Original Article: Determining the Relationship Between Systemic Immune-Inflammation Index (SII) and Acute Pain Intensity After Femoral Fracture Surgery in Hip Arthroplasty Candidates

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A B S T R A C T

Background: The Systemic Immune-Inflammation Index (SII) has emerged as a reliable marker of systemic inflammation and has been associated with various postoperative outcomes in surgical patients. However, its relationship with acute postoperative pain in patients undergoing hip arthroplasty for femoral fractures remains underexplored. **Objective:** This study aims to investigate the correlation between the SII and acute pain intensity in patients undergoing hip arthroplasty for femoral fractures, along with its association with postoperative clinical outcomes such as length of hospital stay (LOHS), ICU admission, and platelet count.

Methods: This prospective observational study was conducted with 112 patients who underwent hip arthroplasty for femoral fractures. Preoperative blood samples were used to calculate the SII, and pain intensity was measured at various time points postoperatively using a visual analog scale (VAS). Clinical outcomes, including LOHS, ICU admissions, and platelet counts, were recorded.

Results: A significant positive correlation was found between the SII and postoperative pain intensity, with higher SII values associated with increased pain levels at 2 and 4 hours postoperatively ($r = +0.745$, $p = 0.005$). Additionally, patients with elevated SII values had significantly longer hospital stays (22 days vs. 17 days, $p = 0.006$), higher ICU admission rates (27.94% vs. 16.60%, $p = 0.036$), and elevated platelet counts. The SII was also significantly correlated with neutrophil and lymphocyte counts, highlighting its role in reflecting the inflammatory response.

Conclusion: The SII appears to be a promising predictor of postoperative pain intensity and adverse clinical outcomes in patients undergoing hip arthroplasty for femoral fractures. Elevated SII values are associated with increased pain, prolonged hospital stays, and higher rates of ICU admission. These findings suggest that the SII could serve as a useful biomarker for assessing postoperative complications and guiding clinical management in surgical patients.

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Introduction

Acute postoperative pain is one of the most common and significant challenges encountered by patients following surgical interventions, particularly in orthopaedic procedures such as hip fracture surgeries. The management of pain is a critical aspect of patient care as it influences recovery, hospital stay duration, and overall patient satisfaction [1-3]. Pain intensity influenced by a variety of factors, including the type of surgery, patient characteristics, and underlying physiological responses, which include inflammation. In this context, the systemic immune-inflammation index (SII) has emerged as a potential biomarker for evaluating the inflammatory response and its association with pain and other postoperative outcomes [4].

Hip fractures, particularly in elderly patients, are a common clinical concern that often requires surgical intervention, such as total hip arthroplasty (THA) or hemiarthroplasty. These fractures are often associated with significant morbidity and a prolonged recovery period, especially in older individuals with comorbidities. The intensity of postoperative pain following hip surgery can be severe, and inadequate pain control linked to numerous adverse outcomes, including delayed rehabilitation, prolonged hospital stays, and poor functional recovery [5-7].

Acute pain following hip surgery arises from multiple sources, including soft tissue damage, bone fractures, and the surgical intervention itself. The inflammation associated with these injuries not only contributes to pain but can also influence recovery by affecting various physiological processes, such as immune response and tissue repair. This makes the role of systemic inflammation particularly relevant in understanding the severity and duration of pain following surgery [8].

The systemic immune-inflammation index (SII) is a composite marker derived from routine blood test components: neutrophil count, platelet count, and lymphocyte count. This index has garnered attention as an indicator of the body's systemic inflammatory state. It calculated using the formula:

$$SII = \frac{\text{Neutrophil count} \times \text{Platelet count}}{\text{Lymphocyte count}}$$

The SII is a reflection of both the innate immune response (neutrophils and platelets) and the adaptive immune response (lymphocytes). Increased levels of SII are generally associated with heightened systemic inflammation, which has been linked to various adverse outcomes, such as prolonged hospital stays, increased complication rates, and worse prognosis in various clinical conditions, including cancer, cardiovascular diseases, and surgical recovery [9-11].

In the context of orthopaedic surgery, particularly hip fracture surgery, systemic inflammation plays a crucial role in the patient's recovery process. The inflammatory response is essential for tissue healing, but excessive inflammation can lead to complications such as increased pain, delayed recovery, and higher rates of postoperative infections. Therefore, understanding the relationship between SII and acute postoperative pain is critical in predicting patient outcomes and optimizing pain management strategies [12-14].

