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Heterogeneity of Pollen Food Allergy Syndrome in Seven Southern European Countries: the @IT.2020 Multicenter Study

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Abstract

Background: Pollen food allergy syndrome (PFAS) is a frequently underdiagnosed disease due to diverse triggers, clinical presentations, and test results. This is especially relevant in geographic areas with a broad spectrum of pollen sensitization, such as Southern Europe.

Objectives: To elucidate similarities and differences of PFAS in nine Southern European centers and identify associated characteristics and unique markers of PFAS.

Methods: As part of the @IT.2020 Multicenter Study, 815 patients with seasonal allergic rhinitis (SAR), aged 10-60 years, were recruited in seven countries. They completed questionnaires regarding SAR, comorbidities, family history, and PFAS, underwent skin prick testing (SPT) and serum IgE testing.

Results: Of the 815 patients, 167 (20.5%) reported PFAS reactions. Most commonly, eliciting foods were kiwi (58, 34.7%), peach (43, 25.7%), and melon (26, 15.6%). Reported reactions were mostly local (216/319, 67.7%), occurring within five minutes of contact with elicitors (209/319, 65.5%). Associated characteristics included positive IgE to at least one panallergen (profilin, PR-10, or nsLTP) ($p=.007$), maternal PFAS (OR:3.716, $p=.026$), and asthma (OR:1.752, $p=.073$). Between centers, heterogeneity in prevalence (Marseille: 7.5% vs. Rome: 41.4%, $p<.001$) and of clinical characteristics was apparent. Cypress played a limited role, with only 1/22 SPT mono-sensitized patients reporting a food-reaction ($p<.073$).

Conclusions: PFAS is a frequent comorbidity in Southern European SAR patients. Significant heterogeneity of clinical characteristics in PFAS patients amongst the centers was observed, and may be related to the different pollen sensitization patterns in each geographical area. IgE to panallergen(s), maternal PFAS, and asthma could be PFAS-associated characteristics.

Keywords

Oral Allergy Syndrome, Panallergen, Pollen Food Allergy Syndrome, Seasonal Allergic Rhinitis, Southern Europe

Abbreviations

ARIA Allergic Rhinitis and its Impact on Asthma

ATH Athens

IgE Immunoglobulin E

IQR Interquartile Range

IST Istanbul

IZM Izmir

MAR Marseille

MES Messina

nsLTP non-specific Lipid Transfer Protein

OR Odds Ratio

PFAS Pollen Food Allergy Syndrome

POR Porto

PR-10 pathogenesis-related class 10 proteins

ROM Rome

SAR Seasonal Allergic Rhinitis

SD Standard Deviation

SPT Skin Prick Test

TIR Tirana

VAL Valencia

Conflict of interest

Dr. Couto reports personal fees from Roche, outside the submitted work; Dr. Delgado reports personal fees from Laboratórios Vitoria, SA, outside the submitted work; Dr. Makris reports personal fees from Novartis, personal fees from Astra Zeneca, personal fees from Sanofi, personal fees from GSK, personal fees from Mylan, outside the submitted work; Dr. Pahus reports personal fees from GlaxoSmithKline, personal fees from Astra Zeneca, personal fees from Chiesi, outside the submitted work; Dr. Papadopoulos reports personal fees from Novartis, personal fees from Nutricia, personal fees from HAL, personal fees from MENARINI/FAES FARMA, personal fees from SANOFI, personal fees from MYLAN/MEDA, personal fees from BIOMAY, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, personal fees from ASIT BIOTECH, personal fees from Boehringer Ingelheim, grants from Gerolymatos International SA, grants from Capricare, outside the submitted work; Simone Pelosi reports other from TPS Production srl, during the conduct of the study. Dr. Psarros report personal fees from Novartis Hellas, Takeda, Astra Zeneca, Sanofi outside the submitted work; Dr. Sackesen reports grants from MSD to support laboratory tests for the study 'Effects of the montelukast therapy on asthma and allergic inflammation in children with food allergy' and from Abbott to support "Metabolomics study in children with food allergy", outside the submitted work; Dr. Tripodi reports other from TPS Production srl, during the conduct of the study; Dr. Xepapadaki reports personal fees from Uriach, personal fees from Novartis, personal fees from Nestle, personal fees from Nutricia, outside the submitted work; Dr. Matricardi reports grants from Deutsche Forschungsgemeinschaft, grants and personal fees from Hycor Biomedical, grants and personal fees from Euroimmun, personal fees and non-financial support from Thermo Fisher Scientific, outside the submitted work;

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Authors' contribution

XA, SA, AB, BB, SCS, LC, DC, MC, LD, ARB, CD, MVD, JAF, OG, AG, DH, TMH, DTJ, FK, BL, RL, MM, AM, EM, AN, AÖ, LP, IP, NGP, AMP, MP, AP, FP, CS, IF, ST, VV, VV, PX, DY, PMM, SD participated in the clinical coordination and patient recruitment/monitoring. ASA, MAB,

EC, AG, BL, EP, JS, MT, AT, performed and supervised the collection of aerobiological data in the study. SP, ST provided the technical infrastructure for symptom monitoring. TL, EP, TMH performed data management and statistical analysis under the supervision of PMM and SD. LT, SD, PMM wrote the manuscript. All co-authors reviewed the text.

Introduction

Pollen Food Allergy Syndrome (PFAS) is a hypersensitivity reaction that can occur in patients with seasonal allergic rhinitis (SAR) after contact with certain foods due to sensitization to cross-reactive pollen and/or food allergens^{1,2}. Prevalences of PFAS in patients with pollen allergies ranging from 9.6% to 55% have been reported worldwide³⁻⁵. Typical symptoms affect the oropharynx, including itching, stinging, pain, and edema, appearing within minutes of contact with the offending food⁴ and lasting minutes to hours⁴⁻⁶. In around five percent of cases, more severe symptoms affecting other organ systems (e.g. skin, gastrointestinal, cardiovascular, and respiratory systems) have been reported⁷⁻⁹. Rarely, patients suffered from life-threatening anaphylaxis¹⁰⁻¹³.

Regional differences in pollen sensitization patterns influence the prevalence, elicitors, and typical symptoms of PFAS¹⁴.

While much is known about the typical sensitization pattern for PFAS in Northern Europe¹⁵, less information is available for Southern Europe. Studies regarding PFAS in Italy, Turkey, and Spain have been published but show little overlap in methodology and are therefore difficult to compare¹⁶⁻¹⁸. Additionally, different pollen are present in Southern Europe¹⁹. One of these is cypress pollen, a primary cause of SAR in the Mediterranean²⁰. The exact role of cypress pollen in relation to PFAS is yet unknown and subject of current research²¹⁻²⁴.

PFAS cross-reactions are caused by plant-food allergens that share sequence-, structure-, and function-similarities with pollen allergens. Due to their wide-spread nature, these are known as panallergens^{25,26}. In this study the focus was placed on the following panallergen families: profilins, PR-10, and non-specific Lipid Transfer Proteins (nsLTP)²⁷. While the first two categories are markers of PFAS based on a primary sensitization to aeroallergens, the latter are currently categorized as class I food allergens which, due to their cross-reactivity with airborne allergens may elicit also respiratory symptoms^{1,28}. However, recent evidence suggests, that the nsLTP molecule Ole e 7 from olive pollen may play a role as primary sensitizer in peach allergic patients from areas with extensive exposure to olive pollen²⁹. Independently from the different perspectives on primary sensitization, nsLTP play an important role in pollen and food allergies in the Mediterranean region and is therefore being considered in the present analysis.

Currently, no study has been published describing PFAS in Southern Europe with a unified methodology. As greater understanding of this complex syndrome is vital for the proper diagnosis

of and care for patients, we have examined the clinical history, characteristics, and diagnostic results of patients in nine study centers from seven Southern European countries using a uniform method. Furthermore, we focused on finding the connections between PFAS and both cypress pollen and nsLTP in our cohort.

Materials and Methods

Study population—The @IT.2020 Observational Longitudinal Multicenter Clinical Study was conducted to determine the impact of component resolved diagnostics and mobile health on the diagnosis of SAR in Southern Europe. In this context, we recruited patients suffering from SAR in nine study centers in seven Southern European countries between November 2017 and May 2018 (Porto (POR), Portugal; Valencia (VAL), Spain; Marseille (MAR), France; Rome (ROM) and Messina (MES), Italy; Tirana (TIR), Albania; Athens (ATH), Greece; Istanbul (IST) and Izmir (IZM), Turkey). The patients fulfilled the following inclusion criteria: 1) age 10 to 18 years for children or 19 to 60 years for adults; 2) a good understanding of the national language or one of the languages offered in the Allergy monitor® application (TPS software production, Rome, Italy); 3) availability of a smart phone; 4) written informed consent. Exclusion criteria consisted of: 1) prior pollen allergen immunotherapy; 2) any severe chronic disease; 3) living further than 30 km away from the local aerobiological center used for pollen counts. The study was approved by the local ethics committees.

Study design—

T0 questionnaire—Under the supervision of an allergy specialist, the patients or legal guardians completed a questionnaire regarding social demographics, clinical history of SAR and asthma, comorbidities, and family history. After indicating whether they had ever ingested one of the 15 selected known PFAS-associated foods (peach, apple, almond, apricot, soybean, cherry, pear, watermelon, melon, sesame, banana, carrot, fennel, kiwi, celery) or “others”, patients were asked about the type and timing of potential resulting symptoms. Possible symptoms were: 1) pruritus throat/mouth/tongue; 2) vesicles to the oral cavity; 3) skin redness; 4) urticaria; 5) swelling of eyes/eyelids; 6) swelling of tongue/face; 7) difficulty talking/swallowing; 8) nose closed/running; 9) cough/wheezing/respiratory difficulties; 10) vomiting; 11) diarrhea; 12) palpitations/tachycardia; 13) pallor/hypotension; 14) loss of consciousness. Of these symptoms, 1), 2), 6), and 7) were classified as local reactions, while the rest was categorized as systemic. The possible times to onset of symptoms were divided into five categories: 1) ≤ 5 minutes; 2) 6–20 minutes; 3) 21–60 minutes; 4) 61–120 minutes; 5) ≥ 120 minutes. The selection of included

foods was based the experience from previous studies as well as expert opinion^{13,16}. Symptom assessment has been adapted from a validated questionnaire³⁰.

