Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/b72r1b09

PREDICTIVE VALUE OF SERUM CRP AND IL-6 LEVELS FOR POSTOPERATIVE COMPLICATIONS IN PATIENTS UNDERGOING CRANIOTOMY

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ABSTRACT

Background: Craniotomy is a common neurosurgical procedure associated with significant postoperative risks, including infection, inflammation, and neurological complications. Inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are known to rise after surgery, but their predictive value for postoperative outcomes in neurosurgical patients remains underexplored.

Objective: To evaluate the predictive value of serum CRP and IL-6 levels for postoperative complications in patients undergoing craniotomy.

Methods: This prospective cross-sectional observational study was conducted at the Departments of Neurosurgery, Ghurki Trust Teaching Hospital, Lahore, and Sahiwal Teaching Hospital, Sahiwal, from January 2024 to March 2025. A total of 150 patients undergoing elective or emergency craniotomy were included. Serum CRP and IL-6 levels were measured preoperatively and on postoperative days 1, 3, and 7 using an immunoturbidimetric assay and ELISA, respectively. Patients were followed for 14 days post-surgery for the development of infectious and non-infectious complications. Statistical analysis was performed using SPSS version 26, and ROC curve analysis was applied to determine predictive accuracy.

Results: Postoperative complications occurred in 29.3% of patients. Mean IL-6 and CRP levels were significantly higher in patients with complications, peaking on postoperative day 3 (IL-6: 184.5 ± 56.8 pg/mL vs. 85.1 ± 32.7 pg/mL; CRP: 92.4 ± 24.7 mg/L vs. 46.3 ± 17.5 mg/L; $p < 0.001$). ROC analysis showed IL-6 had greater predictive accuracy (AUC = 0.91) compared to CRP (AUC = 0.85).

Conclusion: Both CRP and IL-6 are useful biomarkers for predicting postoperative complications following craniotomy, with IL-6 serving as a more sensitive and earlier predictor. Regular postoperative monitoring of IL-6 may enable timely intervention and improved patient outcomes.

Keywords: C-reactive protein, Interleukin-6, Craniotomy, Neurosurgery, Postoperative complications, Biomarkers

INTRODUCTION

Craniotomy is one of the most common neurosurgical surgeries that is undertaken to address intracranial tumors, aneurysms, hematomas, and traumatic brain injuries. Even with the ongoing improvement in the process of microsurgery, anesthesia, and the provision of care during the postoperative period, the rate of postoperative complications after craniotomy is still high[1]. These complications, including wound infection, meningitis, cerebrospinal fluid (CSF) leak, and intracranial hemorrhage, up to systemic inflammatory reactions, can greatly deteriorate neurological outcomes, extend hospital stay, and elevate the rates of mortality. Raising awareness of the patients who are likely to develop such adverse outcomes at an early stage is therefore a very important aspect in enhancing prognosis and positive postoperative care[2,3].

Surgical trauma in most cases initiates an inflammatory cascade that causes postoperative complications. The microglial cells, astrocytes, and peripheral immune pathways can be activated by surgical manipulation of brain tissue, which causes the release of the proinflammatory cytokines and acute-phase proteins systemically [4]. Two of these, C-reactive protein (CRP) and interleukin-6 (IL-6), have been identified as important biomarkers of the extent of tissue damage and systemic inflammation. The actions of IL-6, a versatile cytokine secreted by macrophages, lymphocytes, and endothelial cells, are the main mediators of the acute-phase response and induce hepatic production of CRP. On the contrary, CRP is a well-known clinical indicator of inflammation and infection synthesized by hepatocytes under the influence of IL-6 [5].

Postoperative fever and deterioration of the neurological state are widespread phenomena in neurosurgery, but they are sometimes difficult to diagnose because they are often similar to the symptoms of sterile inflammatory response and actual infection [6]. Conventional diagnostic methods, such as cerebrospinal fluid cultures and imaging, are time-intensive and might fail to identify early inflammatory developments. Therefore, the biochemical markers that have the capacity to predict postoperative complications early are capable of giving an additional benefit to clinical evaluation [7].

