What plays a role in the severity of Atopic Dermatitis in children?

1. Introduction

Atopic dermatitis (AD) is a chronic relapsing, pruritic, inflammatory skin disease [1]. This disorder is associated with many comorbid conditions leading to impaired overall health and increased healthcare utilization [2]. It has been one of the most common chronic diseases of the present time and affects 15 to 20 percent of the child population worldwide [3]. The onset is most commonly observed at the age of 3 to 6 months, with approximately 60% of patients developing eczema in the first year of their lives and 90% of patients by the age of 5 [1].

In order to prevent a disease that is remarkably common and has wide detrimental effects, it is essential to determine the risk factors of the disease, however, the pathogenesis of AD is not entirely understood [4].

With this single-centred cross-sectional study, we aimed at investigating the clinical characteristics of pediatric patients with AD and identifying the factors associated with the severity of the disease.

2. Materials and Methods

2.1.Clinical assessment

In our retrospective cross-sectional study, the data of the patients who applied between December 2019 and December 2020 were obtained from the hospital records. A total of 304 pediatric patients attending to Mardin State Hospital Pediatric Allergy Outpatient Clinic between December 2019 and December 2020, and diagnosed with AD according to Hanifin Rajka criteria [5, 6], at the time of admission were included in this study. The individuals with a previous diagnosis of AD, with dermographism, having dermatological diseases other than AD, under treatment, or having a special diet were excluded.

The data on patients' age at admission, age at onset of symptoms, the presence of atopy history in their family, the cigarette smoke exposure, and area of residence were collected from the patients' records. Family history of atopy was defined as having at least one parent or sibling with physician-diagnosed asthma, AD and/ or allergic rhinitis [7].

Disease severity was determined according to the SCORAD index: The patients with a score below 25 were classified as mild, 25-50 as moderate, and above 50 as severe AD [8].

The eosinophil levels and eosinophil percentages were obtained from the complete blood counts.

Epidermal prick tests (EPT) were performed on all of the patients. The panels consisting of the 16 most common allergens in Turkey including food allergens (cow's milk, egg white, egg yolk, wheat, hazelnut, peanut, soybean, fish species, sesame, walnut) and aeroallergens (*Dermatophagoides farinae*, *Dermatophagoides pteronyssunus*, *Alternaria tenuis*, *Penisilium notatum*, *Aspergillus fumigatus*) were used for EPT [9]. Histamine was used as positive control while 0.9% NaCl solution as negative control. The commercial extracts (brand name: Allergopharma; D-21462 Reinbek, Germany) were applied for EPT. The prick tests were performed to the volar or dorsal of the forearms after cleaning the areas with alcohol and by using skin prick test applicators (Medblue one 020013, Turkey). The wheal diameter that occurred 15 minutes after the tests had been applied was measured. The test was considered positive if the wheal diameter was at least 3 mm greater compared to the negative control [10]. Patients with positive results in EPT were accepted as "sensitized". All epidermal prick tests were done and evaluated by the same clinician. Thus, standardization was achieved in the application and evaluation of the tests.

The individuals found to be "sensitive" in the epidermal prick tests were undergone oral food challenge (OFC) with the food allergen to which they were sensitive. Those who had positive results in OFC were diagnosed with food allergy (FA).

The study protocol was approved by the Ethical Committee of Artuklu University, Turkey. An informed written consent was obtained from the caregivers of the participants.

2.2.Statistical analyses

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY). Results were indicated as means (standard deviations) for variables with a normal distribution and as medians (interquartile range) for variables with skewed

distribution. The statistical significance of differences between the groups was tested using the Chi-squared test and Fisher's exact test for categorical parameters; Mann-Whitney U test and Kruskal-Wallis test for continuous parameters. Spearman's rank correlation coefficients were assessed as measures of correlation between variables of interest. To assess factors associated with SCORAD scores we applied linear regression modeling. The variables that reach a p-value <0.10 in the univariate analysis were included in a multiple linear regression analysis to investigate factors independently associated with SCORAD scores. Values of p <0.05 were considered to be statistically significant.

3. Results

A total of 304 pediatric patients with AD were enrolled in the study. The mean age at admission was 8.1 (±4.8) months and the mean age at the onset of symptoms was 4.5 (±3) months. There was a slight male predominance in the whole study group (64% male, 36% female).