Skin Prick Tests (SPT)– SPTs were performed by local physicians on the volar surface of both forearms using 1 mm Osterballe type metal lancets and allergen extracts from mugwort, wall pellitory, olive tree, hazel tree, birch, bermuda grass, juniper ash, ragweed, *D. pteronyssinus*, cat, dog, histamine control, saline control (Stallergenes Greer, London, UK), timothy grass, *Alternaria*, plane tree, *Salsola kali* (Russian thistle), and mixed grasses (ALK Abelló, Hørsholm, Denmark). All results were noted 15 minutes after application of the extracts. Positive results were defined as wheal diameters ≥ 3 mm after subtraction of the negative control. For the current analysis regarding PFAS, results obtained from *D. pteronyssinus*, cat, and dog dander SPTs were not included.

IgE results–Serum was obtained and tested for IgE antibodies to multiple extracts and molecules using the EUROLINE Southern European Pollen Profile (EUROIMMUN Medizinische Diagnostika AG, Lübeck, Germany), a semi-quantitative, validated, customized multiplex immunoblot assay method³¹. Results were expressed in kU/l and considered positive at levels ≥ 0.35 kU/l. This current analysis focused on Bet v 2, Phl p 12 (profilins), Bet v 1, Cor a 1, Que a 1 (PR-10), and Art v 3, Ole e 7 (nsLTP).

Statistics – Results were calculated using IBM SPSS Statistics 25, Armonk, NY, USA. All categorical data was summarized as numbers (n) and frequencies (%). Quantitative data was given as mean and standard deviation (SD) or median and interquartile range (IQR). Further analysis was performed using logistic regression analysis to calculate the influence of select variables on the outcome of PFAS. Hierarchical regression analysis was used to investigate possible associated characteristics for PFAS based on backward stepwise logistic regression using Wald's method. Significance of differences between the centers were calculated using Pearson-Chi² test for frequencies, Kruskal-Wallis test for medians, ANOVA for means. When comparing two groups, Pearson-Chi² test was used to calculate the significance for frequencies, Mann-Whitney-U test for medians and t-test for means. Values of $p < .05$ were considered significant.

Results

Study population –815 patients (mean age 26.1 yrs. (13.6); 441/815, 54.1% male) from nine study centers were included. 167 of them (20.5%) reported reactions to at least one PFAS-associated food. The age and sex distribution amongst these patients showed no significant

difference to those without PFAS (25.2 yrs. and 82/167 male (49.1%) vs. 26.3 yrs. and 359/648 male (55.4%)) [Table 1].

PFAS in Southern Europe

- **Clinical characteristics** – Compared to patients without PFAS, patients with PFAS had a lower age at onset of SAR (9 yrs. vs. 12 yrs., $p < .003$), a higher prevalence of maternal PFAS history as well as of additional allergic comorbidities, especially anaphylaxis and urticaria ($p < .001$ for all), but also asthma and atopic dermatitis ($p = .001$ and $p = .006$, respectively). By contrast, no significant differences were observed in disease duration, severity, and quality according to Allergic Rhinitis and its Impact on Asthma (ARIA) classification [Table 1].
- **PFAS-associated foods** – While kiwi (58/167, 34.7%), peach (43/167, 25.7%), and melon (26/167, 15.6%) were most commonly named as elicitors, 44.9% of the patients reported reactions to foods not listed in the questionnaire [Figure 1].
- **PFAS symptoms and time to reaction** – A total of 319 reactions were reported. Frequent symptoms were oral pruritus (252, 79.0%), swelling of the tongue/face (49, 15.4%), and urticaria (48, 15.0%) [Figure 2]. Loss of consciousness (1, 0.3%), palpitations/tachycardia (2, 0.6%), oral vesicles (5, 1.6%), and pallor/hypotension (6, 1.9%) were least frequently reported.

The majority of reactions occurred within 5 minutes of contact with the offending food (209, 65.5%) [Figure 2]. 216 reported reactions (67.7%) consisted solely of oral symptoms [Figure 3].

Systemic reactions were reported by 40.7% (68/167) of the patients [Table e1], most commonly to soy (2/4, 50.0%), peach (17/43, 39.5%), almond (7/20, 35.0%), apple (5/15, 33.3%), sesame (2/6, 33.3%), kiwi (19/58, 32.8%), and cherry (5/17, 29.4%) [Figure 3]. Patients suffering from systemic symptoms showed a significantly higher prevalence of anaphylaxis ($p < .001$) [Table e1].

- **Atopic reactivity** – Patients with PFAS tested positive to a higher mean number of allergens in SPTs than those without (5.0 vs. 3.7, $p < .001$) but did not show a larger mean wheal diameter [Table 2]. In IgE testing, PFAS patients had higher frequency of mono- or multi-panallergen positive results. The prevalence of positive IgE results for the three analyzed panallergen groups, profilin, PR-10, nsLTP, was higher in PFAS positive patients ($p < .001$ for all) [Table 2].
- **PFAS associated characteristics** – The following associated characteristics were identified: 1) positive panallergen IgE results ($p = .007$), especially multi-panallergen (OR:

6.353, $p = .021$) and PR-10 positive results (OR: 5.582, $p = .004$), 2) anaphylaxis (OR: 6.210, $p < .001$), 3) maternal history of PFAS (OR: 3.716, $p = .026$), and 4) asthma (OR: 1.752, $p = .073$)[Table e2]. The model generated by hierarchical regression analysis shows solid diagnostic ability in a Receiver Operating Characteristics Curve with an area under the curve of 0.688[Figure e1].

PFAS in nine different Southern European centers:

The prevalence of PFAS differed significantly between the nine centers ($p < .001$), ranging from 6/80 (7.5%) in **MAR** to 41/99 (41.4%) in **ROM**[Table e4]. Heterogeneity was particularly observed regarding age at SAR onset ($p = .003$), months per year with SAR symptoms ($p = .001$), ARIA severity and frequency (p from $< .001$ to $.080$), number of patients with comorbidities ($p = .035$), and mean number of comorbidities per patient ($p = .016$), especially concerning urticaria and atopic dermatitis ($p = .022$, $p = .018$, respectively).

SPT results varied regarding the number of positive tests and average wheal diameter ($p < .001$). Heterogeneous panallergen IgE results were observed for panallergen negative ($p = .030$) and PR-10 positive results (p -value $< .001$).

A focused description of the unique characteristics of patients with PFAS in each center, in order of decreasing PFAS prevalence, is given below.[Table e1 and e3, Figure 1]

- **ROM** had the highest occurrence of PFAS and 43.9% of these patients also reported urticaria. Reactions to carrot, celery, and fennel were solely reported here. 78% of patients experienced only oral reactions (32/41, $p = .005$). Profilin, PR-10, and nsLTP IgE positivity was observed in 9, 13, and 8 out of 41 patients, respectively.
- In **MES**, patients showed a mean age at onset of SAR of 10 years plus high rates of urticaria and asthma (18/24 and 12/24, respectively). Instead of melon, apricot was the third most frequent elicitor (5/24). Systemic reactions were especially common (14/24). A predominance of nsLTP IgE positivity was shown (4/24).
- **POR** reported patients with young age at onset at 7 years old and 11/24 patients also reported atopic dermatitis. Patients experiencing at least one systemic reaction were common (13/23). Profilin was the predominant panallergen in IgE results (5/24).
- Patients in **TIR** the mean age at onset of SAR was 22 years, high frequency of comorbidities (9/13), especially urticaria (8/13), and solely moderate/severe SAR. Reactions to almond were frequent (4/13). While only 5/13 patients were panallergen negative in IgE tests, 7/13 were PR-10 positive.

- In **ATH**, all 22 patients reported severe SAR with a high number of positive SPTs and large mean wheal diameter. Half of the patients reported experiencing at least one systemic symptom. None were PR-10 IgE positive, instead IgE to nsLTP and profilin were found (5/22, 4/22 respectively).
- **IZM** reported patients with an onset of SAR at 26 years of age, and an average of 2.6 months per year with symptoms. 3/14 patients had mild intermittent SAR and on average the patients had less than 1 comorbidity. Kiwi was by far the most common elicitor. 11/14 patients were IgE negative to all panallergens and none were PR-10 IgE positive.
- In **VAL**, patients typically suffered from SAR during 3.2 months/year on average and reported a high rate of atopic dermatitis (6/10). Moderate/severe intermittent and moderate/severe persistent SAR were equally common at 4/10 each. The most frequently named elicitors included peach (5/10) and almond (5/10). 4/10 patients were IgE positive to nsLTP.
- **IST** showed relatively high age at onset and low frequency of comorbidities. While no reactions to melon were recorded, reactions to almond were common (2/13). A predominance of patients had systemic reactions (7/13). No PR-10 IgE positive patients were found.
- **MAR** reported the lowest prevalence of PFAS (6/80), showing a relatively high age at onset of SAR at 14.5 years old. All PFAS patients had moderate/severe ARIA scores and reported comorbidities, especially urticaria (4/6) and atopic dermatitis (3/6). The patients presented with low average SPT wheal size (4.4 cm) and high rate of positive IgE to PR-10 (3/6).

Specific research questions:

- **The role of cypress in PFAS in Southern Europe** – As an indicator of cypress pollen sensitization, juniper ash extract SPT was performed. 311/815 (38.2%) patients tested positive. 22 of these (7.1%) were mono-sensitized. Only one mono-sensitized patient reported a PFAS reaction, compared to 58/289 of multi-sensitized patients ($p = .073$). Similarly, out of 275 (33.7%) IgE sensitized patients to cypress pollen extract and/or Cup a 1, only 16 (5.8%) were mono-sensitized. None of these patients were PFAS positive, compared to 60/259 of cypress pollen multi-sensitized patients ($p = .029$).

