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ORIGINAL RESEARCH

Association of NLR and Ferritin in Osteoporotic Fractures Among Chinese Older Patients

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Background: Research on the connection between serum ferritin levels and the neutrophil-to-lymphocyte ratio (NLR) in individuals with osteoporotic fractures (OPF) are currently limited. This study aims to investigate the relationship between the NLR and serum ferritin levels, with the goal of offering a more convenience method for assessing iron stores and inflammatory response in clinical settings.

Methods: A retrospective cross-sectional analyzed 4782 patients with OPF. Initial measurements included serum ferritin and NLR. The analysis accounted for various confounders. Furthermore, techniques such as multivariable linear regression, smooth curve fitting, and threshold analysis techniques were utilized.

Results: A strong association was observed between serum ferritin levels and the NLR in patients with OPF ($\beta = 6.36$, 95% CI, 2.02, 10.65, *P*-value < 0.01). The recognized threshold was 5.31. When levels dropped below this point (< 5.31), there was a notable rise in serum ferritin ($\beta = 32.08$; 95% CI, 12.97, 51.20, *P*-value < 0.01). This study discovered a threshold effect between serum ferritin and NLR.

Discussion: Recognizing this threshold effect holds substantial clinical importance, as it could provide a novel approach for assessing inflammation levels and iron reserves in patients with OPF. Higher or lower NLR may be relevant for identifying iron status. Clinicians may assess the iron status of patients with OPF by monitoring NLR, which may serve as an indicator of their iron reserves. This information can facilitate the formulation of targeted strategies for diagnosis and treatment. Nevertheless, further detailed studies are needed to confirm the current results.

Conclusion: The study reveals a threshold effect between serum ferritin and NLR in patients with OPF, showing a positive correlation, particularly when NLR is below 5.31. This discovery reveals that NLR may serve as a biomarker for rapidly evaluating iron reserves in patients with OPF. Therefore, clinicians may incorporate NLR as a potential biomarker for quick iron evaluation to determine the next step of comorbidity screening and treatment plan.

Keywords: serum ferritin, neutrophil-to-lymphocyte ratio, osteoporosis, osteoporotic fractures

Background

Osteoporotic fractures (OPF) represent a significant health issue impacting millions of individuals around the globe.[1–3] In 2010, around 2.33 million individuals with OPF were documented in China, and projections indicate that this figure could rise to 5.99 million by 2050.[4] In osteoporosis, OPF lead to serious traumatic injuries and the weakening of the trabecular structure of the bone,[5,6]. Moreover, OPF also places a considerable strain on both patients' health and the economy.[7,8] Recently, researchers have shifted their focus to the significant impact of inflammation on the development and underlying causes of osteoporosis. A strong connection exists between the risk of osteoporosis and inflammation. Ongoing inflammation may increase the likelihood of both osteoporosis and fractures.[9] Consequently, it is essential to prioritize the immediate prevention of osteoporosis.

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An NLR (neutrophil-to-lymphocyte ratio) measures the ratio between neutrophils and lymphocytes in the blood.[10] In clinical practice, the NLR is commonly used as a marker for inflammation due to its affordability and ease of availability.[11–15] Furthermore, a higher NLR has been associated with various types of cancer.[16–18] Ferritin is an important protein responsible for iron storage, which is essential for regulating iron balance in the body. It functions by sequestering iron and releasing it as required.[19] Measuring serum ferritin has become the favored approach for thoroughly evaluating an individual's iron levels. Clinicians can obtain important information about a person's iron balance by examining serum ferritin concentrations. This data is essential for detecting and addressing issues related to iron metabolism, including both low iron reserves (iron deficiency) and high iron levels (iron overload).[20,21]

Numerous investigations have indicated a link between serum ferritin and inflammation. In particular, these studies have shown that during inflammatory episodes, serum ferritin levels rise above typical baseline values. This suggests that ferritin may be increased as part of the acute phase response in the presence of systemic inflammation. These earlier findings offer preliminary evidence supporting a relationship between the two.[20,22–24] This study also provided similar results. At the same time, NLR serves as a valuable and affordable biomarker for assessing peripheral systemic inflammation. Derived from a standard complete blood count, previous studies have demonstrated that NLR is associated with both the existence and intensity of systemic inflammatory processes within the body.[11–13] Clinical studies have shown a negative correlation between high ferritin levels and bone mineral density, particularly in the elderly, suggesting that elevated ferritin may increase fracture risk due to decreased bone density. NLR is considered a novel inflammatory marker, with elevated levels often associated with a chronic inflammatory state. Chronic inflammation can negatively impact bone metabolism, potentially promoting the development of osteoporosis. Some studies have also found a correlation between increased NLR and decreased bone mineral density. High NLR may reflect heightened inflammation in the body, which is regarded as a risk factor for osteoporosis.[25] Excess iron can catalyze the generation of free radicals, leading to oxidative stress that damages cells and tissues. Osteoblasts exposed to high levels of oxidative stress may experience impaired proliferation, differentiation, and mineralization capabilities. Additionally, iron overload triggers an inflammatory response, promoting the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha TNF-α and IL-6. These cytokines can inhibit osteoblast function while enhancing osteoclast activity, resulting in reduced bone formation and increased bone resorption. Furthermore, the accumulation of excess iron may affect the signaling pathways of osteoblasts, such as those involving the Wnt/β-catenin pathway, thereby suppressing the osteogenic process. Iron overload can also lead to osteoblast apoptosis, further diminishing bone formation.[26]

