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ORIGINAL ARTICLE

Rhinitis, Sinusitis, and Upper Airway Disease

Heterogeneity of pollen food allergy syndrome in seven Southern European countries: The @IT.2020 multicenter study

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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.

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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.

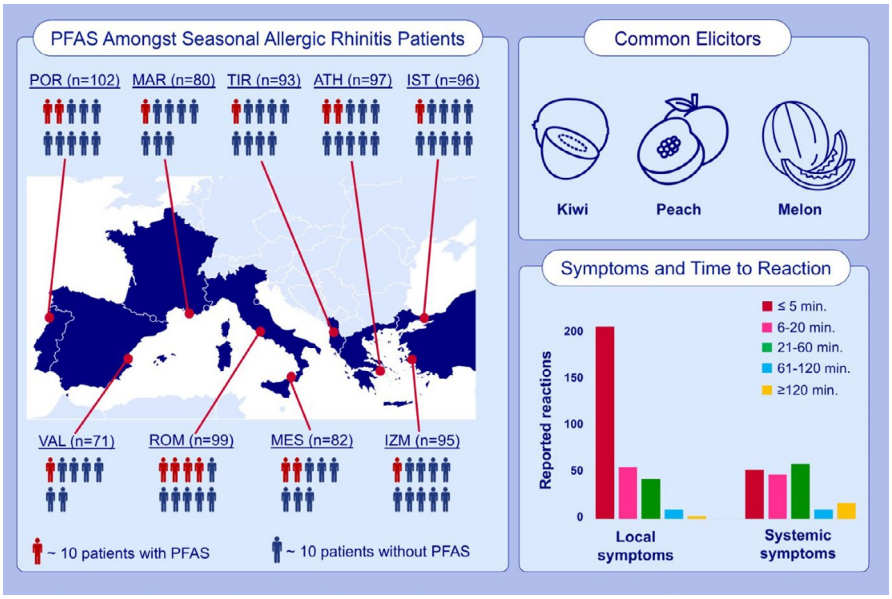
Objectives: To elucidate similarities and differences of PFAS in nine Southern European centers and identify associated characteristics and unique markers of PFAS.

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, and 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 5 min of contact with elicitors (209/319, 65.5%). Associated characteristics included positive IgE to at least one panallergen (profilin, PR-10, or nsLTP) ($p = 0.007$), maternal PFAS (OR: 3.716, $p = 0.026$), and asthma (OR: 1.752, $p = 0.073$). Between centers, heterogeneity in prevalence (Marseille: 7.5% vs. Rome: 41.4%, $p < 0.001$) and of clinical characteristics was apparent. Cypress played a limited role, with only 1/22 SPT mono-sensitized patients reporting a food reaction ($p < 0.073$).

Conclusions: PFAS is a frequent comorbidity in Southern European SAR patients. Significant heterogeneity of clinical characteristics in PFAS patients among the centers was observed and may be related to the different pollen sensitization patterns in each geographic 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



GRAPHICAL ABSTRACT

In Southern Europe, there is a high heterogeneity in clinical characteristics of pollen food allergy syndrome among patients with seasonal allergic rhinitis. Patients frequently report reactions to kiwi, peach, and melon. Most patients report early localized reactions. The map was created using mapchart.net.

Abbreviations: ATH, Athens; IST, Istanbul; IZM, Izmir; MAR, Marseille; MES, Messina; PFAS, pollen food allergy syndrome; POR, Porto; ROM, Rome; SAR, seasonal allergic rhinitis; TIR, Tirana; VAL, Valencia

1 | 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 worldwide.[3-5] Typical symptoms affect the oropharynx, including itching, stinging, pain, and edema, appearing within minutes of contact with the offending food[4] and lasting minutes to hours.[4-6] In around five percent of cases, more severe symptoms affecting other organ systems (e.g. skin, gastrointestinal, cardiovascular, and respiratory systems) have been reported.[7-9] Rarely, patients suffered from life-threatening anaphylaxis.[10-13]

Regional differences in pollen sensitization patterns influence the prevalence, elicitors, and typical symptoms of PFAS.[14]

While much is known about the typical sensitization pattern for PFAS in Northern Europe,[15,16] 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 compare.[17-19] Additionally, different pollens are present in Southern Europe.[20] One of these is cypress pollen, a primary cause of SAR in the Mediterranean.[21] The exact role of cypress pollen in relation to PFAS is yet unknown and subject of current research.[22-25]

Pollen food allergy syndrome cross-reactions are caused by plant-food allergens that share sequence, structure, and function similarities with pollen allergens. Due to their widespread nature, these are known as panallergens.[26,27] In this study, the focus was placed on the following panallergen families: profilins , pathogenesis-related class 10 proteins (PR-10), and non-specific lipid transfer proteins (nsLTPs).[28] 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.[1,29] 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 pollen.[30] Independently from the different perspectives on primary sensitization, nsLTPs play an important role in pollen and food allergies in the Mediterranean region and are 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.

