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REVIEW ARTICLE

Patients' values and preferences for health states in allergic rhinitis—An artificial intelligence supported systematic review

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Abstract

Background: Allergic rhinitis (AR) impacts patients' physical and emotional well-being. Assessing patients' values and preferences (V&P) related to AR is an essential part of patient-centered care and of the guideline development process. We aimed to systematically summarize the information about patients' V&P on AR and its symptoms and impact on daily life.

Methods: We conducted systematic review in a MEDLINE, Embase, PsychInfo, and CINAHL databases. We included studies which quantitatively assessed patients' V&P for specific outcomes in AR by assessing utilities, applying discrete choice approaches, or rating and ranking outcomes. We grouped outcomes as AR symptoms, functional status, and care-related patient experience. Study selection and data extraction were

Abbreviations: AR, allergic rhinitis; ARIA, Allergic Rhinitis and its Impact on Asthma; CoE, certainty of evidence; DCE, discrete-choice experiment; EQ-5D, EuroQol5 Dimension; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HRQoL, health-related quality of life; HUI, Health Utilities Index; PAR, perennial allergic rhinitis; PBI, Patient Benefit Index; PNQ, Patient Needs Questionnaire; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RSUI, Rhinitis Symptom Utility Index; SAR, seasonal allergic rhinitis; SF-6D, Short Form 6 Dimension; SG, standard gamble; SR, systematic review; TTO, time trade-off; V&P, values and preferences; VAS, visual analogue scale; WTP, Willingness to pay.

supported by the Laser AI tool. We rated the certainty of evidence (CoE) using the GRADE approach.

Results: Thirty-six studies (41 records) were included: nine utility studies, seven direct-choice studies and 21 studies of rating or ranking outcomes. Utilities were lower with increased AR severity and with the concomitant presence of asthma, but not with whether AR was seasonal or perennial (CoE = low–high). Patients rated AR symptom-related outcomes as more important than those related to care-related patient experience and functional status (CoE = very low–moderate). Nasal symptoms (mainly nasal congestion) followed by breathing disorders, general and ocular symptoms were rated as the symptoms with the highest impact.

Conclusions: This systematic review provides a comprehensive overview of V&P of patients with AR. Patients generally considered nasal symptoms as the most important. Future studies with standardized methods are needed to provide more information on V&P in AR.

KEYWORDS
allergic rhinitis, health states, systematic review, utility, values and preferences

1 | INTRODUCTION

Allergic rhinitis (AR) is a common condition, affecting approximately 18.1% of population.[1] Its symptoms can vastly reduce the quality of life and pose a high economic burden, primarily because of indirect costs due to lost school days and workdays.[2-4] In fact, studies indicate that AR may significantly affect academic and work performance - AR can lead to a decrease of over 30% in both work and academic productivity.[3,5-7] Considering that, and the fact that AR is highly prevalent among children and individuals of working age, its total impact on work and school productivity may be higher than that of other chronic diseases that predominantly affect older individuals (e.g., coronary heart disease or type II diabetes).[3,8]

Cross-sectional studies indicate that health-related quality of life (HRQoL) of patients with AR can be 25% lower than that of the general population.[9] A comparison of calculated EQ-5D utility index scores showed that the baseline mean utility for patients with AR was similar to those with other chronic conditions like migraine, hypertension, or psoriasis.[10] The decrease in HRQoL highlights the importance of conducting patient-centered research and implementing treatment strategies that consider both the medical and HRQoL components of AR.

Given the relevant burden of AR on patients and society, understanding the values and preferences (V&P) of patients or the relative importance of health outcomes regarding AR and its management is essential for evidence-based decision-making. According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group, V&P are defined as "the relative importance people place on specific outcomes"[11] (a more detailed explanation of the concept and importance of V&P is available in Box 1). Considering them in AR is especially relevant as, for AR, besides drug-related aspects (e.g., the route of administration or the choice between monotherapy or combination therapy), disease-related aspects such as symptom severity and co-morbidities require proper consideration.

Patients' V&P are key for any decision to assess the benefits and harms of an intervention. Together with the risk difference or absolute effect of an intervention, they determine if an intervention does or does not have net health benefits, as well as the magnitude of the benefits. Values constitute, thus, a key criterion in the GRADE Evidence to Decision Framework to be accounted for when formulating guideline recommendations, along with the desirable and undesirable effects of healthcare interventions.[7,12] For adequately considering patients' V&P in guideline development, systematic reviews on that topic are crucial. In fact, summarizing the evidence systematically allows not only to comprehensively assess patients' V&P on all attributes which have been assessed in the literature but also for appraising the quality and gaps of available evidence. Nevertheless, we found no existing systematic review related to the V&P of patients with AR.

Therefore, we conducted a systematic review to gather all available evidence assessing patients' V&P for AR-related health outcomes following previously established methodology.[13,14] This review aims to provide information for those making recommendations about the prevention and treatment of AR and, specifically, to inform the next revision of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines.

2 | METHODS

2.1 | Protocol and registration

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15] We developed (ES, EB, AJN HJS, JLB) and

BOX 1 Key concepts and importance of values and preferences

What are values and preferences?

Values and preferences (V&Ps) express the relative importance that people place on health outcomes. That is, V&P imply assessing the outcomes that the patients judge to be more important. As indicated by the Agency for Healthcare Research Quality (US), such preferences reflect "the degrees of subjective satisfaction, distress or desirability that patients or potential patients associated with particular health outcomes" (these outcomes include, among others, health conditions, different severities of a same condition, and/or specific symptoms). Therefore, V&Ps do not directly deal with whether patients may prefer one treatment over another, but rather with how patients value the different outcomes that may result from the use of an intervention.

Why are values and preferences important?

