 if nasal steroids are used) + (0.243 if asthma medication is used) + (0.380 if other rhinitis relief medication is used)] ×7.577
Three control classes [(0.050 × VAS Global Symptoms) + (0.017 × VAS Eyes) + (0.012 × VAS Nose) + (0.015 × VAS Asthma) + (0.003 × VAS Sleep) + (0.201 if MPAzeflu is used) + (0.799 if nasal steroids are used) + (0.388 if asthma medication is used) + (−0.477 if oral antihistamines are used)] ×9.019
Cluster-based scores (clusters defined based on CARAT and 'WPAI:AS activities')
Worst-controlled versus remainder [(0.033 × VAS Global Symptoms) + (0.011 × VAS Eyes) + (0.023 × VAS Asthma) + (0.008 × VAS Sleep) + (0.652 if MPAzeFlu is used) + (0.765 if nasal steroids are used) + (−0.571 if oral antihistamines are used)] ×11.215
Best-controlled versus remainder [(0.037 × VAS Global Symptoms) + (0.018 × VAS Eyes) + (0.014 × VAS Asthma) + (0.242 if MPAzeFlu is used) + (0.144 × if oral antihistamines are used)] ×13.725
Five control classes [(0.035 × VAS Global Symptoms) + (0.011 × VAS Eyes) + (0.011 × VAS Asthma) + (0.008 × VAS Sleep) + (0.562 if MPAzeflu is used) + (0.521 if nasal steroids are used) + (−0.181 if oral antihistamines are used) + (−0.502 if other rhinitis relief medications are used)] ×13.187
Linear regression-based scores
Single model [(0.5 × VAS Global Symptoms) + (1.6 if nasal steroids are used) + (−1.7 if ocular antihistamines are used) + (1.1 if MPAzeFlu is used) + (−0.2 if oral antihistamines are used) + (1.5 if other rhinitis relief medications are used) + (1.6 if asthma medications are used)] ×1.792
Combined three regression models *Model for VAS<25*: [(0.5 × VAS Global Symptoms) + (0.8 if nasal steroids are used) + (−1.6 if ocular antihistamines are used) + (2.0 if MPAzeFlu is used) + (0.6 if oral antihistamines are used) + (2.5 if other rhinitis relief medications are used) + (0.1 if asthma medications are used)] ×1.786 *Model for 25<VAS<60*: [(0.5 × VAS Global Symptoms) + (2.2 if nasal steroids are used) + (−5.7 if ocular antihistamines are used) + (−0.4 if MPAzeFlu is used) + (1.2 if oral antihistamines are used) + (0.1 if other rhinitis relief medications are used)] ×1.689 *Model for VAS≥60*: [(0.5 × VAS Global Symptoms) + (1.8 if nasal steroids are used) + (0.8 if ocular antihistamines are used) + (−0.4 if MPAzeFlu is used) + (−1.0 if oral antihistamines are used) + (2.5 if other rhinitis relief medications are used) + (5.5 if asthma medications are used)] ×1.650

Note: All scores are expressed on a scale of 0 to 100, with higher values indicating worse allergic rhinitis control. If negative results are obtained, they should be recorded as 0. For each model, coefficients correspond to those obtained using multivariable regression models.

Abbreviations: 'WPAI:AS activities', Work Productivity and Allergy Impairment (ninth question); CARAT, Control of Allergic Rhinitis and Asthma Test; MPAzeFlu, Azelastine-Fluticasone in intra-nasal formulation; VAS, Visual analogue scale.

potential variability associated with differences between children and adults by excluding data from users aged <16 years.

2.6 | Sample size

We did not perform sample size calculation, but rather analysed all valid data from users meeting the eligibility criteria.

2.7 | Data analysis

For the assessment of concurrent validity, Spearman correlation coefficients were computed to measure the correlation between each SMS and EQ-5D VAS, CARAT, VAS Work, 'WPAI:AS work' and 'WPAI:AS activities'.

Test-retest reliability was assessed for each SMS in users with two measurements of a validated comparator (ie EQ-5D VAS, CARAT, VAS Work, 'WPAI:AS work' and 'WPAI:AS activities'), indicating clinical stability. Clinical stability was assumed whenever a user had two consecutive SMSs of less than three or five weeks apart, with results for validated comparators having a difference smaller than the minimal clinically important difference (MCID) value. We used previously described MCID values (namely in the case of CARAT, for which differences ≤3 were considered to be lower than the MCID)[23] or values determined according to distribution-based methods.[18] These included an MCID of 10 points for EQ-5D-VAS, 11% for VAS Work, 14% for 'WPAI:AS work' and 13.5% for 'WPAI:AS activities'. Agreement was assessed by estimating intraclass correlation coefficients (ICCs) using two-way models estimating absolute agreement, based on average measurements.[30]

Finally, responsiveness was assessed for each SMS in users with two measurements of a validated comparator indicating clinical change. Clinical change was assumed whenever a user had two consecutive SMSs of more than three or five weeks apart, with results for validated comparators having a difference equal to or higher than the MCID value. Responsiveness was determined by calculating Cohen's effect size and the standardized response mean (SRM).[31] Cohen's effect size was calculated by dividing the mean difference between the results

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of the two consecutive SMSs by the standard deviation of 'baseline' values. The SRM was calculated by dividing the mean by the standard deviation of the differences between consecutive SMSs. For each of these measures, values of 0.2–0.5 were considered to represent small effect sizes, 0.5–0.8 medium effect sizes and >0.8 large effect sizes.[31]

To assess the accuracy of the best-performing SMSs, we computed areas under multiclass ROC curves (AUC-ROC), comparing the performance of computed SMSs *versus* three classes of AR control (as defined by k-means cluster analysis based on VAS Work and EQ-5D-VAS, see above). In addition, we determined the SMS cut-off points that best distinguished three levels of AR control (best, intermediate and worst), maximizing the compromise between sensitivity and specificity.

