

Peeling the Peanut. Characterizing Peanut Allergy with the new Food Allergy Severity Score

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Peanut allergy is a major cause of severe food reactions worldwide. Together with tree nuts, it remains the most prevalent cause of fatal food anaphylaxis, according to reports from the US and UK [1-3]. Many studies identified severity predictors of peanut allergy to improve risk stratification, including age of allergy onset, atopic comorbidities, or food extract-specific IgE levels [4-6]. It is also known that sensitization to particular peanut molecular allergens entails a higher risk of anaphylaxis, such as seed storage proteins (SSP) [5,7]. Sensitization profiles and clinical presentations may differ according to diet and environmental exposure. In Mediterranean countries, frequent sensitization to peach lipid transfer protein (LTP) and cross reactivity among food LTPs (including peanut's) is widely described [6,8]. On the other hand, sensitization to *Bet v 1* homologues (PR-10) have been identified mostly in Northern Europe, and are associated with birch tree pollen sensitization and milder symptoms, such as oral allergy syndrome [9]. This variability in the clinical presentation of food allergies has emphasized the need for a common language to characterize the severity of reactions worldwide and to better investigate clinical predictors.

The new food allergy severity score (oFASS) is a recently validated tool that allows for the standardization of severity assessment and may contribute to a better identification of predictors [10]. A mild oFASS-3 involves only the oral cavity; a moderate oFASS-3 includes one or more of the following organs/systems: skin, nose, eyes, digestive system or uterus, and may include the oral cavity as well; lastly, a more severe oFASS-3 includes the previous and the involvement

of one or more of the following: larynx, bronchi, cardiovascular and nervous system. This scoring system has more detailed variations, especially oFASS-5, which further stratifies the moderate and severe degrees in two additional steps, resulting in a crescent severity scale from 1 to 5. The aim of this study was to characterize peanut allergy in a Portuguese cohort using this newly-developed severity stratification score.

A cross-sectional study was conducted including patients observed at the Allergy Clinic of a Tertiary Hospital from 2015 to 2022 with the following IgE-mediated peanut allergy criteria: 1) positive (≥ 0.35 kUA/l) specific IgE to peanut extract; 2) reported symptoms to peanut and anaphylaxis classification according to the EAACI guidelines [11]. Demographic, clinical and laboratory variables were correlated with the oFASS-3 and oFASS-5 scores of the patient's worst reaction to search for individual predictors of peanut allergy severity. Statistical analysis was conducted using STATA 16.1. P-values of < 0.050 for correlations were considered statistically significant. Mann-Whitney U testing was used for associations between dichotomic and categorical or continuous variables. Correlation between continuous and categorical data was assessed using Spearman rank coefficient.

Overall, 80 patients with peanut allergy were evaluated – 39 (48.8%) males; median-age 23 (*IQR* 13-30) years. Despite correlating significantly amongst each other ($p < 0.001$), oFAAS-5 had the highest correlation coefficients, both with oFASS-3 ($r=0.911$) and with peanut anaphylaxis ($r=0.824$). Thus, oFASS-5 was used for the characterization of peanut allergy (table 1). Most patients reported an oFASS-5 of 3 (31.2%), with an overall median of 2 (1-3) – potential involvement of the oral cavity, as well as the skin, nose/eyes, uterus or digestive system. No patients reported reactions with an oFASS-5 of 5 (most severe reaction, with confirmed affliction of either cardiovascular or neurologic systems, and possible involvement of other

organs/systems). Despite no gender differences, patients with an earlier allergy onset ($r = -0.410$, $p < 0.001$) and younger age at the time of the most severe reaction ($r = -0.317$, $p = 0.005$) were associated with higher oFASS-5 scores. Atopic background variables (allergic rhinoconjunctivitis, asthma or atopic dermatitis) and reaction co-factors (exercise, alcohol or NSAID use) did not correlate significantly with oFASS-5. Concomitant anaphylaxis to tree nuts was significantly associated with higher oFASS-5 in peanut reactions ($p < 0.001$). The levels of peanut or tree nut sIgE extracts did not correlate with oFASS-5. Blood eosinophil count and total IgE levels were also non-significantly correlated. However, sensitization to the peanut SSP *Ara h 2* was associated with higher oFASS-5 ($p = 0.008$), while *Bet v 1* (a homologue of the peanut PR-10 *Ara h 8*) with lower oFASS-5 ($p = 0.014$). Despite the high prevalence of LTP sensitization (69.8% of 63 measurements), neither *Pru p 3* nor *Ara h 9* were associated with higher peanut oFASS-5.

