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Asthma remission one, none and one-hundred thousand: the relevance of the patient's view

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ABSTRACT

Objective: Achieving remission in severe asthma holds paramount importance in elevating patient quality of life and reducing both individual and societal burdens associated with this chronic condition. This study centers on identifying pivotal patient-relevant endpoints through standardized, reproducible methods, while also developing a patient-centric definition of remission, essential for effective disease management.

Methods: A discrete choice experiment (DCE) was conducted to assess patients' perceptions on the four primary criteria for defining severe asthma remission, as outlined by the SANI survey. Additionally, it investigated the correlation between these perceptions and improvements in the doctor-patient therapeutic alliance during treatment decision-making.

Results: 249 patients (70% aged between 31–60, 59% women and 82% without other pathologies requiring corticosteroids) prioritize the use of oral corticosteroids (OCS, 48%) and the Asthma Control Test (ACT, 27%) in defining their condition, ranking these above lung function and exacerbations. This preference for OCS stems from its direct role in treatment, tangible tracking, immediate symptom relief, and being a concrete measure of disease severity compared to the less predictable and quantifiable exacerbations.

Conclusions: This study explores severe asthma remission from patients' perspectives using clinician-evaluated parameters. The DCE revealed that most patients highly value OCS and the ACT, prefer moderate improvement, and avoid cortisone cycles. No definitive preference was found for lung function status. Integrating patient-reported information with professional insights is crucial for effective management and future research. Personalized treatment plans focusing on patient preferences, adherence, and alternative therapies aim to achieve remission and enhance quality of life.

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Introduction

Asthma, a chronic respiratory condition, manifests through airway inflammation and constriction, leading to symptoms such as wheezing, breathlessness, tightness, and cough (1). This variability in severity arises from diverse triggers, including allergens, respiratory infections, and stress, influenced by both genetic predisposition and environmental factors (2,3).

The escalating global prevalence of asthma, now affecting up to 18% of the population according to the Global Initiative for Asthma (GINA) (4), poses

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significant public health challenges. Severe asthma, comprising around 10% of asthma cases, presents particularly formidable management hurdles due to its persistent symptoms and recurrent exacerbations, profoundly impacting patients' quality of life and health outcomes (5–7).

To mitigate asthma's burden, GINA recommends a comprehensive approach encompassing patient education, healthcare provider assessment, and comprehensive disease monitoring. Key components of asthma management also involve environmental control to minimize exposure to triggers and personalized treatment plans that address comorbidities (7,8).

The evolution of asthma care toward a remission-focused paradigm, guided by Precision Medicine principles, underscores the need for personalized therapeutic approaches targeting underlying inflammatory pathways. However, defining remission in asthma remains contentious, with varying criteria ranging from clinical symptom absence to inflammatory marker normalization (5,9).

Efforts to establish consensus on remission criteria, such as those undertaken by the Severe Asthma Network Italy (SANI), highlight the importance of patient-centric perspectives in defining treatment goals. Effective collaboration between healthcare providers and patients is paramount for optimizing clinical outcomes and enhancing disease management efficacy (10,11).

Incorporating patient-reported outcomes (PROs) into asthma management protocols, facilitated by rigorous research methodologies including the Discrete-Choice Experiment (DCE), fosters shared decision-making and enhances patient engagement in care. While previous DCE studies have primarily focused on treatment efficacy, this study aims to assess patients' views on asthma remission, thereby contributing to a more comprehensive understanding of patient priorities (12–15).

This study aims to determine the most relevant endpoints for asthma remission in patients, considering demographic, clinical, and attitudinal variables. By establishing a patient-centered definition of remission based on existing literature and rigorous research methods, the study seeks to improve disease management strategies tailored to individual patient needs.

Subjects and methods

The SANI survey results (5) indicate that achieving complete and partial clinical remission in severe asthma requires meeting specific criteria, as previously mentioned.

