

Journal Pre-proof

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PII: S2213-2198(21)01144-2

DOI: <https://doi.org/10.1016/j.jaip.2021.10.025>

Reference: JAIP 3908

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 11 July 2021

Revised Date: 6 October 2021

Accepted Date: 7 October 2021

Please cite this article as: Baiardini I, Fasola S, La Grutta S, Trucco E, Canonica GW, Braido F, Rhinitis and asthma patient perspective (RAPP): clinical utility and predictive value, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.10.025>.

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Rhinitis and asthma patient perspective (RAPP): clinical utility and predictive value

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Word count for the abstract: 249

Word count for the text: 2155

ABSTRACT

Background: RhinAsthma Patient Perspective (RAPP) is the only validated tool for the assessment of health-related quality of life (HRQoL) related to asthma and rhinitis in individual patients.

Objective: The aim of this study was to compare the HRQoL burden among countries and to explore the usefulness of RAPP as a complementary measure in disease management.

Methods: In this post hoc analysis of the RAPP International Study, the enrolled population was clustered into patients with controlled rhinitis and controlled asthma (CA/CR), uncontrolled rhinitis and controlled asthma (CA/UR), controlled rhinitis and uncontrolled asthma (UA/CR), uncontrolled rhinitis and uncontrolled asthma (UA/UR).

Results: 575 adult patients were recruited. Significant differences among countries were observed in the mean RAPP score (from 15.7 in Spain to 18.7 in the Philippines), even if the percentage of subjects with an optimal HRQoL ($RAPP < 15$) was not significantly different. Compared to patients with AR and asthma disease control, those with UR/CA, CR/UA, and UR/UA had significantly higher RAPP scores (4.7, 5, and 9.8, respectively). The best cutoffs for detecting uncontrolled diseases were $RAPP \geq 15$ (Sensitivity= 75%, Specificity= 69%, AUC=0.78) for AR; $RAPP \geq 16$ (Sensitivity=78%, Specificity=76%, AUC=0.83) for asthma; and $RAPP \geq 18$ (Sensitivity=86%, Specificity=87%, AUC=0.92) for both AR and asthma.

Conclusions: The present findings provide a better understanding of the individual burden of HRQoL related to asthma and rhinitis in daily practice. In addition, the RAPP estimates how much of the risk for uncontrolled disease depends on uncontrolled AR and asthma, allowing its use as a clinical support tool in clinical management.

What is already known about this topic? The RhinAsthma patient perspective (RAPP) is a well-validated questionnaire to assess the health-related quality of life (HRQoL) of patients with asthma and comorbid allergic rhinitis (AR) in daily practice. It is available in Italian, English, Spanish, Portuguese, and Polish.

What does this article add to our knowledge? In addition to detecting the disease impact from the patient's perspective, RAPP provides an estimate of the risk for uncontrolled AR and asthma.

How does this study impact current management guidelines? RAPP can be used to support shared clinical management.

Keywords: Allergic rhinitis; Asthma; Clinical practice; Health-related quality of life; Questionnaire

Funding: This work was supported by Menarini International Operations Luxembourg S.A. (M.I.O.L.).

Conflict of interest: I. Baiardini reports personal fees for scientific consultations and/or lectures at national and international meetings from Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini, Novartis, Sanofi Genzyme, Astra Zeneca.

G.W. Canonica reports personal fees from A. Menarini, Alk-Abelló, Allergy Therapeutics, AstraZeneca-Medimmune, Boehringer Ingelheim, Chiesi Farmaceutici, Genentech, Guidotti-Malesci, GSK, Hal Allergy, Merck Sharp & Dome, Mundipharma, Novartis, Orion, Sanofi-Aventis, Sanofi Genzyme/Regeneron, Stallergenes Greer, Uriach Pharma, TEVA, Valeas, and ViforPharma.

F. Braidò has received honoraria for lectures at national and international meetings from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Dompè, Guidotti/Malesci, GlaxoSmithKline, Menarini, Novartis, Lallemand Pharma, Biophutura, Levante Pharma, Merck Sharp and Dohme, and Zambon; he has served as consultant for AstraZeneca, Chiesi Farmaceutici, Novartis, Glaxo Smith Kline, Boehringer Ingelheim, Guidotti/MalesciZambon, Csl Behring.

