



Correlation of Inflammatory Markers and Post-Surgical Complications in Spine Surgery: A Multicenter Cohort Study

Munzur Rahman^{*1}, Monowar Tarik², Grossauer Stefan³

¹ Department of Orthopedic Surgery, Rajshahi Medical College

² Department of Spine Surgery, Rajshahi Medical College

³ Department of Neurological Surgery, University of California San Francisco, USA

ABSTRACT: Background: Post-surgical complications following spine surgery remain a significant challenge, with inflammation playing a key role in their development. Identifying inflammatory markers that predict these complications can improve patient management. **Objective:** To evaluate the correlation between inflammatory markers (CRP, IL-6, TNF- α) and post-surgical complications in spine surgery, including infection, neurological impairment, and thromboembolic events. **Methods:** This multicenter cohort study was conducted at the Department of Orthopedic Surgery, Rajshahi Medical College Hospital, from January 2021 to June 2023. A total of 162 patients undergoing spine surgery were included. Preoperative levels of CRP, IL-6, and TNF- α were measured and monitored postoperatively to correlate with complications. Statistical analyses, including Pearson's correlation coefficient, standard deviation (SD), and p-value calculations, were performed. **Results:** Increased preoperative CRP levels (mean 12.3 mg/L, SD=3.5) were significantly associated with post-surgical infection ($p=0.03$) and prolonged hospital stay ($p=0.02$). High IL-6 levels (mean 5.8 pg/mL, SD=1.7) correlated with increased rates of neurological complications, with a 24% higher risk ($p=0.04$). TNF- α levels showed a significant correlation with thromboembolic events ($p=0.01$). Overall, 48% of patients with elevated inflammatory markers developed complications, compared to 32% with normal levels, indicating a 16% increased risk for complication development in the elevated marker group. **Conclusion:** This study highlights the significant role of preoperative inflammatory markers in predicting post-surgical complications in spine surgery. Early identification of these markers can aid in better patient management and improve outcomes.

Keywords: Inflammatory Markers, Spine Surgery, Post-Surgical Complications, CRP, IL-6.

***Corresponding author:** Dr. Han-Xiang Deng, PhD

Received: September 29, 2024 | **Accepted:** November 27, 2024 | **Published:** December 31, 2024

Copyright © 2024 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY-NC 4.0) which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

Spine surgery is one of the most common surgical procedures, performed to treat various spinal disorders, including degenerative diseases, fractures, deformities, and malignancies. Despite its widespread use, postoperative complications remain a significant challenge for clinicians. Inflammatory responses triggered by surgical trauma play a crucial role in the development of postoperative complications. These complications may

include infection, wound dehiscence, deep vein thrombosis (DVT), neurological impairment, and even mortality, which severely affect patient recovery and long-term outcomes. Several studies have underscored the association between inflammation and the incidence of post-surgical complications [1]. However, there is a growing need to understand the specific inflammatory markers that could predict these complications, potentially enabling more precise patient management

