

Original Article

Effect of neutrophil-to-lymphocyte ratio on short-term prognosis of elderly patients with hip fracture

Jihui Zhou^{1*}, Jidong Fu^{2*}, Qiang Zhao^{3*}, Shibang Lin¹, Haiming Zhu¹

¹Department of Traumatic Orthopedics, Maoming People's Hospital, Maoming, Guangdong Province, China;

²Department of Traumatic Surgery, Longnan Hospital of Daqing, The Fifth Hospital Affiliated to Qiqihar Medical University, Daqing, Heilongjiang Province, China; ³Department of Orthopedics, The Second People's Hospital of Rizhao, Rizhao, Shandong Province, China. *Equal contributors and co-first authors.

Received March 22, 2021; Accepted May 24, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Objective: To investigate the effect of neutrophil-to-lymphocyte ratio (NLR) on short-term prognosis in elderly patients with hip fracture. Methods: Altogether, 124 elderly patients with hip fractures who underwent surgery in our hospital were retrospectively studied, and they were divided into survival group (n=98) and death group (n=26) according to their 1-year survival. General data of both groups were collected and compared, and indicators with statistical differences in univariate analysis were further examined by logistic regression analysis. Venous blood samples were drawn from all patients 1 day after the surgery to detect and compare NLR, serum procalcitonin (PCT) and C-reactive protein (CRP) levels between both groups. ROC curve was used to analyze the clinical value of NLR in predicting the prognosis of patients. NLR cutoff value obtained by the ROC curve analysis was adopted to divide the patients into high and low ratio groups, and Kaplan-Meier (K-M) curves were used to assess the survival rate of patients in both groups. Results: There were significant differences in age, gender, marital status, medical history and American Society of Anesthesiologists (ASA) grades between both groups. Logistic regression analysis showed that advanced age (≥ 85 years), male gender, and higher ASA grades (III-IV) were risk factors for short-term poor prognosis in elderly patients with hip fracture. Compared with survival group, NLR, PCT and CRP levels were higher in death group. ROC curve showed that the AUC of NLR predicting patients' prognosis was 0.804 at a cutoff value of 6.939%. K-M curves showed that the overall survival was lower in high-ratio group than in low-ratio group. Conclusion: Advanced age (overall survival was lower in high-ratio group than in low-ratio group), male gender, and higher ASA grades (III-IV) were risk factors for short-term poor prognosis in elderly patients with hip fracture. NLR has some clinical value in predicting and evaluating the prognosis of patients.

Keywords: Neutrophil-to-lymphocyte ratio, elderly, hip fracture, prognosis

Introduction

Elderly people have a higher risk of falling or slipping due to factors such as osteoporosis and slower response, which in turn increases the incidence of hip fractures. Besides, with the development of society and the acceleration of the aging process, the incidence of hip fractures demonstrates an upward trend year after year [1-3]. The data predict that in 2050, there will be 6300,000 patients with hip fractures worldwide, which will pose a serious threat to human health and quality of life [4]. At present, the main clinical treatment for hip fracture is surgery. However, the postoperative prognosis is poor due to the presence of underlying dis-

eases, prolonged bed rest and limited mobility in elderly patients [5, 6]. Studies have shown that deaths in elderly patients with hip fractures often occur in the early postoperative period, and the mortality rate can reach 14-36% within 1 year after surgery [7]. Therefore, it is of great clinical significance to investigate the risk factors and predictors for poor prognosis in elderly patients with hip fracture. The neutrophil-to-lymphocyte ratio (NLR) refers to the ratio of absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) in the peripheral blood. Studies have shown that when the body is under stress or systemic inflammation, the level of peripheral blood NLR decreases, reflecting the severity of the disease [8]. In addition, NLR

has the advantages of cost-effective, stable, and easy to operate. Therefore, it can be used as one of the auxiliary indicators for prognosis evaluation. Previous studies have confirmed that NLR levels are closely related to the prognosis of cardiovascular diseases, tumors and other diseases [9, 10]. For patient with fracture, his or her body is under stress or inflammation. Therefore, this study focuses on whether NLR expresses abnormally in patients with fractures, and if it is valuable in clinical evaluation of prognosis. Given the above considerations, this study investigated the effect of NLR (neutrophil-to-lymphocyte ratio) on the short-term prognosis of elderly patients with hip fractures in order to provide relevant theoretical basis for clinical assessment of prognosis and timely corresponding measures.

