



Pathophysiological Significance of the Neutrophil-to-Lymphocyte Ratio as a Predictor of Delirium after Major Emergency Orthopedic Surgery in the Elderly

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ABSTRACT

Introduction: Older adults undergoing major emergency orthopedic surgery face high risks of postoperative delirium (POD), a debilitating complication. Inflammation and stress, reflected by the neutrophil-to-lymphocyte ratio (NLR), may contribute to POD. This study evaluates NLR as a predictor of POD in this vulnerable cohort.

Material and methods: This study employed a descriptive cross-sectional design at Shohada Hospital, Tabriz, Iran, with 88 elderly patients undergoing major emergency orthopedic surgery. Convenience sampling and Cochran's formula determined sample size. Inclusion criteria focused on age (≥ 65), surgery type, preoperative CBC availability, and post-op assessment capability, while excluding pre-existing cognitive impairment or confounding conditions. Data on demographics, clinical factors, and NLR were collected, with postoperative delirium as the primary outcome.

Results: A total of 88 patients were evaluated, with 26 (29.5%) developing postoperative delirium. Advanced age ($P < 0.001$), higher ASA status ($P = 0.007$), longer surgery ($P = 0.018$) and delay times ($P = 0.005$), lower albumin ($P = 0.001$), and elevated NLR ($P < 0.001$) were associated with delirium. Preoperative NLR ($OR = 1.89$, 95% CI: 1.29-2.77, $P = 0.001$) independently predicted delirium.

Conclusion: Preoperative NLR is a significant independent predictor of postoperative delirium in elderly patients undergoing major orthopedic surgery, suggesting its utility in risk stratification and early intervention strategies for this vulnerable population.

Introduction

Postoperative delirium (POD) is an acute and fluctuating disturbance in attention, awareness, and cognition that commonly develops within hours or days after surgery. It is among the most consequential complications of surgical care in older adults, not only because it can delay recovery but also because it is associated with longer hospital stays, greater likelihood of discharge to institutional care, functional decline, and increased short- and long-term mortality.

POD is best understood as a multifactorial syndrome arising from the interaction between pre-existing vulnerability and acute perioperative insults, rather than as an isolated consequence of anesthesia or surgery [1].

Older adults undergoing major emergency orthopedic surgery constitute a particularly vulnerable population. These procedures are often required after substantial trauma and must be undertaken within a limited timeframe, leaving little opportunity to optimize chronic conditions or complete comprehensive preoperative assessment.

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The combined effects of tissue injury, severe pain, immobility, blood loss, inflammation, and abrupt changes in the patient's surroundings may place considerable stress on physiological systems that are already less resilient with advancing age [2].

The emergency setting may add further risk. Patients may present with dehydration, anemia, infection, metabolic disturbance, or hemodynamic instability, while the need for prompt intervention can constrain the time available for medication review, nutritional support, sleep preparation, and cognitive assessment. During hospitalization, unfamiliar surroundings, disrupted sleep, sensory deprivation, limited mobility, and exposure to sedatives or opioids may compound these stressors. Their cumulative effects can precipitate acute cognitive dysfunction, particularly in patients with pre-existing frailty or cognitive impairment [3].

POD is also clinically challenging because its presentation is variable. Although some patients develop agitation and perceptual disturbance, others exhibit hypoactive symptoms such as reduced responsiveness, withdrawal, or slowed cognition. These less conspicuous presentations can be overlooked in busy postoperative settings or mistaken for fatigue, pain, or residual effects of anesthesia. Delayed recognition may postpone supportive measures, including reorientation, mobilization, sleep protection, hydration, sensory aids, and review of potentially contributing medications [4].

Identifying patients at increased risk before delirium develops is therefore an important component of perioperative care. Established clinical risk factors include advanced age, cognitive impairment, frailty, sensory deficits, multimorbidity, polypharmacy, and functional dependence. However, these characteristics may not be assessed consistently in urgent surgical pathways, where clinical teams must make decisions rapidly and prioritize immediate injury management. A practical risk marker that can be obtained early and interpreted alongside clinical assessment may help direct surveillance and preventive resources to patients who are most likely to benefit [5].