The median SCORAD score of the whole study group was 16 (IQR: 13-24). According to the classification of AD severity, 75.3% (229) of the patients had mild, 20.4% (62) had moderate, and 4.3% (13) had severe AD.

The ages at admission and at the onset of the symptoms were significantly lower in patients with severe and moderate disease than the patients with mild disease (p=0.009, p<0.001) (**Table 1**). There was a negative correlation between the SCORAD score and both age at admission (r=-0.277, p<0.001) and age at onset of the symptoms (r=-0.474, p<0.001) (**Figure 1**). Any significant relationship between the severity of disease and gender were not observed (**Table 1**).

While 38% of the whole study group had FA, this rate was 23.1% in mild cases and 90.7% in moderate and severe cases (**Table 1**). Food sensitization rates were higher in individuals with moderate and severe disease (p<0.001) and patients with FA had significantly higher SCORAD scores [33 (IQR: 22-44) vs 14 (IQR: 12-16); p<0.001] (**Figure 2a**). Furthermore, the median age at the onset of AD symptoms was significantly lower for individuals with FA than the ones without FA [5(IQR: 2-4) vs 2 (IQR: 3-7); p<0.001]. Egg and milk were the leading foods to which the patients were sensitive (**Figure 3**).

The majority of severely affected patients were living in rural areas (**Table 1**) and concerning the whole study group, it was observed that the ones living in rural areas had higher SCORAD scores than the individuals living in urban areas [22 (IQR: 15-39.5) vs 15(IQR:12-22); p<0.001] (**Figure 2b**).

The frequency of familial atopy was 29.6% and significantly higher in the ones with moderate and severe disease than the mild disease (66.5%vs 17.5%; p<0.001) (**Table 1**). Moreover, the SCORAD scores of the patients with familial atopy history were notably higher (35.5(IQR: 21.75-46) vs 14 (IQR:12-19); p<0.001) (**Figure 2c**).

Sixty-five per cent of the patients in the entire study group were exposed to passive cigarette smoking. The frequency of tobacco exposure was remarkably higher in severe and moderate patients than mild patients (90.7% vs. 56.8%; p<0.001) (**Table 1**). Likewise, SCORAD scores were higher in patients exposed to passive cigarette smoking [21(IQR:14.75-38) vs. 13(IQR:12-16); p<0.001] (**Figure 2d**).

The eosinophil count and peripheral eosinophil percentages were significantly higher in severe and moderate cases than mild ones [630(IQR: 450-850) /µl vs. 170(IQR: 80-405) /µl; p<0.001 and 49(IQR:31-65)% vs. 11(IQR:2-33.5) %; p<0.001] (**Table 1**). Both the eosinophil count and percentage found to be positively correlated with SCORAD scores (r=0.531, p<0.001 and r=0.434, p<0.001) (**Figure 4**).

In the multi-regression analysis, we observed that earlier onset of symptoms, having familial atopy, FA, and higher eosinophil counts were independently associated with SCORAD scores (**Table 2**).

4. Discussion

In the present study, we assessed the factors associated with the severity of AD in children. Patients with earlier onset of the symptoms, food sensitivity, positive familial history for atopy, rural area of residence, cigarette smokes exposure, higher blood eosinophil levels were found to be more prone to have severe AD.

We analyzed the severity of AD in our patients by SCORAD index, which has been reported as one of the most reliable and practicable methods [8, 11]. One fourth of the participants in this study were moderate-severe cases. This rate is lower than what is

reported in the former study by Ricci et al [12], which was performed in a pediatric population with a similar number of cases. The previous studies conducted on pediatric AD patients in Turkey have also reported larger proportions of severe cases [13-15]. In the UK, however, the rates of mild, moderate, and severe AD in children reported to be 82, 12, and 6%, respectively; which are comparable to our results [16]. Hence, these differences could be attributed to variations in methodology and populations.

The ratio of mild to severe AD patients likely increases with age [16]. In our study, the individuals showing symptoms at an earlier age had higher SCORAD scores, and the median age of the severe-moderate cases was found to be lower than the mild cases. The regression analysis revealed that younger age was an independent factor associated with a more severe clinical picture in AD. Therefore, cases with early onset of AD symptoms should be monitored more closely due to a high possibility of a severe and persistent clinical course.