The relationship between systemic inflammation and pain is complex and multifactorial. Inflammatory cytokines, such as interleukins and tumor necrosis factor-alpha (TNF-α), are released at the site of injury and contribute to the sensitization of pain receptors, which can lead to hyperalgesia (increased pain sensitivity). In addition to local inflammation, the systemic inflammatory

response can amplify pain perception by influencing central nervous system pathways.

Neutrophils and platelets are key mediators in the inflammatory cascade. Neutrophils are among the first cells to respond to injury, releasing pro-inflammatory cytokines and chemokines that exacerbate local tissue damage. Platelets, which are involved in blood clotting, also release pro-inflammatory substances that contribute to the activation of the immune system and the subsequent inflammatory response. Lymphocytes, on the other hand, play a role in adaptive immunity and are involved in the resolution of inflammation. Alterations in the balance of these cells, as reflected in the SII, may be indicative of an abnormal inflammatory response, which can correlate with more intense pain [15].

Previous studies have shown that elevated levels of SII are associated with various adverse outcomes, including higher levels of pain, longer hospital stays, and an increased need for intensive care in patients undergoing surgery. Research has suggested that SII may be a reliable predictor of postoperative complications, particularly in surgeries involving significant tissue trauma, such as hip fracture repairs. Studies in other surgical disciplines, such as cardiac surgery and cancer resection, have found that elevated SII correlates with poor postoperative recovery and higher pain scores [16-18].

In orthopaedic surgery, SII has proposed as a useful marker to predict the degree of inflammation and its potential impact on recovery. However, the relationship between SII and acute pain intensity following hip fracture surgery remains an area that requires further investigation. Understanding how SII can predict pain intensity in this population could lead to more effective pain management strategies, tailored to individual inflammatory profiles [19-21].

This study aims to determine the relationship between the systemic immune-inflammation index (SII) and acute pain intensity in patients undergoing hip fracture surgery, specifically in candidates for hip arthroplasty. By assessing the association between SII and pain scores, the study seeks to provide valuable insights into how systemic inflammation influences pain perception in the early postoperative period. Additionally, this study will explore whether SII can serve as a predictive marker for pain intensity, potentially guiding clinicians in optimizing pain management protocols [22].

The findings of this study could have significant clinical implications, as they may help to identify patients at risk for severe postoperative pain based on their inflammatory profile. If a strong correlation found, SII used as an objective measure to predict pain levels, allowing healthcare providers to adjust pain management strategies accordingly. This could not only improve patient outcomes but also reduce the incidence of complications associated with inadequate pain control, such as delayed recovery and prolonged hospital stays [23-25].

In summary, the systemic immune-inflammation index (SII) is a promising marker of systemic inflammation that may correlate with pain intensity following hip fracture surgery. By understanding this relationship, healthcare providers could better anticipate pain levels and tailor postoperative care to improve patient outcomes. Future research into SII as a predictor of postoperative pain and recovery is essential to validate its clinical utility and enhance our approach to pain management in surgical patients [26].

Materials and Methods

This prospective, observational study designed to evaluate the relationship between the Systemic Immune-Inflammation Index (SII) and acute pain intensity following hip

arthroplasty in patients with femoral fractures. The study conducted at Shohada and Imam Reza Hospitals, affiliated with Tabriz University of Medical Sciences, during the second half of 2023.

Study Design

The study followed a prospective, cross-sectional design with data collection over a six-month period. This design enabled the assessment of pain intensity and the SII in patients post-surgery and allowed for the identification of correlations between these variables. Data collected at multiple points during the postoperative period (1, 2, 4, and 6 hours). This approach ensured the evaluation of the dynamic changes in inflammatory responses, as indicated by SII, and their relationship with pain and analgesic consumption in the immediate postoperative period.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were as follows: patients aged 50 to 80 years diagnosed with femoral fractures and scheduled for primary hip arthroplasty, including both total hip arthroplasty and hemiarthroplasty procedures. Patients had to have a clear preoperative assessment, indicating that the fractures were suitable for surgical intervention. Additionally, patients who were capable of providing informed consent were included in the study. Exclusion criteria involved several factors to ensure that the results not confounded by comorbid conditions that could influence the immune-inflammatory response or pain perception.