Inflammation is one proposed pathway linking acute surgery and trauma to delirium. Tissue injury can activate peripheral immune responses and increase the release of inflammatory mediators. These signals may influence the central nervous system through communication between peripheral immune pathways and the brain, changes in blood-brain barrier function, and activation of resident immune cells. In older individuals, age-related changes in immune regulation and a diminished ability to restore physiological homeostasis may increase susceptibility to these effects [6].

Orthopedic trauma may be particularly relevant to this inflammatory pathway because fractures and major surgical procedures produce substantial tissue

damage and can trigger a systemic stress response. The resulting physiological changes may occur alongside blood loss, pain, reduced oxygen delivery, infection, or other complications that affect brain function. In a patient with limited cognitive or physiological reserve, the combined burden of these insults may contribute to the onset of delirium. The extent to which systemic inflammatory markers capture this vulnerability remains an important question in geriatric emergency surgery [7].

The neutrophil-to-lymphocyte ratio (NLR) is a readily available index calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. It can be derived from a routine complete blood count, a test commonly obtained during emergency assessment and preoperative evaluation. NLR combines information from two components of the immune response: neutrophilia, which may accompany acute inflammation or physiological stress, and relative lymphopenia, which may arise during stress-related changes in immune-cell distribution or function. This combination has led to interest in NLR as a broad indicator of systemic inflammatory and stress-related activity [8].

The potential relevance of NLR to delirium is biologically plausible, although the ratio should not be interpreted as a direct measure of brain inflammation. Neutrophil activation can be accompanied by the release of inflammatory mediators, proteolytic enzymes, and reactive oxygen species, which may contribute to endothelial dysfunction and altered microvascular integrity. At the same time, lymphocyte reduction may reflect changes in adaptive immune responses and immune regulation. Together, these changes may indicate an inflammatory state that could increase vulnerability to neurocognitive disturbance during a major perioperative stressor [9].

The relationship between NLR and postoperative delirium may also reflect the broader physiological stress response rather than inflammation alone. Trauma, pain, catecholamine release, infection, hypoxia, and medication exposure can influence circulating leukocyte counts and may occur concurrently with the development of delirium. Thus, an elevated NLR could be associated with delirium because it captures the intensity of the acute illness or injury, because it reflects a relevant inflammatory process, or through a combination of these mechanisms. Clarifying this distinction is important when considering the biological and clinical meaning of the association [10].

Despite its practical advantages, NLR has limitations as a candidate predictor. Its value can be influenced by the timing of blood sampling, recent trauma, infection, chronic inflammatory conditions, corticosteroid treatment, hydration status, and other factors that alter leukocyte counts. In emergency orthopedic patients, trauma itself may change

neutrophil and lymphocyte levels before surgery, making it important to define when NLR is measured and to interpret it in the context of the patient's clinical condition. Consequently, NLR should complement rather than replace clinical assessment [11].

Published findings on NLR and delirium may also differ because studies use varying populations, blood-sampling time points, delirium assessment tools, and analytical approaches. Differences in the prevalence of baseline cognitive impairment, fracture type, surgical urgency, comorbidity, and perioperative care can further affect observed associations. In addition, incomplete adjustment for important factors such as age, frailty, pre-existing cognitive status, infection, anemia, and medication exposure may make it difficult to determine whether NLR provides information beyond established clinical predictors [12].

The clinical value of NLR therefore depends not only on whether it is associated with POD, but also on whether it contributes meaningfully to risk assessment in the population in which it is used. A useful marker should be available early enough to inform care, be interpretable in routine practice, and provide information that complements relevant clinical variables. If an elevated preoperative NLR identifies patients who warrant closer observation, it could support timely delirium screening and reinforce preventive measures. Its usefulness, however, should be established in the specific context of major emergency orthopedic surgery rather than assumed from findings in other patient groups [13].

