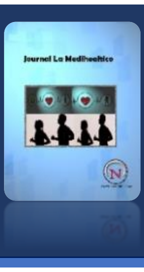
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Serum Interleukin-6 Levels are Positively Correlated with the Severity of Acne Vulgaris

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Abstract

Acne vulgaris is a chronic inflammatory disease that affects the pilosebaceous unit. This disease occurs on the skin of the face, body, back, and other areas of the body, and can leave scars on the skin which can be temporary or permanent. Recent data shows that the inflammatory process is the initial process in the pathogenesis of acne, several pro-inflammatory cytokines, one of which is interleukin 6 (IL-6), which plays a role in acne vulgaris. Analytical observational study with a cross-sectional approach. The research was carried out from February - November 2023 at the Skin and Venereology Polyclinic, RSUP Prof. Dr. I.G.N.G. Ngoerah Denpasar and the Clinical Pathology Laboratory of Prof IGNG Ngoerah Hospital. The sample consisted of 47 samples of patients with acne and 20 samples without acne aged 8 - 45 years who were selected through consecutive sampling according to inclusion and exclusion criteria. A sample of 3 milliliters of venous blood is taken which will then be checked for IL-6 with an ELISA kit. Data analysis with SPSS version 24 and p value <0.05 is significant. The mean IL-6 serum levels in the acne group was 110.2 ± 88.3 pg/ml while in the non-acne group it was 26.7 ± 23.7 pg/ml. There was a significant difference in the category of IL-6 levels in the acne and non-acne groups (95% CI 55.1 - 155.3, p<0.001). The correlation analysis of IL-6 levels with the severity of acne was strongly positive (r=0.951, p<0.001).

Introduction

Acne vulgaris or commonly called acne, is a chronic inflammatory disease that affects the pilosebaceous unit. This disease occurs on the skin of the face, body, back, and other areas of the body, and can leave scars on the skin which can be temporary or permanent. Generally, acne vulgaris appears at puberty, and can be experienced until adulthood. Acne vulgaris has a degree of severity that can be influenced by various internal and external factors. Apart from affecting appearance, acne vulgaris can also affect the sufferer's mental health. Treatment and healing patterns for acne vulgaris differ from one individual to another, so an approach to trigger factors and appropriate treatment is needed in the management of acne vulgaris.

In 2010, The Global Burden of Disease Study stated that acne vulgaris was the eighth most common skin disease experienced by patients. Meanwhile, in Indonesia, acne vulgaris is found in almost 80 to 90 percent of the population. Apart from that, a study conducted by Alsulaimani et al. (2020), stated that there were 182 acne vulgaris sufferers, with a proportion of 10% of all dermato-venerology patients at Adam Malik Hospital. Most sufferers are aged 16 years – 20 years, which is 45.6 percent of the entire population. Meanwhile, research conducted in 2021 at IGNG Ngoerah Hospital, Denpasar, stated that the prevalence of acne vulgaris was 65.41 percent with the highest age range being 10-30 years. Based on the degree of severity, 82.87 percent of patients had mild degrees, 15.08 percent of patients had moderate degrees, and 2.05 percent of patients had severe degrees. (Primasari & Praharsini, 2021) In general, severe acne vulgaris is often found in men. Meanwhile, hormonal acne vulgaris is often found in women, which is related to periodic menstrual cycles. (Alsulaimani et al., 2020; Daou, 2020)

The pathogenesis of acne vulgaris is still not well understood. There are several factors that cause acne, namely abnormal sebum production, changes in keratinization with follicular blockage, Cutibacterium acnes (C. acnes) colonization, congenital neuroendocrine dysregulation and adaptive immunity with the induction of an inflammatory process. (Chilicka, 2022). The inflammatory process is said to be the initial process in the pathogenesis of acne, and there is evidence that the initial CD4 lymphocytic infiltration is the primary inflammatory event. There are several pro-inflammatory cytokines, one of which is interleukin 6 (IL-6) which plays a role in acne vulgaris. The cytokine IL-6 is known to be induced via lipopolysaccharide in certain bacteria as a messenger for cytokines and growth factors. The cytokine IL-6 facilitates the production of neutrophils, various cytokines, proteases, and free radicals. The cytokine IL-6 can also induce T-cell differentiation, B-cell maturation and immunoglobulin production. (Shrihari, 2017)

