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Pathologic Evaluation of the Association Between the Systemic Immune-Inflammation Index and the Severity of Acute Postoperative Pain Following Femoral Fracture Surgery in Elderly Patients

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A B S T R A C T

Introduction: Femoral fracture surgery in elderly patients is frequently followed by substantial acute postoperative pain, which may be influenced not only by surgical trauma but also by systemic inflammatory and immune responses. Because the Systemic Immune-Inflammation Index may reflect this biological susceptibility, the present study aimed to pathologically assess its association with the severity of acute postoperative pain after femoral fracture surgery.

Material and methods: This descriptive cross-sectional study was conducted at Shahid Madani Hospital, Tabriz, on 93 elderly patients selected by convenience sampling, with sample size estimated using Cochran's formula. Demographic, clinical, laboratory, surgical, and postoperative pain data were collected. The Systemic Immune-Inflammation Index was calculated from preoperative platelet, neutrophil, and lymphocyte counts, and its association with acute postoperative pain severity was statistically evaluated.

Results: Patients with severe postoperative pain had markedly higher preoperative SII than those with moderate or mild pain (1801.2±789.6 vs 1280.5±542.7 and 850.2±386.4; P<0.001), along with higher inflammatory markers, lower hemoglobin and albumin, longer operations, greater blood loss, more opioid use, delayed mobilization, and longer hospitalization (all P<0.05). SII correlated with pain intensity (highest 24-hour NRS: r=0.574, P<0.001) and independently predicted severe pain (OR=2.86, 95% CI 1.54-5.31), with good accuracy (AUC=0.812).

Conclusion: Preoperative SII appears to be a clinically useful biomarker for identifying patients at increased risk of severe acute postoperative pain. Its independent association with pain severity and acceptable diagnostic performance suggest that SII may support early perioperative risk stratification and help guide individualized analgesic planning, particularly in patients with an elevated inflammatory burden before surgery.

Introduction

Femoral fractures are among the most consequential injuries affecting older adults, not only because of their frequency but also because of their profound impact on mobility, independence, and survival.

As populations age worldwide, the burden of fragility-related orthopedic trauma continues to increase, placing major pressure on surgical services, rehabilitation systems, and long-term care resources.

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In elderly patients, femoral fracture surgery is often unavoidable and time-sensitive, yet the perioperative course is frequently complicated by frailty, multiple comorbidities, sarcopenia, chronic inflammation, and reduced physiologic reserve. Within this vulnerable context, acute postoperative pain is not merely an expected symptom of tissue injury; it is a clinically significant outcome that can shape respiratory function, early mobilization, delirium risk, sleep quality, rehabilitation adherence, and overall recovery trajectory. Poorly controlled pain after femoral fracture surgery may delay ambulation, prolong hospitalization, and contribute to persistent disability, making it a central issue in geriatric orthopedic care rather than a secondary postoperative concern [1].

The biological and clinical complexity of pain in elderly patients extends beyond the nociceptive consequences of bone trauma and surgical manipulation. Aging is accompanied by structural and functional changes in the peripheral and central nervous systems, altered pain perception, dysregulated inflammatory signaling, and increased susceptibility to both hyperalgesia and undertreatment. Moreover, pain expression in older adults may be influenced by cognitive impairment, anxiety, depression, sensory deficits, and communication barriers, all of which complicate accurate assessment and targeted management. In femoral fracture surgery, the pain experience is further intensified by soft-tissue damage, periosteal disruption, intramedullary instrumentation, and the inflammatory response triggered by both the fracture itself and the surgical procedure. Consequently, postoperative pain severity in this population likely reflects not only operative characteristics and analgesic strategies, but also a deeper interplay between systemic immune activation, tissue response, and host vulnerability. Understanding this broader pathobiological landscape is essential if clinicians are to move beyond symptomatic treatment and toward more individualized perioperative pain prediction and prevention [2].

