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# Comparison of Heat Shock Protein (HSP)-70 and Interleukin-6 Levels Pre and Post Operation in Chronic Rhinosinusitis Patients

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**KEYWORDS**

Heat Shock Protein-70, Interleukin-6, Chronic Rhinosinusitisstatistik

**ABSTRACT:**

Introduction: Chronic rhinosinusitis (CRS) is a long-term disorder marked by inflammation of the nose and paranasal sinus mucosa. HSP-70 can have a variety of immunological consequences on CRS, including the secretion of proinflammatory cytokines such as IL-6. HSP-70 and IL-6 may have an impact on the outcome of surgery.

Objective: To determine the comparison of HSP-70 and IL-6 levels before and after surgery in patients with chronic rhinosinusitis.

Methods: This is an observational analytical study with a prospective study design that will take place from May to October 2023. Patients with chronic rhinosinusitis who had functional endoscopic sinus surgery (FESS) and met the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 were included in this study. HSP-70 and IL-6 levels were measured in all individuals before and after FESS. SPSS 26.0 was used to analyze the data.

Results: 18 people were included in this study. 13 people (72.2%) were men and 5 people (27.8%) were women. 6 people (33.3%) were <= 35 years old, while the rest were > 35 years old. The mean IL-6 was found to be higher post-operatively (7.36±14.87) compared to pre-operatively (2.92±8.57) and The distinction was crucial (p=0.048). The mean HSP-70 was higher preoperatively (2.79±1.93) than postoperatively (2.06±2.60), However, the difference was insignificant (p=0.184).

Conclusion: HSP-70 levels in patients with CRS pre-operatively were higher than post-operatively. IL-6 levels in patients with CRS preoperatively were lower than postoperatively.

## 1. Introduction

Chronic rhinosinusitis (CRS) is an inflammation of the nasal mucosa and paranasal sinuses that lasts more than three months.[1] A study at Cipto Mangunkusumo Hospital from January to August 2005 found that 69% of 435 patients had CRS, while research at three Makassar hospitals found that 41.5% of all cases handled in the rhinology sub-division had CRS.[2,3] There are studies showing that heat shock proteins (HSP) are emitted due to apoptotic and necrotic cells, which ultimately enhance innate and adaptive immune responses through interactions with pattern recognition receptors.[4-6]

Autoantibodies against HSP70 have previously been linked to asthma severity and higher levels of immunoglobulin E (IgE) and interleukin (IL) -4.[6,7] HSP-70 may have a variety of immunological impacts on CRS. When antigen-presenting cells come into contact with exogenous HSP-70, they release a number of proinflammatory cytokines, including tumor necrosis factor a, IL-1b, 5 IL-6, and IL-12. Other study suggests that HSP70 may perform an anti-inflammatory function in some inflammatory disorders, a phenomenon known as the "heat shock paradox".[8] The most prevalent proinflammatory mediator discovered in the nose is IL-6, which is released in response to inflammatory sensitization caused by IL-1, TNF-alpha, bacterial products, and viral infections and is important in activating hematopoiesis and neuronal development. In the mucosa, T and B lymphocyte activation and proliferation, immunoglobulin secretion, basement

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membrane thickening, subepithelial fibrosis, and osteogenesis cell maturation are seen.[9,10] Several studies have revealed a link between HSP-70 and IL-6 with the severity of chronic rhinosinusitis as well as the outcome of surgery.[11] Therefore, knowing more about the relationship between HSP-70 and IL-6 may be able to understand the severity and prevention of chronic rhinosinusitis.

## 2. Methods

### Participants and Study Design

This study was conducted at RSUP Dr. Wahidin Sudirohusodo Makassar as an observational analytical study with a prospective study design. This study will run from May to October 2023. This study included patients aged 17-60 years with chronic rhinosinusitis who underwent functional endoscopic sinus surgery (FESS) and met the criteria of the European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Patients with a history of previous FESS, a history of serious systemic disease (kidney, liver, malignant, autoimmune, and heart disease), atrophic rhinitis, severe septal deviation, septal perforation, and synechiae, and pregnant are excluded from this study

### Research Ethics

This study was conducted after receiving ethical approval from the Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University, with the following number: 454/UN.6.4.5.31/PP36/2023. Every action in this study is carried out after obtaining written approval (informed consent) from the patient or family.