Acne vulgaris is a skin disease that requires appropriate attention and treatment for each individual. Updated therapy and understanding regarding acne vulgaris can be realized through laboratory-based checks, one of which is checking the pro-inflammatory cytokine IL-6. As explained in the previous paragraph, IL-6 levels can provide information about the level of inflammation occurring in the body. Acne vulgaris itself is an inflammatory process that occurs on the skin of the face, body, back, which has different levels of severity. So, based on this, researchers are interested in finding out more about the correlation between serum interleukin-6 (IL-6) levels and the severity of acne vulgaris.

Methods

This research was conducted using an analytical observational method with a cross-sectional approach to determine the relationship between serum IL-6 levels and the severity of acne vulgaris in patients at Prof IGNG Ngoerah Hospital. The research was conducted at the Skin and Venereology Polyclinic of Prof. IGNG Ngoerah General Hospital for eight months, starting in February 2023 to November 2023. The accessible population was all acne vulgaris patients aged 8-35 years who visited the Skin and Venereology Polyclinic of Prof. IGNG Ngoerah Hospital in the period March 2023 to October 2023 with a sampling method in the form of consecutive sampling. The patient inclusion criteria were all patients who visited the polyclinic, Indonesian citizens (WNI), aged 8-45 years, good general condition, and willing to sign informed consent. Patient exclusion criteria are subjects who are pregnant and breastfeeding, have infectious diseases, a history of autoimmune diseases (such as psoriasis, vitiligo, SLE), a history of chronic diseases such as hypertension, rheumatoid arthritis, chronic kidney failure, chronic liver disease, diabetes mellitus, malignancy, atopic dermatitis, bronchial asthma, receiving corticosteroid treatment, hormonal pills, diuretics) in the last 4 weeks.

The procedure for this research begins with selecting samples that meet the inclusion criteria, signing informed consent. Venous blood sampling for serum IL-6 examination. Samples were taken from the cubital vein as much as 3 ml. The blood collection area was previously disinfected with 70% alcohol. Prepare 1 vacutainer tube that has been labeled (name of sample, date of sampling). The tube filled with venous blood was then centrifuged at 3000 rpm for 5 minutes to obtain serum. Serum samples were put into aliquot tubes that were labeled (name of sample, date of sample collection) then the tubes were stored at -70°C. 1 3 ml tube of blood is inverted 5 times until homogeneous, let stand for 30-40 minutes until the blood clots, the

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blood sample is immediately centrifuged at around 1500 rpm for 15 minutes, separate the serum then put it into 3 labeled sample cups (lab no., IL- serum, name) each contains 0.5 ml of serum, stored in a deep freezer (-400), sample stability at -400C is ≥ 6 months. If all serum samples have been collected, IL-6 levels are measured using the ELISA method. Data analysis was carried out using the Statistical Package for Social Sciences (SPSS) program, version 23.

Result and Discussion

This study involved 67 subjects, of which there were 47 acne patients and 20 non-acne patients. The characteristics of the research subjects can be seen in Table 1.1. The mean age of the subjects was 26.38 ± 7.77 for the acne group, and 25.32 ± 9.27 for the non-acne group. There were 8 people (53.3%) samples with acne, and 7 people (46.7%) samples without acne in the 8-18 year age group. There were 38 people (73%) samples with acne, and 14 (27%) samples without acne in the age group >18 years. There were 13 (65.0%) men and 35 (68.10%) women in the acne group. The severity of acne was divided into mild, moderate and severe acne, of which 7 (15.6%) people experienced mild acne, 35 (68.10%) people experienced moderate acne, and 19 (42.2%) people experienced severe acne.

