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How to predict postoperative delirium in geriatric patients with hip fracture as soon as possible? A retrospective study

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Abstract

Purpose Inflammation may play a role in the mechanism of postoperative delirium (POD), a severe complication among older postoperative patients. The purpose of this study was to investigate the risk factors of POD in postoperative patients with hip fracture, especially the inflammation marker– neutrophil–lymphocyte ratio (NLR).

Methods This retrospective investigation utilized data from the Seventh Medical Center of People's Liberation Army. 1,242 Eligible patients with hip fracture (829 females), median age 81 years, mean neutrophil-lymphocyte ratio (NLR) 5.28, were enrolled. Receiver operating characteristic (ROC) curve was performed to identify the optimal cut point of NLR for POD. The relationship between NLR and POD occurrence, NLR and POD duration were analyzed by multivariable analysis.

Results ROC curve showed that the optimal cut point of NLR for POD was NLR ≥ 7.6. Multivariate logistic regression analysis showed that NLR ≥ 7.6 (odds ratio [OR] 2.75, [95% confidence interval [CI] 1.51 to 5.02], $p = 0.001$), stroke (OR 1.05, [95% CI 1.02 to 1.09], $p = 0.005$), complications, general anesthesia, long length of stay were risk factors of POD, with the largest effect for NLR ≥ 7.6. NLR ≥ 7.6 (β 0.59, [95% CI 0.209 to 0.886], $p = 0.038$), older age (β 0.054, [95% CI 0.009 to 0.099], $p = 0.019$), previous stroke (β 0.908, [95% CI 0.085 to 1.731], $p = 0.031$), and previous heart failure (β 1.679, [95% CI 0.448 to 2.910], $p = 0.008$) suggested long POD duration.

Conclusions This study demonstrates an association between NLR and postoperative delirium in geriatric hip fracture patients, and contribute new evidence to support NLR as a potential marker for prediction of POD and POD duration.

Keywords NLR, Risk factors, Hip fracture, Delirium, Delirium duration

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Introduction

Hip fracture has the highest incidence and associated costs of all fractures among 60 years and older. Postoperative delirium (POD), with an incidence of up to 54% in geriatric patients with hip fracture, is one of the major complications in this population [1, 2]. It has been proven to be an independent risk factor not only for mortality but also for institutionalization and dementia. Being a preventable condition with available effective prevention approaches, identifying higher risk factors of POD in patients with hip fracture will be beneficial for early recognition, prevention, and obtaining the best surgical outcomes.

At present, potential preoperative risk factors for POD underscores four fields: (1) demographic, such as age and body mass index [3, 4]; (2) pre-existing cognitive impairment and mental disorders [5, 6], assessed by neuropsychological scales or information from medical records for additional history of dementia diagnosis; (3) preoperative physical condition [7–9], such as numbers of medical comorbidities, acute medical conditions, and the American Society of Anesthesiologists (ASA) rating scale; and (4) surgery related factors, such as preoperative waiting time, hyponatremia, intraoperative blood pressure deviations [10, 11]. There are some limitations in these risk factors. First, there is synergy between the factors, such as age and cognitive impairment. For many people, aging is associated with relatively little cognitive decline [12]. The interaction of advancing age and cognitive impairment may generate conflicting results. Second, except for being measured objectively, risk factors should be related to the pathogenesis of POD. Third, it should be cost effective. Cognition assessment is often not conducted prior to operation due to longer completion time, which may cause discomfort to the patients.

The exact pathogenesis and physiology of how POD occurs remains unclear. While one possible pathophysiological mechanism for POD is inflammation [13, 14]. Several cytokines and inflammatory markers have already been detected in serum and cerebrospinal fluid during delirium [15]. Neutrophils play an important role in first-line defense during inflammation, while lymphocytes regulate the inflammatory response. In various stressful situations, the physiological response of the immune system is characterized by an increase in neutrophils and a decrease in lymphocytes. Therefore, the blood neutrophil-to-lymphocyte ratio (NLR) has been largely investigated to mirror the inflammatory status. In a retrospective study conducted in 2016, in 2301 patients underwent radical prostatectomy for prostate cancer, NLR is an independent prognostic factor for overall survival and prostate cancer-specific survival [16]. In another retrospective study, comprising 100 eligible upper tract urothelial cancer patients, baseline NLR evaluation may be a valuable predictor and prognosticator of defined disease progression and of upper tract recurrence risk [17]. Peripheral inflammatory response, triggered by surgery, trauma, or infection, is often accompanied by endothelial dysfunction and blood-brain barrier (BBB) disruption. Increased peripheral inflammatory mediators, such as neutrophils, enter the central nervous system, activate astrocytes and microglia, and lead to synaptic remodeling and dysfunction, which ultimately contribute to the occurrence of POD [18]. Previous studies have reported increased NLR in delirium in elderly patients [19–21]. While the relationship between NLR and POD occurrence has not been evaluated in elderly patients with hip fracture, as well as the relationship between NLR and POD duration.