S. Fasola, E. Trucco and S. La Grutta have not potential conflict of interest.

Abbreviations used

ACT - Asthma Control Test

AR - allergic rhinitis

ARIA – Allergic Rhinitis and its Impact on Asthma

AUC - area under the ROC curve

BMI – body mass index

CIs - confidence intervals

CR/CA - controlled rhinitis and controlled asthma

- 77 CR/UA - controlled rhinitis and uncontrolled asthma
- 78 GINA - Global Initiative for Asthma
- 79 GRS - Global Rating Scale
- 80 HRQoL - health-related quality of life
- 81 MID - minimal important difference
- 82 OR - odds ratio
- 83 PRO - patient-reported outcome
- 84 RAPP - RhinAsthma Patient Perspective
- 85 ROC - receiver operating characteristic
- 86 SE - sensitivity
- 87 SF-12 - Short Form-12
- 88 SP - 1-specificity
- 89 UR/CA - uncontrolled rhinitis and controlled asthma
- 90 UR/UA - uncontrolled rhinitis and uncontrolled asthma
- 91 VAS - Visual Analog Scale
- 92

93

94 **INTRODUCTION**

95 Health-related quality of life (HRQoL) (1) is a patient-reported outcome (PRO) (2-4) of
96 critical importance in the management of chronic diseases. It is traditionally included in research
97 studies and clinical trials to assess the impact of respiratory allergy and its treatment from the patient
98 perspective. Starting in the 1990s, thanks to the development of questionnaires that are specific for
99 asthma (5), allergic rhinitis (AR) (6), and both conditions (7-9), a growing number of studies have
100 included the assessment of HRQoL as an endpoint, allowing us to determine the subjective disease
101 burden (10, 11). Moreover, HRQoL data from research have been used to compare treatment options
102 in effectiveness trials and to integrate existing measurements of safety and efficacy in the drug
103 development process and regulatory review (12).

104 Recent years have seen increasing interest in incorporating PROs into clinical practice with
105 greater awareness of the importance of patient-oriented approaches (13-17). For healthcare
106 professionals, PROs are a supportive tool during clinical consultation to better detect and manage
107 disease and its treatment-related effects (18). Moreover, the routine collection of PROs improves
108 communication (19) and shared decision-making (20) and has a positive impact on patient outcomes
109 (21).

110 The National Quality Forum (22) and the International Society for Quality of Life Research
111 (23) developed specific guidance to properly assess patients' perspectives in routine care settings.
112 The availability of questionnaires with well-defined psychometric and practical features
113 is the first step towards adoption and inclusion of PROs in clinical practice.

114 RhinAsthma Patient Perspective (RAPP) (24) was originally developed and validated in Italy
115 to be implemented in a real-world setting to assess the HRQoL of adult patients suffering from AR
116 and asthma. It was devised on the basis of the concept of united airway diseases. AR and asthma
117 represent different manifestations of a single underlying disease (25,26). They often coexist; up to
118 80% of asthma patients suffer from AR, and over 40% of AR patients have asthma (27). Moreover,

the impact of comorbid asthma and AR on clinical outcomes, PROs, and costs has been well characterized (28-30).

The RAPP satisfies the psychometric criteria (22) and pragmatic characteristics (31) that are requested for use in clinical practice. It is short (8 items), user friendly, and simple to score. The scores range from 8 to 40 (higher scores indicate a greater impact on HRQoL), and a cutoff point of 15 showed the best sensitivity and specificity in discriminating the achievement of an optimal HRQoL. Moreover, the high responsiveness to change and the minimal important difference (MID) (two points) increase the interpretability and actionability of the questionnaire and allow its use in making clinical decisions. Specific version for children (32) is available in Italy.