- **PFAS and nsLTP in Southern Europe** –26/167 (15.6%) of the patients reporting symptoms to one or more of the 15 PFAS-associated foods were nsLTP IgE positive [Table 2]. The most frequent elicitors of clinical symptoms amongst this group were peach (12, 46.2%), kiwi (10, 38.5%), and almond (8, 30.8%). Half of the nsLTP IgE positive patients reported at least one systemic symptom [Figure 4]. No significant differences between patients with and without sensitization to nsLTP were observed with regard to clinical characteristics [Table e4].

Discussion

In our analysis of PFAS based on a cohort of 815 Southern European patients, we discovered: 1) an overall prevalence of 20.5% of PFAS in patients suffering from SAR in Southern Europe; 2) substantial heterogeneity in prevalence and clinical characteristics of PFAS amongst the different centers; 3) a significant lack of PFAS in cypress pollen mono-sensitized patients; 4) a high frequency of systemic reactions in nsLTP IgE positive patients.

The overall prevalence of PFAS in our study falls within the range of previous reports, but is much lower than the frequency of PFAS amongst birch pollen allergic patients in Northern Europe¹⁴. This can be explained by the decreased role of birch pollinosis in Southern Europe^{14,32}, with a lower sensitization to Bet v 1 and a higher sensitization to Bet v 2¹⁵. This is reflected by our data, showing an equal distribution of sensitization to PR-10, profilin, and nsLTP. Furthermore, the most commonly reported reactions were to foods typically associated with nsLTP or profilin: kiwi, peach, and melon. This reflects similar findings as previous studies performed in Italy and Turkey, where kiwi and peach were also reported as the most common elicitors^{16,17}.

In terms of symptoms, our data show a fast onset and a predominance of oral pruritus. This corroborates current literature, where reactions are described as mainly oral and with a rapid onset². Yet contrary to previous publications on PFAS, where systemic symptoms only comprised 5% of all reactions⁸, 32.3% of the reported reactions in our cohort included at least one systemic symptom. This may be explained by the frequency of nsLTP sensitization in Southern Europe³³, as these molecules are heat and acid resistant and therefore more likely to cause extraoral symptoms²⁸.

Within Southern Europe, a vast heterogeneity of pollen has been reported^{19,34}. This heterogeneity can lead to variance in sensitization patterns and therefore in the development of SAR and PFAS, even within the same country as shown by Mastroilli et al¹⁶. In our study, a difference in latitude appears to have a bigger impact on the heterogeneity of PFAS than longitudinal differences. This could be due to changes in climatic zones with accordingly differing

vegetation. The present analysis aimed at elucidating these potential differences with a uniform methodological approach in several countries and was able to describe a high degree of heterogeneity, certain similarities, as well as certain unexpected observations.

While a low frequency of birch sensitization has previously been reported in the South of France (1.05%)³², we found a high rate of PR-10 IgE sensitization in **MAR** PFAS patients (3/6). This could indicate that patients may have been exposed to birch in a different geographical area. Surprisingly, PFAS positive patients in **TIR** suffered from severe allergic disease and many comorbidities. This is in contrast to previous epidemiological studies from the same geographic region, where low asthma severity has been reported³⁵. Additionally, in 1999, Priftanji et al. described that only 2.7% of the tested patients were SPT positive for *Betula*³⁶, yet our cohort of PFAS patients was predominantly PR-10 IgE positive.

Mastorilli et al. reported in 2016 a PFAS frequency of 16.9%¹⁶ in Southern Italy, while **MES** showed a higher rate of PFAS 24/82 (29.3%) in our study. This may be explained by an increased incidence in allergic diseases, since our study recruited patients almost 10 years later than Mastorilli et al.. However, both studies showed an early onset of SAR and a predominance of nsLTP IgE positivity¹⁶.

Amongst PFAS patients in **ATH**, our cohort reported a higher rate of IgE to profilin (18.2%) than previously reported (10.9%)³⁷. As LTP syndrome has been described as a common allergenic syndrome in Greece³⁸, it is not surprising that the prevalence of nsLTP IgE positive patients amongst our cohort was 22.7%. The absence of sensitization to PR-10 in **ATH** is noticeable and corroborates current literature³⁹.

The high prevalence of IgE to profilin in our PFAS cohort in **POR** is similar to that found in central Portugal by Tavares et al.⁴⁰ and can be explained by the predominance of Urticaceae (including pellitory of the wall) and grass pollen in Portugal⁴¹.

The frequency of peach and almond as causative foods for PFAS-reactions in **VAL** reported by our study shows some similarity to findings by Flores et al.¹⁸, where peach and nuts were the most common elicitors. Their results showed walnut as the main symptom-causing nut¹⁸, which was not included in our questionnaire. The high prevalence of nsLTP sensitization found in our cohort corroborates previous reports for the region⁴².

Compared to an earlier study focusing on PFAS in Italian children¹⁶, our cohort in **ROM** reported fewer reactions to banana and watermelon. Peach, kiwi, and melon were the three most common elicitors in both central Italian groups. While a higher frequency of urticaria as comorbidity was reported in the present study, the frequency of asthma as a comorbidity was lower than reported by Mastorilli et al. 2016¹⁶. In addition to a high frequency of IgE to profilins and PR-10, our study found a high rate of positive IgE to nsLTP.

The results from **IST** and **IZM** shared some similarities with a previous study. While the overall prevalence of PFAS in Turkey reported by our study was lower than the previously reported 19.3%¹³, kiwi was by far the most common elicitor of PFAS in both studies¹⁷. Asthma was the most frequent comorbidity of PFAS positive patients in Turkey both in our cohort and in the previous study¹⁷.

Interesting results regarding the role of cypress in PFAS in Southern Europe –Patients with both cypress pollen allergy and PFAS reactions to peach have been described in literature^{22,23}. These two allergic reactions have been linked through molecular similarities between the cypress molecule Cup s 7 and the peach molecule Pru p 7²¹. While such cases have been published, in our analysis no patients with cypress-pollen-mono-sensitization (based on SPT or IgE results) reported peach PFAS. This result concurs with recent findings by Asero et al. 2020, that mono-sensitization to Pru p 7 is rare among cypress pollen hypersensitive patients in Italy²⁴. It also supports the authors' conclusion, that peach and cypress pollen might share other, currently unknown cross-reactive molecules.

Limitations – We acknowledge certain limitations of this study. First, the diagnosis of PFAS was based on the clinical history and no objective measurement of reaction, such as prick-by-prick testing or oral food challenges, was performed. Second, the IgE test performed was developed for the diagnosis of seasonal pollen allergies in Southern Europe and no specific panallergen molecules found in PFAS-associated foods were included in the test. Third, the focus of our study was placed on patients attending allergy clinics in different centers. Therefore, the present project is not an epidemiological study representative of the included countries.

Conclusion – While some overall similarities within Southern Europe can be seen, the region shows significant heterogeneity in many aspects of its clinical characteristics. These can frequently be explained by the differing pollentypes in the area and the differing development of allergic disease. Unlike patients with PFAS in Northern Europe, patients in Southern Europe report more reactions to peach, melon, and kiwi and suffer more frequently from systemic reactions. Cypress-pollen mono-sensitized patients were significantly less likely to report PFAS than multi-sensitized patients and no link to peach was supported by our findings.

Outlook – Further insight may be provided by studies focusing on prick-by-prick tests and/or oral challenges and more specific IgE testing with a broader panel of panallergens.

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Statement of Contribution

Patient recruitment and data collection:

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References

1. Werfel T, Asero R, Ballmer-Weber BK, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy*. 2015;70(9):1079-1090. doi:10.1111/all.12666
2. Poncet P, Sénéchal H, Charpin D. Update on pollen-food allergy syndrome. *Expert Rev Clin Immunol*. 2020 Jun;16(6):561-578. doi: 10.1080/1744666X.2020.1774366.
3. Bedolla-Barajas M, Kestler-Gramajo A, Alcalá-Padilla G, Morales-Romero J. Prevalence of oral allergy syndrome in children with allergic diseases. *Allergol Immunopathol (Madr)*. 2017;45(2):127-133. doi:10.1016/j.aller.2016.04.017
4. Bircher AJ, Van Melle G, Haller E, Curty B, Frei PC. IgE to food allergens are highly prevalent in patients allergic to pollens, with and without symptoms of food allergy. *Clin Exp Allergy J Br Soc Allergy Clin Immunol*. 1994;24(4):367-374. doi:10.1111/j.1365-2222.1994.tb00248.x
5. Guvenir H, Dibek Misirlioglu E, Buyuktiryaki B, et al. Frequency and clinical features of pollen-food syndrome in children. *Allergol Immunopathol (Madr)* 2020; 48:78–83.
6. Li JD, Du ZR, Liu J, Xu YY, Wang RQ, Yin J. Characteristics of pollen-related food allergy based on individual pollen allergy profiles in the Chinese population. *World Allergy Organ J*. 2020 May 15;13(5):100120. doi: 10.1016/j.waojou.2020.100120.
7. Osawa Y, Ito Y, Takahashi N, Sugimoto C, Kohno Y, Mori S, Morikawa T, Kato Y, Okamoto M, Kanno M, Takabayashi T, Fujieda S. Epidemiological study of oral allergy syndrome in birch pollen dispersal-free regions. *Allergol Int*. 2020 Apr;69(2):246-252. doi: 10.1016/j.alit.2019.09.008. Epub 2019 Nov 7.
8. Price A, Ramachandran S, Smith GP, Stevenson ML, Pomeranz MK, Cohen DE. Oral Allergy Syndrome (Pollen-Food Allergy Syndrome). *Dermatitis*. 2015;26(2):78. doi:10.1097/DER.0000000000000087
9. Asero R, Ariano R, Aruanno A, Barzaghi C, Borrelli P, Busa M et al. Systemic allergic reactions induced by labile plant-food allergens: Seeking potential cofactors. A multicenter study. *Allergy*. 2020 Oct 20. doi: 10.1111/all.14634. Epub ahead of print.