The purpose of this study was (1) to investigate whether NLR could serve as a potential marker for POD in geriatric patients with hip surgery; (2) whether NLR was associated with POD duration in geriatric patients with hip surgery.

Methods

Design

We performed a retrospective analysis of demographic, clinical, and delirium data in consecutive hip fracture patients at the Department of Orthopedics, the Seventh Medical Center of People's Liberation Army, between January 2012 and December 2020. Informed consent was obtained from all patients and the study was approved by the Seventh Medical Center of People's Liberation Army Institutional Review Board.

Patients

All single hip fracture patients aged 60 years or older with a surgical treatment in our center between January 2012 and December 2020 were included in this study (n=1466). A hip fracture was defined as a femoral neck fracture (dislocated or not dislocated) or an intertrochanteric fracture. Patients were excluded if they could not walk independently or with the aid of tools before injury (n=19), caused by high energetic trauma (n=41) or pathological fracture (n=15), companied by preoperative dementia (n=65), companied by disease or taking medicines that could affect the NLR value in the last three weeks (n=13). Patients with data missing (n=18) and died during the perioperative period (n=53) were also excluded (Fig. 1). Each patient was identified by two senior orthopedists and fulfilled the criteria above.

Patients with Garden type I and II femoral neck fracture had been treated with cancellous screws. Patients with Garden type III and IV femoral neck fracture underwent hip arthroplasty. Sliding hip screw (SHS) and intramedullary nail were allocated to the treatment of stable