Healthcare interventions (such as pharmacological interventions) are associated with outcomes corresponding to desirable or undesirable effects. Considering V&Ps allow decision makers to better understand the balance between such desirable and undesirable effects.

As an example, an H1-antihistamine for the treatment of allergic rhinitis may lead to a 30% reduction in nasal symptoms (desirable health effect) but also to a 30% increase in the risk of side effects (undesirable health effect). If patients placed more importance on nasal symptom improvement (benefits/desirable health effects) than on the risk of having side effects (undesirable health effects), then the balance of benefits and harms would favor the use of the antihistamine.

V&Ps, therefore, inform on how patients value the different health states that may result from the use of an intervention. This is important, as it allows decision makers and guideline developers to better understand the balance between desirable and undesirable effects of an intervention and, therefore, to formulate more patient-centered recommendations. From a clinical point of view, it is also relevant to understand what typically patients value more (e.g., what are the symptoms that are associated with the highest impact) in order to support decisions meeting more adequately patients' preferences.

What are utilities?

"Utilities" are the most common way of quantitatively measuring V&Ps. Outcomes/health states associated with higher utilities are also those associated with higher desirability (the maximum utility value is 1, corresponding to "perfect health"; a utility value of 0 corresponds to "being dead"). As an example, let us consider that:

- having poorly controlled allergic rhinitis is associated with an utility of 0.80;
- having well-controlled allergic rhinitis but experiencing bitter taste due to the use of medication is associated with an utility of 0.85.

In this case, patients place more value on having well-controlled allergic rhinitis and experiencing bitter taste than of having poorly controlled allergic rhinitis.

registered the protocol for this review in PROSPERO (registration number CRD42022326825).

2.2 | Criteria for considering studies for this review

We included studies assessing the V&P of participants of any age who had AR (or the V&P of their caregivers in the case of children with AR) in any geographical region. We included studies assessing patients with all types of AR with or without comorbidities. We excluded studies including some patients with AR as comorbidity, but not presenting separate results for those patients with AR. We also excluded studies reporting other types of rhinitis (e.g., non-allergic rhinitis).

We included only original quantitative studies that assessed patients' V&P for specific outcomes in AR. Studies with the following characteristics were eligible:

- Studies assessing patient utilities and health status values—studies that examined how patients value alternative health states using measurement techniques such as standard gamble, time trade-off, visual analog scale (VAS), or mapping results from generic instruments measuring health-related quality of life (e.g., EuroQol5 Dimension (EQ-5D), Short Form 6 Dimension (SF-6D), The Health Utilities Index (HUI)).
- Discrete-choice experiments—studies that examined patients' choices when they were presented with a decision aid, using probabilistic trade-off techniques, discrete choice, willingness to pay or randomized controlled trials for preferences, among others.
- Rating or ranking of treatment outcomes studies—studies assessing health states by quantitatively exploring the patients' views, attitudes, satisfaction, or preferences on outcome importance through questionnaires or scales that were not utility measurement techniques.

We excluded case reports, case series, health economic evaluation studies without original utility elicitation, studies only reporting HRQoL information without utilities or health status values, studies evaluating not patient-reported data (e.g., analyses of health records), and qualitative or quantitative studies that explored patients' views, attitudes or preferences only related to different treatment options without addressing the importance of the outcomes. We did not place restrictions on publication date, status, or language.

2.3 | Search methods for identification of studies

We searched Medline (via Ovid), Embase (via Ovid in original review and Elsevier in update), PsychInfo (via Ovid), and CINAHL (via EBSCO) on April 14, 2022, performing an updated search on September 5, 2023. We used a combination of terms related to AR and a search filter for patient V&P developed by Selva et al.[16] The full original electronic bibliographic search strategy is presented in the Tables E1–E4. To ensure comprehensiveness, we supplemented the searches with a citation search performed in Litmaps,[17] Research Rabbit,[18] and Laser AI.[19] We applied backward and forward citation analysis of the included studies and related systematic literature reviews, cost-effectiveness, or cost-utility studies. We also searched the conference abstracts of the International Society for Quality of Life[20] and the Society for Medical Decision Making.[21]

2.4 | Selection of studies

After (i) deduplication performed in Laser AI (machine learning deduplication algorithm) supplemented with manual verification, and (ii) a pilot exercise with a previously prepared screening guide, three reviewers (ES, EB, JLB) independently screened titles and abstracts for eligibility using the Laser AI tool. Reviewers resolved disagreements by consensus or through the decision of a third reviewer using a dedicated Laser AI panel. Subsequently, paired full-text screening was independently conducted by three reviewers (ES, EB, JLB) using the Laser AI tool.[19] We resolved any discrepancies by consensus or with the help of the third reviewer, if necessary.

2.5 | Data abstraction and analysis

After assessment of potential multiple records of the same study, two reviewers independently extracted data from all included quantitative studies using Laser AI and Microsoft Excel. Extracted data included author name, publication year, participant information (age and sex distribution, among others), sample size, methodological characteristics required to assess the risk of bias and directness of the information, survey techniques, and information about V&P. The extraction process was supported by Laser AI machine learning functionalities (using controlled vocabularies previously created in the tool)—potentially relevant data were automatically extracted by Laser AI and then verified by the reviewers. All discrepancies were discussed and resolved by consensus.

2.5.1 | Data analysis and result presentation

During the full-text screening, we classified studies into three categories according to the method used to elicit V&P[22]: (i) utility studies, (ii) direct-choice studies, and (iii) studies of rating or ranking the importance of outcomes.

We did not assess attributes related only to the treatment itself (e.g., administration form or costs, because they were outside of the scope of this systematic review), unless they were part of rank in the study.