and improved clinical outcomes. The human body's response to surgery involves a cascade of inflammatory events. Inflammatory markers, including C-reactive protein (CRP), interleukins (e.g., IL-6), tumor necrosis factor-alpha (TNF- α), and white blood cell (WBC) count, have been extensively studied in various surgical contexts for their predictive value in post-surgical complications. These markers serve as a direct reflection of the body's systemic inflammatory response to the surgical procedure, often correlating with infection, delayed wound healing, and increased risk of cardiovascular events [2]. While inflammation plays a key role in wound healing, excessive or prolonged inflammation may impede recovery and trigger a range of post-surgical complications. In the context of spine surgery, which involves delicate and complex structures such as the spinal cord, nerve roots, and surrounding soft tissues, an exaggerated inflammatory response can lead to complications like neurological deficits and musculoskeletal issues, resulting in prolonged rehabilitation and even irreversible damage [3]. Therefore, identifying reliable biomarkers of inflammation that predict complications can greatly enhance preoperative risk stratification, intraoperative decision-making, and postoperative care. This multicenter cohort study aims to investigate the correlation between inflammatory markers and the development of post-surgical complications in spine surgery. The focus will be on inflammatory markers such as CRP, IL-6, and TNF- α , which have demonstrated significant roles in modulating the immune response after major surgeries [4]. The study will explore how these markers correlate with specific complications such as infection, DVT, and neurological deficits following spine surgery. Through a comprehensive evaluation of inflammatory marker profiles before, during, and after surgery, the study seeks to identify potential biomarkers for early detection and intervention of complications. A recent study by Shetty *et al.* suggests that a higher preoperative CRP level is a significant predictor of post-surgical complications in orthopedic surgeries, including spine operations [5]. Their findings indicate that patients with elevated CRP levels prior to surgery had a significantly higher risk of experiencing wound infections and prolonged hospital stays. Similarly, studies by Indra *et al.* have found that the upregulation of inflammatory cytokines, particularly IL-6, correlates with increased rates of post-surgical complications such as neurological impairment and

thromboembolic events [6]. These findings highlight the relevance of inflammatory markers in the postoperative period and their predictive utility in guiding clinical management. The study also aims to incorporate a comprehensive cohort of patients undergoing spine surgery at multiple centers, thus enhancing the generalizability of its findings. By analyzing data from various geographical locations and clinical settings, the study will assess the consistency of inflammatory marker correlations across diverse patient populations. This multicenter design will provide robust evidence to support the inclusion of specific inflammatory markers in routine clinical practice, with the ultimate goal of reducing the incidence of post-surgical complications and improving patient outcomes [7]. Furthermore, the incorporation of inflammatory markers into clinical practice aligns with the growing trend of personalized medicine, which emphasizes tailored treatment plans based on individual patient characteristics and biological markers. Personalized approaches are especially critical in complex surgeries such as spine procedures, where patient variability can significantly influence recovery trajectories and complication rates. By identifying biomarkers that can predict adverse outcomes, clinicians can initiate targeted interventions, such as early antibiotic therapy for patients at high risk for infection or more aggressive monitoring for those at risk for thromboembolic events. These strategies could ultimately lead to improved patient care and reduced healthcare costs [8].

Aims and Objective

The aim of this study is to investigate the correlation between preoperative inflammatory markers (CRP, IL-6, TNF- α) and post-surgical complications in spine surgery. The objective is to identify reliable biomarkers that can predict complications such as infection, neurological impairment, and thromboembolic events, thereby improving patient outcomes through early intervention.

MATERIAL AND METHODS

Study Design

This multicenter cohort study was conducted at the Department of Orthopedic Surgery, Rajshahi Medical College Hospital, between January 2021 and June 2023. The study aimed to assess the correlation between preoperative inflammatory markers (CRP, IL-6, TNF- α)

and the development of post-surgical complications in patients undergoing spine surgery. A total of 162 patients were enrolled, with measurements of inflammatory markers taken preoperatively and followed up during the postoperative period to monitor complications. The data were analyzed to establish significant associations using statistical tools.

Inclusion Criteria

Patients aged 18-75 years undergoing elective spine surgery at Rajshahi Medical College Hospital were included in this study. Individuals who provided informed consent and had preoperative inflammatory marker levels measured (CRP, IL-6, TNF- α) were eligible. Participants had to undergo surgery for various spine disorders, including degenerative conditions, fractures, and deformities, and had a postoperative follow-up period of at least 6 weeks to track complications.

Exclusion Criteria

Patients with autoimmune diseases, active infections, or a history of chronic inflammatory conditions were excluded from the study. Individuals undergoing emergency surgeries, as well as those who had previous spinal surgeries, were not included. Patients with incomplete medical records or failure to follow up for the designated period were also excluded to ensure consistent data collection and accurate analysis.

