Association Between Neutrophil-To-Lymphocyte Ratio and Postoperative Fatigue in Elderly Patients with Hip Fracture

Baosheng Jing
Anqing Hospital Affiliated to Anhui Medical University
Jinjing Wang
Medical School of Nanjing University
Dangui Chen
Anqing Municipal Hospital, Anqing Hospital Affiliated to Anhui Medical University
Huming Dai
Anqing Hospital Affiliated to Anhui Medical University
Jinrui Liu
Anqing Hospital Affiliated to Anhui Medical University
Cheng Chen
Anqing Hospital Affiliated to Anhui Medical University
Mingjun Dai
Anqing Hospital Affiliated to Anhui Medical University
Jing Hu
Anqing Hospital Affiliated to Anhui Medical University
Jianjun Wang
Anqing Hospital Affiliated to Anhui Medical University
Zhengfeng Lu
lzf@szgk.net

The Second Affiliated Hospital of Soochow University

Research Article

Keywords: postoperative fatigue, neutrophil-to-lymphocyte ratio, hip fracture

Posted Date: February 4th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1308661/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Heliyon on December 1st, 2023. See the published version at https://doi.org/10.1016/j.heliyon.2023.e22314.

Abstract

Background and purpose: Postoperative fatigue (POF) is a common and distressing post-operative symptom. This study aimed to explore the relationship between neutrophil-to-lymphocyte ratio (NLR) and POF in elderly patients with hip fracture.

Method: Elderly patients (age ≥ 65 years) with acute hip fracture admitted to the Department of Orthopedics of Anqing Hospital affiliated to Anhui Medical University from June 2018 to June 2020 were included. Fatigue was assessed using the Fatigue Severity Scale at the 3-month follow-up postoperatively. Univariate and multivariate analyses were performed to explore the associations between NLR and POF. The diagnostic performance of NLR was analysed using Receiver Operating Characteristic (ROC) curve analysis and the Delong test.

Result: A total of 321 elderly patients with hip fractures were included; 120 (37.4%) of them were diagnosed with POF. Univariate analysis indicated significant differences in NLR, platelet-to-lymphocyte ratio (PLR), education, neutrophil count, lymphocyte count, Hamilton Depression Scale (HAMD) and Insomnia Severity Index (ISI) scores ($P<0.05$). Multivariate analysis indicated neutrophil count (odds ratio [OR], 1.46; 95% confidence interval [CI] 1.27–1.67), lymphocyte count (OR 0.32, 95% CI 0.19–0.53), NLR (OR1.81, 95% CI 1.50–2.17) and PLR (OR 1.005, 95% CI 1.001–1.009) were significantly associated with POF. The areas under the ROC curves (AUCs) of neutrophil count, lymphocyte count, NLR and PLR were 0.712, 0.667, 0.775 and 0.605, respectively. The Delong test indicated that NLR had the best diagnostic performance ($p < 0.05$).

Conclusion: NLR independently predicts POF in elderly patients with acute hip fracture.

Introduction

Postoperative fatigue (POF) is a common postoperative complication commonly described as excessive sleepiness, laziness and emotional disorder, which mainly occurs during the disease treatment process or postoperative rehabilitation[1, 2]. The prevalence of POF was about 30% during the first month postoperatively[3]. Several risk factors of POF have been reported; however, some remain controversial. Some studies suggested that age, sleep quality, educational level and other psychological factors were associated with POF[4-6]. Other studies have shown that POF was not significantly associated with preoperative anxiety, depression, stress and sex[7]. POF is frequently neglected, especially in elderly patients with hip fractures[8]. However, it can hinder a patient’s ability to participate in early rehabilitation, resulting in prolonged hospital stays, decreased quality of life and inability to resume daily life or work[9].

The neutrophil-to-lymphocyte ratio (NLR) is currently a new indicator of systemic inflammation and can reflect the body’s inflammatory state. Generally, the higher the inflammation level, the higher the NLR. Normal NLR ranges have been reported to be between 0.78 and 3.53[10, 11]. Previous studies have suggested that high NLR is associated with poor prognosis in surgical patients[12]. NLR has also been reported to play an important role in the occurrence and progression of emotional diseases, such as depression and fatigue; however, its specific mechanism needs to be further investigated[13, 14].