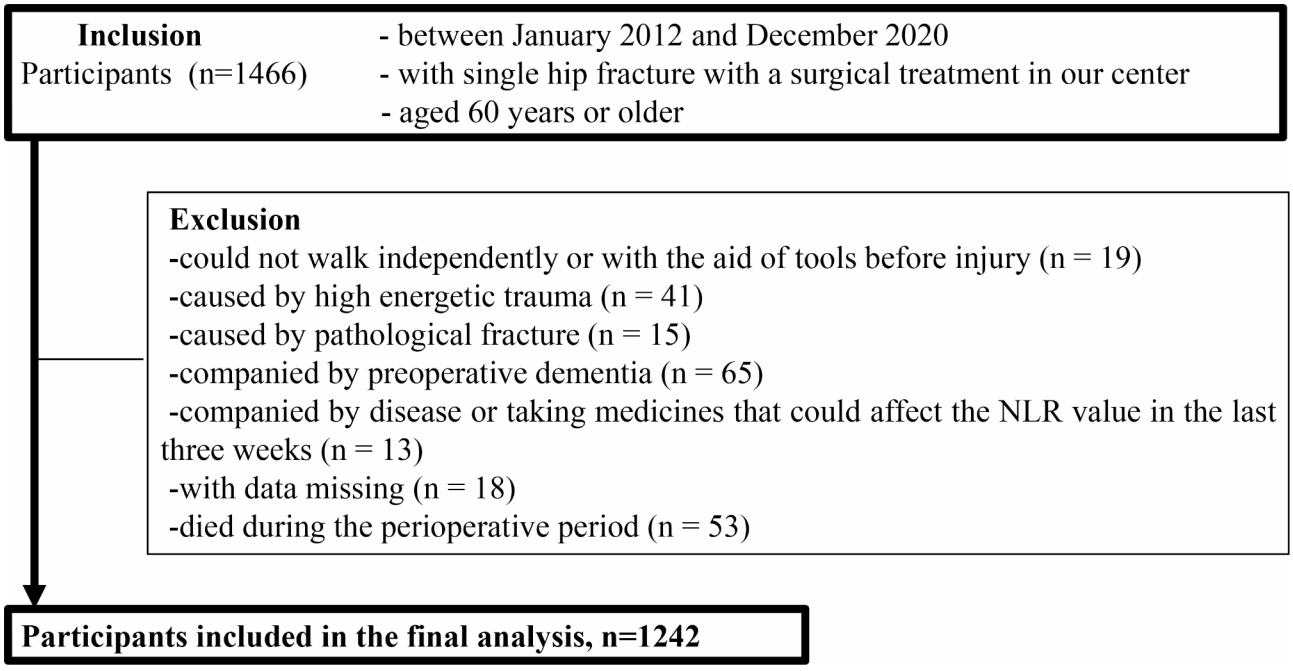

Fig. 1 The flow chart of the study

intertrochanteric and unstable intertrochanteric, respectively [22].

POD and dementia assessment

Delirium was assessed according to the Diagnostic and Statistical Manual of Mental Disorders and the Confusion Assessment Method (CAM) [23]. Patients had to meet the criteria for signs and symptoms according to the four features of the CAM: (1) acute change in the fluctuation of mental state; (2) lack of concentration; (3) confused thinking; and (4) changes in the level of consciousness. Patients' symptoms and signs of delirium were observed and recorded every day by attending doctors until they are discharged. A final diagnosis for POD on each patient was generated after consulting with neurologists at the time of clinical assessment. Delirium duration was extracted from the medical records.

The diagnosis of preoperative dementia was based on Mini-Mental State Examination (MMSE) within 24 h of admission, taking medicines for treating dementia, or previously diagnosed as dementia.

Data

Data including age, gender, past medical history (hypertension, coronary heart disease, diabetes mellitus, cardiac dysrhythmia, heart failure, stroke, renal insufficiency, and mental disorders), post-injury factors (admission to operating time, fracture type, NLR, and length of stay), surgery related factors (type of anesthesia, surgical approach, preoperative sodium, postoperative sodium, alterations of circadian blood pressure, and perioperative complications), and delirium (time of occurrence and duration) were obtained by reviewing their medical records. NLR was defined as the neutrophil count divided by the lymphocyte count. The perioperative complications of hip fracture were all kinds of adverse events during hospitalization that could lead to prolonged hospital stays, increased hospital costs, and even death, such as acute myocardial infarction, new-onset severe arrhythmias, acute cardiac insufficiency, gastrointestinal bleeding, lung infections, acute cholecystitis, and poor wound healing.

Study variables

We obtained data on a wide range of factors that might contribute to delirium in patients after hip fracture surgery. Sixteen variables were grouped into the following categories: (1) sociodemographic data (age and gender; $n=2$ variables), (2) past medical history (hypertension, coronary heart disease, diabetes mellitus, cardiac dysrhythmia, heart failure, stroke, renal insufficiency, and mental disorders; $n=8$ variables), (3) post-injury factors (admission to operating time, fracture type, NLR at admission, and length of stay; $n=4$ variables), and (4) surgery related factors (anesthesia, perioperative complications, preoperative sodium, postoperative sodium, alterations of circadian blood pressure, and surgical approach; $n=6$ variables). Nocturnal dip index was used to estimate the degree of circadian blood pressure alterations: Nocturnal dip index = (diurnal average MAP- nocturnal lowest MAP)/diurnal average MAP×100%. The MAP was calculated as: MAP=DBP+1/3*(SBP-DBP).

Based on nocturnal dip index, the patients were divided into normal circadian blood pressure subgroup (≥10%) and reduced circadian blood pressure subgroup (<10%).

There were three kinds of variables in this model. Continuous variables: age, admission to operating time, neutrophils, lymphocytes, preoperative sodium, postoperative sodium, and length of stay. Dichotomous variables: gender, fracture type, anesthesia, hypertension, coronary heart disease, diabetes mellitus, cardiac dysrhythmia, heart failure, stroke, renal insufficiency, alterations of circadian blood pressure, and mental disorders. Patients receive either regional anesthesia (spinal, epidural, or both techniques combined with no sedation) or general anesthesia (intravenous, inhalational, or combined anesthetic agents). Categorical variables: type of surgery (intramedullary nail, cancellous screws, sliding hip screw, hip arthroplasty).