All analyses were performed using R software (version 4.0).

2.8 | Ethics

MASK-air® is CE1 registered and follows the GDPR regulations. An independent review board approval was not required for this specific study as it is an observational study. All data were anonymized prior to the study (including geolocation-related data) using k-anonymity, and users agreed to the analysis of their data in the terms of use (translated into all languages and customized according to the legislation of each country, allowing the use of the results for research purposes).

3 | RESULTS

3.1 | Descriptive results

We assessed 317,176 observations (days of MASK-air® use) from 17,780 different users (mean age ± standard deviation = 36 ± 13 years; 56% women). The frequency of users and observations by country is given in Table S4. There were 160,471 (51%) days without treatment. Regarding European users, 222,025 days were recorded, of which 105,388 (47%) were without treatment.

3.2 | Concurrent validity of symptom-medication scores

The concurrent validity of all tested scores is displayed in Table S5. Table 2 displays the concurrent validity results for the mCSMS, the mixed CSMS and the best-performing score obtained with each data-driven approach. Consistent results were observed both when all users and only European users were studied.

In comparison with VAS Work, the mCSMS and the factor analysis-based SMS performed less well than the others. For cluster-based SMSs, Spearman correlation coefficients in comparison with VAS Work ranged from 0.73 to 0.83, while for the mixed CSMS and linear regression-based scores, they ranged from 0.80 to 0.81 (Figure S2). An overall worse performance of the mCSMS and the factor analysis-based SMS was also observed for the remaining comparators (Figure S3). In fact, in comparison with the EQ-5D VAS, the mCSMS displayed a correlation coefficient of −0.46, compared to between −0.53 and −0.56 for the remaining scores. On the other hand, compared to CARAT, the mCSMS displayed a correlation coefficient of −0.50, compared to between −0.55 and −0.59 for the remaining scores. Weaker correlations were also observed when comparing the mCSMS to WPAI:AS than when comparing it to the remaining scores.

The same patterns of correlation were found when assessing individual countries with over 10,000 days of reporting in the dataset, with a similar ranking order of SMSs (Figure 1; Table S6). Correlations between VAS Work and the different SMSs (except mCSMS) were very similar in all countries, except for Brazil. Wider across-country differences were observed for other comparators.

3.3 | Test-retest reliability

Table S7 presents the full results of the test-retest reliability analysis, while Table 3 presents the summary data of the best-performing SMSs for each approach. Intraclass correlation coefficients >0.75 were observed for most of the performed analyses, indicating high reliability in clinically stable users.

3.4 | Responsiveness

Table S8 presents the full results of the responsiveness analysis, while Table 4 presents the summary data of the best-performing SMSs. Except for the mCSMS, large effect size measures were observed for all SMSs when compared to VAS Work. When compared to EQ-5D-VAS or to WPAI:AS, effect sizes were mostly moderate, while low effect sizes were observed when CARAT was used as the comparator.

3.5 | Selection of scores

Among hypothesis-driven scores, the mixed CSMS clearly displayed a better performance than the mCSMS (Tables 2-4). Among data-driven scores, differences were smaller, with cluster-based approaches faring more often better than the linear regression-based SMSs. On the other hand, given the insufficient number of observations, it was not always possible to assess the responsiveness of the SMSs defined by cluster-based methods with clusters defined according to CARAT and WPAI:AS. Therefore, we propose to use the cluster-based score with clusters defined according to VAS Work and EQ-5D VAS values (in particular, that based on the formula: [(0.037 × VAS Global Symptoms) + (0.033 × VAS Eyes) + (0.020 × VAS Nose) + (0.027 × VAS Asthma) + (0.450 if MPAzeFlu is used) + (0.424 if nasal steroids are used) + (0.243 if asthma medication is used) + (0.380 if other rhinitis relief medication is used)] × 7.577). If

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TABLE 2 Concurrent validity of hypothesis-driven and data-driven symptom-medication scores: Spearman correlation coefficients [95% confidence intervals] (Number of observations) for the correlation between each symptom-medication score and each validated comparator