The research question, which is the primary objective of applying the DCE methodology, aimed to assess patients' perceptions of the four key criteria used to define severe asthma remission. This assessment was conducted to examine the improvement in the doctor-patient therapeutic alliance during treatment decision-making. A total of 249 subjects were enrolled in the project through the patient association "Respiriamo Insieme", which played a crucial role in disseminating the survey. They shared a direct link to the online DCE questionnaire across multiple communication channels, including their website, Facebook, Instagram, and newsletter.

The Discrete Choice Experiment, utilizing Conjoint Analysis methodology, effectively gauges the relative importance of attributes defining clinical conditions when employing an adequate sample size. The null hypothesis posits that, on average, the 4 criteria possess equivalent levels of importance. Conversely, the alternative hypothesis suggests the presence of a hierarchical order of significance among patients, notably acknowledging their awareness of the heightened importance attributed to the criterion endorsed by the HEALTHY group. The study seeks to elucidate the alignment between criteria outlined by experts and their endorsement by patients' lived experiences. To establish a hierarchical order of importance among attributes, employing questions requiring ranking or rating *via* Likert scales would have been a plausible approach. However, the decision to employ the DCE was predicated on its superior capacity to prompt respondents to make choices. The DCE method presents respondents with two concrete clinical scenarios, prompting them to choose their preferred option. This allows for the assessment of the relative importance of each attribute in their decision-making process.

Attributes were chosen based on a literature review, focusing on SANI's proposed criteria for defining asthma remission. Three representative levels were selected for each attribute, including attainment, failure, and an intermediate level.

The task involved making forced choices between two profiles, each representing hypothetical, yet realistic, clinical conditions. These profile pairs were generated using a random procedure to adhere to orthogonality and balancing criteria (Sawtooth software). Figure 1 illustrates an example of task choice, wherein attribute definitions were simplified to enhance respondent comprehension. For instance, Forced Expiratory Volume in 1 s (FEV1), representing respiratory function, was denoted as "lung function".

The number of attributes aligns with the recommendation put forth by the SANI group, totaling 4.