For utility studies, we provided utilities and disutilities associated with the disease as a whole as well as according to the severity level, presence of comorbidities, and disease stage. In addition, we reported utilities and disutilities for each individual symptom. To prevent the overlap of results, when both utility values and health state values (e.g., EQ-5D VAS) were presented in the study, we extracted only the utility values. Given the high heterogeneity of data, meta-analysis was not performed. Instead, results on utilities and disutilities were presented narratively and using descriptive statistics.

We summarized the results of discrete choice studies using tables of pairwise comparisons, displaying attributes from all included studies in a matrix. Filled cells of the matrix show the proportion of times when a certain attribute in each pair was preferred,[23] for example, if the time to first dose benefit and time to maximum relief had both been assessed by three different studies and time to first dose benefit was preferred in all of them, this would be shown as 3/3, favoring time to first dose benefit.

For studies assessing the rating or ranking of health states (i.e., non-utility studies), to facilitate the analysis and interpretation of the relative importance of outcomes/attributes, we categorized such outcomes/attributes into three groups: (i) functional status, (ii) care-related patient experience, and (iii) symptoms. We presented the percentage of studies in which each outcome was ranked as the most and second most important health state. Definitions on the groups and on the analysis methods are displayed in Appendix S1.

2.6 | Risk of bias and indirectness of the results of the included studies

To assess risk of bias and indirectness of the included studies, we used the ROBVALUE and DIRECTVALU tools recently developed and validated by our research group at the McMaster GRADE Center (Karam et al. manuscript in review)[24] (details in Appendix S1). A single reviewer assessed risk of bias and indirectness and a second reviewer double-checked the assessment. Any disagreements were resolved by discussion and/or arbitration by a third author. We were not able to assess the risk of bias in the four direct-choice studies for which only conference abstracts were available and, thus, did not include them in the full analysis.

2.7 | Certainty of evidence

In addition to evaluating the quality of individual studies, we gauged the overall confidence in the evidence utilizing the GRADE approach.[13] The certainty of evidence (CoE) for each health state was categorized as "high," "moderate," "low," or "very low."

3 | RESULTS

3.1 | Search results

We identified 15,409 records in the databases (Figure E1). After excluding 4526 duplicates, we screened 10,883 titles and abstracts. We were unable to locate the full text for seven records, even after contacting with the study authors. We reviewed 296 full texts for eligibility and included 38 reports.[25-62] Two additional studies[63,64] were identified through a citation search, and one unpublished study was included.[65]

We identified 36 studies (comprising a total of 41 reports—33 full-text articles and 8 conference abstracts) for inclusion in the systematic review.

3.2 | Description of included studies and study quality

The 36 included studies assessed 43,155 participants (Table 1) and were published between 1998 and 2023. The sample size ranged between 100 and 3656 patients. Most studies assessed adults. Studies

TABLE 1 Descriptive study characteristics.

	Utility studies	Direct-choice studies	Studies of rating or ranking outcomes
Number of studies	9	7	21
Number of publications	11	10	22
Publication type available			
Full text	10	3	21
Abstract	0	4	0
Publication year			
<2012	3	1	11
2012–2022	8	9	10
Study characteristics			
Elicitation method/measurement tool	EQ-5D: 4 SG: 3 Rating scales: 8 RSUI: 2 TTO: 1	DCE: 6 WTP: 3 Contingent choice[a]: 1	Questionnaire[b]: 21
Sample size (overall)	15,609	6444	21,572
Respondent type	Adults: 9 Children: 1	Adults: 5 Caregivers: 2 Not reported: 2	Adults: 16 Children: 3 Caregivers: 5 Adults+children: 3
Geographical region			
Europe	4	3	11
North America	1	1	8
South America	–	–	1
Middle East	1	–	1
Asia	3	–	1
Africa	–	–	–
Australia and Oceania	–	2	1
Not reported	–	1	2

Abbreviations: DCE, discrete-choice experiment; EQ-5D, EuroQol five-dimensions; RSUI, Rhinitis Symptom Utility Index; SG, standard gamble; TTO, time trade-off; WTP, willingness to pay.

[a]Direct assessment (5-point Likert scale transformed to values from 0 to 100).

[b]Questionnaires include Patient Needs Questionnaire, Patients Benefit Questionnaire, Assessment of Patient Preferences for Relief of Symptoms instrument, Allergies in Latin America Survey, Patient Voice Allergy Survey and unspecified questionnaires related to AR.

were mainly conducted in Europe and North America. Studies rating or ranking treatment outcomes were the most common ones (21 studies), followed by direct-choice studies (7 studies) and studies of utilities (9 studies). Twenty-five studies did not provide information on how participants were classified/diagnosed with AR or only reported that "patients had been diagnosed by a physician." In only three of the remaining studies, the AR diagnosis involved both symptoms and skin tests and/or specific IgE. None of the included primary studies reported the inclusion of participants with local allergic rhinitis. Tables E5–E7 present the details of each study. Detailed information about the risk of bias and indirectness of included studies are presented in Tables E8–E13.

3.3 | Relative importance of outcomes

3.3.1 | Utility studies

Ten studies assessed utilities and health state values for AR (Table 2). In relation to severity, higher utilities in adult patients (range between 0.70 and 0.97) were observed for health states related to mild AR (CoE = low–high) (Table 2). A similar range was observed for the study in which AR diagnosis involved both clinical assessment and skin test and/or specific IgE. For health states related to severe AR, utilities ranged between 0.43 and 0.90 (CoE = low–high).

Four studies assessed utilities in the presence of concomitant asthma (two studies as self-reported asthma and other two as physician-diagnosed asthma), reporting that asthma associated with a reduction in the utilities of adult patients with AR (range = 0.73–0.97 for the presence of concomitant asthma vs 0.83–0.98 in its absence, CoE = low–high). Utilities rated by children were substantially lower than those rated by adults for all health states.