Sample Size and Sampling Method

The study targeted a sample size of 112 patients, which calculated based on the formula for determining sample size for a population with a dependent variable. The calculation considered a significance level (alpha) of 0.05, a beta error of 0.84 (statistical power of 80%), and an effect size of 0.45, with an estimated dropout rate of 10%. A pilot study conducted to determine the expected values of the variables involved. The sample size calculation, with these parameters, resulted in 112 patients as the minimum required sample size.

Data Collection and Procedure

Data collection included demographic and clinical characteristics of the patients, such as age, gender, body mass index (BMI), and relevant medical history (e.g., hypertension, diabetes, cardiovascular disease). The focus was on collecting data related to the SII, pain intensity, and analgesic use post-surgery.

Systemic Immune-Inflammation Index (SII)

Blood samples collected from each participant preoperatively (at hospital admission) to calculate the SII, which was determined using the following formula:

$$SII = \frac{\text{Neutrophil count} \times \text{Platelet count}}{\text{Lymphocyte count}}$$

The laboratory analysis performed at the central hospital laboratory, where the neutrophil, platelet, and lymphocyte counts were measured using standard automated hematology analyzers.

Pain Measurement

Pain intensity assessed using the Visual Analog Scale (VAS), which has been widely validated for measuring pain intensity in clinical settings. Pain scores recorded at specific time points post-surgery: 1 hour, 2 hours, 4 hours, and 6 hours after surgery. The VAS allowed patients to indicate their perceived pain level on a 10-point scale, where 0 indicated no pain and 10 represented the worst possible pain.

Analgesic Consumption

The amount of meperidine (pethidine), a commonly used opioid analgesic in postoperative pain management, recorded for each patient at the same intervals. This used as a surrogate measure for the severity of pain and the patient's need for pain management.

Hemodynamic Parameters

Heart rate and mean arterial pressure (MAP) monitored at the same time points as pain measurement, as they may correlate with the inflammatory response and pain intensity. These parameters recorded to assess their relationship with the SII.

Duration of Hospital Stay and ICU Admission

Additional outcomes measured were the length of hospital stay (LOHS) and the need for intensive care unit (ICU) admission. These data collected from patient records. ICU admission considered a significant outcome due to its relevance in the recovery trajectory of patients undergoing major surgery, especially those with elevated SII, which might indicate a heightened inflammatory state.

Data Analysis

Data analysis performed using SPSS software version 25.0. Descriptive statistics, including means, standard deviations, and frequencies, were used to summarize demographic and clinical data.

Ethical Considerations

The ethical approval for this study obtained from the Ethics Committee of Tabriz University of Medical Sciences, with the approval code IR.TBZMED.REC.1403.154. The study adhered to the ethical principles outlined in the Declaration of Helsinki, and informed consent obtained from all participants prior to their inclusion in the study. Patients informed about the nature of the study, the procedures involved, and the voluntary nature of their participation. Confidentiality of patient information strictly maintained, and all data anonymized for analysis. The risks and benefits of participation clearly explained, and participants assured that they could withdraw from the study at any time without affecting their medical care.

Results

In this study, we evaluated the relationship between the Systemic Immune-Inflammation Index (SII) and acute pain intensity following hip arthroplasty in patients with femoral fractures. The results showed significant correlations between the SII and pain scores, as well as analgesic consumption during the early postoperative period. Furthermore, the study highlighted the association of SII with other clinical outcomes such as length of hospital stay (LOHS) and the need for intensive care unit (ICU) admission. The analysis was performed at several time points (1, 2, 4, and 6 hours post-surgery), and the results were structured into three key tables.

The demographic and clinical characteristics of the patients summarized in Table 1. The study involved 112 patients, with a mean age of 65.4 years (±8.2). There were 55 male and 57 female participants, with no significant differences in terms of age, gender, ASA score, or surgical duration between the two groups. The mean BMI was 27.8 kg/m^2 (±3.4). The majority of patients had femoral fractures due to trauma, and the types of hip arthroplasties performed included both total hip arthroplasty and hemiarthroplasty.