Table 1. Characteristics of Research Subjects

Characteristic	**Acne status** **N (%), rerata** ± SD	
	Acne **(N= 47)**	**Not Acne** **(N= 20)**
Age (years) 8 – 18 years > 18 years old	26.38±7.77 8 (53,3%) 38 (73%)	25.32± 9.27 7 (46,7%) 14 (27%)
Gender Man Woman	 12 (65,0%) 35 (68,10%)	 5 (35,0%) 15 (31,9%)
Acne Severity Light Keep Heavy	 8 (17,1%) 19 (40,4%) 20 (42,5%)	 - - -
Smoking History Smoke No Smoking	 4(80%) 43(69,4%)	 1(20%) 19(30,6%)
History of the disease	0(0%)	0(0%)
Treatment History Crim retinoid	 15(100%)	 0(0%)
Kadar IL-6 (pg/ml) Normal Tall	110.2 ±88.3 2 (9,1%) 45 (100%)	26.7 ±23.7 20 (90,9%) 0 (0,0%)

Data source: Standard Deviation

The data normality test in this study was carried out using the Shapiro-Wilk test, it was found that the data was normally distributed only for the IL-6 level variable in the moderate acne group ($p>0.05$). The IL-6 variable in the mild, severe acne group and IL-6 levels in the non-acne group were not normally distributed ($p<0.05$) (Table 2).

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Table 2. Data Normality Test Results

	Acne Degrees	P value
IL-6	Not acne	0,026
	Light degree	0,010
	Medium degree	0,136
	Degree of weight	0,001

*Data distribution is normal if the value is p>0.05. Test normality with Shapiro-Wilk test

The data homogeneity test was carried out using the Levene test, data can be said to be homogeneous if the p value is > 0.05 and vice versa, it can be said to be inhomogeneous if the p value is < 0.05. The Levene test results showed that the data was not homogeneous based on the p value (p<0.05) on IL-6 levels. (Table 3).

Table 3. Data Homogeneity Test Results

Variable	P value
IL-6 levels	0,01

*Data is homogeneous if the value of p>0.05. Homogeneity test with *Levene test*

Bivariate relationship analysis was carried out using the chi-square test between IL-6 level categories and acne categories, namely acne and non-acne. The test results are shown in table 4, the results were significant (p<0.05), with a confidence interval (95% CI) of 55.1-155.3. The relative risk value obtained is 42.1.

Table 4. Analysis of IL-6 Grade Category Differences Between Acne and Non-Acne

Variable	Rerata IL-6		IK 95%	P value
	Acne	Not Acne		
Category IL-6 with non-acne status	110.2 ±88.3	26.7 ±23.7	55,1-155,3	<0.001*

***Significant data if p< 0.05

Correlation analysis in this study was carried out using the Spearman test between IL-6 levels and the severity of acne, namely mild, moderate and severe. Based on the results of the analysis (table 5), significant results were obtained for both variables with a p value <0.001 (p<0.05), and a 95% confidence index value in the range 1.29 – 1.88. The results of the correlation analysis were found to be strong and in the same direction for both variables (correlation coefficient 0.951).

Table 5. Correlation Test of IL-6 Levels with the Severity of Acne Vulgaris

Variable	IL-6 levels	IK 95%	P value
Acne Severity	Correlation (r)	0,951	
	P value	1,29-1,88	<0.001*
	Total (n)	67	

*Significant when p<0.05; correlation analysis with the Spearman test

Multivariate analysis was preceded by a chi-square test between categories of IL-6 levels and smoking history and previous treatment. Based on the results of the analysis (table 6), significant results were obtained from the treatment history variable (p<0.05). Next, a multivariate examination was carried out using logistic regression and the results were not significant for both variables (p>0.05) (table 7)

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Table 6. Chi-square *Test* on Smoking History and Treatment Variables

Variable	I 95%	P value
Smoking History	0,059 -5,4	0,528
Treatment History	0,49-0,76	0,002