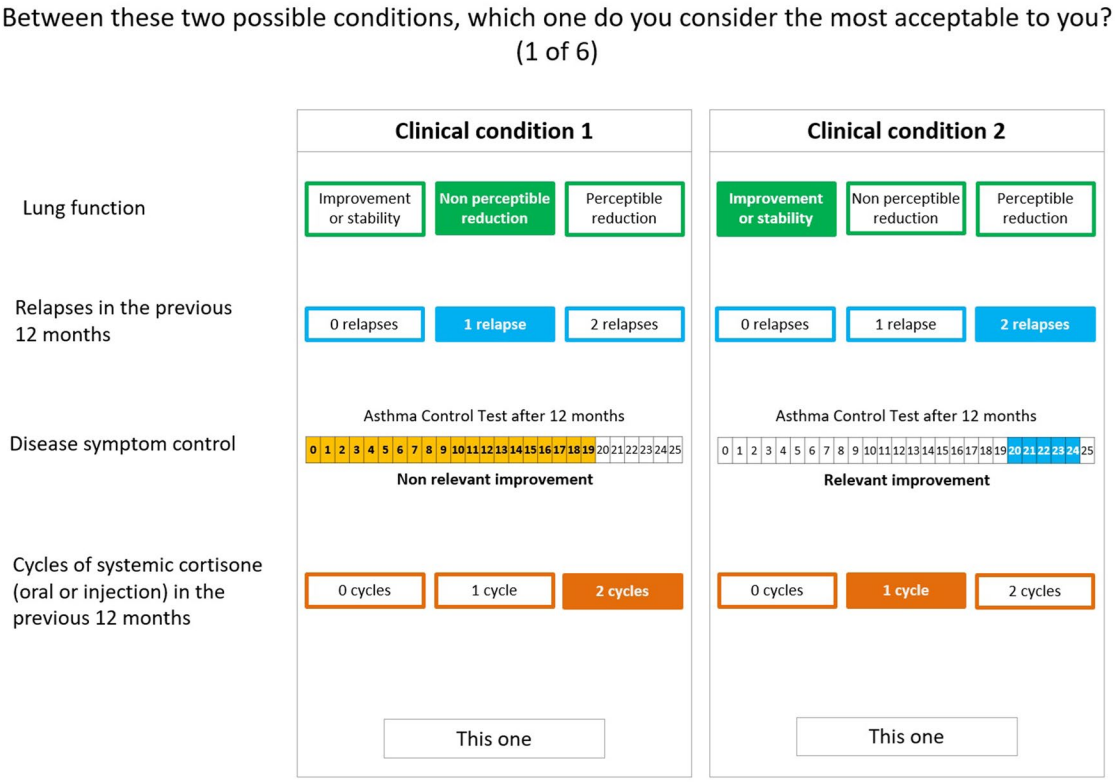

Figure 1. Example of task choice.

Table 1. Experimental design of the DCE study.

Attributes	Levels
Exacerbations in the last 12 months	0 1 2
OCS use in the last 12 months	0 1 2
ACT after 12 months of treatment	25 points: complete improvement 20–24 points: relevant improvement 0–19 points: not relevant improvement
Change in lung function over the last 12 months	Stability No perceivable reduction Perceivable reduction

This facilitated patients' selection between full profiles without encountering difficulty. Partial profiles are often employed when the number of attributes exceeds 7 or when respondents encounter difficulties in comparing overly multidimensional profiles. Additionally, restricting the choice to only 2 profiles, rather than 3 or 4 as occasionally done in DCE studies, enhanced patient engagement. The board, consisting of expert clinicians and patients, collectively decided against including an opt-out option in each comparison, based on their opinions.

The experimental design (Table 1) corresponds to the criteria proposed by the SANI group and was evaluated in terms of orthogonality, balance, and precision of the estimates (Supplementary Material – Experimental Design Simulation).

The tasks of the questionnaire were motivated and explained to the patients with ad-hoc explicative texts.

Beyond task choices, the questionnaire comprised well-defined instrument variables, whose effect was planned to be measured. In particular and in accordance with the research questions, age (4 classes: 18–30, 31–45, 46–60, 61–75), sex (M, F) and comorbidities (present, absent) were asked to participants to assess whether they could modulate patients' preferences.

Patient participation was solicited through referrals by clinicians or engagement with the patient association, lacking a formal sampling plan. As a result, generalizing findings to the entire severe asthma patient population is not feasible due to the absence of random sampling. However, the comparison between subgroups based on the instrumental variables allowed us to evaluate the stability of the estimates. As regards the sample size, based on the Orme formula ($n \geq 500*c/(a*t)$, where a = number of alternatives, c = number of levels in the largest attribute and t = number of choice tasks, 125 patients would have been sufficient. Yet, by running a simulation *via* the Sawtooth software, we observed that with 250 patients we would have obtained standard errors for

PW (Preference Weight) estimates lower than 0.05 (threshold recommended by the DCE guidelines).

The project, akin to an opinion poll, falls under Italian law exempting it from Ethical Committee or Institutional Review Board approval. Participating patients were informed by the Patients' Association and opted in after reviewing project details, including the assurance of questionnaire anonymity.

Statistical analysis

To measure Preference Weights (PWs), the Choice-Based-Conjoint analysis Hierarchical Bayes procedure was used, as recommended and provided by Sawtooth Software (CBC/HB algorithm). According to the Bayesian approach, the *a posteriori* probability combines the probability that a respondent will select a specific concept in a choice task given a specific set of utilities (likelihood) along with the probability that the respondent's utilities are consistent with the pattern of utilities observed in the rest of the respondents (sample density acting as *a priori* probability). The parameter estimates from the model can be interpreted as relative preference weights (PWs). These indicate the average preference for one attribute level over the others. They also reflect the relative utility strength for each attribute level, where more positive numbers indicate higher utility and negative numbers indicate disutility. The average utilities are obtained by rescaling the utilities using the zero-centred "diffs" method. In this method, for each individual, the total sum of utility differences between the worst and best levels of each attribute (across all of them) is equal to the number of attributes times 100. These rescaled utilities are then used to calculate the Relative Importance (RI) of each attribute on the mean PWs. RI reflects how much difference each attribute could make in the total utility of a product. That difference is the range in the attribute's utility values. The percentages of those ranges allow to obtain a set of attribute importance values that add to 100.

