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Original Article

# IL-1β Expression of Patients with Chronic Rhinosinusitis is negatively correlated with Lund-Mackay score

**Lidya Allo Datu Turupadang[1*], Muhammad Fadjar Perkasa[1], Abdul Qadar Punagi[1], Azmi Mir'ah Zakiah[1], Burhanuddin Bahar[2], Muhammad Husni Cangara[3]**

*[1]Department of Otorhinolaryngology - Head and Neck Surgery, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia*
*[2]Department of Nutrition, Faculty of Public Health, Hasanuddin University, Makassar, South Sulawesi, Indonesia*
*[3]Department of Anatomic Pathology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia*

**Corresponding Author:**
Name: Lidya Allo Datu Turupadang, MD
Email: lidya987@gmail.com

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**ABSTRACT**

**Introduction:** IL-1β is one of the proinflammatory cytokines which is commonly found in various diseases, including Chronic Rhinosinusitis (CRS). It has been widely targeted as a therapeutic approach for inflammatory diseases. However, study of IL-1β expression and its correlation with CT-Scan grading scores in CRS is still scarce. **Objective:** To investigate IL-1β expression based on immunohistochemical examination and analyse its correlation with Lund-Mackay score in CRS with and without polyps. **Method:** This analytic observational study was done on 50 patients: 25 subjects in the CRS with Nasal Polyps (CRSwNP) group and 25 subjects in the CRS without Nasal Polyps (CRSsNP) group. The uncinate process was taken for immunohistochemical examination of IL-1β. Lund-Mackay score was calculated based on CT-Scan of the paranasal sinus. **Result:** IL-1β expression in CRSsNP (mean=36.38) was significantly higher than that in the CRSwNP (mean=14.62) with p<0.001. Lund-Mackay score in CRSwNP was higher (mean=35.22) compared to CRSnNP group (mean=15.78) with p<0.001.

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There was a moderate negative correlation (-0.403) between IL-1β expression and Lund-Mackay score ($p<0.05$). **Conclusion:** There was a moderate negative correlation between IL-1β expression and Lund-Mackay score. The IL-1β and the Lund-Mackay score in CRSwNP were lower and higher, respectively, than in CRSsNP.



## 1. INTRODUCTION

Chronic rhinosinusitis (CRS) is often encountered in daily medical practice. The prevalence is quite varied, with an approximate incidence rate of 10.9% in Europe, 12% in America, 11% in South Korea, and 8% in China.[1] This disease deserves special attention as it is associated with multi-factorial etiology and significant interference in quality of life which leads to substantial costs. Chronic rhinosinusitis can be divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) which are distinguished from nasoendoscopy and CT-Scan. There are several criteria for the classification of rhinosinusitis based on CT scan images, one of them is “Lund-Mackay” scoring system. This system is more often used and recommended because it is uncomplicated and has a high sensitivity and specificity.[2]

Cytokines play a major role in the pathophysiology of CRS. IL-1β is one of the cytokines which is found in the inflammatory process of CRS and plays a role in proliferation, differentiation, and pyroptosis.[1, 3] During innate immunity, IL-1β activates T cells and monocytes, regulates the expression of number of cytokines and inflammatory proteins, thereby increasing transendothelial migration of eosinophils and recruitment of neutrophils, which results in clinical symptoms.[4]

IL-1β is initially produced as an inactive precursor, termed pro IL-1β, in response to pathogen associated molecular patterns (PAMPs). Pro IL-1β is a pathogen-carrying molecule, which binds to pattern recognition receptors (PRRs) on macrophages in the sinonasal mucosa. Induced cells then encounter further PAMPs and danger associated molecular patterns (DAMPs), which are endogenous molecules released by dead cells, to induce the secretion of the active molecule IL-1β.[5] Immunohistochemical examination can be utilized to visualize the distribution of IL-1β in the tissue by using an antigen-antibody reaction. Currently, IL-1β blockage is developed as a therapeutic target for local and systemic inflammatory conditions.[6] However, there are still few studies about IL-1β based on immunohistochemistry in CRS, especially those that assess its correlation with CT-Scan grading.