Table 1 Patients' characteristics

Factors	Values ($n=1242$)
Sociodemographic data	
Age (IQR), years	81(75–89)
Sex(male), *n* (%)	413(33.3%)
Past medical history	
Hypertension, *n* (%)	718(57.8%)
Diabetes mellitus, *n* (%)	351(28.3%)
Cardiac dysrhythmia, *n* (%)	138(11.1%)
Stroke, *n* (%)	389(31.3%)
Coronary heart disease, *n* (%)	306(24.6%)
Heart failure, *n* (%)	69(6.2%)
Renal insufficiency, *n* (%)	66(5.3%)
Post-injury factors	
admission to operating time (IQR), days	32.00 ± 18.40
fracture type	
Intertrochanteric	705(56.8%)
Femoral neck	537(43.2%)
Neutrophils (10^9/L) (IQR) 6.50(5.20–8.10)	
Lymphocytes (10^9/L) (IQR) 1.20(0.90–1.60)	
NLR at admission 5.28(3.75–7.61)	
Length of stay (IQR), days 11.00(9.00–15.00)	
Surgery related factors	
Anesthesia	
general anesthesia	370(29.8%)
Regional anesthesia	872(70.2%)
Type of surgery	192 (54.2%)
Intramedullary nail	639(51.4%)
Sliding hip screw	65 (5.2%)
Hip arthoplasty	372 (30.0%)
Cancellous screws 166 (13.4%)	
Perioperative complications 188(15.1%)	
Delirium	177 (14.3%)
Time of occurrence	
Occurs within 1–3 days after surgery	142(80.2%)
Occurs after 3 days after surgery	35(19.8%)
Duration	4.72 ± 2.56d
Symptoms last for 1–3 days	107(60.5%)
Symptoms last for 4–7 days	58(32.8%)
Symptoms last more than 7 days	12(6.8%)

IQR, interquartile range;

Statistical analysis

We compared patients with delirium and those without using univariate analysis. Continuous variables were expressed as means ± standard deviation (SD) or median (interquartile range, IQR) according to the distribution. The Shapiro-Wilk test was used to assess normal distribution. Differences between groups were analyzed using the independent Student's t test for normally distributed variables, and Wilcoxon rank-sum test for non-normally distributed variables. Categorical variables were shown as frequencies (percentages), and compared by $\chi 2$ test. ROC curve analysis was used to calculate the optimal cut point of NLR for POD. Multivariate logistic regression analyses were used to identify independent risk factors for POD. Variables eligible for inclusion in the multivariate models included those significant at $P<0.05$ in univariate analyses. Linear regressions were used to determine the association between the selected the factors and POD duration. All statistical analyses were performed using SPSS software (version 24.0), and a $P<0.05$ was considered statistically significant.

Results

Subjects' characteristics

A total of 1,242 geriatric patients with hip fracture were eligible for the study. Table 1 shows the patients characteristics. The median age of the study participants was 81 years. The median length of the primary in-hospital stay was 11 days. Of the included patients, 413 (33.3%) were male, 829 were female. Hypertension was the most prevalent medical condition (57.8%) followed by stroke (31.3%), diabetes (28.3%), cardiovascular diseases (24.6%), cardiac dysrhythmia (11.1%), heart failure (6.2%), mental disorders (5.4%), and renal insufficiency (5.3%).

The incidence of delirium on admission was 14.3% (177/1242 patients), which was consistent with incidence of POD in previous studies. Because of exclusion the patients with dementia to reduce the interference of dementia on the delirium, the prevalence is lower than other studies. The majority of them (142 (80.2%)) had a delirium within 3 days after operation. The mean duration days of delirium was 4.72 ± 2.56. In our study, the mean leucocyte count, the neutrophil count, and NLR were 6.50×10^9, 1.20×10^9, and 5.28, respectively.