10. Kim M, Ahn Y, Yoo Y, et al. Clinical manifestations and risk factors of anaphylaxis in pollen-food allergy syndrome. *Yonsei Med J* 2019; 60:960–968.
11. Skypala IJ. Can patients with oral allergy syndrome be at risk of anaphylaxis? *Curr Opin Allergy Clin Immunol*. 2020 Oct;20(5):459-464. doi: 10.1097/ACI.0000000000000679. PMID: 32842037.
12. Florido Lopez JF, Quiralte Enriquez J, Arias de Saavedra Alías JM, Saenz de San Pedro B, Martín Casañez E. An allergen from *Olea europaea* pollen (Ole e 7) is associated with plant-derived food anaphylaxis. *Allergy*. 2002;57 Suppl 71:53-9. doi: 10.1034/j.1398-9995.2002.057s71053.x.
13. Asero R, Celi G, Scala E. Labile plant food allergens: Really so harmless? Case series and literature review. *Allergy*. 2020 Jun;75(6):1517-1518. doi: 10.1111/all.14184. Epub 2020 Jan 31.
13. Mastroianni C, Cardinale F, Giannetti A, Caffarelli C. Pollen-Food Allergy Syndrome: A not so Rare Disease in Childhood. *Medicina (Mex)*. 2019;55(10):641. doi:10.3390/medicina55100641
14. Biedermann T, Winther L, Till SJ, Panzner P, Knulst A, Valovirta E. Birch pollen allergy in Europe. *Allergy*. 2019;74(7):1237-1248. doi:10.1111/all.13758
15. Movérare R, Westritschnig K, Svensson M, et al. Different IgE Reactivity Profiles in Birch Pollen-Sensitive Patients from Six European Populations Revealed by Recombinant Allergens: An Imprint of Local Sensitization. *Int Arch Allergy Immunol*. 2002;128(4):325-335.
16. Mastroianni C, Tripodi S, Caffarelli C, et al. Endotypes of pollen-food syndrome in children with seasonal allergic rhinoconjunctivitis: a molecular classification. *Allergy*. 2016;71(8):1181-1191. doi:10.1111/all.12888
17. Özdemir SK, Özgüçlü S. Pollen food allergy syndrome in Turkey: Clinical characteristics and evaluation of its association with skin test reactivity to pollens. *Asian Pac J Allergy Immunol*. 2018;36(2):77-81. doi:10.12932/AP0881

18. Flores E, Cervera L, Sanz ML, Diaz-Perales A, Fernández J. Plant Food Allergy in Patients with Pollinosis from the Mediterranean Area. *Int Arch Allergy Immunol*. 2012;159(4):346-354. doi:10.1159/000338282
19. Hoffmann TM, Acar Şahin A, Aggelidis X, et al. "Whole" vs. "Fragmented" approach to EAACI Pollen Season Definitions: A Multicenter Study in Six Southern European Cities. *Allergy*. doi:10.1111/all.14153
20. Castillo Marchuet MJ, Luengo O, Cardona V. Cypress Pollen Allergy in a Mediterranean Area. *J Investig Allergol Clin Immunol*. 2020;30(1):67. doi: 10.18176/jiaci.0444. Epub 2019 Sep 18.
21. Sénéchal H, Šantrůček J, Melčová M, Svoboda P, Zídková J, Charpin D, Guilloux L, Shahali Y, Selva MA, Couderc R, Aizawa T, Poncet P. A new allergen family involved in pollen food-associated syndrome: Snakin/gibberellin-regulated proteins. *J Allergy Clin Immunol*. 2018 Jan;141(1):411-414.e4. doi: 10.1016/j.jaci.2017.06.041. Epub 2017 Aug 4.
22. Caimmi D, Barber D, Hoffmann-Sommergruber K, et al. Understanding the molecular sensitization for Cypress pollen and peach in the Languedoc-Roussillon area. Accessed January 16, 2020. <https://europepmc.org/article/med/23205629>
23. Hugues B, Didierlaurent A, Charpin D. Cross-reactivity between cypress pollen and peach: a report of seven cases. *Allergy*. 2006;61(10):1241-1243. doi:10.1111/j.1398-9995.2006.01156.x
24. Asero R, Abbadessa S, Aruanno A, Barilaro G, Barzaghi C, Bignardi D, et al. Detection of Gibberellin-Regulated Protein (Peamaclein) Sensitization among Italian Cypress Pollen-Sensitized Patients. *J Investig Allergol Clin Immunol*. 2020 Jul 30:0. doi: 10.18176/jiaci.0542. Epub ahead of print. PMID: 32732184.
25. Hauser M, Roulias A, Ferreira F, Egger M. Panallergens and their impact on the allergic patient. *Allergy Asthma Clin Immunol Off J Can Soc Allergy Clin Immunol*. 2010;6(1):1. doi:10.1186/1710-1492-6-1
26. Ferreira F, Hawranek T, Gruber P, Wopfner N, Mari A. Allergic cross-reactivity: from gene to the clinic. *Allergy*. 2004;59(3):243-267. doi:10.1046/j.1398-9995.2003.00407.x
27. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI Molecular Allergology User's Guide. *Pediatr Allergy Immunol*. 2016;27:1-250. doi:10.1111/pai.12563

28. Bogas G, Muñoz-Cano R, Mayorga C, Casas R, Bartra J, Pérez N, Pascal M, Palomares F, Torres MJ, Gómez F. Phenotyping peach-allergic patients sensitized to LTP and analysing severity biomarkers. *Allergy*. 2020 Jun 14. doi: 10.1111/all.14447. Epub ahead of print.
29. Oeo-Santos C, Navas A, Benedé S, Ruíz-León B, Díaz-Perales A, Vogel L, Moreno-Aguilar C, Jurado A, Villalba M, Barderas R. New insights into the sensitization to nonspecific lipid transfer proteins from pollen and food: New role of allergen Ole e 7. *Allergy*. 2020 Apr;75(4):798-807. doi: 10.1111/all.14086. Epub 2019 Nov 6.
30. Skypala IJ, Calderon MA, Leeds AR, Emery P, Till SJ, Durham SR. Development and validation of a structured questionnaire for the diagnosis of oral allergy syndrome in subjects with seasonal allergic rhinitis during the UK birch pollen season. *Clin Exp Allergy*. 2011;41(7):1001-1011. doi:10.1111/j.1365-2222.2011.03759.x
31. Di Fraia M, Arasi S, Castelli S, et al. A new molecular multiplex IgE assay for the diagnosis of pollen allergy in Mediterranean countries: A validation study. *Clin Exp Allergy*. 2019;49:341-349. doi:10.1111/cea.13264
32. Charpin D, Ramadour M, Lavaud F, et al. Climate and Allergic Sensitization to Airborne Allergens in the General Population: Data from the French Six Cities Study. *Int Arch Allergy Immunol*. 2017;172(4):236-241. doi:10.1159/000471511
33. Rial MJ, Sastre J. Food Allergies Caused by Allergenic Lipid Transfer Proteins: What Is behind the Geographic Restriction? *Curr Allergy Asthma Rep*. 2018;18:56. doi:10.1007/s11882-018-0810-x
34. D'Amato G, Cecchi L, Bonini S, et al. Allergenic pollen and pollen allergy in Europe. *Allergy*. 2007;62(9):976-990. doi:10.1111/j.1398-9995.2007.01393.x
35. Mesonjesi E, Piluri Ziu E, Gupta R, Strachan D, Priftanji A. The prevalence and time trend of asthma in Albanian children in 2011 – Alb ISAAC. *Clin Transl Allergy*. 2015;5(S2):P8, 2045-7022-5-S2-P8. doi:10.1186/2045-7022-5-S2-P8
36. Priftanji AV, Qirko E, Layzell JCM, Burr ML, Fifield R. Asthma and allergy in Albania. *Allergy*. 1999;54(10):1042-1047. doi:10.1034/j.1398-9995.1999.00108.x

37. Iliopoulou A, Petrodimitopoulou M, Konstantakopoulou M, et al. Profilin sensitization and its clinical relevance to a population of atopic adults in Greece. *Rev Fr Allergol*. 2018;58(2):72-76. doi:10.1016/j.reval.2017.11.001
38. Karantoumanis D, Savvatanos S, Konstantinopoulos AP, et al. PD19 - Co-recognition of lipid transfer protein in pollen and foods in a Greek pediatric population. *Clin Transl Allergy*. 2014;4(Suppl 1):P19. doi:10.1186/2045-7022-4-S1-P19
39. Lyons SA, Clausen M, Knulst AC, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L et al. Prevalence of Food Sensitization and Food Allergy in Children Across Europe. *J Allergy Clin Immunol Pract*. 2020 Sep;8(8):2736-2746.e9. doi: 10.1016/j.jaip.2020.04.020. Epub 2020 Apr 21. PMID: 32330668.
40. Tavares B, Machado D, Loureiro G, Cemlyn-Jones J, Pereira C. Sensitization to profilin in the Central region of Portugal. *Sci Total Environ*. 2008;407(1):273-278. doi:10.1016/j.scitotenv.2008.08.013
41. Pereira C, Valero A, Loureiro C, et al. Iberian study of aeroallergens sensitisation in allergic rhinitis. *Eur Ann Allergy Clin Immunol*. 2006;38(6):186-194.
42. Barber D, de la Torre F, Feo F, et al. Understanding patient sensitization profiles in complex pollen areas: a molecular epidemiological study. *Allergy*. 2008;63(11):1550-1558. doi:10.1111/j.1398-9995.2008.01807.x

Legend to figures

Figure 1 -Number of reported PFAS reactions to 15 different PFAS-associated foods. The number of reported reactions is shown for the nine different centers: Porto (light blue), Valencia (orange), Marseille (grey), Rome (yellow), Messina (royal blue), Tirana (green), Athens (dark blue), Istanbul (brown), and Izmir (dark grey).

Figure 2 –Symptoms reported by patients with PFAS after contact with PFAS-eliciting foods and times at onset. Symptoms are split into two categories: local symptoms (left) and systemic symptoms (right). The times at onset are grouped into five categories: ≤ 5 min. (blue), 6-20 min. (orange) 21-60 min. (grey), 61-120 min. (yellow), and >120 min. (dark blue).

Figure 3 –Number of reported PFAS reactions to the questioned PFAS-associated foods, categorized by oral symptoms only (blue) and (oral and) systemic symptoms (orange).

Figure 4 - Frequency of panallergen positive IgE results in patients who only reported oral symptoms (blue) versus those who reported (oral and) systemic symptoms (orange) to any of the questioned PFAS-associated foods. Results are shown based on different panallergen groups: profilins (Bet v 2 and Phl p 12), PR-10 (Bet v 1, Cor a 1, and Que a 1), and nsLTPs (Art v 3 and Ole e 7).