## 2. METHODS

This study was a cross sectional with observational analytic model. Participants were obtained from the ENT polyclinic of Hasanuddin University hospital, Makassar, South Sulawesi, Indonesia. Subjects who met the criteria were asked to sign an informed consent before they were enrolled in this study. This research has met the requirements

of the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University with the recommendation of ethical approval number 688/UN4.6.4.5.31/PP36/2020

Subjects whose complaints did not improve with adequate standard medical therapy were divided into two groups (CRSwNP and CRSsNP) and underwent Functional Endoscopic Sinus Surgery (FESS). Samples of the uncinate mucosa were fixated with 10% neutral buffer formalin and processed at the anatomical pathology laboratory, Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia. The immunohistochemical examination procedure was carried out using IL-1β Monoclonal Antibody (Bioenzy). The Lund-Mackay score was calculated based on cross coronal CT-Scan of the paranasal sinuses without contrast before the FESS procedure. The score range is 0-24 which was divided into two groups, score ≤12 and score >12.

Data were analyzed with SPSS version 23 (SPSS Inc. Chicago, IL, USA)**.** Mann-Whitney U-test with a significance level of <0.05 was used to examine the comparison of IL-1β expression and Lund-Mackay score between CRSwNP and CRSsNP groups. Spearman correlation test was conducted to see the correlation between IL-1β expression and Lund-Mackay score.

## 3. RESULTS

The total participants were 50 subjects which consisted of 25 CRSwNP patients and 25 CRSsNP patients. The majority of participants were women (31, 62%). The age group of 18-28 years was the most prevalent age group (20, 40%) followed by the 29-39 years age group (13, 26%) while 40-50 years was the least commonly found age group (7, 14%). All participants complained of rhinorrhea and 62% did not report any smelling disorder. Most samples had moderate symptoms of nasal obstruction (22, 44%), rhinorrhea (36, 72%), and facial pain (27, 54%) (Table 1).

**Table 1**. Distribution of age, gender, phenotype, and participant complaints

| Variable | n (Total = 50) | % |
|---|---|---|
| **Age (Years)** | | |
| 18-28 | 20 | 40 |
| 29-39 | 13 | 26 |
| 40-50 | 7 | 14 |
| >50 | 10 | 20 |
| **Sex** | | |
| Woman | 31 | 62 |
| **Phenotype** | | |
| CRS with polyps | 25 | 50 |
| CRS without polyps | 25 | 50 |

| | | |
|---|---|---|
| **Complaint** | | |
| *Nasal Obstruction* | | |
| None | 6 | 12 |
| Mild | 16 | 32 |
| Moderate | 22 | 44 |
| Severe | 6 | 12 |
| *Rhinorrhea* | | |
| None | 0 | 0 |
| Mild | 1 | 2 |
| Moderate | 36 | 72 |
| Severe | 13 | 26 |
| *Facial Pain* | | |
| None | 3 | 6 |
| Mild | 14 | 28 |
| Moderate | 27 | 54 |
| Severe | 6 | 12 |
| *Smelling Disorder* | | |
| None | 31 | 62 |
| Mild | 12 | 24 |
| Moderate | 5 | 10 |
| Severe | 2 | 4 |

**IL-1β expression in the CRSwNP and CRSsNP groups**

The range of IL-1β expression in CRS with polyps is 4%–136% and the range of IL-1β expression in CRS without polyps was 56% – 95.6%. Table 2 showed differences in the mean of IL-1β expression in CRSwNP (14.62) and CRSsNP (36.38). This result showed that the expression of IL-1β in CRSsNP was significantly higher than in CRSwNP ($p<0.05$). Figure 1 depicted that IL-1β expressed in the uncinate mucosa of CRSwNP was fewer than in CRSsNP patiens.