Table 7. Multivariate Test Results with Logistic Regression

Variable	B	S.E	df	P value	Exp (B)
Smoking History	-			-	
Treatment History	-20.733	10377.785	1	0,998	0,000

The subject characteristics of this study involved 67 subjects, of which 47 patients had acne and 20 patients did not have acne. The mean age of the object was 26.38 ± 7.77 for the acne group and 25.32 ± 9.27 for the non-acne group, where the age of acne occurrence was dominated by teenagers - adults. This is similar to research by Koko Aksu et al. (2012) who conducted research on adolescents aged 15 - 16 years (with an odds ratio (OR) of 3.3) and adolescents aged 17-18 years (with an OR of 2.6) (Koku Aksu et al., 2012) . Another study by Say et al. (2022) which stated that the incidence of acne in patients aged 21 - 24 years had an OR of 0.728, while the incidence in samples aged 18 - 20 years was with an OR of 0.806 (Say et al, 2022). A study by Jaber et al. (2020) stated that the incidence of acne was dominated by teenagers and young adults aged 15 – 35 years (Jaber et al., 2020). A meta-analysis by Heng & Chew (2020) states that the onset of acne is generally associated with the onset of puberty, when there is an increase in sebum production. High sebum production will trigger the growth of P. acnes, which will trigger an inflammatory response and the formation of acne lesions (Heng & Chew, 2020).

There were 13 (65.0%) men and 35 (68.10%) women in the acne group, and 5 (35.0%) men and 15 (31.9%) women in the non-acne group. acne. This research states that women have a higher incidence of acne vulgaris than men. The results of this study are in accordance with research by Shah et al. (2021), which stated that women (81.7%) had a higher prevalence of acne than men (18.3%) (Shah et al, 2021). A study by Witkam et al. (2024), states that women have a higher tendency to experience acne vulgaris than men in adolescence (with a percentage of 62% in women, and 45% in men). Women are also said to have a higher incidence of severe acne than men (Witkam et al., 2024). Meanwhile, research by Wibisono et al. (2020) at RSUD Dr. Soetomo Surabaya, stated that women have a higher prevalence of acne vulgaris (78.23%) compared to men (21.77%) (Wibisono et al., 2020). More severe conditions of acne vulgaris are often found in women at puberty, which is associated with an earlier onset of puberty in women compared to men. Apart from that, acne vulgaris in women is also associated with the monthly menstrual cycle which causes an increase in the hormones progesterone and estrogen, so acne vulgaris is more often found in women. (Heng & Chew, 2020).

Based on the severity of acne, research divides it into 3 categories, namely mild, moderate and severe acne. A total of 7 (15.6%) people experienced mild acne, 35 (68.10%) people experienced moderate acne, and 19 (42.2%) people experienced severe acne. The results of this study are in line with research by Jaber et al. (2020), which states that the proportion of acne severity is 42.1% mild, moderate 51.3%, and severe 6.6%, which shows the highest proportion of mild acne. Research by Ragab et al. (2019), states that the proportion of acne severity is 10% for mild acne, 73.3% for moderate acne, and 16.7% for severe acne. This research shows that the highest proportion of acne severity is moderate. There are several things that can influence the severity of acne, including a genetic history from a family that has a history of acne vulgaris. A meta-analysis result using loose meta-analysis criteria stated that a family history of acne vulgaris can increase the risk of increasing the degree of acne vulgaris. Another factor that can influence the severity of acne is skin type, where oily skin type and seborrheic skin type are said to be associated with moderate to severe acne vulgaris (Heng & Chew, 2020).