	EQ–5D VAS	CARAT	VAS Work	'WPAI:AS activities'	'WPAI:AS work'
A. mCSMS - modified combined symptom-medication score					
All users	−0.46 [−0.49;−0.44] (3432)	−0.50 [−0.53;−0.46] (1638)	0.59 [0.59;0.60] (120959)	0.61 [0.58;0.64] (2556)	0.58 [0.55;0.62] (1813)
European users	−0.49 [−0.52;−0.46] (2802)	−0.52 [−0.57;−0.48] (1245)	0.61 [0.60;0.61] (90087)	0.64 [0.61;0.67] (1815)	0.61 [0.58;0.65] (1428)
Non-European users	−0.38 [−0.46;−0.30] (630)	−0.36 [−0.45;−0.25] (393)	0.55 [0.54;0.56] (30872)	0.53 [0.47;0.58] (741)	0.46 [0.37;0.54] (385)
B. Mixed combined symptom-medication score					
All users	−0.53 [−0.55;−0.50] (3355)	−0.55 [−0.58;−0.51] (1608)	0.81 [0.80;0.81] (118725)	0.67 [0.65;0.70] (2496)	0.64 [0.61;0.67] (1758)
European users	−0.55 [−0.58;−0.51] (2729)	−0.59 [−0.62;−0.55] (1217)	0.81 [0.81;0.81] (88555)	0.69 [0.66;0.72] (1764)	0.66 [0.63;0.69] (1380)
Non-European users	−0.50 [−0.55;−0.43] (626)	−0.40 [−0.48;−0.32] (391)	0.80 [0.80;0.81] (30170)	0.62 [0.57;0.67] (732)	0.55 [0.48;0.63] (378)
C. Cluster-based scores with clusters based on VAS Work and EQ–5D VAS values [best-controlled days versus the remainder]					
All users	*−0.55 [−0.57;−0.52] (3643)*	−0.58 [−0.61;−0.55] (1748)	*0.83 [0.83;0.83] (128123)*	0.69 [0.67;0.71] (2696)	0.67 [0.64;0.70] (1919)
European users	*−0.57 [−0.60;−0.55] (2980)*	−0.60 [−0.64;−0.56] (1341)	*0.83 [0.83;0.83] (94399)*	0.71 [0.69;0.74] (1927)	0.69 [0.65;0.72] (1520)
Non-European users	*−0.47 [−0.54;−0.41] (663)*	−0.50 [−0.59;−0.41] (407)	*0.83 [0.82;0.83] (33724)*	0.64 [0.59;0.68] (769)	0.60 [0.53;0.66] (399)
D. Cluster-based scores with clusters based on CARAT and 'WPAI:AS activities' values [best-controlled days versus the remainder]					
All users	−0.55 [−0.58;−0.54] (3643)	*−0.59 [−0.62;−0.55] (1748)*	0.83 [0.83;0.84] (128123)	*0.70 [0.68;0.71] (2696)*	0.67 [0.64;0.69] (1919)
European users	−0.57 [−0.60;−0.55] (2980)	*−0.61 [−0.65;−0.57] (1341)*	0.84 [0.83;0.84] (94399)	*0.72 [0.69;0.74] (1927)*	0.69 [0.65;0.71] (1520)
Non-European users	−0.50 [−0.56;−0.44] (663)	*−0.48 [−0.57;−0.38] (407)*	0.84 [0.83;0.84] (33724)	*0.64 [0.59;0.68] (769)*	0.59 [0.51;0.65] (399)
E. Linear regression-based score					
All users	*−0.56 [−0.56;−0.51] (3643)*	−0.56 [−0.59;−0.52] (1748)	*0.81 [0.80;0.81] (128123)*	0.68 [0.65;0.70] (2696)	0.64 [0.61;0.67] (1919)
European users	*−0.56 [−0.58;−0.53] (2980)*	−0.59 [−0.62;−0.55] (1341)	*0.81 [0.80;0.81] (94399)*	0.69 [0.67;0.72] (1927)	0.66 [0.63;0.69] (1520)
Non-European users	*−0.50 [−0.56;−0.44] (663)*	−0.42 [−0.51;−0.32] (407)	*0.80 [0.80;0.81] (33724)*	0.62 [0.58;0.67] (769)	0.56 [0.48;0.64] (399)

Note: Text in italics indicates the comparators used in the generation of the respective data-driven scores. The colour code reflects the effect sizes – the highest correlation coefficients are marked in green, while the lowest are marked in red.

Abbreviations: 'WPAI:AS: activities', Work Productivity and Allergy Impairment: Activity Specific - Percent activity impairment due to allergy; 'WPAI:AS: work', Work Productivity and Allergy Impairment: Percent overall work impairment due to allergy; CARAT, Control of Allergic Rhinitis and Asthma Test; VAS, Visual analogue scale.

the cluster or other data-driven score cannot be implemented, the mixed CSMS may be used, being preferable to the mCSMS.

Based on a distribution approach (standard deviation divided by two), the MCID for the recommended cluster-based score was of 10 points, while for the mixed CSMS, it was of 15 points. The cluster-based score was found to have a high accuracy (AUC-ROC = 0.904), with values<15.8 indicating good AR control, and values >35.3 indicating worse AR control (Table 5; Figure 2). The mixed CSMS also presented high accuracy (AUC-ROC = 0.820), with values<20.0 indicating good AR control, and values >59.0 indicating poorer control.