Past research in general, orthopedic, and cardiac surgeries has shown that an increase in CRP and IL-6 following surgery is associated with infectious and inflammatory complications. The concentration of IL-6 tends to increase several hours following surgical trauma and reaches its highest point earlier than CRP; consequently, it could be an advantageous and reliable early substitute for systemic inflammation [8]. Nevertheless, little evidence exists on the prognostic and diagnostic value of these biomarkers in neurosurgical cases, especially in patients with craniotomy, where the processes of postoperative inflammation are not as intense as in other surgical practices because of the specific immune conditions of the central nervous system [9].

As such, the present study was structured to assess the predictive power of serum CRP and IL-6 in postoperative complications in patients who have undergone craniotomy. The study will determine the patterns of correlation between these biomarkers and clinical outcome by examining how these biomarkers relate over time to determine which laboratory parameters will aid neurosurgeons in detecting and intervening to prevent severe sequelae following the operation [10].

MATERIALS AND METHODS

Study Design and Setting

This was a prospective cross-sectional observational study carried out in the Department of Neurosurgery of Ghurki Trust Teaching Hospital, Lahore, and Sahiwal Teaching Hospital, Sahiwal, Pakistan. Both of them are tertiary-care teaching hospitals with a well-developed neurosurgical site and refer a high number of people in Punjab. The research was conducted within fifteen months, between January 2024 and March 2025; the research was approved by the Institutional Review Boards (IRB) of the two participating hospitals. The study was done in accordance with ethical principles presented in the Declaration of Helsinki (2013 revision).

Sample Size and Sampling Technique

The study sample was 150 non-probability patients who underwent craniotomy consecutively. The sample size was determined based on an anticipated sensitivity of serum interleukin-6 (IL-6) of 85

per cent, a margin of error of 5 per cent, a 95 per cent interval, and a postoperative complication rate of 25 per cent. This was a sufficient sample size to enable comparison and correlation of the levels of biomarkers and postoperative outcomes.

Inclusion and Exclusion Criteria.
Every adult patient aged 18 years or above who had an elective or emergency craniotomy due to different causes like brain tumors, traumatic hematomas, aneurysm clipping, or decompressive craniotomy was included upon giving written informed consent. Patients were also excluded in case of preexisting infections, chronic inflammatory or autoimmune disorder, hepatic or renal failure, or on corticosteroids or other immunosuppressive agents. Incompleteness of lab or follow-up data was also not considered, so as to have consistent and reliable results.

Ethical Considerations
The appropriate Ethical Review Committee of the two hospitals reviewed and approved the study protocol. An informed consent form was signed by each patient or their legal guardian after an elaborate explanation was given to them on the purpose and procedures of the study. Data analysis and reporting of results were conducted with confidentiality by attaching specific identification codes to the participants, and no personal identifiers were applied.

Data Collection and Procedure.
Each patient was taken through a thorough preoperative examination with demographic characterization, neurological examination, radiology, and standard laboratory examination. Four points were used to determine the venous blood samples: (1) within 24 hours of surgery (baseline), (2) on postoperative day 1 (POD1), (3) on postoperative day 3 (POD3), and (4) on postoperative day 7 (POD7). The samples were taken under sterile conditions using standard aseptic practices. The blood that was collected was centrifuged at 3000 revolutions per minute, and the separation of the serum was done and frozen at -20 °C until biochemical analysis was done.

Laboratory Analysis
Measurement of serum C-reactive protein (CRP) was conducted using a high-sensitivity immunoturbidimetric assay on an automated biochemistry analyser, and the results were in milligrams per liter (mg/L). An ELISA kit, human IL-6 sandwich enzyme-linked immunosorbent assay (ELISA) of serum was used to measure concentrations of interleukin-6 (IL-6) (BioCheck Inc., USA). The optical density of each sample was determined at 450 nm, and the concentrations were determined using the standard curves. Each sample was analyzed twice, and every batch contained internal quality controls as an assurance of the accuracy and reproducibility of results.