Table 1. Clinical characteristics of patients with and without PFAS in Southern Europe

	With PFAS (n=167)		Without PFAS (n=648)		Odds Ratio	P- Value
Male [n (%)]	82	49.1	359	55.4	1.288	.146
Age (y) [mean (SD)]	25.2	13.1	26.3	13.7	0.994	.318
Family history						
Atopic relative in immediate family [n (%)]	126	75.5	449	69.3	1.362	.120
Sibling(s) with PFAS [n (%)]	5	3.0	16	2.5	1.219	.703
Father with PFAS [n (%)]	1	0.6	6	0.9	0.645	.685
Mother with PFAS [n (%)]	13	7.8	12	1.9	4.474	<.001***
Allergic rhinitis						
Age at onset (y) [median (IQR)]†	9	12	12	14	0.973	.003**
Disease duration (y) [median (IQR)]†	9	13.5	8	12	1.013	.097
Months/year with symptoms [mean (SD)]	4.8	2.4	4.7	2.4	1.016	.659
ARIA severity						
Mild intermittent [n (%)]	6	3.6	35	5.4	-	.297
Mild persistent (ref.: mild intermittent) [n (%)]	9	5.4	51	7.9	1.029	.960
Mod./severe intermittent (ref.: mild intermittent) [n (%)]	27	16.2	125	19.3	1.260	.637
Mod./severe persistent (ref.: mild intermittent) [n (%)]	125	74.9	437	67.4	1.669	.259
ARIA quality						
Unclassified [n (%)]	19	11.7	108	16.7	-	.073
Rhinitis sneezer/runner (ref.: unclassified) [n (%)]	123	73.7	417	64.4	1.677	.055
Rhinitis blocker (ref.: unclassified) [n (%)]	25	15.0	123	19.0	1.155	.663
Other allergic comorbidities						
Number of patients with comorbidities [n (%)]	111	66.5	298	46.0	2.328	<.001***
Number of comorbidities [mean (SD)]	1.2	1.0	0.7	0.8	1.748	<.001***
Asthma [n (%)]	51	30.5	123	19.0	1.877	.001**
Anaphylaxis [n (%)]	26	15.6	23	3.6	5.001	<.001***
Urticaria [n (%)]	63	37.7	131	20.2	2.391	<.001***
Atopic dermatitis [n (%)]	50	29.9	129	19.9	1.719	.006**
Other [n (%)]	4	2.4	22	3.4	0.698	.514

PFAS: pollen food allergy syndrome; n: number; SD: standard deviation; IQR: interquartile range; ref.: reference

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

†Due to incomplete data sets, 2 patients were excluded

Table 2. Atopic reactivity of patients with and without PFAS in Southern Europe

	With PFAS (n=167)		Without PFAS (n=648)		Odds Ratio	P- Value
Skin prick test (SPT)						
Positive SPT to seasonal aeroallergen(s) [§] [mean (SD)]	5,0	3,1	3,7	2,7	1,166	<.001***
Average SPT size of seasonal aeroallergens (mm) [§] [mean (SD)]	6,1	1,6	6,0	1,7	1,028	,589
IgE results						
No panallergen [n (%)] [†]	102	61,1	559	86,3	-	<.001***
Mono-panallergen (ref.: no panallergen) [n (%)] [†]	53	31,7	79	12,2	3,677	<.001***
Multi-panallergen (ref.: no panallergen) [n (%)] [†]	12	7,2	10	1,5	6,576	<.001***
Profilins [n (%)] [†]	26	15,6	42	6,5	2,661	<.001***
PR-10-like allergenic proteins [n (%)] [†]	26	15,6	26	4,0	4,411	<.001***
nsLTPs [n (%)] [†]	26	15,6	33	5,1	3,436	<.001***

PFAS: pollen food allergy syndrome; n: number; SD: standard deviation; IQR: interquartile range; ref.: reference

* p<0.05; ** p<0.01; *** p<0.001

[§] Testpanel included: juniper ash, birch, hazel, olive, timothy grass, bermuda grass, wall pellitory, ragweed, salsola kali, plane tree, alternaria

[†] Testpanel included: profilins (Bet v 2, Phi p 12), PR-10-like allergenic proteins (Bet v 1, Cor a 1, Que a 1), and nsLTPs (Art v 3, Ole e 7)

