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What is already known about this topic? Several classifications of systemic adverse reactions during allergen immu-notherapy have been proposed, but no comparison has been made until now.

What does this article add to our knowledge? Our analysis allows physicians to compare different international classifications of systemic adverse reactions due to allergen immunotherapy with their own severity criteria in daily clinical practice, measuring the specific degree of correlation achieved.

How does this study impact current management guidelines? The need for a revision and reassignment of some Medical Dictionary for Regulatory Activities terms and the usefulness of specific classifications are suggested.

BACKGROUND: Several classifications of systemic adverse reactions (SARs) during allergen immunotherapy have been proposed, but the comparison of their usefulness in daily clinical practice is lacking.

OBJECTIVE: The present post hoc analysis was aimed at investigating the practicality of the most relevant international classifications proposed by the European Academy of Allergology and Clinical Immunology (EAACI), the American Academy of Asthma, Allergology and Clinical Immunology/American College of Allergy, Asthma and Immunology (AAAACI/ACAAI), and the World Allergy Organization (WAO) using data provided by the longitudinal European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI) based on daily clinical practice in 3 countries in Europe.

METHODS: One hundred nine SARs over 4363 allergen immunotherapy courses were classified as mild (n=78 [71.5%]), moderate (n=27 [24.8%]), and severe (n=4 [3.7%]) by EASSI-doctors, which served as a criterion standard. Every SAR was further classified according to the following grading systems: EAACI 2006 Grading System (EAACI2006), WAO 2010 Grading System (WAO2010), WAO 2017 Grading System (WAO2017), and AAAAI/ACAAI Grading System. All SAR rankings were also cross-compared among each other (Kendall correlation coefficient Tau-b). In general, a low epinephrine use was identified, severe reactions occurred within 15 minutes, and milder reactions were skin only.

RESULTS: The analysis indicated disparities in mild and moderate SARs in the different grading systems. The correlation between EASSI-severity and EAACI2006, WAO2010, WAO2017, and AAAAI/ACAAI Grading System was 0.639, 0.502, 0.315, and 0.663, respectively ($P < .001$ in all cases). However, correlation of severe reactions was good. The best correlation with the onset of the reaction and the number of System Organ Class involved were detected in WAO grading systems.

CONCLUSIONS: Despite having a lower correlation than EAACI and AAAAI/ACAAI, the WAO grading appears to provide a moderate correlation among these classifications. The analysis might help to inform clinicians and investigators on selecting the most appropriate classification.

Key words: Allergen immunotherapy; Systemic adverse reactions; MedDRA; Epinephrine; Classification

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Abbreviations used

AAAAI/ACAAI- American Academy of Asthma, Allergology and Clinical Immunology/American College of Allergy, Asthma and Immunology
AIT- allergen immunotherapy
EAACI2006- European Academy of Allergology and Clinical Immunology 2006 Grading System
EASSI- European Survey on Adverse Systemic Reactions in Allergen Immunotherapy
MCA- multiple correspondence analysis
MedDRA- Medical Dictionary for Regulatory Activities
RQ- Reaction Questionnaire
SAR- systemic adverse reaction
SCIT- subcutaneous allergen immunotherapy
SLIT- sublingual immunotherapy
SOC- System Organ Class
WAO- World Allergy Organization
WAO2010- World Allergy Organization 2010 Grading System
WAO2017- World Allergy Organization 2017 Grading System

INTRODUCTION

It has been more than 100 years since Noon[1] published the results of the first subcutaneous allergen immunotherapy (SCIT) study. Shortly afterwards, systemic allergic reactions (SARs) due to allergen immunotherapy (AIT) were reported. From that moment onwards several attempts to find the best way to classify SARs were made but none seem to fit with daily clinical practice. Therefore, they are likely not to be used by practicing allergists. The European Academy of Allergology and Clinical Immunology 2006 Grading System (EAACI2006) is the official scale for SARs due to SCIT used in Europe[2] in both clinical research and clinical practice. The American Academy of Asthma, Allergology and Clinical Immunology/American College of Allergy, Asthma and Immunology (AAAAI/ACAAI) Grading System has been used to collect safety data of AIT in the United States.[3,4] The lack of consensus on how to report SARs makes it difficult to compare safety outcomes from different health care settings and countries and does not help doctors make critical decisions on management and future treatment options.[5,6] In addition, most available classifications are based on the timing of the SAR and the presence of symptoms. Regarding timing, many efforts have been made to identify the time elapsed between exposure to the allergen and when symptoms and signs first appear.[2-5] Only the 2010 World Allergy Organization (WAO) Grading System (WAO2010) classification stipulates that the reaction severity should be determined once the event is over so that the physician would be able to consider all factors related to the SAR, the treatment needed to reverse the consequences of the SAR, and actions to remediate identified issues and any subsequent problem, if any.[5] Moreover, there is much overlap in symptoms related to SARs, making it sometimes difficult to uniformly name them; so the problem of "speaking the same language" arises.[5] Recently Cox et al[6] have suggested a modification of the WAO SAR grading system trying to better characterize all SARs from any cause. They support the idea that the clinical judgment made after the event is resolved provides additional information very useful to classify SARs. A summary of the different criteria used by EAACI2006,[2] AAAAI/ACAAI Grading System,[3,4] and WAO2010[5] to classify SARs to AIT is summarized in Table I.