4 | DISCUSSION

A validated CSMS is needed in AR, from clinical practice to clinical trials. The current study using real-world data obtained from 17,780 patients in 25 countries showed that (i) both a mixed CSMS and several

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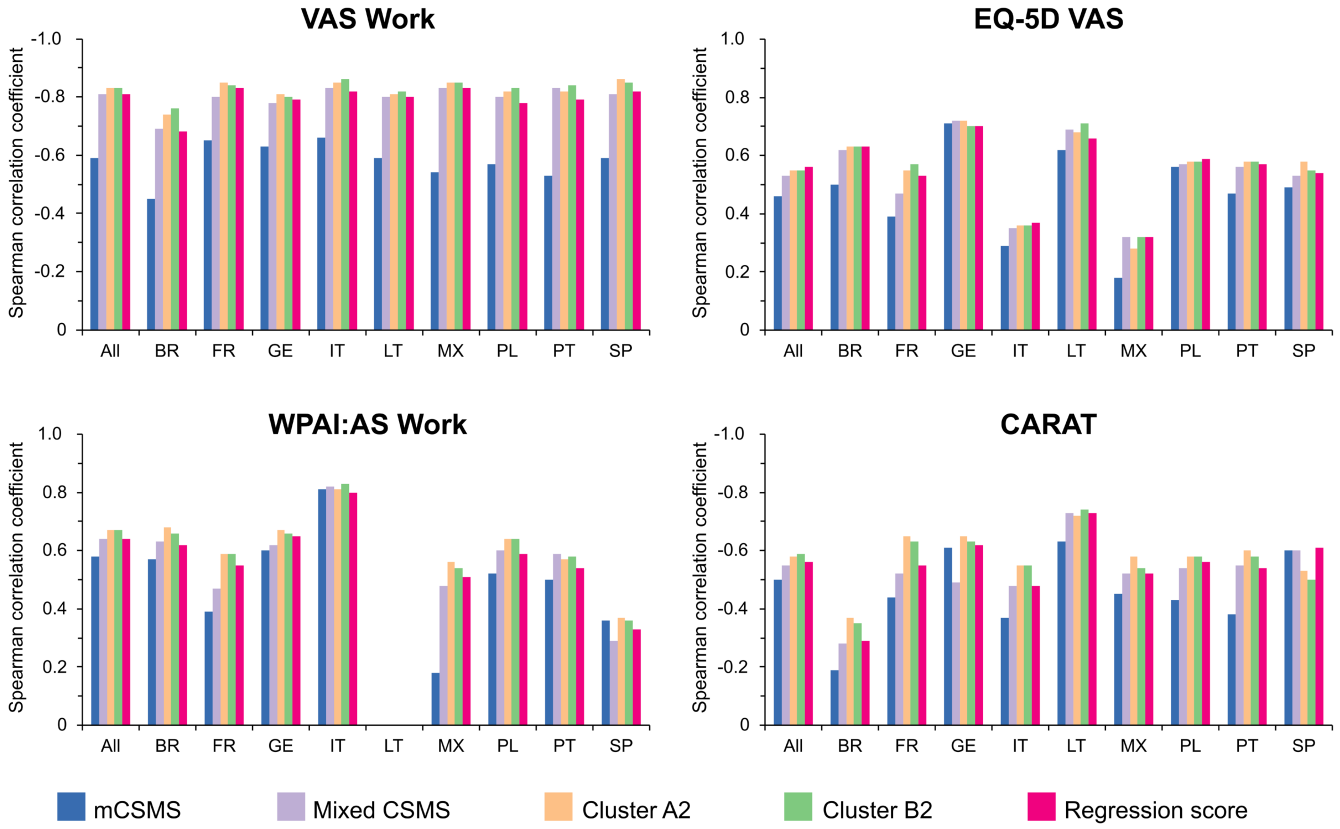

FIGURE 1 Concurrent validity of the selected scores in different countries. CARAT, Control of Allergic Rhinitis and Asthma Test; Cluster A2, Cluster-based score with clusters based on VAS Work and EQ-5D VAS values [best-controlled days versus the remainder]; Cluster B2, Cluster-based score with clusters based on CARAT and 'WPAI:AS activities' values [best-controlled days versus the remainder]; Mixed CSMS, mixed hypothesis-driven and data-driven combined symptom-medication score; mCSMS, modified combined symptom-medication score; regression, linear regression-based score; VAS, Visual analogue scale; WPAI:AS, Work Productivity and Activity Impairment: Allergic Specific. All, All countries; BR, Brazil; FR, France; GE, Germany; IT, Italy; LT, Lithuania; MX, Mexico; PL, Poland; PT, Portugal; SP, Spain

data-driven SMSs based on MASK-air® data were moderately-to-highly correlated with all tested comparators of quality of life and work, and had a high test-retest reliability and (ii) these validity results are reproducible across different European countries. Overall, this points to the possibility of developing CSMSs using mixed- or purely data-driven approaches. Importantly, the same ranking order of SMSs was found for all four outcomes, pointing to a high consistency of results. These four outcomes include measures on quality-of-life (EQ-5D-VAS, 'WPAI:AS activities') and on work (VAS Work and 'WPAI:AS work'). These two major outcomes (i) are deeply impacted by AR, (ii) have an impact associated with AR control, (iii) have a social impact, (iv) are associated with well-being and (v) include tools that can be used to formulate utilities, for economic evaluation studies. Of note, regarding VAS Work, there does not appear to be any cultural or linguistic barriers to this scale (except for Brazil, where, possibly, the question was not adapted), suggesting that VAS Work can be used with a similar value in all countries tested.