Patients with current symptoms reported lower health state values than patients without symptoms.[28] Regarding specific symptoms, in two studies,[29,32] utilities (measured by VAS) were lower for severe nasal congestion and severe rhinorrhea compared to severe sneezing, severe throat itching, and severe itchy eyes (CoE = low). When utilities were elicited with the standard gamble technique, severe itchy eyes were rated by US patients as the least preferred AR symptom (CoE = low). By contrast, Kumanomidou[27] found that higher severity of nasal symptoms (nasal congestion, sneezing, and rhinorrhea) displayed a stronger correlation with utility values than ocular symptoms (itchy eyes, watery/teary eyes). Tamayama[33] reported that patients with AR and current nasal symptoms had nonsignificantly higher utilities than those without current nasal symptoms (CoE = low).

Information on disutilities is presented in Table E14.

3.3.2 | Direct-choice experiment studies

The table of pairwise comparisons of attributes related to health outcomes assessed in direct-choice experiments is presented in Table E15. Most of the studies had only been published as conference posters, impairing the assessment of the CoE in most cases.

Attributes related to reduction and relief of symptoms were rated as more important for adult patients than the risk of side effects. Patients also showed a preference for more efficacious treatments than for treatments acting faster.

There were no studies reporting preferences for children as utilities or attributes. We included only two studies that also reported health outcome preferences among parents of children with AR. Parents showed a preference for a higher reduction of risk of systemic reactions, compared to adults with AR.

3.3.3 | Studies of rating or ranking of outcomes

Adult sample

In the adult sample (16 studies), there were 13 studies[45,46,48,49,50,54,56,57,58,59,60,63,64] in which AR symptoms were ranked as the most important and bothersome attributes (i.e., they were ranked as having the same or higher importance than functional status and care-related patient experience attributes). However, in eight of the 13 studies[45,48,49,54,58,60,63] variables related to the functional status or care-related patient experience were not assessed. Certainty of evidence was very low to moderate. The summary of findings for studies of rating or ranking of outcomes for adult patients is presented in Table 3 and Table E16.

Regarding specific symptoms, in 11 of 14 studies, a nasal symptom was ranked as the most and/or second most important attribute (CoE = low-moderate).[28,45,46,48,54,56,57,60,61,63,64]

All the analyzed nasal symptoms were ranked as the most or second most important attribute in at least one study. Notably, eight studies identified nasal congestion as the most important attribute[45,46,48,54,55,60,63,64] (CoE = low–moderate). One of those studies was that in which patients had been diagnosed both based on their clinical history and skin tests and/or specific IgE.

An ocular symptom was ranked as the most or the second most important attribute in three studies out of 13.[49,56,61] In particular, itchy eyes were identified as the most important or second most important in two studies[49,56] (CoE = low). In five studies out of eight,[46,50,58,59,64] a non-nasal respiratory symptom (namely, breathing difficulties) was identified as the most or second most important attribute (CoE = moderate).

Ear symptoms were never ranked as the most important attributes for patients (CoE = low). In two studies,[45,54] some general symptoms (e.g., headache) were ranked as the second most important health state (CoE = very low–low). In two studies,[50,61] itching was ranked as the most or second most important attribute (CoE = moderate).

Care-related patient experience outcomes were only assessed in six studies.[28,46,50,61,62,64]

In four of these studies, outcomes related to the effectiveness of treatments (fast relief, long lasting relief, complete treatment relief,

TABLE 2 Summary of findings for utility studies.

	Adults					
	Direct methods					Indirect methods
	Standard gamble		TTO	Rating scale		Equation 5D
Health state	Europe/ North America	Asia	Asia	Europe/North America	Asia/ Middle East	Asia/Middle East
Utility for different AR severity						
AR none/mild[32]						
AR mild[25,29,33]			0.96		0.82	0.87
AR mild/moderate[32]						
AR moderate[29,36]			0.94		0.71	
AR moderate/severe[25,32]						0.74
AR severe[29,33]			0.89		0.56	
AR severest[33]			0.83		0.43	
SAR none[27]						1.000[c]
SAR mild[27]						0.943[c]
SAR moderate[27]						0.909[c]
SAR severe[27]						0.849[c]
SAR most severe[27]						0.767[c]
Summary	In the adult population with different severity of AR, the results vary between each study because of different methods to elicit values and preferences and different geographical regions. Generally, patients value the mildest health states more than those severe. Utilities measured in Asian population by time-trade-off method range between 0.83 for severest AR and 0.94 for mild AR. The results of the same group of patients measured by rating scale are between 0.43 and 0.82. In the case of indirect methods, the results are consistent with the previous one—the worse disease severity, the worse utility. For EQ-5D tool, the range is 0.74–1.00 and for RSUI 0.67–0.79 (Europe/North America) and 0.49–0.82 (Asia/ Middle East).					
Utility for different AR severity + symptoms						
AR mild (with current nasal symptoms)[33]			0.97			
AR mild (without current nasal symptoms)[33]			0.96			
AR moderate (with current nasal symptoms)[33]			0.96			
AR moderate (without current nasal symptoms)[33]			0.93			
AR severe (with current nasal symptoms)[33]			0.90			
AR severe (without current nasal symptoms)[33]			0.87			
AR severest (with current nasal symptoms)[33]			0.83			
AR severest (without current nasal symptoms)[33]			0.82			

