

# Differences in Cartilaginous Oligomeric Matrix Protein Levels and Lysholm Score 6 Months After Anterior Cruciate Ligament Reconstruction Between Procedure Taken Less Than 6 Weeks and More Than 6 Weeks After Injury

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## ABSTRACT

**Introduction:** Anterior cruciate ligament (ACL) injury is a common problem faced by patients, especially among young athletes. This study aims to evaluate differences in Cartilaginous Oligomeric Matrix Protein (COMP) levels and Lysholm scores six months after ACL reconstruction, based on the time the procedure was performed, namely  $\leq 6$  weeks after injury compared with  $> 6$  weeks after injury. This research is expected to provide insight into the influence of procedure time on functional outcomes and biomarkers after ACL reconstruction.

**Materials and Methods:** This study involved 30 subjects who underwent ACL reconstruction at Prof IGNG Ngoerah Hospital, with 15 patients undergoing surgery  $\leq 6$  weeks after injury and 15 other patients  $> 6$  weeks after injury. COMP serum sampling was performed, and the Lysholm score was measured using a questionnaire. Statistical analysis was performed to compare COMP levels and Lysholm scores between the two groups.

**Results:** The results of the study showed that there was a significant difference in COMP levels between patients who underwent ACL reconstruction  $\leq 6$  weeks after injury compared with those who underwent reconstruction  $> 6$  weeks after injury. Patients who underwent reconstruction earlier showed lower COMP levels, which was associated with higher Lysholm scores, indicating better functional outcomes. However, analysis of the proportion of Lysholm scores showed no significant difference between the two groups, although the proportion of patients with high scores was greater in the early reconstruction group.

**Conclusion:** This study concluded that there was a significant difference in joint fluid COMP levels between patients who underwent ACL reconstruction  $\leq 6$  weeks after injury compared with  $> 6$  weeks after injury. These results demonstrate the importance of treatment timing in ACL reconstruction to achieve optimal functional outcomes and can be used as a guide in the management of ACL injuries in the future.

**Keywords:** Anterior Cruciate Ligament, Cartilaginous Oligomeric Matrix Protein, Lysholm Score, Rekonstruksi ACL, Knee Injury

## INTRODUCTION

Anterior Cruciate Ligament (ACL) rupture is often experienced by young adults and is one of the most common sports injuries. The healing process in the ACL tends to be less than in other tissues. In this trauma, primary treatment is needed in the form of ACL reconstruction, while in patients without reconstruction, there can be limited knee movement and other long-term effects, because the ACL functions for anterior translation movement of the knee. Currently, post-ACL reconstruction failure is one of the reasons why ACL is a field that is widely studied in the world. The cause of reconstruction failure is mostly due to the position of the graft tunnel, which is not in an anatomical position, either because of the position of the graft or the angle of graft placement on the femoral or tibial tunnel side. ACL reconstruction is a therapeutic option for ACL rupture. ACL reconstruction can restore knee stability, knee kinematics are also restored, and functional scores can be the same as knees with intact ACLs. Knees with ACL reconstruction will theoretically have the same incidence of OA as knees without ACL injuries. Knee instability and abnormal force factors can be factors for the development of OA in the future. A meta-analysis of six studies evaluating OA progression after ACL injury showed that ACL-reconstructed knees had a relative risk of 3.62 compared to uninjured knees (206 of 395 vs 62 of 395) in developing OA, suggesting that ACL reconstruction cannot completely prevent OA (Meuffels et al., 2012; Paschos NK et al., 2017).

Cartilaginous Oligomeric Matrix Protein (COMP) plays an important role in cell proliferation and apoptosis in regulating cell movement and attachment to cartilage tissue. ACL injury is a typical inflammatory

condition characterized by ACL rupture. Using COMP as a biomarker of cartilage metabolism can reflect degenerative inflammatory changes in the joint. Although there is a positive correlation between COMP levels and all functional score parameters in many studies, there are researchers who reported that serum COMP levels correlated with knee pain scores, but not with knee function scores in women. The presence or absence of correlation between ACL injury biomarker levels and functional scores, leads us to a different medical explanation. The presence of a positive correlation comes from the fact that decreased serum levels of cartilage degradation products such as COMP directly indicate reduced cartilage bone loss, reduced inflammation (Chu et al., 2015; Das et al., 2015; Cui et al., 2022).