In 2013, a European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI) was conducted to prospectively collect AIT SAR in daily clinical practice in 3 European countries: France, Germany, and Spain.[7,8] In this study and according to their clinical experience in the field, doctors graded AIT SARs' severity on the basis of symptoms, duration, administered treatment, and seriousness. To unify the collection of data, the use of Medical Dictionary for Regulatory Activities (MedDRA) was proposed and followed.[7] MedDRA is the dictionary of medical terms recommended by the European Medicines Agency to report adverse reactions of drugs in general and gives universally accepted terms to designate specific symptoms and some of these terms are grouped into System Organ Class (SOC).[9,10] One relevant limitation of MedDRA in the field of allergic diseases is that it does not include anaphylaxis as a term and that is because it is not a symptom but a clinical condition with a constellation of symptoms and the specific requirement of being life-threatening.[11,12]

The present analysis was aimed at investigating the usefulness of the most relevant current international classifications (EAACI2006, AAAAI/ACAAI, and WAO2010) and the new proposed modification (World Allergy Organization 2017 Grading System [WAO2017]) according to our data provided by daily clinical practice to identify the one that best fits with doctors' scale of severity.

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TABLE I. Methodology for the categorization of SARs according to the different international grading systems (EAACI2006, WAO2010, and AAAAI/ACCAI)

Grading system	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
EAACI2006	Regardless of the severity, any of the following nonspecific symptoms: blood pressure decrease (sensation), sensation of foreign body, fatigue, headache, nausea, vomiting, dizziness, tachycardia	Regardless of severity if any of the following: abdominal pain, chest discomfort, chest tightness, diarrhea, dysphagia; or, if any of the following and mild severity: asthma, bronchospasm, cough, dysphonia, dyspnea, erythema, rhinitis, urticaria, wheezing, conjunctivitis	Any of these symptoms when severity is moderate and onset is 15 min or later: asthma, bronchospasm, dyspnea, generalized erythema, generalized pruritus, rhinitis, urticaria, wheezing, conjunctivitis, laryngeal edema	Any of these symptoms when intensity is moderate and the onset is earlier than 15 min: generalized erythema, generalized pruritus, urticaria, angioedema/ laryngeal edema and wheezing; or any of the following regardless of the onset if severe intensity: asthma, angioedema, bronchospasm, dyspnea, generalized erythema, generalized pruritus, urticaria, flushing, wheezing	When hypotension or loss of consciousness is present	NA
WAO2010 AIT	NA	Only a single organ affected with any of these symptoms in a mild severity reaction: angioedema, erythema, generalized erythema, pruritus generalized, urticaria, flushing, cough, dysphonia, rhinitis, dizziness, syncope, headache, blood pressure decrease (subjective feeling), fatigue, sensation of foreign body, nausea, dysphagia, tachycardia	Whenever 2 organs affected with mild severity reaction; or, if any of the following alone with mild severity: asthma, bronchospasm, chest discomfort, chest tightness, wheezing, dyspnea, vomiting, abdominal pain or diarrhea	If any of the following alone with moderate severity: asthma, bronchospasm, chest discomfort, chest tightness, dyspnea or wheezing; or, if laryngeal edema with mild severity	If any of the following alone with severe affection: asthma, bronchospasm, chest discomfort, chest tightness, dyspnea, or wheezing; or, if alone any of the following regardless of severity: hypotension or loss of consciousness	Death
AAAAI/ ACAAI	NA	If mild severity, 1 or more of the following: generalized erythema, generalized pruritus, flushing, rhinitis, conjunctivitis, erythema, generalized erythema, urticaria, chest discomfort, chest tightness, angioedema, laryngeal edema	If any of the following with mild or moderate severity: asthma, bronchospasm, dyspnea, wheezing; or, when moderate severity if any of the following: rhinitis, cough, dysphonia, urticaria, abdominal pain, diarrhea, dysphagia, nausea, vomiting, chest discomfort, chest tightness	If any of the following along with severe presentation: asthma, bronchospasm, dyspnea, wheezing; or, any of the following regardless of the severity of the reaction: hypotension, loss of consciousness	NA	NA

NA, Not applicable.

METHODS

Detailed information on the EASSI methodology and results has been previously described.[7,8,13] Briefly, data on 4316 patients under AIT (4363 courses because some patients received more than 1 AIT at the time of the study) were prospectively collected from the first day they had started AIT by subcutaneous (SCIT) or sublingual (sublingual immunotherapy [SLIT]) routes until a mean of 12.7 ± 3.37 months of follow-up. Information on SARs was uniformly registered by means of 31 MedDRA terms and 9 MedDRA SOC[9] in the Adverse Reaction Questionnaire (RQ).[7] One hundred nine SARs were collected, 97 (89%) in SCIT and 12 (11%) in SLIT. Doctors classified them as mild (n = 78 [71.5%]),

moderate (n = 27 [24.8%]), and severe (n = 4 [3.7%]) once the SAR ended.[8]

To perform the *post hoc* analysis, data from several questions in RQ were analyzed and reclassified according to EAACI2006,[2] WAO2010,[5] WAO2017,[6] and AAAAI/ACAAI Grading System[3,4] (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Answers of the following questions were recorded:

- "Type of adverse reaction according to the MedDRA classification for SARs, including MedDRA terms" (RQ question 7).
- "Medication used to treat the reaction" (RQ question 8).
- "Severity of the reaction" ("mild" if symptoms do not interfere with daily activities, "moderate" if strong symptoms that interfere in daily activities, and "severe" if unacceptable symptoms that interfere considerably in daily activities" (RQ question 8).
- "Elapsed time from last AIT administration to the SAR expressed in days, hours, or minutes" (RQ question 13). This variable was defined as "onset" and classified as follows: 1 (SAR in the first 15 minutes); 2 (SAR between 16 and 30 minutes); 3 (SAR between 31 and 120 minutes); 4 (SAR later than 121 minutes).

As for anaphylaxis, symptoms allocated in the previously mentioned questions 7 and 13 were evaluated to classify SAR as anaphylactic because this term is not included in MedDRA. Thus, every single symptom or sign recorded during the prospective study was grouped into 4 categories (skin and/or mucosa, respiratory compromise, gastrointestinal symptoms, and decreased blood pressure and/or organ dysfunction) according to the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network criteria.[12] When 2 or more of these groups of symptoms appeared, anaphylaxis was suspected. The recodification was automatically performed and later independently revised by 3 doctors (C.V., P.R., and M.C.).