History of smoking: 4 people (80%) smoked in the acne group, 1 person (20%) smoked in the non-acne group, 43 people (69.4%) did not smoke in the acne group, and 19 people (30.6%) non-smokers in the non-acne group. In this study, a statistical test was calculated in the form of a bivariate smoking test with acne status in the sample, which obtained a p value > 0.05 (p = 0.528) and the 95% CI value was 0.059 - 5.4, which means there is no significant difference. The results of this study differ from those mentioned by Aldaham et al. (2015) who stated that IL-6 levels were significantly related to smoking, especially in active smokers (Aldaham et al,, 2015). Research by Al-tameemi et al. (2022), stated that IL-6 increased drastically in patients with a history of smoking when compared with patients who did not smoke, with the amount of IL-6 being 2.58 ± 0.98 pg/mL in patients with a history of smoking and 1.85 ± 0.62 pg/mL in patients without a history of smoking (Al-tameemi et al., 2022). Exposure to cigarette smoke can cause increased oxidative stress which causes vascular inflammation. Increased oxidative stress and immune responses can trigger B and T cell proliferation which reduces the generation, activity and autoantibodies of immunosuppressive cells (Treg cells) and increases the expression of inflammatory mediators such as IL-6, IL-8 and TNF. Differences in results in this study could be caused by the number of samples, as well as bias in the sample and researcher interviews (Wang et al., 2022).

Treatment history revealed the use of retinoid cream in 15 people (100%) of the severe acne samples. In this study, a statistical test was calculated in the form of a bivariate test of treatment history with acne status in the sample, which obtained a p value <0.05 (p = 0.002) and the 95% CI value was 0.49 – 0.76, which means there is a difference. significant. Therapeutic modalities for acne vulgaris include topical therapy, systemic therapy, and invasive therapy. Research by Jaber et al. (2020), states that the modalities frequently used by acne vulgaris sufferers are facial cleansers (48%), scrub cream (35%), topical antibiotics (24.2%), oral antibiotics (21.6%), Roaccutane (20 .9%), using a face mask (27.5%), and using invasive laser therapy (3.3%). There is a relationship between the severity of acne vulgaris and the use of drugs. The more severe the degree of acne vulgaris, the greater the use of scrub creams, oral antibiotics, and Roaccutane (Jaber et al., 2020). Research by Wibisono et al. (2020), states that patients with comedonal lesions are generally given topical treatment, while patients with papulo-pustular and conglobatic lesions are given a combination of topical and oral medications. This is in accordance with this study which stated that the majority of samples were in the moderate and severe acne category, so the research samples used topical treatment in the form of retinoid ointment. (Wibisono et al., 2020).

Normality test results using the Shapiro-Wilk test. The normality test is intended to see the distribution of research data. It is said to be normally distributed if the normality test shows a p value > 0.05 and vice versa it is said to be abnormally distributed if the p value < 0.05. In this study, data was found to be normally distributed only for the IL-6 level variable in the moderate acne group (p>0.05). The IL-6 variable in the mild, severe acne group and IL-6 levels in the non-acne group were not normally distributed (p<0.05). The data homogeneity test was carried out using the Levene test, data can be said to be homogeneous if the p value is > 0.05 and vice versa, it can be said to be inhomogeneous if the p value is < 0.05. The Levene test results showed that the data was not homogeneous based on the p value (p<0.05) on IL-6 levels. Because the data obtained was not normally distributed, the next hypothesis test was carried out using a non-parametric test.

In this study, a bivariate relationship analysis was carried out using the chi-square test between the IL-6 level category and the acne category, namely acne and non-acne. The test results showed significant results (p<0.05), with a confidence interval (95% CI) of 55.1-155.3. The relative risk value obtained is 42.1. Meanwhile, correlation analysis using the Spearman test between IL-6 levels and the severity of acne, namely mild, moderate and severe. Based on the results of the analysis, significant results were obtained for both variables (p<0.05), with a

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strong and unidirectional correlation between the two variables (correlation coefficient 0.951). The results of a similar study by Ragab et al. (2019) which stated that there was a significant association of IL-6 in acne patients with a p value <0.001. It is stated that IL-6 is a contributing cause of acne vulgaris. However, genetic variations of IL-6 on the chromosome are said to have no significant relationship with the severity of acne vulgaris (Ragab et al., 2019). The results of research by Elhanboli (2021) stated that there was an increase in serum levels of IL-6, IL-10, IL-12, IL-17, IL-19, IL-31, IL-26, IL-37, and IL-38 in acne vulgaris compared to healthy control patients without acne vulgaris. Significant results showed an increase in serum levels of IL-6, IL-10, 1L-7, IL-19, IL-31, IL-36, and IL-38 in patients with severe acne vulgaris when compared with those with moderate and moderate degrees of acne vulgaris light (Elhanboli, 2021).