A recent multinational project aimed at transcultural adaptation and validation of the RAPP in English (33), Spanish (34), Portuguese (35), and Polish (36) confirmed that the questionnaire has the recommended psychometric properties in each language. The full questionnaire (Appendix E1) and a summary of the validation process (Appendix E2) are available in this article's Online Repository at www.jaci-inpractice.org.

The results of this international study offered the opportunity to compare HRQoL in the involved countries and to explore RAPP usefulness as a complementary measure in disease management. To achieve this goal, the ability of RAPP to differentiate patients with impaired HRQoL due to uncontrolled AR, uncontrolled asthma, or both has been explored.

138

139 **METHODS**140 **Study design and participants**

141 This is a post hoc analysis of the RAPP International study, which was a multicenter,
142 observational perspective study approved by the Ethics Committee of the University of Genoa
143 (approval no. P.R. 333REG2106) and ratified by the local ethics committees. The methodology and
144 the results have been described previously (33-36). In brief, for each country, adult patients diagnosed
145 with asthma and rhinitis according to Global Initiative for Asthma (GINA) (37) and Allergic Rhinitis
146 and its Impact on Asthma (ARIA) (38) documents attending a specialist center for a visit were asked
147 to be enrolled in the study. Patients were evaluated twice, with an interval of 4 weeks between the
148 visits. At each visit, patients completed the RAPP (24), and three other validated PROs: the Short
149 Form-12 (SF-12) (39), a questionnaire to assess health status; the Asthma Control Test (ACT) (40),
150 to evaluate the level of asthma control; and the symptomatologic Visual Analog Scale (VAS), a well-
151 accepted measure to monitor AR control (41). At the second visit, patients were asked to complete a
152 Global Rating Scale (GRS) (42) to detect any change in health.

153 Between the two visits, patients received treatment according to the current guideline
154 recommendations.

155 The analyzed endpoints of this post hoc analysis were: 1) the differences in terms of patient
156 characteristics and RAPP scores across countries; 2) the usefulness of RAPP as a complementary tool
157 in disease management of patients with upper and lower respiratory allergy. To this aim, recruited
158 patients were divided into four classes according to the level of control for the upper (43) and lower
159 (40) airways: controlled rhinitis and controlled asthma ($ACT > 19$ and $VAS \leq 5$, CR/CA), uncontrolled
160 rhinitis and controlled asthma ($ACT > 19$ and $VAS > 5$, UR/CA), controlled rhinitis and uncontrolled
161 asthma ($ACT \leq 19$ and $VAS \leq 5$, CR/UA), uncontrolled rhinitis and uncontrolled asthma ($ACT \leq 19$ and
162 $VAS > 5$, UR/UA).

A convenient data sampling method was used to recruit a total of 150 patients in each country. As the current analysis was post hoc, no sample size calculations were required and therefore all analyses are descriptive only, as well as the calculated p-values.

Statistical analysis

Patient characteristics were summarized through the mean and the standard deviation (SD) for quantitative variables and through absolute (no.) and percentage (%) frequencies for categorical variables. Comparisons among centers were carried out using the Kruskal-Wallis test for quantitative variables and the chi-square test for categorical variables. Fisher's exact test was used if one or more cells of the contingency table were below 5.

Pairwise group differences in the RAPP total score were assessed through Tukey's honest multiple comparisons by means of 95% familywise confidence intervals (CIs).

The ability of RAPP to discriminate between each disease status (UR/CA, CR/UA, and UR/UA) and the baseline status (CR/CA) was assessed by receiver operating characteristic (ROC) curves, representing 1-specificity (SP) and sensitivity (SE) for different RAPP cutoffs. The discriminating ability was considered fair if the 95% CI of the area under the ROC curve (AUC) did not include 0.5. For each ROC curve, the best cutoff was identified as the RAPP total score maximizing Youden's *J* statistic (sensitivity+specificity-1). For each detected cutoff, we reported SE, SP, overall accuracy, and the odds ratio (OR) from the 2-by-2 confusion matrix. We also adjusted the OR by age, gender, body mass index (BMI), education, employment status, smoking habits, atopy, rhinitis severity, and asthma severity through multivariable logistic regression models.