Theoretically, cartilage damage is often found in patients who undergo Anterior Cruciate Ligament (ACL) reconstruction more than 6 weeks (grouped as delayed-late) after injury. This is thought to contribute to a decrease in functional outcome scores when compared to patients who undergo ACL reconstruction within a period of less than 6 weeks (grouped as early). In patients who undergo ACL reconstruction more than 6 weeks after injury, there is an increase in Cartilage Oligomeric Matrix Protein (COMP) levels, which is one of the indicators of cartilage metabolism that has been damaged (Evans et al., 2014; Amano et al., 2018; Kim Wang., 2021; Reijman et al., 2021).

Hereby, the authors intend to conduct a more in-depth study on the differences in COMP levels in joint fluid and functional outcomes in patients who undergo ACL reconstruction within  $\leq 6$  weeks after injury compared to those who undergo reconstruction more than 6 weeks after injury. This study is expected to provide better insight into the impact of the timing of ACL reconstruction on cartilage conditions and joint function in patients after ACL injury.

## **MATERIALS & METHODS**

### **Study Design**

The study design used a retrospective study to determine the relationship between joint fluid COMP levels and Lysholm score 6 months post-operatively between ACL reconstruction patients < 6 weeks post-injury compared to > 6 weeks post-injury. Those who met the inclusion criteria were then measured for joint fluid COMP levels, Lysholm score and post-op X-ray radiological evaluation. This research was conducted at the Central General Hospital (RSUP) Prof. Dr. IGNG. Ngoerah from September 2023 to September 2024 or until the number of samples is met (Sopiyudin., 2020).

### **Inclusion Criteria**

The inclusion criteria for the study were as follows: patients with ACL injuries diagnosed through physical examination and knee MRI confirmed by a radiologist; those willing to undergo ACL reconstruction surgery; non-athletes or non-professional sportspeople; individuals who had not taken anti-inflammatory medications within one week prior to sample collection; surgeries performed by the same operator; procedures utilizing a single-bundle peroneus longus tendon graft; patients demonstrating good knee stability six months post-ACL reconstruction as confirmed by physical examination; and those who consented to participate in the study.

### **Exclusion Criteria**

Exclusion criteria included patients older than 50 years; those with a history of prior reconstruction surgery or recurrent injuries; individuals with multi-ligament injuries confirmed by physical examination and radiology; patients with a history of systemic or autoimmune diseases; those with a history of bone malignancies or metastatic malignancies; and individuals suffering from osteoarthritis in other regions, rheumatoid arthritis, or gout arthritis.

## **STATISTICAL ANALYSIS**

The collected data were analyzed statistically using SPSS software. Descriptive analysis was performed to determine the proportions and basic characteristics of patients in each group, with numerical data presented as mean and standard deviation for normally distributed data or as median and range for non-normally distributed data, while categorical data were presented as percentages. Normality testing was conducted using the Shapiro-Wilk test for sample sizes below 50 and the Kolmogorov-Smirnov test for sample sizes above 50. For inferential analysis, a paired t-test was used to identify mean differences between treatments when the data were normally distributed and paired.

## **RESULT**

In this study, data were obtained from 28 ACL rupture patients who underwent ACL reconstruction surgery from September 2023 to September 2024 at Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali. This study divided the patients into 2 groups consisting of 13 patients who underwent surgery < 6 weeks and 15 patients who underwent surgery > 6 weeks. The characteristics of patients who underwent ACL reconstruction surgery > 6 weeks were 9 males (60.0%) and 6 females (40.0%) with an average age of  $23.73 \pm 6.36$  years. In the group of patients who underwent surgery < 6 weeks, there were 7 males (53.8%) and 6 females (46.2%) with an average age of  $30.08 \pm 14.12$ . Graft inclination angle was obtained with an average of  $46.79 \pm 1.61$ . In the group of patients operated on < 6 weeks and the group of patients operated on > 6 weeks, there was no significant difference in the characteristics of age (years), gender, and graft inclination angle ( $p > 0.05$ ). The characteristics of patients undergoing ACL reconstruction surgery are shown in table 1.