In older patients undergoing emergency orthopedic procedures, delirium risk is likely to arise from the interaction of host vulnerability, inflammatory activity, injury severity, and perioperative exposures. NLR offers a simple means of summarizing two circulating leukocyte components that may change during acute stress, but its association with POD in this setting requires focused evaluation. Accordingly, this study aimed to assess the pathophysiological significance of the neutrophil-to-lymphocyte ratio and determine its value as a predictor of postoperative delirium in elderly patients undergoing major emergency orthopedic surgery.

Material and methods

Study Design:

This descriptive cross-sectional study was conducted at Shohada Hospital in Tabriz, Iran. It investigated the association between the neutrophil-to-lymphocyte ratio (NLR) and postoperative delirium among older adults undergoing major emergency orthopedic surgery.

Sampling and Sample Size:

Participants were recruited using convenience sampling from eligible patients evaluated at Shohada Hospital, Tabriz. The required sample size was estimated as 88 using Cochran's formula for a single population proportion: $n = Z^2 \times p \times (1-p) / d^2$. The calculation assumed a 95% confidence level ($Z=1.96$), maximum variability ($p=0.50$), and an acceptable precision of $d=0.105$, yielding a target sample size of approximately 88 participants.

Inclusion and Exclusion Criteria

Patients were eligible if they were 65 years of age or older, were admitted to Shohada Hospital for major emergency orthopedic surgery, and had an available preoperative complete blood count from which the NLR could be calculated. Participants also needed to be assessable for delirium after surgery, either through direct evaluation or review of their clinical records. Patients were excluded if they had delirium before surgery, a documented history of dementia or another condition that prevented reliable assessment of postoperative mental status, or an active neurological or psychiatric disorder substantially affecting cognition. Additional exclusion criteria included active hematologic malignancy or a major hematologic disorder likely to distort leukocyte counts; current immunosuppressive or cytotoxic treatment; a concurrent severe infection or inflammatory condition likely to markedly alter the NLR; incomplete essential clinical or laboratory records; and death or transfer before postoperative delirium assessment could be completed. These criteria should be checked against the study protocol and actual data collection procedures before submission.

Data Collection and Study Variables:

Demographic and baseline variables included age, sex, and relevant preoperative characteristics documented in the medical record. Clinical variables included the reason for emergency admission, type of orthopedic injury, procedure performed, and available indicators of baseline health and comorbidity. The timing of admission, surgery, and postoperative assessment was recorded where available. Preoperative laboratory data included the neutrophil and lymphocyte counts from the complete blood count; the NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The timing of blood sampling relative to surgery was documented to support consistent interpretation of this inflammatory marker.

The primary outcome was the occurrence of delirium after surgery, determined using the assessment method documented in the study protocol and medical records. Delirium-related variables included its presence or absence and, when recorded, the time of onset and duration.

Postoperative clinical variables included relevant complications and other recorded outcomes during the observation period. Data were extracted using a structured collection form, checked for completeness, and coded before analysis. Only variables available in the study records should be retained in the final manuscript; specify the delirium instrument and postoperative observation period if these were defined in the protocol.

Statistical Analysis:

Continuous variables were summarized as means and standard deviations, and categorical variables as frequencies and percentages. The distribution of continuous data was assessed using the Shapiro-Wilk test and visual inspection of histograms or Q-Q plots. Between-group comparisons of normally distributed continuous variables were conducted using the independent-samples *t* test, while categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The association between NLR and postoperative delirium was examined using logistic regression; variables considered clinically relevant or showing evidence of association in univariable analyses could be entered into a multivariable model to estimate adjusted odds ratios with 95% confidence intervals. Receiver operating characteristic (ROC) curve analysis was used to assess the discriminatory performance of NLR, with the area under the curve (AUC) and an appropriate threshold reported. All tests were two-sided, and *P*<0.05 was considered statistically significant.

