CMMB

ORIGINAL PAPERS

https://doi.org/10.31689/rmm.2025.32.3.285

Relationship Between Peripheral Blood Eosinophil Count, Tissue Eosinophil Dominance and Serum Specific Immunoglobulin E Levels with Primary Chronic Rhinosinusitis Phenotype

Anna Mailasari Kusuma DEWI[1*], Krisna Dini SEPTIANI[1], Yanuar Iman SANTOSA[1], Riece HARIYATI[1], Kanti YUNIKA[1]

Abstract

Background: European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 proposed a novel primary chronic rhinosinusitis (CRS) phenotype classification. As the endotype and phenotype of primary CRS are highly heterogeneous, clinical evaluation to match these endotypes and corresponding clinical biomarkers with these novel phenotypes is still limited. This study aimed to evaluate the correlation between clinical inflammatory biomarkers and primary CRS phenotype. Materials and Methods: A retrospective study of 78 adult patients diagnosed with primary CRS was conducted. Peripheral eosinophil count, serum-specific immunoglobulin E (ssIgE), and primary CRS phenotyping data were collected from the electronic health record database of Dr. Kariadi General Hospital Semarang. The Chi-square test and phi coefficient were used to assess the correlation between variables. Results: Most patients have polysensitization allergen patterns, predominated by house dust mites (Tyrophagus putrescentiae, Dermatophagoides microceras, and Dermatophagoides farinae) and grass pollens (Bermuda grass, mix grass, and Timothy grass). peripheral eosinophil count and ssIgE are significantly correlated to primary CRS phenotype ($r=+0.407$, $p<0.001$; $r=+0.342$, $p=0.002$; respectively). We also found a small portion of some peculiar conditional probabilities of having non-eCRS given patients have peripheral eosinophilia and positive ssIgE (6.2% and 17.3%, respectively). Conclusion: peripheral eosinophils count and ssIgE are correlate to the CRS phenotype.

Keywords: Immunoglobulin E, Peripheral Eosinophil, Primary Chronic Rhinosinusitis, Endotype, Phenotype

[1]Department of Otorhinolaryngology-Head and Neck Surgery Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

***Corresponding author:**
Anna Mailasari Kusuma DEWI, Department of Otorhinolaryngology-Head and Neck Surgery Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
E-mail: anna_drtht@fk.undip.ac.id

INTRODUCTION

Primary chronic rhinosinusitis (CRS) is a disease that has many underlying cause (like a fungal infection, tumor, or dental problem) is present.[1] Primary CRS usually classified based on phenotype or clinical manifestations and the presence or absence of nasal polyps on nasal endoscopy.[2] There are two types of CRS, first one is primary CRS with nasal polyps / *chronic rhinosinusitis with nasal polyps* (CRSwNP) and second one is primary CRS without nasal polyps / *chronic rhinosinusitis without nasal polyps* (CRSsNP).[1] This phenotype-based classification of primary CRS does not use cellular pathophysiological mechanisms underlying the primary CRS phenotype, which may have a detrimental impact on therapeutic *outcomes* of primary CRS.[3–5] This is the main weakness of the classification of primary CRS based only on phenotype.

Endotype or cellular pathophysiological mechanism of primary CRS is based on the inflammatory response.[1,2,6] Phenotype of primary CRS is based on the classical paradigm of T helper (Th) 1 and Th2 cells, where CRS with nasal polyps (CRSwNP) is characterized by an inflammatory response by Th2 cells and CRS without nasal polyps (CRSsNP) by Th1.[1,2,6] Previous studies related to the characterization of endotypes of CRSwNP and CRSsNP phenotypes still show heterogeneous results.[1,2,6] Classification of inflammatory responses has developed and is based on increased expression of Th1, Th2, and Th17 cells, where the CRSwNP endotype is characterized by Th2 expression (type 2 inflammation) and CRSsNP is characterized by Th1 and/or Th17 expression (non-type 2 inflammation).[6] A hypothetical explanation for this phenomenon is the heterogeneity of the phenotype classification of CRSwNP and CRSsNP.[7]

Phenotype classification of primary CRS has evolved over time by incorporating the endotypes and phenotype subtypes of CRSwNP and CRSsNP.[5] *European Position Paper on Rhinosinusitis and Nasal Polyps* (EPOS) 2020 divides the phenotypes of primary CRS based on anatomical distribution, endotype dominance and subtypes CRSwNP and CRSsNP.[8]EPOS 2020 to classify re-classification of primary CRS phenotypes that are more specific than phenotype classification based on the presence/absence of nasal polyps to reduce the heterogeneity of primary CRS phenotypes. The merging of endotypes in the classification of CRSwNP and CRSsNP subtypes can also be a threat to the homogeneity of primary CRS phenotype reclassification, where an endotype can underlie more than one subtype of CRSwNP and CRSsNP.[6,9] Studies to prove the homogeneity of the merging of CRSwNP and CRSsNP endotypes and subtypes in the EPOS 2020 reclassification are still limited.