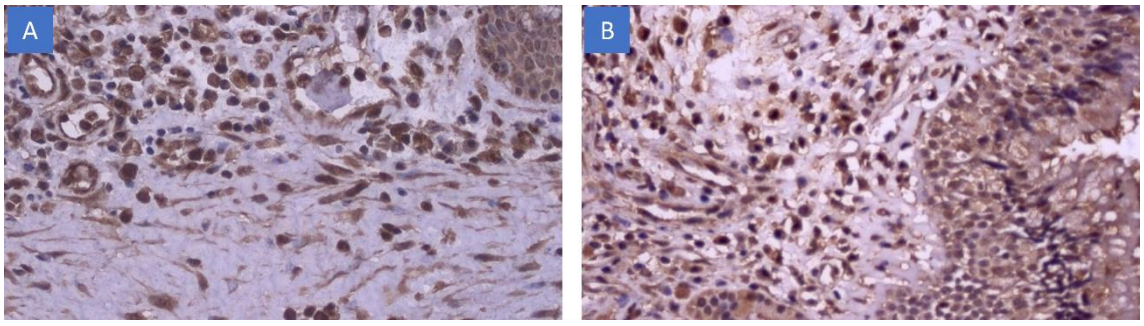


**Figure 1.** IL-1β expression shown by brown cells on immunohistochemical examination. IL-1β expressed in the uncinate mucosa of a). CRSwNP fewer than in b). CRSsNP patiens. The figure also shows that there are fewer inflammatory cells in CRSwNP than in CRSsNP

**Table 2.** Expressions IL-1β in CRS with and without polyps

| CRS phenotype | Min (%) | Max (%) | Mean | P-value |
|---|---|---|---|---|
| CRSwNP (n=25) | 4 | 136 | 14.62 | <0.001 |
| CRSsNP (n=25) | 56 | 95.6 | 36.38 | |

Analysis: Mann-Whitney U Test

### Lund-Mackay score in the CRSwNP and CRSsNP groups

Table 3 shows that more than half of the sample (29, 58%) had a Lund-Mackay score ≤ 12. However, there was a difference in Lund-Mackay score based on the CRS phenotype. Most of Lund-Mackay score in CRSwNP was >12 (72%) while in CRSsNP most of this score was ≤ 12 (88%). Table 4 shows the significant difference between the Lund-Mackay scores on CRSwNP and CRSsNP. The mean score of Lund-Mackay in CRSwNP (35.22) was higher with a score range of 5-24 compared to CRSsNP (15.78) with a score range of 2-21 ($p < 0.05$).

**Table 3.** Lund-Mackay score by CRS phenotype

| CRS Phenotype | Lund-Mackay score | | P-value |
|---|---|---|---|
| | ≤12 n (%) | >12 n (%) | |
| Total (n = 50) | 29 (58.0%) | 21 (42.0%) | |
| CRSwNP (n=25) | 7 (28.0%) | 18 (72.0%) | <0.001 |
| CRSsNP (n=25) | 22 (88.0%) | 3 (12.0%) | |

**Table 4.** Analysis of Lund-Mackay Score in CRS with and without polyps

| CRS phenotype | Min (%) | Max (%) | Mean | P-value |
|---|---|---|---|---|
| CRSwNP (n=25) | 5 | 24 | 35.22 | <0.001 |
| CRSsNP (n=25) | 2 | 21 | 15.78 | |

Analysis: Mann-Whitney U Test

### Analysis of the correlation between IL-1β expression and Lund-Mackay score in CRS with and without polyps

The results showed that there was a significant correlation between the expression of IL-1β with the Lund-Mackay score (p=0,004). Statistical analysis showed a negative correlation between the expression of IL-1β with the Lund-Mackay score with moderate correlation strength value (0.403). This means that the higher the IL-1β expression, the lower the Lund-Mackay score is (Table 5).

**Table 5.** Expression Correlation of IL-1β and Lund-Mackay Score

| | | LMK Score |
|---|---|---|
| **IL-1β** | Correlation Coefficient | –.403 |
| | Sig. (2-tailed) | .004 |
| | N | 50 |

Analysis: Spearman Correlation Test

## 4. DISCUSSIONS

This study showed that most cases of CRS occurred in the productive age group of 18-28 years and in women. The incidence of CRS was more likely to occur in the young productive age group because they are more often exposed to environmental factors such as air pollution and cigarette smoke compared to other age groups. These environmental factors can damage the respiratory tract mucosa which ultimately interferes with the mucociliary clearance system. This is in accordance with a previous study conducted by Triola, S (2019) in Padang which received the most samples under 40 years old at 71.43%. A different finding was seen in another study which reported that the highest incidence of CRS occurred in subjects above 40 years old (48.89%).[7, 8] One theory postulates that estrogen affects with the state of the nasal mucosa. During hormonal instability, the vascularization of the nasal mucosa may be disrupted and results in cell damage, impaired oxygenation and impaired function of the nasal mucosa.(7) Another theory states that there are differences in response to medical therapy, where the anti-inflammatory effect of steroid drugs may be more effective in men.[9] The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 suggests that microbial factors, environmental factors, and host factors such as allergies, immunodeficiency, anatomical abnormalities, mucociliary dysfunction, odontogens, and

trauma have important roles in the incidence of CRS. This could explain the differences in the characteristics of age and sex in different regions.[1]

