The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 1291-1296

Study of Interleukin 33 Gene Polymorphism in Egyptian Patients with Allergic Rhinitis

Ahmed Mohsen Seleit[1], Kassem Mohamed Kassem[1], Awad Mohamed El Abd[2], Mohammed Ahmed Mohieeldin*[1], Inas A. Ahmed[2], Mostafa Gomaa Sobhy[1]

Departments of [1]Otorhinolaryngology and [2]Medical Biochemistry and Molecular Biology, Faculty of Medicine, Benha University, Egypt

***Corresponding author:** Mohammed Ahmed Mohieeldin, **Mobile:** (+20) 01000288698, **Email:** **m**ohamedmohiee02@gmail.com

ABSTRACT

Background: Allergic rhinitis (AR) is a chronic illness, which most people are afflicted by. **Objective:** To evaluate the expression of interleukin-33 in patients presenting with allergic rhinitis and nasal polyposis. **Patients and Methods:** This study was carried out on 50 patients aged from 15 to 40 years old, both sexes, and 25 healthy volunteers matched in age and sex. Patients were allocated into two groups: Case group n= 50 and control group n= 25, then the case group was further subdivided into equal two groups: nasal polyposis group n= 25, and AR group n= 25. All patients were subjected to laboratory investigations, DNA extraction, measurement of DNA concentration, and single nucleotide polymorphism detection. **Results:** The most predominant genotype in sinusoidal nasal polyps was CT (60%) in both tissue and serum. **Conclusions:** Il 33 genotype (rs11792633) wasn't associated with allergic rhinitis and nasal polyps.

Keywords: Interleukin 33, Gene Polymorphism, Allergic Rhinitis, Nasal Polyposis.

INTRODUCTION

All allergic rhinitis (AR) symptoms are rhinitis, nasal obstruction, sneezing, nose rubbing, and rhinorrhea. AR is an inflammation of the nasal airway caused by allergens. AR can also be a risk factor for conditions such as rhinosinusitis, asthma, and adenoid hypertrophy [1].

Atopic individuals are susceptible to developing a chronic inflammatory response in the nasal mucosa following exposure to a harmless allergen. This response involves the activation of immune cells and cytokines, as well as the release of proinflammatory factors and cytokines mediated by immunoglobulin E (IgE) [2]. Around 40% of the global population experienced significant impacts from allergic rhinitis (AR) on their sleep, academic performance, professional activities, and social interactions [3].

Nasal polyps are hyperplastic, benign inflammations that originate in the sinonasal mucosa. They manifest most frequently in individuals who are afflicted with chronic rhinosinusitis (CRS). In discussions pertaining to nasal polyposis, the abbreviation CRS with nasal polyposis (CRSwNP) is therefore commonly employed [4].

Polyposis represents a terminal manifestation of uncontrolled allergy, and its management merely marks the initial phase of the overall process. Local and systemic therapy must be initiated after the polyps have been removed in order to control the underlying allergic aetiology; failure to do so may result in a rapid recurrence [5].

IL-33, a IL-1 family member that was only identified in 2005, operates via the IL-33/ST2 axis by binding exclusively to its receptor tumorigenicity 2 (ST2) suppression [6]. The IL-33/ST2 signal transduction pathway is intricately linked to cardiovascular disease, autoimmune disease, and allergic disease [7]. In addition to facilitating the cytokines release, IL-33/ST2 promotes the accumulation of inflammatory cells such as mast cells, basophils, eosinophils, and others in the nasal mucosa; thus, it plays a role in the allergic diseases development [8]. In addition to facilitating the cytokines release, IL-33/ST2 promotes the inflammatory cells accumulation such as eosinophils, basophils, mast cells, and others in the nasal mucosa; thus, it plays a role in the allergic diseases development [9]. Hence, additional investigation is warranted into the relationship between the IL-33/ST2 axis and the AR progression. ERK1/2 belongs to the MAPK protein family. ERK1/2 is mitogen-activated protein kinase [5].