2 | MATERIALS AND METHODS

2.1 | 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; and 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 AllergyMonitor® application (TPS software production, Rome, Italy); (3) availability of a smartphone; and (4) written informed consent. Exclusion criteria consisted of (1) prior pollen allergen immunotherapy; (2) any severe chronic disease; and (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.

2.2 | Study design

2.2.1 | 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; and (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 min; (2) 6–20 min; (3) 21–60 min; (4) 61–120 min; and (5) ≥120 min. The selection of included foods was based on the experience from previous studies as well as expert opinion.[17,28] Symptom assessment has been adapted from a validated questionnaire.[31]

2.2.2 | Skin prick tests (SPTs)

Skin prick tests 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, *Dermatophagoides pteronyssinus*, cat, dog, histamine control, saline control (Stallergenes Greer), timothy grass, *Alternaria*, plane tree, *Salsola kali* (Russian thistle), and mixed grasses (ALK Abelló). All results were noted 15 min 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.

2.2.3 | 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), a semi-quantitative, validated, customized multiplex immunoblot assay method.[32] 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).

2.3 | Statistics

Results were calculated using IBM SPSS Statistics 25. All categorical data were summarized as numbers (*n*) and frequencies (%). Quantitative data were 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-chi-square test for frequencies, Kruskal-Wallis test for medians, and ANOVA for means. When comparing two groups, Pearson-chi-square test was used to calculate the significance for frequencies, Mann-Whitney U-test for medians, and t-test for means. Values of $p < 0.05$ were considered significant.

3 | RESULTS

3.1 | Study population

815 patients (mean age 26.1 years (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 among these patients showed no significant difference to those without PFAS (25.2 years and 82/167 male (49.1%) vs. 26.3 years and 359/648 male (55.4%)) (Table 1).

3.2 | PFAS in Southern Europe

- *Clinical characteristics*: Compared to patients without PFAS, patients with PFAS had a lower age at onset of SAR (9 years vs. 12 years, $p < 0.003$), a higher prevalence of maternal PFAS history as well as of additional allergic comorbidities, especially anaphylaxis and urticaria ($p < 0.001$ for all), but also asthma and atopic dermatitis ($p = 0.001$ and $p = 0.006$, 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 min 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 ($p < 0.001$) (Table e1).

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	0.146
Age (y) [mean (*SD*)]	25.2	*13.1*	26.3	*13.7*	0.994	0.318
Family history						
Atopic relative in immediate family [n *(%)*]	126	*75.5*	449	*69.3*	1.362	0.120
Sibling(s) with PFAS [n *(%)*]	5	*3.0*	16	*2.5*	1.219	0.703
Father with PFAS [n *(%)*]	1	*0.6*	6	*0.9*	0.645	0.685
Mother with PFAS [n *(%)*]	13	*7.8*	12	*1.9*	4.474	<0.001***
Allergic rhinitis						
Age at onset (y) [median (*IQR*)][a]	9	*12*	12	*14*	0.973	0.003**
Disease duration (y) [median (*IQR*)][a]	9	*13.5*	8	*12*	1.013	0.097
Months/year with symptoms [mean (*SD*)]	4.8	*2.4*	4.7	*2.4*	1.016	0.659
ARIA severity						
Mild intermittent [n *(%)*]	6	*3.6*	35	*5.4*	—	0.297
Mild persistent (ref.: mild intermittent) [n *(%)*]	9	*5.4*	51	*7.9*	1.029	0.960
Mod./severe intermittent (ref.: mild intermittent) [n *(%)*]	27	*16.2*	125	*19.3*	1.260	0.637
Mod./severe persistent (ref.: mild intermittent) [n *(%)*]	125	*74.9*	437	*67.4*	1.669	0.259
ARIA quality						
Unclassified [n *(%)*]	19	*11.7*	108	*16.7*	—	0.073
Rhinitis sneezer/runner (ref.: unclassified) [n *(%)*]	123	*73.7*	417	*64.4*	1.677	0.055
Rhinitis blocker (ref.: unclassified) [n *(%)*]	25	*15.0*	123	*19.0*	1.155	0.663
Other allergic comorbidities						
Number of patients with comorbidities [n *(%)*]	111	*66.5*	298	*46.0*	2.328	<0.001***
Number of comorbidities [mean (*SD*)]	1.2	*1.0*	0.7	*0.8*	1.748	<0.001***
Asthma [n *(%)*]	51	*30.5*	123	*19.0*	1.877	0.001**
Anaphylaxis [n *(%)*]	26	*15.6*	23	*3.6*	5.001	<0.001***
Urticaria [n *(%)*]	63	*37.7*	131	*20.2*	2.391	<0.001***
Atopic dermatitis [n *(%)*]	50	*29.9*	129	*19.9*	1.719	0.006**
Other [n *(%)*]	4	*2.4*	22	*3.4*	0.698	0.514