Materials and methods

General data

A total of 124 elderly patients with unilateral hip fractures who received surgical treatment in our hospital from January 2017 to January 2019 were enrolled in this retrospective study. The patients were divided into the survival group (n=98) and the death group (n=26) according to the survival status after 1 year. The study was approved by the ethics committee of the hospital (Approval No. 2017-26). All the patients have signed the informed consent form for the study.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with primary hip fracture underwent surgery; (2) Patients without history of fracture; (3) Old patients; (4) Patients and their families were informed and signed informed consent.

Exclusion criteria: (1) Patients with other vital organ dysfunction or acute or chronic infection; (2) Patients with incomplete clinical data; (3) Patients died perioperatively; (4) Patients complicated with fracture of other parts of the body; (5) Patients with poor compliance.

Methods

General data of patients were collected, including age, gender, income, marital status, education level, history of underlying diseases, medical insurance, body mass index (BMI), surgical

and anesthesia methods. Grouping by age was referred to relevant literature [11-13].

The next day after surgery, 2 tubes of 5 mL fasted venous blood were drawn from all patients in the morning, stored in anticoagulant tubes for immediate detection. One was used for detection of NLR using DxH800 automatic hematology analyzer (Beckman Coulter, USA). The other was centrifuged at 3,000 r/min for 5 min to separate serum for the measurement of PCT levels via enzyme-linked immunosorbent assay (Spectra-Max Paradigm Multi-Mode Microplate Reader, Molecular Devices, USA) and C-reactive protein (CRP) levels via immunoturbidimetry (Roche/Hitachi Cobas c501 analyzer, Roche, Switzerland).

All patients were followed up for 1 year after surgery, and their survival status was recorded.

Outcome measures

Primary outcome measures: The NLR levels were compared between the survival group and the death group; the clinical value of NLR in predicting the prognosis of patients was analyzed by ROC curve, and the survival rate of the NLR high ratio group and low ratio group was assessed by Kaplan-Meier (K-M curve).

Secondary outcome measures: General data were compared between the survival group and the death group; indicators with statistical differences in univariate analysis were subsequently examined by logistic regression analysis; CRP (C-reactive protein) and PCT (procalcitonin) levels were compared between the two groups.

Statistical analysis

SPSS 22.0 software was adopted for statistical analysis. Enumeration data were presented as n (%). Measurement data conforming to normal distribution were expressed as mean $\pm$ standard deviation ($\bar{x} \pm sd$) and were analyzed by t-test. Enumeration data were compared by χ^2 test. Indicators with statistical differences in univariate analysis were subsequently analyzed by multiple logistic regression. ROC curve (Receiver operating characteristic curve) was used to analyze the clinical value of NLR in predicting the prognosis of patients, and K-M curve (Kaplan-Meier) was utilized to evaluate