**Lund-Mackay Score, IL-1β Expression, and Their Correlation in Chronic Rhinosinusitis**

In this study, the Lund-Mackay score on the majority of subjects was ≤ 12. This finding was consistent with a study by Min et al with an average score of 6.83 and in contrast to Younis, et al (2016), where the average score obtained was 14.01. However, unlike in this study, both studies did not differentiate scores based on the CRS phenotype.[8, 10] In CRSwNP, more score was >12 with a score range of 5-24 while in CRSsNP more score was ≤12 (88%) with a score range of 2-21. These results were in line with Savastano, et al (2014) who found the average score of CRSwNP was 18. Another study found that the average score of CRSsNP was 8 with a score range of 5-12.[11, 12] The Lund-Mackay Score System was created to see the degree of inflammation of the paranasal sinuses and the presence of obstruction from ostiomeatal complex.

The expression of IL-1β by all samples confirmed that IL-1β is a major proinflammatory cytokine in CRS. Infected nasal mucosa showed increased IL-1β expression and was associated with an increase in mucus production.[13] The results of this study also showed a significant difference between IL-1β expression in CRSwNP and CRSsNP where the IL-1β expression in CRSsNP was higher compared to CRSwNP. This finding was different from Plewka, et al. who found that IL-1β was more common in CRSwNP. They also found that IL-1β was expressed in various layers of the nasal mucosa of CRS patients, most of which were in the stroma. The study found that the greatest difference in IL-1β expression between CRSwNP polyps and CRSsNP was found in the endothelium.[14] Meanwhile, in this study, IL-1β expression was examined in the stroma.

The differences of IL-1β expression could be due to the effect of oral steroid medication. Our sample who suffered from CRSwNP had received high-dose oral and intranasal corticosteroid, while the CRSsNP did not receive high-dose oral corticosteroid therapy. Previous study has stated that CRSwNP treated with steroids showed a decrease in NLR. This protein is known to form an inflamosome that produces IL-1β through the caspase-1 pathway.[15] Saber A, et al also found that the expression of NLRP3, which plays a role in the production of IL-1β, was higher in CRSwNP. However, after administration of steroids there was a decrease in NLRP3 expression. A similar finding was also obtained in another study that showed a decreased IL-1β expression following steroid administration for three months.[16, 17] Langereis, et al conducted a study on the effects of steroids on the secretion of IL-1Ra and IL-1β and found that steroids work by suppressing the secretion of TNF-α which plays a role in pro IL-1β production which leads to a reduction in IL-1β excretion.[18]

Based on EPOS 2020, the latest classification of CRS does not solely depend on polyp phenotypes and is instead classified into primary and secondary, which are further grouped based on anatomy and dominant endotype.[1] Cytokines are not only the key regulator of cellular interactions but also as biomarkers of different endotypes.[15] Thus,

the expression of IL-1β based on the presence or absence of polyps is still not adequate to explain the pathogenesis of inflammation in CRS. In addition, proinflammatory cytokines that are involved in the incidence of CRS are not only IL-1β but also other cytokines that play a role in both innate and adaptive immunity.[1] This might explain the results of this study where there was negative correlation with moderate strength between IL-1β expression and Lund-Mackay score on CRS. Research conducted by Min, et al (2015) found that there was no correlation between IL-1β and the Lund-Mackay score. However, the IL-1β identification method, which used ELISA from nasal rinse specimen, was different from the current study.[8] The presence of IL-1β expression in this study outlined the involvement of this interleukin in the pathophysiology of CRS, rendering IL-1β to be a potential therapeutic target in CRS.

## 5. CONCLUSION

IL-1β was expressed in all CRS patients and was lower in CRSwNP than in CRSsNP and the Lund-Mackay score was higher in CRSwNP than in CRSsNP. There was a negative correlation with moderate strength between IL-1β expression and Lund-Mackay score which was thought to be caused by steroid medication.

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**Conflict of Interest Statement:**

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.