Inflammation has emerged as a key mechanistic bridge between tissue injury and pain amplification. Following fracture and surgical intervention, local trauma initiates a cascade of cellular and molecular events involving neutrophils, monocytes, platelets, cytokines, chemokines, and endothelial mediators. These inflammatory processes are necessary for tissue repair, yet they also sensitize peripheral nociceptors and facilitate central pain transmission. Cytokines such as interleukin-6, tumor necrosis factor-alpha, and interleukin-1 beta can lower the activation threshold of sensory neurons, increase spontaneous firing, and prolong pain signaling beyond the immediate period of tissue insult. In older adults, this inflammatory response may be exaggerated, prolonged, or maladaptively regulated because of immunosenescence and chronic low-grade inflammation, sometimes described as inflammaging. As a result, systemic inflammatory status before surgery may influence the magnitude of postoperative pain in ways that are clinically measurable and potentially prognostically meaningful. This has led to growing interest in simple hematologic indices that capture the interaction between innate immunity, thrombosis, and inflammatory burden in surgical populations [3].

Among these emerging biomarkers, the Systemic Immune-Inflammation Index has attracted attention as a composite indicator derived from platelet, neutrophil, and lymphocyte counts. By integrating elements of inflammatory activation and immune regulation into a single parameter, this index may provide a more comprehensive reflection of host response than isolated leukocyte subtypes alone. Elevated neutrophils generally indicate acute inflammatory activation, lymphopenia may reflect physiologic stress and impaired adaptive immune balance, and platelet elevation is increasingly recognized as a marker of inflammatory and thromboinflammatory activity rather than hemostasis alone. The combination of these components in the Systemic Immune-Inflammation Index has been studied across oncology, cardiovascular disease, critical care, and surgical settings, where it has shown associations with prognosis, complications, and disease severity. Its appeal lies in its accessibility, low cost, reproducibility, and routine availability from standard blood counts, making it especially attractive in resource-variable clinical environments where rapid risk stratification is needed [4].

From a pathologic perspective, the Systemic Immune-Inflammation Index may be especially relevant in the setting of trauma and postoperative pain because it mirrors several biologic pathways involved in nociceptive sensitization. Neutrophil predominance reflects early inflammatory recruitment and mediator release at sites of injury; platelets contribute to microvascular activation, cytokine signaling, and tissue cross-talk; and reduced lymphocyte counts may signal systemic stress, neuroendocrine imbalance, and impaired immunologic modulation. Together, these processes may create a pro-inflammatory internal milieu that heightens pain sensitivity after surgery. In elderly patients with femoral fractures, such mechanisms may be further intensified by preexisting atherosclerosis, diabetes mellitus, malnutrition, anemia, and impaired tissue perfusion, all of which can alter both inflammatory behavior and pain processing. Therefore, a biomarker that captures this systemic inflammatory-immune state could

plausibly correlate with postoperative pain severity and serve as a clinically useful adjunct in identifying patients at higher risk for difficult pain control or delayed functional recovery [5].

Although a growing body of literature has evaluated inflammatory biomarkers in relation to postoperative complications, infection, mortality, and healing, comparatively less attention has been devoted to their specific association with acute pain outcomes after orthopedic trauma surgery in the elderly. Traditional pain prediction models often emphasize age, sex, fracture type, anesthesia method, surgical duration, and analgesic regimen, but these factors alone do not fully explain the marked variability in pain intensity observed among patients who undergo similar procedures. Some individuals experience relatively controlled postoperative discomfort, whereas others develop severe early pain despite standardized management. This discrepancy suggests that patient-specific biological determinants may be at work. In recent years, interest has shifted toward identifying preoperative laboratory markers that may help explain this heterogeneity. Yet the role of the Systemic Immune-Inflammation Index in this context remains insufficiently defined, particularly in geriatric femoral fracture populations where both inflammatory dysregulation and pain-related complications are especially common [6].