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

[a]Due to incomplete data sets, 2 patients were excluded.

*$p < .05$; **$p < .01$; ***$p < .001$.

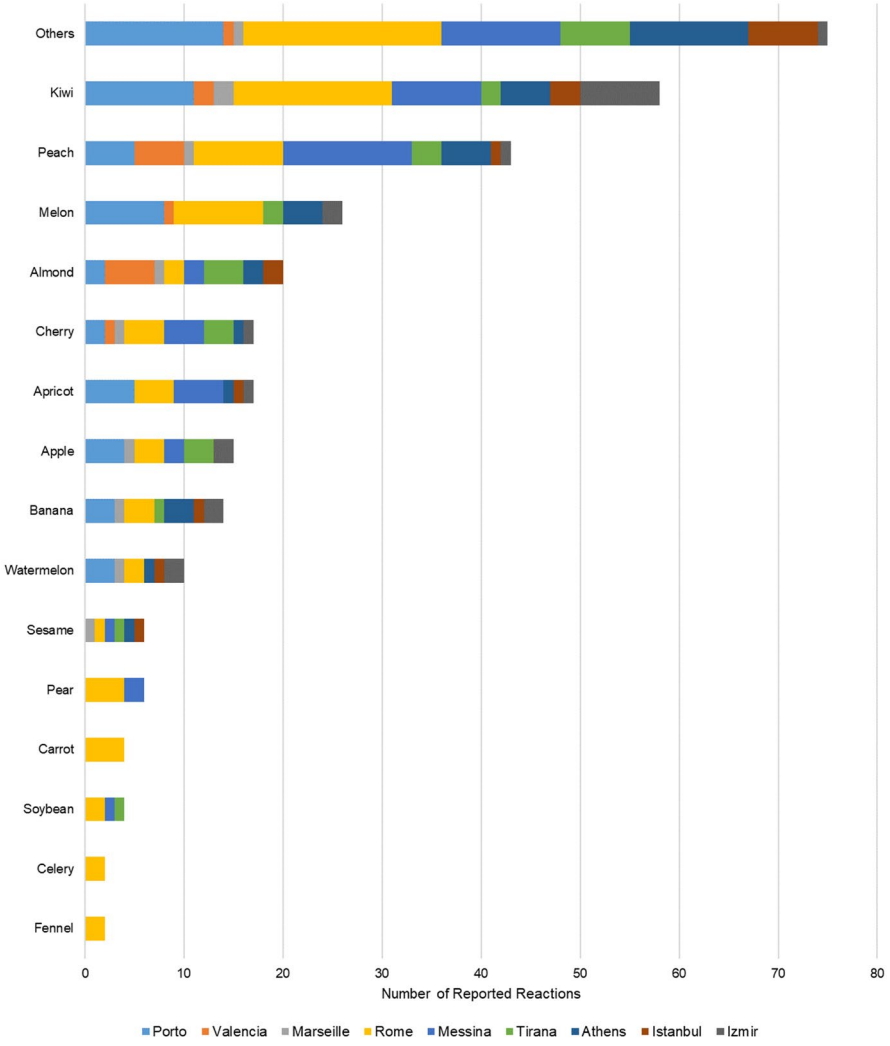


FIGURE 1 Number of reported PFAS reactions to 15 different PFAS-associated foods. The number of reported reactions is shown for the nine different centers: Porto (light blue), Valencia (orange), Marseille (gray), Rome (yellow), Messina (royal blue), Tirana (green), Athens (dark blue), Istanbul (brown),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

- *Atopic reactivity*: Patients with PFAS tested positive to a higher mean number of allergens in SPTs than those without (5.0 vs. 3.7, $p < 0.001$) 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, and nsLTP, was higher in PFAS-positive patients ($p < 0.001$ for all) (Table 2).
- *PFAS-associated characteristics*: The following associated characteristics were identified: (1) positive panallergen IgE results ($p = 0.007$), especially multi-panallergen-positive (*OR*: 6.353, $p = 0.021$) and PR-10-positive results (*OR*: 5.582, $p = 0.004$), (2) anaphylaxis (OR: 6.210, $p < 0.001$), (3) maternal history of PFAS (*OR*: 3.716, $p = 0.026$), and (4) asthma (*OR*: 1.752, $p = 0.073$) (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).