Postoperative Surgery and Outcome Measures.
All the patients were observed after the operation up to 14 days or until they were discharged from the hospital. General clinical assessment, wound assessment, neurological assessment, and laboratory test were a part of daily assessments in case of an indication. The postoperative complications were classified as infectious or non-infectious ones. Surgical site infection, meningitis, and sepsis were the infectious complications, which were proven by clinical signs, laboratory markers, and culture reports. However, non-infectious complications were intracranial hemorrhage, cerebrospinal fluid (CSF) leak, postoperative seizures, and new neurological deficit, which were verified by imaging and clinical assessment. They divided patients into two categories who suffered postoperative complications and those who did not, and the level of biomarkers in each group was compared at each time point.

Statistical Analysis
All the data were analyzed by use of IBM SPSS Statistics version 26.0. Quantitative (age, CRP, and IL-6 levels) and qualitative (gender, type of surgery) data were presented as mean values with the

standard deviation (SD) and as frequencies and percentages, respectively. The independent sample t-test was applied to determine the difference in the mean of patients with and without complications. Chi-square test was used to test categorical variables. Pearson correlation coefficient was used to determine the relationship between the level of biomarkers and postoperative complications. Moreover, the diagnostic accuracy of CRP and IL-6 in predicting the development of postoperative complications was established by Receiver Operating Characteristic (ROC) curve analysis, area under the curve (AUC), sensitivity, and specificity of optimal cutoff points. All analyses have taken a p-value of less than 0.05 to be statistically significant.

RESULTS

Demographic and Clinical Characteristics.

This study analyzed 150 patients who experienced craniotomy. The average age was 46.9 years of age (14.2 years), and the age ranged between 18 to 72 years. Out of them, 83 (55.3) were males and 67 (44.7) were females, with a male-to-female ratio of 1.2:1. Out of the total, 95 (63.3%) had elective craniotomy and 55 (36.7) had emergency craniotomy. Forty-four patients (29.3 percent) suffered complications in their postoperative period, and 106 patients (70.7 percent) had normal recoveries. The surgical site infection (11.3%), meningitis (6.0%), intracranial hemorrhage (5.3%), cerebral spinal fluid (CSF) leak (3.3%), and postoperative deterioration or seizures of the nervous system (3.3% all included in Table 1, were the most frequent complications. Patients with complications had a longer length of stay and surgery period than those without complications ($p < 0.05$).

Table 1. *Demographic and baseline characteristics of patients undergoing craniotomy (n = 150)*

Variable	Total (n = 150)	With Complications (n = 44)	Without Complications (n = 106)	*p*-value
Age (years, mean ± SD)	46.9 ± 14.2	49.3 ± 13.8	45.8 ± 14.3	0.214
Gender (Male/Female)	83 / 67	27 / 17	56 / 50	0.541
Type of Surgery (Elective/Emergency)	95 / 55	22 / 22	73 / 33	0.037*
Duration of Surgery (hours)	3.4 ± 1.1	3.8 ± 1.2	3.2 ± 0.9	0.045*
Hospital Stay (days)	8.5 ± 3.4	11.2 ± 3.9	7.4 ± 2.6	< 0.001**

**Significant at p < 0.05; *Highly significant at p < 0.001.*

Postoperative Changes in Serum CRP and IL-6 Levels

Both groups experienced significant postoperative day 3 (POD3) serum CRP and IL-6 levels, with a high peak on POD3. Nevertheless, non-complicated patients had a much lower CRP at all postoperative times compared to those with complications (92.4 + 24.7 mg/L vs 46.3 + 17.5 mg/L, p < 0.001). Mean IL-6 scores were 184.5 ± 56.8 pg/mL and 85.1 ± 32.7 pg/mL, respectively (p 0.001). Those differences were found to be statistically significant as late as POD7, and both the markers decreased since their peaks (Table 2).