					Children		
					Direct methods		
	RSUI				Rating scale		
Europe	Europe/North America	Asia/Middle East	No. of studies/ respondents	Certainty of evidence	Europe	No. of studies/ respondents	Certainty of evidence
	0.79[f]		1/100	⨁⨁◯◯ [Ind, Imp][j,k]			
		0.82[f]	3/2224	⨁⨁⨁◯ [R][g,h]			
	0.70[f]		1/100	⨁⨁◯◯ [Ind, Imp][j,k]			
		0.70[f]	2/416	⨁⨁◯◯ [R Imp][h,k]			
	0.67[f]		2/1908	⨁⨁⨁⨁			
		0.49[f]	2/416	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/246	⨁⨁◯◯ [Ind, Imp][i,k]			
			1/246	⨁⨁◯◯ [Ind, Imp][i,k]			
			1/246	⨁⨁◯◯ [Ind, Imp][i,k]			
			1/246	⨁⨁◯◯ [Ind, Imp][i,k]			
			1/246	⨁⨁◯◯ [Ind, Imp][i,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			

(Continues)

TABLE 2 (Continued)

Health state	Adults					
	Direct methods					Indirect methods
	Standard gamble		TTO	Rating scale		Equation 5D
	Europe/ North America	Asia	Asia	Europe/North America	Asia/ Middle East	Asia/Middle East
Summary	In adult parents with AR and without nasal symptoms, utility values measured by time-trade-off method differ according to disease severity from 0.82 for severest AR to 0.96 for mild AR. In terms of patients with AR and current nasal symptoms, the utility range is 0.83–0.97. The utility values were stable regardless of the patients' current nasal symptoms.					
Utility for AR +/−symptoms						
AR (with current nasal symptoms)[33]			0.92			
AR (without current nasal symptoms)[33]			0.90			
Summary	Symptomatic patients with current nasal symptoms reported higher utility values compared to asymptomatic patients (0.92 vs. 0.90), although the observed difference is possibly due to chance.					
Utility related to AR treatment						
AR (controlled)[25]						0.9
AR (not controlled)[25]						0.7
AR only (good control)[a]						
AR only (partial control)[a]						
AR only (poor control)[a]						
AR + asthma (good control)[a]						
AR + asthma (partial control)[a]						
AR + asthma (poor control)[a]						
Summary	Patients with AR (Asia/Middle East) whose symptoms were well-controlled reported higher utility values (both measured with EQ-5D-3L and EQ-VAS) compared to subjects with symptoms not well controlled. In European countries, both patients with allergic rhinitis alone and those with concomitant asthma reported higher utility values when their diseases were well controlled compared to patients without disease control. Patients with allergic rhinitis and allergic rhinitis with asthma, whose symptoms were poorly controlled, reported similar utility values.					
Utility for AR +/−comorbidities						
PAR (without asthma)[30]	0.842					
PAR (with well-to-partly controlled asthma)[30]	0.849					
PAR (with uncontrolled asthma)[30]	0.818					
SAR (without asthma)[27]						0.92[c,d]
SAR (with asthma)[27]						0.77[c,d]
AR (with asthma)[26]						

					Children		
					Direct methods		
	RSUI				Rating scale		
Europe	Europe/North America	Asia/Middle East	No. of studies/ respondents	Certainty of evidence	Europe	No. of studies/ respondents	Certainty of evidence
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/300	⨁⨁◯◯ [R Imp][h,k]			
			1/1808	⨁⨁◯◯ [R, Ind][g,i]			
			1/1808	⨁⨁◯◯ [R, Ind][g,i]			
0.87–0.98			1/7905	⨁⨁◯◯ [R, Ind][g,l]			
0.84–0.95			1/7905	⨁⨁◯◯ [R, Ind][g,l]			
0.73–0.84			1/7905	⨁⨁◯◯ [R, Ind][g,l]			
0.84–0.97			1/7905	⨁⨁◯◯ [R, Ind][g,l]			
0.81–0.94			1/7905	⨁⨁◯◯ [R, Ind][g,l]			
0.73–0.87			1/7905	⨁⨁◯◯ [R, Ind][g,l]			
			1/1454	⨁⨁⨁⨁	0.655	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.650	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.638	1/1082	⨁⨁⨁⨁
			1/246	⨁⨁◯◯ [Ind, Imp][g,k]			
			1/246	⨁⨁◯◯ [Ind, Imp][g,k]			
0.836			1//2128	⨁⨁◯◯ [R, Ind][g,l]			

(Continues)

TABLE 2 (Continued)

