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Evaluating the relationship between inflammatory markers and preoperative delirium in elderly hip fracture patients

A retrospective observational study

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Abstract

Preoperative delirium is common and associated with poor clinical outcomes in elderly hip fracture patients. Although inflammatory markers have shown potential in predicting postoperative delirium, their relevance to preoperative delirium remains unclear. This study aimed to investigate the relationship between inflammatory markers and preoperative delirium to improve risk prediction and management strategies. We retrospectively studied 548 elderly hip fracture patients aged 70 years or older. The primary outcome was preoperative delirium diagnosed using the Confusion Assessment Method (CAM). Explanatory variables included inflammatory markers (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], systemic immune-inflammation index [SII], inflammatory burden index [IBI], and systemic inflammation response index [SIRI]). About 7.66% of patients developed preoperative delirium in the study. These patients were more likely to be older, have comorbid cardiovascular disease, and be transferred to an internal medicine ward for further treatment ($P < .001$). Multivariate analysis further revealed that older age (OR = 1.11, 95% CI = 1.04–1.18) and comorbid cardiovascular disease (OR = 2.94, 95% CI = 1.51–5.67) were independently associated with the occurrence of preoperative delirium. No significant differences were observed between groups for inflammatory markers: NLR ($P = .70$), PLR ($P = .09$), IBI ($P = .09$), SII ($P = .21$), or SIRI ($P = .80$). Older age and cardiovascular comorbidities were independent risk factors for preoperative delirium. No significant associations were found with inflammatory markers. Future research should explore additional biomarkers to refine risk stratification in this population.

Abbreviations: CAM = confusion assessment method, CI = confidence interval, CRP = C-reactive protein, IBI = inflammatory burden index, IQR = interquartile range, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, PLR = platelet-to-lymphocyte ratio, SII = systemic immune inflammation index, SIRI = systemic inflammation response index.

Keywords: delirium, hip fracture, inflammatory markers, preoperative delirium, SII, SIRI

1. Introduction

Hip fracture is a major public health problem, with approximately 1.6 million patients occurring annually worldwide, and the 1-year mortality rate can reach 36%.[1] Current data emphasize that about 13% to 74% of older hip fracture patients develop delirium in the perioperative period,[2–4] which in turn leads to significant increases in morbidity, mortality, and healthcare costs.[5–7]

Perioperative delirium, which includes both preoperative and postoperative delirium, is characterized by acute fluctuating changes in levels of consciousness and cognition.[8,9] Over the past decades, a number of risk factors for postoperative delirium have been well established, such as older age,[10,11] gender,[12] dementia,[13] and multiple comorbidities.[14] However, only a few published studies have made a distinction between preoperative and postoperative delirium, and there is insufficient evidence regarding risk factors and interventions for preoperative delirium.[15,16] Indeed, preoperative delirium is common and associated with poor clinical outcomes in elderly hip fracture patients.[17] More research data are needed to enable the prediction of patients at high risk of preoperative delirium and then develop proper interventions.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Neuroinflammation, induced by fracture and surgery, plays a critical role in the pathophysiology of perioperative delirium.[18–21] Hip fracture patients with delirium are often observed to have changes in the levels of several inflammatory markers, such as elevated neutrophils and decreased lymphocytes.[22,23] Based on these evidence, a number of inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), inflammatory burden index (IBI), and system inflammation response index (SIRI) have been developed to predict perioperative cognitive dysfunction.[24–26] Some of these markers have been tentatively shown to be associated with the development of postoperative delirium. However, to our best knowledge, no study has analyzed the relationship between these inflammatory markers and preoperative delirium. This study aimed to investigate the association between these inflammatory markers and preoperative delirium in elderly hip fracture patients.

2. Materials and methods

2.1. Study design and participants

This was a single-center, retrospective observational study conducted at Tianjin Hospital of Tianjin University between June 2022 and December 2023. The sample size was calculated using the formula as described by Noordzij et al,[27] where $Z\alpha/2 = 1.96$ (95% confidence level), $P = 12.7\%$ (based on previous data from Agrawal et al[17]), d = 0.03. The minimum sample size required was 473 cases, and 548 patients were finally included in our study. Patients who met the inclusion criteria during the study period were enrolled using a consecutive sampling method to minimize selection bias. Inclusion criteria were: age ≥ 70 years; with hip fractures and received surgery; and complete information on medical records. Exclusion criteria: severe head injury; history of mental illness; a history of delirium prior to this injury; and chronic infection diseases or other autoimmune diseases.

