Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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LETTER

Prospective (e-diary) vs retrospective (ARIA) measures of severity in allergic rhinoconjunctivitis: An observational compatibility study

To the Editor,

Severity assessment in relation to allergen exposure is an essential part of the diagnostic work-up for seasonal allergic rhinoconjunctivits (AR). Regularly recorded patient-reported symptom data may support the physician's decision-making on etiological diagnosis and therapeutic success of a pharmacological treatment

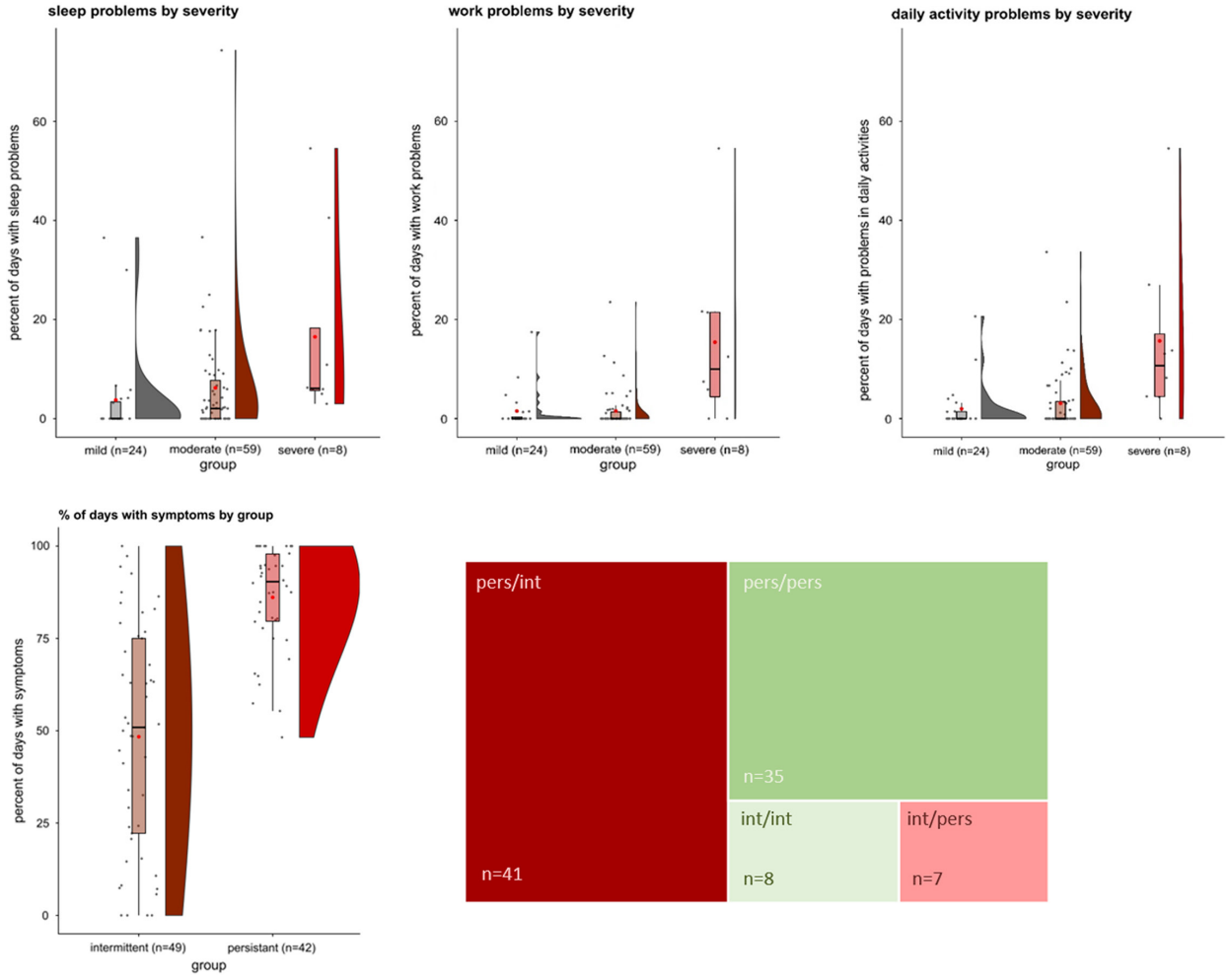

FIGURE 1 Prospectively recorded impact of allergic symptoms on sleep (top left), work (top middle), and daily activities (top right) in patient groups retrospectively classified after the pollen season according to ARIA severity classification as mild (grey), moderate (dark red), or severe (red). Further, the percentage of prospectively recorded days with symptoms is indicated (bottom left) for patients retrospectively classified as intermittent (dark red) or persistent (red) according to ARIA classification after the pollen season. Tiles (bottom right) indicate the number of matches (green tiles) or mismatches (red tiles) in persistence classification according to ARIA when obtained retrospectively vs prospectively

or allergen-specific immunotherapy (AIT).[1] Although several mobile applications facilitate the prospective collection of symptom data via e-diaries, severity measures often still rely on retrospective questionnaires and studies on data quality and validation in longitudinal data sets are scarce.[2,3] In this analysis, we aim to investigate whether and how prospectively acquired measures of disease severity (e-diary) relate to those retrospectively assessed via the Allergic Rhinitis and its Impact on Asthma (ARIA) questionnaire[4] in grass pollen allergic patients.

Within the observational @IT.2020 pilot project, 91 patients (average age 13.7 years (SD 3.2), 58/91 (64%) male) with a diagnosis of seasonal AR living in Rome, Italy, provided complete data sets for all study visits and recorded symptoms, medication intake and quality of life measures via the AllergyMonitor® e-diary app.