Health state	Adults					
	Direct methods					Indirect methods
	Standard gamble		TTO	Rating scale		Equation 5D
	Europe/ North America	Asia	Asia	Europe/North America	Asia/ Middle East	Asia/Middle East
Summary	In adult European/North American patients with PAR and the similar level of disease severity with concomitant asthma, the lowest utility is 0.818 in PAR patients with uncontrolled asthma. Surprisingly, the higher utility was observed in patients with PAR and well-to-partly controlled asthma (0.849) than PAR without asthma (0.842). In the pediatric populations results of mean utility are substantially lower than in adults—range 0.638 (PAR + uncontrolled asthma) to 0.655 (PAR without asthma). In the subpopulation of adult patients from Asia region, the utility of SAR measured by EQ-5D was 0.77 for patients with asthma and 0.92 for those without asthma. These values were lower than those observed in the European population in the same scale, which had a utility score of 0.836						
Utility for different AR severity +/−comorbidities						
SAR mild (without asthma)[30]	0.880					
SAR mild (with well-to-partly controlled asthma)[30]	0.872					
SAR moderate (without asthma)[30]	0.864					
SAR moderate (with well-to-partly controlled asthma)[30]	0.847					
SAR severe (with well-to-partly controlled asthma)[30]	0.845					
SAR mild (with uncontrolled asthma)[30]	0.844					
SAR severe (without asthma)[30]	0.831					
SAR moderate (with uncontrolled asthma)[30]	0.828					
SAR severe (with uncontrolled asthma)[30]	0.812					
Summary	Mean utilities for SAR in adults according to the disease severity (measured by standard gamble method) vary from 0.812 (severe SAR) to 0.880 (mild SAR). Concomitant asthma causes significant decrease in the utility value. The lowest utility, 0.812, was calculated for adults with severe SAR and uncontrolled asthma. For the pediatric population, utilities (measured by rating scales) were lower than in adults and ranged between 0.666 (severe AR) and 0.705 (mild SAR). Also in this subpopulation, asthma caused utility decrease. Mean child-generated utilities for SAR with comorbidity were 0.635 for uncontrolled asthma and severe SAR, and 0.677 for well-to-partly controlled asthma and mild SAR. Adult patients also value more controlling asthma symptoms, if they appear, than having a more severe status of AR, which means that asthma is a more bothersome disease for patients than AR. Similar results are presented also for pediatric patients—for children, more important is having well o partly controlled asthma symptoms if it is a concomitant disease than having milder AR status.						
Utility of specific outcomes (multiple symptoms + duration)						
Moderate stuffy nose and itchy eyes (1–3 days)[29]		0.88[f]			0.56[f]	
Moderate stuffy nose and itchy eyes (4–7 days)[32]	0.62[f]			0.31[f]		
Moderate stuffy nose and runny nose (4–7 days)[32]	0.64[f]			0.23[f]		
Moderate stuffy nose and runny nose (8–14 days)[29]		0.75[f]			0.42[f]	
Severe stuffy nose, itchy eyes, and itchy throat/ moderate runny nose and sneezing (1–3 days)[32]	0.44[f]			0.08[f]		
Severe stuffy nose, itchy eyes, and itchy throat/ moderate runny nose and sneezing (4–7 days)[29]		0.46[f]			0.15[f]	
Severe stuffy nose/moderate runny nose and itchy eyes (4–7 days)[29,32]	0.57[f]	0.64[f]		0.16[f]	0.26[f]	

					Children		
					Direct methods		
	RSUI				Rating scale		
Europe	Europe/North America	Asia/Middle East	No. of studies/ respondents	Certainty of evidence	Europe	No. of studies/ respondents	Certainty of evidence
			1/1454	⨁⨁⨁⨁	0.705	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.677	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.675	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.668	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.663	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.643	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.666	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.647	1/1082	⨁⨁⨁⨁
			1/1454	⨁⨁⨁⨁	0.635	1/1082	⨁⨁⨁⨁
		0.86[f]	1/116	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.63[f]		1/100	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.64[f]		1/100	⨁⨁◯◯ [Ind, Imp][j,k]			
		0.73[f]	1/116	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.41[f]		1/100	⨁⨁◯◯ [Ind, Imp][j,k]			
		0.4[f]	1/116	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.5[f]	0.61[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			

(Continues)

TABLE 2 (Continued)

Health state	Adults					
	Direct methods					Indirect methods
	Standard gamble		TTO	Rating scale		Equation 5D
	Europe/ North America	Asia	Asia	Europe/North America	Asia/ Middle East	Asia/Middle East
Severe stuffy nose/moderate runny nose, itchy eyes, and itchy throat (1–3 days)[29,32]	0.63[f]	0.76[f]		0.19[f]	0.4[f]	
	Severity of symptoms, number of symptoms, and their duration were correlated with utility values.					
Utility of specific outcomes (single symptoms)[b]						
Severe sneezing[29,32]	0.69[f]	0.76[f]		0.23[f]	0.33[f]	
Severe throat itching[29,32]	0.68[f]	0.75[f]		0.20[f]	0.32[f]	
Severe itchy eyes[29,32]	0.61[f]	0.75[f]		0.2[f]	0.32[f]	
Severe nasal congestion[29,32]	0.68[f]	0.61[f]		0.17[f]	0.27[f]	
Severe rhinorrhea[29,32]	0.66[f]	0.61[f]		0.19[f]	0.27[f]	
Summary	In US and Chinese samples, severe sneezing and severe throat itching were rated as the most preferred. Utilities for severe nasal congestion and severe rhinorrhea (measured by Vas) were least preferred by patients. Utility scores (measured by SG) for severe itchy eyes varied between the US and Chinese subgroups. US patients rated this health state as the least preferred, probably due to geographic variations in disease characteristics.					

Note: The green shades reflect the health state with the highest utility values, while the red identifies the health state with the lowest utility among patients with allergic rhinitis, taking into account the regional distribution and elicitation method.

Abbreviations: Imp, certainty of evidence was lowered due to imprecision, ⨁⨁⨁⨁ high certainty of evidence, ⨁⨁⨁◯ moderate certainty of evidence, ⨁⨁◯◯ low certainty of evidence; Inc, certainty of evidence was lowered due to inconsistency; Ind, certainty of evidence was lowered due to indirectness; R, certainty of evidence was lowered due to risk of bias.

[a]Data from Vieira RJ et al.—manuscript under review.

[b]A corner symptom state was defined as one symptom at the worst possible level of severity (i.e., most severe) and frequency (i.e., 8–14 days).

[c]The combined data of 2019 and 2020.

[d]Values extracted from the graphs.

[e]100 was anchored as no rhinitis-related symptoms (i.e., best possible state) and 0 was anchored as severe rhinitis related symptoms for 8–14 days (i.e., worst possible state).

[f]A scale of 0–1, where 0 indicated the worst symptom(s) and 1 represented no symptom(s).

[g]We rated down certainty of evidence because in Al-Digheari 2018 response rate was low: 47.4%.

[h]We rated down certainty of evidence because in Tamayama 2009 response rate was low: 51%.

[i]We rated down the certainty of evidence for indirectness because an indirect measurement tool was used to elicit the utility of outcomes.

[j]We rated down the certainty of evidence for indirectness because an indirect measurement tool was used to elicit the utility of outcomes with scale of 0 to 1, where 0 indicated the worst symptom(s) and 1 represented no symptom(s).