The correlation between the 4 grading systems and EASSI score of severity was assessed by using Kendall correlation coefficient Tau-b. In addition, all SAR rankings were cross-compared among each other and also against 2 EASSI parameters: the severity reported by the doctor participating (from now onwards: EASSI-severity) and the use of epinephrine/adrenaline.

To analyze the relationship between symptoms, onset, and severity of the SAR, multiple correspondence analysis (MCA) was applied. MCA helps to describe patterns of relationships distinctively using geometrical methods by locating each variable/unit of analysis as a point in a low-dimensional space. MCA is useful to map both variables and individuals, so allowing the construction of complex visual maps whose structuring can be interpreted. The first 2 dimensions were used to visualize the correlation of the variables. Statistical analyses were carried out in R using the package "FactoMineR,"[14] which is freely available at http://cran.r-project.org.

RESULTS

All SARs classified as severe by EASSI-doctors corresponded with the highest level of every other classification system used for comparison (EAACI2006, WAO2010, WAO2017, and AAAAI/ACAAI Grading System) (Table II). However, differences were found for mild and moderate SARs. Thus, regarding EAACI2006, 3 cases cataloged as moderate by EASSI-doctors were assigned to grade 0 (moderate headache in 2 cases and a case of vomiting and ethmoiditis) and 1 mild EASSI-severity event was sorted as grade 3 (mild angioedema). The correlation between EASSI-severity and EAACI2006 classification was high (Tau-b = 0.639) and significant ($P < .0001$).

TABLE II. Overall distribution of all systemic reactions due to AIT: According to the EASSI-severity and current international grading classifications

	EAACI2006*				
EASSI-severity	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Mild	12_0	65_{10}	0	1	78
Moderate	3_0	3_0	20_5	1	27
Severe	0	0	0	4_2	4
Total	15	68	20	6	109
	WAO2010†				
EASSI-severity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Mild	41_0	37_{10}	0	0	78
Moderate	6_0	8_2	13_3	0	27
Severe	0	0	0	4_2	4
Total	47	45	13	4	109
	WAO2017‡				
EASSI-severity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Mild	43_0	7_1	28_9	0	78
Moderate	7_0	6_2	14_3	0	27
Severe	0	0	0	4_2	4
Total	50	13	42	4	109
	AAAAI/ACAAI§				
EASSI-severity	**Grade 1**	**Grade 2**	**Grade 3**		**Total**
Mild	54_3	24_7	0		78
Moderate	0	27_5	0		27
Severe	0	0	4_2		4
Total	54	51	4		109

Overall distribution of all reactions according to the EASSI-severity, recoded for the following:

*EAACI2006. The EAACI classification ranges from 0 to IV; because there were no events graded IV (anaphylactic shock), it was not represented in the table. The subfix represents the number of epinephrine doses administered in each set of SAR (ie, 20_5 = in 20 reactions, 5 received epinephrine).

†WAO2010. The WAO classification ranges from 1 to 5; because there were no events graded 5 (death), it was not represented in the table. The subfix represents the number of epinephrine doses administered in each set of SAR (41_0 = in 41 reactions, 0 received epinephrine).

‡WAO2017. The WAO2017 classification ranges from 1 to 5; because there were no events graded 5, it was not represented in the table. The subfix represents the number of epinephrine doses administered in each set of SAR (28_9 = in 28 reactions, 9 received epinephrine).

§The AAAAI/ACAAI Grading System used in safety surveillance surveys. The AAAAI/ACAAI classification ranges from 1 to 3. The subfix represents the number of epinephrine doses administered in each set of SAR (ie, 54_3= in 54 reactions, 3 received epinephrine).

According to WAO2010, 6 reactions considered moderate by EASSI-doctors were included in WAO2010's grade 1 (headache in 2 cases and symptoms limited to skin in 4). The correlation between EASSI-severity and WAO2010 classification was moderate (Tau-b = 0.502) but significant ($P < .0001$). When recoded according to the Cox et al[6] modification, 28 cases recorded as mild by EASSI-doctors were now assigned to grade 3, so severity increased with the new evaluation.

Accordingly, the correlation with EASSI classification is lower with WAO2017 (Tau-b = 0.315; $P < .001$) than with the previous version, WAO2010. Finally, discrepancies between

AAAAI/ACAAI classification and EASSI-severity were found in cases considered mild for EASSI-doctors but moderate in this grading system due to the appearance of respiratory symptoms. The correlation between EASSI-severity and AAAAI/ACAAI classification was the highest (Tau-b = 0.663; $P < .0001$).

When performing the same analysis stratified by the onset of the SAR, no relevant changes occur. Even though some SARs happened after the 30 minutes of observation, all SARs classified as severe were present in the first 30 minutes after the administration of the dose.

Finally, 18.3% (n = 20) of events fulfilled the criteria of anaphylaxis. One of the 4 cases considered severe by EASSI-doctors was not included in the definition of anaphylaxis because it consisted of severe bronchospasm without other manifestations. Nine and 8 anaphylactic reactions were respectively classified as mild and moderate by EASSI-doctors because of the implication of 2 or more organs but with mild or moderate intensity. The correlation between EASSI-severity and anaphylaxis was low (Tau-b = 0.296; $P = .002$).

Interestingly, only 17 (15.6%) SARs received epinephrine, 6 not being coded as anaphylaxis. Likewise, 9 anaphylaxis cases were not treated with epinephrine and, surprisingly, 50% of the severe SARs were not treated with epinephrine.