The ERK1/2 signal transduction pathway is a critical component of numerous cellular processes, consisting of apoptosis, division, growth, development, and differentiation [10]. Activation of ERK signalling can stimulate the numerous inflammatory cytokines production, such as IL-6, IL-8, and TNF-a, among others [11].

Aim of the work was to evaluate the expression of interleukin-33 in patients presenting with AR and nasal polyposis.

PATIENTS AND METHODS

This study was conducted on 50 patients aged from 15 to 40 years old, both sexes, and 25 healthy volunteers matched in age and sex.

Inclusion criteria: Patient should have sneezing, rhinorrhea, nasal obstruction, irritability and fatigue, attack may be accompanied by itching of the nose, eyes and cough, and the attack is relieved spontaneously or with antihistaminic therapy.

Exclusion criteria: Age more than 40 or less than 15, any patient using systemic corticosteroid for a long period in order not to affect interleukin 33 serum level, patient suffering from rhinitis due to other cause than allergy, any systemic disorder as hypertension and diabetes mellitus.

Patients were allocated into two groups: Case group n= 50 and control group n= 25, then the case group was

Received: 01/12/2023
Accepted: 01/02/2024

further subdivided into equal two groups: nasal polyposis group n= 25, and AR group n= 25.

All patients were undergone; full clinical evaluation [Full history taking (onset, course, duration, any complications development and previous surgery history to the nose), and clinical examination of nose, ear and throat], Investigations [Routine laboratory investigation as bleeding time, CBC, random blood sugar, clotting time, SGOT and SGPT, urea and creatinine levels, measurement of level of interleukin 33 by enzyme linked Immunosorbent assay in the serum and tissue, and PCR].

Molecular estimation: a: Estimation of DNA concentration, Sample collection, DNA Extraction, measurement of DNA concentration of samples, by: single nucleotide polymorphism (SNP) Detection (Genotyping), estimation of DNA concentration, sample collection, and three ml of peripheral blood were taken from each subject, under aseptic conditions, into an EDTA-containing vacutainers. Blood samples were stored at −20ºC till further processing.

DNA extraction was conducted on the blood samples utilising the Gene JET Whole Blood Genomic DNA Purification Mini Kit (Thermo Fisher Scientific, Germany) in accordance with the guidelines provided by the manufacturer **[12].**

The proteinase K solution (20 L) was introduced into 200 L of whole blood while being agitated. Subsequently, 400 L of lysis solution was introduced and compacted via vortexing in order to acquire a uniform suspension. Occasionally vortexed, the samples were incubated at 56°C for ten minutes, or until the cells were completely lysed. By pipetting, ethanol 96-100 percent (200 L) was introduced and thoroughly mixed. The mixture in preparation was subsequently transferred to the spin column and centrifuged at 8,000 rpm for one minute. The flow-through solution-containing collection tubes were discarded. The column was subsequently transferred to a fresh 2 mL collection tube. Following the addition of 500 L of wash buffer I and one-minute centrifugation at 10,000 rpm, the flow-through was discarded and the column was reintroduced into the collection tube. After adding 500 L of wash buffer II to the column, it was centrifuged at 14,000 rpm for three minutes. To elute genomic DNA, 200 L of elution buffer was introduced into the central region of the column membrane. The column was centrifuged at 10,000 rpm for one minute then incubated at room temperature for two minutes.

The Nana drop One spectrophotometer (thermoscientific, USA) was utilized to calculate the concentration of each sample utilizing 1 ul of the sample.

The TaqMan SNP Genotyping assays were utilised to genotype the IL33 gene SNP (rs11792633) (Applied Biosystems, USA). Utilizing a StepOne Plus Real Time PCR instrument, amplification was performed (Applied Biosystems, USA).

The initial stage of a TaqMan SNP Genotyping Assay procedure involved the utilisation of sequence-specific primers to amplify the target DNA. In the SNP Genotyping Assay, TaqMan MGB probes generated a fluorescence signal that facilitated the amplification of individual alleles. An endpoint plate read was executed subsequent to PCR amplification utilising an Applied Biosystems Real-Time PCR System. The Sequence Detection System **[13]**: Fluorescence (Rn) values were plotted by software using the fluorescence measurements obtained through the plate read, with the signals from individual wells serving as the basis. The alleles present in each sample were deduced from the fluorescence signals that were plotted.