Figure 1 –

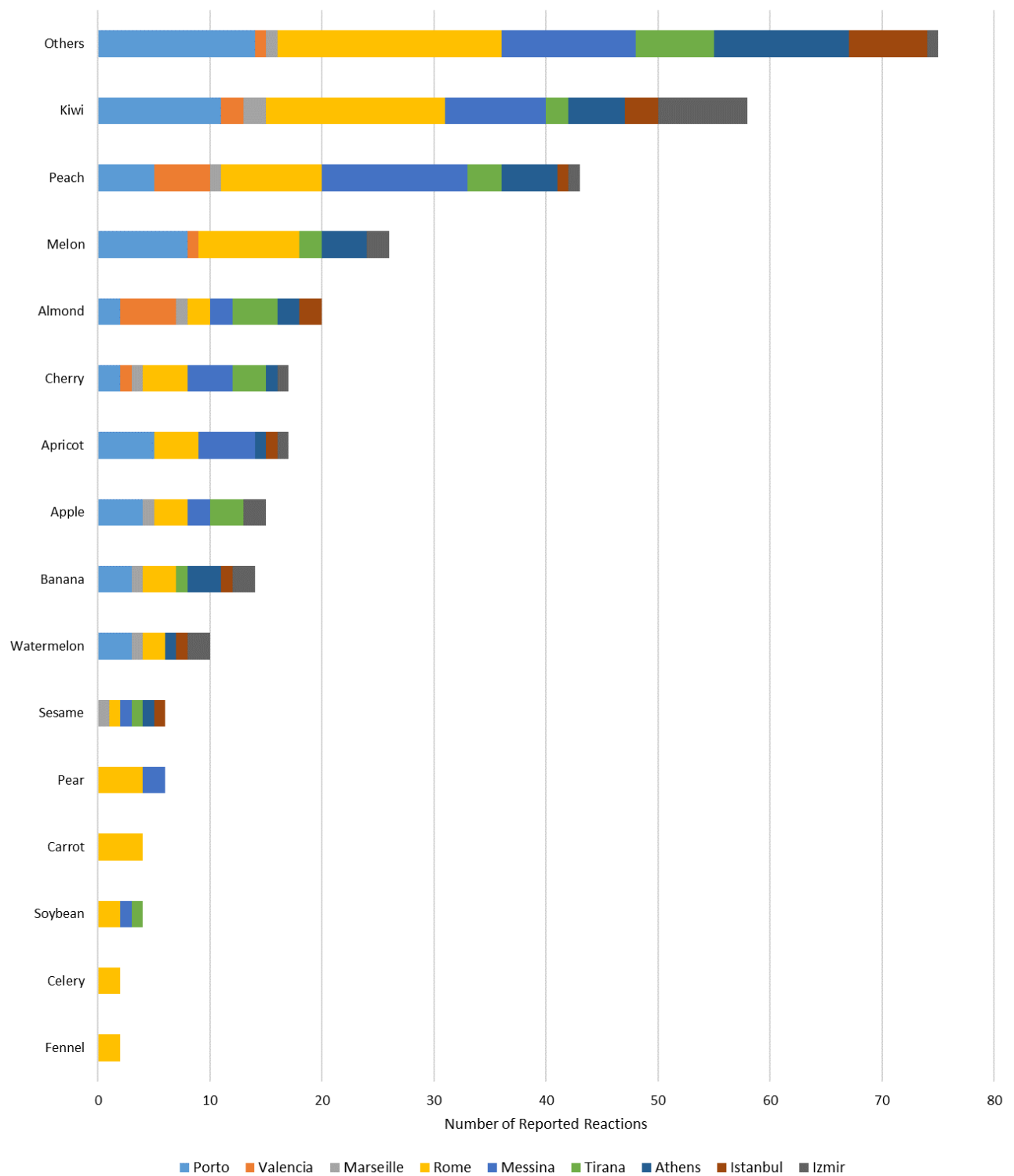


Figure 2 –

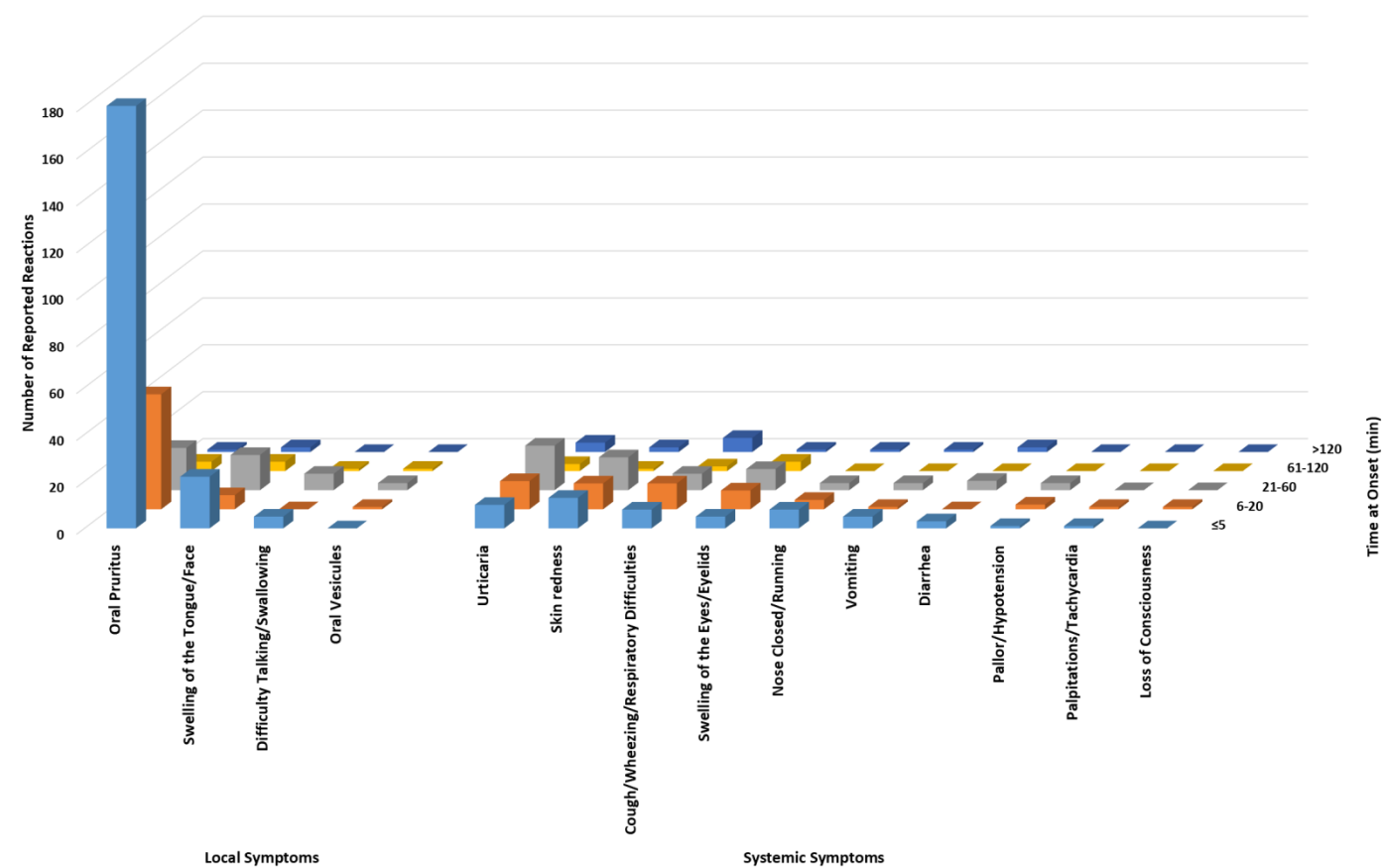


Figure 3 –

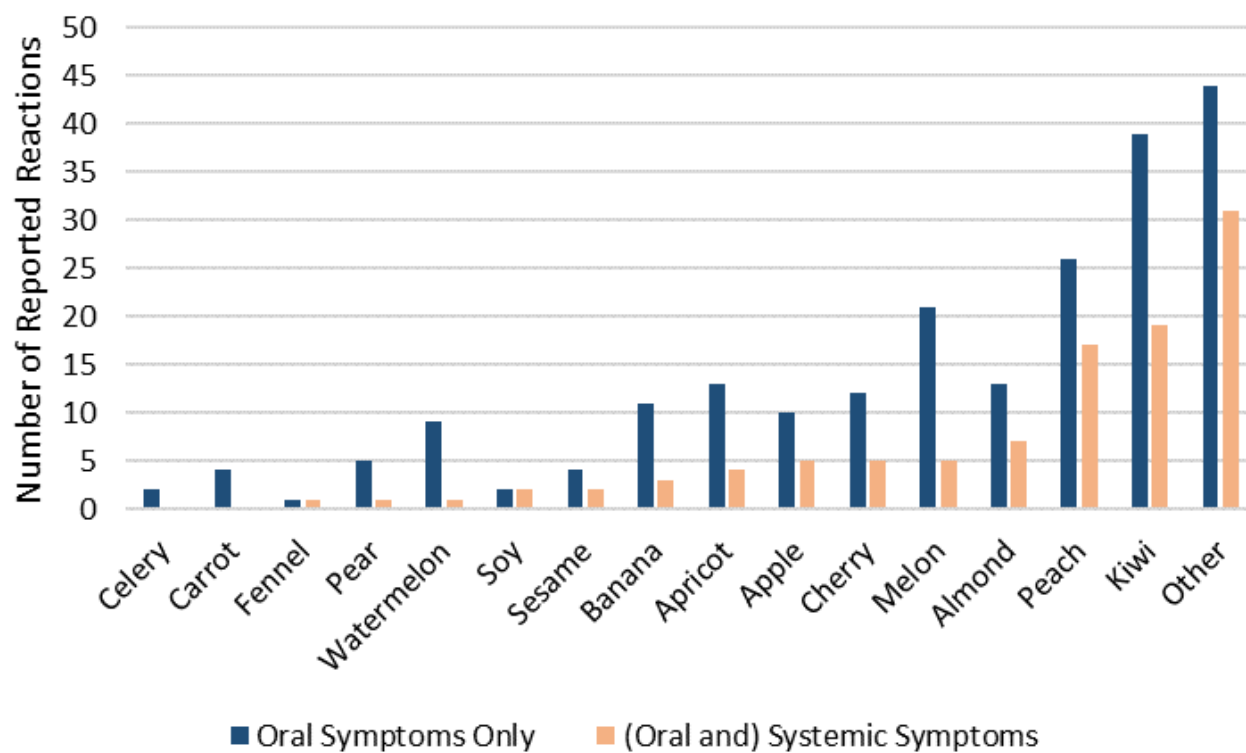
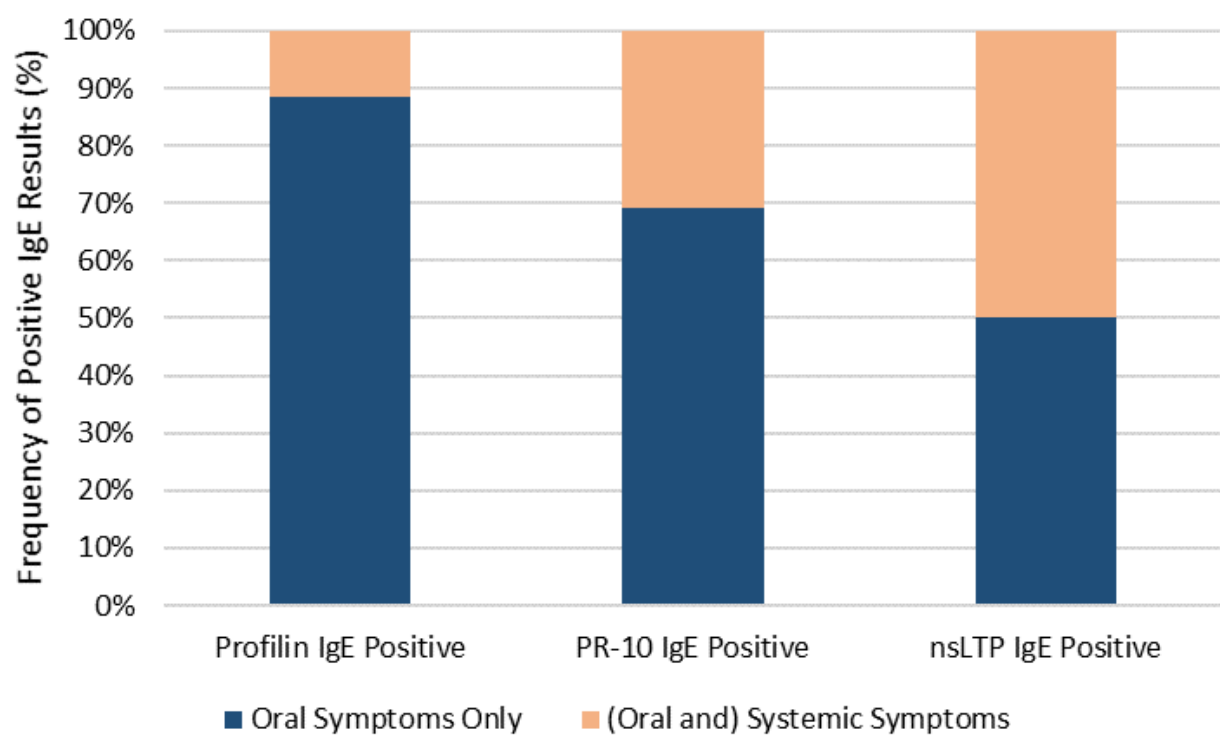
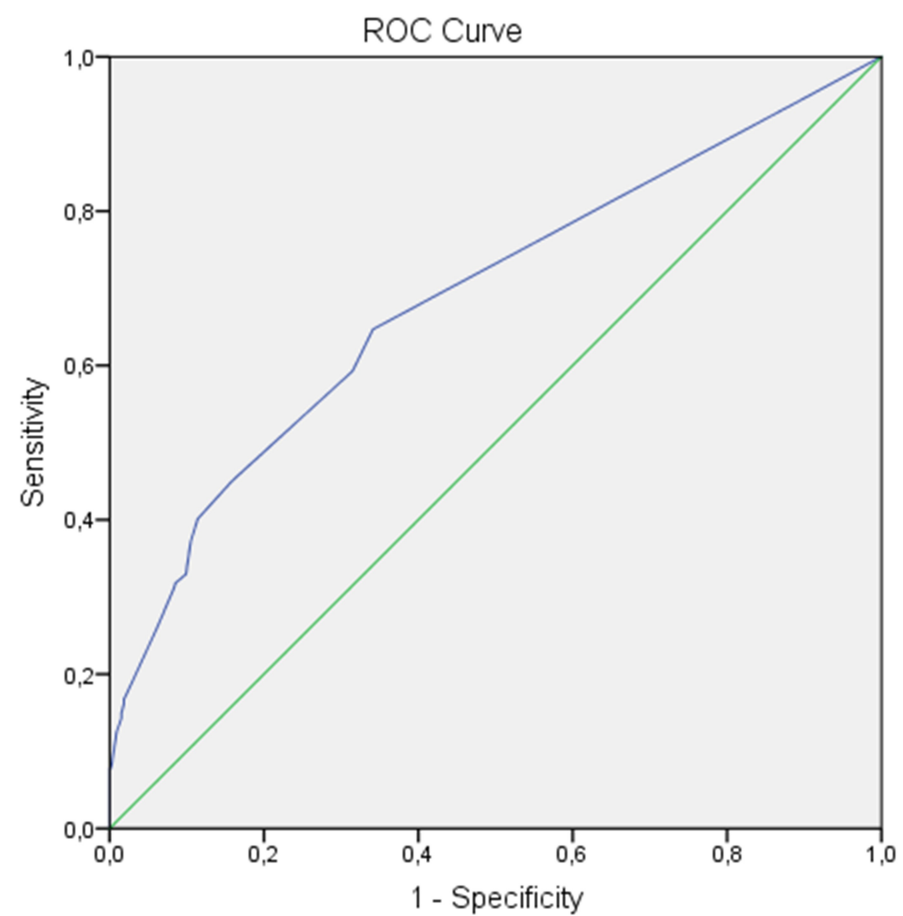


Figure 4 –





Diagonal segments are produced by ties.