All statistical analyses were performed using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

187

188 **RESULTS**189 **Patient characteristics and RAPP scores across countries**

190 A total of 575 patients were recruited: 150 (26.1%) from the Philippines, 127 (22.1%) from
 191 Poland, 149 (25.9%) from Portugal, and 149 (25.9%) from Spain. On average, patients were younger
 192 in Poland (34.8 years). A higher percentage of females were recruited in the Philippines (74.0%).
 193 Table 1 summarizes the patient characteristics by center. A lower percentage of current smokers was
 194 observed in Portugal. Almost all the subjects were atopic (from 94.6% in Portugal to 100% in Poland).
 195 The highest percentage of uncontrolled asthma was observed in the Philippines (59.4%), while the
 196 highest percentage of uncontrolled rhinitis was observed in Spain (55.8%). Significant center
 197 differences were observed in the mean RAPP total score (from 15.7 in Spain to 18.7 in the
 198 Philippines), even if the percentage of subjects with a good HRQoL ($RAPP < 15$) was not significantly
 199 different.

200

201 **Analysis according to diseases control**

202 A total of 263 subjects (45.7%) were in the CR/CA group (both diseases controlled); 134
 203 subjects (23.3%) were in the UR/CA group (uncontrolled rhinitis only). A total of 73 subjects were
 204 in the CR/UA group (uncontrolled asthma only), while 105 subjects were in the UR/UA group (both
 205 diseases uncontrolled). Figure 1 represents the RAPP total score distribution by class. The mean (SD)
 206 RAPP total scores by group were 13.5 (SD=4.1) in CR/CA, 18.1 (SD=5.1) in UR/CA, 18.5 (SD=4.4)
 207 in CR/UA, and 23.3 (SD=5.8) in UR/UA. Table 2 summarizes the pairwise mean differences between
 208 the four classes. Mean RAPP total scores were significantly different for all the class pairs, except
 209 for CR/UA and UR/CA.

210

211 **ROC analyses**

212 Figure 2 shows the ROC curves for the three disease outcomes. When having uncontrolled
213 rhinitis was used as the outcome, the AUC was 0.78 (95% CI: 0.73, 0.83). When having uncontrolled
214 asthma was used as the outcome, the AUC was 0.83 (95% CI: 0.78, 0.87). When having both diseases
215 uncontrolled was used as the outcome, the AUC was 0.92 (95% CI: 0.89, 0.95).

216 The optimal RAPP cutoffs and the relevant performance indicators are reported in Table 3 for each
217 disease outcome. The best cutoff for detecting uncontrolled rhinitis (UR/CA vs. CR/CA) was
218 $RAPP \geq 15$ (SE=75%, SP=69%, accuracy=71%, OR=6.8, adjusted OR=7.0). The best cutoff for
219 detecting uncontrolled asthma (CR/UA vs. CR/CA) was $RAPP \geq 16$ (SE=78%, SP=76%,
220 accuracy=76%, OR=11.1 adjusted OR=14.4). The best cutoff for detecting an uncontrolled status of
221 both diseases (UR/UA vs. CR/CA) was $RAPP \geq 18$ (SE=86%, SP=87%, accuracy=86%, OR=39.1,
222 adjusted OR=42.0).

223

224

225 **DISCUSSION**

226

227 The impact of asthma and comorbid rhinitis on the symptoms, control, and HRQoL are a main
228 component of disease management. PROs are increasingly being recommended as a part of routine
229 practice to provide a standardized method for detecting the patient's perspective (2). User guides to
230 implement PROs in clinical practice have well defined the psychometric standards and practical
231 characteristics that the questionnaires should have (22,23).

232 In recent years, the pathogenic view of AR and asthma has changed, and epidemiological and
233 clinical evidence has confirmed the link between the upper and lower airways (25-27). In light of the
234 concept of "united airway disease", the clinical routine should guarantee an integrated approach to
235 optimize outcomes.

236 The RAPP (24) is the first validated tool for individual assessment of HRQoL in management
237 of upper and lower respiratory allergy, and it is now available in five languages (24, 33-36). The tool
238 is clinically applicable in daily practice: patients may fill in and score it in a few minutes, and the
239 result interpretation is immediate.

