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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 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

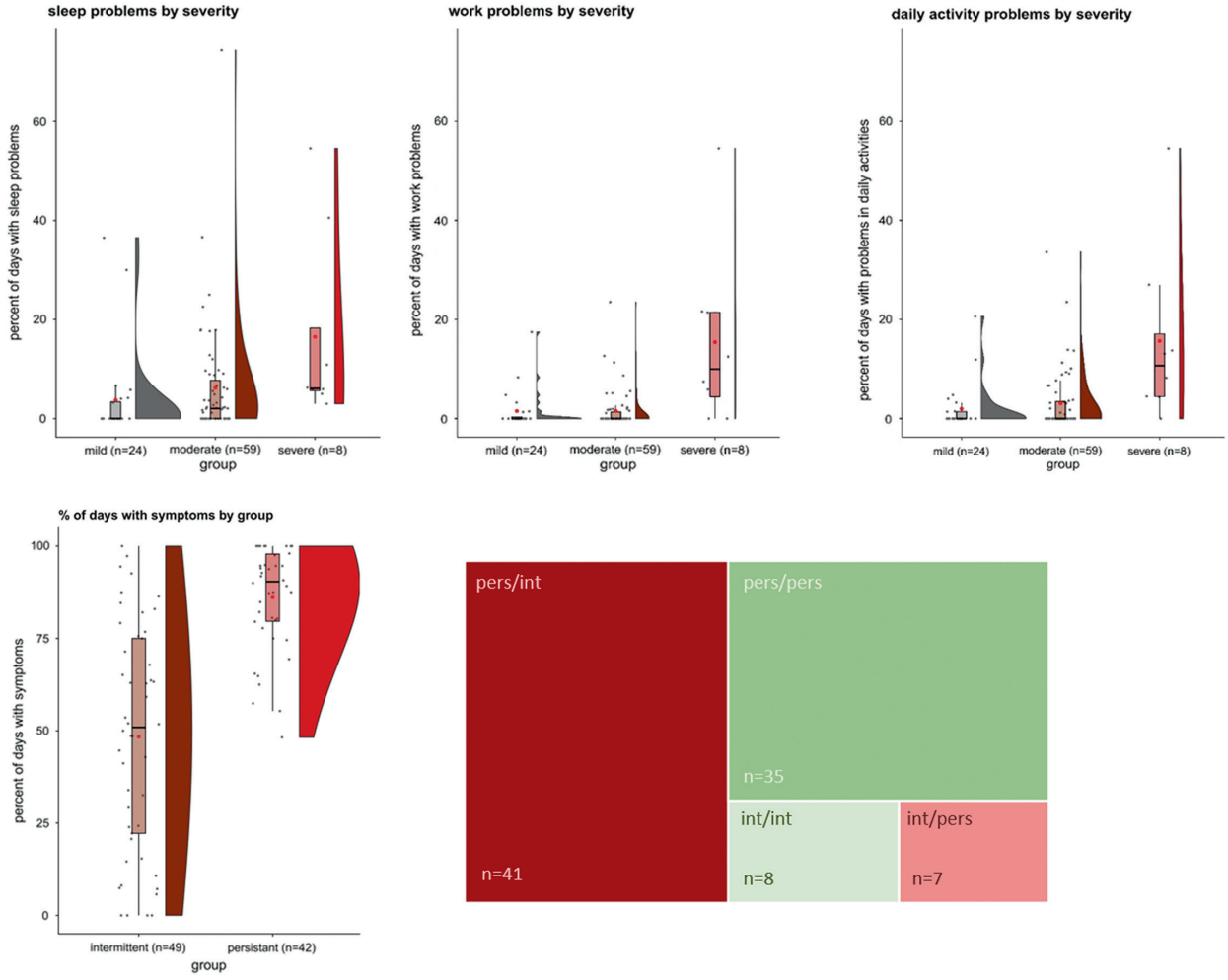

FIGURE 1 Prospectively recorded impact of allergic symptoms on sleep (top left), work (top middle), and daily activities (top right) in patient groups retrospectively classified after the pollen season according to ARIA severity classification as mild (grey), moderate (dark red), or severe (red). Further, 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

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 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