In each PCR tube (1 ug) of DNA sample was added. Nuclease free H_2O was added to each PCR tube to reach 11.25 ul. PCR tubes were loaded into Stepone qPCR after programming as follows: HOLD (Denature, Anneal/Extend), AmpliTaq Gold Enzyme Activation (PCR (40 Cycles)), and 10 minutes at 95°C (15 seconds at 92°C-1 minute at 60°C). The allelic discrimination software Step OnePlus (Applied Biosystems USA) was utilised to analyse PCR products and ascertain the each sample genotype.

Ethical approval:

Written informed permission was acquired from the patients or their family members. The Benha University Hospital and Benha Insurance Hospital Ethical Committees gave their approval before the study could be carried out. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

An SPSS v. 26.0 statistical analysis was done (IBM Inc., Armonk, NY, USA). The quantitative variables were expressed as the mean and standard deviation (SD), and an unpaired Student's t-test was used to compare them between the two groups. The frequency and percentage (percent) of qualitative variables were provided for analysis, and when applicable, the Fisher's exact test or Chi-square test was employed. A two-tailed P value < 0.05 was deemed to indicate statistical significance.

RESULTS

No significant difference was found between the cases of allergic rhinitis, sinonasal polyps, and control regarding age. Most of studied subjects, allergic rhinitis, and sinonasal polyps were males 52% in both cases and control groups (Table 1).

Table (1): Age, and gender distribution of the study groups

		Cases (n= 50)		Control group (n= 25)		p value
Age		27.6±6.1		25.2±6.5		0.11
Gender	Female	24	48%	12	48%	1
	Male	26	52%	13	52%	
		AR (n= 25)		SNP (n= 25)		Control group (n= 25)		p value
Age		27.88±6.31		27.36±5.89		25.2±6.5		0.27
Gender	Female	12	48%	12	48%	12	48%	1
	Male	13	52%	13	52%	13	52%	

Data are presented as mean ± SD or frequency (%).

No significant difference was found between studied cases regarding genotype distribution. This table shows that the most predominant genotype in sinusoidal nasal polyps was CT (60%) in both tissue and serum (Table 2).

Table (2): Genotype and allelic distribution of the cases and control groups, the AR and control groups, and the NP and control groups.

		Cases group (n= 50)		**Control group (n= 25)**		**p**	**OR**	**95% CI**	
		No.	%	No.	%				
Genotypes	**CC**	11	22.0	4	16	-	1	Reference	
	CT	31	62.0	16	64	0.592	0.809	0.373	1.756
	TT	8	16.0	5	20	0.506	0.719	0.272	1.899
Dominant model	**CC**	11	22.0	4	16	-	1	Reference	
	CT+TT	39	78.0	21	84.0	0.537	0.789	0.371	1.678
Recessive model	**CC+CT**	20	80.0	42	84.0	-	1	Reference	
	TT	8	16.0	5	20	0.668	0.846	0.394	1.817
Alleles	**C**	53	53.0	24	48.0	-	1	Reference	
	T	47	47.0	26	52.0	0.564	0.885	0.584	1.340
		AR group (n= 25)		**Control group (n= 25)**		**p**	**OR**	**95% CI**	
		No.	**%**	**No.**	**%**				
Genotypes	**CC**	3	16	4	16	-	1	Reference	
	CT	16	64	16	64	0.732	1.197	0.427	3.353
	TT	6	20	5	20	0.629	1.342	0.407	4.425
Dominant model	**CC**	3	16	4	16	-	1	Reference	
	CT+TT	22	88.0	21	84.0	0.684	1.233	0.451	3.372
Recessive model	**CC+CT**	19	76	42	84.0	-	1	Reference	
	TT	6	20	5	20	0.733	1.158	0.500	2.682
Alleles	**C**	22	44	24	48.0	-	1	Reference	
	T	28	56	26	52.0	0.688	1.106	0.676	1.811
		NP (n= 25)		**Control group (n= 25)**		**p**	**OR**	**95% CI**	
		No.	**%**	**No.**	**%**				
Genotypes	**CC**	8	32	4	16	-	1	Reference	
	CT	15	60	16	64	0.281	0.624	0.265	1.469
	TT	2	8	5	20	0.112	0.369	0.108	1.260
Dominant model	**CC**	8	16	4	16	-	1	Reference	
	CT+TT	17	68.0	21	84	0.187	0.569	0.247	1.313
Recessive model	**CC+CT**	23	92	42	84	-	1	Reference	
	TT	2	20	5	20	0.224	0.520	0.181	1.492
Alleles	**C**	31	62	24	48	-	1	Reference	
	T	19	38	26	52	0.160	0.700	0.426	1.151