### Research Flow

Patients with chronic rhinosinusitis who undergo FESS first provide informed permission. After that, rinse your nose before and after FESS to check HSP-70 and IL-6 levels, and then compare before and after surgery.

### Statistic analysis

The data in this study was analyzed using the IBM SPSS Statistics v.26.0 computer software. The respondents' characteristics were assessed. Age is represented by mean and standard deviation, as well as frequency and percentage. Before and after surgery, HSP-70 and IL-6 levels were examined. FESS was evaluated using the Wilcoxon signed rank test. P-values less than 0.05 are considered significant.

## 3. Results

This study included 20 people who had chronic rhinosinusitis. However, two research participants were removed due to excessively high postoperative IL-6 levels. As a result, the study only comprised 18 research subjects. The following table shows the gender and age distribution of research subjects:

**Table 1.** Distribution of Research Subject Characteristics

| Characteristics | n (18) | % |
|---|---|---|
| Gender | | |
| Women | 5 | 27,8 |
| Men | 13 | 72,2 |
| Age (Mean±SD) | 43,6±14,1 | |
| <= 35 years | 6 | 33,3 |
| 36 - 45 years | 3 | 16,7 |
| 46 - 55 years | 4 | 22,2 |
| > 55 years | 5 | 27,8 |

This study's participants were mostly male (13(72.2%)) compared to females (5(27.8%)). When compared to other age groups, the age group =35 years is the most prevalent (33.3%).

According to figures 1 and 2, four samples (22.2%) had a drop in IL-6 levels after surgery. There were 14 samples (77.8%) that had an increase in IL-6 levels following surgery. Table 2 demonstrates that the post-surgery mean level of IL-6 (7.36) was greater than the pre-surgery level (2.92). According to statistical testing, this difference is statistically significant ($p<0.05$).

**Table 2.** IL-6 Levels Preoperatively and Postoperatively

| **Variable** | **n** | **Mean** | **SD** | **Median** | **Min** | **Max** | **p** |
|---|---|---|---|---|---|---|---|
| IL-6 Level Pre-operative | 18 | 2,92 | 8,57 | 0,84 | 0,18 | 37,16 | 0,048* |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Post-operative | 18 | 7,36 | 14,87 | 1,12 | 0,47 | 58,90 |