Table 1: Demographic and Clinical Characteristics of the Study Population

Parameter	High SII Group (n=56)	Low SII Group (n=56)	P-value
Age (years)	65.2 (±7.8)	65.6 (±8.5)	0.719
Gender (M/F)	28/28	27/29	0.892
ASA Score (I/II)	32/24	33/23	0.821
Surgical Duration (min)	120 (±15)	118 (±12)	0.605
BMI (kg/m^2)	28.1 (±3.6)	27.6 (±3.2)	0.358

Table 2 presents the correlation analysis between the SII and pain intensity as measured by the Visual Analog Scale (VAS). A significant positive correlation found between SII levels and pain intensity in the first 4 hours following surgery. The correlation was strongest at the 2-hour mark (r = +0.745, p = 0.005), suggesting that elevated SII values were associated with higher pain scores. These findings underscore the potential role of SII as a marker of postoperative pain intensity.

Table 2: Correlation between Systemic Immune-Inflammation Index (SII) and Postoperative Pain Intensity (VAS)

Time Point	SII	Pain Intensity (VAS)	r-value	P-value
1 Hour	820.5 (±103.2)	4.2 (±1.3)	+0.415	0.033
2 Hours	830.1 (±106.7)	5.3 (±1.2)	+0.745	0.005
4 Hours	840.2 (±108.3)	6.1 (±1.1)	+0.658	0.009
6 Hours	850.4 (±112.5)	6.5 (±1.0)	+0.612	0.011

In Table 3, the relationship between SII and various clinical outcomes, including the need for ICU admission, length of hospital stay (LOHS), and platelet count, detailed. Patients with higher SII levels had significantly longer hospital stays (22 days vs. 17 days, p = 0.006), more frequent ICU admissions (27.94% vs. 16.60%, p = 0.036), and increased platelet counts (P < 0.001). These results suggest that an elevated SII may be associated with a more severe inflammatory response, potentially influencing both recovery time and complications.

Table 3: Analysis of Systemic Immune-Inflammation Index (SII) and Postoperative Outcomes

Parameter	High SII Group (n=56)	Low SII Group (n=56)	P-value
Length of Hospital Stay (days)	22 (±5.4)	17 (±4.1)	0.006
ICU Admission (%)	27.94%	16.60%	0.036
ICU Stay (days)	5.25 (±2.3)	3.75 (±1.8)	0.041
Platelet Count (x10^9/L)	300 (±90)	250 (±85)	<0.001
Lymphocyte Count (x10^9/L)	1.2 (±0.5)	1.6 (±0.6)	<0.001

Discussion

The findings from this study provide valuable insights into the relationship between the Systemic Immune-Inflammation Index (SII) and postoperative outcomes, particularly pain intensity, in patients undergoing hip arthroplasty for femoral fractures [27-29]. Our results demonstrate that higher SII values correlate with increased pain intensity and a more severe postoperative course, including

prolonged hospital stays, increased ICU admissions, and elevated platelet counts. These observations highlight the clinical significance of the SII as a potential marker for assessing postoperative pain and inflammatory response [30-32].

One of the most striking findings of this study was the significant correlation between the SII and postoperative pain intensity, particularly in the first four hours following surgery. Pain is a complex and multifactorial experience, influenced by both physiological and psychological factors. The acute inflammatory response, which closely related to the SII, plays a pivotal role in the modulation of pain. In our study, we found that higher SII levels were associated with increased pain scores, particularly at the 2-hour postoperative mark, with a correlation coefficient of +0.745 ($p = 0.005$). This finding is consistent with existing literature that suggests a strong link between systemic inflammation and heightened pain perception following surgery [33-35].

Several studies have shown that inflammatory mediators, such as cytokines (e.g., interleukin-6, TNF-α), are released during the early postoperative period and contribute to pain sensitization. In particular, the increase in neutrophils, platelets, and white blood cells, all components of the SII, may enhance the nociceptive response, leading to higher pain levels. Inflammation-induced sensitization of the nervous system could lead to an exaggerated pain response in patients with higher SII scores. Thus, it is plausible that the elevated SII reflects a more pronounced inflammatory response, which could lead to increased pain intensity and the need for greater analgesic consumption, as observed in our study [36].

The significant correlation between the SII and pain intensity underscores the potential of the SII as a predictive marker for postoperative pain management. By identifying patients with higher SII values, clinicians may be able to anticipate the need for more aggressive pain control measures in the immediate postoperative period. This could ultimately improve patient comfort and satisfaction while reducing the risk of complications associated with inadequate pain management [37].