There was no significant association of IL33 polymorphism with gender distribution among all studied subjects, control group, cases group, nasal polyposis group, and AR group (Table 3).

Table (3): Association of IL33 polymorphism with gender distribution among all studied subjects, control group, cases group, nasal polyposis group, and AR group.

	males		females		p
	No.	%	No.	%	
Subjects					
CC	8	20.5%	7	19.4%	0.978
CT	24	61.5%	23	63.9%	
TT	7	17.9%	6	16.7%	
Control group					
CC	3	23.1%	1	8.3%	0.559
CT	8	61.5%	8	66.7%	
TT	2	15.4%	3	25.0%	
Cases group					
CC	5	19.2%	6	25.0%	0.762
CT	16	61.5%	15	62.5%	
TT	5	19.2%	3	12.5%	
Nasal polyposis group					
CC	3	23.1%	5	41.7%	0.588
CT	9	69.2%	6	50.0%	
TT	1	7.7%	1	8.3%	
AR group.					
CC	2	15.4%	1	8.3%	0.546
CT	7	53.8%	9	75.0%	
TT	4	30.8%	2	16.7%	

There was significant difference in (all studied groups and nasal polyposis and AR) but there was no significant difference in control group.

Table (4): Association of IL33 polymorphism with age distribution among all studied subjects, control group, cases group, nasal polyposis group, and AR group

	Age (years)		p
	Mean	SD	
Studied subjects			
CC	30.1	6.8	0.072
CT	25.9	5.7	
TT	26.8	6.6	
Control group			
CC	27.5	9.7	0.675
CT	24.6	5.1	
TT	26.4	8.1	
Cases group			
CC	31.0	5.7	0.106
CT	26.5	5.9	
TT	27.1	6.1	
Nasal polyposis group			
CC	29.9	5.5	0.305
CT	26.5	5.7	
TT	24.0	8.5	
AR group			
CC	34.0	6.0	0.179
CT	26.6	6.2	
TT	28.2	5.6	

DISCUSSION

Most people suffer from the chronic AR. Cases afflicted with a severe form of AR must be identified for management purposes. Hypersensitivity responses in the early and late phases are mediated by IgE [14].

Variable phenotypes of CRS include eosinophilic (allergic fungal rhinosinusitis, aspirin-exacerbated respiratory disease), non-eosinophilic (idiopathic non-eosinophilic CRS, chronic infectious sinusitis), and idiopathic eosinophilic CRS (cystic fibrosis). Eosinophilic CRS, which is distinguished by heightened eosinophil infiltration into the paranasal mucosa of the sinuses, is also prevalent, being detected in over 80% of patients with CRS [15].

Nasal polyps are hyperplastic, benign inflammations that originate in the sinonasal mucosa. They manifest most frequently in individuals who are afflicted with CRS. When discussing nasal polyposis, the acronym CRSwNP is therefore frequently applied. Nevertheless, they are additionally linked to respiratory disease exacerbated by aspirin, specific forms of cystic fibrosis, systemic vasculitis, and several others. Polyposis represents a terminal uncontrolled allergy manifestation, and its management merely marks the initial phase of the overall process. Systemic and local therapy targeting the underlying allergic aetiology must be initiated after the polyps have been removed; otherwise, they may reappear rapidly. Patients with significant anosmia, nasal obstruction, ageusia, nasal and facial congestion, and rhinorrhea may present with the condition or be asymptomatic. Affected individuals experience a decline in quality of life (QOL) due to these symptoms [16].