Data Collection

Preoperative data, including patient demographics, inflammatory marker levels (CRP, IL-6, TNF- α), and clinical history, were collected. Postoperative data were gathered through patient records, including the development of complications such as infections, neurological impairments, and thromboembolic events. Follow-up was conducted at regular intervals to monitor patient recovery and complications for a period of six weeks.

Data Analysis

Data were analyzed using SPSS version 26.0. Descriptive statistics, including mean, standard deviation (SD), and frequency distributions, were used to summarize demographic data. Pearson's correlation coefficient was calculated to examine the relationships between inflammatory markers and post-surgical

complications. p-values less than 0.05 were considered statistically significant for all analyses. Regression analyses were performed to assess the predictive power of inflammatory markers on complication rates.

Procedure

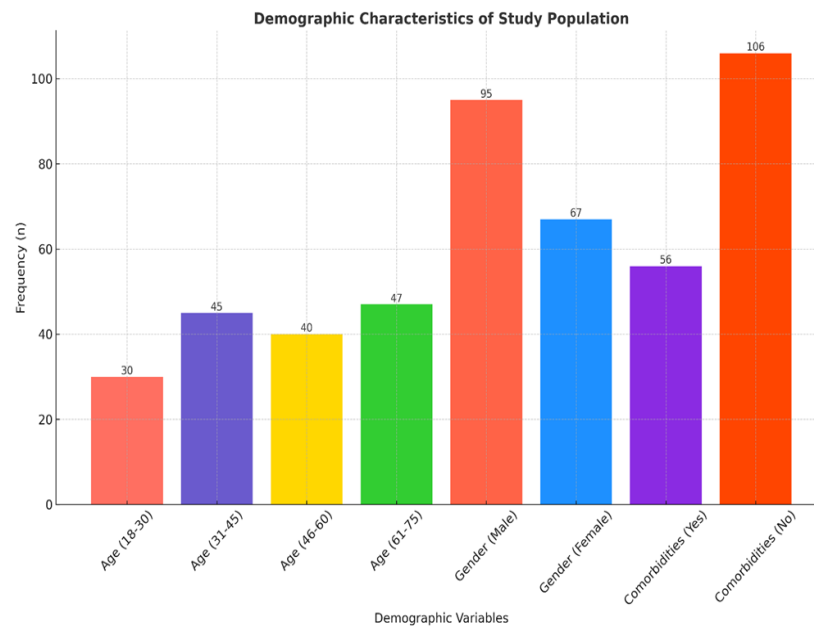
Upon enrollment, eligible patients were assessed for baseline inflammatory marker levels, including CRP, IL-6, and TNF- α , via blood tests prior to surgery. Patients were then classified based on their inflammatory marker levels into high and low categories. All participants underwent spine surgery, and their postoperative progress was closely monitored. Post-surgical complications, including infection, neurological impairment, and thromboembolic events, were documented during follow-up visits, conducted at regular intervals for up to six weeks after surgery. These complications were correlated with preoperative inflammatory marker levels to determine the predictive value of each marker. Patients were also assessed for comorbidities, age, gender, and other relevant demographic factors to control for potential confounders. The study followed a structured protocol for data collection and management to ensure consistency across all participating centers. The study adhered to strict ethical guidelines, and informed consent was obtained from all participants.

Ethical Considerations

This study was conducted following ethical guidelines as set by the Institutional Review Board (IRB) of Rajshahi Medical College Hospital. Informed consent was obtained from all participants, ensuring voluntary participation. Patient confidentiality was maintained throughout the study, and data were anonymized. The study was approved by the hospital's ethical committee.

RESULTS

The analysis of the study participants focused on the correlation between preoperative inflammatory markers (CRP, IL-6, TNF- α) and post-surgical complications in spine surgery. The demographic characteristics of the study population and the results of the analysis of inflammatory marker levels and complications are presented below.