Ethical Considerations:

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (approval

code: IR.TBZMED.FMD.REC.1403.037). Patient information was handled confidentially and used only for research purposes. Informed consent was obtained where required by the approved protocol, and all study procedures were conducted in accordance with the relevant institutional and ethical guidelines.

Results

A total of 88 elderly patients undergoing major emergency orthopedic surgery were evaluated, among whom 26 (29.5%) developed postoperative delirium (Table 1). Patients who experienced delirium were significantly older (77.8 ± 5.9 vs. 72.7 ± 6.7 years; *P* < 0.001), had a higher prevalence of American Society of Anesthesiologists (ASA) physical status class III or higher (65.4% vs. 33.9%; *P*=0.007), experienced longer surgical delays (33.1 ± 11.5 vs. 26.4 ± 9.0 hours; *P*=0.005), and had extended operative times (118.2 ± 26.1 vs. 104.4 ± 23.0 minutes; *P*=0.018) compared with those who did not develop delirium. Notably, marked differences were observed in the preoperative inflammatory and laboratory profiles. The delirium cohort exhibited a significantly higher preoperative neutrophil-to-lymphocyte ratio (NLR) (7.8 ± 2.4 vs. 4.1 ± 1.2 ; *P*<0.001), driven by elevated absolute neutrophil counts (10.1 ± 2.8 vs. $7.4 \pm 2.2 \times 1000$ per microliter; *P*<0.001) and reduced absolute lymphocyte counts (1.4 ± 0.5 vs. $2.0 \pm 0.6 \times 1000$ per microliter; *P*<0.001). Furthermore, serum albumin levels were significantly lower in the delirium group (3.5 ± 0.5 vs. 3.9 ± 0.4 g/dL; *P*=0.001), whereas differences in sex, body mass index, and major comorbid conditions were not statistically significant (*P*>0.05).

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of Patients with and Without Postoperative Delirium

Variable	Total Cohort (N=88)	Delirium Group (n=26)	Non-Delirium Group (n=62)	P-value
Demographics	-	-	-	-
Age (years), Mean $\pm$ SD	74.2 ± 6.8	77.8 ± 5.9	72.7 ± 6.7	<0.001
Sex (Male/Female), n (%)	41 (46.6) / 47 (53.4)	13 (50.0) / 13 (50.0)	28 (45.2) / 34 (54.8)	0.678
Clinical Characteristics	-	-	-	-
BMI (kg/m ²), Mean $\pm$ SD	25.4 ± 3.1	24.9 ± 3.3	25.6 ± 3.0	0.339
ASA Physical Status $\geq$ III, n (%)	38 (43.2)	17 (65.4)	21 (33.9)	0.007
Comorbidities	-	-	-	-
— Diabetes Mellitus, n (%)	29 (33.0)	11 (42.3)	18 (29.0)	0.230
— Hypertension, n (%)	51 (58.0)	17 (65.4)	34 (54.8)	0.360
— Cardiovascular Disease, n (%)	23 (26.1)	10 (38.5)	13 (21.0)	0.089
Surgical Details	-	-	-	-
Fracture Type (Hip / Non-hip), n (%)	56 (63.6) / 32 (36.4)	20 (76.9) / 6 (23.1)	36 (58.1) / 26 (41.9)	0.098
Anesthesia Type (General / Regional), n (%)	31 (35.2) / 57 (64.8)	11 (42.3) / 15 (57.7)	20 (32.3) / 42 (67.7)	0.369
Surgery Duration (min), Mean $\pm$ SD	108.5 ± 24.6	118.2 ± 26.1	104.4 ± 23.0	0.018