240 Disease control is the key outcome in the treatment of asthma and AR (44). Reaching this goal
241 offers the opportunity to reduce or even avoid the impact of respiratory allergies on HRQoL.

242 This post hoc analysis of a large cross-sectional study provided new insights into the HRQoL of
243 patients with AR and asthma in a real-life setting.

244 Our results indicate that the rate of patients who achieved disease control varies and is significantly
245 different across countries, ranging from 36 to 56.7% for both AR and asthma controlled, from 4.7 to
246 43% for AR or asthma uncontrolled, and from 5.5 to 6.9% for both uncontrolled. These findings are
247 in agreement with the results of numerous studies evaluating control in respiratory allergies. The
248 REALISE study reported uncontrolled asthma in 45% and 49.7% of patients in Europe and Asia,
249 respectively (45). In a large multicenter study performed in 12 European countries, the percentage of

patients with suboptimal asthma control was 56.7% (46). Available literature data on AR control showed that this goal is achieved in approximately 40-45% of patients (47,48), independent of the treatment. The high variability we found could be due to the different sociodemographic (gender, age, education level, employment status) and clinical (atopy, disease severity) features of patients in each center. The limited number of selection criteria (adult age, AR and asthma diagnosis according guidelines, and willingness to participate in the study) affected eligibility for recruitment. However, the statistical analyses we performed in each country during the validation process, excluded the possible effect of sociodemographic features on RAPP answers.

In contrast, the percentage of subjects with an optimal HRQoL was not significantly different across countries. More than half of the patients still failed to achieve this goal, with percentages ranging from 54.3 to 66.7%.

Failure to reach optimal HRQoL is strictly related to the level of AR and asthma control.

Median RAPP scores lower than 15, indicating optimal HRQoL, were detected only for patients in which AR and asthma were controlled. This result is in line with previous studies that showed an association between disease control and HRQoL (49). Moreover, the comparison across classes of disease control allowed us to detect how much the RAPP score increases when patients are not controlled, all largely exceeding the MID. Indeed, having uncontrolled AR or asthma, compared to achieving control in both diseases, results in 4.7 and 5 extra points, respectively. This slight difference confirms how, from patient's viewpoint, when disease control is not achieved, no matter if related to upper and lower respiratory tracts, HRQoL scores get worse. In patients with both uncontrolled AR and asthma, RAPP was 5.1 points higher than in patients with uncontrolled AR and controlled asthma and 4.8 points higher than in patients with controlled AR and uncontrolled asthma. The findings indicate that both AR and asthma control are perceived by patients in terms of HRQoL, with differences that are not only statistically but also clinically significant.

No statistically significant difference was detected in the mean RAPP score between patients who achieved the control in one of the two diseases. However, ROC analyses identified increasing cutoffs

values of the RAPP score (15, 16, 18) associated with an increasing ability (in terms of sensitivity, specificity, and AUC) to forecast uncontrolled rhinitis, uncontrolled asthma, or uncontrolled rhinitis and asthma). (Fig. 2). In particular, a RAPP score ≥ 18 (namely 4 points higher than the optimal HRQoL) increases the odds of having uncontrolled rhinitis and asthma by 39.1 times. After adjusting for sociodemographic and clinical outcomes through multivariable logistic regression models, the odds ratio improved. These results suggest that, independent of the characteristics of the patients, the RAPP score is able to predict the likelihood of uncontrolled AR and asthma. A simple tool as RAPP could be easily be incorporated into routine assessment of patients with upper and lower respiratory allergy to better tailor treatment decisions to patients' needs.

Some limitations should be considered in the evaluation of our results. Patient selection bias cannot be excluded because patients were recruited from specialist centers and the sample was nonrandomized. In addition, the data were analyzed for the whole study population, however, there was some country-specific variations among respondents in terms of demographic and clinical characteristics.