Elderly patients are susceptible to brittle fractures, especially hip fractures, and their mortality within 1 year is as high as 30%[15-17]. Hip fractures are usually caused by low-energy trauma, and most patients need surgical treatment[18]. Surgically treated elderly patients have a worse outcome than younger patients owing to poor body resistance, decreased immunity and other co-existing diseases[19]. Previous studies have confirmed that inflammation was associated with the occurrence of POF in abdominal surgery[20]. However, the relationship between NLR and POF in elderly patients with hip fractures has not been reported. Therefore, this study aimed to evaluate the inflammatory factors associated with POF and the predictive value of NLR on POF in elderly patients with acute hip fractures.

Methods

Study population

Patients with acute hip fracture admitted to the Department of Orthopedics in Anqing Hospital affiliated with Anhui Medical University from June 2018 to June 2020 were included in this study. All patients completed the surgical treatment under general anaesthesia within 3–5 days after admission. The inclusion criteria were as follows: (1) age ≥ 65 years, (2) acute femoral neck fracture treated with surgery and (3) written informed consent. The exclusion criteria included the following: (1) previous history of fatigue, mental disorder or positive family history; (2) acute infection, shock or any other serious systemic diseases; (3) stroke, dementia or any other neurological diseases; (4) chronic diseases such as cancer and heart failure; (5) obvious post-operative complications and (6) lack of critical data.

Data collection

All participants completed a basic sociodemographic and medical history questionnaire face-to-face within 24 h after admission. The following specific variables were recorded: age, sex, height, weight, educational level, history of hypertension and diabetes mellitus. Body mass index (BMI) was calculated as weight in kilograms divided by height in square metres. History of hypertension was defined as the use of antihypertensive agents, systolic blood pressure of > 140 mmHg or diastolic blood pressure of >90 mmHg before or at least 2 weeks.

History of diabetes was defined as fasting plasma glucose level of ≥126 mg/dl (7.0 mmol/L) or the use of anti-diabetic medications.

Laboratory tests

Blood samples were obtained from the elbow vein in all patients between 6:00 and 7:30 AM. Routine blood tests (including platelet, C-reactive protein, leucocyte count, neutrophil count and lymphocyte count) were performed at the central laboratory of the Anqing Municipal Hospital. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The platelet-to-lymphocyte ratio (PLR) was calculated by dividing the absolute platelet count by the absolute lymphocyte count.

Measurements of fatigue and related parameters

All participants completed the neuropsychological scale evaluation 3 months after discharge. The Fatigue Severity Scale (FSS) was used to evaluate the fatigue degree of patients and to confirm in patients with POF[8], including a total of nine questions, with 1–7 points for each question. The total score was ≥36 points, or the average score of ≥4 points indicates fatigue.

Depression symptoms and sleep status were assessed using the 24-item Hamilton Depression Scale (HAMD-24) and Insomnia Severity Index (ISI), respectively[21, 22]. The HAMD-24 Scale includes 24 items: 14 items with a score of 0–4 and 10 items with a score of 0–2. The higher the score, the more severe the depression. The ISI scale is mainly used to evaluate the degree of insomnia, including a total of seven items, with 0–4 points for each item. Higher scores indicate a heavier degree of insomnia. In addition, the Visual Analogue Scale (VAS) was used to evaluate postoperative pain. The higher the score, the more severe the pain[23].

All scale evaluations were completed by two professionally trained clinicians. If they disagree, the superior physician makes the decision.

Statistical analysis

Demographic and clinical characteristics of all patients stratified by NLR tertiles were expressed as frequencies and proportions for categorical variables, mean (SD) or median (interquartile) for continuous variables. Differences in continuous variables were compared using one-way analysis of variance and Kruskal–Wallis test. Categorical variables were analysed using the chi-squared test or Fisher's exact test. Univariate and multivariate logistic regression models were used to evaluate the association between inflammatory parameters (including NLR) and POF. In multivariate-adjusted models, hypertension, diabetes, educational level, LSNS, ISI, HAMD and VAS ($p < 0.2$ in univariate analysis). We performed receiver operating characteristic (ROC) curve analysis using the pROC package and compared ROC curves using the DeLong test. All statistical analyses were performed using Statistical Package for the Social Sciences Statistics 25.0 software and R 4.1.3 software. A *P*-value of <0.05 was considered statistically significant. The Bonferroni correction method was used for multiple comparisons.