3.3 | PFAS in nine different Southern European centers

The prevalence of PFAS differed significantly between the nine centers ($p < 0.001$), 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 ($p = 0.003$), months per year with SAR symptoms ($p = 0.001$), ARIA severity and frequency (p from <0.001 to 0.080), number of patients with comorbidities ($p = 0.035$), and mean number of comorbidities per patient ($p = 0.016$), especially concerning urticaria and atopic dermatitis ($p = 0.022$ and $p = 0.018$, respectively).

Skin prick test results varied regarding the number of positive tests and average wheal diameter ($p < 0.001$).

Heterogeneous panallergen IgE results were observed for panallergen-negative ($p = 0.030$) and PR-10-positive results (p-value < 0.001).

A focused description of the unique characteristics of patients with PFAS in each center, in order of decreasing PFAS prevalence, is given below (Tables e1 and e3; Figure 1).

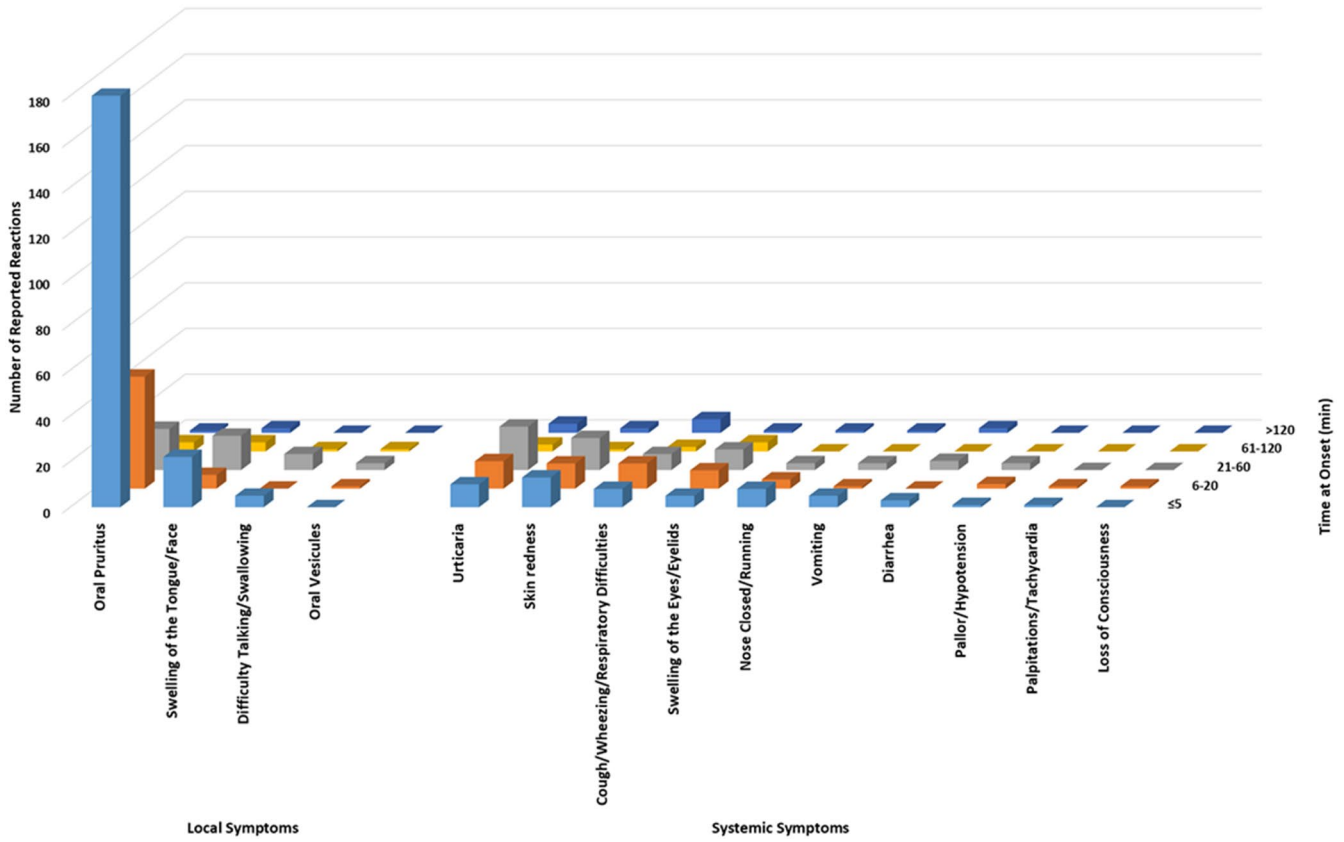


FIGURE 2 Symptoms reported by patients with PFAS after contact with PFAS-eliciting foods and times at onset. Symptoms are split into two categories: local symptoms (left) and systemic symptoms (right). The times at onset are grouped into five categories: ≤5 min (blue), 6–20 min (orange) 21–60 min (gray),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

- 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, $p = 0.005$). Profilin, PR-10, and nsLTP IgE positivity were 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, 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 had a mean age at onset of SAR of 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 was found (5/22 and 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 <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. 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).

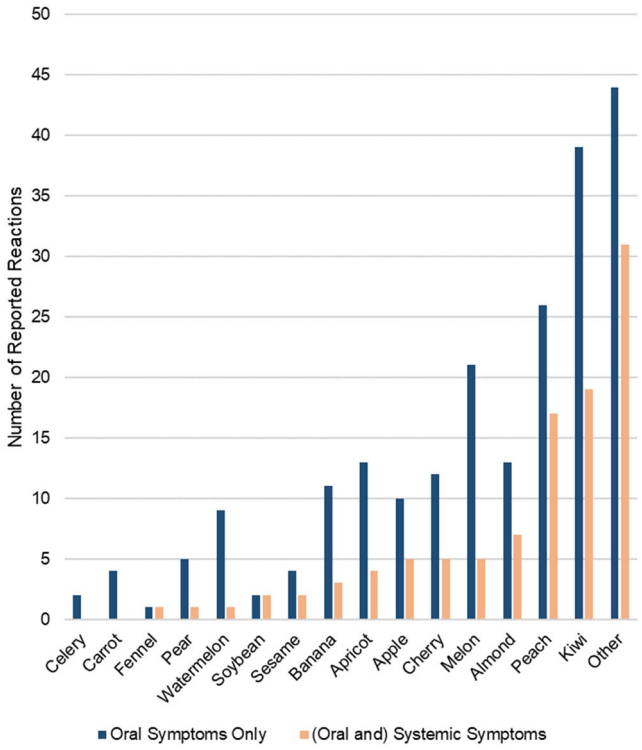