Currently, there are several questionnaires assessing the control of AR, including CARAT, the Allergic Rhinitis Control Test[32] and the Rhinitis Control Assessment Test (RCAT).[33] However, these questionnaires assess rhinitis symptoms for a period longer than one day. In addition, RCAT does not have a specific question on AR medication, while for CARAT, there is one single question that does not discriminate between asthma and AR medication or between medication classes. Differently from these existing questionnaires, the developed SMSs assess AR symptoms and medication use simultaneously for the period of a single day. Further rhinitis control scores have been proposed by different groups and have been validated to some extent. Examples are (i) the Satisfaction Scale for Patients Receiving Allergen Immunotherapy questionnaire, comprising four categories covering a questionnaire of 16 rhinitis-specific items[34] and (ii) the Patient Benefit index, which provides a satisfaction index for the treatment based on 25 questions. These control scores can be quickly filled in by patients, correlate well with certain domains of health-related quality-of-life, and their floor effects are low.[3] However, they lack multi-language translations and their questions only cover the retrospective burden of the disease.

The existence of valid and reliable CSMSs is particularly important as they can represent endpoints in AIT or AR medication trials[1] and in real-life observational studies. Such CSMSs can also be used in clinical practice to assess patients' daily AR control, helping clinicians to identify potential control patterns (and, thus, potential types of pollen patients may be allergic to), to adjust AR medication and to stratify patients for AIT or other rhinitis treatments.[2] This

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TABLE 3 Test-retest reliability of hypothesis-driven and data-driven symptom-medication scores: Intraclass correlation coefficients [95% confidence intervals] (Number of observations) for each symptom-medication score in relation to each validated comparator

	EQ−5D VAS	CARAT	VAS Work	'WPAI:AS activities'	'WPAI:AS work'
A. mCSMS - modified combined symptom-medication score					
5-week assessment	0.83 [0.78;0.87] (215)	0.80 [0.70;0.86] (103)	0.83 [0.82;0.84] (4382)	0.83 [0.77;0.88] (149)	0.87 [0.81;0.91] (106)
3-week assessment	0.84 [0.79;0.88] (202)	0.83 [0.75;0.89] (94)	0.84 [0.83;0.85] (4333)	0.83 [0.76;0.88] (142)	0.87 [0.80;0.91] (99)
B. Mixed combined symptom-medication score					
5-week assessment	0.77 [0.69;0.83] (212)	0.78 [0.66;0.85] (102)	0.84 [0.83;0.86] (4304)	0.84 [0.77;0.89] (143)	0.79 [0.68;0.86] (100)
3-week assessment	0.78 [0.70;0.84] (199)	0.81 [0.70;0.87] (93)	0.84 [0.83;0.86] (4253)	0.85 [0.79;0.90] (137)	0.81 [0.71;0.87] (95)
C. Cluster-based scores with clusters based on VAS Work and EQ−5D VAS values [best-controlled days versus the remainder]					
5-week assessment	*0.82 [0.76;0.86] (240)*	0.83 [0.74;0.88] (117)	*0.89 [0.88;0.90] (4520)*	0.88 [0.83;0.91] (164)	0.79 [0.69;0.85] (118)
3-week assessment	*0.84 [0.79;0.88] (225)*	0.85 [0.76;0.90] (106)	*0.90 [0.89;0.90] (4475)*	0.89 [0.84;0.92] (156)	0.84 [0.77;0.89] (109)
D. Cluster-based scores with clusters based on CARAT and 'WPAI:AS activities' values [best-controlled days versus the remainder]					
5-week assessment	0.84 [0.76;0.89] (96)	*0.80 [0.70;0.87] (99)*	0.87 [0.85;0.88] (1777)	*0.91 [0.85;0.95] (56)*	0.74 [0.48;0.87] (35)
3-week assessment	0.84 [0.75;0.90] (89)	*0.79 [0.68;0.87] (90)*	0.87 [0.85;0.88] (1763)	*0.92 [0.85;0.95] (53)*	0.84 [0.68;0.92] (32)
E. Linear regression-based score					
5-week assessment	*0.77 [0.68;0.83] (240)*	0.78 [0.68;0.85] (117)	*0.84 [0.83;0.86] (4520)*	0.83 [0.76;0.88] (164)	0.72 [0.59;0.81] (118)
3-week assessment	*0.78 [0.70;0.84] (225)*	0.81 [0.72;0.87] (106)	*0.85 [0.83;0.86] (4475)*	0.83 [0.76;0.88] (156)	0.79 [0.69;0.85] (109)

Note: Text in italics indicates the comparators used in the generation of the respective data-driven scores. The colour code reflects the effect sizes –high intraclass correlation coefficients are marked in green.

Abbreviations: 'WPAI:AS: activities', Work Productivity and Allergy Impairment: Activity Specific—Percent activity impairment due to allergy; 'WPAI:AS: work', Work Productivity and Allergy Impairment: Percent overall work impairment due to allergy; CARAT, Control of Allergic Rhinitis and Asthma Test; VAS, Visual analogue scale.

would potentially improve their effectiveness and have a relevant impact on reimbursement strategies. The automatic calculation of these CSMSs is an additional factor facilitating their application in the clinical practice. While the MASK-air® app is an obvious candidate for the computation of CSMSs in the clinical practice, computer-based calculators, or even print versions, can be specifically developed and used for that purpose (particularly as the CSMS formulae are available in Table 1).