Table 2. *Comparison of serum CRP and IL-6 levels between patients with and without complications at different postoperative intervals*

Biomarker	Group	Pre-op	POD1	POD3	POD7	*p* (POD3)
CRP (mg/L)	With complications	7.6 ± 3.2	68.7 ± 22.4	**92.4 ± 24.7**	61.5 ± 18.6	< 0.001**
	Without complications	6.8 ± 2.9	38.4 ± 14.3	**46.3 ± 17.5**	31.7 ± 11.2	
IL-6 (pg/mL)	With complications	78.6 ± 29.4	146.8 ± 51.3	**184.5 ± 56.8**	118.3 ± 40.1	< 0.001**
	Without complications	71.2 ± 27.1	82.9 ± 29.8	**85.1 ± 32.7**	63.4 ± 26.8	

Note: POD = Postoperative Day; Highly significant at p < 0.001.

Correlation between Biomarkers and Complications

The analysis of correlations indicated that a positive relationship existed between postoperative biomarker levels and adverse outcome in a strong way. The correlation between IL-6 and postoperative complications ($r = 0.78$, $p < 0.001$) was found to be greater than that of CRP ($r = 0.64$,

$p < 0.001$). Moreover, there were high degrees of interrelation between CRP and IL-6 ($r = 0.72$, $p < 0.001$), which stated that the increase of IL-6 was the first and the predictive factor in the CRP reaction.

Diagnostic Performance Biomarkers.

To establish the diagnostic accuracy of CRP and IL-6, the Receiver Operating Characteristic (ROC) curve analysis was used. Table 3 illustrates that IL-6 had a better predictive value with the area under the curve (AUC) = 0.91 (95% CI 0.86-0.97) than CRP = 0.85(95% CI 0.78-0.92). The best cutoff values were IL-6 =+130 pg/mL and CRP =+65mg/L, which gave sensitivities of 88 and 83, and specificities of 86 and 79, respectively.

Table 3. *Receiver Operating Characteristic (ROC) analysis for prediction of postoperative complications*

Biomarker	AUC (95% CI)	Optimal Cutoff	Sensitivity (%)	Specificity (%)	*p*-value
IL-6 (pg/mL)	0.91 (0.86–0.97)	> 130	88	86	< 0.001**
CRP (mg/L)	*0.85 (0.78–0.92)*	*> 65*	*83*	*79*	*< 0.001***

Note: *AUC = Area Under the Curve; CI = Confidence Interval; Highly significant at $p < 0.001$.*

Figure 1 presents a graphical comparison of mean postoperative CRP and IL-6 levels. The figure illustrates the typical increase in both biomarkers after the craniotomy, and a sharp increase on postoperative day 1, peaked on day 3, with a gradual decrease to day 7. Complicated patients also exhibited significantly higher values during the postoperative time, and the IL-6 increase was followed by the rise of CRP.