[k]We rated down because of the small sample size of the included study creating uncertainty due to random error.

[l]We rated down certainty of evidence because low response rate (risk of bias).

and reduction of complaints and symptoms) were ranked as the most or second most important attributes[28,50,61,62] (CoE = very low–moderate). Outcomes related to safety, frequency of medication use, and mode of application were never considered among the two most important attributes, except in one study.[50]

Health states related to the functional status were assessed in seven studies.[28,46,50,57,59,61,64] Among functional status attributes, only those related to physical function were ever ranked as the most or second most important health state/attribute[50,59,61] (CoE = moderate).

Children/caregivers sample

Seven studies assessing children or their caregivers[48,51,52,54,56,58,63] were included in the relative importance analysis (Table 4, Table E17). Most of these studies only assessed symptom-related attributes. Similar to the adult population, a nasal symptom was frequently ranked as the most or second most important attribute[48,52,54,55,58,63] (CoE = low). In particular, nasal congestion was identified as the most important attribute in five studies[48,52,54,56,63] (CoE = low). In one study,[51] all three attribute categories were analyzed, and attributes pertaining to care-related patient experience

					Children		
					Direct methods		
	RSUI				Rating scale		
Europe	Europe/North America	Asia/Middle East	No. of studies/ respondents	Certainty of evidence	Europe	No. of studies/ respondents	Certainty of evidence
	0.61[f]	0.72[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.68[f]	0.69[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.68[f]	0.68[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.62[f]	0.68[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.7[f]	0.61[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			
	0.68[f]	0.61[f]	2/216	⨁⨁◯◯ [Ind, Imp][j,k]			

(treatment relief) and functional status (daily activities) were ranked as the most important or second most important attributes (CoE = low).

3.4 | Mixed population

Three studies assessed mixed (children and adults) populations[44,47,55] (Table 5, Table E18). Nasal symptoms were always considered among the most important health states/attributes (CoE = very low–low).

3.5 | Presentation of results by type of attribute

Presentation of results by type of attribute is available in Appendix S1 and Tables E19–E22.

4 | DISCUSSION

To our knowledge, this is the first systematic review in V&P of patients with AR, even though there had been previous systematic

TABLE 3 Summary of findings for studies of rating or ranking of outcomes (Adults only).

Health state/outcome	% of times the outcome was most important*	% of times outcome was second most important*	Number of studies/ respondents	Certainty of evidence
Functional status				
Cognitive function	0.00%	0.00%	6/5465	⨁⨁◯◯-⨁⨁⨁◯ Low–moderate certainty
Emotional function	0.00%	0.00%	7/9027	⨁⨁⨁◯ Moderate certainty
Physical function	**28.57%**	**14.29%**	7/9027	⨁⨁⨁◯ Moderate certainty
Sexual function	0.00%	0.00%	5/1830	⨁⨁⨁◯ Moderate certainty
Social function	0.00%	0.00%	6/5465	⨁⨁◯◯-⨁⨁⨁◯ Low-moderate certainty
Care-related patient experience				
Outcome/E	**50.00%**	**16.67%**	6/2079	⨁◯◯◯-⨁⨁⨁◯ Very low–moderate certainty
Outcome/S	0.00%	0.00%	5/1830	⨁⨁⨁◯ Moderate certainty
Related to treatment	0.00%	**16.67%**	6/2079	⨁⨁⨁◯ Moderate certainty
Symptoms				
Ear	0.00%	0.00%	3/5451	⨁⨁◯◯ Low certainty
General	**8.33%**	**25.00%**	12/14,728	⨁◯◯◯-⨁⨁⨁◯ Very low–moderate certainty
Nasal	**64.29%**	**14.29%**	14/13,584	⨁⨁◯◯-⨁⨁⨁◯ Low–moderate certainty
Ocular	**7.69%**	**15.38%**	13/10549	⨁◯◯◯-⨁⨁⨁◯ Very low–moderate certainty
Respiratory	**27.27%**	**18.18%**	11/13,513	⨁◯◯◯ -⨁⨁⨁◯ Very low-moderate certainty

Note: * and Bold values Percentage was calculated over all studies evaluating a given attribute.

reviews conducted for other respiratory diseases, like chronic obstructive pulmonary disease or asthma.[13,66,67]

Lower utilities were associated with increased AR severity. There were no such major differences between seasonal and perennial AR. These results suggest that severity displays a higher impact on utilities than the seasonal or perennial type of AR. Previous studies have found that AR severity played a more decisive role in quality of life, sleep and work impairment than duration.[68] The concomitant presence of asthma was also associated with lower utilities. Despite the across-study diversity, we observed that patients rated the nasal symptoms as the most important and bothersome ones. We observed lower utility values for nasal congestion, rhinorrhea, or sneezing compared to other AR symptoms. After nasal symptoms, ocular symptoms (e.g., watery, teary, or itchy eyes) showed the lowest associated utilities. Consistent results were obtained from rating or ranking studies for adults—in most of the included studies, among AR symptoms, nasal symptoms were the ones that bothered patients the most and nasal congestion was identified as particularly important. In direct-choice studies, we observed that patients have a strong preference for symptoms relief. Attributes related to the reduction of symptoms were more important for adult patients than the risk of side effects.

The main strength of our systematic review is its wide scope—we included any kind of studies assessing patients' V&P on AR. We decided to exclude all studies that explored patients' V&P related to different treatment options to focus mainly on disease-related aspects. We developed a sensitive search strategy with the use of a validated search filter for the V&P developed by Selva et al.[16] We searched not only standard databases but also grey literature, which allowed us to find additional relevant references.