Interleukin 6 (IL-6) acts as a cytokine that triggers inflammation and also as a myokine that reduces inflammation. In humans, IL-6 is produced by the IL-6 gene. In addition, osteoblasts produce IL-6 to trigger osteoclast formation. Smooth muscle cells in the tunica media contain many blood vessels and also produce IL-6 as a cytokine that triggers inflammation. The role of IL-6 as a myokine that relieves inflammation is carried out by inhibiting the effects of TNF-alpha and IL-1, and activating IL-1ra and IL-10 (Daou, 2020; Allen, 2020). IL-6 correlates with inflammatory markers such as C-reactive protein, which may increase the value of IL-6 as an inflammatory mediator. The IL-6 gene 572 C allele plays a role in the production of IL-6 in acne vulgaris, and it is further stated that the severity of acne and certain cytokine gene polymorphisms have a correlation. Keratinocytes and sebocytes have been shown to secrete IL-6, which may suggest that IL-6 has a role in acne vulgaris. (Ragab et al., 2019)

Research Strengths and Weaknesses

This study was able to prove that IL-6 has a strong positive correlation with the severity of acne vulgaris. The results of this study illustrate the role of IL-6 in the pathogenesis of acne development and the severity of acne vulgaris as a pro-inflammatory cytokine. However, the weakness of this research is that it is limited to the environment in the area where the sample subjects were selected, so that it can be proven in various places with different sample conditions through diet, metabolic indices, and the role of genetic factors in the development of acne vulgaris and increased levels of IL-6.

Furthermore, it is known that there are several aspects that influence the production of IL-6 in the body. Apart from the inflammatory process and oxidative stress, there is a genetic role for each individual which can contribute to the occurrence of moderate to severe acne vulgaris. Dietary factors are also said to have a role in the amount of IL-6 cytokines. Some foods are said to increase inflammation in the body, such as highly processed foods that are high in sugar and salt. Food with a high content of sugar, salt, flavoring agents, colorings, emulsifiers, and going through various kinds of processing and storage processes is called ultra-processed food. Foods and drinks that fall into the ultra-processed food category include ice cream, sausages, chips, packaged bread, cereal, biscuits, carbonated drinks, flavored yogurt, soup and instant noodles, and alcoholic drinks. Dos Santos et al. (2023), stated that there was a relationship between frequent consumption of ultra-processed food, which was associated with an increase in IL-6 concentrations in the body. This is related to ultra-processed foods which are associated with increased body weight and the occurrence of inflammatory processes. Increased inflammation in the body will increase the response of cytokines and other inflammatory mediators in the body, in this case increasing the production of IL-6. Apart from that, there is a role of pro-inflammatory cytokines such as TNF, IL-6, IL-10, 1L-7, IL-19, IL-31, IL-36, and IL-38 which can also play a role in the pathogenesis of acne vulgaris.

Conclusion

The conclusion of this study is that there is a difference in the mean serum IL-6 levels in acne vulgaris samples, namely with a mean of 110.2 ± 88.3 pg/ml higher compared to non-acne samples, namely with a mean of 26.7 ± 23.7 pg/ml at RSUP Prof. Dr. I.G.N.G Ngoerah, and there is a strong positive correlation between serum IL-6 levels and the severity of acne vulgaris with a strong positive correlation coefficient (r) value of 0.951 and p<0.001 at RSUP Prof. Dr. I.G.N.G Ngoerah.

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