Decreased IL-6 Levels more than 9.46 pg/ml and TNF-α Levels more than 14.43 pg/ml as Predictors of Functional Outcome of Oxford Knee Score 6 Weeks Post Total Knee Arthroplasty in Kellgren-Lawrence Grade IV Osteoarthritis Patients

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ABSTRACT

Introduction: Knee osteoarthritis (OA) occurs when there is a disruption of the dynamic balance between degradation and tissue synthesis. Operative management with Total Knee Arthroplasty (TKA) is considered a late-stage therapeutic option. One of the reasons for the TKA is to reduce pain and improve knee movement function. However, the research has not extensively covered the impact of these proinflammatory cytokines and mechanical variables that emerge after the surgery and it is still unclear how they relate to post-TKA outcomes. This study aims to further prove the relationship between the magnitude of the decrease in inflammatory markers IL-6 and TNF-α with the functional output of post-TKA as measured by the Oxford Knee Score.

Methods: This investigation is a retrospective cohort. With a total of 28 patients of grade IV Knee OA based on Kellgren-Lawrence Classification who were candidates for TKA surgery between January 2022 until April 2022. Blood samples were obtained the day before surgery and six weeks thereafter. The Oxford Knee Score (OKS) was used to evaluate the patient’s functional status after surgery. Subjects were divided into two groups depending on whether or not they had reduced IL-6 and TNF-α levels to below the cut-off point by 6 weeks postoperatively, as calculated using ROC analysis. Chi-square tests were used to demonstrate the test's validity, and Pearson correlation test is also performed.

Results: Average difference in TNF-α levels was 20.19 (CI = 8.58564-31.81007), which is statistically significant at the 0.002 level (p 0.05), according to the findings of a paired t-test. When comparing IL-6 levels using a paired t-test, a mean difference of 10.52 (IC = 3.32833-17.70738) was found, which is statistically significant at the 0.002 level (p 0.05). TNF-α levels were considered to have been reduced at a cut off value of 14.43 pg/mL with an AUC of 0.837. As for IL-6, the threshold for a reduced level was 9.46 pg/mL with an AUC of 0.837. OKS was also associated with a 6.0-fold lower relative risk between lowered TNF-α and IL-6 levels.

Conclusion: There is a positive link between OKS and the reduction in IL-6 and TNF-α serum levels that occurs 6 weeks after surgery. Decreased level of serum IL-6 more than 9.56 pg/mL and TNF-α more than 14.43 pg/mL can be used as a predictor of good OKS after 6 weeks post TKA.

Keywords: Interleukin-6, oxford knee score, total knee arthroplasty, tumor necrosis factor α.

I. INTRODUCTION

Knee osteoarthritis (OA) affects 27.8% of over-45s people [1]. Symptomatic knee OA affects 40% of men and 47% of women. As a source of significant morbidity in aged patients, understanding the pathogenesis and therapy of OA is critical to enhance surgical outcomes [2]. Osteoarthritis (OA) arises when joint tissue breakdown and synthesis are disrupted. Pain is the first symptom of OA, particularly after knee overuse. TKA is a late-stage therapy option when non-operative management fails. TKA reduces pain and improves knee function but not all post-TKA patients are functionally equal. Inflammatory and mechanical mechanisms both contribute to the etiology of knee OA According to the Kellgren Lawrence classification, mechanical abnormalities can be recognized clinically and radiologically with OA severity; the Kellgren-Lawrence IV grade indicates the need for TKA. Earlier study
described the post-TKA inflammatory process in knee OA patients, using Interleukin-6 (IL-6) as an accurate and sensitive cytokine measure. The greatest IL-6 levels were identified 3 days postoperatively and recovered to normal 6 weeks later [1], [2].

Cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) play the most important roles in the pathogenesis and severity of OA disease, whereas IL-15, IL-17, IL-21, and chemokines and their receptors, such as MCP-1/ CCL2, IL-8/CXCL8, and CXCL1, are also involved [3]. Previous study found that 30% of TKA patients were unhappy with the functional outcome. Previous studies focused on preoperative factors, including patient factors and expectations, to improve the outcome. In order for doctors and patients to weigh the risks and advantages of an operation, it is crucial to determine which patients are at high risk for negative outcomes. To further improve their surgical outcomes, these patients may additionally undergo targeted therapies against inflammatory variables [4], [5]. Based on these, the authors are interested in investigating the role of inflammatory markers in these patients and to further prove the relationship between the decrease in the inflammatory markers IL-6 and TNF-α with post-TKA functional outcome as measured by the Oxford Knee Score (OKS).

II. METHODS

The purpose of this retrospective cohort study was to examine the levels of TNF-α and IL-6, both of which have been linked to the progression of knee osteoarthritis, in patients 6 weeks after TKA surgery. Patients with post-TKA knee OA were included in the sample, and they were chosen at consecutively. Patients with knee OA grade IV based on the Kellgren-Lawrence Classification who received TKA at Prof. Dr. IGNG Ngoerah General Hospital Denpasar during the period of time and meets the inclusion criteria: 1) The patient was diagnosed with grade IV knee OA based on the Kellgren-Lawrence Classification based on the results of plain radiographs of the knee; 2) male of female gender; 3) Aged 50-75 years old; 4) Planned and agree to get TKA procedure; 5) Agree to participate in the research.

Research samples were collected at Prof. Dr. IGNG Ngoerah Hospital Outpatient Clinic, and TKA surgeries were performed at the Central Surgical Operating Theatre and the Amerta Wing Operating Theatre. The sampling for this study take place over the course of four months, from January to April of 2022. Examination of IL-6 and TNF-α was carried out by laboratory examination and serum samples were taken on the day before the surgical procedure and 6 weeks after surgery. If previously the patient was taking Non-Steroid Anti-Inflammatory Drugs (NSAIDs), then these drugs were discontinued 7 days before the serum test. The follow-up will occur within a month's time, from March to May of 2022. Functional scores were assessed in the form of postoperative OKS. The study subjects were then grouped into two groups based on reduction level of the cut-off point in IL-6 and TNF-α levels with the outcome of the Oxford Knee Score (OKS) at 6 weeks postoperatively. Furthermore, in the sample, statistical analysis was carried out using SPSS software version 25.0 for Windows.

III. RESULTS

In the study, a total of 28 patients were obtained (Table I). Of the total 28 patients, 9 patients (35.71%) were men while 19 patients (64.29%) were women, 13 patients (46.3%) were affected on the right side of the knee while 15 patients (53.57%) were affected on the left knee side.

Based on the normality test on TNF-α and IL-6 data, it was found that all variables were normally distributed with p value > 0.05 (Table II).

Based on the results of the paired t-test (Table III) for TNF-α levels, the mean difference in TNF-α levels before and 6 weeks after Total Knee Arthroplasty was 20.19 (CI = 8.58564 - 31.81007) which was statistically significant with p value 0.002 (p < 0.05). The results of the paired t-test of IL-6 levels showed that the difference in the mean levels of IL-6 before and 6 weeks after Total Knee Arthroplasty was 10.52 (IC = 3.32833 - 17.70738) which was also statistically significant with p value 0.002 (p < 0.05).

In this study, it was found that the cut-off point for decreasing TNF-α levels was 14.43 with a sensitivity of 85.7% and specificity of 85.7% and p value = 0.035. The strength of the under-curve area is 0.837, which means it has a predictive power of 83.7% (Fig. 1).

While the cut-off point for decreasing IL-6 levels was 9.46 with a sensitivity of 85.7% and specificity of 85.7% and p value = 0.013. The strength of the area under the curve was 0.898, which means it had a predictive power of 89.8% (Fig. 2).