Some CRSwNP phenotype sub types with fusion endotypes can be classified based on the dominance of eosinophils and mononuclear cells.[10] Eosinophil dominance is a downstream cascade of Th2 cell inflammatory responses and mononuclear cell dominance is a downstream cascade of Th1 cell inflammatory responses.[6] Spectral inflammatory responses allow for a shift in the dominance of Th2 to Th1 inflammatory responses and vice versa.[11] The spectrum of inflammatory responses has expanded along with the development of the inflammatory response paradigm based on increased expression of Th1, Th2, and Th17 cells.[6,11] The downstream cascade of Th17 cell inflammatory responses is neutrophil expression.[12] Classification of CRSwNP subtypes by combining endotype broader spectrum of inflammatory responses has resulted in new phenotype subtypes, namely those based on eosinophil and non-eosinophil dominance.[4] This classification of CRSwNP subtypes results in eCRS and non-eCRS subtypes.

Certain biomarkers can be used to determine the dominance of the inflammatory response, identify relevant endotypes, and approach primary CRS therapy.[2,9] Relevant biomarkers can be identified along the inflammatory response signaling pathway, either upstream or downstream.[6] Preoperative biomarker examination in primary CRS patients can determine endotype, predict phenotype, and plan primary CRS management approaches, including the classification of eCRS and non-eCRS diagnosed based on the cellular dominance of nasal polyp mucosa after endoscopic sinus surgery.[4]

The number of peripheral blood eosinophils and increased serum specific IgE concentrations are the lower cascade of type 2 inflammatory responses that can be elaborated as biomarkers to determine type 2 endotypes and predict eCRS phenotypes.[11] Spectral nature of the inflammatory response allows the number of peripheral eosinophils and peripheral IgE concentrations to also determine non-type 2 endotypes and predict non-eCRS phenotypes.[6,11] Previous studies related to the characterization of CRSwNP and CRSsNP phenotypes with therapeutic blood eosinophil counts and serum specific IgE concentrations have shown varying

results.[2,13] Research related to the characterization of biomarkers, such as peripheral blood eosinophils and serum specific IgE concentrations in eCRS and non-eCRS phenotypes is still limited.

This study aims to prove the relationship between the number of peripheral blood eosinophils and serum specific IgE concentrations with primary CRS phenotypes, namely eCRS and non-eCRS. The study may contribute to proving the homogeneity of re-classification of primary CRS phenotypes in EPOS 2020 and the use of peripheral blood eosinophil and specific IgE biomarker examinations in post -operative management of primary CRS.

METHOD

This research was observational study used a cross-sectional design. The study was conducted at Dr. Kariadi Central General Hospital (RSUP) Semarang, during April–May 2022. The sampling method in this study was *consecutive sampling* . The sample in this study were primary CRS patients at Dr. Kariadi Central General Hospital Semarang during January 2021 – March 2022 with inclusion criteria patient 18–60 years old and had complete CT scan that capable of detecting tissues within a solid organ[14,15], specific IgE, anatomical pathology, and nasoendoscopy data records at Dr. Kariadi Central General Hospital. Patients will be excluded if they experience odontogenic sinusitis, fungal rhinosinusitis, nasal tumors, and immunodeficiency. Final number of samples in this study was 76 patients.