Results

A total of 249 subjects participated in the study. All patients were above 18 years old, and the responses were directly provided by the patients. Among them, 69% were between 31 and 60 years old, 59% women and 82% did not have other pathologies requiring corticosteroids. All the characteristics asked to patients are reported in Table 2. Their distributions, except for comorbidities, are in line with the severe asthma patient general population. Patient preference scores were assessed in subgroups (Table 3) defined based on the three instrumental variables of the study design (age, sex, and presence of comorbidities).

Patients attribute the highest importance to the criterion of corticosteroids intake. As shown in Figure 2, the importance of this criterion accounted for 48% of the total (95% CI: 46%, 51%). The second criterion was symptoms (ACT) with a relative importance (RI) of 27% (95% CI: 24%, 29%). The other two criteria (pulmonary function and exacerbations) exhibited less importance.

The analysis of the preference scores by levels (Figure 3) revealed that the greatest utility for patients is not having to resort to cortisone (PW = +70; 95% CI: 61, 79) and the comparison with the levels more "welcoming" than the other criteria (no exacerbations, significant symptomatic improvement, and

Table 2. Respondents' characteristics.

From whom did you receive the invitation to participate in this research?	From my doctor	*n* (%)	1 (0.4)
	From the patient association	*n* (%)	214 (85.9)
	Other	*n* (%)	34 (13.7)
What age group do you belong to?	18-30	*n* (%)	42 (16.9)
	31-45	*n* (%)	81 (32.5)
	46-60	*n* (%)	91 (36.5)
	61-75	*n* (%)	35 (14.1)
Gender	F	*n* (%)	147 (59)
	M	*n* (%)	102 (41)
Education	Junior high school	*n* (%)	44 (17.7)
	Senior high school	*n* (%)	131 (52.6)
	University	*n* (%)	74 (29.7)
Have you been diagnosed with severe asthma?	Yes	*n* (%)	243 (97.6)
	No	*n* (%)	6 (2.4)
Disease duration	Years	median (IQR)	21 (10-25)
At which center were you diagnosed with severe asthma? (Italian Region)	Abruzzo	*n* (%)	1 (0.4)
	Calabria	*n* (%)	2 (0.8)
	Campania	*n* (%)	18 (7.2)
	Emilia-Romagna	*n* (%)	3 (1.2)
	Friuli-Venezia-Giulia	*n* (%)	3 (1.2)
	Lazio	*n* (%)	67 (26.9)
	Liguria	*n* (%)	4 (1.6)
	Lombardia	*n* (%)	14 (5.6)
	Piemonte	*n* (%)	14 (5.6)
	Puglia	*n* (%)	3 (1.2)
	Sardegna	*n* (%)	2 (0.8)
	Sicilia	*n* (%)	5 (2)
	Toscana	*n* (%)	101 (40.6)
	Umbria	*n* (%)	1 (0.4)
	Veneto	*n* (%)	11 (4.4)
Have you been or are you currently being treated with biological drugs?	Yes	*n* (%)	216 (86.7)
	No	*n* (%)	30 (12)
	I don't know	*n* (%)	3 (1.2)
Do you suffer from other pathologies requiring corticosteroids besides asthma?	Yes	*n* (%)	44 (17.7)
	No	*n* (%)	205 (82.3)
Do you work?	Yes	*n* (%)	205 (82.3)
	No	*n* (%)	44 (17.7)
Do you participate in sports activities?	Yes	*n* (%)	100 (40.2)
	No	*n* (%)	149 (59.8)

Table 3. Respondents' characteristics: subgroups by the three predefined main instrument variables: age, sex and comorbidity.

