

# The Comparison of Inflammation Response in Chronic Rhinosinusitis Patients with Nasal Polyp and Without Nasal Polyp: A Study on Interleukin 33 and Eosinophil Contents

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## ABSTRACT

**Background:** The research aimed to perceive the comparison of inflammation response (IL-33 and eosinophil contents) in chronic rhinosinusitis with nasal polyp and without nasal polyp, and the pathomechanism of nasal polyp incident on chronic rhinosinusitis.

**Method:** This was the cross sectional research with 40 patients. Each sample underwent IL-33 serum content examination, and nasal mucosa swab.

**Results:** The research result indicates that IL-33 serum contents were significantly higher ( $p < 0.05$ ) in patients with Chronic Rhinosinusitis without Nasal polyp than with Nasal polyps, While the number of eosinophils content in chronic rhinosinusitis with nasal polyps was significantly higher ( $p < 0.05$ ) than without nasal polyps

**Conclusion:** IL-33 has higher content on chronic rhinosinusitis without nasal polyp, IL-33 increases eosinophil content in chronic rhinosinusitis without nasal polyp, and the eosinophil has higher content on chronic rhinosinusitis with nasal polyp.

**Keywords:** *Chronic Rhinosinusitis, Nasal polyp, Interleukin 33, Eosinophil*

## INTRODUCTION

Rhinosinusitis is a disease commonly found in everyday practice. In the United States according to the National Ambulatory Medical Care Survey in 2001 12.3 million health care visits were attributed to chronic rhinosinusitis (SSR) or 1.3% of total visits per year. Chronic rhinosinusitis is a problem for general practitioners and ear, nose, throat (ENT) experts given the complex etiology and high prevalence. In Europe, rhinosinusitis is thought to account for 10% to 30% of the population. In the United States in 1996, total health spending directly related to rhinosinusitis was estimated at 5.6 billion dollars. Of that figure, 58.7% (about 3.5 billion dollars) is related to SSR. It is estimated that 13.4-25 million doctor visits per year are associated with rhinosinusitis and / or its consequences. As many as 14% of the American population had at least one episode of rhinosinusitis during their lifetime and about

15% were estimated to have SSR. New rhinosinusitis incident in adult patients who came to the Rhinology Subdivision of ENT Department Cipto Mangunkusumo hospital January-August 2005 from 435 patients, 69 % (300 sufferers) suffered from rhinosinusitis, in Makassar from three teaching hospitals for the period 2003-2007 were reported as many as 41.5% of all cases handled by Rhinology Subdivision.<sup>1,2,3,4</sup>

Chronic rhinosinusitis can be divided into two subtypes: chronic rhinosinusitis without nasal polyps and rhinosinusitis with nasal polyps. Both groups of rhinosinusitis differ in terms of inflammatory profiles and their remodeling processes, differences in these may affect prognosis, comorbid asthma, appropriate surgical procedures, , and pharmacological management.<sup>5</sup>

Further research on T-helper (Th) cells has found that there is a role of Th cells in the pathogenesis of chronic rhinosinusitis with nasal polyps. Th cells

themselves are divided into Th1 and Th2 based on the resulting cytokines. Th1 cells produce interferon (IFN)  $\gamma$ . IFN- $\gamma$  and Th1 cytokines increase defense against primary intracellular microbes, by activating neutrophils and macrophages. While Th2 cells are associated with eosinophil inflammation, and Th2 cells produce IL-4, IL-4, IL-33, and IL-13.<sup>6</sup>

Chronic rhinosinusitis with nasal polyps often accompanied by eosinophilic inflammatory Th2 cells, whereas chronic rhinosinusitis without nasal polyps is characterized by most Th1 cell response.<sup>7</sup> IL-33 is more abundant in chronic rhinosinusitis mucosal tissue with nasal polyp than without nasal polyps. Chronic polynomial rhinosinusitis is subdivided into two types of disease based on the level of eosinophilic inflammation, especially for people in East Asia: eosinophilic chronic rhinosinusitis (ECRS) and non-eosinophilic chronic rhinosinusitis (NECRS).<sup>8</sup>

This study aims to see the inflammatory responses (IL-33 content) in chronic rhinosinusitis with nasal polyps and without nasal polyps and the pathomechanism of nasal polyps in chronic rhinosinusitis.

**METHOD**

*Research Site:*

This study was conducted in outpatient clinic of Dr. Wahidin Sudirohusodo Hospital, and other hospitals in Makassar, Molecular Biology Laboratory of education hospital Unhas, and Pathology Anatomy Laboratory of Education Hospital Unhas for period of January – March 2018

*Design and Research Variables:*

The design of this study is cross sectional with analytic observasional. The independent group of this study was patient with chronic rhinosinusitis without nasal polyp and with nasal polyp, while the dependent variable was the inflammatory response (IL-33 content).