FIGURE 3 Number of reported PFAS reactions to the questioned PFAS-associated foods, categorized by oral symptoms only (blue) and (oral and) systemic symptoms (orange)

3.4 | 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 ($p = 0.073$). 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 ($p = 0.029$).
- *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 among 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).

4 | 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 among the different centers; (3) a significant lack of PFAS in cypress pollen mono-sensitized patients; and (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 among birch pollen allergic patients in Northern Europe.[15] This can be explained by the decreased role of birch pollinosis in Southern Europe,[15,33] with a lower sensitization to Bet v 1 and a higher sensitization to Bet v 2.[16] 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.[17,18]

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 onset.[2] Yet, contrary to previous publications on PFAS, where systemic symptoms only comprised 5% of all reactions,[8] 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 Europe,[34] as these molecules are heat and acid resistant and therefore more likely to cause extraoral symptoms.[29]

Within Southern Europe, a vast heterogeneity of pollen has been reported.[20,35] 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 Mastrorilli et al.[17] 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, and certain unexpected observations.

While a low frequency of birch sensitization has previously been reported in the South of France (1.05%),[33] 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 geographic 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 reported.[36] Additionally, in 1999, Priftanji et al. described that only 2.7% of the tested patients were SPT-positive for *Betula*,[37] yet our cohort of PFAS patients was predominantly PR-10 IgE-positive.