Results

After applying the aforementioned eligibility criteria, a total of 321 patients were included in the final analyses (Figure 1). The mean age of all patients was 72.5 ± 6.5 years; 198 (41.7%) of them were men. The prevalence of POF was 120 (37.4%). All patients were surgical treated, and 8 of them were excluded because of post-operative complications.

Table 1 shows baseline characteristics of included patients by NLR tertiles.

Univariate analysis indicated significant differences in leucocyte count, neutrophil count, lymphocyte count, C-reactive protein level, ISI score and VAS score among the three groups ($p < 0.05$). However, no difference was observed on age, sex, BMI, hypertension, diabetes, educational level, haemoglobin, platelet and LSNS score among these groups ($p > 0.05$, Table 1). The incidence of POF significantly increased across the NLR tertiles (10.2% vs. 41.0% vs. 61.1% for tertile 1 vs. tertile 2 vs. tertile 3, respectively). Table 2 shows the baseline characteristics of included patients with and without POF. Compared with patients without POF, those with POF had higher educational levels, neutrophil count, NLR, PLR, ISI score and HAMD score and lower lymphocyte count ($p < 0.05$, Table 2).

Results of univariate and multivariate logistic regression models assessing the association between inflammation-related indicators and POF are shown in Table3. In the unadjusted model, neutrophil count (odds ratio [OR], 1.44; 95% confidence interval [CI] 1.26–1.64), lymphocyte count (OR 0.30, 95% CI 0.18–0.49), NLR (OR 1.74, 95% CI 1.48–2.06) and PLR (OR 1.005, 95% CI 1.002–1.009) were significantly associated with POF. Multivariate adjustments did not significantly alter the results (neutrophil count [OR 1.46, 95% CI 1.27–1.67]; lymphocyte count [OR 0.32, 95% CI 0.19–0.53]; NLR [OR 1.81, 95% CI 1.50–2.17]; PLR [OR 1.005, 95% CI 1.001–1.009]; Table 3).

To compare the performance of significant inflammatory indicators (including neutrophil, lymphocyte, NLR and PLR), ROC curve analysis was performed, and the area under the ROC curve (AUC) was calculated. The AUC values of neutrophil count, lymphocyte count, NLR and PLR were 0.712, 0.667, 0.775 and 0.605, respectively. Among these indicators, NLR had the highest AUC. The Delong test results of NLR and PLR ($p < 0.001$), NLR and neutrophil count ($p < 0.001$), and NLR and lymphocyte count ($p < 0.001$) showed significant differences. The best NLR cut-off value was 2.35, with a sensitivity of 56% and a specificity of 85% (Figure 2).

Discussion

This study evaluated the association between inflammatory indicators and POF and the predictive value of blood NLR for POF. Our results demonstrated patients with POF had a higher NLR. Multivariate regression indicated NLR, PLR, neutrophil count and lymphocyte count were significantly associated with POF. Among them, NLR had the best performance, with the highest AUC for diagnosis and independently associated with POF. Moreover, we found that the best NLR cut-off value in patients with POF was 2.35.

In this study, the prevalence of POF was 37.5%, which was consistent with a study by Nancy[8]. In addition to inflammatory parameters, their significant differences were observed in sleep disorder and postoperative depression between POF and non-POF groups. The results were consistent with those of previously published studies, indicating that mental health-related factors play an important role in the occurrence and development of POF[2, 24].

Inflammatory factors have been reportedly associated with fatigue in several studies [25]. Inflammation and mental stresses can promote the secretion of interleukin 1 β (IL-1β) by microglia in the brain, and elevated interleukin levels may lead to central nervous system disorders associated with nitric oxide and serotonin levels. These inflammatory factors affect the limbic system areas, such as the hippocampus, which induces the POF occurrence. Therefore, microglial activation is considered a common inflammatory pathway, resulting in fatigue[26-28].