*Samples*

The sampling technique was performed randomly. In this study all patients who have been diagnosed as chronic rhinosinusitis based on the history, the ENT diagnostic examination were undergone CT scan of paranasal sinus coronal view. The sample size is 40 patients were divided into 2 groups. Patients in the first

group (20 patients) categorized as chronic rhinosinusitis with nasal polyps, and the second groups categorized as chronic rhinosinusitis without nasal polyps. Patients from both groups were examined for IL-33 serum content.

*Exclusion Criteria:*

Patients with severe systemic disease (kidney disease, liver disease, malignancy, autoimmune disease, and heart disease), sinonasal tumors, patients with a history of Endoscopic sinus surgery, severe septal deviation, septal perforation, rhinitis atrophy, serum sample lysis.

**Statistical Analysis:**

Data were analyzed using Statistical Package for Social Sciences (SPSS) software (version 23.0 for Windows; SPSS Inc, Chicago, IL).

*Research Ethics Aspect:*

The study permit was obtained from Biomedical Research Ethics Committee on Human Faculty of Medicine Universitas Hasanuddin (Register No. 31 / H4.8.4.5.31 / PP36-KOMETIK/2018).

**RESULTS**

**Characteristics** From a sample of 40 people, aged 21 to 40 years, with a mean age of 30.40 for chronic rhinosinusitis with nasal polyps and 31.70 for chronic rhinosinusitis without nasal polyps, and consisted of 15 men and 25 women.

**Table 1. Characteristics of Research Subjects in Each Group**

Characteristics	Groups		P
	With Nasal polyps (n=20)	Without Nasal polyps (n=20)	
Age (Mean)	30,40	31,70	0,435*
Gender (M/F)			0,774**
Male	7	8	
Female	13	12	

**Content of IL-33 Serum**

Table 2 shows that serum content of IL-33 and IL-4 patients with chronic rhinosinusitis are higher than

controls; respectively for IL-33 serum (Median 788.50 vs. 154.71). The results of the Mann-Whitney test showed significant difference ( $p < 0.05$ ) between the two groups.

**Table 2. Comparison of serum IL-33 content between Chronic Rhinosinusitis and Control group**

Variable	Chronic Rhinosinusitis		P
	Yes (n=40)	No (n=10)	
Level of IL-33 serum; Mean±SD(Median)	668,16±382,51 (788,50)	151,85±9,71 (154,71)	<0,001*

### Level of IL-33 Serum and Eosinophil Count

Table 3 shows that serum IL-33 content were significantly higher ( $p < 0.05$ ) in patients with Chronic Rhinosinusitis without Nasal polyp than with Nasal polyps (median 859.65 vs 214.77). While the number of eosinophils counts in nasal polyps was significantly higher ( $p < 0.05$ ) than without Nasal polyps (median = 3.0 vs 2.0).

**Table 3. Comparison of IL-33, and eosinophil counts of Chronic Rhinosinusitis with Nasal polyps and Without Nasal polyps**

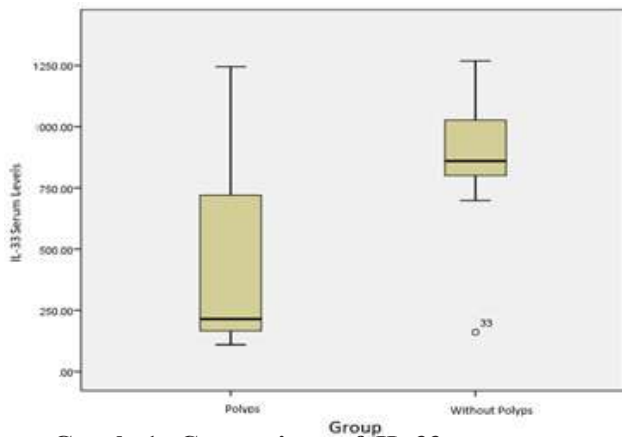
Variable	Chronic Rhinosinusitis		P
	Nasal polyp (n=20)	Without Polyp (n=20)	
Level of IL-33 serum; Mean±SD(Median)	443,33±370,96 (214,77)	892,99±237,27 (859,65)	<0,001*
Eosinophil Count	1 – 4 (3,0)	1 – 4 (2,0)	0,001*

### Content of Eosinophil Counts

Table 4 shows that the distribution of eosinophil counts in the Chronic Rhinosinusitis with Nasal polyp group is more categorized as ++++ and +++ (40.0% and 30.0%) than those categorized as ++ and + (20.0% and 10.0%); whereas in the Chronic Rhinosinusitis without nasal polyp group is more categorized + and ++ (50.0% and 30.0%) than +++ and ++++ (15.0% and 5.0%); Chi-square test results showed significant differences ( $p < 0.05$ ).