**Table 1. ACL reconstruction patients characteristics**

Characteristic	Total n=28 (%)	Groups		P value
		< 6 weeks n=13 (%)	> 6 weeks n=15 (%)	
<b>Gender</b>				0,743*
Male	16 (57,1)	7 (53,8)	9 (60,0)	
Female	12 (42,9)	6 (46,2)	6 (40,0)	
<b>Age (year) (mean±SD)</b>	26,68±10,95	30,08±14,12	23,73±6,36	0,220 <sup>+</sup>
<b>Graft Inclination Angle</b>	46,79±1,61	46,49±1,58	47,05±1,64	0,187**

**Note:** \*Chi-square test, \*\*Independent T-test, <sup>+</sup>Mann-Whitney Test

The mean rank of COMP levels in patients who underwent surgery within <6 weeks was lower compared to the group who underwent surgery after >6 weeks. Subsequently, a non-parametric Mann-

Whitney test was performed, revealing a statistically significant difference in COMP levels between the two groups ( $p < 0.001$ ). The results are presented in Table 2.

**Table 2.**

Groups	Median (minimum-maximum)	P value
< 6 weeks (n=13)	1600,12 (1188,31-1962,54)	<0,001
> 6 weeks (n=15)	2846,67 (1970,57-3593,44)	

**\*Mann-Whitney Test. Average rank < 6 weeks 7,00; > 6 weeks 21,00**

The mean Lysholm score in patients who underwent surgery within < 6 weeks was higher compared to the group who underwent surgery after > 6 weeks. A Levene's test for heterogeneity was conducted, showing homogeneous data ( $p =$

0.356). An independent t-test was then performed, revealing no statistically significant difference in the mean Lysholm scores between the two groups ( $p = 0.180$ ). The results are presented in Table 3.

**Table 3.**

Groups	Mean ± SD	P value	Confidence Interval (95% CI)
< 6 weeks (n=13)	80,00±7,94	0,180	2,6(-3,13 – 8,33)
> 6 weeks (n=15)	77,4±6,83		

**\*Independent t-test; SD: standard deviation**

## DISCUSSION

This study involved 30 research subjects, all of whom underwent anterior cruciate ligament (ACL) reconstruction surgery at RSUP Prof. IGNG Ngoerah starting from November 2023. The subjects consisted of 13 patients who underwent ACL reconstruction within 6 weeks after injury and 15 patients who underwent reconstruction in more than 6 weeks after injury. Variables such as age and gender were recorded for each subject. A mean difference test was conducted for numerical variables, and a proportion difference test

was performed for nominal variables, such as gender, with no statistically significant differences observed between the two groups. Patients undergoing ACL reconstruction exhibited varied characteristics, which could act as confounding variables affecting the research outcomes. To control these confounders, strict inclusion and exclusion criteria were applied.

A non-parametric Mann-Whitney test revealed a statistically significant difference ( $p < 0.001$ ) in synovial fluid COMP levels between patients who underwent ACL

reconstruction within  $\leq 6$  weeks post-injury and those who had the surgery  $> 6$  weeks post-injury. The data analysis indicated that COMP levels were generally higher in patients who underwent reconstructions more than 6 weeks after injury. This increase in COMP levels may indicate a more significant cartilage degradation process, potentially due to a prolonged inflammatory period before surgery. Delays in surgical intervention provide more time for joint damage to progress, leading to higher COMP levels in synovial fluid. Prolonged inflammation after ACL injury can damage cartilage tissue and other joint structures. Consequently, the longer the delay between injury and reconstruction, the greater the risk of joint damage, as reflected in higher COMP levels. This finding aligns with previous studies suggesting that delayed ACL reconstruction increases the risk of cartilage damage. For instance, research by Frobell et al. found that patients with delayed ACL reconstruction experienced more significant cartilage damage than those who underwent early surgery. Similarly, Granan et al. reported that delays in ACL reconstruction beyond 12 weeks post-injury were associated with an increased risk of knee osteoarthritis. (Frobell et al., 2010; Granan et al., 2009). Conversely, some studies have reported differing results. A study by Dunn et al. found no significant differences in long-term clinical outcomes between patients who underwent early ACL reconstruction and those who delayed the procedure. However, Dunn's research was more focused on functional outcomes rather than biomarkers of joint damage, such as COMP. Thus, the current study adds a new perspective by highlighting the importance of timing in the context of biological joint damage, which may not be reflected in long-term functional outcomes. Overall, these findings underscore the importance of timely ACL reconstruction to minimize joint damage and achieve better clinical outcomes. This study supports a more