Based on the results of independent t-test (Table IV), the average OKS score in the TNF-α group with decreased levels of >14.43 pg/mL, the mean OKS score in the group was 28.86 ± 3.24.The mean difference between the two groups was 10.86 (CI = 6.368 - 15.346) which was statistically significant with p < 0.001 (p < 0.05).

Based on the results of independent t-test (Table V), the average OKS score in the group with decreased IL-6 levels > 9.46 pg/mL and IL-6 levels decreased < 9.46 pg/mL, the average OKS score was found in the group with decreased IL-6 levels > 9.46 pg/mL was 39.43 ± 3.59 while in the group with decreased levels of IL-6 < 9.46 pg/mL it was 28.86 ± 4.14.

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<tr>
<th>TABLE I: STUDY DEMOGRAPHICS</th>
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<th>TABLE II: SHAPIRO WILK'S NORMALITY TEST</th>
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Based on the results of the Pearson test, it was found that the r value of TNF-α levels before and after Total Knee Arthroplasty was 0.743, which means there is a strong positive correlation (r = 0.743 - < 0.8) and statistically significant (P value < 0.05) with the patient's Oxford Knee Score after Total Knee Arthroplasty (Table VI). This means that the greater the difference in TNF-α levels before and after Total Knee Arthroplasty, the higher the patient's Oxford Knee Score after Total Knee Arthroplasty.

The mean difference between the two groups was 10.57 (CI = 6.054 – 15.089) which was statistically significant with p < 0.001 (p < 0.05).

Based on the results of the Pearson test, it was found that the r value of IL-6 levels before and after Total Knee Arthroplasty was 0.880, which means that there is a strong positive correlation (r = 0.88 - < 1) and statistically significant (P value < 0.05) with the patient's Oxford Knee Score after Total Knee Arthroplasty (Table VII). This means that the greater the difference in IL-6 levels before and after Total Knee Arthroplasty, the higher the patient's Oxford Knee Score after Total Knee Arthroplasty.

The table below (Table VIII) show a decrease in TNF-α levels >14.43 pg/mL as a good predictor of the Oxford Knee Score at 6 weeks after Total Knee Arthroplasty (TKA) in patients with Kellgren-Lawrence IV Osteoarthritis. The analysis obtained a relative risk (RR) of 6,000 so that patients with decreased levels of TNF-α > 14.43 pg/mL had a 6-fold possibility of producing a good Oxford Knee Score (OKS) compared to decreased levels of TNF-α < 14.43 pg/mL with CI (0.953-37.764) and p value = 0.008.

The Table IX shows a decrease in IL-6 levels >9.46 pg/mL as a good predictor of the Oxford Knee Score at 6 weeks after Total Knee Arthroplasty (TKA) in patients with Kellgren-Lawrence IV Osteoarthritis.

![Fig. 1. ROC curve of decreased TNF-α levels.](image)

![Fig. 2. ROC curve of decreased TNF-α levels.](image)
The analysis obtained a relative risk (RR) of 6.000 so that patients with decreased levels of IL-6 < 9.46 pg/mL had a 6-fold possibility of producing a good Oxford Knee Score (OKS) compared to decreased levels of IL-6 < 9.46 pg/mL with CI (0.953-37.764) and p value = 0.008.

IV. DISCUSSION

In this study, the total sample was 28 patients. From all research subjects, the average age of the patients was 64.50 ± 7.63 years, the gender of the research subjects was 9 (35.71%) male and 19 (64.29%) female. A total of 13 samples underwent TKA surgery on the right knee and 15 samples on the left knee. The sex distribution of patients obtained in this study is in line with epidemiological reports in several previous studies. This is also consistently found in studies by Cui et al., where women are said to suffer from knee joint OA more. In another study by Spitaels et al., knee OA patients were also more common in the female group than in the male group [6], [7].