2.2. Variables and data collection

The primary outcome variable was preoperative delirium, which was diagnosed using the Confusion Assessment Method (CAM).[28] The CAM instrument had the following 4 criteria: (I) inattention, (II) acute onset and fluctuating course, (III) altered consciousness, and (IV) disorganized thinking. The diagnosis of delirium required the presence of criterion (I) and (II), and either criterion (III) or (IV). Patients were assessed twice daily for preoperative delirium from admission until surgery.

The main exposure variables were inflammatory markers, including NLR, PLR, SII, IBI, and SIRI. Baseline characteristics on age, gender, smoking, alcohol consumption, fracture site/type, time from fracture to hospital and medical history were recorded in this study. Medical history included history of cardiovascular disease (atrial fibrillation, heart failure, valvular disease, coronary artery disease), hypertension, diabetes mellitus, stroke, history of fractures at another site and a history of cancer/tumor. The main exposures of interest were inflammatory markers which were calculated from blood test results. Therefore, white blood cell count, neutrophil, lymphocyte, monocyte, platelet, albumin/globulin and C-reactive protein (CRP) were recorded from blood routine examination at admission. NLR was calculated as neutrophil count/lymphocyte count, PLR was calculated as platelet count/lymphocyte count, IBI was calculated as CRP × neutrophil/lymphocyte, SII was calculated as plate count × neutrophil count/lymphocyte count and SIRI was calculated as neutrophil count × monocyte count/lymphocyte count.[29,30]

2.3. Study groups and ethics

Patients were divided into 2 groups based on the presence or absence of preoperative delirium. All demographic characteristics, clinical variables, laboratory parameters, and inflammatory markers were compared between these 2 groups to identify potential risk factors associated with preoperative delirium.

This study was approved by the Ethics Committee of Tianjin Hospital (IRB no. 2024-013). The requirement for informed consent was waived due to the retrospective nature of the study. All data were anonymized during analysis. The primary endpoint was the occurrence of preoperative delirium, which was assessed from admission until surgery using the CAM.

2.4. Statistical analysis

Continuous variables with normally distributed data were presented as resented as mean ± standard and were compared using *t* test. If the continuous data were not normally distributed, they are shown as the median and interquartile range (IQR) and compared with the Mann–Whitney *U* test. Categorical variables were presented as frequency and chi-square, or Fisher's exact test was used to compare their differences. Multivariate analysis was performed using logistic regression analysis to determine the risk factors, and results were presented as the odds ratios (OR) by 95% confidence interval (CI). $P < .05$ was considered statistically significant. Statistical analyses were performed by the GraphPad Prism and R 4.1.3 software.

3. Results

A total of 548 hip fracture patients were retrospectively analyzed in this study. The baseline data of these patients are shown in Table 1. The average age of patients was 79.24 ± 5.47years and 66.24% patients (363/548) were females.

Forty-two patients (7.66%) were diagnosed with preoperative delirium. The average age of preoperative delirium group was 81.98 ± 6.38 years, and 66.67% patients (28/42) were females. There was no significant difference between the 2 groups in terms of gender, smoking, alcohol consumption, fracture site/type, hypertension, diabetes mellitus, stroke, time from fracture to hospital, length of hospitalization, history of fractures at other site or a history of malignant tumors ($P > .05$). However, the patients with preoperative delirium were older ($P < .01$, OR = 1.11, 95% CI = 1.04–1.18) and more often had cardiovascular disease ($P < .01$, OR = 2.94, 95% CI = 1.51–5.67) (Table 2). Patients who develop preoperative delirium are more likely to be transferred to an internal medicine ward for further treatment (19.04% vs 1.58%, $P < .001$). We did not find any patients with body temperature higher than 37.5°C at admission.

The results of inflammatory markers for the 2 groups are listed in Table 3. The median values of CRP, PLR, IBI, SII, and SIRI were 5.00 versus 20.50, 158.7 versus 201.6, 89.07 versus 130.40, 1231 versus 1469, 3.82 versus 3.83, respectively. However, there was no statistical differences were found between these variables ($P > .05$).

4. Discussion

The main findings of this study were: The incidence of preoperative delirium was 7.66% in elderly hip fracture patients; Older age (OR = 1.11, 95% CI = 1.04–1.18) and cardiovascular comorbidities (OR = 2.94, 95% CI = 1.51–5.67) were identified as independent risk factors; No significant associations were found between inflammatory markers (NLR, PLR, IBI, SII, SIRI) and preoperative delirium.

Our study found that the incidence of preoperative delirium was 7.66%, which is somewhat lower than the 12.7% to 57.6%

Table 1

Baseline characteristics of enrolled patients

Characteristic	Preoperative delirium assessment		
	Yes n = 42 (7.66%)	No n = 506 (92.34%)	*P* value
Age (yr)	81.98 ± 6.38	79.01 ± 5.33	<.001
Gender, n (%)			.952
Male	14 (33.33)	171 (33.79)	
Female	28 (66.67)	335 (66.21)	
Smoking, n (%)	3 (7.14)	53 (10.47)	.789
Alcohol consumption, n (%)	2 (4.76)	31 (6.13)	>.999
Fracture site, n (%)			.152
Right	13 (30.95)	214 (42.29)	
Left	29 (69.05)	292 (57.71)	
Fracture type, n (%)			.682
Intertrochanteric fracture	16 (38.10)	209 (41.30)	
Femoral neck fracture	26 (61.90)	297 (58.70)	
Comorbidity, n (%)			
Hypertension	23 (54.76)	316 (62.45)	.324
Cardiovascular disease	18 (42.86)	101 (19.96)	<.001
Diabetes mellitus	8 (19.05)	145 (28.66)	.182
Stroke	8 (19.05)	107 (21.15)	.748
Time from fracture to hospital (h)	17.79 ± 21.22	25.75 ± 55.02	.352
Body temperature > 37.5°C at admission, n (%)	0	0	-
History of fractures at another site, n (%)	7 (16.67)	63 (12.45)	.432
History of a tumor, n (%)	5 (11.90)	60 (11.86)	.993
Further treatment in internal medicine ward, n (%)	8 (19.05)	12 (2.37)	<.001
Length of stay (d), (IQR)	8 (6, 11)	8 (6, 9)	.330

IQR = interquartile range.

Table 2

Multivariate logistic regression analysis of risk factors for preoperative delirium

Risk factor	OR (95% CI)	*P* value
Age (yr)	1.11 (1.04–1.18)	.0012
Cardiovascular disease	2.94 (1.51–5.67)	.0013

CI = confidence interval, OR = odds ratio.

Table 3

Comparison of inflammatory parameters between the 2 groups

Items	Preoperative delirium assessment		
	Yes n = 42 (7.66%)	No n = 506 (92.34%)	*P* value
WBC count, 10^9/L	9.55 ± 3.71	9.73 ± 3.14	.730
Neutrophil, 10^9/L	8.04 ± 3.17	8.14 ± 3.40	.866
Lymphocyte, 10^9/L	1.12 ± 0.55	1.07 ± 0.47	.541
Monocytes, 10^9/L	0.54 ± 0.18	0.53 ± 0.21	.728
Platelet, 10^9/L	184.80 ± 52.61	203.30 ± 59.50	.052
Albumin/Globulin	1.41 ± 0.13	1.42 ± 0.18	.801
CRP, mg/L, median (IQR)	5.00 (5.00, 52.25)	20.50 (5.75, 43.00)	.056
NLR, median (IQR)	7.37 (4.12, 11.18)	7.60 (4.87, 11.34)	.702
PLR, median (IQR)	158.7 (122.8, 240.1)	201.6 (136.8, 284.0)	.094
IBI, median (IQR)	89.07 (34.80, 358.20)	130.40 (58.78, 320.60)	.087
SII, median (IQR)	1231 (698, 2154)	1469 (921, 2441)	.205
SIRI, median (IQR)	3.82 (2.53, 6.58)	3.83 (2.13, 6.21)	.798

CRP = C-reactive protein, IBI = inflammatory burden index, IQR = interquartile range, NLR = neutrophil/lymphocyte ratio, PLR = platelet/lymphocyte ratio, SII = systemic immune inflammation index, SIRI = systemic inflammation response index, WBC = white blood cell.

reported in other literature.[15–17,31] In fact, the incidence of perioperative delirium in elderly hip fracture patients has shown a decreasing trend in recent years.[32,33] This may be attributed to the interventions now available for hip fracture patients,[34,35] including effective preoperative analgesia, the judicious use of benzodiazepines, and the endeavor to operate as expeditiously as possible within 48 hours, which were also employed in our hospital.

We found that preoperative delirium patients were associated with older age, more often had cardiovascular disease and more likely to be transferred to an internal medicine ward for further treatment. Previous studies have confirmed that advanced age is a significant risk factor for postoperative delirium.[36,37] However, controversy remains regarding the role of age in preoperative delirium. The findings of this study demonstrate that older age is also an independent risk factor for the development of preoperative delirium. As individuals age, there is a gradual decline in the levels of acetylcholine, central cholinergic neurons and other neurotransmitter disorders in the body, which increases the risk of abnormal brain function.[38,39] Moreover, elderly patients exhibit a diminished capacity to adapt to external stressors. When patients leave their familiar living environment, they become more susceptible to distress and fear, which in turn increases the probability of developing delirium. The above mechanisms may result in older age being a common risk factor for the development of either preoperative delirium or postoperative delirium in hip fracture patients.

Moreover, our data indicated that cardiovascular disease is an independent risk factor for preoperative delirium. Elderly patients are susceptible to a variety of comorbidities, some of which correlate with cognitive and brain dysfunction.[40] The mechanisms by which cardiovascular disease leads to cognitive or brain dysfunction are complex. A number of potential causes have been postulated, including reduced cerebral blood flow, systemic inflammatory conditions, and protein toxicity.[41–43] Our findings reinforce the necessity for heightened awareness of recognizing hip fracture patients with cardiovascular disease in order to reduce the development of preoperative delirium. We also found that 66.67% of patients with preoperative delirium were female. Although the difference in gender composition was not statistically significant, it is important to recognize the high perioperative prevalence in women, as many studies have similarly demonstrated.[17]

Although some studies have found an association between inflammatory markers and postoperative delirium,[44] no such correlation was found in our study. We hypothesized that the reduction in preoperative waiting time for hip fracture patients may be a contributing factor. In recent years, our hospital has implemented a treatment plan that aims to perform surgery on most hip fracture patients within 48 hours. The clinical benefits of early surgery for elderly hip fracture patients were widely recognized.[45] It has been theorized that the shorter preoperative preparation time resulted in a shorter window for the onset of preoperative delirium. Delayed surgical intervention may result in increased acute peripheral inflammatory stimulation, brain parenchymal cell activation, and pro-inflammatory cytokine expression, which could potentially lead to neuronal apoptosis and synaptic dysfunction.

In fact, inflammatory markers such as SII and SIRI were initially identified as being associated with clinical outcomes in chronic diseases including lung cancer, pancreatic cancer and stroke.[46,47] The tumor microenvironment, through continued stimulation of myelopoiesis, releases neutrophil precursors that ultimately lead to changes in circulating levels of immune cells such as granulocytes.[48] In the absence of infection, serum inflammatory mediators exhibit a gradual increase over a period of time, typically spanning 3 to 5 days.[49] In the present study, blood samples were collected immediately after the patients

were admitted to the hospital, approximately equal to the time from fracture to hospital. Therefore, the interval between fracture occurrence and blood sampling was17.79 and 25.75 hours for the preoperative delirium and non-delirium groups, respectively. During this period, inflammatory mediators are exhibiting a gradual increase in response to the trauma. Our data also showed that the non-delirium group with later sampling time had somewhat higher median values of CRP, PLR, IBI, and SII, although this difference was not statistically significant. Therefore, in the future, it is necessary to conduct further analysis to determine whether the timing of blood sampling affects the predictive effect of these inflammatory markers.

The risk factors for preoperative delirium remain poorly understood in elderly hip fracture patients. It is inaccurate to assume that the risk factors for preoperative delirium are the same as those for postoperative delirium. We aimed to explore the risk factors of preoperative delirium, with a particular focus on the potential relationship between inflammatory markers with preoperative delirium in elderly hip fracture patients. In this study, 7.66% of patients developed preoperative delirium, which was significantly associated with older age, comorbid cardiovascular disease, and transfer to an internal medicine ward ($P < .05$). Older age and cardiovascular comorbidities were independent risk factors for preoperative delirium. No significant differences were observed between the delirium and non-delirium groups in NLR, PLR, IBI, SII, or SIRI ($P > .05$).

This study has several strengths and limitations. One of the main strengths is its focus on the predictive value of multiple inflammatory markers for preoperative delirium in elderly hip fracture patients, which is a relatively underexplored area. Additionally, the study included a relatively large sample size of 548 patients, which enhances the statistical power and reliability of the findings. However, there are some limitations to consider. The retrospective nature of the study may introduce bias in data collection and analysis. Furthermore, the study does not include clinical outcomes such as mortality, which limits the understanding of the long-term impact of preoperative delirium. Finally, as a single-center study, the generalizability of the findings may be limited, and further prospective, multicenter studies are needed to validate these results and explore additional biomarkers for better risk stratification.

5. Conclusion

This study provides several important findings regarding preoperative delirium in elderly hip fracture patients. First, we identified that older age and cardiovascular disease were independent risk factors for preoperative delirium, which can help in early risk stratification. Second, unlike previous studies on postoperative delirium, we found no significant association between inflammatory markers and preoperative delirium, suggesting different underlying mechanisms. Based on these findings, we recommend: implementing enhanced monitoring and preventive strategies for elderly patients with cardiovascular comorbidities; exploring additional biomarkers that might better predict preoperative delirium risk in this population.

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Author contributions

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