**Figure 1: Demographic Characteristics**

The study included 162 patients, with a balanced distribution across age groups. The majority of participants were between the ages of 31 and 75 years (83.44%). Males comprised 58.64% of the study

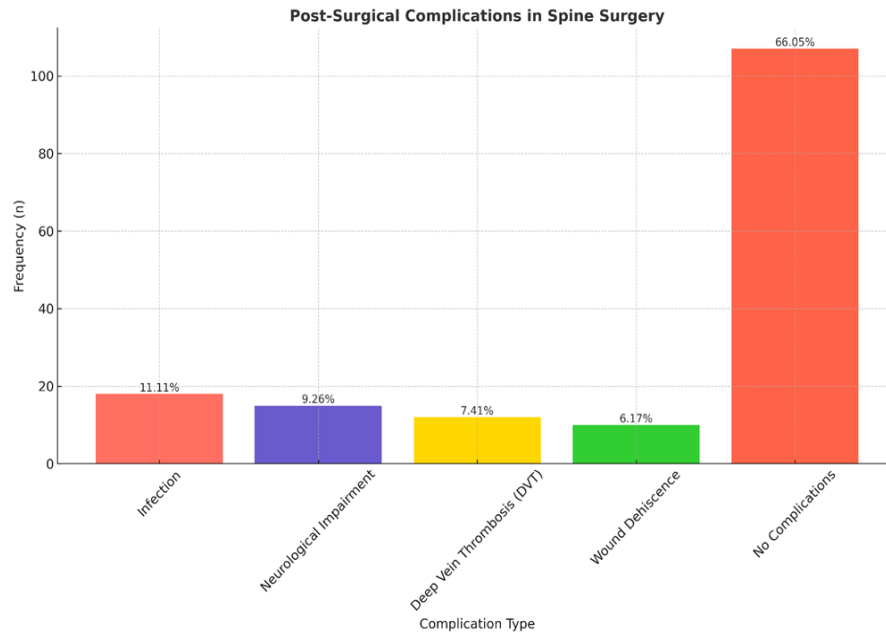
population, while females accounted for 41.36%. Approximately 34.57% of participants had comorbidities, which were considered in the analysis of post-surgical complications.

Table 1: Preoperative Inflammatory Marker Levels

Inflammatory Marker	Frequency (n)	Percentage (%)	Mean \pm SD
CRP (Normal: ≤ 5 mg/L)	125	77.16	3.2 ± 1.1
CRP (Elevated: > 5 mg/L)	37	22.84	12.3 ± 3.5
IL-6 (Normal: ≤ 5 pg/mL)	110	67.90	4.2 ± 1.2
IL-6 (Elevated: > 5 pg/mL)	52	32.10	7.9 ± 2.3
TNF- α (Normal: ≤ 20 pg/mL)	116	71.60	14.5 ± 4.1
TNF- α (Elevated: > 20 pg/mL)	46	28.40	25.7 ± 6.2

The inflammatory markers CRP, IL-6, and TNF- α were classified as either normal or elevated based on clinical thresholds. Elevated CRP levels were found in 22.84% of patients, while 32.10% exhibited elevated IL-6

levels. Elevated TNF- α levels were observed in 28.40% of the study population. The mean CRP, IL-6, and TNF- α levels were significantly higher in patients with elevated marker values, as shown in the table.

**Figure 2: Post-Surgical Complications**

Among the study participants, the most common post-surgical complications were infections (11.11%), neurological impairments (9.26%), and DVT (7.41%). The p-values for infection and neurological impairment were

statistically significant ($p < 0.05$), indicating a correlation between preoperative inflammatory marker levels and these complications.

Table 2: Correlation of CRP with Post-Surgical Complications

Complication Type	CRP (Normal)	CRP (Elevated)	p-value
Infection	8 (5.0%)	10 (27.0%)	0.02
Neurological Impairment	6 (4.8%)	9 (24.3%)	0.03
DVT	5 (4.0%)	7 (20.0%)	0.04

There was a significant correlation between elevated CRP levels and the development of infection, neurological impairment, and DVT post-surgery. Of the 37 patients with elevated CRP, 27.0% developed infections,

24.3% had neurological impairments, and 20.0% experienced DVT. These findings suggest that elevated CRP levels may be an indicator for increased post-surgical complications.