*Wilcoxon Signed Rank Test

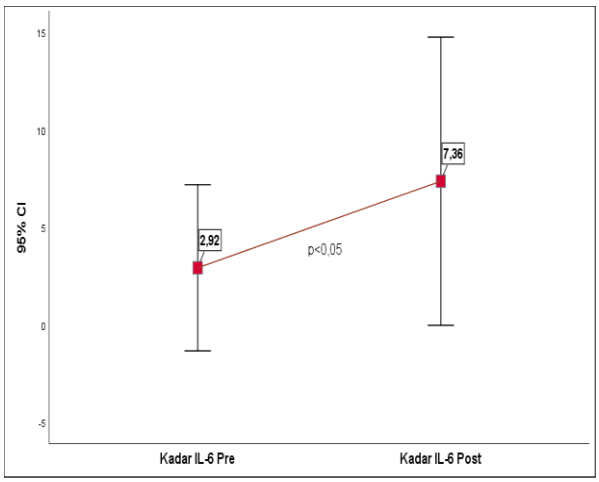


**Figure 1.** Comparison of Pre- and Post-Operative IL-6 Levels

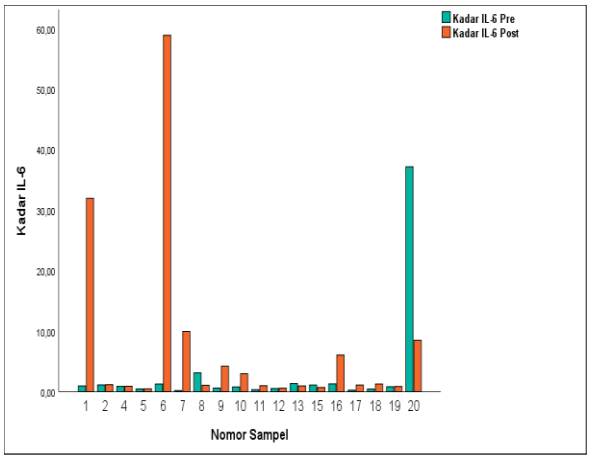


**Figure 2**. Comparison of individual IL-6 levels in pre- and post-operative samples

According to figures 3 and 4, 13 samples (72.2%) had a drop in HSP-70 levels after surgery. There were 5 samples (27.8%) that had an increase in HSP-70 levels after surgery. According to table 3, the post-operative mean level of HSP-70 (2.06) was lower than the pre-operative level (2.79). According to statistical testing, this difference is not statistically significant (p>0.05).

**Table 3.** HSP-70 Levels Preoperatively and Postoperatively

| Variable | n | Mean | SD | Median | Min | Max | p |
|---|---|---|---|---|---|---|---|
| HSP-70 Level | | | | | | | |
| Pre-operative | 18 | 2,79 | 1,93 | 2,41 | 0,43 | 9,42 | 0,184 |
| Post-operative | 18 | 2,06 | 2,60 | 1,03 | 0,07 | 8,34 | |

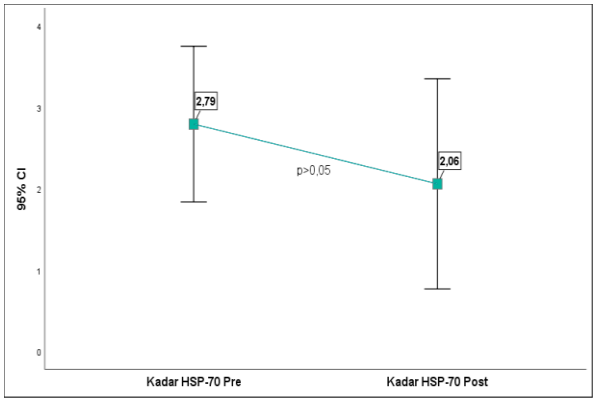


**Figure 3**. Comparison of Pre- and Post-Operative HSP-70 Levels

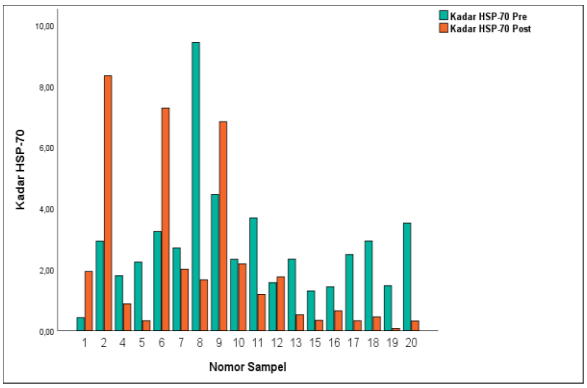


**Figure 4**. Comparison of Individual HSP-70 Levels in Pre- and Post-Operative Samples

## 4. Discussion

The study's findings revealed that mean IL-6 levels were greater post-operatively than pre-operatively, and this difference was statistically significant. There is no study

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to back up these claims. The findings of a research conducted by Marlina L, et al (2020) on 20 CRS patients contradict the findings of this study, in which CRS patients were given the same medication, namely nasal irrigation, nasal corticosteroids, and the antibiotic amoxicillin clavulanate for 14 days. IL-6 levels were measured before and after 14 days of therapy. As a result of the medication, there was a drop in IL-6.[12] IL-6 is a Th2-type cytokine that promotes fibroblast proliferation and collagen production. T and B lymphocytes, macrophages, eosinophils, epithelial cells, and fibroblasts are among the cells that produce IL-6.[13] However, its method of action in the chronic inflammatory function of CRS remains unknown.[14]