Our study aims to investigate the connection between NLR and iron status, as well as evaluate the patterns of NLR and ferritin during inflammation progression in patients with OPF.

Materials and Methods

Research Design and Participant Characteristics

This research was conducted as a retrospective analysis, utilizing patient information collected from January 2017 to August 2023 at The First People's Hospital of Kunshan. The study included a total of 4782 patients diagnosed with osteoporosis who had recently experienced fractures necessitating surgical intervention. Participants in the study were carefully selected from our hospital's electronic medical records, ensuring that only individuals meeting specific inclusion criteria were included.

Research Design and Participant Characteristics

This research was conducted as a retrospective analysis using patient information collected from January 2017 to August 2023 at our hospital. A total of 4,782 patients with OPF who had recently suffered fractures requiring surgical intervention were included in the study. Osteoporosis represents a primary focus of our research group, particularly given the significant increase in fracture risk among the elderly population suffering from this condition. The implications of these fractures extend beyond the affected individuals, placing a considerable burden on both patients and their families. All participants in this study had suffered fractures within the past six years and had subsequently been hospitalized for surgical procedures. The selected population included elderly individuals aged 50 and older residing in the eastern coastal regions of China, specifically those who had experienced fractures. These patients underwent surgical treatment at the First People's Hospital of Kunshan City.

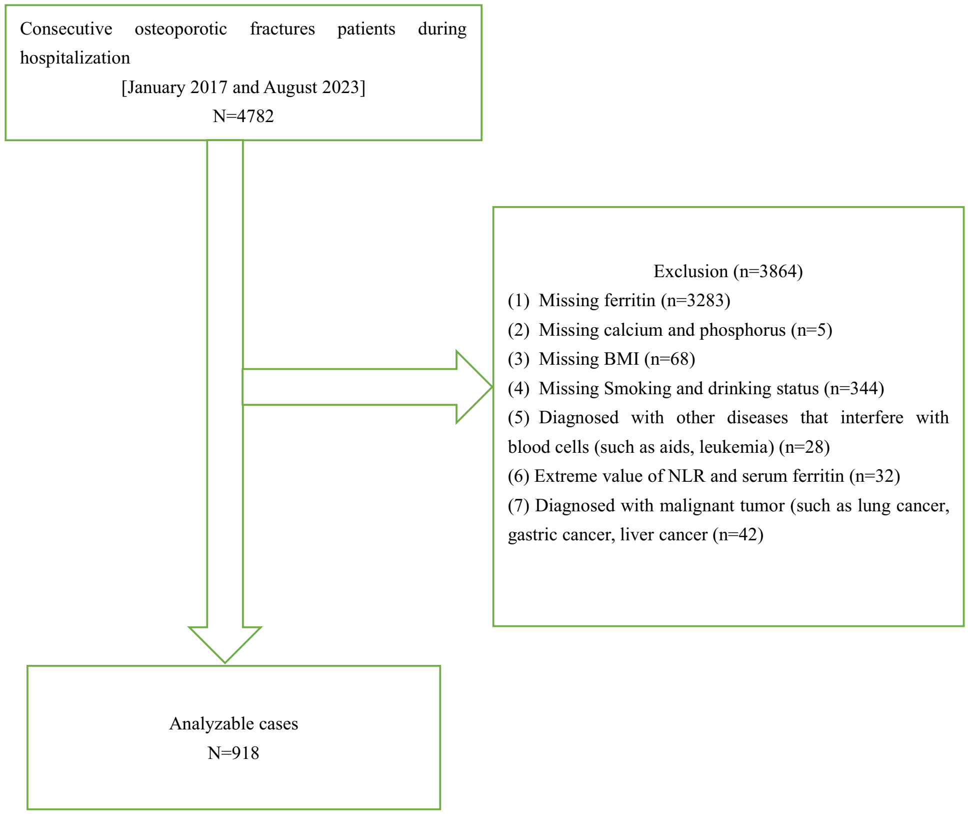

Figure 1 Research workflow diagram. This flowchart illustrates the selection process for patients.