Although some studies report slightly female predominance [17,18], the majority of the patients, particularly those with severe disease were male in our study population. Besides, in consistency with the former studies [19], we couldn't reveal any significant relations between the severity of AD and patient’s gender.

FA can coexists with AD in infancy [20]. In two-fifths of our patients, AD is accompanied by food sensitivity and consistent with the literature [16], egg and milk sensitivity were the most common triggers prevalent. Almost all of our moderate and severe cases had FA. These results were similar to previous studies, suggesting that in the first two years of life, the majority of infants with moderate to severe disease shows sensitization to food allergens, whereas those with mild disease are less sensitized [21,22]. In a retrospective study, it was observed that the patients with FA developed AD at earlier ages [23]. Similar to this study, we revealed that AD symptoms appeared earlier in the cases accompanied by FA, and severity scores of these cases were significantly higher than the ones without FA.

Recently the prevalence and incidence of AD have been increasing. A major theory explaining this trend, in general, is the ‘hygiene hypothesis' that supports an inverse

relationship between AD and exposure to endotoxin, early daycare, farm animal, and dog pets in early life [24,25]. As part of the 'hygiene hypothesis,' it has been thought that AD is more common in urban than in rural communities [26]. In the context of this hypothesis, we analyzed the association between the area of residence and the severity of AD. Contrary to the previous studies, we found that the individuals living in rural areas had higher SCORAD scores than the ones living in urban areas. Longitudinal cohort studies conducted in this particular region of Turkey are needed to explain this difference and reveal any causation.

Population-based studies have indicated that the strongest risk factor is a positive family history for atopic diseases, particularly for AD [27]. Approximately 70 percent of individuals with AD have a positive family history of atopic diseases [28]. Patients with one atopic parent have two to threefold increased risk of developing AD. Moreover the risk increases to three to fivefold in case both parents are atopic [1]. In our study, almost all of the severe cases had a positive family history of atopic diseases. The SCORAD scores of the patients with familial atopy history were significantly higher. We can postulate that positive family history for atopic diseases increases the possibility of a more severe clinical course for patients with AD.

Early studies have shown that cigarette smoke in the environment increases children's risk of allergic sensitization [29]. A meta-analysis reviewed 86 studies, from 39 countries, investigated the association of active smoking, passive smoking exposure, and maternal smoking during pregnancy with childhood AD, and concluded that childhood AD was significantly associated with passive smoking exposure [30]. In our study, 90.7% of severe and moderate cases had passive cigarette smoking exposure and those with passive cigarette smoking exposure had a significantly higher SCORAD score. These results indicate that passive tobacco exposure increases the severity of AD. Therefore, it is strongly recommended that all caregivers should stop smoking.

Eosinophilia in patients with AD is usually mentioned as a nonspecific finding [31]. However, recent studies have determined a positive correlation between peripheral eosinophilia and the severity of AD [13,32]. Comparable to these studies, we found that the blood eosinophil count and the eosinophil percentage of moderate and severe

cases were higher than mild cases. Besides, a positive correlation was established between patients' SCORAD scores and the eosinophil counts and percentages. Since they can be practically evaluated and have potential utility in clinical practice; blood eosinophil count and percentage can be very valuable parameters for assessing the severity of AD in children.

As far as we know, this study was one of the few studies evaluating children with AD in this particular region of Turkey. Because of the retrospective cross-sectional nature and relatively small sample size of our study, our findings on investigating possible factors associated with the increased severity of AD were limited. Especially, the socioeconomic or cultural level of the patients, that may affect the parameters (such as passive cigarette smoking, living in rural areas) that we consider in assessing the severity of AD could not be evaluated within the scope of our study. Further studies are still needed to clarify the factors playing a role in severe AD in the pediatric population.

5. Conclusion

Our findings show that early-onset, food sensitivity, having familial atopy history and passive smoke exposure play a significant role in severe AD, consistent with the previous reports. On the contrary, living in rural areas was found to be associated with severe AD. Since it is remarkably correlated with SCORAD scores, we can postulate that eosinophil count can be used as a marker to assess the severity of AD in children.