Time to Surgery (hours), Mean $\pm$ SD	28.4 $\pm$ 10.2	33.1 $\pm$ 11.5	26.4 $\pm$ 9.0	0.005
Preoperative Laboratory Data	-	-	-	-
White Blood Cell Count ($\times 10^3/\mu\text{L}$), Mean $\pm$ SD	10.8 $\pm$ 3.1	12.4 $\pm$ 3.3	10.1 $\pm$ 2.8	0.002
Absolute Neutrophil Count ($\times 10^3/\mu\text{L}$), Mean $\pm$ SD	8.2 $\pm$ 2.7	10.1 $\pm$ 2.8	7.4 $\pm$ 2.2	<0.001
Absolute Lymphocyte Count ($\times 10^3/\mu\text{L}$), Mean $\pm$ SD	1.8 $\pm$ 0.6	1.4 $\pm$ 0.5	2.0 $\pm$ 0.6	<0.001
Neutrophil-to-Lymphocyte Ratio (NLR), Mean $\pm$ SD	5.2 $\pm$ 2.1	7.8 $\pm$ 2.4	4.1 $\pm$ 1.2	<0.001
Hemoglobin (g/dL), Mean $\pm$ SD	11.6 $\pm$ 1.5	11.2 $\pm$ 1.6	11.8 $\pm$ 1.4	0.089
Serum Creatinine (mg/dL), Mean $\pm$ SD	1.1 $\pm$ 0.3	1.2 $\pm$ 0.4	1.0 $\pm$ 0.3	0.041
Serum Albumin (g/dL), Mean $\pm$ SD	3.8 $\pm$ 0.5	3.5 $\pm$ 0.5	3.9 $\pm$ 0.4	0.001

Note: Continuous variables are presented as Mean $\pm$ SD and compared using the independent-samples t-test. Categorical variables are presented as n (%) and compared using the chi-square test or Fisher's exact test, as appropriate. ASA=American Society of Anesthesiologists; BMI=Body Mass Index.

To determine the independent predictors of postoperative delirium, univariable and multivariable logistic regression analyses were conducted (Table 2). In the univariable analysis, advanced age (OR=1.12, 95% CI:1.04-1.21, P=0.003), ASA physical status class III or higher (OR=3.68, 95% CI:1.41-9.61, P=0.008), prolonged time to surgery (OR=1.07, 95% CI:1.02-1.13, P=0.007), longer surgical duration (OR=1.25, 95%

CI:1.03-1.52, P=0.024), lower serum albumin levels (OR=2.85, 95% CI:1.42-5.71, P=0.003), and elevated preoperative NLR (OR=2.18, 95% CI:1.52-3.13, P<0.001) were significantly associated with the development of delirium. After adjusting for confounding clinical and demographic covariates in the multivariable model, preoperative NLR remained a robust and independent predictor of postoperative delirium (adjusted OR=1.89, 95% CI:1.29-2.77, P=0.001), indicating that each single-unit elevation in preoperative NLR conferred an 89% increase in the odds of delirium occurrence. Conversely, other clinical variables did not maintain statistical significance in the fully adjusted model (P>0.05).

Table 2. Univariable and Multivariable Logistic Regression Analyses for Predictors of Postoperative Delirium

Predictor Variable	Univariable OR (95% CI)	P-value	Multivariable Adjusted OR (95% CI)	P-value
Age (per 1-year increase)	1.12 (1.04-1.21)	0.003	1.08 (0.98-1.19)	0.118
ASA Physical Status (Class III or higher vs Class I-II)	3.68 (1.41-9.61)	0.008	2.14 (0.68-6.73)	0.192
Time to Surgery (per 1-hour delay)	1.07 (1.02-1.13)	0.007	1.04 (0.98-1.11)	0.215
Duration of Surgery (per 10-minute increase)	1.25 (1.03-1.52)	0.024	1.11 (0.87-1.42)	0.402
Fracture Type (Hip vs Non-hip)	2.41 (0.84-6.90)	0.102	1.62 (0.45-5.83)	0.461
Preoperative Serum Albumin (per 1 g/dL decrease)	2.85 (1.42-5.71)	0.003	1.95 (0.82-4.63)	0.131
Preoperative NLR (per 1-unit increase)	2.18 (1.52-3.13)	<0.001	1.89 (1.29-2.77)	0.001

Note: OR=Odds Ratio; CI=Confidence Interval; ASA=American Society of Anesthesiologists; NLR=Neutrophil-to-Lymphocyte Ratio.