Risk factors for POD occurrence in geriatric patients with hip fracture

Figure 2 shows the ROC curve of NLR predicting delirium after operation, and NLR ≥ 7.613 were useful markers

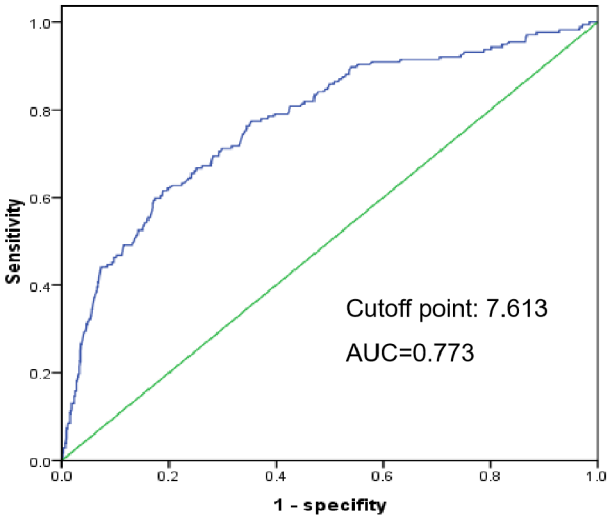

Fig. 2 ROC curve of NLR predicting delirium after operation

for predicting POD. The cutoff value of NLR predicting delirium after operation was 7.613. Area under the curve was 0.773, and the sensitivity and specificity were 61.6% and 88.1%, respectively. We therefore defined NLR≥7.613 as high NLR. The results of the univariable analysis of POD risk factors are displayed in Table 2. The results suggest the risk of POD is increased by previous heart failure (p=0.030), previous diabetes (p=0.019), previous stroke (p=0.011), high NLR (p=0.000), long time to surgery (p=0.002), general anesthesia (p=0.029), perioperative complications (p=0.000), long length of stay (p=0.031). No significant higher risk of delirium was found for age, gender, type of hip fracture, preoperative sodium, postoperative hyponatremia, circadian blood pressure alterations, previous hypertension, previous cardiovascular diseases, previous cardiac dysrhythmia, previous renal insufficiency, previous mental disorders, and surgical approach.

Significant associations observed in univariable analysis were included in a multivariable model (Table 3). The multivariable model showed that high NLR (odds ratio [OR] 7.790, [95% confidence interval [CI] 5.350 to 11.341], p=0.000), stroke (OR 1.520, [95% CI 1.034 to 2.235], p=0.033), perioperative complications (OR 2.815, [95% CI 1.805 to 4.390], p=0.000), general anesthesia (OR 1.555, [95% CI 1.051 to 2.299], p=0.027), long admission to operating time (OR 2.106, [95% CI 1.281 to 3.462], p=0.003) were significant independent prognostic factors for the development of a delirium, with the largest effect for increased NLR. Based on the above independent risk factors and their corresponding regression coefficients, a predictive model of POD in elderly hip fracture patients was construct. A visual presentation of the simplified nomogram is depicted in Fig. 3.

Table 2 Univariate analysis of postoperative delirium in elderly patients with hip fracture

Variables	Delirium group (n=177)	no delirium group (n=1065)	p -value
Sociodemographic data			
age(IQR), years	81(74,85)	80(74,86)	0.94
gender, *n* (%)			0.29
males	65(36.7%)	348(32.7%)	
female	112(63.3%)	717(67.3%)	
Past medical history			
hypertension	102(57.6%)	616(57.8%)	0.96
coronary heart disease	37(20.9%)	269(25.3%)	0.21
diabetes mellitus	37(20.9%)	314(29.5%)	0.02
cardiac dysrhythmia	23(13.0%)	115(10.8%)	0.39
heart failure	17(9.9%)	52(5.5%)	0.03
stroke	70(39.5%)	319(30.0%)	0.01
renal insufficiency	8(4.5%)	58(5.4%)	0.61
Post-injury factors			0.00
increased NLR group	109(61.6%)	200(18.8%)	0.00
admission to operating time(≥2d)	151(85.3%)	592(74.4%)	0.00
fracture type			0.80
intertrochanteric	102(57.6%)	603(56.6%)	
femoral neck	75(42.4%)	462(43.4%)	
length of stay	12(9–16)	11(9–14)	0.03
Perioperative complications	50(28.2%)	138(13.0%)	0.00
Surgery related factors			
anesthesia			0.03
general	65(36.7%)	305(28.6%)	
regional	112(63.3%)	760(71.4%)	
surgical approach			0.41
Intramedullary nail	86(48.6%)	553(51.9%)	
Sliding hip screw	12(6.8%)	53(5.0%)	
Hip arthoplasty	50(28.2%)	322(30.2%)	
Cancellous screws	29(16.4%)	137(12.9%)	

IQR, interquartile range;