				Do you suffer from other conditions that require the use of corticosteroids in addition to asthma?		
Age				Y	N	Total
18-30	Sex	F	N	3	23	26
			% of Total	7.1%	54.8%	61.9%
		M	N	1	15	16
			% of Total	2.4%	35.7%	38.1%
	Total		N	4	38	42
			% of Total	9.5%	90.5%	100.0%
31-45	Sex	F	N	12	41	53
			% of Total	14.8%	50.6%	65.4%
		M	N	0	28	28
			% of Total	0.0%	34.6%	34.6%
	Total		N	12	69	81
			% of Total	14.8%	85.2%	100.0%
46-60	Sex	F	N	13	35	48
			% of Total	14.3%	38.5%	52.7%
		M	N	5	38	43
			% of Total	5.5%	41.8%	47.3%
	Total		N	18	73	91
			% of Total	19.8%	80.2%	100.0%
61-75	Sex	F	N	5	15	20
			% of Total	14.3%	42.9%	57.1%
		M	N	5	10	15
			% of Total	14.3%	28.6%	42.9%
	Total		N	10	25	35
			% of Total	28.6%	71.4%	100.0%
Total	Sex	F	N	33	114	147
			% of Total	13.3%	45.8%	59.0%
		M	N	11	91	102
			% of Total	4.4%	36.5%	41.0%
	Total		N	44	205	249
			% of Total	17.7%	82.3%	100.0%

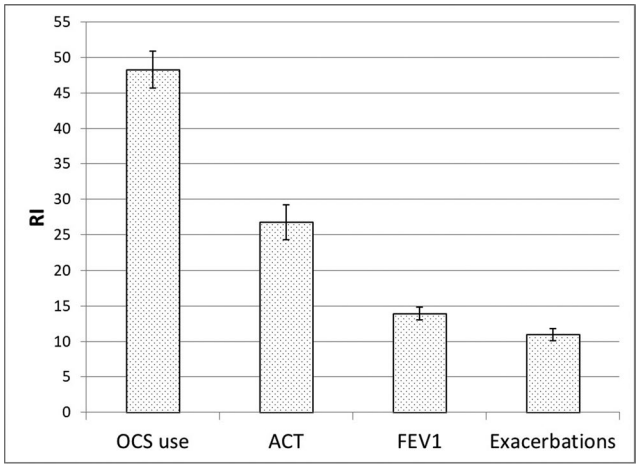

Figure 2. Relative Importance (RI) of the four criteria in study according to patient preferences. RI reflects how much difference each attribute could make in the total utility of a product. That difference is the range in the attribute's utility values. The percentages of those ranges allow to obtain a set of attribute importance values that add to 100.

stability of lung function) was consistently significant ($p < 0.01$, Sidak adjustment). Conversely, having to resort to 2 courses of cortisone in the last year corresponds to the greatest disutility for patients (PW= −84; 95% CI: −75, −95). The pattern of patient preferences between different ACT levels didn't match expectations. The level assumed to be in-between, with noticeable symptomatic improvement, was actually preferred over the one thought to be the best, where symptoms completely disappeared (ACT = 25). The disutility associated with an ACT score below 20 was significantly greater than the one linked with the least desirable levels of the two attributes (experiencing 2 exacerbations per year and perceiving reduction in respiratory function). Also, note that the difference between stability and no noticeable reduction in respiratory function was not significant after Sidak's correction for multiple comparisons.

The patterns shown in Figure 3 were evaluated for each of the subgroups defined by the combinations between the levels of the three main instrumental variables, excluding those with numbers lower than 10 and no difference emerged based on the characteristics of the patients (Supplementary material – Figures S1, S2, S3, S4).