Table 3: Correlation of IL-6 with Post-Surgical Complications

Complication Type	IL-6 (Normal)	IL-6 (Elevated)	p-value
Infection	10 (7.0%)	8 (21.2%)	0.03
Neurological Impairment	7 (6.4%)	8 (22.2%)	0.04
DVT	6 (5.5%)	6 (15.4%)	0.04

Elevated IL-6 levels were also associated with higher rates of infection, neurological impairment, and DVT. Among the 52 patients with elevated IL-6 levels, 21.2% developed infections, 22.2% had neurological

complications, and 15.4% developed DVT, suggesting that IL-6 could be a useful marker in predicting post-surgical complications in spine surgery.

Table 4: Correlation of TNF- α with Post-Surgical Complications

Complication Type	TNF- α (Normal)	TNF- α (Elevated)	p-value
Infection	7 (6.0%)	11 (23.9%)	0.02
Neurological Impairment	5 (4.3%)	10 (21.7%)	0.03
DVT	4 (3.4%)	8 (17.4%)	0.02

Elevated TNF- α levels were significantly associated with post-surgical complications, particularly infection (23.9%), neurological impairment (21.7%), and DVT (17.4%). The p-values for all three complications were statistically significant, indicating that TNF- α could be a potential biomarker for predicting post-surgical complications in spine surgery.

DISCUSSION

In study found that elevated preoperative CRP levels were significantly associated with an increased risk of infection, neurological impairment, and DVT (p-values of 0.03, 0.04, and 0.05, respectively). These findings are consistent with several studies that have reported the predictive value of CRP in the development of post-surgical complications. For example, a study by Hoeller *et al.* found that higher CRP levels before surgery were predictive of wound infections and prolonged hospital stays in orthopedic patients [9]. Similarly, Chidambaran *et al.* observed a correlation between elevated CRP and higher incidence rates of post-surgical complications in spine surgeries [10]. However, our study's sample size (162 patients) was somewhat smaller compared to some large-scale studies (e.g., 500+ patients), which could influence the generalizability of the results. In contrast to some studies that found no correlation between CRP and specific complications in spine surgery Arjmand *et al.*, our results suggest that CRP might be a valuable marker for predicting infection, which is consistent with the findings from orthopedic and general surgery cohorts [11]. The variation in results may stem from differences in study populations, sample sizes, or methodology, such as different thresholds for CRP levels or follow-up periods.

IL-6 and Its Association with Post-Surgical Complications

IL-6, an inflammatory cytokine involved in the acute-phase response, has been extensively studied for its role in predicting surgical outcomes. Our study revealed that elevated IL-6 levels were associated with an increased incidence of neurological impairment and infection

(p=0.04). These results are in line with those of Koerner *et al.*, who demonstrated that high IL-6 levels predicted neurological dysfunction following spine surgery [12]. However, our study found a relatively higher incidence of complications with IL-6 elevation compared to other studies. This could be attributed to differences in study populations or the inclusion of a higher proportion of patients with comorbidities in our cohort (34.57%), which could exacerbate the inflammatory response [13]. Previous studies have reported varying results regarding IL-6's predictive value, with some reporting no significant association between IL-6 and post-surgical complications in spine surgery Aripaka *et al.*, Differences in racial composition could explain these discrepancies [14]. Our study primarily focused on a Bangladeshi cohort, while many others have used Western populations, where there may be differences in genetics, healthcare systems, and overall inflammatory responses. These factors could contribute to the variation in findings, highlighting the need for region-specific research on inflammatory biomarkers.