Table 1. Comparison of general data between the two groups

Characteristics	Survival group (n=98)	Death group (n=26)	χ^2	P
Gender			5.660	0.017
Male	35	16		
Female	63	10		
Age (years)			12.052	0.001
≥ 0	25	16		
60-84	73	10		
Income (¥)			0.002	0.966
<3000	57	15		
≥ 5000	41	11		
Marital status			5.192	0.023
Married	62	10		
Unmarried	36	16		
Education level			0.106	0.949
Primary School or under	21	5		
High school	42	12		
College or above	35	9		
Medical insurance			0.584	0.445
Yes	75	18		
No	23	8		
Hypertension			5.192	0.023
Yes	36	16		
No	62	10		
Diabetes			4.269	0.039
Yes	16	9		
No	82	17		
Cardiovascular disease			5.802	0.016
Yes	22	12		
No	76	14		
BMI (kg/m ²)			0.179	0.672
≥ 6	61	15		
<24	37	11		
ASA classes			6.154	0.013
I-II	64	10		
III-IV	34	16		
Surgical method			1.184	0.757
Intramedullary nail	47	11		
Hollow screw	21	5		
DHS	16	4		
Joint replacement	14	6		
Anesthesia			0.345	0.842
Spinal	43	13		
General	27	6		
Nerve block	28	7		

Note: BMI: body mass index; ASA: American Society of Anesthesiologists.

Results

Comparison of general data between the two groups

The results showed that there were significant differences in gender, age, marital status, medical history (hypertension, diabetes, and cardiovascular and cerebrovascular diseases), and American Society of Anesthesiologists (ASA) grades between the two groups (all $P < 0.05$), while no statistical difference was observed in income, education, medical insurance, BMI, operation and anesthesia methods ($P > 0.05$). See **Table 1**.

Logistic regression analysis results

Values were assigned to indicators with statistical differences in univariate analysis: for gender, 1= "male" and 0= "female"; for age, 1= "aged ≥ 85 years old"; 0= "60-84 years old"; for marital status, 1= "married" and 0= "unmarried"; for medical history, 1= "hypertension" and 0= "none"; 1= "diabetes" and 0= "none"; 1= "cardiovascular and cerebrovascular diseases" and 0= "none"; for ASA grades, 1= "ASA III-IV"; and 0= "ASA I-II". Logistic regression analysis was performed with forward LR. The results showed that advanced age (I differences in univariate analysis: for gender, 1= "male" and 0= "female"; for age, 1= "aged ≥ 85 years old"; 0= "60-84 years old"; for marital status, < 0.05). See **Table 2**.

Comparison of NLR, CRP and PCT levels between the two groups

the survival rate of NLR high ratio and low ratio groups. Statistical differences were accepted at $P < 0.05$.

The levels of NLR, CRP, and PCT were $5.61 \pm 1.28\%$, 45.54 ± 8.79 mg/L, and 1.56 ± 0.23 μ g/L in the survival group, and $7.22 \pm 1.42\%$,

Table 2. Logistic regression analysis results

Indicators	Age (≥85)	Gender (male)	ASA classes (III-IV)
β	2.145	0.773	0.337
SE	0.344	0.319	0.398
Wald	33.984	8.996	3.988
P	<0.001	0.027	<0.001
OR	5.576	2.013	2.302
95% CI			
Lower limit	4.421	1.089	1.008
Upper limit	17.452	3.741	5.426

Note: ASA: American Society of Anesthesiologists.

59.21±9.94 mg/L, and 3.89±0.46 µg/L in the death group, respectively, and the differences were statistically significant between the two groups ($P<0.001$). See **Table 3**.

ROC curve results

The results showed that the AUC for NLR predicting patients' prognosis was 0.804 at a cut-off value of 6.939%, with the sensitivity and specificity of 0.615 and 0.918, respectively ($P<0.001$), as shown in **Table 4** and **Figure 1**.

Survival analysis results

The results showed that 124 patients were divided into the low ratio group (100 cases) and the high ratio group (24 cases) with an NLR cut-off value of 6.939. Among them, 90 patients survived and 10 patients died in the low ratio group, with an average survival time of 11.62 (11.34, 11.91) months and a survival rate of 90.00%. In the high ratio group, 8 patients survived and 16 patients died, with an average survival time of 9.10 (7.95, 10.24) months, and a survival rate of 33.33%. There was a significant difference in the overall survival rate between the two groups ($\chi^2=48.133$, $P<0.001$). See **Figure 2**.