This study has several strengths, including (i) the application of different methodological approaches to generate CSMSs, (ii) the assessment of different properties of hypothesis-driven and data-driven scores and (iii) the consistency of sub-analyses specifically assessing data from Europe or specific countries. It was based on the analysis of a large volume of real-world data, with the structure of the MASK-air® app precluding the existence of missing data within each daily questionnaire response. Moreover, the daily monitoring VASs used within the context of the SMSs had already been shown to have sound concurrent validity and moderate-high test-retest reliability and responsiveness.[18]

This study also has some important limitations. In particular, there is no gold-standard measure of daily control of AR to compare with hypothesis-driven and data-driven scores. In fact, EQ-5D-VAS may have suboptimal specificity for respiratory symptoms (hence, the weaker correlation coefficients observed with EQ-5D-VAS as a comparator compared to VAS Work). On the other hand, while CARAT assesses AR control, it concerns a four-week period. To overcome this limitation, we opted for assessing the properties of the different SMSs in relation to several different scales quantifying quality-of-life and the impact of AR on work productivity and activities.

Another important limitation concerns the relatively small sample sizes for assessment of responsiveness in relation to comparators such as EQ-5D-VAS, CARAT or WPAI:AS (even precluding the full assessment of the responsiveness of one data-driven SMS). This limitation stems from the fact that (i) responsiveness can only be assessed in users with two consecutive assessments some time apart (in this case, more than three or five weeks) and indicating clinical change and (ii) response to EQ-5D-VAS, CARAT or WPAI:AS is not

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TABLE 4 Responsiveness of hypothesis-driven and data-driven symptom-medication scores: Effect size measures (Number of observations) for each symptom-medication score in relation to each validated comparator

	EQ–5D VAS		CARAT		VAS Work		'WPAI:AS activities'		'WPAI:AS work'	
	ESM I	ESM II	ESM I	ESM II	ESM I	ESM II	ESM I	ESM II	ESM I	ESM II
A. mCSMS - modified combined symptom-medication score										
5-week assessment	0.65 (70)	0.67 (70)	0.20 (34)	0.24 (34)	0.82 (949)	0.77 (949)	0.57 (42)	0.54 (42)	0.60 (35)	0.59 (35)
3-week assessment	0.53 (90)	0.53 (90)	0.16 (44)	0.21 (44)	0.81 (1248)	0.77 (1248)	0.56 (58)	0.56 (58)	0.59 (41)	0.56 (41)
B. Mixed combined symptom-medication score										
5-week assessment	0.65 (69)	0.64 (69)	0.25 (32)	0.28 (32)	0.98 (936)	0.93 (936)	0.68 (40)	0.62 (40)	0.66 (34)	0.60 (34)
3-week assessment	0.52 (89)	0.52 (89)	0.25 (42)	0.31 (42)	0.98 (1231)	0.94 (1231)	0.67 (55)	0.65 (55)	0.62 (40)	0.56 (40)
C. Cluster-based scores with clusters based on VAS Work and EQ–5D VAS values [best-controlled days versus the remainder]										
5-week assessment	*0.55 (81)*	*0.60 (81)*	0.32 (38)	0.34 (38)	*0.95 (975)*	*1.01 (975)*	0.71 (50)	0.68 (50)	0.63 (41)	0.54 (41)
3-week assessment	*0.45 (104)*	*0.49 (104)*	0.28 (50)	0.35 (50)	*0.97 (1275)*	*1.02 (1275)*	0.67 (68)	0.63 (68)	0.61 (48)	0.53 (48)
D. Cluster-based scores with clusters based on CARAT and 'WPAI:AS activities' values [best-controlled days versus the remainder]										
5-week assessment	-[a]	-[a]	-[a]	-[a]	0.88 (415)	0.92 (415)	-[a]	-[a]	-[a]	-[a]
3-week assessment	0.49 (35)	0.64 (35)	*0.30 (38)*	*0.34 (38)*	0.89 (560)	0.96 (560)	-[a]	-[a]	-[a]	-[a]
E. Linear regression-based score										
5-week assessment	*0.57 (81)*	*0.55 (81)*	0.18 (38)	0.19 (38)	*0.97 (975)*	*0.92 (975)*	0.70 (50)	0.64 (50)	0.59 (41)	0.51 (41)
3-week assessment	*0.46 (104)*	*0.46 (104)*	0.21 (50)	0.25 (50)	*0.98 (1275)*	*0.96 (1275)*	0.71 (68)	0.64 (68)	0.62 (48)	0.55 (48)

Note: Text in italics indicates the comparators used in the generation of the respective data-driven scores. The colour code reflects the effect sizes—the highest effect size measures (corresponding to high responsiveness) are marked in green, while the lowest are marked in red.

Abbreviations: 'WPAI:AS: activities', Work Productivity and Allergy Impairment: Activity Specific—Percent activity impairment due to allergy; 'WPAI:AS: work', Work Productivity and Allergy Impairment: Percent overall work impairment due to allergy; CARAT, Control of Allergic Rhinitis and Asthma Test; ESM I, Cohen's effect size; ESM II, standardized response mean; VAS, Visual analogue scale.

[a]Insufficient (<30) number of participants.