Upon admission, each of these elderly patients underwent routine blood biochemical tests within 24 hours. Additionally, dual-energy X-ray absorptiometry scans were performed, revealing a diagnosis of osteoporosis in line with the clinical assessment.

All evaluations were performed using the first fasting blood sample, which was collected within 24 hours of hospital admission. OPF denotes fractures that occur due to bone density reduction, with the spine often being the most frequently impacted region. Osteoporosis was identified using the criteria outlined below: (1) BMD (bone mineral density) T-score ≤ −2.5 Exclusion criteria included: (1) missing or incomplete data (n=3762); (2) diagnosed with additional conditions affecting blood cells, such as leukemia or AIDS (n=28); (3) extreme values of NLR and serum ferritin (n=32); (4) identified with cancerous growths, including lung cancer, gastric cancer and liver cancer (n=42). As illustrated in (Figure 1), the final analysis included 918 hospitalized patients diagnosed with OPF after the selection criteria were applied. This research adhered to the guidelines outlined in the Declaration of Helsinki and received approval from the Ethics Committee of our hospital (approval No: 2021-06-016-K01). To guarantee an unbiased study, patient identities were kept confidential, and all participants gave written informed consent after being thoroughly informed.

Exposure and Outcome Variables

NLR was obtained by calculating the total peripheral neutrophil to lymphocyte ratio. Lymphocyte and neutrophil levels were measured utilizing a computerized blood cell counter (Sysmex XN-10 (B4) hematology analyzer). In this research, the outcome variable was serum ferritin, and the evaluation method employed a Roche Elecsys 170 analyzer. For further analysis, serum ferritin levels were divided into tertiles.

Covariates

The covariates considered in the study were age, sex, body mass index (BMI), hypertension, diabetes, alcohol consumption, smoking status, phosphorus, total cholesterol (TC), urea nitrogen (UN), uric acid (UA), serum calcium and albumin. All clinical parameters were assessed following an overnight fast in the first three days of admission to the hospital.

Statistics

All measurements were conducted with a consistent device and by the same operator, and the outcomes were reported as mean ± standard deviation (SD), median (25th percentile, 75th percentile) or percentage frequency (%) for both continuous and categorical data. Univariate variables were examined using either Pearson's chi-square test or Fisher's exact test for analysis. For the assessment of continuous variables, we employed t-tests or Mann–Whitney *U*-tests, depending on the normality of the data distribution. Next, to assess the association between serum ferritin and the NLR in hospitalized patients with OPF, we applied linear multivariate regression models. Furthermore, all data are derived from the (Supplementary).

Generalized estimating equations (GEE) were employed with suitable covariate adjustments to investigate the independent association between serum ferritin and NLR in hospitalized patients with OPF. The analysis included three models: a basic model (Model 1), a minimally adjusted model (Model 2) that accounted for age, gender, and BMI, and a fully adjusted model (Model 3) that additionally considered these factors including age, gender, BMI, hypertension, diabetes, alcohol consumption, smoking status, phosphorus, TC, UN, UA, serum calcium and albumin, American Society of Anesthesiologists score (ASA). At the outset, an analysis of the variance inflation factor revealed collinearity among the covariates. Covariates were chosen for adjustment based on two criteria: (1) a change of ≥ 10% in the matched odds ratio (OR) when including or excluding covariates in either the basic or full models; (2) covariates that had a *P*-value of less than 0.1 in univariate analyses.

Additionally, we developed non-linear associations utilizing a generalized additive model (GAM). Upon identification, piecewise linear regression models assessed the threshold effects of smoothed curves. Maximum likelihood models using a recursive method automatically identified breakpoints at which curves displayed distinct inflection points.

Study Site

Our research department is the Department of Orthopedics at The First People's Hospital of Kunshan. The hospital is located in Kunshan, and our affiliated school is Gusu School of Nanjing Medical University, located in Suzhou, Jiangsu, China. The study site is Kunshan Biomedical Big Data Innovation Application Laboratory which is located in the First People's Hospital of Kunshan.

All data analyses were conducted using Empower Stats (X&Y Solutions, Inc., Boston, MA, USA) and R software version 3.6.3. A *P*-value lower than 0.05 was considered significant.

Results

Features of Patients

(Table 1) presents an overview of the initial characteristics of hospitalized patients (n = 918) admitted from January 2017 to August 2023, categorized into the designated NLR tertiles. These patients had a mean age of 68.83 ± 11.28 years, mean NLR level of 7.02 ± 5.23, and mean serum ferritin of 334.08 ± 323.74 ug/L.