Another possible mechanism is that inflammation damages the blood–brain barrier and cell structure in the brain and results in POF occurrence [29, 30]. Inflammatory factors affect the release of neurotransmitters in the brain, change hippocampal neuroplasticity and fatigue[31-34] .Surgical trauma not only leads to systemic inflammatory immune response but also activates the neuroendocrine system in the body, causing changes in the serotonin, tryptophan, dopamine and norepinephrine levels, which are considered to be associated with neuropsychiatric symptoms such as POF[35].

Neutrophils and lymphocytes in the peripheral blood system are redistributed in the case of surgical trauma, and activated neutrophils release reactive oxygen, myeloperoxidase and proteolytic enzymes, which damage the blood–brain barrier and brain parenchyma. Lymphocytes have protective effects on the brain. In the postoperative stress state, lymphocytes in the circulatory system are decreased in number and redistributed to the lymphoid tissue, thus accelerating cell apoptosis and resulting in fatigue[36]. Mark *et al.* proposed that peripheral inflammation mainly causes fatigue by destroying the blood–brain barrier and affecting the vagus nerve activity. The vagus nerves control many breathing-related organs through the parasympathetic nerve and regulate the oxygen demand, resulting in fatigue[37]. The inflammatory mechanism that leads to POF can be summarised as follows: on the one hand, it causes fatigue by affecting changes of the brain parenchyma and neurotransmitters; on the other hand, it causes fatigue through peripheral nerves, especially the vagus nerve. However, its underlying mechanisms need to be further investigated.

The strengths of the study include relatively large sample size, prospective design and its analytic strategy. However, several limitations need to be addressed. First, this was a single-centre study; therefore, the results may not be generally applicable to all patients. Second, we could not directly infer causality owing to the cross-sectional nature of the study design. Third, the NLR value was only collected at baseline; therefore, we were unable to analyse the effects of dynamic NLR changes on POF. Fourth, this study only included elderly patients, which limits the generalisation of our findings.

Conclusion

In conclusion, this study aimed to attract attention to POF in patients with hip fractures and indicated that elevated NLR was associated with POF, which will used in future studies as a risk factor of POF. However, whether POF can be prevented by reducing postoperative inflammation remains to be elucidated.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee. All participants or their legally designated surrogates provided informed consent for study participation.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

BSJ and JJW contributed to the concept and design of the study; BSJ conducted the data analysis and wrote the first draft of the manuscript; JJW conducted the data analysis; JH, HMD,JRL,CC,MJD and DGC contributed to data collection; ZFL and JJW contributed to the study design, interpretation of results and critical revision of manuscript.

Acknowledgements

Not applicable.

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Tables

Table 1 Baseline characteristics of patients with acute hip fracture based on tertiles of the neutrophil-to-lymphocyte ratio

Variable	Tertile 1 (1.16-2.17; n=108)	Tertile 2 (2.24-3.47; n=106)	Tertile 3 (3.67-10.80; n=107)	P value
Age, mean(SD), y	72.6 (6.9)	72.1 (6.4)	72.7 (6.5)	0.813
Male, n (%)	68 (63.0)	68 (64.8)	62 (57.4)	0.514
BMI, mean (SD), kg/m^2	24.2 (3.6)	24.5 (3.3)	24.2 (3.2)	0.803
Hypertension, n (%)	88 (81.5)	83 (79.0)	85 (78.7)	0.858
Diabetes, n (%)	37 (34.3)	49 (46.7)	45 (41.7)	0.179
Hyperlipemia, n (%)	14 (13.2)	17 (16.8)	13 (12.1)	
Education level, n (%)				0.052
Illiterate	31 (28.7)	37 (35.2)	36 (33.3)	
Primary school	39 (36.1)	30 (28.6)	33 (30.6)	
Secondary school	21 (19.4)	33 (31.4)	31 (28.7)	
High school or above	17 (15.7)	5 (4.8)	8 (7.4)	
HB, median (IQR), g/L	133.5 (120.3-141)	133.0 (119.5-146.0)	136.5 (127.3-145.0)	0.201
PLT, median (IQR), 10^9	191.5 (160.0-224.5)	192.0 (164.0-230.0)	198.0 (150.0-249.0)	0.808
WBC, median (IQR), 10^9	6.3 (5.6-7.5)	7.9 (6.2-9.5)	6.8 (5.7-7.9)	<0.001
Neutrophils, median (IQR), 10^9	3.3 (2.5-3.9)	4.8 (3.7-5.2)	6.1 (5.0-8.6)	<0.001
Lymphocyte, mean(SD), 10^9	1.8 (1.2-2.2)	1.5 (1.2-2.0)	1.2 (1.0-1.3)	<0.001
CRP, median (IQR), mg/L	2.3 (0.5-7.2)	3.5 (1.5-10.2)	2.3 (0.5-7.2)	0.001
LSNS, median (IQR)	31.5 (19-40)	29.0 (16.0-39.0)	31.5 (19.0-40.0)	0.260
ISI, median (IQR)	1.0 (0-8.0)	3.0 (0-12.0)	1.0 (0-8)	0.003
HAMD, median (IQR)	4.0 (1.3-10)	3.0 (1.0-12.5)	4.0 (1.3-10.0)	0.006
VAS, median (IQR)	4.0 (3.0-5.0)	5.0 (3.5-7.0)	4.0 (3-5)	<0.001
POF, n (%)	11 (10.2)	43 (41.0)	66 (61.1)	<0.001