Supplementary Material

Clinical Characteristics of Pollen Food Allergy Syndrome amongst Patients with Seasonal Allergic Rhinitis in Seven Southern European Countries: Results from the @IT.2020 Multicenter Study

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95 **Legend to figures**

96

97 **Figure E1** - Receiver Operating Characteristics (ROC) Curve for the model generated by the logistic

98 stepwise backward selection (Wald), based on data from mothers with PFAS, anaphylaxis, asthma

99 as comorbidity, and panallergen IgE results (blue line). Compared to reference line (green).

100 Area under the curve: 0.688

101

Table e1. Clinical characteristics of patients with PFAS who reported only oral symptoms compared to those who reported (oral and) systemic symptoms

	Oral Symptoms Only (n=99)		(Oral and) Systemic Symptoms (n=68)		P- Value
Male [n (%)]	47	47,5	35	51,5	,612
Age (y) [mean (SD)]	24,7	12,8	25,9	13,5	,558
Centers					
Porto [n (%)]	11	11,1	13	19,1	,147
Valencia [n (%)]	6	6,1	4	5,9	,961
Marseille [n (%)]	3	3,0	3	4,4	,637
Rome [n (%)]	32	32,3	9	13,2	.005**
Messina [n (%)]	10	10,1	14	20,6	,058
Tirana [n (%)]	9	9,1	4	5,9	,447
Athens [n (%)]	11	11,1	11	16,2	,342
Istanbul [n (%)]	6	6,1	7	10,3	,316
Izmir [n (%)]	11	11,1	3	4,4	,125
Allergic rhinitis					
Age at onset (y) [median (IQR)]†	8	11,3	10	14	,337
Months/year with symptoms [mean (SD)]	4,9	2,4	4,5	2,4	,362
Other allergic comorbidities					
Asthma [n (%)]	28	28,3	23	33,8	,445
Anaphylaxis [n (%)]	7	7,1	19	27,9	<.001***
Urticaria [n (%)]	34	34,3	29	42,7	,277
Atopic dermatitis [n (%)]	26	26,3	24	35,3	,211
Other [n (%)]	1	1,0	3	4,4	,158
Skin prick test (SPT)					
Positive SPT to seasonal aeroallergen(s) [mean (SD)]	5,4	2,9	4,6	3,4	,209
Average SPT size of seasonal aeroallergens (mm) [mean (SD)]	6,2	1,6	6,0	1,7	,486
IgE results					
Profilins [n (%)]‡	23	23,2	3	4,4	.001**
PR-10-like allergenic proteins [n (%)]‡	18	18,2	8	11,8	,261
nsLTPs [n (%)]‡	13	13,1	13	19,1	,294

PFAS: pollen food allergy syndrome; n: number; SD: standard deviation; IQR: interquartile range

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

†Due to incomplete data sets, 1 patient was excluded

‡ Testpanel included: profilins (Bet v 2, Phl p 12), PR-10-like allergenic proteins (Bet v 1, Cor a 1, Que a 1), and nsLTPs (Art v 3, Ole e 7)

Table e2. Results of hierarchical regression analysis of predictors for PFAS in Southern Europe

	Full model (Step 1)			Late-stage specific model (Step 17)		
	OR	95% CI	P-Value	OR	95% CI	P-Value
Male	0,926	0.496-1.730	,810	-	-	-
Age	1,028	0.994-1.062	,108	-	-	-
Centers						
Porto	-	-	,338	-	-	-
Valencia (ref.: Porto)	0,592	0.155-2.251	,441	-	-	-
Marseille (ref.: Porto)	0,167	0.037-0.746	,019*	-	-	-
Rome (ref.: Porto)	0,876	0.282-2.720	,819	-	-	-
Messina (ref.: Porto)	0,806	0.253-2.569	,716	-	-	-
Tirana (ref.: Porto)	0,336	0.079-1.421	,138	-	-	-
Athens (ref.: Porto)	1,182	0.371-3.762	,778	-	-	-
Istanbul (ref.: Porto)	0,500	0.117-2.137	,350	-	-	-
Izmir (ref.: Porto)	0,557	0.152-2.036	,376	-	-	-
Family history						
Atopic relative in immediate family	3,410	0.247-47.031	,360	-	-	-
Sibling(s) with PFAS	0,831	0.228-3.028	,779	-	-	-
Father with PFAS	1,192	0.071-20.148	,903	-	-	-
Mother with PFAS	4,030	0.973-16.693	,055	3,716	1.165-11.845	,026*
Allergic rhinitis						
Age at onset	0,984	0.942-1.028	,476	-	-	-
Months/year with symptoms	0,950	0.826-1.092	,469	-	-	-
ARIA severity						
Mild intermittent	-	-	,430	-	-	-
Mild persistent (ref: mild intermittent)	0,139	0.012-1.576	,111	-	-	-
Mod./severe intermittent (ref: mild intermittent)	0,773	0.206-2.905	,704	-	-	-
Mod./severe persistent (ref: mild intermittent)	0,637	0.182-2.230	,480	-	-	-
ARIA quality						
Unclassified	-	-	,351	-	-	-
Rhinitis sneezer/runner (ref. unclassified)	1,253	0.494-3.180	,635	-	-	-
Rhinitis blocker (ref. unclassified)	0,665	0.210-2.107	,488	-	-	-
Other allergic comorbidities						
Patients with comorbidities	0,881	0.292-2.658	,822	-	-	-
Asthma	1,724	0.704-4.224	,233	1,752	0.949-3.234	,073
Anaphylaxis	6,358	2.209-18.296	,001**	6,210	2.561-15.057	<.001***
Urticaria	1,813	0.734-4.482	,197	-	-	-
Atopic dermatitis	1,160	0.486-2.768	,739	-	-	-
Other	0,217	0.019-2.444	,216	-	-	-
Skin prick test (SPT)						
Positive SPT to seasonal aeroallergen(s)	1,055	0.921-1.208	,440	-	-	-
Average SPT size of seasonal aeroallergens	1,037	0.863-1.246	,700	-	-	-
IgE results						
No panallergen IgE [†]	-	-	,091	-	-	,007**
IgE only to profilins (ref.: no panallergen IgE) [†]	1,550	0.471-5.107	,471	2,113	0.794-5.623	,134
IgE only to PR-10-like allergenic proteins (ref.: no panallergen IgE) [†]	5,023	1.214-20.776	,026*	5,582	1.709-18.232	,004**
IgE only to nsLTPs (ref.: no panallergen IgE) [†]	1,390	0.447-4.325	,569	1,401	0.483-4.058	,535
Multi-panallergen IgE (ref.: no panallergen IgE) [†]	7,421	1.166-47.241	,034*	6,353	1.323-30.503	,021*

PFAS: pollen food allergy syndrome; n: number; OR: odds ratio; CI: confidence interval; ref.: reference

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

[†] Testpanel included: profilins (Bet v 2, Phl p 12), PR-10-like allergenic proteins (Bet v 1, Cor a 1, Que a 1), and nsLTPs (Art v 3, Ole e 7)

Table e3. Clinical characteristics of patients with PFAS in the nine Southern European centers