Univariate Analyses of Factors Associated with Serum Ferritin

In univariate analysis, notable correlations were found between serum ferritin and factors such as serum calcium with a *P*-value less than 0.01, uric acid with a *P*-value less than 0.01, phosphorus with a *P*-value less than 0.01 and NLR with a *P*-value less than 0.01 (Table 2). The results of single factor analysis are similar to previous literature.

Examining the Relationship Between NLR and Serum Ferritin

In the following analysis, three different models were employed to investigate the relationship between NLR and serum ferritin (Table 3). In Model 1 (without adjustments), NLR were significantly related to serum ferritin (β, 7.68; 95% CI: 3.69, 11.67, *P*-value < 0.01). In Model 2, which accounted for age, gender, and body mass index, similar relationships were shown (β, 7.77, 95% CI, 3.76, 11.79, *P*-value < 0.01); The consistency of the effect size across these two models suggests that the relationship between NLR and ferritin is robust, even after accounting for these demographic and anthropometric factors. In Model 3, which further adjusted for age; gender; BMI; hypertension; diabetes; alcohol

Table 1 Patient Characteristics

	Mean+SD / N (%)
Age, years	68.83 ± 11.28
BMI, kg/m^2	23.11 ± 3.45
Phosphorus, mmol/L	1.05 ± 0.23
Albumin, mmol/L	39.50 ± 3.94
Serum calcium, mmol/L	2.21 ± 0.13
TC, mmol/L	4.23 ± 0.91
UN, mmol/L	6.60 ± 5.21
UA, mmol/L	284.58 ± 92.86
Serum ferritin, ug/L	334.08 ± 323.74
NLR	7.02 ± 5.23
	N (%)
Gender, N (%)	
Female	547 (59.98%)
Male	365 (40.02%)
Hypertension, N (%)	
No	784 (85.96%)
Yes	128 (14.04%)
Diabetes, N (%)	
No	875 (95.94%)
Yes	37 (4.06%)
Smoking status, N (%)	
No	836 (91.67%)
Yes	76 (8.33%)
Alcohol consumption, N (%)	
No	855 (93.75%)
Yes	57 (6.25%)
ASA score, N (%)	
1	128 (14.04%)
2	583 (63.93%)
3	197 (21.60%)
4	4 (0.44%)

Notes; This table provides detailed demographic information about the study participants, including age, gender, and baseline health status. The data illustrate the diversity of the sample population and its relevance to the research findings. *P*-value*: Kruskal Wallis Rank Test for continuous variables, Fisher Exact for categorical variables with Expects < 10.

Abbreviations: BMI, body mass index; TC, total cholesterol; NLR, neutrophil-to-lymphocyte ratio; UA, uric acid; UN, urea nitrogen; ASA, American Society of Anesthesiologists score.

consumption; smoking status; phosphorus; TC; serum calcium; ASA; UN; UA; albumin, the relationship remained consistent (β, 6.36, 95% CI: 2.02, 10.69, *P*-value < 0.01). While the effect size decreased, it still indicates a meaningful association, suggesting that even when accounting for a broader array of potential confounding variables, NLR continues to be a significant predictor of serum ferritin levels. This indicated a robust relationship between NLR and serum ferritin in all models. It is also notable that with the inclusion of confounding factors in the model adjustments, the change in the effect size (β) from Model 1 to Model 3 illustrates the impact of these confounders. For example, the reduction in the effect size observed in Model 3 may suggest that certain health conditions or lifestyle factors (such as hypertension or diabetes) are masking the true relationship between NLR and serum ferritin.