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TABLE 5 Accuracy and cut-off points for the best performing combined symptoms and medication scores

Score	AUC[a]	Cut-off points (Sensitivity; Specificity)	
		Best-controlled *versus* remainder	Worst-controlled *versus* remainder
mCSMS – modified combined symptom-medication score	0.835	21.0 (71.6%; 81.3%)	35.0 (86.4%; 70.9%)
Mixed combined symptom-medication score	0.820	20.0 (77.8%; 80.7%)	59.0 (81.7%; 77.3%)
Cluster-based score (clusters based on VAS Work and EQ–5D VAS)	0.904	15.8 (81.5%; 86.6%)	35.3 (92.0%; 77.0%)
Cluster-based score (clusters based on CARAT and WPAI:AS)	0.905	17.3 (82.6%; 85.1%)	42.8 (88.6%; 82.3%)
Linear regression-based score	0.900	18.1 (77.6%; 86.9%)	52.9 (86.4%; 83.8%)

Abbreviations: AUC, Area under the ROC curve; CARAT, Control of Allergic Rhinitis and Asthma Test; VAS, Visual analogue scale; WPAI:AS, Work Productivity and Activity Impairment: Allergic Specific.

[a]For clusters with rhinitis control defined simultaneously based on CARAT and on WPAI:AS: AUC for the mCSMS = 0.811; AUC for the mixed CSMS = 0.723; AUC for the cluster-based score (clusters based on VAS Work and EQ-5D VAS) = 0.856; AUC for the cluster-based score (clusters based on CARAT and WPAI:AS) = 0.857; AUC for the linear regression-based score = 0.845

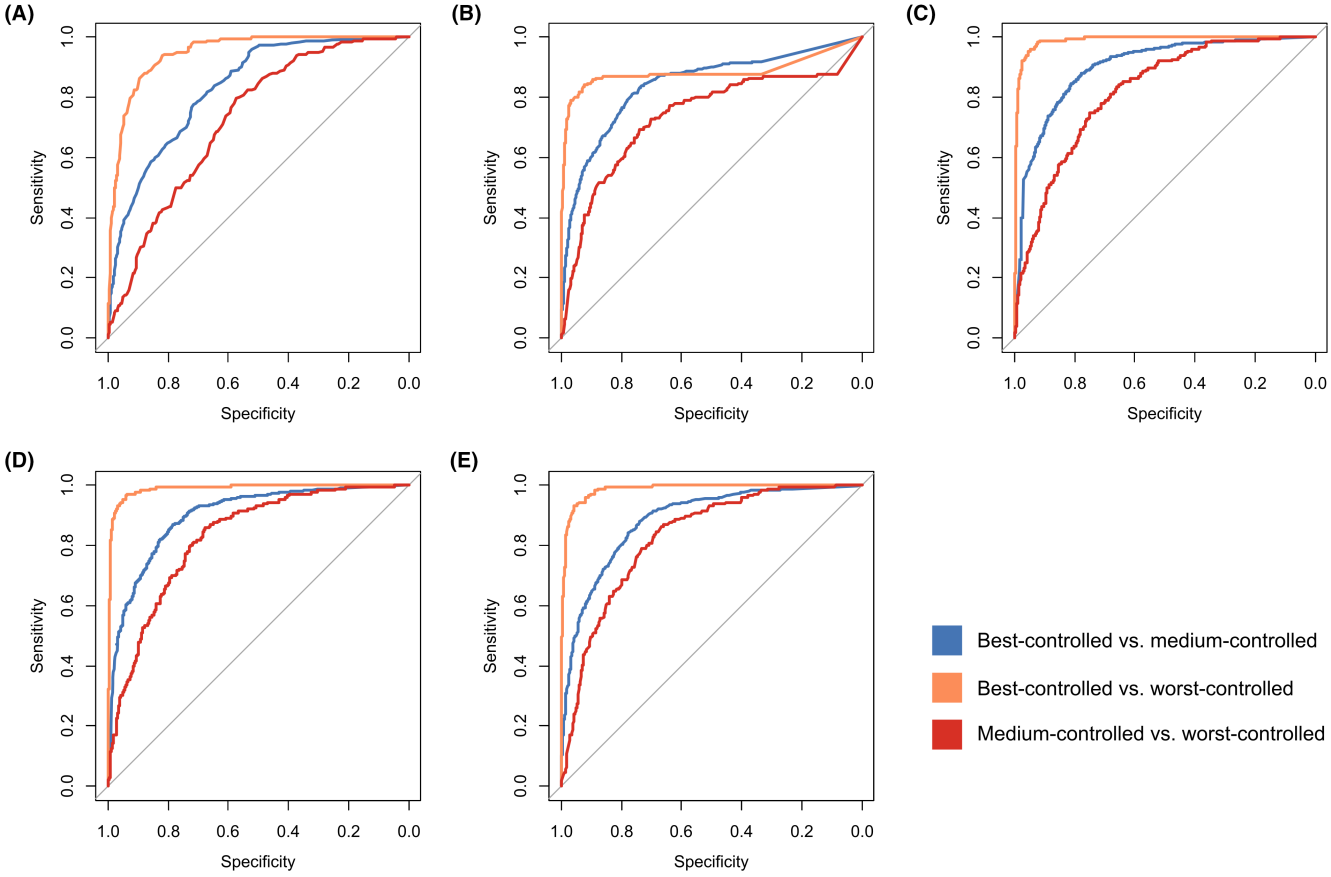

FIGURE 2 ROC curves for the modified combined symptom-medication score (A), for the mixed combined symptom-medication score (B), for the cluster-based score with clusters based on visual analogue scale on the impact of allergic rhinitis on work (VAS Work) and EQ-5D-VAS (C), for the cluster-based score with clusters based on Control of Allergic Rhinitis and Asthma Test (CARAT) and Work Productivity and Activity Impairment: Allergic Specific (WPAI:AS) (D), and for the regression-based score (E)

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mandatory within the daily monitoring of MASK-air®. Limitations in sample size (along with the absence of datasets similar to those analysed) precluded the derivation and validation of data-driven scores in totally different data sets. While this may possibly result in optimistic estimates for the analyses involving comparators used in the generation of the respective SMSs, the impact is not expected to be high. In fact, we performed an ancillary analysis deriving and validating the cluster-based SMS defined according to VAS Work and EQ-5D-VAS on two different sample subsets, obtaining identical results (Table S9).