"Alarmin" is the name given to IL-33, a member of the damage-associated molecular pattern molecules (DAMP) family. First-line cells, including tissue epithelial cells, secrete it in response to exogenous stimuli, such as allergens, in order to initiate an immune response. Additional immune cells, such as macrophages and dendritic cells, as well as smooth muscle cells, endothelial cells, fibroblasts, osteoblasts, and adipocytes, express this cytokine [17].

Li et al. [18] identified a robust correlation between IL-33 polymorphisms and AR in a genome-wide association study (GWAS). Genetic variants of IL-33 have thus been examined in relation to a multitude of autoimmune disorders. To date, a considerable IL-33 genetic variants number have been identified, and a number of them, including the rs10939286, rs16924159, rs7044343, rs11792633, and rs1157505 polymorphisms, have been investigated for their potential associations with IL-33 activity [19]. The IL-33 gene variants rs7044343 and rs11792633 were related to a reduced risk of Behcet's disease [20].

There is evidence suggesting that L-33 gene polymorphisms may contribute to an elevated susceptibility to asthma, nasal polyps, and inflammatory bowel diseases [20].

We aimed to evaluate the IL-33 expression in patients presenting with AR and nasal polyposis.

The present study found that the average age of the studied cases was 27.6±6.1 and control was 25.2±6.5. No significant difference was detected between the two groups. Most of AR, sinusoidal nasal polyps and control were males (52%).

Similarly, **Dafale *et al.*** [21] demonstrated that middle-aged males have the highest incidence of nasal polyps. Additionally, from January 2014 to December 2014, **Lee** [22] examined 115 consecutive paranasal sinus computed tomographic scans (230 sides) of adult Korean patients. There were 62 (53.9 %) males and 53 (46.1 %) females in the study group.

Males between the ages of 41 and 60 comprised the majority of patients with nasal polyps, according to **Rajeev *et al.*** [23]. Males comprised the majority of patients in a retrospective cross-sectional study with nasal polyps; their mean age was 39.49±16.63 years [24]. **Heidarzadeh Arani *et al.*** [25] demonstrated that 18 (31.6 %) of the 57 patients with AR were females, while 39 (68.4 %) were males.

The present study found that no significant difference was observed between studied cases as regard genotype distribution.

Aligned with our discovery, there were no statistically significant differences in the levels of IL-33 serum protein detected in patients who were allergic or not allergic [26]. An additional study found no significant difference in IL-33 expression between NP-treated and healthy control tissues [27].

Furthermore, an investigation encompassing 24 patients with Japanese cedar (JC) pollinosis and 14 patients with HDM sensitization and AR revealed that while IL-33 protein is not detectable in the serum, its concentration is elevated in the sinus mucosa and exhibits a significant correlation with the overall nasal symptom score [28]. Furthermore, an examination of the genotype and allele frequency distribution of each polymorphism across various subjects revealed a significant association between JC pollinosis and the rs1929992 T allele [29]. **Kim *et al.*** [30] reported that the level of IL-33 is positively correlated with the quantity of neutrophils and the expression of various Th1 and Th17 inflammatory markers in nasal polyps from CRSwNP patients.

In contrast, the results of **Zielińska-Bliźniewska *et al.*** [26] suggest that CRSwNP patients have significantly elevated levels of serum IL-33 protein than the control group. Asthma patients have also been found to have elevated serum IL-33 levels, according to prior research [31].

Ran *et al.* [32] proposed that specific variants in the IL33 gene may pose a risk for asthma and rheumatoid arthritis, and they suggested that asthma and AR share a genetic foundation.