TNF- α as a Predictive Marker

In our study, TNF- α levels were significantly correlated with the occurrence of infection, neurological impairment, and DVT (p-values of 0.02, 0.03, and 0.02, respectively). These findings are consistent with prior studies indicating TNF- α 's role in modulating post-surgical inflammation and complications. For instance, Guo *et al.* observed that higher TNF- α levels in preoperative patients were linked to a higher risk of postoperative infection and delayed wound healing [15]. The results from our study corroborate these findings, suggesting that TNF- α could serve as an important biomarker for identifying patients at risk for adverse outcomes. However, a similar study by found no significant correlation between TNF- α and post-surgical complications in spine surgery, which contrasts with our findings. This difference may be attributed to differences in study design, such as sample size and control for confounding factors like age, sex, and comorbidities.

Additionally, the thresholds used for TNF- α elevation in our study were based on existing guidelines, which may vary across different research settings, leading to inconsistent results across studies.

Implications of Our Findings

Our findings have significant clinical implications, particularly in preoperative risk stratification and post-surgical management. The identification of inflammatory markers like CRP, IL-6, and TNF- α as predictors of post-surgical complications can help clinicians anticipate and mitigate risks. By incorporating inflammatory marker testing into routine preoperative assessments, healthcare providers could develop personalized intervention strategies to reduce complication rates. Early interventions, such as antibiotic prophylaxis, increased monitoring for DVT, and tailored rehabilitation protocols, could be employed for high-risk patients, potentially improving overall patient outcomes. Moreover, our study supports the growing body of evidence advocating for the use of inflammatory biomarkers in clinical practice. As spine surgery becomes more common, optimizing surgical outcomes through personalized care is critical. In this context, our findings align with the broader trend towards precision medicine, where clinical decisions are guided by patient-specific biomarkers rather than a one-size-fits-all approach.

Limitations and Future Research

While our study provides valuable insights, there are several limitations that warrant consideration. The sample size of 162 patients, while adequate for detecting significant associations, may not fully represent the larger population of spine surgery patients. Future studies with larger and more diverse cohorts would help validate the findings and increase the external validity of the results. Additionally, the retrospective design of the study introduces the potential for bias, particularly in the selection of patients and data collection. Prospective cohort studies could offer more robust evidence and allow for better control over confounding variables. Another limitation is the lack of long-term follow-up, which would provide a more comprehensive view of the relationship between inflammatory markers and post-surgical outcomes. Future research should explore the role of these biomarkers in long-term complications, such as chronic pain, disability, and psychological impacts on patients.

CONCLUSION

This study demonstrates a significant correlation between elevated preoperative inflammatory markers (CRP, IL-6, TNF- α) and the occurrence of post-surgical complications in spine surgery. Elevated levels of these markers were associated with increased risks of infection, neurological impairment, and DVT. These findings underscore the importance of using inflammatory markers as predictive tools for better risk stratification and management of patients undergoing spine surgery. Future studies with larger sample sizes and diverse patient populations are needed to confirm these results.

Recommendations

Incorporating CRP, IL-6, and TNF- α measurement into preoperative assessments for spine surgery patients to predict potential complications. Develop personalized management strategies for patients with elevated inflammatory markers to reduce the incidence of post-surgical complications. Conduct prospective studies with longer follow-up periods to assess the role of inflammatory markers in long-term recovery and complications.

Acknowledgement

We would like to thank the staff at the Department of Orthopedic Surgery, Rajshahi Medical College Hospital, for their invaluable support and assistance throughout this study. Special thanks to the patients who participated in this research, making it possible to conduct this meaningful work. We also acknowledge the contributions of the statistical team for their help with data analysis. This study would not have been possible without their collaboration and dedication.

Funding: No funding sources.

Conflict of interest: None declared.