**Table 4. Distribution of the category of eosinophil counts of Chronic Rhinosinusitis with Nasal polyps and without Nasal polyps groups**

Group	Eosinophil Count				P*
	+	++	+++	++++	
Nasal polyp (n=20)	2(10,0%)	4(20,0%)	6(30,0%)	8(40,0%)	0,007
Without Nasal polyp(n=20)	10(50,0%)	6(30,0%)	3(15,0%)	1(5,0%)	



**Graph 1. Comparison of IL-33 serum content between group of Nasal polyp and without Nasal polyp Box Plot**

Graph 1 shows that mean content of IL-33 serum of group with chronic rhinosinusitis with nasal polyps are much lower than serum content of IL-33 serum of group with chronic rhinosinusitis without nasal polyps.

**Tabel 5. Correlation between IL-33 content against eosinophils in chronic rhinosinusitis patients with nasal polyps**

Variable	Eosinophil Content		
	n	r	p
IL-33 level	20	0,302	0,097

From table 5 shown that serum IL-33 content were positively correlated with eosinophil content. Although higher IL-33 content followed with higher eosinophil count but not significant correlation in the statistical. ( $p > 0,05$ )

**Tabel 6. Correlation between IL-33 content against eosinophils in chronic rhinosinusitis patients without nasal polyps**

Variable	Eosinophil Counts		
	n	r	p
IL-33 level	20	0,427	0,030

From table 6 shown that serum IL-33 content was positively correlated with eosinophil content ( $r = 0.427$ ;  $p = 0,030$ ), meaning higher serum IL-33 content, the higher the eosinophil counts.

**DISCUSSION**

In this study, samples were obtained between the

ages of 20 and 40 years, with a mean of 30.40 years in chronic rhinosinusitis with nasal polyps, and 31.70 years in chronic rhinosinusitis without nasal polyps. This is in accordance with the research of Chen Y, et al., 2003 where the prevalence of chronic rhinosinusitis increases at age 20-29 years and 50-59 years.

The number of chronic rhinosinusitis patients with nasal polyps and without nasal polyps consisted of 15 men and 25 women. The distribution of sex and age in both groups of chronic rhinosinusitis patients may be considered homogeneous ( $p > 0.05$ ).

Based on the data in table 2 it was shown that the serum content of IL-33 serum with chronic rhinosinusitis were higher than controls; respectively for serum IL-33 (Median 788.50 vs. 154.71), and the result is significant ( $p < 0.05$ ). This is consistent with Ozturan et al., 2015 which found that serum IL-33 content in chronic rhinosinusitis with nasal polyps were higher than those in the control group. the influence of IL-33 on upper respiratory epithelium has an important role in chronic inflammation associated with chronic rhinosinusitis with nasal polyps by increasing the cytokine of Th2, which also mediates the occurrence of eosinophil infiltration.<sup>9,10</sup>

Table 3 and graph 1 showed that serum IL-33 content were significantly higher ( $p < 0.05$ ) in patients with chronic rhinosinusitis without nasal polyps than with nasal polyps (median 859.65 vs 214.77). This is according to research by Smithgall MD, et al., 2008, that IL-33 if synergize with IL-12 can induce NK cells and cell iNKT which resulted in the release of inflammatory mediators IFN- $\gamma$  which can release the release of neutrophils and cause inflammatory responses in chronic rhinosinusitis without nasal polyp.<sup>11</sup>

Based on table 3 data, it shows that the number of eosinophils in nasal polyps was significantly higher ( $p < 0.05$ ) than without nasal polyps (median = 3.0 vs 2.0). In table 4 and graph 3 data also shows that the distribution of eosinophil counts in the nasal polyp group is more categorized as +4 and +3 (40.0% and 30.0%) than those categorized as +2 and +1 (20.0% and 10.0%); whereas in the group without nasal polyps is more categorized as +1 and +2 (50.0% and 30.0%) than +3 and +4 (15.0% and 5.0%); Chi-square test results shown significant differences ( $p < 0.05$ ).

The increasing of eosinophil in chronic rhinosinusitis with nasal polyps is also significantly consistent with

Hulse KE, et al., 2015, which says that eosinophils are elevated in chronic rhinosinusitis with nasal polyps. Eosinophils will produce eosinophil cationic proteins that can cause epithelial cell damage, as well as proinflammatory molecules that contribute to type 2 inflammation, which is associated with the occurrence of nasal polyps.<sup>12</sup>

Based on Table 5 and Table 6 can be seen in both groups of chronic rhinosinusitis with nasal polyps and chronic non-nasal polyps rhinosinusitis, it was found that serum IL-33 content were positively correlated with eosinophil content. The higher the content of IL-33, the higher the eosinophil level but which is significant only in chronic rhinosinusitis without nasal polyps.

### CONCLUSION

This study shown that IL-33 was higher content on chronic rhinosinusitis without nasal polyp, whereas IL-33 increases eosinophil content in chronic rhinosinusitis without nasal polyp, and the eosinophil was higher content on chronic rhinosinusitis with nasal polyp.

**Conflict of Interest :** There is no conflict of interest

**Source of Funding:** Researcher (Self)

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