	TOTAL (n=167)	POR (n=24)	VAL (n=10)	MAR (n=6)	ROM (n=41)	MES (n=24)	TIR (n=13)	ATH (n=22)	IST (n=13)	IZM (n=14)
Number PFAS positive relative to total number recruited [n (%)]	167/815 20,5	24/102 23,5	10/71 14,1	6/80 7,5	41/99 41,4	24/82 29,3	13/93 14,0	22/97 22,7	13/96 13,5	14/95 14,7
Male [n (%)]	82 49,1	14 58,3	3 30,0	4 66,7	19 46,3	11 45,8	8 61,5	12 54,5	5 38,5	6 42,9
Age (y) [mean (SD)]	25,2 13,1	26,5 13,0	25,7 13,7	33,3 7,8	27,3 16,0	23,2 12,7	29,5 8,9	21,7 11,8	25,8 12,0	16,9 8,1
Family history										
Atopic relative in immediate family [n (%)*]	126 75,5	16 66,7	7 70,0	6 100,0	30 73,2	21 87,5	9 69,2	18 81,8	9 69,2	10 71,4
Sibling(s) with PFAS [n (%)*]	5 3,0	0 0,0	0 0,0	0 0,0	2 4,9	3 12,5	0 0,0	0 0,0	0 0,0	0 0,0
Father with PFAS [n (%)*]	1 0,6	0 0,0	0 0,0	0 0,0	0 0,0	0 0,0	0 0,0	1 4,5	0 0,0	0 0,0
Mother with PFAS [n (%)*]	13 7,8	0 0,0	0 0,0	0 0,0	5 12,2	4 16,7	0 0,0	4 18,2	0 0,0	0 0,0
Allergic rhinitis										
Age at onset (y) [median (IQR)]†	9 12	7,0 16,0	13,5 17,8	14,5 18,8	7,0 8,0	10,0 10,8	22,0 16,5	7,5 5,5	18,0 13,0	6,0 4,8
Disease duration (y) [median (IQR)]†	9 13,5	11,0 15,0	6,5 16,0	20,0 10,5	12,0 25,0	9,0 11,8	8,0 8,5	9,0 11,0	8,0 12,0	8,0 10,3
Months/year with symptoms [mean (SD)]	4,8 2,4	5,0 2,9	3,2 1,4	4,8 1,7	4,4 1,8	5,9 3,2	5,9 2,1	5,2 2,0	4,9 2,5	2,6 0,9
ARIA severity										
Mild intermittent [n (%)*]	6 3,6	1 4,2	0 0,0	0 0,0	0 0,0	2 8,3	0 0,0	0 0,0	0 0,0	3 21,4
Mild persistent [n (%)*]	9 5,4	1 4,2	2 20,0	0 0,0	0 0,0	2 8,3	0 0,0	0 0,0	2 15,4	2 14,3
Mod./severe intermittent [n (%)*]	27 16,2	4 16,7	4 40,0	1 16,7	2 4,9	9 37,5	1 7,7	2 9,1	2 15,4	2 14,3
Mod./severe persistent [n (%)*]	125 74,9	18 75,0	4 40,0	5 83,3	39 95,1	11 45,8	12 92,3	20 90,9	9 69,2	7 50,0
ARIA quality										
Unclassified [n (%)*]	19 11,7	0 0,0	1 10,0	0 0,0	0 0,0	3 12,5	3 23,1	2 9,1	5 38,5	5 35,7
Rhinitis sneezer/runner [n (%)*]	123 73,7	19 79,2	5 50,0	5 83,3	39 95,1	19 79,2	10 76,9	15 68,2	6 46,2	5 35,7
Rhinitis blocker [n (%)*]	25 15,0	5 20,8	4 40,0	1 16,7	2 4,9	2 8,3	0 0,0	5 22,7	2 15,4	4 28,6
Other allergic comorbidities										
Number of patients with comorbidities [n (%)*]	111 66,5	16 66,7	8 80,0	6 100,0	29 70,7	18 75,0	9 69,2	13 59,1	3 23,1	9 64,3
Number of comorbidities [mean (SD)]	1,2 1,0	1,3 1,2	1,7 1,2	1,8 0,8	1,2 1,0	1,4 1,1	1,2 0,9	1,0 1,0	0,3 0,6	0,8 0,7
Asthma [n (%)*]	51 30,5	7 29,2	3 30,0	2 33,3	12 29,3	10 41,7	1 7,7	7 31,8	2 15,4	7 50,0
Anaphylaxis [n (%)*]	26 15,6	7 29,2	3 30,0	2 33,3	5 12,2	3 12,5	4 30,8	2 9,1	0 0,0	0 0,0
Urticaria [n (%)*]	63 37,7	5 20,8	5 50,0	4 66,7	18 43,9	12 50,0	8 61,5	7 31,8	1 7,7	3 21,4
Atopic Dermatitis [n (%)*]	50 29,9	11 45,8	6 60,0	3 50,0	14 34,1	8 33,3	3 23,1	3 13,6	1 7,7	1 7,1
Other [n (%)*]	4 2,4	0 0,0	0 0,0	0 0,0	2 4,9	0 0,0	0 0,0	2 9,1	0 0,0	0 0,0
Skin prick test (SPT)										
Positive SPT to seasonal aeroallergen(s) [mean (SD)]	5,0 3,1	4,0 2,4	4,3 2,8	4,8 2,6	7,0 2,9	2,6 2,1	6,3 3,0	6,9 2,7	2,3 1,6	4,3 3,3
Average SPT size of seasonal aeroallergens (mm) [mean (SD)]	6,1 1,6	6,5 1,8	7,0 1,7	4,4 0,8	6,1 1,3	5,5 1,7	6,6 1,4	6,9 1,7	5,0 1,3	5,7 1,7
IgE results										
No panallergen [n (%)*]§	102 61,1	16 66,7	6 60,0	2 33,3	19 46,3	20 83,3	5 38,5	13 59,1	10 76,9	11 78,6
Mono-panallergen [n (%)*]§	53 31,7	7 29,2	3 30,0	3 50,0	15 36,6	3 12,5	7 53,8	9 40,9	3 23,1	3 21,4
Multi-panallergen [n (%)*]§	12 7,2	1 4,2	1 10,0	1 16,7	7 17,1	1 4,2	1 7,7	0 0,0	0 0,0	0 0,0
Profilins [n (%)*]§	26 15,6	5 20,8	1 10,0	1 16,7	9 22,0	0 0,0	1 7,7	4 18,2	2 15,4	3 21,4
PR-10-like allergenic proteins [n (%)*]§	26 15,6	2 8,3	0 0,0	3 50,0	13 31,7	1 4,2	7 53,8	0 0,0	0 0,0	0 0,0
nsLTPs [n (%)*]§	26 15,6	2 8,3	4 40,0	1 16,7	8 19,5	4 16,7	1 7,7	5 22,7	1 7,7	0 0,0

PFAS: pollen food allergy syndrome; POR: Porto; VAL: Valencia; MAR: Marseille; ROM: Rome; MES: Messina; TIR: Tirana; ATH: Athens; IST: Istanbul; IZM: Izmir; n: number; SD: standard deviation; IQR: interquartile range

*p <0.05; **p <0.01; ***p <0.001

† Percentages calculated from total number of PFAS positive patients overall/in the centers

‡ Due to an incomplete data set, 1 patient was excluded

§ Testpanel included: profilins (Bet v 2, Phi p 12), PR-10-like allergenic proteins (Bet v 1, Cor a 1, Que a 1), and nsLTPs (Art v 3, Ole e 7)

Table e4. Clinical characteristics of PFAS patients with and without IgE to nsLTP

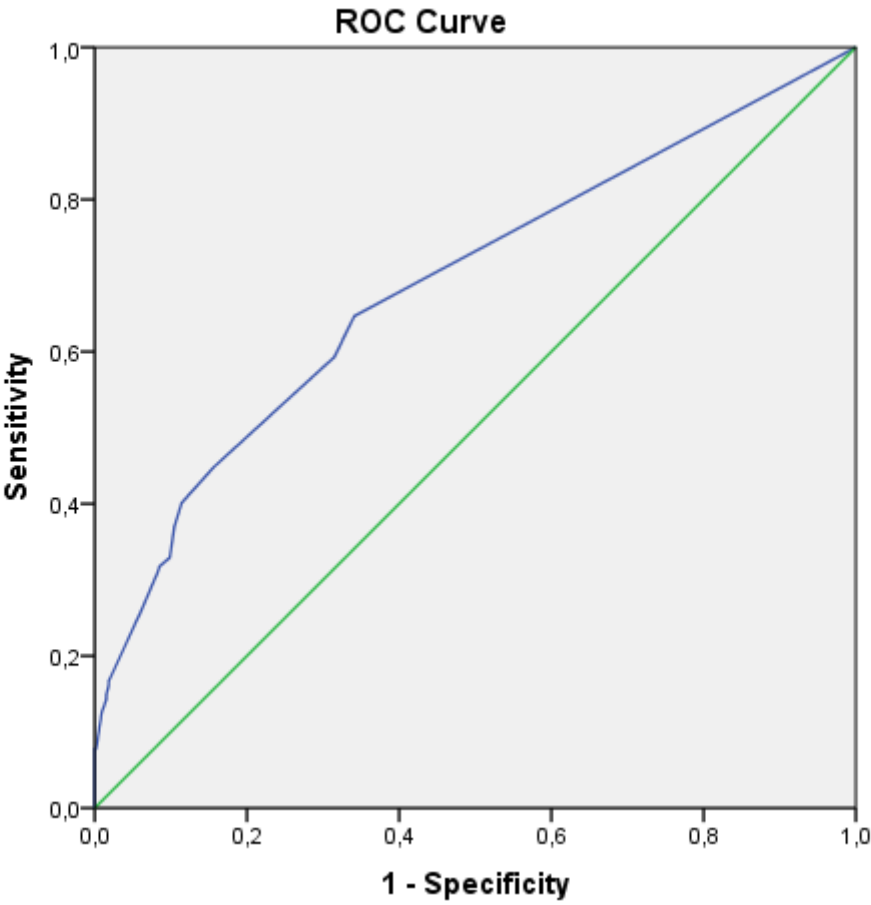
	PFAS - nsLTP Negative Patients (n=141)		PFAS - nsLTP Positive Patients (n=26)		P- Value
Male [n (%)]	67	47,5	15	57,7	,340
Age (y) [mean (SD)]	24,9	12,8	26,4	14,8	,590
Family history					
Atopic relative in immediate family [n (%)]	108	76,6	18	69,2	,459
Sibling(s) with PFAS [n (%)]	4	2,8	1	3,9	,576
Father with PFAS [n (%)]	1	0,7	0	0,0	1,000
Mother with PFAS [n (%)]	10	7,1	3	11,5	,429
Allergic rhinitis					
Age at onset (y) [median (IQR)]†	9	12,8	9	10,5	,878
Disease duration (y) [median (IQR)]†	9	12	10,5	19,5	,239
Months/year with symptoms [mean (SD)]	4,7	2,3	5,3	2,8	,228
ARIA severity					
Mild intermittent [n (%)]	6	4,3	0	0,0	,591
Mild persistent (ref.: mild intermittent) [n (%)]	6	4,3	3	11,5	,148
Mod./severe intermittent (ref.: mild intermittent) [n (%)]	24	17,0	3	11,5	,772
Mod./severe persistent (ref.: mild intermittent) [n (%)]	105	74,5	20	76,9	,791
ARIA quality					
Unclassified [n (%)]	17	12,1	2	7,7	,160
Rhinitis sneezer/runner [n (%)]	100	70,9	23	88,5	
Rhinitis blocker [n (%)]	24	17,0	1	3,9	
Other allergic comorbidities					
Number of patients with comorbidities [n (%)]	94	66,7	17	65,4	,899
Number of comorbidities [mean (SD)]	1,1	1,0	1,3	1,2	,281
Asthma [n (%)]	43	30,5	8	30,8	,978
Anaphylaxis [n (%)]	22	15,6	4	15,4	1,000
Urticaria [n (%)]	53	37,6	10	38,5	,933
Atopic dermatitis [n (%)]	39	27,7	11	42,3	,163
Other [n (%)]	3	2,1	1	3,9	,495
Skin prick test (SPT)					
Positive SPT for seasonal aeroallergen(s) [mean (SD)]	4,8	3,1	6,5	2,9	,012
Average SPT size of seasonal aeroallergens (mm) [mean (SD)]	6,0	1,7	6,4	1,5	,261

PFAS: pollen food allergy syndrome; n: number; SD: standard deviation; IQR: interquartile range; ref.: reference

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

†Due to incomplete data sets, 2 patients were excluded

111 **Figure e1**
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