Table 3 Multivariable analysis for factors associated with POD in elderly patients with hip fracture

	OR	95% CI	p -value
Increased NLR	7.79	5.35;11.34	0.00
Stroke	1.52	1.03;2.24	0.03
Diabetes mellitus	0.68	0.44;1.05	0.08
Length of stay	1.01	0.98;1.03	0.62
Perioperative complications	2.82	1.81;4.39	0.00
Admission to operating time	2.11	1.28;3.46	0.00
General anesthesia	1.56	1.05;2.30	0.03
Heart failure	1.83	1.15;3.49	0.07

NLR, Neutrophil-lymphocyte ratio

Linear regression analysis for factors that associated with POD duration in geriatric patients with hip fracture

The results of single-linear regression of the association between different variables and delirium duration are displayed in Table 4. The results suggest the long

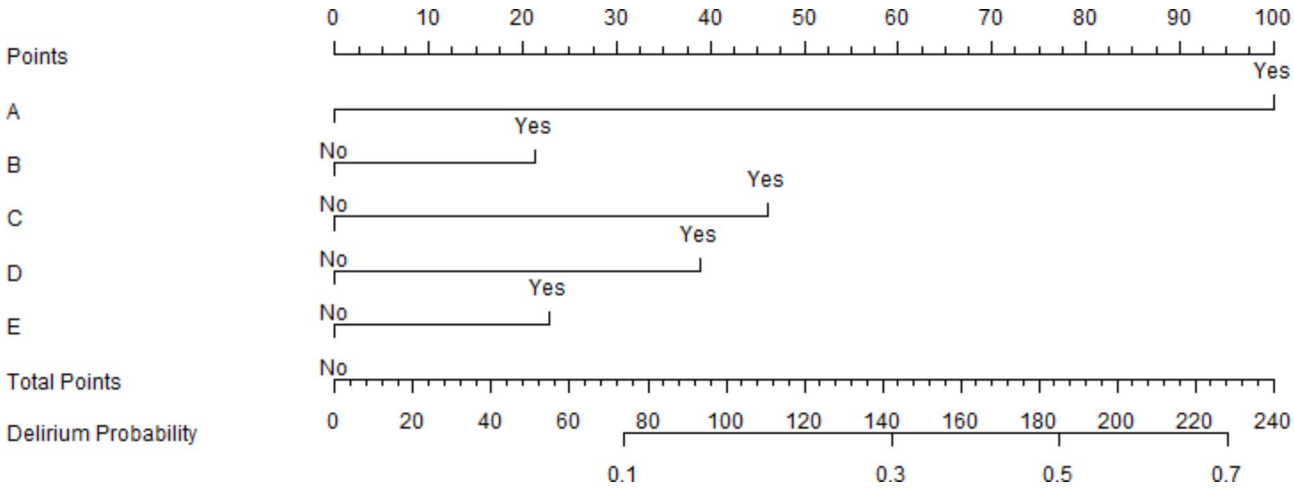

Fig. 3 Nomogram of POD predictive model in elderly hip fracture patients

Table 4 Linear regression analysis for factors associated with POD duration in elderly patients with hip fracture

	Single-linear regression analysis			Multi-linear regression analysis	
	β	95% CI	*p* -value β	95% CI	*p* -value
Age	0.02	-0.02;6.55	0.02 0.05	0.01;0.10	0.02
Male	0.34	-0.45; 1.13	0.40		
Type of fracture	-0.50	-1.27; 0.26	0.20		
Hypertension	-0.04	-0.81; 0.73	0.92		
Coronary heart disease	-0.23	-1.17; 0.71	0.63		
Cardiac dysrhythmia	-1.28	-2.40; -0.16	0.03 -1.05	-2.21;0.11	0.08
Heart failure	1.68	0.41; 2.96	0.01 1.68	0.45;2.91	0.01
Stroke	1.22	0.45; 1.99	0.00 0.91	0.09;1.73	0.03
Diabetes mellitus	0.15	-0.79; 1.08	0.76		
Renal insufficiency	-1.28	-3.11; 0.54	0.17		
Increased NLR	0.17	0.11; 0.23	0.00 0.59	0.21;0.89	0.04
Length of stay	-0.53	-1.64; 0.59	0.35		
General anesthesia	-0.40	-1.22; 0.43	0.35		
Surgical approach	4.53	0.13; 0.56	0.22		
Admission to operating time(≥2d)	0.06	0.01; 0.10	0.01 0.04	-0.01;0.08	0.12
Perioperative complications	0.94	0.11; 1.78	0.03 0.46	-0.44;1.36	0.32
Time of occurrence	-1.33	-2.27; -0.39	0.01 -0.67	-1.64;0.31	0.18