Variables assessed in this study were the absolute peripheral blood eosinophil count, tissue eosinophil dominance, serum specific IgE levels, and primary CRS phenotype. The absolute peripheral blood eosinophil count was calculated based on the division of the leukocyte count by percentage of eosinophil differential count. Examination of the leukocyte count and differential count was performed using the Automated Hematology Analyzer XN-100 (Sysmex, Osaka, Japan). Tissue eosinophil dominance was determined based on semi-quantitative examination of anatomical pathology preparations of tissue samples in the *functional sinus endoscopic surgery (FESS)* procedure. Serum specific IgE examination was performed using *the Enzyme-Allergo-Sorbent test* EUROLINE *Atopy* Indonesia 1 method. (EUROIMMUN, Lübeck, Germany). Primary CRS phenotype assessment based on nasal endoscopy examination, CT scan imaging, and anatomical pathology results according to EPOS 2020. The data source for this research variable is secondary data obtained from medical records. primary CRS patients at Dr. Kariadi General Hospital, Semarang.

Statistical analysis between variable in this study used the chi square test and the strength of the relationship between variables was determined by the Phi coefficient test. If p value <0.05 is significant. *Ethical Clearance* has issued by Commission Ethics Study Health (KEPK) No. 1143/EC/KEPK-RSDK/2022 and permission from the Director of Dr. Kariadi General Hospital Semarang No. DP.02.01/I.II/4266/2022 .

RESULTS

Patient Characteristics

Total of 76 patient were included in this study. The age range of the study sample was between 18–60 years with an average of 33.91 ± 13.2 years. The absolute eosinophil range of the sample was 60.00 – 2400.00 / μL with an absolute eosinophil mean of 433.5 ± 364.2 /μL. The study sample was dominated by primary CRS patients with eCRS phenotype (Table 1).

Table 1. Sample Characteristics

	Amount	Percentage
Gender		
Man	28	35.9%
Woman	50	64.1%
Peripheral Blood Eosinophil Count		
Increase	46	59.0%
Normal	32	41.0%
Tissue Eosinophil Dominance		
Eosinophil	56	71.8%
Non-Eosinophil	22	28.2%
Serum Specific IgE Levels		
Positive	52	66.7%
Negative	26	33.3%
Phenotype of RSK		
eCRS	56	71.8%
Non-eCRS	22	28.2%

The majority of patient in this study experienced sensitization to more than one allergen (59.0%) and only 7.7% of the samples experienced monosensitization. The distribution of allergen sensitization (*sensitization rate) in this study was dominated by the house dust mite allergen group and* grass pollen. The sensitization rate of the house dust mite allergen group house dust is dominated by *Tyrophagus putrescentiae, Dermatophagoides*

microceras, and *Dermatophagoides farinae* **(Table 2).** The distribution of allergen polysensitization to the house dust mite allergen group is shown in **Figure 1.** *Sensitivity rate* of the grass pollen allergen group was dominated by grinting grass *Cynodon dactylon*), mixed grass (sweet vernal grass (*Anthoxanthum odoratum*), grinting grass, Timothy grass (*Phleum pratense*), and Timothy grass **(Table 2).**

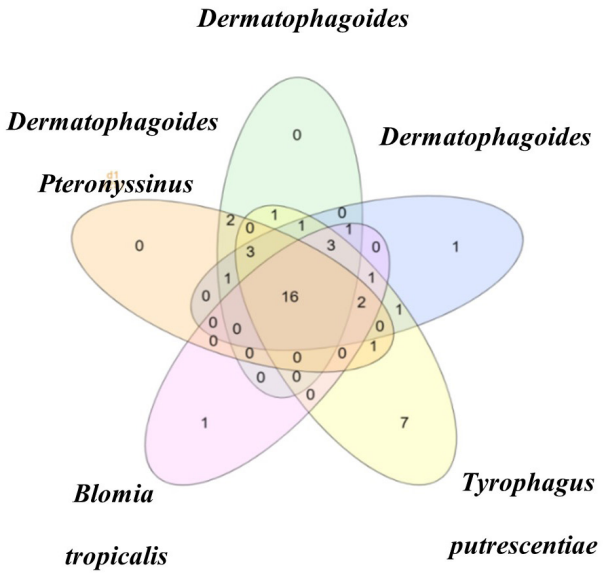

Figure 1. Venn Diagram of House Dust Mite Allergen Sensitization Distribution

Relationship between Peripheral Blood Eosinophil Count and Primary CRS Phenotype

eCRS sample group was dominated by patients with an absolute increase in eosinophils (53.6%), the non-eCRS patient group was dominated by patients with no increase in eosinophils (90.9%). This study showed that there was a relationship between the number of eosinophils and the primary CRS phenotype. The correlation coefficient of the relationship between the number of eosinophils and the primary CRS phenotype was +0.407 (strong positive). The results of the chi square test analysis and correlation coefficient are shown in Table 3.