Abbreviations: HB, Hemoglobin; PLT, platelet; CRP, C-reactive protein; LSNS, Lubben social score; IQR, interquartile interval; ISI, Insomnia Severity Index; HAMD, Hamilton Depression Scale; VAS, Visual Analogue Scale; POF, post-operative fatigue.

Table 2 Baseline characteristics of patients with and without postoperative fatigue

Variable	Non-POF (n=201)	POF(n=120)	P value
Age, mean(SD), y	72.4 (6.7)	72.6 (6.4)	0.791
Male, n (%)	126 (62.7)	72 (60.0)	0.632
BMI, mean (SD), kg/m^2	24.3 (3.5)	24.4 (3.1)	0.745
Hypertension, n (%)	165 (82.1)	91 (75.8)	0.177
Diabetes, n (%)	84 (41.8)	47 (39.2)	0.643
Hyperlipemia, n (%)	29 (14.7)	15 (12.8)	0.639
Highest level of education, n (%)			0.037
Illiterate	69 (34.3)	35 (29.2)	
Primary school	59 (29.4)	43 (35.8)	
Secondary school	48 (23.9)	37 (30.8)	
High school or above	25 (12.4)	5 (4.2)	
HB, median (IQR), g/L	134.0 (123.5-144.0)	134.0 (121.5-145.0)	0.588
PLT, median (IQR), 10^9	192.0 (161.5-229.0)	199.0 (161.5-247.0)	0.653
WBC, median (IQR), 10^9	6.8 (5.8-8.3)	6.9 (5.9-8.4)	0.447
Neutrophils, median (IQR), 10^9	3.9 (3.0-5.0)	5.2 (4.4-6.3)	<0.001
Lymphocyte, median (IQR), 10^9	1.6 (1.2-2.2)	1.2 (1.1-1.7)	<0.001
CRP, median (IQR), mg/L	2.7 (0.6-7.2)	2.3 (0.7-8.6)	0.814
NLR, median (IQR)	2.2 (1.9-3.3)	3.7 (2.5-5.7)	<0.001
PLR, median (IQR)	123.3 (84.7-164.7)	140.0 (105.5-195.3)	0.007
LSNS, median (IQR)	30.0 (19.0-39.0)	33.0 (18.0-40.0)	0.160
ISI, median (IQR)	0 (0-7.0)	2.5 (0-12.0)	0.018
HAMD, median (IQR)	4.0 (2.0-10.5)	6.0 (2.0-14.0)	0.029
VAS, median (IQR)	4.0 (3.0-5.0)	4.0 (4.0-5.0)	0.889

Abbreviations: HB, Hemoglobin; PLT, platelet; WBC, white blood cell; CRP, C-reactive protein; NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LSNS, Lubben social score; IQR, interquartile interval; ISI, Insomnia Severity Index; HAMD, Hamilton Depression Scale; VAS, Visual Analogue Scale; POFS, post-operative fatigue syndrome.