In Table III all *post hoc* classifications' correlations are depicted along with some original parameters from the EASSI as EASSI-severity, the onset of the reaction, and the number of SOCs involved. The highest correlation found was for the couple WAO2010 and WAO2017 (Tau-b = 0.863) and WAO2017 and AAAAI/ACAAI (Tau-b = 0.721) and the lowest between EASSI-severity and WAO2017 (Tau-b = 0.315). When the correlation among epinephrine use and all the classifications is analyzed, the Tau-b is poor (data not shown). The correlation with the onset of the reaction was poor and significant only for WAO's classifications. Finally, the number of SOCs involved in the reaction correlated better with the WAO2010 (Tau-b = 0.535) and WAO2017 (Tau-b = 0.491) classifications than with the others.

Results of MCA plot (FactoMineR) showed the clusters of different symptoms and their association with onset and severity of the SAR vectors projected in the space of dimensions 1 and 2 (Figure 1). Total variance accounted for 16.4% (dimension 1: 8.7%; dimension 2: 7.7%). Briefly, as can be seen in the upper right square, SARs that happened in the first 15 minutes (onset 1) were related to the most severe reactions (severity 2 and 3) and included some of the respiratory symptoms (dyspnea, fatigue, cough, and asthma defined as the presence of dyspnea, cough, and wheezing at the same time) and decreased blood pressure. When wheezing, bronchospasm, chest discomfort, or chest tightness were reported alone, there is a tendency to appear later (between 16 and 30 minutes) but with a similar severity (right lower square). Less severe reactions involved the skin and appeared later (onset 3 and 4) (left squares). When the same analysis was performed including the analyzed classifications, only grade 4 in the EAACI2006 appeared to be unrelated to any other symptoms or classifications.

DISCUSSION

AIT SAR classifications are usually the result of academic initiatives promoted by experts either supported by a specific national or international allergy society[2-6] or focused in 1 study or survey.[15,16] The selection of any of them for reporting SARs in a trial is based on the experience and preferences of the promoters and principal investigators, and represents a delicate decision in the trial design. However, there are no reports to date comparing the most relevant classifications based on real AIT SARs collected prospectively with a homogeneous and consistent methodology. The information included in this article provides an insight into the weaknesses and strengths of each codifying system.

The use of different classifications hampered the comparability of published data on safety outcomes.[5,17] This "comparability" was never addressed before, and the use of the mean Tau-b was an attempt to objectively do so. The Tau-b coefficient provides a relative scale of association where there are no clearcut values for "high" or "low" correlation, but only an assessment in terms of higher or lower compared with others. The analysis of concordance was not possible due to the different number of categories included in each grading system, so we intend to show if each classification tend to vary in the same or different direction than the EASSI-severity. Through the analysis performed, only moderate correlations were observed, and although drawbacks and strengths of each of them were apparent, none of the classifications was shown to be clearly better than the others.

The AAAAI/ACAAI classification was an easy and reliable way to report sensitive data and correlated well with the severity assessed by doctors. It is perhaps less exhaustive and exclusive than others, but its simplicity and its correlation with other more complex classifications such as WAO2010 favors a fast but still accurate assignment that might be an advantage if used for decision making in an ongoing reaction. Despite being slightly inferior to the AAAAI/ACAAI classification, the EAACI2006 classification behaves in a similar way. It has been the classification of choice for reporting SARs by most clinical trials registered by the European Medicines Agency. The main flaws of the EAACI2006 classification are the lack of gastrointestinal symptoms, the rigid definition of "early onset" in 15 minutes, and the lack of precision of some terms ("sensation of foreign body" [grade 0] could be interpreted as "something unspecific is happening" [grade 0] or "laryngeal edema" [grade 3]). Thus, the MCA placed "sensation of foreign body" associated to severity between 2 and 3 and near dysphagia and angioedema, supporting the idea that this symptom could be misinterpreted and should be clarified in MedDRA.

The WAO classification was born in an attempt to uniformly classify SARs during AIT and help doctors to assess more accurately when epinephrine should be used. However, according to the authors, "the final grade will not be determined until the event is over"[5] so it seems contradictory because the statement prevents doctors from making the decision of using epinephrine during an ongoing reaction. Although the correlation with severity is lower than that for both the AAAAI/ACAAI and the EAACI2006 classifications, the WAO classification is more exhaustive and more exclusive. The modification proposed in 2017[6] lowers the correlation of severity in our patients. Finally, the WAO classification of SARs is the one with a better correlation with the use of epinephrine.

The WAO2017 has not been endorsed by WAO. Also, it is important to comment that all these "academic classifications" have not been "clinically validated" although they have been used in many different clinical reports and systematic reviews.

The concept of classifying systemic reaction's severity due to AIT only "after" the event is resolved (WAO2017) has its pros

TABLE III. Correlation between all current classifications analyzed and severity of the reaction according to EASSI-doctors, the onset of the reaction, and the number of SOCs involved

Tau-b Kendall	AAAAI/ACAAI	WAO2010	EAACI2006	WAO2017	EASSI-severity	Onset	No. of SOCS
AAAAI/ACAAI	1.000	0.685 $P < .0001$	0.518 $P < .0001$	0.721 $P < .0001$	0.663 $P < .0001$	−0.144 $P = .071$	0.382 $P < .001$
WAO2010		1.000	0.463 $P < .001$	0.863 $P < .0001$	0.502 $P < .0001$	−0.219 $P = .004$	0.535 $P < .0001$
EAACI2006			1.000	0.412 $P < .001$	0.639 $P < .0001$	−0.090 $P = .242$	0.306 $P < .001$
WAO2017				1.000	0.315 $P < .001$	−0.246 $P = .001$	0.491 $P < .001$
EASSI-severity					1.000	−0.008 $P = .920$	0.273 $P = .003$
Onset						1.000	−0.152 $P = .051$
No. of SOCS							1.000