Relationship of Tissue Eosinophil Dominance with Primary CRS Phenotype

The eCRS sample group showed eosinophil dominance, while the non-eCRS sample group showed non-eosinophil dominance. The results of this study indicate that there is a relationship between tissue eosinophil dominance and primary CRS phenotype. The correlation coefficient of the relationship between tissue eosinophil dominance and primary CRS phenotype is +1,000 (very strong positive). The results of the chi square test and correlation coefficient are shown in Table 3.

Relationship between Serum Specific IgE Levels and Primary CRS Phenotype

The eCRS sample group was dominated by patients with positive IgE results (76.8%) and non-eCRS was dominated by patients with negative IgE results (59.1%). This study showed that there was a relationship between specific IgE and the primary CRS phenotype. The correlation coefficient of the relationship between specific IgE and the CRS phenotype was +0.342 (moderately positive). The results of the *chi square test* and correlation coefficient are shown in table 3.

DISCUSSION

Patient in this study was dominated by eCRS patients. A study by Fujieda showed that there was a shift in the distribution between the proportion of primary CRS patients with eCRS and non-eCRS phenotypes.[16] The shift in the distribution of eCRS phenotypes that would increase as *the cut-off for* eosinophil counts decreased was observed in large fields of view. This was also observed in several studies in various parts of the world.[17]

Distribution of allergen sensitization in this study is different from several previous studies in Indonesia (Bandung and Jakarta).[18,19] Differences in the distribution of allergen sensitization in one country region can be observed in China and South Korea.[18,19] The differences in the distribution of allergen sensitivity can be caused by several factors, such as urbanization, climate crisis, and cross-reactivity.[20,21] Areas with different urbanization impacts have different distributions of sensitivity to certain allergens.[20] The World Bank shows that the rate of urbanization in Semarang is lower than Bandung and Jakarta.[22] The distribution of allergen sensitization in rural areas will also be dominated by grass pollen, where this characteristic was also found in this study.[22] The impacts of the climate crisis, such as changes in average temperature and humidity, can also affect the growth and survival of dust mites. home.[22,23] A study by Faradiba shows that changes in average temperature and humidity due to the climate crisis have the same impact in Bandung and Jakarta, but differently in Semarang.[24]

Table 2. Distribution of Allergen Sensitization

Allergen Groups	Total (%)*	Class 1 (%)	Class 2 (%)	Class 3 (%)	Grade 4 (%)	Grade 5 (%)	Grade 6 (%)
Inhalants							
House Dust Mites							
Tyrophagus putrescentiae (d72)	36 (69.2)	15 (28.8)	17 (32.7)	4 (7.7)	1 (1.9)	0	0
Dermatophagoides microceras (d4)	30 (57.7)	10 (19.2)	12 (23.1)	3 (5.8)	3 (5.8)	3 (5.8)	0
Dermatophagoides farinae (d2)	28 (53.8)	13 (25.0)	9 (17.3)	2 (3.8)	1 (1.9)	4 (7.7)	0
Dermatophagoides pteronyssinus (d1)	25 (48.1)	10 (19.2)	11 (21.2)	0	2 (3.8)	2 (3.8)	0
Blomia tropicalis (d201)	24 (46.2)	11 (21.2)	9 (17.3)	1 (1.9)	1 (1.9)	1 (1.9)	1 (1.9)
Grass Pollen							
Grinting Grass (g2)	20 (38.5)	5 (9.6)	10 (19.2)	3 (5.8)	1 (1.9)	1 (1.9)	0
Grass Mix 5 (gs1)†	19 (36.5)	8 (15.1)	6 (11.5)	3 (5.8)	1 (1.9)	1 (1.9)	0
Timothy Grass (g6)	15 (28.8)	8 (15.4)	5 (9.6)	2 (3.8)	0	0	0
Tree Pollen							
Acacia (t19)	10 (19.2)	8 (15.4)	2 (3.8)	0	0	0	0
Palm oil (t223)	10 (19.2)	7 (13.5)	2 (3.8)	1 (1.9)	0	0	0
Animal Epithelium							
Cat (e1)	9 (17.3)	8 (15.4)	0	0	1 (1.9)	0	0
Dog (e2)	1 (1.9)	1 (1.9)	0	0	0	0	0
Horse (e3)	1 (1.9)	1 (1.9)	0	0	0	0	0
Insect							
German Cockroach (i6)	9 (17.3)	7 (13.5)	2 (3.8)	0	0	0	0
Mushrooms							
Candida albicans (m5)	7 (13.5)	4 (7.7)	2 (3.8)	1 (1.9)	0	0	0
Mushroom Mix (ms1)††	6 (11.5)	3 (5.8)	3 (5.8)	0	0	0	0
Sting (Injection)							
Insect							
Honey Bee Venom (i1)	23 (44.2)	12 (23.1)	8 (15.4)	1 (1.9)	2 (3.8)	0	0