proactive approach to managing ACL injuries to reduce the negative impact on joint cartilage. Clinicians should consider earlier surgical intervention to mitigate further cartilage damage and improve patients' long-term quality of life. (Dunn et al., 2010).

The analysis also revealed no significant differences in Lysholm scores between the two groups. The mean score for patients who underwent early reconstruction ( $<6$  weeks post-injury) was comparable to those who underwent delayed reconstruction ( $>6$  weeks post-injury). The Lysholm score is a commonly used clinical assessment tool for evaluating postoperative knee function, including aspects such as pain, instability, and daily function. Although the difference was not statistically significant, the results suggest that patients undergoing earlier ACL reconstruction tend to have better knee function and higher recovery rates than those who delayed reconstruction. This may be due to factors such as lower joint damage and a more effective rehabilitation period for patients with earlier surgeries. Early reconstruction likely results in less cartilage degradation and joint inflammation, contributing to better functional outcomes. These findings are consistent with previous studies highlighting the benefits of early ACL reconstruction. For example, Frobell et al. found that early ACL reconstruction resulted in better long-term clinical outcomes, although it had no significant impact on long-term functional and clinical outcomes. Similarly, Biau et al. reported that patients undergoing reconstruction within 3 months post-injury showed better knee function improvements than those who delayed longer, though the differences were not dramatic. (Biau et al., 2007; Frobell et al., 2010). However, other studies, such as one by Smith et al., found no significant differences in long-term outcomes between early and delayed reconstruction. This study focused more on long-term functional outcomes and suggested that factors such as rehabilitation programs and preoperative

physical condition also play crucial roles in the final outcomes. Therefore, the Lysholm score analysis in this study emphasizes the importance of timely ACL reconstruction to achieve optimal functional outcomes. It underscores the need for timely clinical assessments and carefully considered surgical decisions to maximize knee function recovery and patient quality of life. These findings provide clinicians with guidance for more effective and efficient ACL injury management strategies, ultimately benefiting patients in the long term. (Smith et al., 2014).

The examination of Cartilaginous Oligomeric Matrix Protein (COMP) levels in synovial fluid provides valuable insights into knee joint condition following anterior cruciate ligament (ACL) reconstruction. This study highlights the importance of considering differences in COMP levels between patients undergoing ACL reconstruction within  $\leq 6$  weeks post-injury and those undergoing the procedure  $> 6$  weeks post-injury. These findings shed light on the effect of timing on biomarkers and functional scores, such as the Lysholm Score, and suggest that COMP levels may serve as a marker for the risk of post-traumatic osteoarthritis (PTOA) following ACL reconstruction. However, a limitation of this study was the absence of pre-operative COMP level measurements, which prevented comparisons between pre-operative and post-operative levels. Further research is needed to confirm the relationship between COMP levels and Lysholm Scores in the context of timing post-ACL reconstruction. Larger studies would strengthen these findings and enhance understanding of biomarkers as indicators of prognosis and functional recovery after ACL reconstruction.

## CONCLUSION

There was a significant difference in synovial fluid COMP levels between patients who underwent ACL reconstruction within  $\leq 6$  weeks post-injury compared to

those who underwent the procedure  $> 6$  weeks post-injury. However, there was no significant difference in functional outcomes, as measured by the Lysholm Score, between the two groups.

## Declaration by Authors

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