Discussion

Elderly patients with hip fractures have higher postoperative mortality due to increasing underlying diseases and old age. Therefore, it is of great clinical significance to explore the risk factors and specific indicators to improve the prognosis of the patients. The results of this study showed that advanced age (≥85 years old), male gender, and higher ASA grades (III-IV)

were risk factors for poor short-term prognosis in elderly patients with hip fracture.

Previous studies are controversial regarding the influence of age on the prognosis of hip fractures [11-14]. Studies have found that with the increase of age, the elderly will develop systemic organ failure and dysfunction as well as lower immunity, resulting in poor stress response to anesthesia, trauma, and surgery, which further increases the risk of postoperative death [11-13]. However, after excluding differences in complications, it has also been shown that age has small influence on the prognosis of patients with hip fractures [14]. The results of this study showed that patients of advanced age (≥85 years old) had a 5.576-fold higher risk of death than patients aged 60 to 84 years. This suggests that adverse events are more likely to occur to elderly patients due to physiological decline and stimulation of trauma and surgery. Therefore, the doctors need to pay attention to these patients and choose appropriate treatments. The effect of gender on the prognosis of patients with hip fracture is somewhat controversial. Previous studies have suggested that compared with females, male patients with hip fractures have higher postoperative mortality due to poor living habits, susceptibility to other underlying diseases, and shorter average life expectancy [15]. However, some studies have found that gender does not negatively affect the prognosis of patients with hip fractures after ruling out the impact of age and underlying diseases [16]. It was revealed in this study that the risk of postoperative death in male patients was 2.013 times higher than that in females. Such conclusion still needs further validation by subsequent investigations. ASA is mainly used to assess the risks of anesthesia and surgery. It can comprehensively reflect the patient's preoperative condition, and higher classes represent worse conditions of the patients [17]. Our study found that compared with grades I-II, patients in grades III-IV had a higher risk of postoperative death.

Hematological parameters are one of the indicators for early assessment of infection in patients [18]. Infection, as the primary factor that affects postoperative healing of open fracture, will seriously threaten the life and health of patients if not diagnosed in time and treated effectively. Both PCT and CRP are common bio-

Table 3. Comparison of NLR, CRP and PCT levels between the two groups

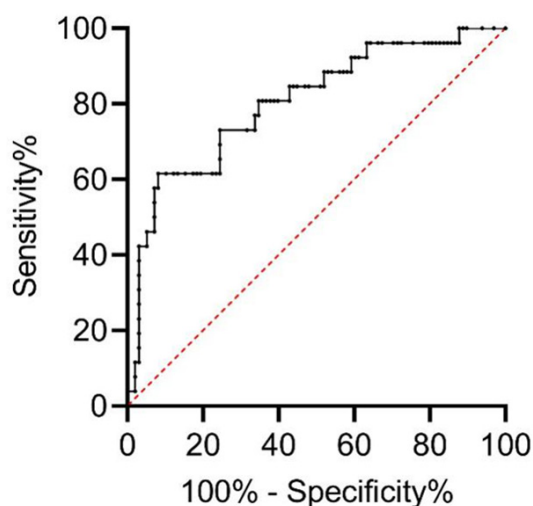
Group	NLR (%)	CRP (mg/L)	PCT (μ g/L)
Survival group (n=98)	5.61 $\pm$ 1.28	45.54 $\pm$ 8.79	1.56 $\pm$ 0.23
Death group (n=26)	7.22 $\pm$ 1.42	59.21 $\pm$ 9.94	3.89 $\pm$ 0.46
t	5.576	6.875	25.011
P	<0.001	<0.001	<0.001

Note: NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; PCT: serum procalcitonin.

Table 4. ROC curve results

Indicators	NLR (%)
Cut-off value	6.939
AUC	0.804
P-value	<0.001
95% CI	
Lower limit	0.705
Upper limit	0.903
Sensitivity	0.615
Specificity	0.918
Positive predictive value	0.724
Negative predictive value	0.905

Note: ROC: The receiver operating characteristic curve; NLR: neutrophil-to-lymphocyte ratio; AUC: area under the curve.