Allergen Groups	Total (%)*	Class 1 (%)	Class 2 (%)	Class 3 (%)	Grade 4 (%)	Grade 5 (%)	Grade 6 (%)
Occupational							
Latex (u85)	9 (17.3)	4 (7.7)	3 (5.8)	2 (3.8)	0	0	0
Give up (u134)	3 (5.8)	3 (5.8)	0	0	0	0	0
Ingestion							
Crab (f23)	21 (40.4)	7 (13.5)	9 (17.3)	2 (3.8)	3 (5.8)	0	0
Mixed Shellfish (fs10)†††	20 (38.5)	8 (15.4)	8 (15.4)	1 (1.9)	2 (3.8)	1 (1.9)	0
Wheat Flour (f4)	13 (25.0)	8 (15.4)	4 (7.7)	1 (1.9)	0	0	0
Almonds *(* f20)	12 (23.1)	5 (9.6)	4 (7.7)	3 (5.8)	0	0	0
Garlic (f47)	10 (19.2)	6 (11.5)	2 (3.8)	1 (1.9)	1 (1.9)	0	0
Tomato (f25)	6 (11.3)	3 (5.8)	3 (5.8)	0	0	0	0
Strawberry (f44)	6 (11.5)	2 (3.8)	3 (5.8)	1 (1.9)	0	0	0
Peanuts (f13)	5 (9.6)	4 (7.7)	1 (1.9)	0	0	0	0
Hazelnut (*f17*)	5 (9.6)	5 (9.6)	0	0	0	0	0
Shrimp (f24)	5 (9.6)	2 (3.8)	1 (1.9)	0	2 (3.8)	0	0
Lobster (f80)	5 (9.6)	2 (3.8)	1 (1.9)	0	2 (3.8)	0	0
Kiwi (f84)	3 (5.8)	3 (5.8)	0	0	0	0	0
Chocolate (f105)	1 (1.9)	1 (1.9)	0	0	0	0	0
Soybeans (f14)	1 (1.9)	1 (1.9)	0	0	0	0	0
Duck Meat (f157)	1 (1.9)	0	1 (1.9)	0	0	0	0
Cod Fish (f3)	1 (1.9)	1 (1.9)	0	0	0	0	0
Salmon Fish (f41)	1 (1.9)	1 (1.9)	0	0	0	0	0
Yeast (f45)	1 (1.9)	1 (1.9)	0	0	0	0	0
Coffee (f74)	1 (1.9)	1 (1.9)	0	0	0	0	0
Gluten (f79)	1 (1.9)	1 (1.9)	0	0	0	0	0
Lamb Meat (f88)	1 (1.9)	1 (1.9)	0	0	0	0	0

* Sensitization Rate

† Sweet vernal grass, grinting grass, Timothy grass, and rye

†† Penicillium notatum, Cladosporium herbarium, Aspergillus fumigatus, Alternaria alternata

††† Spiny lobster, oysters, mussels

Table 3. Relationship between Peripheral Blood Eosinophil Count and Serum Specific IgE Levels with Primary CRS Phenotype

Variables	Primary RSK Phenotype		Correlation Coefficient	p-value
	eCRS	Non-eCRS		
Eosinophil Count				
Increase	30 (53.6%)	2 (9.1%)	+0.407	0.000*
Not Increasing	26 (46.4%)	20 (90.9%)		
Network Domination				
Eosinophil	56 (100.0%)	0 (0.0%)	+1,000	0.000*
Non-Eosinophil	0 (0.0%)	22 (100.0%)		
Specific IgE				
Positive	43 (76.8%)	9 (40.9%)	+0.342	0.002*
Negative	39 (23.2%)	13 (59.1%)		

chi square test

Presence of a polysensitization pattern to several species house dust mites in the study explained the differences in the distribution of sensitization in this study (see Table 2 and Figure 1). Liao et al. showed that polysensitization to dust mite allergens home is cross-reactivity, not co-sensitization.[25] Yu et al. showed that sensitization to *Tyrophagus putrescentiae* can cause cross-reactivity to proteins of other species. mite dust House others, such as *Dermatophagoides Pteronyssinus* and *Dermatophagoides Farinae*.[26] Cross-reactivity can also occur in structurally related proteins, such as *Blomia tropicalis*.[27]