Table 2 Univariate Analyses of Factors Associated with Serum Ferritin

Characteristics	Statistics	β[a] (95% CI) *P*-value
NLR	7.02 ± 5.23	6.36 (2.02, 10.69) < 0.01
Age, years	68.83 ± 11.28	1.43 (−0.85, 3.70) 0.22
Gender, N (%)		
Female	547 (59.98%)	0
Male	365 (40.02%)	−4.69 (−51.46, 42.09) 0.84
BMI, kg/m^2	23.11 ± 3.45	−0.03 (−6.31, 6.26) 0.10
Hypertension		
No	784 (85.96%)	0
Yes	128 (14.04%)	35.27 (−32.00, 102.54) 0.30
Diabetes, N (%)		
No	875 (95.94%)	0
Yes	37 (4.06%)	21.13 (−93.36, 135.62) 0.72
Phosphorus, mmol/L	1.05 ± 0.23	−152.85 (−249.01, −56.69) < 0.01
Albumin, mmol/L	39.50 ± 3.94	−2.66 (−9.46, 4.14) 0.44
Serum calcium, mmol/L	2.21 ± 0.13	261.16 (58.55, 463.77) < 0.01
TC, mmol/L	4.23 ± 0.91	14.42 (−10.67, 39.51) 0.26
UN, mmol/L	6.60 ± 5.21	0.38 (−3.80, 4.56) 0.86
UA, mmol/L	284.58 ± 92.86	0.37 (0.13, 0.60) < 0.01
Smoking status, N (%)		
No	836 (91.67%)	0
Yes	76 (8.33%)	4.23 (−84.58, 93.04) 0.93
Alcohol consumption, N (%)		
No	855 (93.75%)	0
Yes	57 (6.25%)	82.02 (−17.52, 181.56) 0.11
ASA score, N (%)		
1	128 (14.04%)	0
2	583 (63.93%)	−5.99 (−68.80, 56.82) 0.85
3	197 (21.60%)	−22.14 (−103.89, 59.60) 0.560
4	4 (0.44%)	195.46 (−127.62, 518.55) 0.24

Notes: Dependent variable NLR, as a result of univariate analyses for serum ferritin.
Abbreviations: BMI, body mass index; TC, total cholesterol; NLR, neutrophil-to-lymphocyte ratio; UA, uric acid; UN, urea nitrogen; ASA, American Society of Anesthesiologists score.

Table 3 Association Between NLR and Serum Ferritin in Different Models

	Model 1[a] N=918 β (95% CI) *P*-value	Model 2[b] N=918 β (95% CI) *P*-value	Model 3[c] N=918 β (95% CI) *P*-value
NLR	7.68 (3.69, 11.67) < 0.01	7.77 (3.76, 11.79) < 0.01	6.36 (2.02, 10.69) < 0.01
NLR Tertile			
Low	Reference	Reference	Reference
Middle	73.40 (22.61, 124.19) <0.01	72.74 (21.77, 123.71) <0.01	75.77 (23.54, 127.99) <0.01
High	115.78 (64.74, 166.83) <0.01	117.38 (66.01, 168.75) <0.01	104.16 (48.89, 159.43) 0.02

Notes: This table summarizes the main results obtained from the data analysis, including statistical outcomes and their significance levels. It serves as a concise reference for the study's key discoveries. [a] No adjustment. [b] Adjusted for age; gender; BMI. [c] Adjusted for age; gender; BMI; hypertension; diabetes; alcohol consumption; smoking status; phosphorus; total cholesterol; serum calcium; ASA; UN; UA; albumin.
Abbreviations: BMI, body mass index; TC, total cholesterol; NLR, neutrophil-to-lymphocyte ratio; UA, uric acid; UN, urea nitrogen; ASA, American Society of Anesthesiologists score.

Spline Smoothing Graph and Threshold Exploration

First and foremost, the association between NLR and serum ferritin was assessed through graphical methods to ascertain if the relationship exhibited a linear or nonlinear pattern (Figure 2). (B Smooth) Adjusted smoothed curves illustrated this relationship in hospitalized patients with OPF. The upper and lower curves indicate the 95% confidence interval, while the middle curve depicts the relationship between serum ferritin and NLR. (A Scatter) The scatter plot and smooth curve illustrate that when NLR is less than approximately 5, serum ferritin levels exhibit a positive correlation with increasing NLR. Conversely, when the NLR exceeds 5, both serum ferritin and NLR show fluctuations, although the overall trend remains upward. This suggests a more complex relationship between these variables at higher NLR values, warranting further investigation to elucidate the underlying mechanisms.

The threshold effect analysis further accounted for adjustments in age; gender; BMI; hypertension; diabetes; alcohol consumption; smoking status; phosphorus; total cholesterol; serum calcium; ASA; UN; UA and albumin (Table 4). The GAM analysis demonstrated that, when controlling for covariates, clear nonlinear associations existed between NLR and serum ferritin in the OPF population examined in this study. To confirm this threshold nonlinear relationship, segmented linear regression models were utilized. A threshold value of 5.31 for NLR was determined. When NLR fell below this point (< 5.31), there was a significant increase in serum ferritin levels (β, 32.08; 95% CI, 12.97, 51.20, *P*-value < 0.01). In contrast, levels exceeding 5.31 showed no clear relationship between serum ferritin and NLR. These findings underscore a strong association between NLR values below 5.31 and elevated serum ferritin, whereas no significant link was evident above this threshold. When NLR exceeds 5.3, the inflammatory response may reach a critical threshold, resulting in substantial alterations within the immune system. At this point, levels of various cytokines and inflammatory mediators in the body may experience significant changes. These mediators not only influence the synthesis of ferritin but may also inhibit its excessive production through negative feedback mechanisms. Consequently, this leads to a diminished relationship between ferritin levels and NLR, complicating the interpretation of these biomarkers in the context of inflammation.