Discussion

The DCE results provide valuable insights into severe asthma remission. However, it is important to note

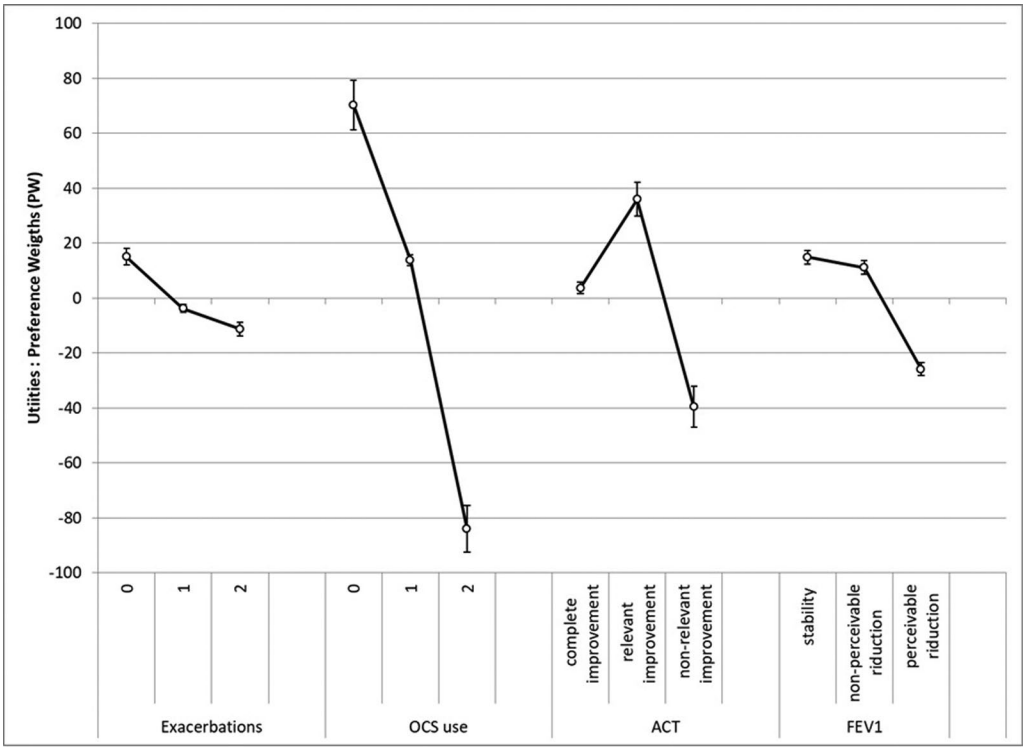

Figure 3. Partworth utilities rescaled using the zero-centred "diffs" method (see Statistical Analysis paragraph for details). These measures can be interpreted as relative preference weights (PWs), indicating the average preference for one attribute level over others.

that nonrandom sampling used in the study may limit the generalizability of these findings. To enhance the stability of conclusions, we conducted subgroup comparisons using instrumental variables. Notably, the majority of participants were females between 46 and 60 years, with a relatively low prevalence of comorbidities.

The analysis of the study reveals that patients attribute a fundamental role in defining their condition to the use of OCS, accounting for 48% of the total, followed by the ACT (Asthma Control Test, with an RI of 27%). On the contrary, it has been demonstrated that the other two criteria, namely lung function and exacerbations, are less important. Patients often prefer to define their condition based on oral corticosteroid (OCS) use rather than exacerbations due to several reasons. Firstly, OCS use represents a direct and tangible aspect of their treatment regimen that is easily trackable and understandable. In contrast, exacerbations may be less predictable and harder to accurately quantify. Secondly, OCS use can offer immediate relief of symptoms, giving patients a sense of control over their condition. Lastly, OCS use may be perceived as a more concrete measure of disease severity or activity compared to exacerbations, which can vary in intensity and duration.

Based on the evidence, the analysis of preference scores suggests that the most significant benefit for patients lies in avoiding cortisone cycles. The trend of PW between the ACT levels is different from expectations, as the level hypothesized as intermediate (relevant symptomatic improvement) is more preferred than the one hypothesized as optimal (complete improvement). It also useful to note that the difference between stable lung function and non-perceivable reduction of respiratory function is not significant. This observation suggests that patients prioritize achieving relevant symptomatic improvement over complete improvement, contrary to expectations. Additionally, it is noteworthy that there was no significant difference between stable lung function and non-perceivable reduction of respiratory function. The findings suggest patients prioritize certain treatment aspects differently than expected. This underscores the need to incorporate patient preferences in defining treatment goals and evaluating treatment effectiveness.

