

## Cumulative Pollen Concentration Curves for Pollen Allergy Diagnosis

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In the Mediterranean area, patients with Seasonal Allergic Rhinitis (SAR) are often polysensitized to a wide array of grasses, trees and weeds [1], whose pollen are abundant mainly due to a mediterranean climate.[2] Global warming further contributes to increasingly extended pollination seasons resulting in wide overlaps between pollen seasons of several clinically relevant taxa.[3]

Given this scenario, pollen calendars are becoming increasingly complex as a tool for aerobiologists and physicians [4,5]. In the attempt of improving the precision of diagnostic work-ups for pollen allergy, daily symptom monitoring via eDiaries and graphical representations of airborne pollen data are progressively used.[6] Unfortunately, diagrams illustrating daily pollen concentrations of many different sources in parallel make the interpretation of each of these curves very difficult. This ultimately leads to difficulties for clinicians in identifying the culprit pollen for the potential prescription of an -specific allergen immunotherapy.[7]

This problem may be solved by using curves based on the cumulative transformation of pollen data. Cumulative pollen concentration sums have been described over 40 years ago [8] but are rarely used in an aerobiological domain [9]. To our knowledge, no reports on the use of cumulative pollen concentration curves in clinical practice exist to date.

In this study, we aimed to investigate whether the graphical representation of cumulative pollen concentrations over time helps to discriminate single pollen concentrations in a complex diagram and whether it is perceived as clinically useful by physicians. To this end, we elaborated curves of pollen concentrations as daily *cumulative* vs *absolute* values based on pollen data collected during the @IT.2020 study, a multicenter project on pollen allergy and allergen immunotherapy in 9 Southern European cities. In this context, aerobiological monitoring was performed from 1<sup>st</sup> January to 31<sup>st</sup> December 2018 on pollen of Cupressaceae, Fagales, Oleaceae, Poaceae, Urticaceae, *Ambrosia* spp., and *Artemisia* spp. taxa. Six cities (Valencia, Marseille, Rome, Messina, Istanbul, Izmir) had complete aerobiological data during the study period [Tables e1 and e2]. Data from the coordinating study center for aerobiological monitoring in Rome was used as a case study [Figure 1].

For the graphical representation of pollen concentrations, two different approaches have been used. Firstly, individual daily pollen concentration values have been represented for seven taxa in one diagram. Secondly, the cumulative pollen concentration was calculated for every day by adding the daily average concentration to the sum of previously counted pollen of the same source.

Following, a workshop with specialized allergists and physicians undergoing allergological training [Table e3] was held in four locations (Rome, Lisbon, Ankara, Tirana) between March and May 2019. In the framework of the workshop, participants completed a survey on the clarity and usability of absolute vs cumulative pollen concentration curves, based on the airborne pollen data obtained in Rome during the year 2018 [Figure 1 and e1]. After a short training on the correct interpretation of graphs based on absolute and cumulative data, physicians answered a questionnaire structured according to: the individual perception of (A) daily and (B) cumulative pollen concentration curves; (C) usability of both curves; (D) usefulness in a clinical setting.

Overall, 112 physicians completed the survey. Most physicians correctly interpreted information on daily absolute and cumulative pollen concentrations taken from both curves ( $n_{abs}=94$ , 83.9%;  $n_{cum}=90$ , 80.4%, respectively) [Table e4]. When asked to evaluate the usefulness of both curves in combination with regard to clinical decision-making, over two thirds ( $n=80$ , 71.4%) of the local physicians judged the information given by both curves as useful from a clinical standpoint. By interpreting each curve alone, only 3.6% ( $n=4$ ) of the physicians judged the information provided by the cumulative values as useful, while 25% ( $n=28$ ) considered the information given by the diagram portraying only daily values, as useful [Table e4]. While information on the highest peak of daily pollen concentration was mainly sought and found using a combination of both curves, the cumulative curve was considered the only graphical tool to identify the highest annual cumulative pollen concentration.

In summary, we found that the graphical representation of cumulative pollen concentrations in addition to absolute daily concentration curves is:

- 1) intuitively interpretable for most study participants with regard to the pollen season start, trend, and conclusion as well as on monthly growth and annual cumulative levels (annual total integral)
- 2) clearly differentiated even when the curves of many pollen types, with overlapping seasonality, are represented together in the same diagram

Our results offer a solution to visualize pollen data of many allergenic pollen types in complex aerobiological areas by combining detailed pollen information easily and effectively in a single diagram. This is of great relevance for the management of patients with IgE sensitization to pollen extracts with overlapping seasons. Given that poly-sensitized pollen-allergic patients are predominant nowadays [10] our data suggest a wide area of application for these complementary methodologies in clinical practice. The characteristics of cumulative pollen concentrations open up a range of possible uses in the analysis of the interaction between exposure to allergenic pollen and data acquired in clinical practice, such as patients' symptoms curves acquired via eDiaries.[11]

A few limitations of the present study need to be considered. First, although we had data from six Mediterranean centers, we selected Rome as a case study, which is not representative for

all aerobiological conditions in the participating centers. This strategy aimed to keep the physician assessment short, limiting attrition and tiredness that could lower answer quality if data from all cities was independently assessed. Moreover, although we acknowledge that there are different aerobiological conditions in different centers / cities that could lead to diverse perceptions on the usefulness of daily absolute or cumulative pollen curves, this proof of concept study is the first comparing these two data representations and showing that both give relevant information to physicians in care of pollen allergic patients. Second, the study was performed based on pollen data of only one year. However, we believe that the conclusions reached by our study are relatively independent of the year of data collection.

In conclusion, our study shows that in Southern European countries the graphical representation of pollen data based on cumulative pollen concentrations is efficient, informative, and perceived as useful for the diagnostic work-up of pollen-allergic patients. This observation builds the base for future investigations, for example on the role of individual thresholds of absolute and cumulative pollen concentrations eliciting symptoms in the majority of sensitized patients.

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## Legend to Figures

**Figure 1.** Daily absolute (yellow) and cumulative (brown) pollen concentrations of Cupressaceae in Rome 2018. Blue areas indicate linearly interpolated data for missing values.