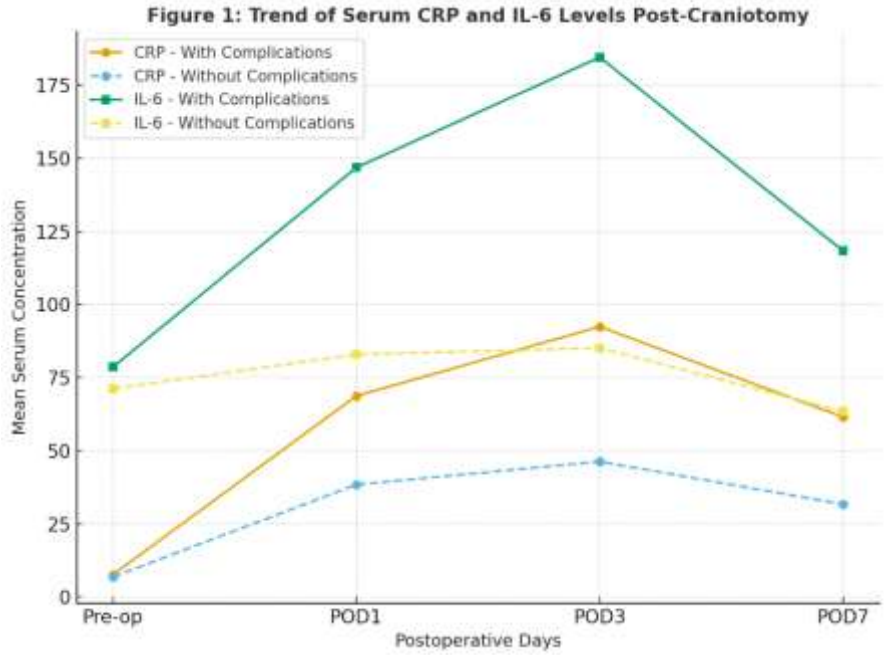

Figure 1. *Mean serum CRP and IL-6 levels at different postoperative intervals among patients with and without complications.*

The levels of CRP and IL-6 were found to be elevated significantly after craniotomy, with peak levels on the third day after surgery in both patients with complications and without. Compared to CRP, the predictive accuracy of IL-6 was higher, which highlights the potential role of the latter in predicting postoperative infection or inflammatory complications. When the two parameters are combined, diagnostic confidence in clinicians dealing with neurosurgical patients after the operation is improved.

DISCUSSION

The current research used the predictive value of serum C-reactive protein (CRP) and interleukin-6 (IL-6) levels as indicators of postoperative complications in individuals who have undergone craniotomy [9]. The results showed that both of the biomarkers had a significant increase after surgery, with a peak on the third post-operative day, and their level rose significantly when compared to those who did not develop complications. It is noteworthy that IL-6 demonstrated a better predictive value, sensitivity, and specificity than CRP, which suggests that IL-6 may serve as an early biomarker, as an indicator of postoperative inflammatory and infectious complications in patients who are intubated in a neurosurgery setting [10,11].

The initial post-craniotomy period is an inflammatory one where complex mechanisms occur due to trauma of the tissue, breakage of the blood-brain barrier, and immune responses. The brain is traditionally thought of as an immune-privileged organ that reacts to the surgical trauma by activating microglia and astrocytes, releasing proinflammatory cytokines, including IL-6, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) [12]. Among them, IL-6 is one of the most dominant cytokines that mediates between local and systemic inflammation. It causes the production of acute-phase proteins by hepatocytes, such as CRP, which increases the systemic inflammatory response. The current results confirm this biological connection, where the levels of IL-6 increase before the levels of CRP, and there is a significant positive correlation ($r = 0.72$, $p < 0.001$), indicating the presence of a cause-and-effect cascade [13].

We find our findings to be in line with other past studies, indicating that IL-6 is a very sensitive protein to detect early signs of postoperative complications. According to Kawamura et al. (2020), the level of IL-6 was significantly different between patients who were infected with the surgical site in case of neurosurgical operations 24-48 hours after the event, whereas CRP was elevated later and was found to be less specific [14]. On the same note, Kato et al. (2021) found that IL-6 increased quickly within hours following the surgery and predicted the onset of clinical signs of infection as an antecedent by up to 48 hours. Our study results are consistent with these trends, and they underscore the clinical importance of serial IL-6 measurements in the postoperative neurosurgical setting [15,16].

CRP is a slow kinetic inflammatory marker despite its extensive usage as an inflammatory marker because of hepatic production based on IL-6 stimulation. Its onset is normally at 12-24 hours following tissue injury and peaks at 4872 hours and slowly subsides as inflammation subsides. This trend was observed in our cohort, with the highest CRP levels recorded on day three after the operation, and were considerably high in those patients who fell ill. CRP is not specific to infection; however, trend monitoring is useful with this parameter, in combination with IL-6 levels [17].