After total knee arthroplasty, Kellgren-Lawrence grade IV knee osteoarthritis patients had a statistically significant decrease in interleukin 6 (p = 0.008; p < 0.05). Reference [8] found that total knee arthroplasty patient’s blood serum interleukin 6 levels increased dramatically on the first day postoperative, and fell to preoperative levels in the second week, and recovered to normal at 6 weeks. High IL-6 levels may indicate postoperative inflammation, according to one study [8]. In other study, [9] similarly found there is a decrease in IL-6 serum level, 48 hours following TKA surgery. According to [10] the average values of interleukin 6 preoperatively, 1 day postoperatively, and 5 days postoperatively were 5.67, 69.74, and 16.80 ng/L. On the 5th day postoperative, serum IL-6 levels dropped. Reference [11] also found that serum IL-6 levels decreased on the 4th day postoperative. After 24 hours of TKA surgery, [8], [9] and [10] all found a rise in IL-6 levels. Regardless of infection, the rise indicates inflammation [8]-[10]. The surgery can also produce inflammation, which raises IL-6 levels in the first several days. IL-6 levels will steadily fall and potentially drop below preoperative levels after 6 weeks after TKA. TKA decreased IL-6 levels by 10.52 pg/mL (p = 0.008) in this study. ROC curve analysis showed that the significant cut-off point was 9.46 pg/mL with predictive power of 89.8%, sensitivity 85.7%, and specificity 85.7%.

TNF-α, from chromosome 6, has 4 exons and 3 introns. Astroglia, microglia, Langerhans cells, Kupffer cells, and alveolar macrophages release TNF-α. TKA surgery reduced TNF-α (p = 0.002, p < 0.05) in Kellgren-Lawrence grade IV knee osteoarthritis patients. Reference [4] discovered that TNF-α levels gradually decreased after surgery. Reference [12] observed that the mean TNF-α concentration was higher in 39 individuals who experienced preoperative pain at rest than in 36 who did not (p = 0.015) and was the only independent predictor of pain preoperatively at rest (OR=13, p = 0.02). Postoperative pain management may enhance joint outcomes in patients with decreased TNF-α values [12], [13]. Reference [14] found that TNF-α induces adhesion molecules and other cytokines to modulate the immune response. This study shows that after TKA, TNF-α levels dropped by 20.19 pg/mL (p = 0.002). The ROC curve showed that 14.43 pg/mL was significant with 83.7% predictive power, 85.7% sensitivity, and 85.7% specificity.

This study also shows that decrease in TNF-α levels >14.43 pg/mL as a good predictor of the Oxford Knee Score at 6 weeks after TKA with relative risk (RR) of 6,000, so that patients had a 6-fold possibility of producing a good OKS compared to decreased levels of TNF-α < 14.43 pg/mL. Also a decrease in IL-6 levels >9.46 pg/mL as a good predictor of the Oxford Knee Score at 6 weeks after TKA with relative risk (RR) of 6,000 so that patients with decreased levels of IL-6 >14.43 pg/mL had a 6-fold possibility of producing a good OKS compared to decreased levels of IL-6 <9.46 pg/mL.

V. CONCLUSION

This study proves the role of decrease in TNF-α and IL-6 levels as predictors of functional output (OKS) in Knee OA KL IV patients after TKA. Patients with Kellgren-Lawrence IV knee osteoarthritis will experience a significant decrease of TNF-α and IL-6 levels at 6 weeks after TKA. The OKS in patients 6 weeks postoperatively whose IL-6 level decreased >9.46 pg/mL was better than patients whose IL-6 level decreased <9.46 pg/mL. Simultaneously, the OKS in patients 6 weeks postoperatively TKA whose TNF-α level decreased >14.43 pg/mL was better than patients whose TNF-α level decreased <14.43 pg/mL. In short, the decrease in TNF-α levels >14.43 pg/mL and IL-6 levels >9.46 pg/mL was a good predictor of the OKS in patients 6 weeks after TKA surgery. Further research is still needed by using more samples, longer follow-up, and with specific varus or valgus deformities to get more accurate results.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES