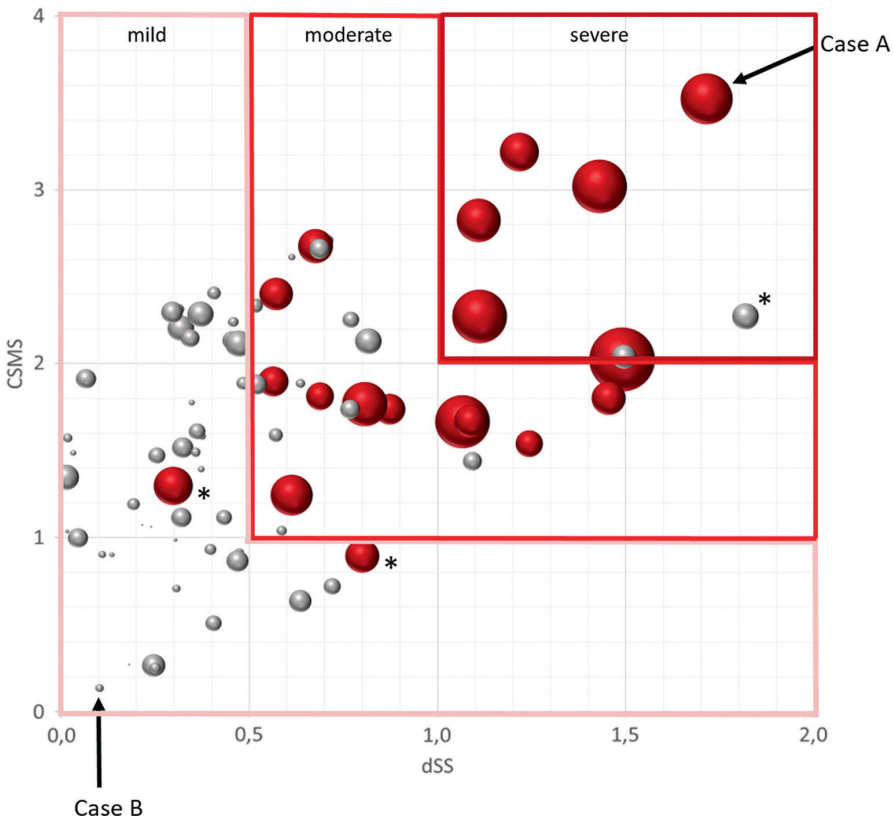

FIGURE 2 Visualization of SAR severity combining average symptoms (dSS, x-axis), average symptoms plus medication (CSMS, y axis), and average subjective impact of symptoms on daily life (VAS, bubble size). Every sphere represents an individual patient with average VAS scores ≥3 marked in red. Colored 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

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

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

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Sputum transcriptome analysis of co-regulated genes related to arachidonic acid metabolism in N-ERD

To the Editor,

Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (N-ERD) is characterized by alteration of arachidonic acid (AA) metabolism. The disease has variable pattern of lipid biomarkers and bronchial inflammation.[1–3] How this heterogeneity is reflected by expression of AA-related genes before and after aspirin therapy remains unknown. We collected induced sputum from 27 participants before aspirin desensitization and after 52-week high-dose aspirin therapy (650 mg/day).[2] Abundance of 87 genes mRNAs, including 15 AA-related ones was assessed in a total RNA from the sputum cells. By a method of unsupervised cluster analysis, the genes expression was used to find co-regulated transcripts, as expression patterns before and after aspirin therapy. We hypothesized that clustering of co-expressed AA-related genes might elucidate the genetic heterogeneity of N-ERD at baseline. Thereafter, we determined effect of a high-dose aspirin therapy on the aggregation of co-regulated AA-related genes to investigate transcriptional changes accompanying beneficial response in 21 out of 27 patients. Gene expression was assessed using a quantitative real-time polymerase chain reaction. The cluster analysis was performed using distances calculated on correlations between the expression of individual genes. Similar expression patterns were classified together as co-regulated genes, thus in separate clusters mRNA expression was independent from one another. The study group characteristics, data collection, and statistics are described in Appendix S1 (Methods, Table E1, Figure E1).

At baseline, five expression clusters were identified (Figure 1, Appendix S1: Figure E2). Each cluster contained genes encoding AA

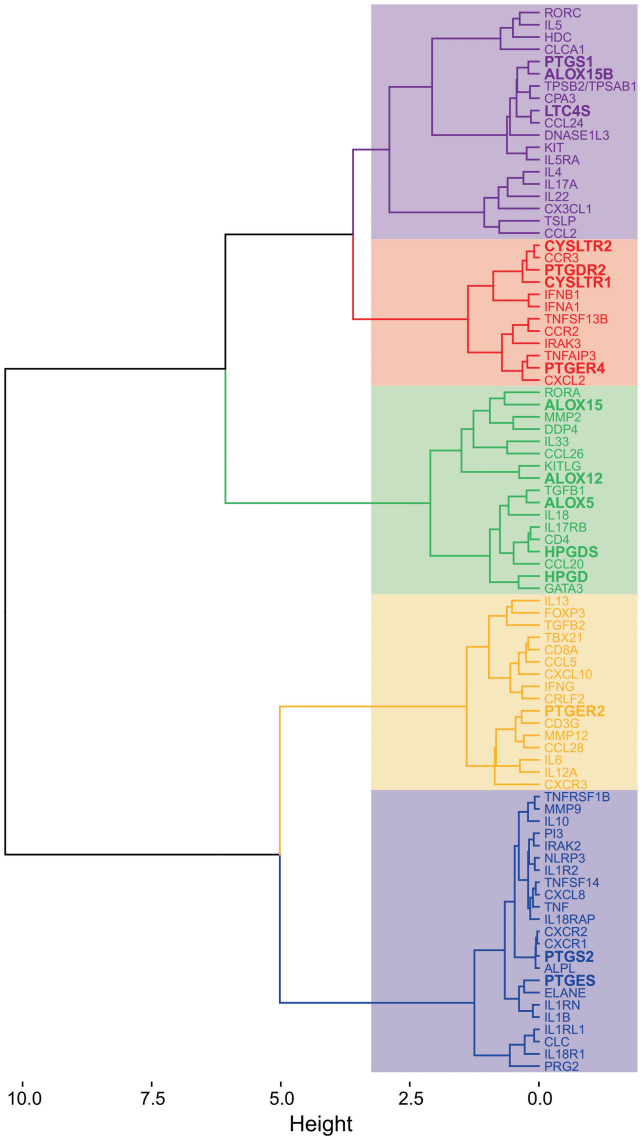

FIGURE 1 Dendrogram showing a hierarchical cluster analysis of 87 genes in sputum cells from patients with NSAID-exacerbated respiratory disease at baseline. Cluster analysis was performed using the Ward method on Spearman's correlation. Each color represents different cluster: blue—cluster number 1, yellow—cluster number 2, green—cluster number 3, red—cluster number 4, and violet—number 5. Genes related to arachidonic acid pathways are in bold