[5] Symptom severity was assessed with daily Symptom Score (dSS),[6] Combined Symptom Medication Score (CSMS),[6] and Visual Analogue Scale (VAS)[3] and these prospective outcomes were compared to the retrospective ARIA severity classification obtained after the pollen season. For our analysis, we used the (i) cumulative dSS/CSMS/VAS; (ii) average dSS/CSMS/VAS; and (iii) number of "high days," surpassing the arbitrarily chosen thresholds of ≥1 for dSS (max. 3), ≥2 for CSMS (max. 6) and ≥3 for VAS (max. 10).

We tentatively divided the severity of AR in our study population as mild (n = 40, 44%), moderate (n = 38, 42%), and severe (n = 13, 14%), according to criteria reported in Table S3. These categories based on prospective monitoring (e-diary) matched in 46/91 (50%) those retrospectively generated by ARIA classification. Extreme inconsistencies were only observed in 4/91 (5%) patients. Moreover, the impact of symptoms on quality-of-life, prospectively measured by daily questions on sleep, work, and daily activity (Figure 1), significantly related to the retrospective classification in mild, moderate, and severe AR. For the frequency of symptoms, the observed differences were more heterogeneous. While patients who retrospectively judged their AR symptoms as persistent, indicated to suffer from allergic symptoms during more than 50% of the recorded days (Figure 1, bottom left), those retrospectively assessing their symptoms as intermittent, showed a broader range of data entries indicating symptoms. This is also reflected in a match/mismatch-analysis between ARIA criteria and e-diary data (Figure 1, bottom right). Interestingly, only 47% (43/91) of the patients showed a match of their retrospective and prospective frequency classification. The largest mismatch group (41/91, 45%) retrospectively judged their symptoms as persistent, while the e-diary entries reflected an intermittent phenotype.

To support the intuitive interpretation of prospectively collected severity data for physicians, we propose a comprehensive bubble chart (Figure 2). This scattergram visualizes for each individual patient (=bubble) the three most frequently used parameters to measure AR severity: (i) symptom score (dSS, x-axis); (ii) symptom-medication score (CSMS, y-axis); and (iii) impact on QoL (VAS, diameter of each bubble). Bubble colors and positions within the graph area give a quick overview on AR severity for individuals and the patient cohort.