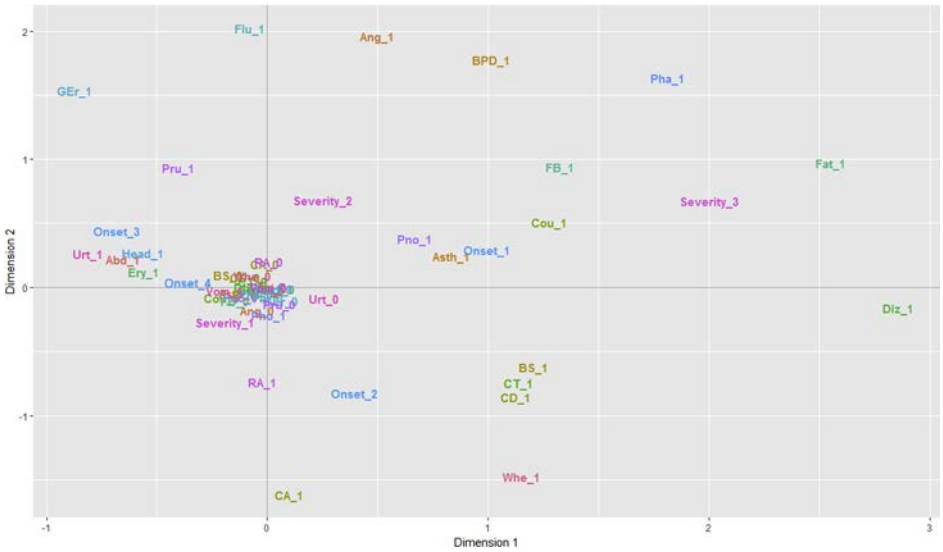

FIGURE 1. MCA representation: *ABD*, Abdominal pain; *ANG*, angioedema; *ASTH*, asthma; *BPD*, blood pressure; *BS*, bronchospasm; *CA*, conjunctivitis; *CD*, chest discomfort; *COU*, cough; *CT*, chest tightness; *DIA*, diarrhea; *DIZ*, dizziness; *ERY*, erythema; *FAT*, fatigue; *FB*, sensation of foreign body; *FLU*, flushing; *GER*, generalized erythema; *HEAD*, headache; *HYP*, hypotension; *LARY*, laryngeal edema; *LOC*, loss of conscience; *NAU*, nausea; *Onset_1*, SAR in the first 15 minutes; *Onset_2*, SAR between 16 and 30 minutes; *Onset_3*, SAR between 31 and 120 minutes; Onset_4, SAR later than 121 minutes; *PHA*, dysphagia; *PHO*, dysphonia; *PNO*, dyspnea; *PRU*, pruritus; *Severity_1*, *Severity_2*, *Severity_3*, according to EASSI's doctors; *SYN*, syncope; *TAC*, tachycardia; *UR*, urticaria; *VOM*, vomiting; *WHE*, wheezing; *1*, present; *0*, absent.

and cons. The major "pro" of classifying the SAR's severity after the event is resolved is that the doctor will have a full knowledge of the symptoms, duration, and response to treatment. However, ("a con") waiting until SAR is resolved could change the interpretation of the first impression of severity, especially if the doctors have not recorded data objectively or evaluation is done by people with no proper information on the event.

We suggest that the academic groups or academic societies that have proposed these grading systems for SAR due to AIT would reevaluate their proposals and provide evidence of clinical validation of each classification. Moreover, as regulatory agencies, such as the Food and Drug Administration, the European Medicines Agency, and Paul-Ehrlich Institute, have used some of these classifications, they should also need to comment on these issues.

Regarding anaphylaxis, and even though the term is not included *per se* in MedDRA, its correlation with epinephrine treatment was better than any SAR classification. The use of epinephrine was somewhat erratic because only 55% of the anaphylactic reactions were treated with it and, on the contrary, it was used in 10 (12.8%) of 78 mild reactions and in 7 (22.5%) of 31 moderate and severe reactions. Its use in mild reactions is not surprising due to its safe profile and the recommendations of the prompt use to avoid the worsening of a reaction.[18] However, its low rate of use in moderate and severe reactions is worrisome, and has already been reported in AIT[19] and in other allergy fields.[20,21] We identified that epinephrine use in SARs due to AIT was based on (1) national guidelines, (2) national clinical parameters, or (3) doctors' individual criteria so the "international guidelines" on epinephrine use appear not to be properly implemented.

Time to onset as a criterion of severity is always taken into account by doctors, but it is not always considered a criterion to change the degree of a SAR, except for EAACI2006. However, there was no correlation between EAACI2006 and the onset of the reaction. On the contrary, WAO2010 and WAO2017

classifications that record onset as a suffix have the best correlation with it. Different cutoff points have been established for the so-called early reactions: 15 minutes,[2] 30 minutes,[17] 60 minutes,[22] or minutes to several hours,[23] whereas other systems do not include a clear time span[3,4] although warn about the potential severity of symptoms occurring "within minutes." Fatal and near-fatal reactions in AIT tend to occur in the first 30 minutes, but not exclusively.[24-26] The inclusion of a rigid definition of time to onset might overlook severe reactions occurring not that acutely, as has been previously discussed, although all severe reactions in EASSI occurred 10 to 20 minutes after AIT administration.

The MCA technique used in this study allows the analysis of the relationships between the variables and different levels of one variable. The results can be seen analytically and visually and, therefore, allow one to reach a rationale interpretation based on previous knowledge on the subject. It is useful to identify discrepancies when similar symptoms were differently identified by doctors and then assigned to a different level of severity. The diversity of terms included in MedDRA to name the same symptom (eg, chest tightness and chest discomfort) is confusing and the selection of the term could provoke a misunderstanding.

The main limitations of the study rely on the *post hoc* nature of the analysis: (1) not all the variables needed for accurately recoding some classifications were recorded as, for example, peak-flow values; (2) the EASSI-severity score for every reaction was recorded according to the EASSI doctor opinion and it does not necessarily represent the real severity, but only his or her impression at the moment; (3) the EASSI-severity itself was used to grade some raw MedDRA symptoms to generate the *post hoc* variables, which could represent a bias. We have tried to minimize it by the use of the standardized computerized way we adopted to recode each reaction rather than on an individual basis.