The clinical importance of clarifying this relationship is considerable. Severe acute postoperative pain after femoral fracture surgery can interfere with deep breathing, coughing, repositioning, participation in physiotherapy, and early weight-bearing, thereby increasing the risk of pulmonary complications, thromboembolism, pressure injury, and prolonged institutional dependence. In elderly patients, intense pain may also precipitate agitation, sleep disturbance, opioid overexposure, urinary retention, constipation, and postoperative delirium, each of which may worsen functional outcomes and lengthen hospital stay. If a readily obtainable preoperative index could help predict which patients are more likely to experience severe acute pain, clinicians could tailor analgesic planning more effectively, allocate closer monitoring, optimize anti-inflammatory and multimodal pain strategies, and counsel caregivers more precisely. Such an approach would align with current trends toward risk-adapted perioperative medicine and would be particularly valuable in high-volume orthopedic centers caring for medically complex older adults [7].

A pathologic framing of this question is also justified because postoperative pain does not arise solely from mechanical injury; rather, it reflects the tissue-level and systemic consequences of inflammation, immune response, vascular activation, and neurochemical sensitization. The Systemic Immune-Inflammation Index may therefore be interpreted not simply as a numerical laboratory result, but as a surrogate marker of the biological environment in which surgical trauma occurs. In the elderly, where baseline homeostasis is often fragile, even modest elevations in systemic inflammatory burden may shift the postoperative response toward amplified pain and slower recovery. This concept has particular relevance in femoral fractures, where the injury itself induces marrow exposure, hemorrhage, soft-tissue disruption, and profound metabolic stress before surgical treatment even begins. Examining the relationship between this index and postoperative pain severity may thus contribute to a more integrated understanding of how systemic pathology influences subjective clinical outcomes, bridging hematologic biomarkers with functional perioperative endpoints [8].

Despite its theoretical promise, several uncertainties remain. It is not yet clear whether the Systemic Immune-Inflammation Index is independently associated with acute postoperative pain severity or whether any observed relationship is largely mediated by confounders such as comorbidity burden, fracture complexity, operative duration, transfusion need, or baseline nutritional status. Likewise, the predictive value of this index in elderly femoral fracture surgery has not been firmly established in routine clinical practice. These unanswered questions underscore the need for focused investigation in well-defined patient cohorts. A clearer understanding of this biomarker's significance could expand current perioperative assessment models and support more biologically informed pain management pathways. Therefore, the present study was designed to pathologically evaluate the association between the Systemic Immune-Inflammation Index and the severity of acute postoperative pain following femoral fracture surgery in elderly patients.

Material and methods

Study Design:

This descriptive cross-sectional study was conducted at Shahid Madani Hospital, Tabriz, Iran, among elderly patients undergoing surgical treatment for femoral fractures. The study evaluated the relationship between the preoperative Systemic Immune-Inflammation Index (SII) and the severity of acute postoperative pain. Eligible patients were assessed during hospitalization, and clinical, laboratory, surgical, and pain-related information was collected using a standardized data collection form.

Sample Size and Sampling

The required sample size was estimated using Cochran's sample-size formula for a single proportion: $n=Z1-\alpha/2p(1-p)/d2$. Assuming a 95% confidence level (Z=1.96), maximum variability (p=0.50), and an absolute precision of approximately 10.2% (d=0.102), the minimum sample size was calculated as 93 patients. Participants were recruited through convenience sampling from eligible elderly patients admitted for femoral fracture surgery until the target sample size was reached.

Inclusion and Exclusion Criteria

The inclusion criteria were age 60 years or older, radiologically confirmed femoral fracture requiring surgical treatment, hospitalization at Shahid Madani Hospital, availability of a complete blood count obtained before surgery, ability to undergo postoperative pain assessment, provision of written informed consent by the patient or legal representative, and availability of complete clinical and perioperative records. Patients were excluded if they had active infection, sepsis, fever of unknown origin, autoimmune or systemic inflammatory disease, hematologic or malignant disorders, chronic liver or advanced renal disease, recent major trauma involving multiple organs, another fracture requiring simultaneous surgery, pathological fracture secondary to malignancy, long-term corticosteroid or immunosuppressive treatment, chemotherapy or radiotherapy, blood transfusion before preoperative blood sampling, or surgery during the preceding three months. Patients with severe cognitive impairment, advanced dementia, delirium, aphasia, reduced consciousness, or communication difficulties preventing reliable pain scoring were also excluded. Additional exclusion criteria included chronic opioid use, documented chronic pain syndromes, incomplete laboratory or pain-assessment data, perioperative death, reoperation during the acute assessment period, and withdrawal of consent.