Multivariable model adjusted for age, ASA physical status, time to surgery, duration of surgery, fracture type, preoperative serum albumin, and NLR. The solid blue curve represents the discriminatory performance of the preoperative NLR across varying decision thresholds, demonstrating an area

under the curve (AUC) of 0.886 (95% CI:0.804-0.968; P<0.001). The dashed gray diagonal line denotes the reference line corresponding to chance discrimination (AUC=0.500). The red circle indicates the optimal cutoff value of 5.45 determined via Youden index, yielding a sensitivity of 88.5% and a specificity of 82.0%. All text, numbers, and symbols are formatted consistently for publication.

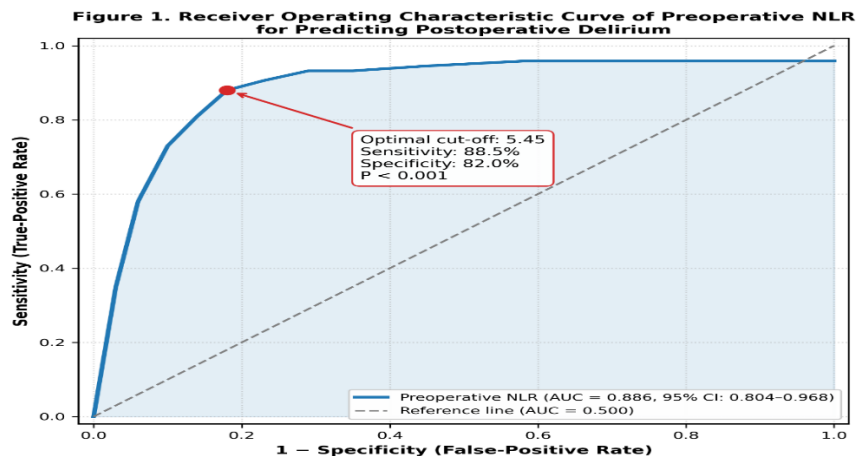


Figure 1. Receiver Operating Characteristic (ROC) Curve of Preoperative Neutrophil-to-Lymphocyte Ratio (NLR) for Predicting Postoperative Delirium.

Discussion

In this cohort of 88 elderly patients undergoing major emergency orthopedic surgery, postoperative delirium occurred in 29.5% and was associated with older age, higher ASA class, longer time-to-surgery and operative duration, a more pronounced preoperative inflammatory profile (higher neutrophils, lower lymphocytes, and higher NLR), and lower serum albumin; importantly, NLR demonstrated strong discriminatory performance (AUC=0.886) and remained an independent predictor after multivariable adjustment (adjusted OR=1.89, 95% CI:1.29-2.77), supporting its value as a clinically accessible biomarker for delirium risk stratification in this high-risk setting.[10][11].

The observed relationship between elevated preoperative NLR and postoperative delirium is biologically plausible because delirium is increasingly recognized as an acute brain dysfunction arising from systemic inflammation, neuroendocrine stress responses, and impaired cerebral homeostasis rather than a purely “psychiatric” complication. Major trauma and urgent orthopedic surgery generate an immediate cytokine surge and innate immune activation, and NLR captures this shift toward neutrophil predominance and relative lymphopenia, both of which reflect stress-mediated myeloid mobilization and adaptive immune suppression. Once systemic inflammatory mediators increase, blood-brain barrier permeability may be altered, facilitating microglial activation and synaptic dysfunction that manifest clinically as delirium. In this context, NLR functions as an integrated surrogate for inflammatory tone and physiologic reserve, explaining why each unit increase was associated with substantially higher odds of delirium even after adjustment for key clinical covariates.[12][13].