The present findings provide a better understanding of the clinical relevance of HRQoL assessment in daily practice. In addition to detecting the disease impact from the patient's perspective, RAPP provides an estimate of risk on uncontrolled AR and asthma. This information, available in real time, gives clinical meaning to subjective experience about disease and treatment, and can be used to support shared disease management.

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448 **Figure legends**

449

450 **Figure 1.** RAPP total score distribution by disease class. The boxplots represent the median (central
451 line), 25th–75th percentiles (box) and min-max (whiskers) of the RAPP total score.

452 **Figure 2.** Receiver operating characteristic curves. Predictor: RAPP total score. Outcome A: being
453 in the UR/CA group (uncontrolled rhinitis and controlled asthma) rather than in the baseline group
454 (CR/CA, i.e. both diseases controlled) (Panel A). Outcome B: being in the CR/UA group (controlled
455 rhinitis and uncontrolled asthma) rather than in the baseline group. Outcome C: being in the UR/UA
456 group (both diseases uncontrolled) rather than in the baseline group.

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Journal Pre-proof

Appendix E1. RhinAsthma Patient Perspective (RAPP)

The following questionnaire will evaluate the impact of rhinitis and asthma in daily life. Please indicate how much you have been bothered during the last 2 weeks by:

1. Stuffy or runny nose, sneezing or itchy nose
2. Itchy eyes, watery eyes, sore eyes and eye redness
3. Difficulty in concentrating
4. Wheezing, cough, chest tightness, shortness of breath
5. Problems in sleeping (i.e., night awakenings)
6. Having to avoid certain areas and environments
7. Having to take drugs
8. Limitation in performing some activities (i.e., working, studying, sports)

Score Scale:

1. Nothing at all
2. A little
3. Enough
4. Much
5. Very much

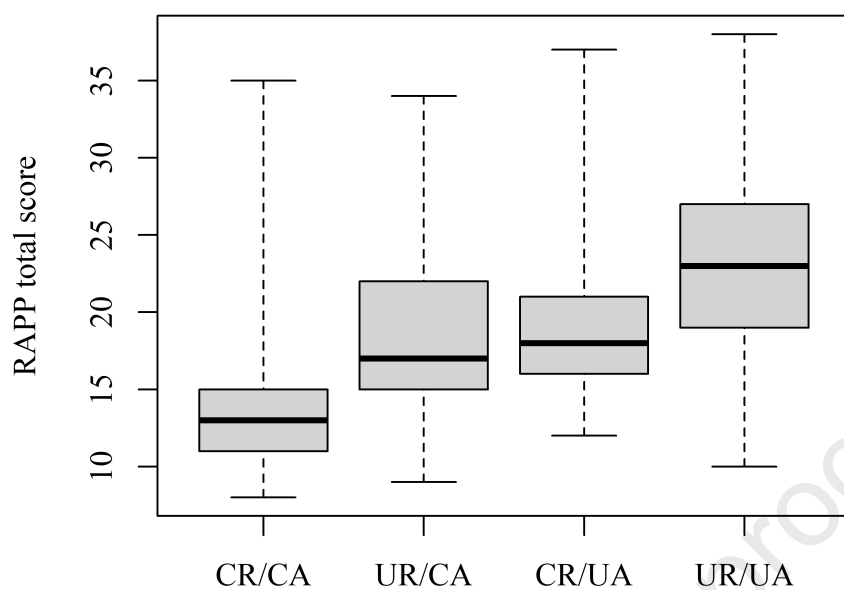
Appendix E2. Cross-cultural adaptation and validation of RAPP in English, Spanish, Portuguese and Polish (33-36).**Adaptation process**

The original Italian version was independently translated. The process of cross-cultural adaptation was conducted according to international guidelines with 2 forward and backward translations.

Validation process

The following psychometric properties have been evaluated:

- Scale's dimension by means of explorative and confirmative factor analysis.
- Internal consistency using Cronbach's alpha on the whole test.
- Reliability by means of interclass coefficient (ICC) and Lin's concordance correlation coefficient (CCC)
- Convergent validity using Spearman's between RAPP and SF-12
- Discriminant validity by means of ANOVA (Fischer's test) comparing patients according to ACT, GINA and ARIA classification of severity.
- Responsiveness by analyzing the correlation between changes in RAPP scores and changes in GRS, VA S and ACT by means of a non-parametric test (Spearman correlation coefficient).
- Minimal important difference (MID) was determined by applying the receiver operating characteristics (ROC) curve method. The entire cohort for one dichotomization point (i.e., 'no change' vs 'any improvement or deterioration') was adopted.