The use of e-diaries to investigate AR severity in a routine setting is still in its infancy. We show that the prospective and retrospective assessment of AR severity are well interrelated, suggesting

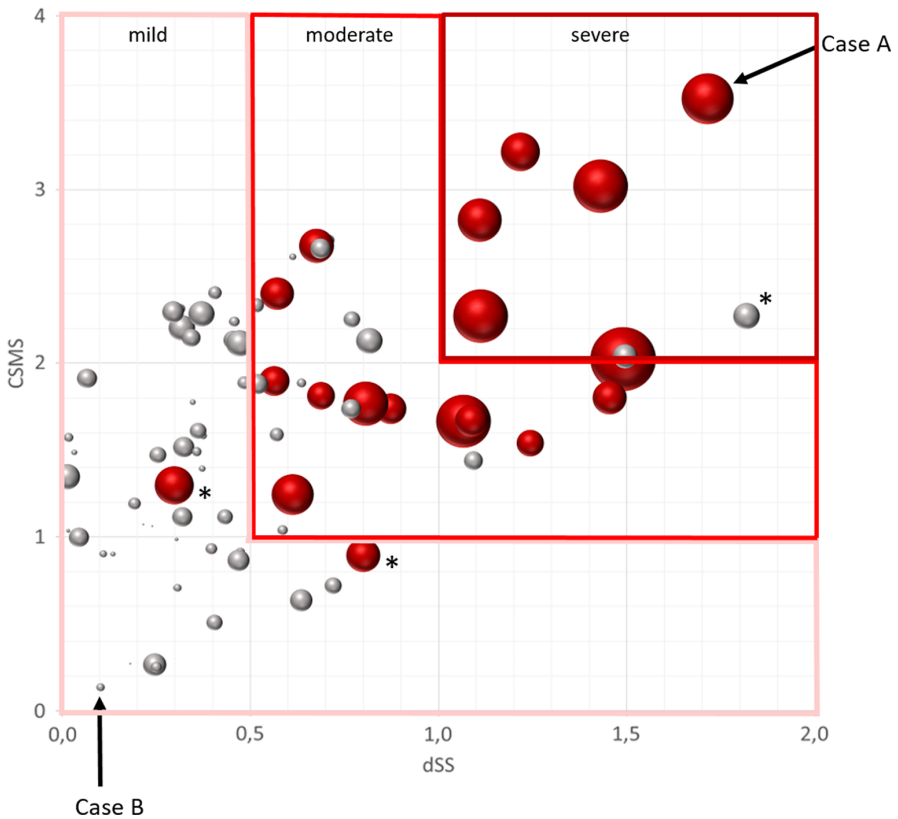

FIGURE 2 Visualization of SAR severity combining average symptoms (dSS, x-axis), average symptoms plus medication (CSMS, y axis), and average subjective impact of symptoms on daily life (VAS, bubble size). Every sphere represents an individual patient with average VAS scores ≥3 marked in red. Colored frames represent arbitrarily established areas of mildly (rose), moderately (red), and severely (dark red) affected patients. Cases A and B refer to sample patients whose features are reported in more detail in the Supporting Information. While patient A presented with persistently high values for dSS, CSMS, and VAS, patient B only indicated minimal values for all three scores. *Patients classified as moderately affected despite average CSMS and/or average dSS, taking their average VAS score into consideration

reciprocal consistency and cross-compatibility. However, our results suggest, that patients remember with less precision the frequency rather than the severity of their symptoms. Further, we propose an observer-friendly interpretation of patient-reported severity measures. More studies are required to develop this novel method, investigating its strengths, weaknesses, and optimal use in routine allergy practice.

AUTHOR CONTRIBUTION

SD data analysis, manuscript preparation and writing, SP data management and data analysis, MdF/SA/SC/DV/FB/IS/VV/EP/MAB/AT/SP data acquisition, review of the manuscript, ST data acquisition, critical review of the manuscript. UG statistical analysis and critical review, PMM data acquisition, supervision of statistical analysis, writing, and critical review of the manuscript.

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CONFLICT OF INTEREST

Dr. Matricardi reports grants and personal fees from Euroimmun AG, during the conduct of the study, grants and personal fees from Thermo Fisher Scientific, personal fees from Hycor Biomedical Inc, outside the submitted work. Salvatore Tripodi and Simone Pelosi are co-founders of TPS Software Production. Simone Pelosi reports personal fees from TPS Software Production. All other authors declared no conflicts of interest.

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SUPPORTING INFORMATION

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