The newly validated oFASS scores proved a useful tool to stratify the severity of peanut allergy in our cohort: it was (1) easy to apply, (2) correlated significantly with peanut anaphylaxis, and (3) provided a numerical information that was not available in “traditional” dichotomic descriptions (e.g., anaphylaxis vs non-anaphylaxis; with skin symptoms vs without).

oFASS characterization was able to identify previously well-known predictors, such as sensitization to SSPs (*Ara h 2*) for severe reactions and PR-10 (*Bet v 1*) for mild reactions. Interestingly, despite frequent sensitization to LTPs in our cohort, neither *Pru p 3* nor the peanut-LTP *Ara h 9* correlated with oFASS-5. This suggests that severity of LTP allergy is highly variable and may depend on the type of food involved. In our study, oFASS identified lower age of peanut allergy onset and concomitant anaphylaxis to tree nuts as predictors of anaphylaxis to peanut, in accordance with findings of the recent EuroPrevall study [5]. There are some limitations to this

study – its retrospective nature led to some missing data, particularly regarding the limited peanut molecular profile that was available, and a larger and more diverse sample size could have strengthened the power of our statistical analysis [12]. However, there is still room to explore the full potential of this tool in peanut allergy – more peanut molecular proteins should be included in future studies, such as the PR-10 *Ara h 8* and other SSPs like *Ara h 1* [13], in order to build detailed sensitization and cross-reactivity profiles. This can potentially improve dietary recommendations and influence decisions regarding food immunotherapy. In addition, there are regional differences in the sensitization patterns of peanut allergy (e.g. Mediterranean vs Northern Europe) that could be better compared with a widespread and multicenter use of the oFASS stratification, allowing more accurate predicting models of severity and deeper understanding of regional impacts.

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Conflict of interest

No conflicts of interest to declare.

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Table 1. Clinical characteristics of peanut allergic patients and oFASS-5 associations

Variables	oFASS-5 (n=80)					Overall	p-value	Spearman coefficient*
	1 n=23 (28.8%)	2 n=22 (27.5%)	3 n=25 (31.2%)	4 n=10 (12.5%)	5 n=0 (0%)			
<i>Demographic data</i>								
Age of food allergy onset, M (n=80)	16	15	8	8		12	<0.001	-0.410
Age of most severe reaction, M (n=80)	28	24	22	16		23	0.005	-0.317
Male gender, n (%) (n=80)	10 (43.5)	12 (54.6)	11 (44.0)	6 (60.0)		39 (48.8)	0.651	
<i>Clinical background, n (%)</i>								
Asthma (n=75)	13 (59.1)	11 (55.0)	14 (56.0)	5 (11.6)		43 (57.3)	0.996	
Allergic rhinoconjunctivitis (n=78)	18 (78.3)	16 (76.2)	18 (72.0)	7 (77.8)		59 (75.6)	0.750	
Atopic dermatitis (n=74)	6 (27.3)	8 (38.1)	10 (43.5)	2 (25.0)		26 (35.1)	0.566	
Co-factors (n=66)	4 (22.2)	4 (20.0)	6 (31.6)	3 (33.3)		17 (25.8)	0.393	
Anaphylaxis to peanut (n=80)	0 (0)	2 (9.1)	22 (88.0)	10 (100.0)		34 (42.5)	<0.001	0.824
Reactions to tree nuts (n=75)	16 (72.7)	15 (75.0)	12 (52.2)	4 (40.0)		47 (62.7)	0.035	
Anaphylaxis to tree nuts (n=46)	0 (0)	0 (0)	6 (50.0)	3 (100.0)		9 (19.6)	<0.001	
<i>Laboratory data</i>								
Total IgE (kU/L), M (n=44)	203	358	238	615		342	0.204	0.176
Blood eosinophil count, M (n=34)	180	300	390	300		250	0.081	0.303
sIgE to Peanut (kU/L), M (n=80)	1.64	2.24	1.94	3.60		1.94	0.151	0.176
Ara h 2 positivity, n (%) (n=37)	0 (0)	2 (15.4)	3 (30.0)	4 (57.1)		9 (25.7)	0.008	
Ara h 9 positivity, n (%) (n=12)	0 (0)	3 (100.0)	3 (75.0)	3 (75.0)		9 (75.0)	0.787	
Pru p 3 positivity, n (%) (n=63)	15 (68.2)	9 (20.4)	14 (31.8)	6 (13.6)		44 (69.8)	0.680	
Bet v 1 positivity, n (%) (n=22)	3 (60.0)	2 (22.2)	0 (0)	0 (0)		5 (22.7)	0.014	

Statistically significant associations in bold; *- used when statistically applicable; M - median; in Variables column, number of patients collected in parentheses reflects available data; anaphylaxis to peanut/tree nuts classified according to EAACI criteria (11)