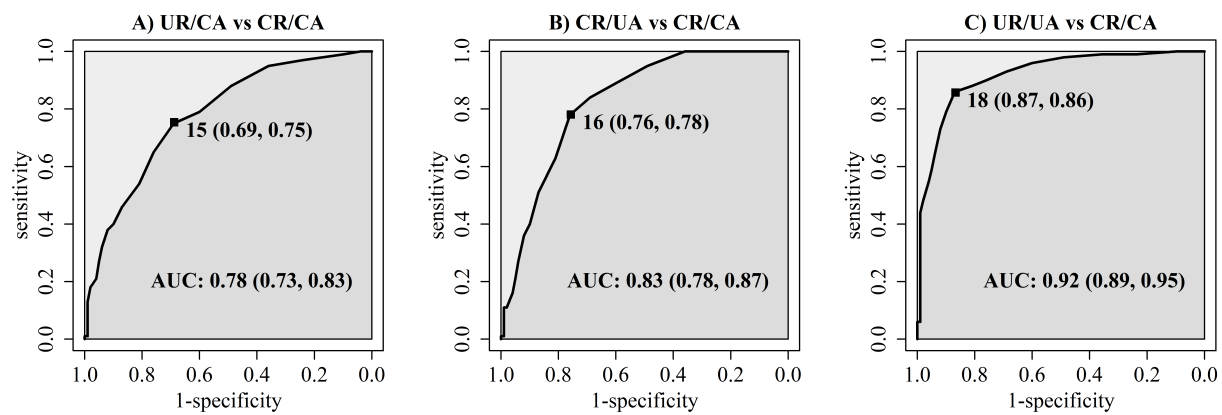


Table 1. Patient characteristics by centre. Data are reported as mean (SD) for quantitative variables and no. (%) for categorical variables.

	Philippines n=150 (26.1%)	Poland n=127 (22.1%)	Portugal n=149 (25.9%)	Spain n=149 (25.9%)	p-value ^s
Age, years	39.3 (15.5)	34.8 (12.5)	36.8 (13.2)	37.7 (10.3)	0.054
Female gender	111 (74.0)	68 (53.5)	98 (65.8)	93 (62.4)	0.005
BMI, kg/m ²	26.6 (7.3)	25.3 (4.6)	24.5 (3.9)	25.1 (5.8)	0.118
Education					<0.001
Primary/middle school	73 (48.7)	66 (52.0)	65 (43.6)	39 (26.2)	
Graduate	77 (51.3)	61 (48.0)	84 (56.4)	110 (73.8)	
Employment status					<0.001
Unemployed/retired	66 (44.0)	32 (25.2)	46 (30.9)	30 (20.1)	
Employed	84 (56.0)	95 (74.8)	103 (69.1)	119 (79.9)	
Smoking habits					<0.001
Never-smoker	106 (70.7)	92 (72.4)	128 (85.9)	91 (61.1)	
Current smokers	27 (18.0)	19 (15.0)	6 (4.0)	28 (18.8)	
Ex-Smoker	17 (11.3)	16 (12.6)	15 (10.1)	30 (20.1)	
Atopy	149 (99.3)	127 (100.0)	141 (94.6)	142 (95.3)	0.003
Rhinitis					<0.001
Intermittent	59 (39.3)	47 (37.0)	43 (28.9)	87 (58.4)	
Persistent	91 (60.7)	80 (63.0)	106 (71.1)	62 (41.6)	
Rhinitis severity					<0.001
Mild	107 (71.3)	52 (40.9)	60 (40.3)	135 (90.6)	
Moderate	43 (28.7)	75 (59.1)	89 (59.7)	14 (9.4)	
Asthma severity (GINA)					<0.001
Step 1	86 (57.3)	9 (7.1)	59 (39.6)	102 (68.5)	
Step 2	2 (1.3)	37 (29.1)	31 (20.8)	16 (10.7)	
Step 3	33 (22.0)	15 (11.8)	18 (12.1)	18 (12.1)	
Step 4	29 (19.3)	27 (21.3)	35 (23.5)	11 (7.4)	
Step 5	0 (0.0)	39 (30.7)	6 (4.0)	2 (1.3)	
ACT total score	18.2 (4.0)	20.9 (3.7)	22.0 (3.2)	23.0 (3.4)	<0.001
VAS	4.7 (2.6)	3.3 (2.9)	5.0 (2.5)	5.3 (2.8)	<0.001
Rhinitis / asthma control					<0.001
VAS≤5 / ACT>19 (CR/CA)	54 (36.0)	72 (56.7)	76 (51.0)	61 (40.9)	
VAS>5 / ACT>19 (UR/CA)	7 (4.7)	19 (15.0)	44 (29.5)	64 (43.0)	
VAS≤5 / ACT≤19 (CR/UA)	34 (22.7)	24 (18.9)	10 (6.7)	5 (3.4)	
VAS>5 / ACT≤19 (UR/UA)	55 (36.7)	12 (9.4)	19 (12.8)	19 (12.8)	
RAPP total score	18.7 (6.4)	16.6 (6.9)	16.9 (5.5)	15.7 (4.6)	<0.001
HRQoL					0.136
Impaired HRQoL (RAPP≥15)	100 (66.7)	69 (54.3)	90 (60.4)	83 (55.7)	
Optimal HRQoL (RAPP<15)	50 (33.3)	58 (45.7)	59 (39.6)	66 (44.3)	