This is the first case-based comparison between different AIT SAR classifications, and the data provided by this article might enable the scientific community to select the most relevant according to the purpose of its use. Despite having a lower correlation than EAACI2006 and AAAAI/ACAAI, the WAO grading systems were the most complete and might be the most reliable for both research and clinical data comparison. It is also helpful for physician decision-making use of epinephrine because of their good correlation with the onset of the SAR. Even though SCIT and SLIT were analyzed and due to the low number of SARs associated with SLIT, our conclusion would apply only for SCIT.

As a conclusion of this evaluation, we can suggest that WAO2010 represents the most comprehensive and factual system to record and classify SARs due to AIT. The EASSI study has proven that (1) it is possible to do a real-life prospective survey in different countries despite language barriers; (2) the use of harmonized terminology (eg, MedDRA) allows all participant doctors to report the SAR due to AIT in a homogeneous manner; (3) country "health care clinical parameters" differences play an important role in the reporting of SARs due to AIT. In some countries, like in Spain, the use of epinephrine is a common practice as soon as any SAR appeared, despite severity, onset, duration, and easy control with other medication; and (4) socioeconomical variables need to be considered when comparisons between countries are conducted. Finally, we would like to make a call to all "academic groups" and/or "academic societies" that have provided these grading systems for SARs due to AIT to reevaluate their proposals in a more pragmatic and factual manner and to provide evidence of "clinical validation" of all these grading systems.

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REFERENCES

1. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;177:1572-3.
2. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling H-J, Valovirta E, et al. Standards for practical allergen-specific immunotherapy. Allergy 2006;61:1-20.
3. Bernstein DI, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. Ann Allergy Asthma Immunol 2010;10:530-5.
4. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract 2014;2:161-7.
5. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010;125:569-74.
6. Cox LS, Sanchez-Borges M, Lockey RF. World Allergy Organization Systemic Allergic Reaction Grading System: is a modification needed? J Allergy Clin Immunol Pract 2017;5:58-62.
7. Calderón MA, Rodríguez del Río P, Vidal C, Just J, Pfaar O, Linneberg A, et al. An EAACI 'European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI)': the methodology. Clin Transl Allergy 2014;4:22.
8. Calderón MA, Vidal C, Rodríguez del Río P, Just J, Pfaar O, Tabar AI, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. Allergy 2017;72:462-72.
9. MedDRA. Available from: http://www.meddra.org/. Accessed August 1, 2011.
10. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003605.pdf. Accessed February 10, 2011.
11. Simons FER, Ardusso LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol 2011;127:587-93.
12. Manivannan V, Decker WW, Stead LG, Li JTC, Campbell RL. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Int J Emerg Med 2009;2:3-5.
13. Rodríguez del Río P, Vidal C, Just J, Tabar AI, Sanchez-Machin I, Eberle P, et al. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a paediatric assessment. Pediatr Allergy Immunol 2017;28:60-70.
14. Le S, Josse J, Husson F. FactoMineR: an R Package for multivariate analysis. J Stat Softw 2008;25:1-18.
15. Madsen F. EAACI 'Standards for practical allergen-specific immunotherapy'. Allergy 2007;62:332.
16. Alvarez-Cuesta E, Bousquet J, Canonica WG, Durham S, Malling H-J, Passalacqua G, et al. Reply to the letter by Dr Fleming Madsen (EAACI 'Standards for practical allergen-specific immunotherapy'). Allergy 2008; 63:939-40.
17. Caminati M, Dama AR, Djuric I, Montagni M, Schiappoli M, Ridolo E, et al. Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. Expert Rev Clin Immunol 2015;11:233-45.
18. Kemp SF, Lockey RF, Simons FER. World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy 2008;63:1061-70.

19. Santos N, Pereira AM, Silva R, Torres da Costa J, Plácido JL. Characterisation of systemic reactions to subcutaneous immunotherapy with airborne allergens and classification according to WAO 2010. Allergol Immunopathol (Madr) 2015;43:25-31.
20. Soller L, Fragapane J, Ben-Shoshan M, Harrington DW, Alizadehfar R, Joseph L, et al. Possession of epinephrine auto-injectors by Canadians with food allergies. J Allergy Clin Immunol 2011;128:426-8.
21. Song TT, Lieberman P. Epinephrine in anaphylaxis: doubt no more. Curr Opin Allergy Clin Immunol 2015;15:323-8.
22. Pfaar O, Jung K, Wolf H, Decot E, Kleine-Tebbe J, Klimek L, et al. Immunological effects and tolerability of a new fast updosed immunologically enhanced subcutaneous immunotherapy formulation with optimized allergen/adjuvant ratio. Allergy 2012;67:630-7.
23. Sastre J, Rodríguez F, Campo P, Laffond E, Marín A, Alonso MD. Adverse reactions to immunotherapy are associated with different patterns of sensitization to grass allergens. Allergy 2015;70:598-600.
24. Moreno C, De San Pedro BS, Millán C, Panizo C, Martín S, Florido F. Exploratory study of tolerability and immunological effect of a short up-dosing immunotherapy phase with a standardised allergen extract derived from pollen of *Olea europaea*. Clin Transl Allergy 2015;5:27.
25. Quiralte J, Justicia JL, Cardona V, Dávila I, Moreno E, Ruiz B, et al. Is faster safer? Cluster versus short conventional subcutaneous allergen immunotherapy. Immunotherapy 2013;5:1295-303.
26. Copenhaver CC, Parker A, Patch S. Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice. Ann Allergy Asthma Immunol 2011;107:441-7.