Our study has several limitations. First, the diversity of utility studies (in the subsets based on which participants were classified, the methods to compute utilities, and the study region) prevented us from doing meta-analysis and exploring potential differences in V&P for patients' subgroups. Likewise, we could not perform a meta-analysis of ranking outcomes, as they (i) presented with different choices to participants and (ii) did not provide a proper effect size to pool. For direct-choice studies, most included studies had solely

TABLE 4 Summary of findings for studies of rating or ranking of outcomes (children/caregivers).

Health state/outcome	% of times the outcome was most important*	% of times outcome was second most important*	Number of studies/ respondents	Certainty of evidence
Functional status				
Cognitive function	0.00%	0.00%	1/345	⨁⨁◯◯ Low certainty
Emotional function	0.00%	0.00%	1/345	⨁⨁◯◯ Low certainty
Physical function	0.00%	**100.00%**	1/345	⨁⨁◯◯ Low certainty
Social function	0.00%	0.00%	1/345	⨁⨁◯◯ Low certainty
Care-related patient experience				
Outcome/E	**100.00%**	0.00%	1/345	⨁⨁◯◯ Low certainty
Outcome/S	0.00%	0.00%	1/345	⨁⨁◯◯ Low certainty
Related to treatment	0.00%	0.00%	1/345	⨁⨁◯◯ Low certainty
Symptoms				
Ear	0.00%	0.00%	3/1417	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty
General	0.00%	**40.00%**	5/1995	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty
Nasal	**71.43%**	14.29%	7/3261	⨁⨁◯◯ Low certainty
Ocular	0.00%	0.00%	7/3261	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty
Respiratory	**16.67%**	0.00%	6/2760	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty

Note: * and Bold values Percentage was calculated over all studies evaluating a given attribute.

TABLE 5 Summary of findings for studies of rating or ranking of outcomes (Mixed population).

Health state/outcome	% of times the outcome was most important*	% of times outcome was second most important*	Number of studies/ respondents	Certainty of evidence
Functional status				
Physical function	0.00%	0.00%	1/569	⨁⨁◯◯ Low certainty
Symptoms				
General	0.00%	**100.00%**	2/1070	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty
Nasal	**100.00%**	0.00%	3/1517	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty
Ocular	**50.00%**	**50.00%**	2/1016	⨁◯◯◯-⨁⨁◯◯ Very low-Low certainty
Respiratory	0.00%	0.00%	1/501	⨁◯◯◯ Very low certainty

Note: * and Bold values Percentage was calculated over all studies evaluating a given attribute.

been presented as conference posters. While possibly their quality may have been a factor precluding their publication, the fact that these studies have only been published in the abstract form rendered unfeasible the assessment of the risk of bias and indirectness due to inadequate information availability. In the case of nonutility rate and ranking studies, studies have been conducted with different, non-validated questionnaires, rendering it difficult to identify a common definition of described outcomes. An additional limitation

is that most studies do not provide sufficient detail on the AR diagnosis methods. However, those few studies reporting that AR has been diagnosed based on clinical history and skin tests or specific IgE displayed results consistent with the remaining studies. In addition, in studies reporting the impact of asthma on utilities in patients with AR, asthma was either self-reported or clinically diagnosed but without further details being provided. Finally, most of the included studies have been sponsored by the industry, something which may increase their risk of bias and have some influence on the obtained results. Overall, due to these limitations, the provided results should be interpreted with caution.

For guideline development on AR, this review can be a source of evidence on the patients' V&P that can be incorporated into an evidence-to-decision framework. This process ensures that recommendations not only reflect the clinical effectiveness of interventions but also account for patients' acceptability, being aligned with patients' priorities. In addition, this systematic review can highlight priorities and indicate new questions that should be formed and addressed in future guideline updates.

For healthcare professionals, this systematic review provides information allowing them to better understand patients' needs and views on AR, facilitating shared decision-making. Patient-centered care requires an understanding of patients' needs, values, and individual circumstances.

This systematic review shows a necessity to conduct further research on V&P of patients with AR. Although the current review provides a wide scope of findings, included primary studies vary in terms of the adopted methodologies and assessed populations, with this diversity possibly explaining some across-study inconsistencies. The variety of approaches highlights the importance of establishing standardized methods in future research, enabling higher comparability with other studies.

Given the comprehensiveness of this systematic review, the presented utility values can be relevant for future health economic evaluation studies. In particular, future cost-utility analysis studies may benefit from taking into account the utilities presented for different AR-related health states. A summary of the implications for research is presented in Table E23.

5 | CONCLUSION

This systematic review provides an informative overview of the existing literature regarding preferences of patients with AR. In general, the severity of AR appeared to have a larger impact on patients' preferences (as measured through utilities) than whether the AR is seasonal or perennial. Overall, patients rated outcomes related to AR symptoms as more important than those related to care-related patient experience or to the impact of AR on the functional status. Among AR symptoms, nasal symptoms (particularly nasal congestion), followed by non-nasal respiratory, and ocular symptoms were the ones that tended to be rated by patients as most important. However, we observed wide diversity of V&P studies in terms of methods to elicit V&P, as well as differences in results among different regions and patients' age groups. Future studies estimating utilities or performing direct-choice experiments should be conducted, in order to convey more robust evidence concerning patients' V&P.

AUTHOR CONTRIBUTIONS

EB, ES, and JLB designed of the study, screened literature, extracted data, and drafted the manuscript; HJS designed the study, interpreted data and critically revised and edited the manuscript; AJN analyzed the data and provided technical support related to AI during the selection and extraction process; BSP, JLB, RJV, AB, JJYN YZ, and TZ participated in manuscript writing and data interpretation and critically revised the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None relevant.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ROLE OF THE FUNDER/SPONSOR

The funder had no role in: (i) the design and conduct of the study; (ii) the collection, management, analysis, and interpretation of the data; (iii) the preparation, review, or approval of the manuscript; and (iv) the decision to submit the manuscript for publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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