6. References

1. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014; 70 (2): 338-351. doi: 10.1016/j.jaad.2013.10.010.
2. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol. 2013; 24 (5): 476-86. doi: 10.1111/pai.12095.
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006; 368 (9537): 733-43. doi: 10.1016/S0140-6736(06)69283-0.
4. Kapur S, Watson W, Carr S. Atopic dermatitis. Allergy Asthma Clin Immunol. 2018; 14 (Suppl 2): 52. doi: 10.1186/s13223-018-0281-6.
5. Hanifin, J. Diagnostic features of atopic eczema. Acta Dermatol Venereol (Stockh) 1980; 60 (**92)**: p. 44-47. doi : 10.2340/00015555924447.
6. Vakharia PP, Chopra R, Silverberg JI. Systematic Review of Diagnostic Criteria Used in Atopic Dermatitis Randomized Controlled Trials. Am J Clin Dermatol 2018; 19 (1): 15-22. doi: 10.1007/s40257-017-0299-4.
7. Böhme M, Wickman M, Lennart Nordvall S, Svartengren M, Wahlgren C. Family history and risk of atopic dermatitis in children up to 4 years. Clinical

& Experimental Allergy. 2003;33(9):1226-31.doi: 10.1046/j.1365-2222.2003.01749.x.

8. Ertam I, Su O, Alper S, Sarıcaoglu H, Karadag AS, et al. The Turkish guideline for the diagnosis and management of atopic dermatitis-2018. TURKDERM-Turkish Archives of Dermatology and Venereology 2018. **52**(1): p. 6-23. doi: 10.4274/turkderm.87143.
9. Kahveci M, Koken G, Şahiner ÜM, Soyer Ö, Şekerel BE. Immunoglobulin E-Mediated Food Allergies Differ in East Mediterranean Children Aged 0-2 Years. Int Arch Allergy Immunol 2020; 181 (5): 365-374. doi: 10.1159/000505996.
10. Heinzerling L, Mari A, Bergmann KC, Bresciani M, Burbach G, et al. The skin prick test - European standards. Clin Transl Allergy 2013; 3 (1): 3. doi: 10.1186/2045-7022-3-3.
11. Oranje AP. Practical issues on interpretation of scoring atopic dermatitis: SCORAD Index, objective SCORAD, patient-oriented SCORAD and Three-Item Severity score. Curr Probl Dermatol 2011; 41: 149-155. doi: 10.1159/000323308.
12. Ricci G, Patrizi A, Baldi E, Menna G, Tabanelli M, et al. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. J Am Acad Dermatol 2006; 55 (5): 765-771. doi: 10.1016/j.jaad.2006.04.064.
13. Akan A, Azkur D, Civelek E, Erkoçoğlu M, Yılmaz-Öztorun Z, et al. Risk factors of severe atopic dermatitis in childhood: single-center experience. Turk J Pediatr 2014; 56 (2):121-126.

14. Ozceker D, Bulut M, Ozbay AC, Dilek F, Koser M, et al. Assessment of IL-31 levels and disease severity in children with atopic dermatitis. Allergol Immunopathol (Madr) 2018; 46 (4): 322-325. doi: 10.1016/j.aller.2017.10.005.
15. Su O, Bahalı AG, Demir AD, Ozkaya DB, Uzuner S, et al. The relationship between severity of disease and vitamin D levels in children with atopic dermatitis. Postepy Dermatol Alergol 2017; 34 (3): 224-227. doi: 10.5114/pdia.2017.66054.
16. Huang E, Ong PY. Severe Atopic Dermatitis in Children. Curr Allergy Asthma Rep 2018; 18 (6): 35. doi: 10.1007/s11882-018-0788-4.
17. Larsen, F.S. and J.M. Hanifin, Epidemiology of atopic dermatitis. Immunology and Allergy Clinics of North America 2002; 22 (1): 1-24. doi : 10.1016/S0889-8561(03)00066-3.
18. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. J Allergy Clin Immunol. 1999; 103 (1 Pt 1): 125-38. doi: 10.1016/s0091-6749(99)70536-1.
19. Ballardini N, Kull I, Söderhäll C, Lilja G, Wickman M, et al. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: a report from the BAMSE birth cohort. Br J Dermatol 2013; 168 (3): 588-594. doi: 10.1111/bjd.12196.
20. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. Front Immunol 2020; 11: 1907. doi: 10.3389/fimmu.2020.01907.