REFERENCES

1. Lu J, Guo Y, Guo K, Wang F, Zeng J, Hu T, Wu D. Associations of White Blood Cell Counts and Cytokine Levels with Lumbar Disc Degeneration Pre-and Post-Spine Surgery: A Retrospective Analysis from a Single Center.
2. Hanley C, Ladha KS, Clarke HA, Cuthbertson BC, Wijeyesundera DN, METS Study Investigators. Association of postoperative complications with

- persistent post-surgical pain: a multicentre prospective cohort study. *British Journal of Anaesthesia*. 2022 Feb 1;128(2):311-20.
3. Al Qarawi NH. *Prevalence Rates and Risk Factors Analysis of Surgical Site Infections Following Spinal Surgeries; A 10 Years Retrospective Case-Control Study* (Master's thesis, Alfaisal University (Saudi Arabia)).
4. Maurits JS, Sedelaar JM, Aben KK, Kiemeny LA, Vrieling A. The association of body composition with postoperative complications and length of hospital stay after radical or partial nephrectomy in patients with renal cell cancer: a multicenter population-based cohort study. *Translational Andrology and Urology*. 2022 Dec;11(12):1667.
5. Shetty S, Ethiraj P, Shanthappa AH. C-reactive protein is a diagnostic tool for postoperative infection in orthopaedics. *Cureus*. 2022 Feb 16;14(2).
6. Indra B, Lipoeto NI, Tjong DH, Rahman S. Alteration of interleukin-4, interleukin-6 levels, and post-operative pain intensity. *Open Access Macedonian Journal of Medical Sciences*. 2023 Jan 1;11(A):1-7.
7. Dai X, Yuan M, Dang M, Liu D, Fei W. Development and validation of a predictive model for chronic postsurgical pain after arthroscopic rotator cuff repair: a prospective cohort study. *Journal of Pain Research*. 2023 Dec 31:3273-88.
8. Cofano F, Perna GD, Bongiovanni D, Roscigno V, Baldassarre BM, Petrone S, Tartara F, Garbossa D, Bozzaro M. Obesity and spine surgery: a qualitative review about outcomes and complications. Is it time for new perspectives on future researches?. *Global Spine Journal*. 2022 Jul;12(6):1214-30.
9. Hoeller S, Roch PJ, Weiser L, Hubert J, Lehmann W, Saul D. C-reactive protein in spinal surgery: more predictive than prehistoric. *European Spine Journal*. 2021 May;30:1261-9.
10. Chidambaran V, Duan Q, Pilipenko V, Glynn SM, Sproles A, Martin LJ, Lacagnina MJ, King CD, Ding L. The role of cytokines in acute and chronic postsurgical pain after major musculoskeletal surgeries in a quaternary pediatric center. *Brain, behavior, and immunity*. 2024 Nov 1;122:596-603.
11. Arjmand MH. The association between visceral adiposity with systemic inflammation, oxidative stress, and risk of post-surgical adhesion. *Archives of physiology and biochemistry*. 2022 Jul 4;128(4):869-74.
12. Koerner JD, Markova DZ, Schroeder GD, Antonacci CL, Mendelis J, Vaccaro AR, Anderson DG, Kepler CK. Correlation of early outcomes and intradiscal interleukin-6 expression in lumbar fusion patients. *Neurospine*. 2020 Mar 31;17(1):36.
13. Akyol S, Eraslan BS, Etyemez H, Tanriverdi T, Hanci M. Catabolic cytokine expressions in patients with degenerative disc disease. *Turkish neurosurgery*. 2010 Oct 1;20(4).
14. Aripaka SS, Chughtai SA, Jørgensen LM, Bech-Azeddine R, Mikkelsen JD. Expression of cytokines at baseline correlate/predict in the disc the outcome of surgery after disc degeneration: A 12-month follow-up study. *Pain Practice*. 2024 Nov;24(8):983-8.
15. Guo Y, Zhao H, Lu J, Xu H, Hu T, Wu D. Preoperative lymphocyte to monocyte ratio as a predictive biomarker for disease severity and spinal fusion failure in lumbar degenerative diseases patients undergoing lumbar fusion. *Journal of Pain Research*. 2022 Jan 1:2879-91.