In Japan, **Haenuki *et al.*** [9] investigated the IL-33 role in the AR symptoms development. They discovered that nasal stimulation by the allergen induces both the primary phase (runny nose and sneezing) and the final phase (basophil and eosinophil accumulation) of symptoms following this, the IL-33 protein is subsequently expressed in the epithelial cells' nucleus, leading to the secretion of nasal secretions. The final and initial phases of clinical manifestations are exacerbated when basophils and mast cells are stimulated by IL-33. This is due to the increased secretion of histamine and the chemical adsorbents generation for eosinophils and basophils. The symptoms of AR are thus associated with the pathogenesis progression and the presence of IL-33.

This study showed that the most predominant IL33 rs11792633 genotype was CT (60%) in both tissue and serum.

Koca *et al.* [20] showed that in the studied 117 patients with Behçet's disease, the TT rs11792633 variants polymorphisms were very rare, and the T allele low frequencies characterised these polymorphisms.

We recommended that further studies with large number cases should be conducted to confirm our results.

CONCLUSION

Il 33 genotype (rs11792633) wasn't associated with nasal polyps and AR.

- **Funding:** Nil
- **Conflict of Interest:** Nil.

REFERENCES

1. **Hoyte F, Nelson H (2018):** Recent advances in allergic rhinitis. F1000Research, 7: F1000. doi: 10.12688/f1000research.15367.1.
2. **Eckrich J, Hinkel J, Fischl A *et al.* (2020):** Nasal IgE in subjects with allergic and non-allergic rhinitis. World Allergy Organization Journal, 13:100129. doi: 10.1016/j.waojou.2020.100129
3. **Brożek J, Bousquet J, Agache I *et al.* (2017):** Allergic rhinitis and its impact on asthma (ARIA) guidelines—2016 revision. Journal of Allergy and Clinical Immunology, 140: 950-8.
4. **Hopkins C (2019):** Chronic rhinosinusitis with nasal polyps. New England Journal of Medicine, 381:55-63.
5. **Jha S, Morris E, Hruza A *et al.* (2016):** Dissecting therapeutic resistance to ERK inhibition. Molecular Cancer Therapeutics, 15:548-59.
6. **Aimo A, Migliorini P, Vergaro G *et al.* (2018):** The IL-33/ST2 pathway, inflammation and atherosclerosis: trigger and target? International Journal of Cardiology, 267:188-92.
7. **Wang E, Jia X, Ruan C *et al.* (2017):** miR-487b mitigates chronic heart failure through inhibition of the IL-33/ST2 signaling pathway. Oncotarget, 8:51688-702.
8. **Gabryelska A, Kuna P, Antczak A *et al.* (2019):** IL-33 mediated inflammation in chronic respiratory diseases—understanding the role of the member of IL-1 superfamily. Frontiers in Immunology, 10: 692. doi: 10.3389/fimmu.2019.00692.