Table 3 Multivariate logistic regression analysis on the association of inflammation-related indicators with POF

	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
WBC	1.08 (0.96-1.21)	0.188	1.13 (0.99-1.29)	0.062
PLT	1.001 (0.997-1.006)	0.546	1.001 (0.996-1.006)	0.725
Neutrophils	1.44 (1.26-1.64)	<0.001	1.46 (1.27-1.67)	<0.001
Lymphocyte	0.30 (0.18-0.49)	<0.001	0.32 (0.19-0.53)	<0.001
CRP	1.01 (1.00-1.03)	0.141	1.02 (1.00-1.04)	0.130
NLR	1.74 (1.48-2.06)	<0.001	1.81 (1.50-2.17)	<0.001
PLR	1.005 (1.002-1.009)	0.007	1.005 (1.001-1.009)	0.015

Model 1, unadjusted; Model 2, adjusted for hypertension, diabetes, education, LSNS, ISI, HAMD, VAS ($p<0.2$ in univariate analysis). Abbreviations: WBC, white blood cell; CRP, C-reactive protein; NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; LSNS, Lubben social score; ISI, Insomnia Severity Index; HAMD, Hamilton Depression Scale; VAS, Visual Analogue Scale.

Figures

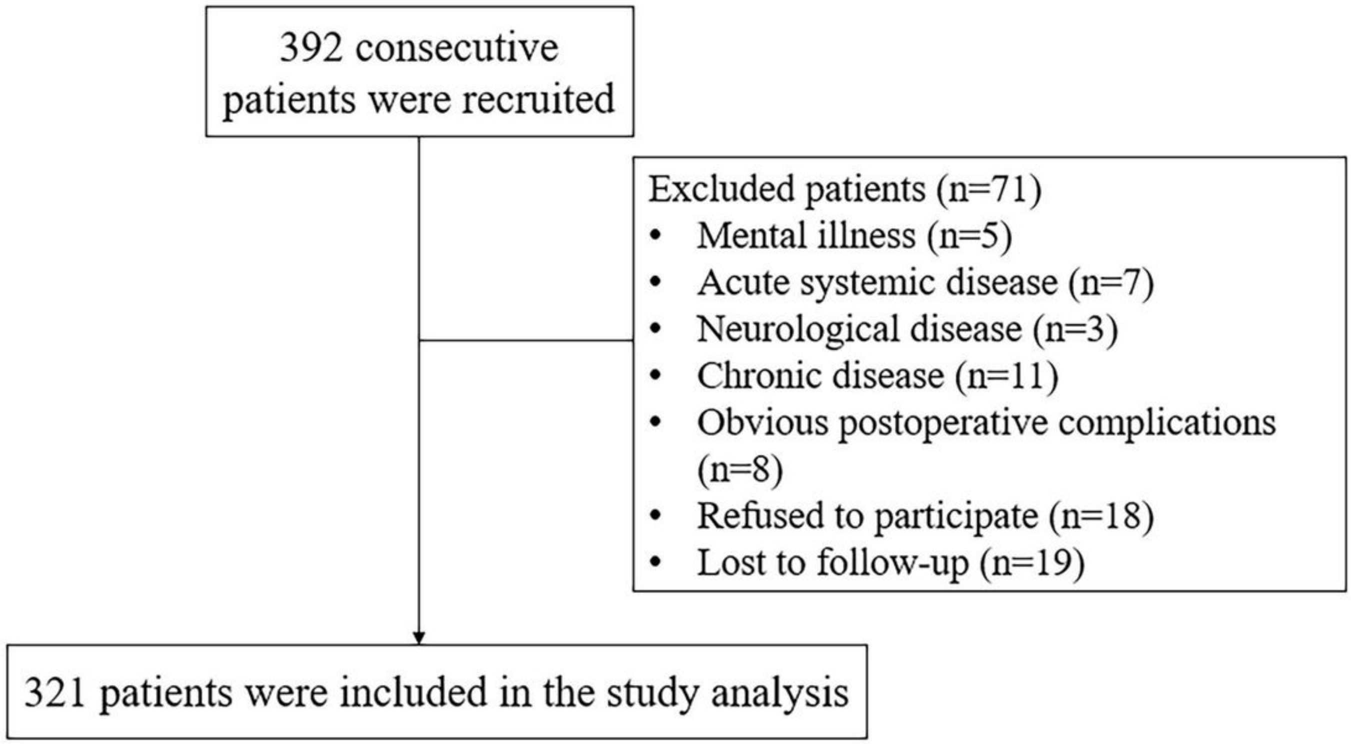

Figure 1

Study population.