Other discrete choice experiments (DCEs) related to decision-making in asthma treatment and Chronic Obstructive Pulmonary Disease (COPD) have been scarce (15–19). Yang et al. (15), in their recent DCE study, underscored the significant importance patients

place on safety and efficacy when considering severe asthma treatments. Their findings revealed that patients, particularly middle-aged women, prioritize factors such as the absence of a black box warning for life-threatening allergic reactions, reductions in severe asthma exacerbations, and improvements in lung function over convenience aspects like dosing frequency and injection device type. Both our study and theirs share the goal of integrating patient-reported information with healthcare professionals' input to enhance personalized treatment plans. By aligning treatment strategies with patient preferences, healthcare providers can elevate the quality of care and achieve better health outcomes for asthma patients.

There is a lack of consensus in the literature regarding the definition of optimization and stabilization of lung function in the context of the above-mentioned topic. Several studies have reported interpatient variability in lung function, which correlates with the anticipated decline in lung function associated with aging. This highlights the need to define patient populations based on longitudinal changes over time. Additionally, pathological alterations in the airway and changes in lung function throughout the progression of the disease may render it unfeasible for patients to return to a state of "normal" lung function (20,21). Identifying factors linked to lung function decline and developing treatments to alter disease progression pose ongoing challenges, crucial also because lung function and exacerbations remain critical criteria for patients and their remission. Evaluating the effect of early intervention to halt the onset of asthma or disease progression is also crucial, as early intervention might halt or delay the progression of the disease (22–24). Despite experiencing a period of symptom remission, individuals with asthma may still harbor an underlying active disease process that could potentially continue to progress. Overall, DCE results indicate that patients with severe asthma attribute the highest importance to the criterion of corticosteroid intake, followed by symptomatic improvement (ACT). These findings may suggest that achieving asthma remission may require attention to controlling OCS intake and improving symptoms. Additionally, the preference for avoiding OCS use may indicate an opportunity to develop alternative therapies that reduce dependence on these drugs. The observed trend in preference scores for different treatment levels suggests that personalized management, considering patients' individual preferences, could be essential for optimizing treatment outcomes and aiming for remission. These results can inform future clinical practice by encouraging a more patient-centred approach and enabling treatment customization based on patients' preferences and individual needs in severe asthma management. Furthermore, biologic drugs are highly beneficial in severe asthma management, signifying a substantial progress in treatment and providing personalized therapy options. They are able to reduce exacerbations as well as improve lung function, maintaining good symptoms control and allowing for OCS reduction (25).

The use of DCE based on Conjoint Analysis undoubtedly enables us to assess the alignment and compatibility between data from scientific literature and the practical experiences of patients diagnosed with severe asthma. Based on this analysis, it is reasonable to conclude that the concept of disease remission varies depending on the patient's characteristics, such as age, sex, lifestyle habits, treatment adherence, and the presence or absence of comorbidities, which can serve as physical and psychological barriers to achieving therapeutic goals (26). The management of asthma frequently proves challenging when unidentified exacerbating factors persist. Specific medications, such as non-steroidal anti-inflammatory drugs and blockers, have the potential to exacerbate asthma symptoms (27–30). Gastro-oesophageal reflux commonly co-occurs with asthma; however, evidence supporting that treating reflux influences asthma control is currently lacking (31). Rhinosinusitis often coexists with difficult-to-treat asthma. However, while rhinosinusitis may contribute to overall respiratory symptoms and affect the quality of life in individuals with asthma, its management may not always directly correlate with asthma outcomes such as exacerbation frequency, lung function, or asthma control. Therefore, addressing rhinosinusitis alone may not necessarily lead to improvements in asthma outcomes (32).