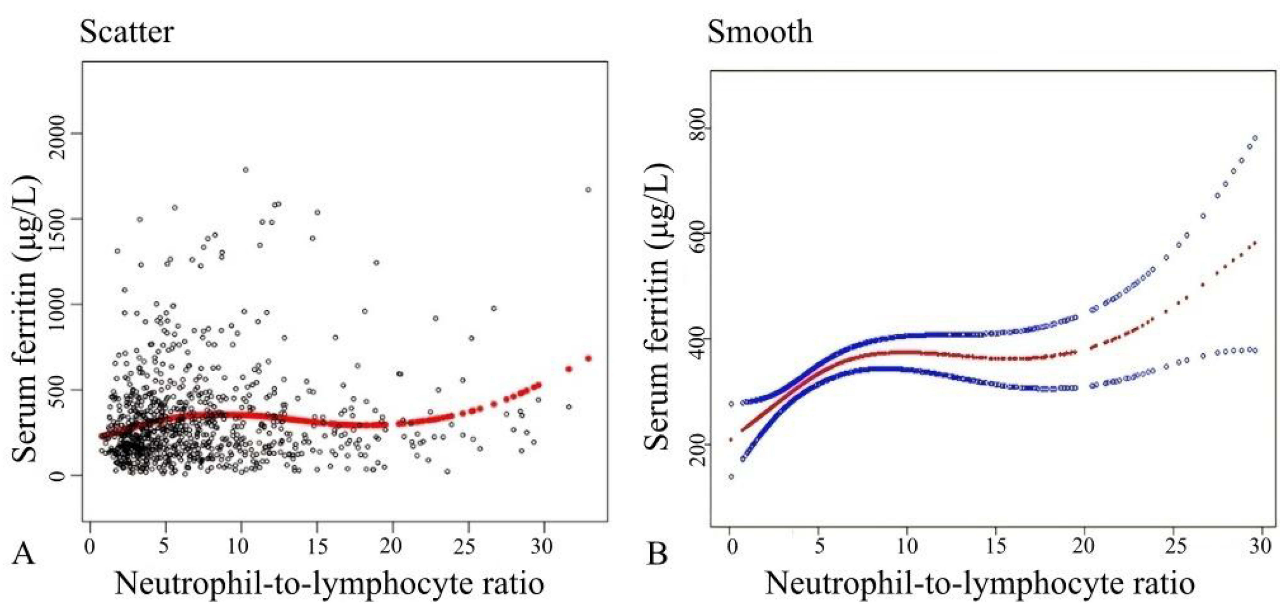

Figure 2 The association between serum ferritin levels and NLR. Adjusted smoothed curves illustrated this relationship in hospitalized patients with OPF. A generalized additive model indicated a thresholded non-linear association between serum ferritin and NLR. The upper and lower curves indicate the 95% confidence interval, while the middle curve depicts the relationship between serum ferritin and NLR. The models were refined to account for different covariates. In Model 3, the red curve displayed an inflection point (K) at 5.31. NLR and Serum Ferritin: Smooth curve (**A**) and Scatter plot (**B**).

Table 4 Threshold Effect Analysis Examining the Relationship Between NLR and Serum Ferritin

Outcome	Model3[a]
	β (95% CI) *P*-value
Model A[b]	
One line effect	6.36 (2.02, 10.69) < 0.01
Model B [c]	
Serum ferritin turning Point (K),	5.31
< K	32.08 (12.97, 51.20) < 0.01
> K	1.87 (−3.53, 7.28) 0.50
LRT test [d]	< 0.01

Notes: Threshold effect analysis examining the relationship between the neutrophil-to-lymphocyte ratio (NLR) and serum ferritin levels. The results are presented in two models. [a] Adjusted for age; [b] Linear analysis, *P*-value < 0.05 indicates a linear relationship. [c] Non-linear analysis. [d] *P*-value < 0.05 means Model B is significantly different from Model A, which indicates a non-linear relationship.

Abbreviations: BMI, body mass index; TC, total cholesterol; NLR, neutrophil-to-lymphocyte ratio; UA, uric acid; UN, urea nitrogen; ASA, American Society of Anesthesiologists score.