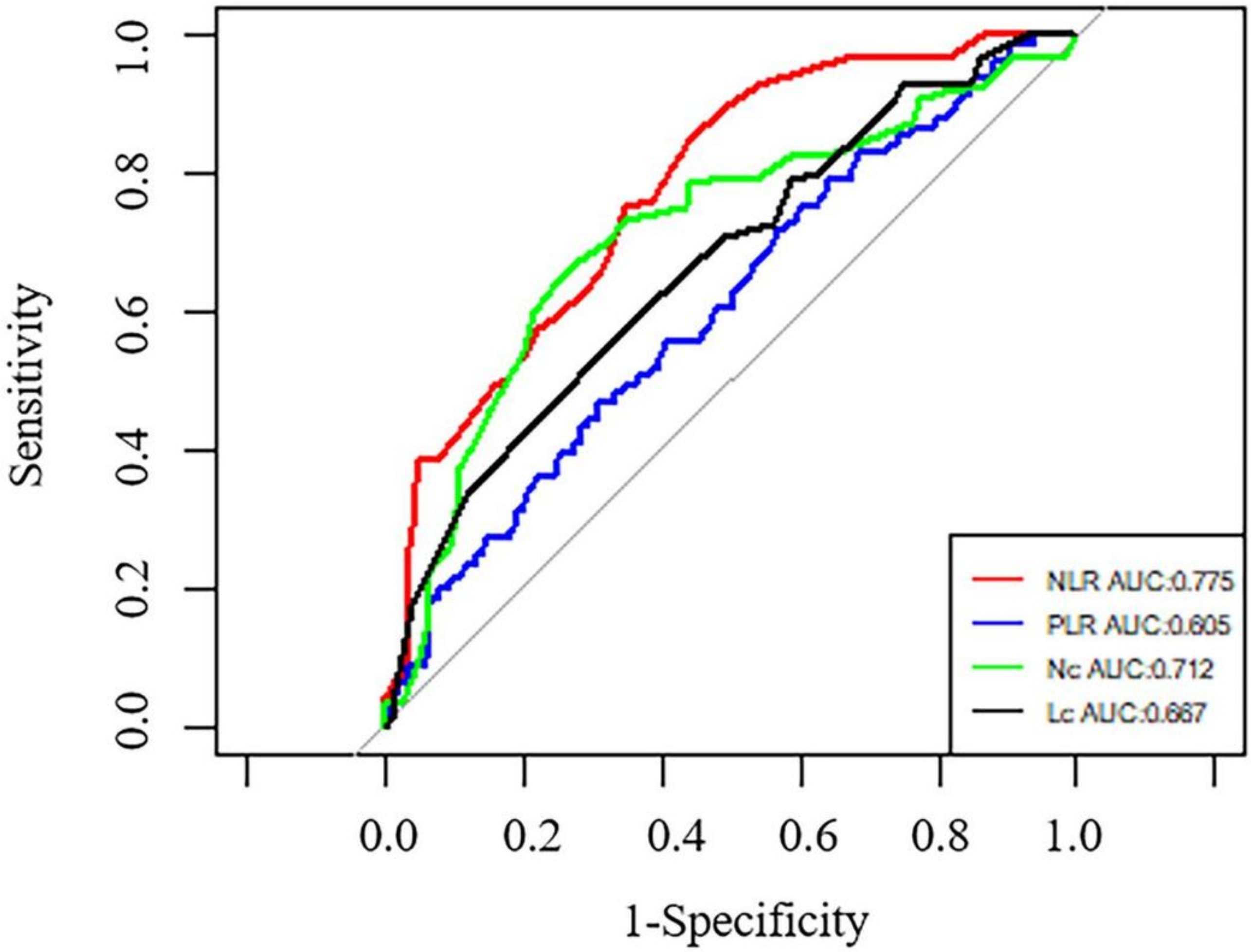

Figure 2

The Receiver Operating Characteristic Curve analysis of NLR, PLR, Nc and Lc for patients with POF. Abbreviations: NLR, Neutrophil lymphocyte ratio; PLR, Platelet lymphocyte ratio; Nc, neutrophils; Lc, Lymphocyte; POF, post-operative fatigue.