Study Procedure

After enrollment, demographic and clinical information was recorded, including age, sex, body mass index, smoking status, fracture mechanism, fracture location and pattern, affected side, time from injury to hospital admission, and interval between admission and surgery. Medical history was reviewed for diabetes mellitus, hypertension, cardiovascular disease, chronic pulmonary disease, osteoporosis, previous fractures, and other relevant comorbidities. Preoperative laboratory variables included neutrophil, lymphocyte, platelet, and total leukocyte counts, hemoglobin, hematocrit, C-reactive protein, erythrocyte sedimentation rate, serum albumin, creatinine, and blood glucose. The SII was calculated from the final complete blood count obtained before surgery using the formula: platelet count × neutrophil count/lymphocyte count. All blood-cell counts were expressed in consistent units before calculation. Perioperative variables included the type of anesthesia, surgical procedure, implant type, operative duration, estimated blood loss, intraoperative and postoperative transfusion, and postoperative analgesic regimen. Acute pain intensity was evaluated using the 11-point Numerical Rating Scale, ranging from 0 (no pain) to 10 (the worst imaginable pain), at predefined intervals during the first 24 hours after surgery, including 6, 12, and 24 hours postoperatively. The highest score recorded during this period was considered the primary pain-severity measure. Pain was categorized as mild (scores 1-3), moderate (scores 4-6), or severe (scores 7-10). Additional postoperative variables included rescue analgesic use, total opioid consumption converted to intravenous morphine equivalents, time to initial mobilization, postoperative complications, and length of hospital stay. Laboratory measurements were performed by the hospital laboratory, while pain assessments were completed by trained clinical personnel using uniform instructions.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics. Continuous variables were assessed for normality using the Shapiro-Wilk test, histograms, and Q-Q plots and were found to be normally distributed; therefore, they were reported as mean and standard deviation. Categorical variables were presented as frequencies and percentages. The independent-samples Student's t-test was used to compare continuous variables between two pain groups, while one-way analysis of variance with an appropriate post hoc test was applied to comparisons across mild, moderate, and severe pain categories. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Pearson's correlation coefficient was used to examine the association of SII with pain scores and other continuous variables. Multivariable linear regression was performed to assess the independent relationship between SII and continuous postoperative pain scores after adjustment for potential confounders, whereas ordinal or binary logistic regression was used for categorized pain severity, as applicable. Variables with clinical relevance or a univariable P value below 0.20 were considered for multivariable modeling. Regression assumptions, multicollinearity, and model fit were evaluated. Receiver operating characteristic curve analysis was used to determine the discriminatory ability of SII for severe postoperative pain, and the

optimal cutoff was identified using the Youden index; the area under the curve, sensitivity, specificity, positive predictive value, and negative predictive value were calculated with 95% confidence intervals. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of Tabriz University of Medical Sciences (ethics code: IR.TBZMED.REC.1403.154). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant or, when appropriate, from a legally authorized representative. Participation was voluntary, and patients could withdraw at any stage without any effect on their treatment. Personal identifiers were removed from the dataset, all information was kept confidential, and the collected data were used exclusively for research purposes.

Results

As shown in Table 1, the 93 participants had a mean age of 73.8 ± 8.1 years, and 55.9% were female. Intertrochanteric fracture was the most frequent fracture type (44.1%), while spinal anesthesia was used in 66.7% of patients. The mean preoperative Systemic Immune-Inflammation Index was 1354.6 ± 721.3. Within 24 hours after surgery, the mean maximum NRS score was 5.8 ± 2.1, with moderate and severe pain reported in 46.2% and 32.3% of patients, respectively (Table 1).