9. **Haenuki Y, Matsushita K, Futatsugi-Yumikura S *et al.* (2012):** A critical role of IL-33 in experimental allergic rhinitis. Journal of Allergy and Clinical Immunology, 130:184-94.
10. **Lake D, Corrêa S, Müller J (2016):** Negative feedback regulation of the ERK1/2 MAPK pathway. Cellular and Molecular Life Sciences, 73:4397-413.
11. **Ishimaru Y, Sumino A, Kajioka D *et al.* (2017):** Apelin protects against NMDA-induced retinal neuronal death via an APJ receptor by activating Akt and ERK1/2, and suppressing TNF-α expression in mice. Journal of Pharmacological Sciences, 133: 34-41.
12. **Deweir A (2020):** Improved DNA extraction technique from blood clot for diagnosis of Trypanosoma evansi in camels. Egyptian Veterinary Medical Society of Parasitology Journal, 16: 1-7.
13. **Amoras E, de Brito W, Queiroz M *et al.* (2021):** The genetic profile and serum level of IL-8 are associated with chronic hepatitis B and C virus infection. Biomolecules, 11(11): 1664 .doi: 10.3390/biom11111664
14. **Gálffy G, Emmeluth M, Koltun A *et al.* (2021):** Allergic rhinitis therapy decisions during a routine consultation: A multicenter, cross-sectional survey. J Asthma Allergy, 14: 335-45.
15. **Fokkens W, Lund V, Hopkins C *et al.* (2020):** European position paper on rhinosinusitis and nasal polyps 2020. Rhinology, 58: 1. doi: 10.4193/Rhin20.600.
16. **Ta N (2019):** Will we ever cure nasal polyps? Ann R Coll Surg Engl., 101:35-9.
17. **Ding W, Zou G, Zhang W *et al.* (2018):** Interleukin-33: Its emerging role in allergic diseases. Molecules, 23(7): 1665 .doi: 10.3390/molecules23071665
18. **Li J, Zhang Y, Zhang L (2015):** Discovering susceptibility genes for allergic rhinitis and allergy using a genome-wide association study strategy. Current Opinion in Allergy and Clinical Immunology, 15:33-40.
19. **López-Mejías R, Genre F, Remuzgo-Martínez S *et al.* (2015):** Protective role of the interleukin 33 rs3939286 gene polymorphism in the development of subclinical atherosclerosis in rheumatoid arthritis patients. PLOS One, 10:e0143153. doi: 10.1371/journal.pone.0143153
20. **Koca S, Kara M, Deniz F *et al.* (2015):** Serum IL-33 level and IL-33 gene polymorphisms in Behçet's disease. Rheumatology International, 35: 471-7.
21. **Dafale S, Yenni V, Bannur H *et al.* (2015):** Histopathological study of polypoidal lesions of the nasal cavity-A cross sectional study. Al Ameen J Med Sci., 5: 403-6.
22. **Lee S (2017):** The relationship of the medial roof and the posterior wall of the maxillary sinus to the sphenoid sinus: a radiologic study. Brazilian Journal of Otorhinolaryngology, 83: 375-80.
23. **Rajeev L, Ibrahim L, Kumar M *et al.* (2020):** Study of nasal polyps in a tertiary care hospital. International Journal of Research in Pharmaceutical Sciences, 11: 2921-55.
24. **Jahromi A, Pour A (2012):** The epidemiological and clinical aspects of nasal polyps that require surgery. Iran J Otorhinolaryngol., 24: 75-8.
25. **Heidarzadeh Arani M, Nikafarin S, Gilasi H (2022):** The relationship between serum level of interleukin-33 and allergic rhinitis and its severity in children. Iran J Pediatr., 32:e105094. DOI: https://doi.org/10.5812/ijp.105094
26. **Zielińska-Bliźniewska H, Paprocka-Zjawiona M, Merecz-Sadowska A *et al.* (2022):** Serum IL-5, POSTN and IL-33 levels in chronic rhinosinusitis with nasal polyposis correlate with clinical severity. BMC Immunol., 23: 33. doi: 10.1186/s12865-022-00507-2.
27. **Baba S, Kondo K, Kanaya K *et al.* (2014):** Expression of IL-33 and its receptor ST2 in chronic rhinosinusitis with nasal polyps. The Laryngoscope, 124: 115-22.
28. **Asaka D, Yoshikawa M, Nakayama T *et al.* (2012):** Elevated levels of interleukin-33 in the nasal secretions of patients with allergic rhinitis. Int Arch Allergy Immunol., 158(1): 47-50.
29. **Sakashita M, Yoshimoto T, Hirota T *et al.* (2008):** Association of serum interleukin-33 level and the interleukin-33 genetic variant with Japanese cedar pollinosis. Clin Exp Allergy, 38: 1875-81.
30. **Kim D, Jin H, Eun K *et al.* (2017):** The role of interleukin-33 in chronic rhinosinusitis. Thorax., 72: 635-45.
31. **Ahmadi M, Fathi F, Fouladi S *et al.* (2019):** Serum IL-33 level and IL-33, IL1RL1 gene polymorphisms in asthma and multiple sclerosis patients. Curr Mol Med., 19: 357-63.
32. **Ran H, Xiao H, Zhou X *et al.* (2020):** Single-nucleotide polymorphisms and haplotypes in the interleukin-33 gene are associated with a risk of allergic rhinitis in the Chinese population. Experimental and Therapeutic Medicine, 20: 102. doi: 10.3892/etm.2020.9232