An additional limitation concerns the fact that medication registration in MASK-air® is dependent on a scroll list which differs across countries. Therefore, medication use may not be registered (resulting in misclassification) in the cases of (i) medication bought in a country different from the one the user lives in, or (ii) recently commercialized medication not yet available in the scroll list.

Finally, the assessed SMSs may not be generalizable to all AR patients. Not only may they not be generalizable for children, but also there is a potential overrepresentation of younger adults, of patients more concerned about their health (as the latter may be more prone to using health apps more regularly), and of more affluent patients (who may have an easier access to smartphone apps). In addition, data-driven SMSs may be more tailored for application in working users, as VAS Work or WPAIS:AS were used in their computation. Therefore, a potential worse performance of data-driven SMSs in retired or unemployed patients may not be excluded. Finally, while we used data from patients from all countries where MASK-air® is available, European users are overrepresented, and sensitivity analyses assessing the performance of the models on European users tended to display better results than those on non-European users. Future studies applying and assessing the developed CSMS in non-European patients should therefore be conducted.

It is important to highlight the fact that this study assessed several SMSs using previously collected data. Future prospective evaluations are thus required. The possibility of the automatic computation of any of these SMSs via a mobile app may allow for them to automatically change with the provision of further data, adapting to the assessment of different populations.

In conclusion, we assessed the properties of hypothesis-driven and data-driven SMSs using MASK-air®. The mixed CSMS and the cluster-based data-driven scores were found to have moderate-high concurrent validity, high test-retest reliability and moderate responsiveness, rendering them as potential candidates for primary endpoints in future AIT and AR medication trials, in AR real-world data studies and in the clinical practice. In line with international initiatives aiming to harmonize trial designs and outcome measures in AR for better comparability of intervention effects, this analysis is an important further step in optimizing the future care of allergic patients.

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CONFLICT OF INTEREST

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Compositions and Methods for Using the Same pending, and a patent Microfluidic Device and Diagnostic Methods for Allergy Testing Based on Detection of Basophil Activation pending. NGP reports personal fees from Novartis, Nutricia, HAL, MENARINI/FAES FARMA, SANOFI, MYLAN/MEDA, BIOMAY, AstraZeneca, GSK, MS D, ASIT BIOTECH, Boehringer Ingelheim, grants from Gerolymatos International SA, Capricare. OP reports grants and personal fees from ALK-Abelló, Allergopharma, from Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, from Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, ASIT Biotech Tools S.A., Laboratorios LETI/LETI Pharma, Anergis S.A., Glaxo Smith Kline, personal fees from Astellas Pharma Global, grants from Biomay, Pohl-Boskamp, Inmunotek S.L., personal fees from MEDA Pharma/MYLAN, Mobile Chamber Experts (a GA2LEN Partner), Indoor Biotechnologies, EUFOREA, ROXALL Medizin, Novartis, Sanofi-Aventis and Sanofi Genzyme, Med Update Europe GmbH, streamedup! GmbH, John Wiley and Sons, AS, Paul-Martini-Stiftung (PMS). SR reports that her department has received grants from ALK, Allergy Therapeutics and Mylan BV and acted as consultant for Sanofi Genzyme and Novartis. ATB reports grants and personal fees from AstraZeneca, GSK (GlaxoSmithKline), Novartis, Sanofi, Teva, Mundipharma, personal fees from Bial, grants from Leti. SW reports other from GSK, AZ, ALK, SANOFI, PEDIAPHARM, MEDEXAS, NOVARTIS, COVIS and President Canadian Allergy Asthma and Immunology Foundation Board of Asthma Canada. TZ reports and Organizational affiliations: Commitee member: WHO-Initiative 'Allergic Rhinitis and Its Impact on Asthma' (ARIA), Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI), Board Chairman: European Centre for Allergy Research Foundation (E CARF)—President: Global Allergy and Asthma European Network (GA2LEN), Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO).

AUTHORS' CONTRIBUTIONS

BSP participated in methodology, formal analysis and writing—original draft. LFA participated in methodology and writing—review & editing. OP, JAF and JB participated in conceptualization, formal analysis, supervision and writing—original draft. All remaining authors participated in data collection and writing—review & editing.

DATA AVAILABILITY STATEMENT

Data that underlie the results reported in this article (along with the analytic code)—beginning 12 months and ending 36 months following article publication—can be made available upon reasonable request to researchers who provide a methodologically sound proposal. Proposals should be addressed to jean.bousquet@orange.fr. To gain access, data requestors will need to sign a data access agreement that follows the General Data Protection Regulation.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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