In CRS, there occurs pathogenic invasion of the nasal epithelium. Inflammation causes the nasal epithelium to emit different chemokines, one of which is IL-6.[15] When nasal irrigation with isotonic saline solution (0.9% NaCl) or intranasal corticosteroids is administered, pro-inflammatory mediators are prevented from being produced. As a result, medication administered after nasal irrigation can lower IL-6 levels.[12] It is, however, distinct from surgical conditions. IL-6 is critical in the immune response to surgical damage. The inflammatory response is a defense mechanism that seeks to repair damaged tissue and adapt to stress by reestablishing equilibrium. However, if the inflammatory response is misregulated, it can result in pathogenic conditions and chronic inflammation.[16] Longbottom ER, et al (2017) and Souza JN, et al (2022) found that post-operative patients had higher IL-6 levels than the control group.[17,18] IL-6 levels may rise following surgery. Surgical operations raise systemic IL-6 concentrations. The degree of elevation is proportional to the extent of tissue injury.[18]

The findings of this study also revealed that mean post-operative HSP-70 levels were lower than pre-operative levels. This difference, however, is not statistically significant. There is no prior study to back up our findings. However, we expect that surgery will lessen the inflammatory condition in SRS compared to non-surgery conditions in SSR, so HSP70 was shown to be lower post-surgery compared to pre-surgery. Aside from the inflammatory reaction to external threats (insults), the heat shock response is the primary homeostatic response. Heat shock proteins (HSPs) are a family of proteins that have a vital cytoprotective role. HSP70 is an HSP that is low or non-existent in healthy people, but its expression increases during disease. HSP functions primarily as a molecular companion, promoting cell protein folding, reducing protein aggregation, and destroying misfolded proteins.[20]

HSP-70 can assess surgical outcomes as well as indicate the severity of chronic rhinosinusitis. HSP70 levels were shown to be lower in chronic rhinosinusitis patients who received steroid therapy, according to Adji IS et al (2016). This decrease is due to the steroid's anti-inflammatory properties, which allows the inflammatory condition in chronic rhinosinusitis to subside and reduce HSP-70 levels.[20] This issue, however, appears to be different if the patient receives surgical intervention. Kimura F, et al (2004) discovered that HSP70 levels were higher in post-operative participants than in pre-operative subjects. HSP70 levels increased on days 0 and 1, then gradually dropped until day 7. Circulating HSP70 has been shown to have a crucial role in the postoperative inflammatory response. HSP70 is a stress-inducible protein that acts as a molecular chaperone to protect cells from harm by controlling protein folding, assembly, transport, and degradation.[21]

HSP-70 has anti-inflammatory properties as well. Wounds can contain high levels of HSP-70, which is hypothesized to protect against tissue injury by maintaining proper protein synthesis and structure, mending damaged proteins, and accelerating tissue wound healing. HSP-70 is found in keratinocytes, particularly in the higher layers of the epidermis, as well as fibroblasts, macrophages, and endothelium. The anti-inflammatory and cell proliferation actions of intracellular HSP-70 aid in wound healing. Extracellular HSP-70 is passively released after cell death or actively released via the exosome system, and it has an influence on wound debris cleaning by enhancing macrophage phagocytic capabilities.[20]

Our findings show a correlation between HSP-70 and IL-6 levels before and after FESS in CRS patients. Unfortunately, we did not consider various confounding factors that could have influenced this comparison, such as age, gender, or concomitant disorders like diabetes mellitus.

## 5. Conclusion

HSP-70 levels in patients with chronic rhinosinusitis were higher preoperatively than postoperatively.

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Preoperative IL-6 levels in patients with chronic rhinosinusitis were lower than postoperative values.

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