In addition to pain intensity, our study also explored the relationship between the SII and other clinical outcomes, such as length of hospital stay (LOHS), ICU admission, and platelet count. We found that patients with higher SII levels had significantly longer hospital stays (22 days vs. 17 days, $p = 0.006$), higher rates of ICU admission (27.94% vs. 16.60%, $p = 0.036$), and increased platelet counts. These findings suggest that a higher SII is associated with a more severe postoperative course and may indicate a heightened inflammatory state that can contribute to delayed recovery [38-40].

The relationship between the SII and hospital stay is particularly noteworthy. It has well established that inflammation is a key driver of complications following surgery, including infections, delayed wound healing, and prolonged recovery. The increased inflammatory burden, as reflected by the SII, may impede the healing process and lead to extended hospitalization. Furthermore, elevated platelet counts, which observed in the high SII group, are indicative of ongoing systemic inflammation. Platelets not only play a central role in hemostasis but also interact with inflammatory mediators, exacerbating the inflammatory response and potentially contributing to postoperative complications. Elevated platelet levels have been associated with an increased risk of thrombosis and infection, both of which can lead to prolonged hospital stays [41-43].

Our study also observed a higher rate of ICU admissions in patients with elevated SII levels, which may be reflective of the more severe

inflammatory response and its associated complications. The need for ICU care often arises in the context of respiratory or hemodynamic instability, both of which closely linked to systemic inflammation. The association between SII and ICU admission suggests that patients with higher inflammatory burden may require more intensive monitoring and care, further emphasizing the need for early identification of patients at risk for postoperative complications [44-46].

The SII, which is a composite index that incorporates neutrophil, lymphocyte, and platelet counts, offers a comprehensive measure of the systemic immune-inflammatory response. The components of the SII have individually linked to various adverse outcomes in surgical patients. For example, neutrophils play a central role in the early stages of inflammation, and their increased presence is often associated with infection, wound dehiscence, and other postoperative complications. Similarly, platelets are involved in both inflammation and coagulation, and elevated platelet counts have correlated with poor outcomes in a variety of surgical settings.

In our study, the high SII group had significantly higher neutrophil, platelet, and white blood cell counts, while lymphocyte counts were significantly lower. These findings suggest that the systemic inflammatory response more pronounced in these patients, potentially contributing to both the increased pain levels and the adverse postoperative outcomes observed. The low lymphocyte count, in particular, is a marker of immune suppression, which may increase the risk of infections and other complications in the postoperative period. These results align with previous research that has shown the SII to be a reliable marker of systemic inflammation and a predictor of poor outcomes in various surgical populations [47].

Our findings suggest that the SII could be a valuable tool for predicting postoperative pain intensity and clinical outcomes in patients undergoing hip arthroplasty. By measuring SII levels preoperatively and in the early postoperative period, clinicians may be able to identify patients at higher risk for prolonged pain, extended hospital stays, and ICU admissions. This information could guide clinical decision-making, allowing for more tailored pain management strategies and closer monitoring of high-risk patients [48].

Furthermore, the SII could potentially serve as a biomarker for assessing the effectiveness of anti-inflammatory interventions in the postoperative setting. Future research could explore whether targeting the inflammatory response with pharmacologic agents, such as corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), could reduce pain intensity and improve postoperative outcomes in patients with elevated SII levels. Additionally, prospective studies are needed to further validate the predictive value of the SII in larger, more diverse patient populations, and to explore its potential role in predicting long-term outcomes, such as functional recovery and complications [49].

While this study provides promising results, it is not without limitations. First, the study conducted at a single center, which may limit the generalizability of the findings. Additionally, the sample size, though adequate for preliminary analysis, expanded in future studies to enhance statistical power. Another limitation is the lack of a long-term follow-up, which would have allowed for the assessment of SII's predictive value for long-term outcomes, such as functional recovery and chronic pain. Finally, while the SII correlated with pain intensity and clinical outcomes, the study did not explore the underlying mechanisms by which inflammation influences

pain and recovery, which warrants further investigation.

Conclusion

In conclusion, the findings of this study suggest that the Systemic Immune-Inflammation Index (SII) is a significant predictor of acute postoperative pain and adverse clinical outcomes in patients undergoing hip arthroplasty for femoral fractures. Higher SII values were associated with increased pain intensity, longer hospital stays, higher ICU admission rates, and increased platelet counts. These results support the potential use of the SII as a useful marker for assessing the inflammatory response and predicting postoperative complications. Future research needed to confirm these findings and to explore the mechanisms by which systemic inflammation influences pain and recovery after surgery.

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