21. Illi S, von Mutius E, Lau S, Nickel R, Grüber C, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immuno 2004; 113 (5): 925-931. doi: 10.1016/j.jaci.2004.01.778.
22. De Benedictis FM, Franceschini F, Hill D, Naspitz C, Simons FE, et al. The allergic sensitization in infants with atopic eczema from different countries. Allergy 2009; 64 (2): 295-303. doi: 10.1111/j.1398-9995.2008.01779.x.
23. Kijima A, Murota H, Takahashi A, Arase N, Yang L, et al. Prevalence and impact of past history of food allergy in atopic dermatitis. Allergol Int 2013; 62 (1): 105-112. doi: 10.2332/allergolint.12-OA-0468.
24. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? Br J Dermatol 2005; 152 (2): 202-216. doi: 10.1111/j.1365-2133.2004.06436.x.
25. Flohr, C. and L. Yeo, Atopic dermatitis and the hygiene hypothesis revisited, in Pathogenesis and Management of Atopic Dermatitis. 2011, Karger Publishers. p. 1-34. doi: 10.1159/000323290.
26. Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, et al. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. Br J Dermatol 2010; 162 (5): 964-973. doi: 10.1111/j.1365-2133.2010.09689.x.
27. Apfelbacher CJ, Diepgen TL, Schmitt J. Determinants of eczema: population-based cross-sectional study in Germany. Allergy 2011; 66 (2): 206-213. doi: 10.1111/j.1398-9995.2010.02464.x.
28. Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, et al. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. Br J Dermatol 2009; 161 (5): 1166-1172. doi: 10.1111/j.1365-2133.2009.09412.x.

29. Lannerö E, Wickman M, van Hage M, Bergström A, Pershagen G, et al. Exposure to environmental tobacco smoke and sensitisation in children. Thorax 2008; 63 (2): 172-176. doi: 10.1136/thx.2007.079053.

30. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. Expert review of clinical immunology. 2017;13(1):15-26. doi: 10.1080/1744666X.2016.1212660.

31. Bieber, T. Atopic dermatitis. N Engl J Med 2008; 358: 1483-1494. doi: 10.1056/NEJMra074081.

32. Özdoğru EE, Gönülal M. Atopic dermatitis, inhalant allergy and food allergy: A paediatric approach. Dermatol Ther 2020: e14542. doi: 10.1111/dth.14542.

Table1. Comparison of the clinical and laboratory characteristics of patients in order to AD severity

	Mild (n=229)	**Moderate & Severe (n=75)**	***p value***
Age at admission *(months)*	7 (IQR: 5-11)	6 (IQR: 4-7)	**0.009**
Age at the onset of symptoms *(months)*	4 (IQR: 2.5-6)	2 (IQR: 1-3)	**<0.001**
Gender of the patients (Male/Female) *[n (%)/n(%)]*	144 (62.9) /85 (37.1)	51 (68)/24 (32)	0.42
Patients with food allergy *[n(%)]*	53 (23.1)	68 (90.7)	**<0.001**
Patients living in rural areas *[n(%)]*	56 (24.5)	37 (49.3)	**<0.001**
Family history of atopy *[n(%)]*	40 (17.4)	50 (66.7)	**<0.001**
Cigarette smoke exposure *[n(%)]*	130 (56.8)	68 (90.7)	**<0.001**
Eosinophil count *(μl)*	170 (IQR: 80-405)	630(IQR: 450-850)	**<0.001**
Peripheral eosinophil percentage *(%)*	11(IQR: 2-33.5)	49 (IQR: 31-65)	**<0.001**

Abbreviations: *Values in table are presented as the number of patients with/without the percentage in parenthesis, as the median with the interquartile range (IQR) in parenthesis as appropriate*

Table 2. Linear regression analysis of factors associated with greater SCORAD scores

Table 2. Linear regression analysis of factors associated with greater SCORAD scores