Mastrorilli et al. reported in 2016 a PFAS frequency of 16.9%[17] 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

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)[a] [mean (*SD*)]	5.0	*3.1*	3.7	*2.7*	1.166	<0.001***
Average SPT size of seasonal aeroallergens (mm)[a] [mean (*SD*)]	6.1	*1.6*	6.0	*1.7*	1.028	0.589
IgE results						
No panallergen [n *(%)*][b]	102	*61.1*	559	*86.3*	-	<0.001***
Mono-panallergen (ref.: no panallergen) [n *(%)*][b]	53	*31.7*	79	*12.2*	3.677	<0.001***
Multi-panallergen (ref.: no panallergen) [n *(%)*][b]	12	*7.2*	10	*1.5*	6.576	<0.001***
Profilins [n *(%)*][b]	26	*15.6*	42	*6.5*	2.661	<0.001***
PR-10-like allergenic proteins [n *(%)*][b]	26	*15.6*	26	*4.0*	4.411	<0.001***
nsLTPs [n *(%)*][b]	26	*15.6*	33	*5.1*	3.436	<0.001***

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

[a]Test panel included mugwort, wall pellitory, olive tree, hazel tree, birch, bermuda grass, juniper ash, and ragweed.

[b]Test panel 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).

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

10 years later than Mastrorilli et al. However, both studies showed an early onset of SAR and a predominance of nsLTP IgE positivity.[17]

Among PFAS patients in ATH, our cohort reported a higher rate of IgE to profilin (18.2%) than previously reported (10.9%).[38] As LTP syndrome has been described as a common allergenic syndrome in Greece,[39] it is not surprising that the prevalence of nsLTP IgE-positive patients among our cohort was 22.7%. The absence of sensitization to PR-10 in ATH is noticeable and corroborates current literature.[40]

The high prevalence of IgE to profilins in our PFAS cohort in POR is similar to that found in central Portugal by Tavares et al.[41] and can be explained by the predominance of Urticaceae (including pellitory of the wall) and grass pollen in Portugal.[42]

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,[19] where peach and nuts were the most common elicitors. Their results showed walnut as the main symptom-causing nut,[19] which was not included in our questionnaire. The high prevalence of nsLTP sensitization found in our cohort corroborates previous reports for the region.[43]

Compared to an earlier study focusing on PFAS in Italian children,[17] 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 Mastrorilli et al.[17] 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%,[18] kiwi was by far the most common elicitor of PFAS in both studies.[18] Asthma was the most frequent comorbidity of PFAS-positive patients in Turkey both in our cohort and in the previous study.[18]

4.1 | 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.[23,24] These two allergic reactions have been linked through molecular similarities between the cypress molecule Cup s 7 and the peach molecule Pru p 7.[22] 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.[25] that mono-sensitization to Pru p 7 is rare among cypress pollen hypersensitive patients in Italy. It also supports the authors' conclusion that peach and cypress pollen might share other, currently unknown cross-reactive molecules.

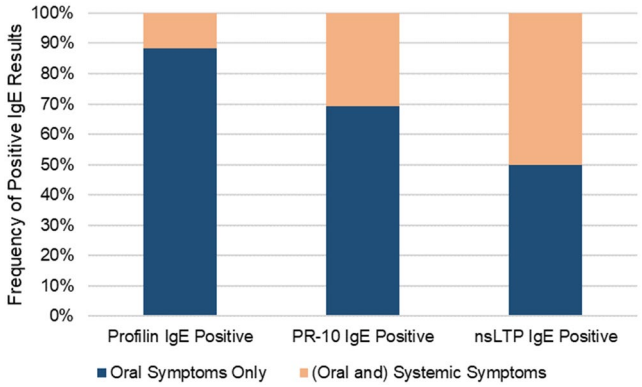


FIGURE 4 Frequency of panallergen-positive IgE results in patients who only reported oral symptoms (blue) versus those who reported (oral and) systemic symptoms (orange) to any of the questioned PFAS-associated foods. Results are shown based on different panallergen groups: profilins (Bet v 2 and Phl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

4.2 | 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.

4.3 | 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 pollen types 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.

4.4 | 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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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, and personal fees from Mylan, outside the submitted work; Dr. Pahus reports personal fees from GlaxoSmithKline, personal fees from Astra Zeneca, and 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, and grants from Capricare, outside the submitted work; and Simone Pelosi reports other from TPS Production srl, during the conduct of the study. Dr. Psarros reports personal fees from Novartis Hellas, Takeda, Astra Zeneca, and 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, and personal fees from Nutricia, outside the submitted work; and Dr. Matricardi reports grants from Deutsche Forschungsgemeinschaft, grants and personal fees from Hycor Biomedical, grants and personal fees from Euroimmun, and personal fees and non-financial support from Thermo Fisher Scientific, outside the submitted work.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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