Discussion

Bone fractures lead to increased inflammation due to tissue damage that triggers an inflammatory response for healing. The immune system activates in response to the injury, releasing pro-inflammatory cytokines and growth factors necessary for repair. Additionally, fractures can cause local blood vessels to dilate, increasing blood flow to the area and bringing immune cells and nutrients. The healing process also involves the activation of osteoclasts and osteoblasts, which produce inflammatory mediators while remodeling the fractured bone. In the case of open fractures or soft tissue injuries, the risk of infection can further elevate inflammation. These mechanisms are integral to the normal healing process, but if not properly regulated, they can contribute to prolonged inflammation.[27]

The connection between serum ferritin and NLR has been infrequently studied, and the available literature offers only limited insights.[28] Previous research has demonstrated a potential link between serum ferritin and inflammation, indicating that ferritin levels tend to rise during inflammatory processes.[20,22–24] Moreover, regardless of age or gender, the effects of increased serum ferritin levels due to infection are directly related to the initial serum ferritin measurement at each phase.[29] When serum ferritin is used as an indicator of inflammation, numerous studies have shown that the inflammatory processes in the body lead to elevated levels of C-reactive protein (CRP), a widely recognized acute phase response protein.[30] This inflammatory response is linked to increased serum ferritin levels, emphasizing the connection between these biomarkers in relation to inflammation.[31]

One possible explanation for the findings is that elevated serum ferritin levels may be more closely associated with markers of cellular damage instead of those related to cell counts. This implies that serum ferritin might serve as a better indicator of underlying cellular harm rather than simply reflecting shifts in cell population.[32] At the same time, NLR represents the balance between neutrophils and lymphocytes, serving as an indicator of inflammation intensity.[33] Ferritin serves as a biochemical indicator of the body's iron levels and is increased during periods of chronic inflammation.[34] In the context of inflammation or infection, key inflammatory markers such as CRP and ferritin, along with cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), experience a rapid increase.[35] Research has shown a positive relationship between serum ferritin levels and both CRP and IL-6.[36] Among them, IL-6 especially increases ferritin synthesis and decrease iron transport. Damaged bone tissues and activated immune cells secrete IL-6. IL-6 stimulates liver cells to produce acute phase proteins, including CRP. This occurs through the activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, specifically through STAT3. CRP serves as a biomarker for inflammation and contributes to immune responses. IL-6 and CRP trigger the production of ferritin in hepatocytes. This occurs through: Activation of the transporter, which regulates iron release from macrophages. Increased synthesis of ferritin, and other signaling pathways that respond to heme and iron levels.[37] Damaged bone tissues and activated immune cells secrete IL-6. IL-6 stimulates liver cells to produce acute phase proteins, including CRP. This occurs through the activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, specifically through STAT3. CRP serves as a biomarker for inflammation and contributes to immune responses. IL-6 and CRP trigger the production of ferritin in hepatocytes. This occurs through: Activation of the transporter, which regulates iron release from macrophages. Increased synthesis of ferritin, and other signaling pathways that respond to heme and iron levels. IL-6 also inhibits the action of TNF-α and thus induces production of ferritin protein.[38] Therefore, additional research is necessary to explore the connection between inflammatory processes and the regulators of iron metabolism. However, When IL-6 and CRP levels exceed certain thresholds, the liver's capacity to produce ferritin becomes saturated, limiting further increases in ferritin despite elevated IL-6 and CRP levels. This may explain why serum ferritin is no longer positively correlated with values when NLR exceeds the threshold.

In the clinical care of patients with osteoporotic fractures, it is crucial to monitor the NLR and ferritin levels,[39] while ferritin is involved in iron metabolism and also serves as a biomarker of inflammation and iron status.[40] This research indicates that serum ferritin levels have an inverse relationship with bone density in individuals with osteoporosis, implying that higher ferritin levels could contribute to an increased risk of developing osteoporosis. Excess iron can catalyze the generation of free radicals, leading to oxidative stress that damages cells and tissues. Osteoblasts exposed to high levels of oxidative stress may experience impaired proliferation, differentiation, and mineralization capabilities. Additionally, iron overload triggers an inflammatory response, promoting the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha TNF-α and IL-6. These cytokines can inhibit osteoblast function while enhancing osteoclast activity, resulting in reduced bone formation and increased bone resorption. Furthermore, the accumulation of excess iron may affect the signaling pathways of osteoblasts, such as those involving the Wnt/β-catenin pathway, thereby suppressing the osteogenic process. Iron overload can also lead to osteoblast apoptosis, further diminishing bone formation.[41,42] Additionally, an increase in NLR is associated with a higher risk of fragility fractures in elderly patients with osteoporosis.[43] Regarding treatment approaches, alongside conventional anti-osteoporosis therapies like bisphosphonates and selective estrogen receptor modulators, it is essential to take into account the impact of inflammation and iron metabolism on osteoporotic fractures. Tracking ferritin concentrations can assist healthcare providers in evaluating patients' iron reserves and identifying any inflammatory processes associated with iron metabolism.[44,45] Indeed, the NLR is a readily accessible marker. Our study found that NLR exhibits a positive association with ferritin within a specific range, suggesting that elevated NLR levels often coincide with higher ferritin levels in patients. Conversely, lower NLR values may indicate reduced ferritin levels. Significantly, we identified a threshold at which this positive association is evident.