Neutrophilia in the delirium group likely reflects enhanced catecholamine- and cortisol-driven demargination, bone marrow release, and endothelial activation that occur after fracture-

related tissue injury and perioperative stress. Neutrophils are not only markers but also mediators of organ dysfunction through release of reactive oxygen species, proteases, and neutrophil extracellular traps, which can amplify systemic inflammation and microvascular dysregulation. Concurrent lymphopenia may indicate impaired cell-mediated immune regulation and an exaggerated stress response; reduced lymphocyte trafficking and apoptosis during acute illness have been associated with worse outcomes and may predispose to dysregulated neuroinflammation. Therefore, the combined metric (NLR) can outperform absolute counts because it embeds two pathophysiologic directions innate immune escalation and adaptive immune suppression both of which are relevant to delirium vulnerability in the elderly.[14][15].

The discriminatory capacity observed for preoperative NLR (AUC=0.886) suggests that inflammatory priming before incision is an important determinant of postoperative neurocognitive complications, particularly in emergency settings where optimization time is limited. Older adults frequently present with baseline “inflammaging,” endothelial dysfunction, and reduced cognitive reserve; when a superimposed inflammatory hit occurs, even modest additional immune activation may cross a threshold for acute cerebral dysfunction. The identified cutoff (NLR=5.45) with relatively high sensitivity and specificity is clinically appealing because it could support rapid bedside triage for intensified delirium-prevention bundles, such as minimizing deliriogenic medications, optimizing analgesia, ensuring early mobilization, and prioritizing reorientation and sleep hygiene.[16][17].

The finding that delirium patients were older and more frequently ASA class III or higher aligns with established concepts of frailty and physiologic vulnerability. Age likely captures cumulative cerebrovascular burden, subclinical

neurodegeneration, and impaired cholinergic neurotransmission, which can reduce the brain's tolerance to inflammatory and metabolic stressors. Higher ASA class may reflect a composite of cardiopulmonary disease, metabolic derangements, and reduced functional reserve, each of which can contribute to cerebral hypoperfusion, impaired oxygen delivery, and susceptibility to delirium triggers such as pain, anemia, and polypharmacy. Notably, these clinical risk markers lost statistical significance in the multivariable model, which may indicate that NLR partially mediates the effect of systemic illness severity through an inflammatory pathway, or alternatively that sample size limited power for detecting independent contributions once correlated covariates were included.[18][19].

Prolonged time to surgery and longer operative duration were also associated with delirium in unadjusted analyses, which is consistent with the notion that both prolonged nociceptive stress and extended immobilization worsen inflammatory burden and increase exposure to precipitating factors such as fasting, sleep disruption, and opioid requirements. Delay to surgery may also serve as a proxy for preoperative instability or logistical barriers that prolong pain and stress hormone secretion, amplifying neutrophilia and lymphopenia. Similarly, longer operative time can reflect surgical complexity, increased tissue trauma, and larger inflammatory response, thereby potentiating postoperative delirium. That these variables did not remain significant after adjustment may suggest that their effect is channeled through the same biological axis captured by NLR, or that the adjusted model prioritized the strongest, most proximal marker of systemic inflammatory stress.[20][21].

Lower serum albumin in the delirium group is another biologically coherent finding, as albumin is both a marker of nutritional status and a negative acute-phase reactant that declines in systemic inflammation. Hypoalbuminemia can worsen pharmacokinetics (increasing free fractions of protein-bound drugs), reduce antioxidant capacity, and impair endothelial stability, potentially increasing blood-brain barrier vulnerability and neuroinflammatory signaling. In the perioperative elderly population, low albumin may also indicate sarcopenia and frailty, both associated with reduced resilience to surgical stress and higher delirium risk. The attenuation of albumin's association in the multivariable model may reflect collinearity with NLR or the possibility that albumin provides a broader measure of chronic vulnerability, whereas NLR better captures the acute inflammatory state immediately preceding surgery.[22][23].