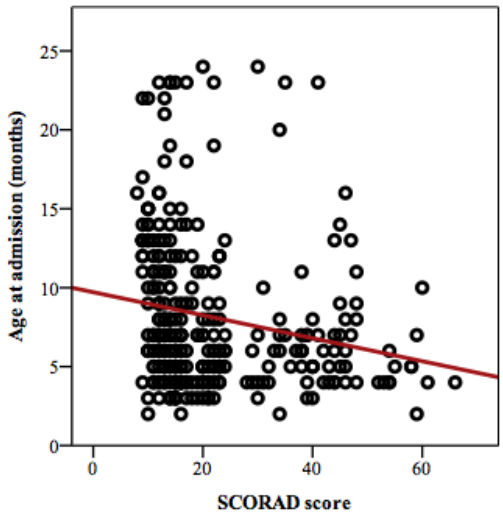
	Univariate linear regression			**Multiple linear regression**		
	B coefficient	**95% CI**	**p**	**B coefficient**	**95% CI**	**p**
Age at the onset of symptoms	-0.396	-1.93 to -1.045	<0.001	-0.74	-0.58 to -0.01	**0.04**
Food allergy	0.74	17.76 to 21.75	<0.001	0.50	11.1 to 15.54	**<0.001**
Gender	-0.04	-4.10 to 2.01	0.5			
Region of residency	-0.26	-10.93 to -4.39	<0.001	-0.05	-3.40 to 0.49	0.14
Family history of atopy	0.54	7.28 to -10.41	<0.001	0.20	3.42 to 7.98	**<0.001**
Cigarette smoke exposure	0.38	7.62 to 13.3	<0.001	0.04	-0.80 to 3.20	0.23
Eosinophil count	0.54	0.011 to 0.015	<0.001	0.27	0.005 to 0.008	**<0.001**

Abbreviations: *SCORAD, Scoring Atopic Dermatitis Index, CI: coefficient interval*

Figüre Legends

Figure 1. Correlation between the SCORAD score and age [**(a)** at admission and **(b)** at the onset of the syptoms] *(r, Spearman's rank correlation)*

a.



b.

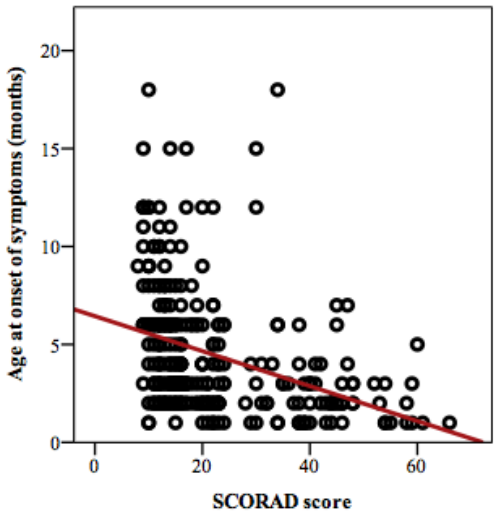
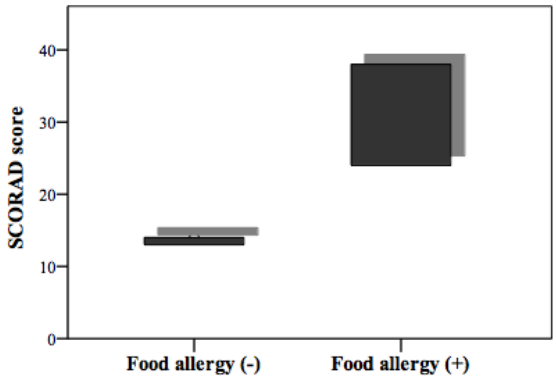
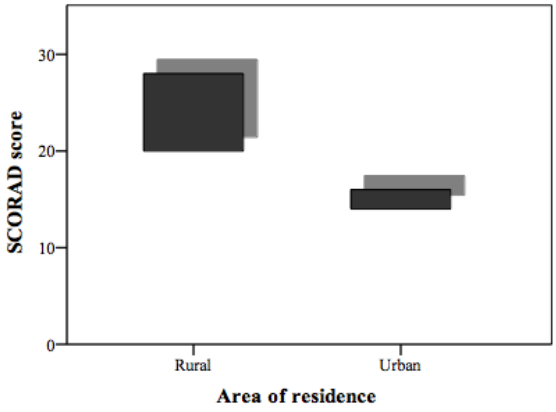


Figure 2. Comparison of SCORAD scores of patients in the context of **(a)** food allergy, **(b)** the area of residence, **(c)** family history of atopy and **(d)** passive smoke exposure.