This article is the first to thoroughly investigate the relationship between the NLR and serum ferritin levels specifically in elderly patients suffering from osteoporotic fractures. A nonlinear relationship between them has been discovered. This insight adds complexity to our understanding of how these biomarkers interact and suggests that the relationship may not be straightforward. Recognizing this nonlinear dynamic could have important implications for clinical assessments and interventions related to both ferritin and NLR in patient management. Moreover, it identifies an innovative threshold effect, a finding that has not been previously reported in the literature. Within this threshold, a significant positive correlation between NLR and ferritin levels is observed, suggesting that as the NLR increases, serum ferritin also tends to rise, indicating a potential link between systemic inflammation and iron metabolism in this vulnerable population. The identification of this threshold effect is particularly noteworthy, as it opens new avenues for clinical practice. By providing a clear cutoff point for evaluating these biomarkers, healthcare practitioners may be able to rapidly assess serum iron reserves in older individuals with osteoporosis. This capability is critical, as it can lead to timely interventions aimed at improving patient outcomes. If NLR approaches or exceeds the threshold, clinicians should consider retesting ferritin levels in patients with osteoporotic fractures, as ferritin testing is not routinely performed for all patients. If ferritin levels are found to be significantly elevated, clinicians should adjust the patient's dietary structure to limit the intake of iron-rich foods. Furthermore, it is essential for healthcare providers to continuously monitor the serum ferritin status of retested patients to exclude potential underlying conditions such as tumors, hepatitis, and infections following fractures.

This article also presents some limitations. Firstly, as a cross-sectional study, it can only identify the correlation between the two variables without establishing causative relationships. Furthermore, the study population consists exclusively of elderly patients aged 50 and above with osteoporotic fractures from the eastern coastal regions of China. This specificity may limit the generalizability of the findings. Therefore, further investigations are required to elucidate the underlying mechanisms at play, and we suggest that future research involves larger cohorts that include participants from diverse racial backgrounds and age groups to enhance the robustness of our findings, particularly through prospective cohort studies and longitudinal designs that aim to deepen our understanding of the temporal relationships and causative factors influencing NLR and serum ferritin levels in patients with OPF. Additionally, exploring intervention studies that aim to modulate NLR or ferritin levels in this population could provide valuable insights into potential therapeutic strategies. Such studies might investigate the effects of dietary modifications, pharmacological treatments, or lifestyle changes on these biomarkers. Implementing these research approaches will help clarify the implications of NLR and ferritin in the management of OPF and contribute to evidence-based practices in clinical settings.

Conclusion

The findings of this study indicated a threshold effect between serum ferritin levels and the NLR in patients with osteoporotic fractures. Overall, serum ferritin is positively correlated with NLR. In particular, a significant positive association was observed between serum ferritin and NLR when the latter was under 5.31. And a threshold effect has been discovered. At this threshold, serum ferritin levels showed a notable increase. According to existing literature, the normal value of NLR ranges from approximately 1 to 3. This observation implies that in patients with OPF presenting with NLR values within or slightly above the normal range, routine hemogram results obtained in the emergency department can be effectively employed to predict and assess the patient's iron status. Therefore, clinicians may incorporate NLR as a potential biomarker for iron evaluation, subsequently conducting further diagnostic tests such as serum iron studies and total iron binding capacity to formulate an appropriate treatment plan. Early recognition of iron imbalance, whether deficiency or overload, facilitates precise interventions that may improve patient prognosis and decrease osteoporosis-associated complications, thus provide reference for the next step of diagnosis and treatment. Nonetheless, further detailed analyses and long-term studies are essential to confirm the validity of the findings from this research. To enhance the understanding of the relationship between inflammatory markers and iron metabolism, future studies should focus on longitudinal and interventional approaches. This is crucial for validating results across diverse populations, including various regions in China and different ethnic groups worldwide. Such research would provide a comprehensive understanding of how genetic, environmental, and dietary factors influence these biomarkers.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author Ke Lu on reasonable request.

Ethics Approval

We received ethical approval from the Affiliated Kunshan Hospital of Jiangsu University (approval No. 2021-06-015-K01), and was compliant with the Declaration of Helsinki.

Consent to Participate

Informed consent was obtained from all individual patients included in the study. Patients signed informed consent regarding publishing their data.

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Disclosure

The authors declare that they have no competing interests in this work.

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