Relationship between the number of peripheral blood eosinophils and the primary CRS phenotype in this study is in line with previous studies. The dominance of eosinophils in nasal polyp tissue is a lower cascade of type 2 inflammatory response. The dominance of eosinophils in nasal polyp tissue is associated with an increase in the number of peripheral blood eosinophils. Wu et al. showed that the percentage of peripheral blood eosinophils is related to the percentage of tissue eosinophils ($r_\rho = 0.56, p < 0.001$) with a positive slope.[28] This result show that in some cases where the percentage of peripheral blood eosinophils is normal, the percentage of tissue eosinophils increases (tissue eosinophil dominance). Similar conditions can also explain the occurrence of peripheral eosinophilia in non-eCRS phenotypes. Cellular pathophysiological mechanism that allows this process is the spectral inflammatory response.[11] Spectral nature of the inflammatory response can be explained through cross-regulation of the cellular mechanisms of inflammatory response (Figure 2).[2,6] Cross-regulation can be observed at *benchmark level* of each inflammatory response. Cross-regulation may also occur at the upper or lower cascades of each inflammatory response.[29,30] The implication of cross-regulation is that dominant response cells can exist alone or in conjunction with other inflammatory responses.[2] This mechanism allows for a variety of inflammatory responses that can be experienced by primary CRS patients.[6,9]

Relationship between serum specific IgE levels is also in line with previous studies. Tissue specific IgE production is a downstream cascade of type 2 inflammatory responses. Specific IgE production in nasal polyp tissue is associated with serum specific IgE concentrations. Han et al. showed that serum total IgE concentrations were associated with tissue total IgE concentrations ($r_p = 0.39, p < 0.001$), with a positive slope.[31] This suggests that relatively low serum total IgE levels may reflect increased tissue total IgE concentrations. Han et al. showed that the distribution of serum total IgE concentrations was skewed to the right.[32] This was also found in this study, where the majority of positive specific IgE results were distributed in classes I and II (Table 2). The spectral nature of the inflammatory response may explain the presence of specific IgE production findings is not limited to eCRS phenotype, but also non-eCRS.[11] The cross-regulatory mechanism that can explain this condition is the dominance of Th17 which can then activate Th2 through various mechanisms, such as Th17 plasticity.[30] The results of allergen sensitization in primary CRS patients are not limited to inhalant allergens. but also other groups of allergens such as food, and contribute to primary SSR management but not in pathophysiological mechanisms.[32,33]

Limitation of this study is that upstream cascade biomarker examination *of* inflammatory response and T *helper cell dominance was not performed* to obtain a complete picture of the endotype. Allergen protein examination is also needed to determine allergen sensitization in polysensitization cases.

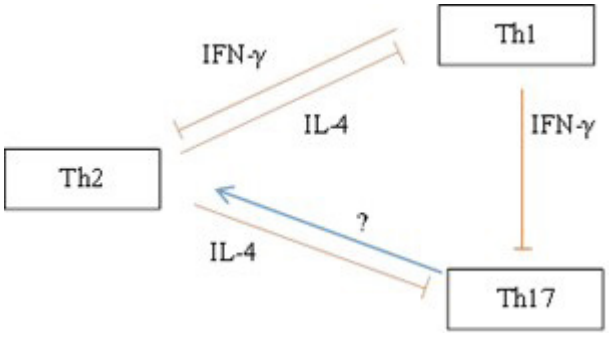

Figure 2 Spectrum of Cross-Regulation of the Inflammatory Response

CONCLUSION

Number of peripheral blood eosinophils and serum specific IgE levels are associated with the phenotype of primary CRS.

SUGGESTION

Cascade biomarker examination of inflammatory response, *helper T cells*, and allergen protein structure. The use of primary CRS phenotypes, eCRS and non-eCRS, in further studies to identify the relationship between biomarkers and phenotypes will obtain homogeneous results between previous studies.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies.

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