The observed differences in leukocyte profiles and creatinine, alongside nonsignificant differences in several comorbidities, may point to the limitations of using comorbidity labels alone to estimate risk in urgent surgical care. Chronic disease diagnoses do

not necessarily reflect the patient's acute physiologic trajectory at admission, whereas laboratory markers can capture the "current state" of immune activation, hydration, renal perfusion, and catabolic stress. Mildly higher creatinine in the delirium group may represent reduced renal reserve or peri-traumatic hypoperfusion, both of which can increase susceptibility to delirium through metabolic disturbances and reduced clearance of sedatives and analgesics. However, the clinical impact of small creatinine differences is likely modest compared with the more pronounced inflammatory signal, reinforcing the concept that delirium risk in this context is multifactorial but strongly influenced by systemic inflammation.[24][25].

From a mechanistic standpoint, the link between systemic inflammation and delirium can be framed through neuroimmune crosstalk: peripheral cytokines and damage-associated molecular patterns trigger microglial priming and astrocytic responses, altering neurotransmitter balance (particularly cholinergic and dopaminergic pathways) and disrupting synaptic plasticity. Elderly patients often have primed microglia due to aging and comorbidities, producing an exaggerated central response to peripheral inflammatory stimuli. Neutrophil-driven inflammation may contribute to microvascular dysfunction and endothelial activation, with downstream effects on cerebral perfusion and oxygen utilization. Lymphopenia may also signal impaired immunoregulation, allowing a more sustained inflammatory response that prolongs delirium risk beyond immediate postoperative hours.[26][27].

Clinically, these data support incorporating NLR into perioperative delirium risk frameworks, particularly where rapid decision-making is necessary and resource constraints limit comprehensive geriatric evaluation. A preoperative NLR above the identified threshold could prompt targeted measures: prioritizing early surgery when feasible, choosing anesthesia and analgesia strategies that minimize hypotension and excessive sedation, optimizing hemodynamics and oxygenation, and implementing structured delirium prevention bundles in the recovery and ward settings. Importantly, the goal is not to "treat NLR," but to use it as an objective trigger for intensified surveillance and mitigation of modifiable precipitating factors. Such an approach may be especially valuable in emergency orthopedic pathways, where delirium carries substantial downstream consequences including prolonged hospitalization, functional decline, and increased mortality.[28][29].

Several considerations are relevant when interpreting these findings. First, NLR is nonspecific and can be influenced by occult infection, chronic inflammatory disease, corticosteroid exposure,

dehydration, or hematologic disorders, which may not be fully captured by routine clinical documentation. Second, the timing of blood sampling relative to trauma, resuscitation, and analgesic administration can affect leukocyte dynamics, and repeated measurements could provide additional prognostic information beyond a single preoperative value. Third, although the multivariable model suggests independent predictive value, the sample size and event count impose constraints on model complexity and precision; external validation in larger cohorts and across different orthopedic emergency populations is necessary before establishing universal thresholds. Nonetheless, the magnitude of association and the strong AUC observed here indicate that the inflammatory signal captured by NLR is not trivial and warrants further prospective evaluation.[30][31].

Conclusion

Overall, the present findings advance the concept that postoperative delirium after major emergency orthopedic surgery in the elderly is tightly linked to preoperative systemic inflammatory stress, and that NLR provides a practical window into this pathophysiology. By integrating neutrophil predominance and lymphocyte suppression into a single, widely available index, NLR appears to identify patients in whom neuroinflammatory vulnerability is already heightened before operative stress is added. Future work should examine whether incorporating NLR into multimodal prediction tools improves calibration and clinical utility, and whether NLR-guided care pathways can reduce delirium incidence through earlier prevention, optimized perioperative physiology, and structured postoperative monitoring.

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Conflicts of interest

The authors declare that they have no competing interests.

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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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