**Figure 1.** ROC curve results.

logical parameters. PCT is mainly secreted by thyroid C cells, and remains at a low level under normal physiological conditions. However, when patients have infection, a large number of PCT will be secreted by macrophages as well as monocytes in the liver under the stimulation of factors such as endotoxin, resulting in a marked

increase of PCT levels in serum [19, 20]. CRP is an acute-phase inflammatory protein featuring an early appearance and rapid increase. When the body develops infectious diseases, CRP levels will rise to varying degrees [21, 22]. The results of this study revealed that compared with patients in the death group, patients in the survival group had lower postoperative PCT and CRP levels, suggesting that the above indicators may have certain correlation with the prognosis of patients with hip fracture. However, this study did not observe the dynamic changes of each indicator, so it still needs to be further validated by subsequent studies. As a biomarker produced by stress-stimulated body, NLR has been widely used in clinical diagnosis and prognostic evaluation. Studies have found that macrophages promote the elevation of neutrophil levels by secreting granulocyte colony-stimulating factor when the body is exposed to infection or stimulation [23]. However, pathogens, once invading human body, will lead to immune dysfunction, disorders of immune system, and a decrease of lymphocytes. Therefore, when the body is infected by pathogens, there will be an increase in neutrophil levels and a decrease in lymphocyte levels under the stimulation of inflammatory factors. Also, compared with other biomarkers, NLR is cost-effective, easy to be tested, and faster in result reading. These advantages suggest that NLR can be used as a clinical marker to reflect the degree of stress response under infection. Previous studies have mostly focused on NLR expression during infectious diseases. Our study found that in patients with hip fracture, compared with those in the survival group, patients who died 1 year after surgery had higher NLR levels at day 1 after the operation, and when the NLR cutoff value was 6.939%, the area under the ROC curve for NLR predicting patient prognosis was 0.804, suggesting that it has some clinical value in predicting patient prognosis. At the cut-off value of 6.939%, the patients were divided into NLR high ratio group and low ratio group. The K-M curve showed that the overall survival rate was lower in the high ratio group than in the low ratio group, which further confirmed that NLR level may affect the prognosis of patients.

However, this study also had the shortcomings. For example, the changes of each indicator

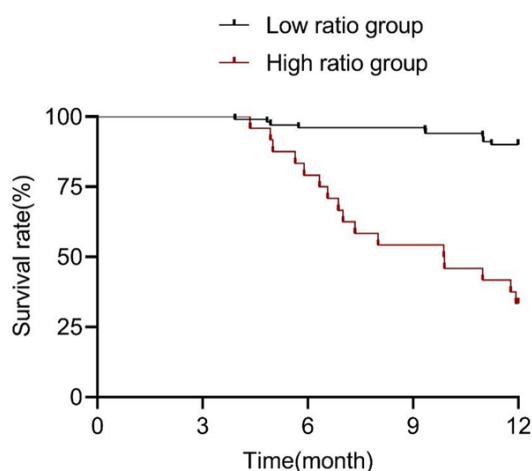


Figure 2. K-M curve. K-M: Kaplan-Meier.

were not dynamically observed, and this was a single-center study with small sample size. Therefore, multicenter studies with larger sample size are needed to further observe and confirm the dynamic changes of NLR.

In conclusion, advanced age, male gender, and higher ASA grades (III-IV) are risk factors for poor short-term prognosis in elderly patients with hip fractures. NLR has certain clinical value in predicting and evaluating the prognosis of patients.

Acknowledgements

This work was supported by the High-level Hospital Construction Research Project of Maoming People's Hospital.

Disclosure of conflict of interest

None.

Address correspondence to: Shibang Lin, Department of Traumatic Orthopedics, Maoming People's Hospital, No. 101 Weimin Road, Maoming 525000, Guangdong Province, China. Tel: +86-0668-292-2191; Fax: +86-0668-2922191; E-mail: drshibanglin@163.com

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