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TABLE E1. Classification of 109 SARs according to EASSI-severity, EAACI2006, AAAAI/ACCAI, WAO2010, and WAO2017

No.	Symptoms	Adrenaline	Onset	Time to resolution	Severity	Anaphylaxis	AAAAI/ACCAI Grading System	EAACI2006	WAO2010	WAO 2017
1	Conjunctivitis + Rhinitis	No	3 h	3 h	Mild	No	1	I	2	2
2*	Asthma	No	15 min	2 h	Moderate	No	2	II	3	3
3	Bronchospasm + Conjunctivitis + Wheezing	Yes	20 min	2 h	Mild	No	2	I	2	3
4*	Conjunctivitis + Rhinitis	No	8 h	4 d	Moderate	No	2	II	2	2
5*	Vomiting	No	1 min	60 min	Mild	No	1	0	2	1
6*	Angioedema	No	7 min	30 min	Mild	No	1	III	1	1
7*	Conjunctivitis + Rhinitis	No	1 h	45 d	Mild	No	1	I	2	2
8	Bronchospasm	No	10 min	60 min	Moderate	No	2	III	3	3
9	Asthma + Chest tightness	No	1 d 5 h	3 d	Moderate	No	2	II	3	3
10*	Bronchospasm + Fatigue	No	5 h	10 d	Moderate	No	2	II	3	3
11*	Cough	No	1 d	1 d	Mild	No	1	I	1	1
12*	Vomiting	No	45 d	8 d	Moderate	No	2	0	2	1
13*	Dysphonia	No	10 min	2 h	Mild	No	1	I	1	1
14*	Vomiting	No	1 min	60 min	Mild	No	1	0	2	1
15	Generalized erythema	No	5 d	20 d	Mild	No	1	0	1	1
16	Chest tightness + Wheezing	No	15 min	60 min	Mild	No	2	I	2	3
17	Bronchospasm	No	20 min	4 h	Severe	No	3	III	4	4
18	Abdominal pain	No	1 min	1 d 1 h	Mild	No	1	I	2	3
19	Cough + Dyspnea + Dizziness + Fatigue + Feeling bad	No	15 min	2 h	Moderate	No	2	II	3	3
20	Dyspnea + Erythema + Generalized pruritus	No	2 h	20 h	Mild	Yes	2	I	2	3
21	Angioedema + Erythema + Generalized pruritus	No	1 h	20 h	Moderate	No	2	II	1	1
22	Chest tightness + Weakness + Cough + Dizziness + Feeling bad	No	15 min	90 min	Moderate	No	2	I	3	3
23	Feeling bad	No	30 min	90 min	Mild	No	1	0	1	1
24	Urticaria	No	90 min	12 h	Mild	No	1	I	1	1
25	Headache + Feeling bad	No	8 h	2 d	Mild	No	1	0	2	2
26	Dyspnea	No	30 min	30 min	Mild	No	2	I	2	3
27	Rhinitis	No	1 h	2 d	Mild	No	1	I	1	1
28	Generalized erythema	No	5 d	20 d	Mild	No	1	0	1	1
29	Dyspnea	No	90 min	60 min	Mild	No	2	I	2	3
30	Dyspnea + Wheezing	No	30 min	90 min	Moderate	No	2	II	3	3
31	Feeling bad	No	30 min	3 h	Mild	No	1	0	1	1
32	Cough	No	1 d	11 d	Mild	No	1	I	1	1
33	Feeling bad	No	30 min	60 min	Mild	No	1	0	1	1
34	Dyspnea + Generalized erythema + Urticaria	No	45 min	21 h	Mild	Yes	2	I	2	3
35	Erythema + Urticaria	No	30 min	2 h	Mild	No	1	I	1	1
36	Feeling bad	No	45 min	10 min	Mild	No	1	0	1	1
37	Erythema	No	1 d	14 d	Mild	No	1	I	1	1
38*	Chest tightness + Chest discomfort	No	15 min	15 min	Moderate	No	2	I	3	3
39	Rhinitis	No	3 d	1 d	Mild	No	1	I	1	1
40	Erythema + Urticaria	No	5 h	7 d	Mild	No	1	I	1	1
41	Generalized erythema + Pruritus + Urticaria	No	8 h	10 h	Mild	No	1	I	1	1

(continued)