NLR, Neutrophil-lymphocyte ratio

POD duration is associated with age(p=0.023), previous heart failure (p=0.010), previous cardiac dysrhythmia (p=0.025), previous stroke (p=0.002), increased NLR (p=0.000), operation waiting time (p=0.012), perioperative complications (p=0.027), and delirium onset (p=0.006). Significant associations observed in single-linear regression were included in multi-linear regression model (Table 4). Strong linear correlations have been found between older age (β 0.054, [95% CI 0.009 to 0.099], p=0.019), previous stroke (β 0.908, [95% CI 0.085 to 1.731], p=0.031), heart failure (β 1.679, [95% CI 0.448 to 2.910], p=0.008), high NLR (β 0.59, [95% CI 0.209 to 0.886], p=0.038) and long POD duration.

Discussion

The delirium incidence in our study was 14.3% (177/1242). Delirium symptoms occurred 1–3 days after surgery in 142 patients 142(80.2%), and lasted for 1–3 days in 107 patients (60.5%). In this study, we found that high NLR, previous stroke, perioperative complications, general anesthesia, operation waiting time are independently associated with POD, with the largest effect for increased NLR. This is the first study to evaluate the role of NLR as a risk factor for developing delirium in POD patients.

Inflammatory factors may be useful for predicting POD. One potential mechanism for POD is inflammation, compounded with stress and repair causes

inflammatory chemicals to be systemically released throughout the body during the surgical procedure. At present, inflammatory markers, including CRP, IL-6, IL-1β, TNF-α, S-100β, IL-8, IL-10, and IL-1ra, had been measured preoperatively in POD patients [24, 25]. Only increased CRP and IL-6 were found in POD in some studies. The roles of CRP and IL-6 in predicting POD were inconsistent. Chen et al. and Dong et al. revealed that IL- 6 level and preoperative CRP concentrations may serve as potent predictors of POD in patients undergoing coronary artery bypass graft and laparoscopic surgery for colon carcinoma, respectively [26, 27]. While the sensitivity and specificity value were not showed. Lv et al. suggested that a suitable cut-off value of preoperative IL-6 levels (95.45 pg/ml) as an indicator for predicting POD, which generated a sensitivity value of 71.0% and a specificity value of 69.8% [28]. Baukje Brattinga et al. failed to find the significant association between CRP, IL-6 and POD in older oncological patients [29]. The possible reasons of the inconsistent results may be heterogeneity in study populations, differences in timing of measurement, variability in assay methods, confounding factors, and small sample sizes. More research is needed to determine the role of CRP and IL-6 in predicting POD. In addition, these markers are not routinely used in the clinic.

In many recent studies, the NLR has been used and validated as an inflammatory marker in certain diseases characterized by systemic or local inflammatory response. It has been found to be increased in elderly patients with delirium, psychiatric disorders and total hip arthroplasty. Kotfis K et al. conclude that NLR can be used as a potential marker for prediction of early-onset delirium after acute ischemic stroke [30]. He R et al. showed that NLR≥3.5 was an independent risk factor for delirium after total hip arthroplasty, and NLR can be used as a potential marker for prediction of delirium in elderly patients with total hip arthroplasty for hip fracture [31]. While the association between NLR and POD in geriatric hip fracture patients have not been investigated. In our study, the prevalence of POD was significantly higher in increased NLR group than in low NLR group. And the baseline NLR in the hip fracture patients was significantly associated with POD. On the basis of the results, controlling inflammation may be a potential treatment to reduce POD.