[§]Kruskal-Wallis (quantitative variables), Chi-square (categorical variables) or Fisher's exact test (for atopy and asthma severity). Significant p-values are in bold. CR: controlled rhinitis. CA: controlled asthma. UR: uncontrolled rhinitis. UA: uncontrolled asthma.

Table 2. Pairwise group differences in the RAPP total score and 95% family-wise confidence intervals (CI) from Tukey's honest multiple comparisons. CR: controlled rhinitis. CA: controlled asthma. UR: uncontrolled rhinitis. UA: uncontrolled asthma.

Group comparison	Mean RAPP total score difference (95% CI)
UR/CA - CR/CA	4.7 (3.4, 5.9)
CR/UA - CR/CA	5 (3.4, 6.6)
UR/UA - CR/CA	9.8 (8.4, 11.2)
CR/UA - UR/CA	0.3 (-1.5, 2.1)
UR/UA - UR/CA	5.1 (3.5, 6.7)
UR/UA - CR/UA	4.8 (3, 6.7)

Significant differences are in bold.

Table 3. Area under the ROC curve (AUC) and performance indicators associated with the optimal RAPP cut-off by disease outcome: sensitivity, specificity, overall accuracy, and odds ratio. CR: controlled rhinitis. CA: controlled asthma. UR: uncontrolled rhinitis. UA: uncontrolled asthma.

	UR/CA vs. CR/CA	CR/UA vs. CR/CA	UR/UA vs. CR/CA
AUC (95% CI)	0.78 (0.73, 0.83)	0.83 (0.78, 0.87)	0.92 (0.89, 0.95)
Cut-off point	RAPP $\geq$ 15	RAPP $\geq$ 16	RAPP $\geq$ 18
Sensitivity	75%	78%	86%
Specificity	69%	76%	87%
Overall accuracy	71%	76%	86%
Odds ratio (95% CI)	6.8 (4.3, 11.0)	11.1 (6.1, 21.2)	39.1 (20.9, 77.5)
Adjusted [§] odds ratio (95% CI)	7.0 (4.2, 11.9)	14.4 (7.3, 29.9)	42.0 (20.4, 94.4)

[§]Adjusted by age, gender, BMI, education, employment status, smoking habits, atopy, rhinitis severity and asthma severity through multivariable logistic regression models.