TABLE E1. *(Continued)*

No.	Symptoms	Adrenaline	Onset	Time to resolution	Severity	Anaphylaxis	AAAAI/ACCAI Grading System	EAACI2006	WAO2010	WAO 2017
42	Cough + Dyspnea + Generalized pruritus + Feeling bad	Yes	15 min	24 h	Moderate	Yes	2	II	3	3
43	Bronchospasm + Chest tightness + Generalized pruritus	Yes	15 min	20 min	Mild	Yes	2	I	2	3
44	Urticaria	No	2 h	3 h	Mild	No	1	I	1	1
45	Asthma + Rhinitis	No	2 h	2 d	Mild	No	2	I	2	3
46	Chest tightness + Urticaria	No	90 min	30 min	Mild	No	1	I	2	2
47	Conjunctivitis + Generalized pruritus + Rhinitis	No	4 h	4 h	Mild	Yes	1	I	2	2
48	Dyspnea + Generalized pruritus + Rhinitis	No	1d	1 d	Moderate	Yes	2	II	3	3
49	Angioedema + Cough + Generalized erythema + Generalized pruritus + Feeling bad	Yes	1 h	45 min	Moderate	Yes	2	II	2	2
50*	Angioedema + Dysphagia	No	4 h	6 h	Moderate	No	2	I	2	2
51	Feeling bad	No	30 min	60 min	Mild	No	1	0	1	1
52	Generalized pruritus + Urticaria	No	2 h	4 h	Mild	No	1	I	1	1
53	Angioedema + Asthma + Bronchospasm + Cough + Dysphagia + Dyspnea + Rhinitis + Feeling bad	No	10 min	60 min	Severe	Yes	3	III	4	4
54	Asthma + Bronchospasm + Chest tightness	Yes	5 min	2 d	Mild	No	2	I	2	3
55	Cough + Erythema + Generalized pruritus	Yes	30 min	30 min	Mild	Yes	1	I	2	2
56	Erythema	No	30 min	15 min	Mild	No	1	I	1	1
57	Erythema	No	20 min	30 min	Mild	No	1	I	1	1
58	Generalized pruritus	No	8 h	1 d	Mild	No	1	0	1	1
59	Bronchospasm + Cough + Dyspnea	Yes	45 min	15 min	Mild	No	2	I	2	3
60	Dyspnea	No	15 min	15 min	Mild	No	2	I	2	3
61	Dyspnea + Urticaria	YES	3 h	6 h	Moderate	Yes	2	II	3	3
62	Urticaria	No	90 min	10 h	Mild	No	1	I	1	1
63	Headache	No	3 h	2 d	Moderate	No	2	0	1	1
64	Dyspnea + Urticaria	No	10 min	60 min	Mild	Yes	2	I	2	3
65	Asthma + Cough + Dyspnea + Enrojecimiento	No	4 h	6 h	Mild	No	2	I	2	3
66	Rhinitis	No	3 h	1 d	Mild	No	1	I	1	1
67	Rhinitis	No	3 h 20 min	80 min	Mild	No	1	I	1	1
68	Rhinitis	No	30 min	2 h	Mild	No	1	I	1	1
69	Angioedema + Asthma + Blood pressure decreased	Yes	15 min	2 h	Mild	Yes	2	I	2	3
70	Bronchospasm + Conjunctivitis + Rhinitis	Yes	20 min	60 min	Mild	No	2	I	2	3
71	Urticaria	No	2 h	3 h	Mild	No	1	I	1	1
72	Asthma + Dysphagia	No	12 h	7 h	Mild	No	2	I	2	3
73	Asthma + Bronchospasm + Chest tightness + Cough + Wheezing	No	30 min	30 min	Mild	No	2	I	2	3

(continued)

TABLE E1. *(Continued)*

No.	Symptoms	Adrenaline	Onset	Time to resolution	Severity	Anaphylaxis	AAAAI/ACCAI Grading System	EAACI2006	WAO2010	WAO 2017
74	Chest tightness + Conjunctivitis + Dizziness + Erythema + Rhinitis	No	20 min	30 min	Mild	Yes	1	I	2	2
75	Urticaria	No	60 min	30 min	Mild	No	1	I	1	1
76	Angioedema	No	2 h	3 h	Moderate	No	2	II	1	1
77	Angioedema	No	30 min	2 h	Moderate	No	2	II	1	1
78	Rhinitis	No	8 h	1 d	Mild	No	1	I	1	1
79	Asthma	No	6 h	2 h	Mild	No	2	I	2	3
80	Rhinitis	No	6 h	1 d	Mild	No	1	I	1	1
81	Urticaria	No	1 h	1 d	Mild	No	1	I	1	1
82	Asthma	No	6 h	1 d	Mild	No	2	I	2	3
83	Asthma	No	1 d	3 d	Moderate	No	2	II	3	3
84	Urticaria	No	90 min	10 h	Mild	No	1	I	1	1
85	Asthma	No	22 h	60 min	Mild	No	2	I	2	3
86	Urticaria	No	2 h	1 d	Mild	No	1	I	1	1
87	Rhinitis	No	3 h	60 min	Mild	No	1	I	1	1
88	Abdominal pain + Urticaria	No	2 h + 30 min	3 h	Moderate	No	2	II	2	3
89	Urticaria	No	10 h	2 h	Mild	No	1	I	1	1
90	Bronchospasm + Conjunctivitis + Wheezing	Yes	20 min	2 h	Mild	No	2	I	2	3
91	Rhinitis	No	15 min	30 min	Mild	No	1	I	1	1
92	Chest tightness + Conjunctivitis + Rhinitis + Urticaria	Yes	30 min	2 h	Mild	Yes	1	I	2	3
93	Asthma + Erythema	Yes	10 min	30 min	Severe	Yes	3	III	4	4
94	Cough + Erythema + Urticaria	Yes	2 h	20 min	Moderate	Yes	2	II	2	2
95	Cough	No	90 min	15 min	Mild	No	1	I	1	1
96	Urticaria	No	90 min	12 min	Mild	No	1	I	1	1
97	Headache	No	3 h	2 d	Moderate	No	2	0	1	1
98	Asthma + Bronchospasm + Urticaria	Yes	3 h	1 d	Moderate	Yes	2	II	3	3
99	Angioedema + Generalized erythema + Generalized pruritus + Urticaria	No	3 h	10 h	Moderate	No	2	II	1	1
100	Chest tightness + Chest discomfort	No	4 h	12 h	Mild	No	1	I	2	3
101	Headache	No	2 h	6 h	Mild	No	1	0	1	1
102	Chest tightness + Chest discomfort	Yes	5 min	2 h	Mild	No	1	I	2	3
103	Urticaria	No	12 h	6 h	Mild	No	1	I	1	1
104	Bronchospasm + Cough + Rhinitis + Urticaria	Yes	20 min	6 h	Severe	Yes	3	III	4	4
105	Bronchospasm + Dyspnea	No	30 min	60 min	Mild	No	2	I	2	3
106	Conjunctivitis + Cough+ Dyspnea + Rhinitis	No	30 min	60 min	Mild	No	2	I	2	3
107	Conjunctivitis + Generalized erythema + Generalized pruritus + Rhinitis	No	30 min	6 h	Moderate	Yes	2	II	2	2
108	Rhinitis + Urticaria	No	5 h	2 h	Moderate	Yes	2	II	2	2
109	Dyspnea	No	5 min	30 min	Mild	No	2	I	2	3

*SAR related to SLIT.