Severe asthma presents a significant challenge for physicians. To effectively manage this condition, a comprehensive approach is crucial. This approach relies heavily on close collaboration between patients and healthcare providers. Working together, they can develop individualized treatment plans that address each patient's unique needs. However, striking a balance is essential. The analysis process must be accurate, precise, and replicable to ensure reliable findings. At the same time, it must acknowledge the possibility of distinct, individualized outcomes, as patients with severe asthma will respond differently to treatment. In this context, the DCE methodology, using Conjoint Analysis, is valuable for determining a unified and clinically valid definition. This analytical tool is a ground-breaking approach that hits a unique balance between standardized methodology and personalized

outcome adjustment. It allows researchers to present respondents with hypothetical scenarios and systematically analyze their preferences and choices. It enables the exploration of complex decision-making processes, providing valuable insights into how individuals weigh different attributes when making choices. By incorporating both standardized elements and personalized adjustments, the DCE tool offers a versatile and powerful means of understanding and predicting human behavior in various contexts.

The analysis of DCE results allows us to determine which remission-related endpoints are truly relevant for healthcare professional, as identified in the SANI survey, to ensure effective disease management. Considering the possibility that clinical attributes deemed important by patients may differ from those supported by scientific evidence, the identification of physician important endpoints is important:

- to ensure optimal disease management;
- to improve patient clinical outcomes;
- to monitor patients' progress in achieving treatment goals;
- to identify at-risk patients;
- to promote better communication and coordination in managing disease.

Furthermore, the intertwining of information from patients and healthcare professionals forms a complex and pivotal dynamic in severe asthma management and achieving remission. Patient perspectives provide insights into daily challenges, perceived symptoms, and triggers. Meanwhile, physicians offer objective data from diagnostic tests, pulmonary function evaluations, and treatment responses through clinical assessment. This harmonious interaction of information could facilitate a comprehensive evaluation of patients' condition and therefore enhance severe asthma management.

This study acknowledges a specific limitation: the diagnosis of severe asthma relies on self-reported information from patients. Looking ahead, the authors intend to establish a standardized definition of asthma remission using reproducible methodologies. This objective aims to enhance the consistency and reliability of remission criteria across diverse clinical contexts and research studies. Additionally, the authors plan to delve into the dynamics between patients and healthcare providers. Their focus will be on identifying commonalities and differences in perceptions and asthma management approaches. Understanding these dynamics is pivotal for improving patient-centred care and optimizing treatment outcomes. By addressing these areas, the authors aspire to contribute to more precise and effective strategies for managing asthma.

Conclusions

Asthma is recognized as the most prevalent respiratory condition, with approximately 10% of asthma patients experiencing severe disease. It therefore becomes imperative to establish clear criteria for evaluating remission in such cases, considering perspectives from both physicians and patients.

To the best of our knowledge, this is the very first study on the concept of remission as defined by patients' preferences, based on parameters evaluated by clinicians. The Discrete Choice Experiment underscores essential attributes that delineate clinical remission in severe asthma from the patient's perspective. The majority of patients, primarily middle-aged women without comorbidities, attribute significance to oral corticosteroids (OCS) followed by the Asthma Control Test (ACT). Patients prefer avoiding cortisone cycles. When comparing distinct levels of improvement measured by the Asthma Control Test (ACT), patients tend to prefer moderate improvement over complete improvement. However, there is no clear preference between having stable lung function or a slight reduction in respiratory function. Our upcoming research focuses on integrating patient-reported information with healthcare professionals' input to accurately assess and manage severe asthma. This endeavor holds great promise for developing personalized treatment plans tailored to individual needs. These plans can prioritize patient preferences, such as minimizing corticosteroid use, while simultaneously ensuring effective symptom control and disease management. Additionally, healthcare professionals could emphasize the importance of regular monitoring and adherence to treatment, regardless of the specific preferences of the patients. Furthermore, further research and clinical trials could be conducted to explore alternative treatment options that align more closely with patient preferences and goals, ultimately aiming to achieve complete remission and improve patient quality of life.

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Declaration of interest

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Data availability statement

Raw data are available under request.

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