Table 1. Baseline demographic, clinical, laboratory, and perioperative characteristics of the study population

Variable	Total population (n=93)
Age, years	73.8 ± 8.1
Sex, male	41 (44.1)
Sex, female	52 (55.9)
Body mass index, kg/m²	25.9 ± 3.7
Current smoking	14 (15.1)
Diabetes mellitus	27 (29.0)
Hypertension	49 (52.7)
Cardiovascular disease	24 (25.8)
Chronic pulmonary disease	11 (11.8)
Osteoporosis	38 (40.9)
Previous fracture history	17 (18.3)
Low-energy fall	76 (81.7)
High-energy trauma	17 (18.3)
Femoral neck fracture	34 (36.6)
Intertrochanteric fracture	41 (44.1)
Subtrochanteric fracture	18 (19.4)
Right-sided fracture	48 (51.6)
Left-sided fracture	45 (48.4)
Time from injury to admission, hours	9.6 ± 5.4
Time from admission to surgery, hours	38.7 ± 16.9
White blood cell count, ×10³/µL	9.8 ± 2.6
Neutrophil count, ×10³/µL	7.1 ± 2.3
Lymphocyte count, ×10³/µL	1.4 ± 0.5
Platelet count, ×10³/µL	246.8 ± 68.5
Systemic Immune-Inflammation Index	1354.6 ± 721.3
Hemoglobin, g/dL	11.3 ± 1.6
Hematocrit, %	34.7 ± 4.8
C-reactive protein, mg/L	18.9 ± 11.6
Erythrocyte sedimentation rate, mm/h	31.4 ± 15.2
Serum albumin, g/dL	3.6 ± 0.5
Serum creatinine, mg/dL	1.1 ± 0.3
Fasting blood glucose, mg/dL	126.5 ± 38.9
Spinal anesthesia	62 (66.7)
General anesthesia	31 (33.3)
Dynamic hip screw fixation	28 (30.1)

Proximal femoral nail fixation	39 (41.9)
Hemiarthroplasty	26 (28.0)
Operative duration, minutes	78.5 ± 21.7
Estimated blood loss, mL	312.4 ± 126.8
Perioperative blood transfusion	29 (31.2)
Rescue analgesic requirement	36 (38.7)
Morphine-equivalent opioid consumption, mg	8.9 ± 4.6
Highest NRS pain score within 24 hours	5.8 ± 2.1
Mild pain, NRS 1-3	20 (21.5)
Moderate pain, NRS 4-6	43 (46.2)
Severe pain, NRS 7-10	30 (32.3)
Time to first mobilization, hours	31.6 ± 14.8
Length of hospital stay, days	6.4 ± 2.3

As shown in Table 2, patients with severe postoperative pain had a significantly higher mean SII than those with moderate or mild pain (1801.2 ± 789.6 vs. 1280.5 ± 542.7 and 850.2 ± 386.4, respectively; P<0.001). Severe pain was also associated with higher inflammatory markers, lower hemoglobin and albumin levels, longer operative duration, greater blood loss, increased opioid consumption, delayed mobilization, and prolonged hospitalization (all P<0.05) (Table 2).

Table 2. Comparison of clinical, laboratory, and perioperative characteristics according to acute postoperative pain severity