Previous stroke is another factor that associated with developing POD. Radiological evidence of cerebral ischemia can be seen in 7–10% of older surgical patients, and this is associated with more than double the risk of POD [32]. It may be likely that a stroke itself leads to inevitable disturbances in cerebral neurotransmitters and a disturbance of cerebral networking, with more severe stroke leading to a higher risk of delirium [33]. At present, the relationship between anesthesia and postoperative delirium is not clear. Abbott et al. [34] showed that decrease in delirium in patients receiving regional anesthesia compared with those receiving general anesthesia. While Bryson et al. [35] reported a relationship between postoperative delirium and certain drugs in general anesthesia, such as fentanyl and propofol. In our study, general anesthesia was one of the risk factors of POD in nonagenarians with hip fracture. Accordingly, exposure to general anesthesia should be avoided on such patients. Our results showed that the time interval between admission and operation was negatively associated with POD among nonagenarians. Delay between admission and operation leads to increased long time in bed, pain, dehydration, and inverted sleep rhythm, which may result the POD among nonagenarians. The result found in the elderly patients with hip fracture, was in line with the result in our previous study with nonagenarians. Therefore, it is important to manage the waiting time to reduce the incidence of POD.

Not only delirium occurrence, but also delirium duration is the concern of clinicians. Most studies suggested that delirium is a transient disease, and can quickly return to normal after 3–5 days, while some reports showed that delirium could last for a long time. The mean duration of delirium in the elderly patients was 4.72 days. We focused on delirium duration to further characterize patients who have already developed delirium. High NLR level, older age, previous stroke and cardiac insufficiency have shown to be associated with longer duration of POD. The second major finding of this study is that high NLR level is also associated with long delirium duration in hip fracture patients after surgery. Previous studies have shown that POD is a common complication of the central nervous system shortly after surgery, while the duration time is still not clear. In our study, an episode of delirium was detected mostly within 3 days after operation, and was associated with NLR level. It has been supposed to be related with excessive inflammatory reaction. Significantly elevated NLR level may involve in the elevated stimulation to central nervous system, the resultant neuro-inflammation promotes a state of cholinergic failure, predisposing to delirium. In the nonagenarians of hip fracture, delirium after surgery is inevitable and symptoms last for 3 days (71.4%), symptoms last for 4–7 days (17.9%), and symptoms last for more than 14 days (10.7%) have been reported. While in the elderly hip fracture patients after surgery, the symptoms last for more than 14 days. Longer duration of POD could be found in patients with previous stroke and previous heart failure. The main reason may be impaired cerebral perfusion, which is common in stroke patients [36]. Cerebral perfusion abnormalities have been demonstrated in cardiac insufficiency patients, because they often have systemic hypotension that could lead to further insults to cerebral

perfusion. Saller T et al. observed increased tau levels and neurofilament light levels in patients with cardiac surgery and POD [37]. Detection of the two increased markers of neuroaxonal injury in patients with POD after cardiac surgery provides insights into the neuropathological mechanisms of POD. The systemic inflammatory state recognized in patients with cardiac insufficiency may exacerbate delirium and extend delirium duration [38].

Some limitations of this study are worth considering. First, we relied on a single baseline NLR value, lack of dynamic change of NLR, which may provide additional information about development for POD. Larger studies with repeated measurements of NLR over time are needed to confirm the results that NLR can be used as a predictive marker for POD. Second, delirium was assessed by CAM in our study according to the Guidelines. Mental disorder, lack of concentration, and confused thinking may co-exist in patients with dementia, which make dementia hard to diagnose. Therefore, patients with dementia were excluded, which limits the generalizability of the results.

Conclusion

In this study, we evaluated the association between preoperative condition and POD in patients with hip fracture and found significantly higher NLR in patients with POD compared to those without. The study contributes new evidence to support NLR as a potential marker for prediction of POD and POD duration. General anesthesia should be used with caution in hip fracture patients with high NLR to reduce the incidence of POD.

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Author contributions
ZSJ, STS, ZJZ, WYL, GYH, and WXW are the investigators responsible for project design and protocol writing. ZSJ and WXW have participated in sample size calculation and statistical analysis planning. STS, ZJZ, WYL, and GYH have contributed to study background, general design and study variable definition. ZSJ and WXW have contributed to the preparation of the project and the manuscript. All authors have read and approved the manuscript.

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Data availability
The datasets generated during the current study are available by request to the corresponding author after approval from the Seventh Medical Center of People's Liberation Army Institutional Review Board.

Declarations

Ethical approval and consent to participate
Informed consent was obtained from all patients and the study was approved by the Seventh Medical Center of People's Liberation Army Institutional Review Board.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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