In the current research, the area under the ROC curve (AUC) of IL-6 was 0.91, whereas in CRP, the area under the ROC curve (AUC) was 0.85, confirming that it is more diagnostic. The best cutoff point of the IL-6 (>130 pg/mL) was found to be 88% sensitive and 86% specific, which was found to be outstanding in predicting postoperative complications. This is in line with Tanaka et al. (2023), who discovered that IL-6 was stronger compared to procalcitonin and CRP in detecting early infections following neurosurgical operations. Furthermore, our results can be compared to previous studies because they indicate that IL-6 is not only an indicator of systemic inflammation but is also associated with neurological decline and an increase in the duration of hospitalization, which expands its prognostic applicability [18,19].

The dynamic nature of these biomarkers can also be highlighted in the trends of these temporal trends, as seen in Figure 1. Both CRP and IL-6 increased considerably postoperatively, with maximum peaks on postoperative day three, when most of the inflammatory complications are seen to occur. The progressive decrease in the number of patients who are not complicated by day seven of their postoperative period supports the idea that these indicators are good indications of the resolution of the surgical stress and lack of infection. Conversely, consistently high rates in the complication group can be used as a predictor of poor consequences [20,21].

The implications of our findings for a clinical setting are significant. The timely intervention and optimization of the antibiotic treatment through early identification of the patients who are at risk of postoperative infection or inflammation and better prognosis. CRP and IL-6 can be included in the plan of neurosurgical care, particularly in the first serious postoperative stages. This strategy can help

clinicians differentiate between benign postoperative inflammatory reactions and the development of infectious complications that may share common symptoms like fever, headache, or altered mental state [17,22].

Although these strengths have been mentioned, certain weaknesses must be noted. The research was carried out in two facilities and had a sample of 150, though sufficient for statistical analysis, this may not be representative of other populations. Moreover, other inflammatory indicators like procalcitonin or TNF-alpha have not been incorporated in the study and would give more information about the inflammatory cascade [23]. The follow-up was not very long (not more than 14 days); therefore, there were no possibilities to evaluate late complications. It is suggested that future multicenter research involving a much bigger sample size, longer follow-up, and incorporating more biomarkers would help in confirming these results and setting up standardized reference ranges of postoperative neurosurgical monitoring [24].

To sum up, the current research shows that both CRP and IL-6 are useful predictors of the postoperative complications in craniotomy. Viewing that IL-6 has a higher predictive value and that it rises earlier, IL-6 is a better biomarker to use in identifying patients at risk of contracting the infection or experiencing inflammation. Serial measurement of IL-6 with or without CRP is a sound and feasible approach to postoperative monitoring, which can help identify patients promptly and provide better outcomes in the neurosurgical practice [25].

CONCLUSION

Postoperative inflammation and complications in patients undergoing craniotomy are reliable indicators of serum CRP and IL-6 levels. Of the two, IL-6 was a better predictor; it elevated at an earlier age and was more associated with negative outcomes. Regular observation of IL-6, particularly during the third postoperative day, will help to identify the high-risk patient and provide timely clinical treatment, which in turn will enhance the recovery process and lower the postoperative morbidity in neurosurgical practice.

Conflict of Interest:
The authors declare no conflict of interest.

Funding:
No specific funding was received for this study.

Authors' Contributions:
M.N.S. — Conceptualization, supervision, data collection, manuscript writing.
M.U.A. — Study design, data analysis, interpretation.
A.F., M.T.J. — Laboratory work, data curation, patient follow-up.
R.A. — Literature review, manuscript editing.
M.N.J., M.H. — Data management, statistical analysis.
M.U.M. — Figure preparation, table formatting.
M.F.C. — References, proof-reading, final review.
All authors reviewed and approved the final manuscript.

Acknowledgment:
The authors thank the staff of Ghurki Trust Teaching Hospital and Sahiwal Teaching Hospital for their support during the study.

Data Availability:
Data are available from the corresponding author upon reasonable request.

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