Variable	Mild pain (n=20)	Moderate pain (n=43)	Severe pain (n=30)	P-value
Age, years	72.1 ± 7.6	73.5 ± 8.0	75.4 ± 8.5	0.331
Female sex	10 (50.0)	24 (55.8)	18 (60.0)	0.767
Body mass index, kg/m²	25.1 ± 3.5	25.8 ± 3.6	26.6 ± 3.9	0.365
Diabetes mellitus	3 (15.0)	11 (25.6)	13 (43.3)	0.047
Hypertension	8 (40.0)	23 (53.5)	18 (60.0)	0.382
Cardiovascular disease	4 (20.0)	10 (23.3)	10 (33.3)	0.495
White blood cell count, ×10³/μL	8.4 ± 2.0	9.7 ± 2.4	10.9 ± 2.8	0.003
Neutrophil count, ×10³/μL	5.7 ± 1.7	6.9 ± 2.0	8.4 ± 2.5	<0.001
Lymphocyte count, ×10³/μL	1.7 ± 0.5	1.4 ± 0.4	1.1 ± 0.4	<0.001
Platelet count, ×10³/μL	226.5 ± 59.4	244.7 ± 64.8	263.4 ± 75.2	0.169
Systemic Immune-Inflammation Index	850.2 ± 386.4	1280.5 ± 542.7	1801.2 ± 789.6	<0.001
Hemoglobin, g/dL	12.0 ± 1.4	11.4 ± 1.5	10.7 ± 1.6	0.014
C-reactive protein, mg/L	12.5 ± 7.8	18.0 ± 9.9	24.4 ± 13.8	0.001
Erythrocyte sedimentation rate, mm/h	24.2 ± 11.7	30.6 ± 13.9	37.3 ± 17.4	0.009
Serum albumin, g/dL	3.9 ± 0.4	3.6 ± 0.5	3.4 ± 0.5	0.002
Time from admission to surgery, hours	31.7 ± 13.1	37.9 ± 15.8	44.6 ± 18.4	0.021
General anesthesia	5 (25.0)	13 (30.2)	13 (43.3)	0.342
Operative duration, minutes	66.8 ± 17.9	77.6 ± 19.8	87.6 ± 23.7	0.003
Estimated blood loss, mL	238.5 ± 94.6	301.8 ± 111.7	376.9 ± 139.4	<0.001
Perioperative blood transfusion	3 (15.0)	12 (27.9)	14 (46.7)	0.045
Rescue analgesic requirement	2 (10.0)	14 (32.6)	20 (66.7)	<0.001
Morphine-equivalent opioid consumption, mg	4.2 ± 2.3	8.1 ± 3.4	13.1 ± 4.8	<0.001
Highest NRS score within 24 hours	2.7 ± 0.5	5.2 ± 0.8	8.3 ± 0.9	<0.001
Time to first mobilization, hours	22.4 ± 9.7	30.7 ± 12.5	39.1 ± 16.5	<0.001
Length of hospital stay, days	4.9 ± 1.5	6.2 ± 2.0	7.7 ± 2.6	<0.001

As presented in Table 3, the Systemic Immune-Inflammation Index showed significant positive correlations with postoperative pain scores at 6, 12, and 24 hours, with the strongest association observed for the highest pain score within the first 24 hours (r=0.574, P<0.001). In adjusted analyses, higher SII remained independently associated with greater pain severity and increased odds of severe

postoperative pain. ROC analysis further demonstrated good predictive performance, with an AUC of 0.812, 76.7% sensitivity, and 73.0% specificity (Table 3).

Table 3. Correlation, regression, and diagnostic performance of the Systemic Immune-Inflammation Index for severe acute postoperative pain

Variable	Statistical estimate	95% CI	P-value
Correlation with NRS score at 6 hours	r = 0.482	0.305–0.628	<0.001
Correlation with NRS score at 12 hours	r = 0.536	0.373–0.666	<0.001
Correlation with NRS score at 24 hours	r = 0.497	0.323–0.641	<0.001
Correlation with highest NRS score within 24 hours	r = 0.574	0.420–0.696	<0.001
Linear regression for highest NRS score, β coefficient	β = 0.41	0.24–0.58	<0.001
Logistic regression for severe postoperative pain, odds ratio	OR = 2.86	1.54–5.31	0.001
Optimal SII cutoff for severe pain	1450.0	—	—
Area under the ROC curve	0.812	0.721–0.903	<0.001
Sensitivity at cutoff	76.7%	57.7–90.1	—
Specificity at cutoff	73.0%	60.3–83.4	—
Positive predictive value	57.5%	42.2–71.7	—
Negative predictive value	86.8%	74.7–94.5	—
Accuracy	74.2%	64.1–82.7	—

As shown in Figure 1, the Systemic Immune-Inflammation Index demonstrated good discriminative ability for identifying patients at risk of severe acute postoperative pain, with an area under the curve of 0.812. This finding indicates that preoperative SII had a clinically meaningful predictive performance, with a balanced sensitivity and specificity at the optimal cutoff point. Overall, the ROC profile supports the potential value of SII as a useful preoperative biomarker for early risk stratification of postoperative pain severity.