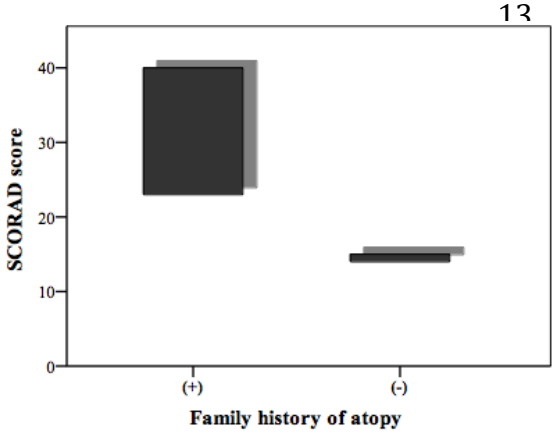
a.



b.



c.



d.

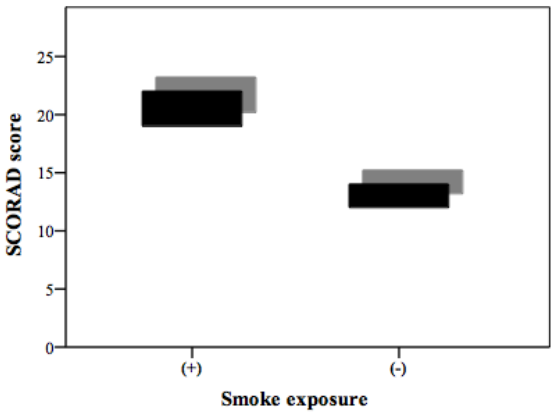


Figure 3. Distribution of the frequency of food sensitivity in patients according to the food type

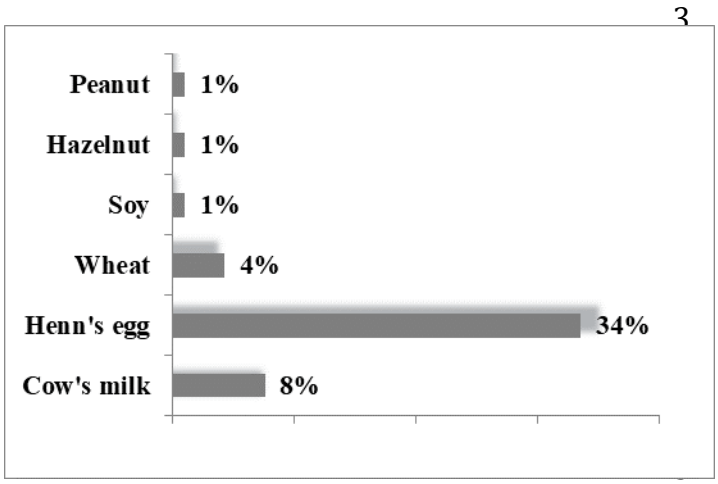
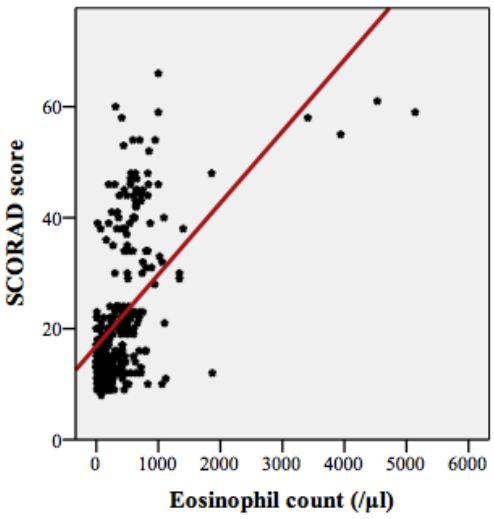


Figure 4 . Correlation between SCORAD scores and **(a)** the eosinophil count , **(b)** peripheral *(r, Spearman's rank correlation)*

a.



b.