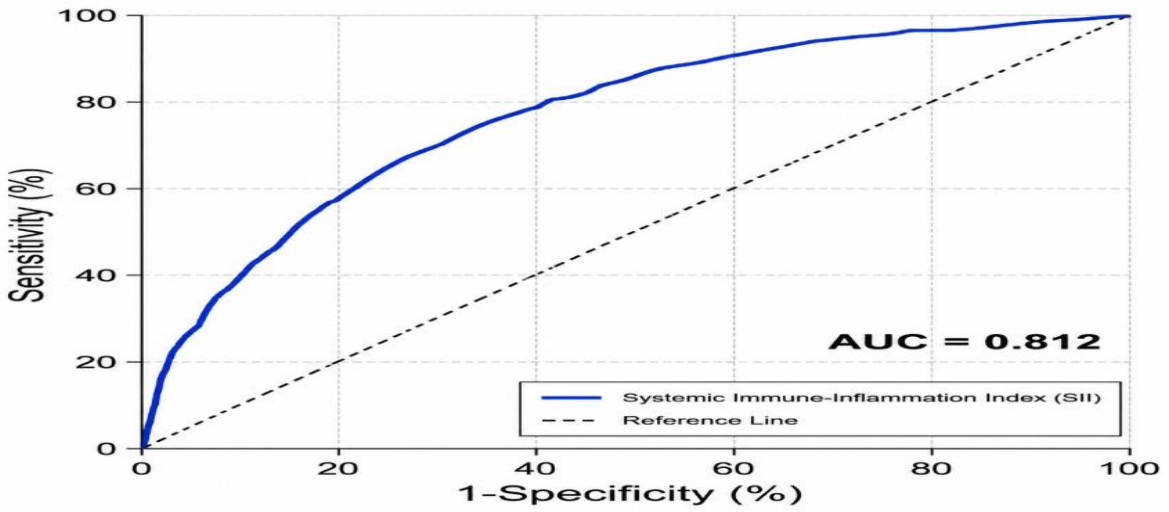

Figure 1. Receiver Operating Characteristic Curve of the Systemic Immune-Inflammation Index for Predicting Severe Acute Postoperative Pain

Discussion

In this cohort of elderly patients undergoing femoral fracture surgery, a higher preoperative Systemic Immune-Inflammation Index was consistently associated with greater acute postoperative pain severity and a less favorable perioperative course. Patients with severe pain had substantially higher SII values than those with moderate or mild pain, alongside higher leukocyte-based inflammatory markers, lower hemoglobin and albumin levels, longer time to surgery, longer operative duration, greater blood loss, more frequent transfusion, higher rescue analgesic use, increased opioid consumption, delayed mobilization, and prolonged hospitalization. Moreover, SII correlated positively with pain scores across the first 24 postoperative

hours and remained an independent predictor of severe pain in adjusted models. Its diagnostic performance was clinically meaningful, with an AUC of 0.812 and an optimal cutoff of 1450, supporting its potential utility as a preoperative marker for pain risk stratification in this population [10,11].

These findings are biologically plausible because the SII integrates three key cellular components of the systemic inflammatory response: neutrophils, platelets, and lymphocytes. An elevated SII reflects intensified innate immune activation and relative suppression of adaptive immune balance, a pattern that may amplify nociceptive signaling before surgical injury even occurs. In elderly patients with femoral fractures, tissue trauma from the fracture itself is already sufficient to trigger cytokine release, endothelial activation, and leukocyte recruitment; surgery then acts as a second inflammatory insult. In such a context, a higher preoperative SII may identify patients entering the operation in a primed pro-inflammatory state, making them more vulnerable to peripheral and central sensitization after surgery. This mechanism may explain why SII was not merely associated with pain category but also correlated with serial postoperative NRS values and with the highest pain intensity within 24 hours. The independent regression findings further suggest that SII captures clinically relevant inflammatory information beyond standard demographic and perioperative variables, reinforcing its potential mechanistic link with postoperative hyperalgesia rather than acting only as a nonspecific marker of illness severity [12,13].

The accompanying laboratory profile in the severe-pain group strengthens this interpretation. Higher white blood cell and neutrophil counts, lower lymphocyte counts, and higher CRP and erythrocyte sedimentation rate together indicate a more activated inflammatory milieu, while the progressive rise in SII across pain categories suggests that this composite index may better summarize the overall inflammatory burden than any single parameter alone. Neutrophils are increasingly recognized as active participants in pain generation through release of proteases, reactive oxygen species, prostaglandins, and pro-inflammatory cytokines that sensitize peripheral nociceptors. Platelets may also contribute by interacting with leukocytes and endothelium and by releasing serotonin and other mediators involved in pain processing. Conversely, lymphopenia may reflect physiologic stress and impaired immune regulation, both of which can favor exaggerated inflammatory signaling. Therefore, the observed relationship between higher SII and more severe pain likely reflects a convergence of amplified inflammatory drive and reduced immunologic equilibrium. This may be especially important in geriatric fracture patients, in whom age-related immune dysregulation can intensify and prolong the inflammatory response to trauma and operative intervention [14,15].

Another notable aspect of the results is the coexistence of elevated SII with lower hemoglobin and albumin concentrations in patients with severe pain. These associations are clinically meaningful because anemia may worsen tissue hypoxia and fatigue, potentially lowering pain tolerance and delaying functional recovery, while hypoalbuminemia often reflects poor nutritional reserve, systemic inflammation, or both. Albumin is also a negative acute-phase reactant, so lower levels may indicate an ongoing inflammatory state consistent with elevated SII. In elderly patients, frailty, catabolic stress, and reduced physiologic reserve may cause these factors to cluster, producing a phenotype characterized by inflammation, malnutrition, impaired healing, and heightened postoperative vulnerability. This could help explain why severe pain was linked not only to laboratory abnormalities but also to slower mobilization and longer hospital stay. Pain in such patients may therefore be understood not as an isolated symptom but as one manifestation of a broader adverse perioperative biological state. From this perspective, SII may be valuable precisely because it identifies patients in whom inflammatory activation intersects with diminished reserve, thereby increasing the likelihood of difficult postoperative recovery [16,17].

The perioperative variables also provide important context for interpreting the association between SII and pain severity. Patients with severe pain experienced longer delays from admission to surgery, longer operations, more blood loss, and more frequent transfusion, all of which may intensify physiologic stress and inflammatory activation. Delayed surgery can prolong exposure to fracture-related pain and immobilization, while longer and more invasive procedures may increase tissue injury and cytokine release. Greater blood loss and transfusion may further contribute to postoperative pain through immunomodulation, oxidative stress, and delayed recovery. At the same time, these relationships are likely bidirectional. Patients who enter surgery with a higher inflammatory burden may be more clinically fragile, more prone to difficult perioperative courses, and less resilient in the face of surgical stress, thereby requiring more analgesia and mobilizing later. The increased need for rescue analgesics and higher morphine-equivalent consumption in the severe-pain group fits this model and indicates that the association between SII and pain has practical therapeutic consequences. Thus, preoperative SII may serve not only as a marker of pain susceptibility

but also as a broader indicator of perioperative complexity in elderly femoral fracture surgery [18,19].

Conclusion

The diagnostic findings are particularly relevant from a clinical standpoint. An AUC of 0.812 indicates good discrimination, and the sensitivity and specificity observed at the cutoff of 1450 suggest that preoperative SII may be useful for identifying patients at elevated risk of severe acute postoperative pain before surgery. Although the positive predictive value was moderate, the high negative predictive value implies that a lower SII may help reassure clinicians that severe pain is less likely, whereas an elevated SII could prompt more proactive analgesic planning, closer monitoring, and optimization of modifiable factors such as anemia, nutrition, and inflammatory status where feasible. These results should nevertheless be interpreted with caution. SII is not disease-specific, and it can be influenced by comorbidities, occult infection, medication exposure, dehydration, and other peri-fracture stressors. In addition, the observational nature of the data precludes causal inference, and the findings should ideally be validated in larger prospective cohorts with standardized pain protocols and external calibration of the proposed cutoff. Even so, the present study supports the concept that the preoperative inflammatory state is closely linked to postoperative pain expression and that SII may offer a simple, inexpensive, and clinically accessible biomarker for personalized perioperative pain risk assessment in elderly fracture patients.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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