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Association of neutrophil to high-density lipoprotein cholesterol ratio with fragility fracture in osteoporotic patients: a case-control study

Liman Wang[1,2†], Dan Xu[1,2†], Meijiao Chen[1,2] and Xuhui Huang[1,2*]

Abstract

Background Systematic inflammation plays an important role in the pathogenesis of osteoporosis. Neutrophil to high-density lipoprotein cholesterol ratio (NHR) has been considered as a novel inflammatory marker. To date, the clinical association between NHR and fragility fracture is not yet well-known. Thus, the present study explored whether NHR levels in patients with osteoporosis were associated with an increased risk of fragility fracture.

Methods This case-control study included 271 osteoporotic patients with and without a history of fragility fracture from January 2017 to December 2021. Laboratory tests and physical examinations were conducted in all participants, and NHR was calculated.

Results The mean NHR levels in patients with fragility fractures were significantly higher compared to those without fragility fractures (2.91 ± 1.18 vs. 2.21 ± 0.91, $P < 0.001$). Additionally, there was a significant positive correlation between NHR and fragility fracture ($r = 0.310$, $P < 0.001$). Moreover, we could detect a statistical increment of the area under receiver operating characteristics curve (from 0.681 to 0.805, $P < 0.001$) upon the combination of NHR and Fracture Risk Assessment Tool (FRAX) score for determining the presence of fragility fracture among the study patients. In multivariable logistic regression models, elevated NHR level was an independent risk factor for fragility fracture (adjusted OR: 1.924, 95% CI: 1.443–2.564, $P < 0.001$) when adjusted for alkaline phosphatase and FRAX score.

Conclusions As a valuable and convenient inflammatory biomarker calculated from routine blood examinations, NHR might help to identify individuals with osteoporosis who are at high risk of fragility fracture.

Keywords Neutrophil to high-density lipoprotein ratio, Osteoporosis, Fracture risk, Bone turnover markers, FRAX

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Background

Osteoporosis, a systemic metabolic disorder caused by decreased bone mass and bone microstructural degradation, has become a common public health problem in aging societies [1, 2]. It is estimated that approximately 30% of females and 20% of males 55 years of age or older occur fragility fractures in their lifetime throughout the world [3]. Moreover, fragility fracture is strongly associated with high morbidity and mortality in older adults, imposing a considerable socioeconomic burden [4]. Bone mineral density (BMD) is the gold standard for diagnosing osteoporosis [1]. Although BMD is inversely correlated with fragility fracture risk, a majority of patients with fragility fracture have a normal or osteopenic range of BMD [5]. It has been well established that the Fracture Risk Assessment Tool (FRAX) is widely used to identify individuals at high risk of fragility fracture. However, the sensitivity and specificity of FRAX for predicting fragility fracture have not yet reached optimal levels [6]. Hence, it is urgent to search for novel and efficient biomarkers that can early discriminate fragility fracture risk independent of or combined with FRAX.

Increasing evidence suggests that inflammatory response activation contributes to the development of osteoporosis [7–10]. Furthermore, several inflammatory biomarkers, such as systemic immune-inflammation index (SII), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and interleukin-6, are independently associated with a higher risk of fragility fracture [11–14]. The neutrophil to high-density lipoprotein cholesterol (HDL-C) ratio (NHR) has been newly recognized as a simple, easily accessible, and economical biochemical marker of systemic inflammation. In fact, NHR is associated with poor outcomes in various diseases [15–19]. Activated neutrophils can contribute to osteoclast activation by expressing receptor activator of nuclear factor-κB ligand (RANKL), which promotes bone resorption [20]. On the other hand, HDL-C has been considered as an important predictor for fragility fracture [21]. According to these findings, NHR may be used as a potential biomarker for fragility fracture risk prediction.

To the best of our knowledge, the relationship between NHR and the risk of fragility fracture remains uncertain in the clinical setting. Therefore, the current study is undertaken to explore whether a high level of NHR is independently associated with the presence of fragility fracture in subjects with osteoporosis.

Methods

Study participants

The case-control study was performed at the endocrinology department at Fujian Provincial Hospital in Fuzhou, People's Republic of China. In the current work, a total of all consecutive 1107 osteoporotic patients admitted to the hospitals were retrospectively reviewed from January 2017 to December 2021. The enrolled patients were postmenopausal women aged ≥ 45 years who had no menstruation for at least 12 months or men aged ≥ 50 years. Patients who satisfied any of the following criteria were excluded from the analysis: (a) those taking hypolipidemic drugs or medications that could affect bone metabolism (e.g. glucocorticoids therapy, estrogen replacement therapy); (b) those with a history of medical conditions affecting bone health (e.g. malabsorption syndromes, cancer, rheumatic diseases, hyperthyroidism or hypothyroidism, hyperparathyroidism or hypoparathyroidism, asthma or chronic obstructive pulmonary disease); (c) those with concomitant acute or chronic infections; (d) those with a history of abnormal liver function or chronic renal failure; (e) those with high-energy traumatic fractures or pathological fractures; and (f) those with incomplete baseline data. Ultimately, the exclusion left 271 eligible patients included in the study, namely 182 cases without fragility fracture and 89 cases with fragility fracture (Fig. 1). This study was conducted in accordance with the principles of Helsinki Declaration. Permission to accomplish the study was received from the Ethics Committee of Fujian Provincial Hospital (K2022-01-010). The current study waived the requirement for written informed consent from enrolled patients because of its retrospective design.

Clinical characteristics

Clinical data including demographic characteristics, lifestyle, smoking history, alcohol consumption, parental history of hip fractures, medication use, as well as a thorough medical history (including incident clinical fragility fractures, dyslipidemia, diabetes mellitus, hypertension, chronic kidney disease, etc.) were recorded for each patient. Smoking and alcohol status was categorized as either current, ever, or never. Standing height (m) and body weight (kg) were measured while the patient was dressed in lightweight clothing and without shoes before breakfast. Body mass index (BMI) was calculated according to the patient's weight and height (kg/m^2). Waist circumference was measured in duplicate horizontally at the umbilicus level in a relaxed standing position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined using an automatic sphygmomanometer in a sitting position after at least five minutes of rest.

Biochemical assessment

In all patients, venous blood samples were routinely collected after at least 10 h of overnight fasting. Neutrophil and lymphocyte counts were subsequently performed by an automated hematology analyzer (JMXN-3000, Sysmex Corporation, Kobe, Japan). Biochemical parameters,

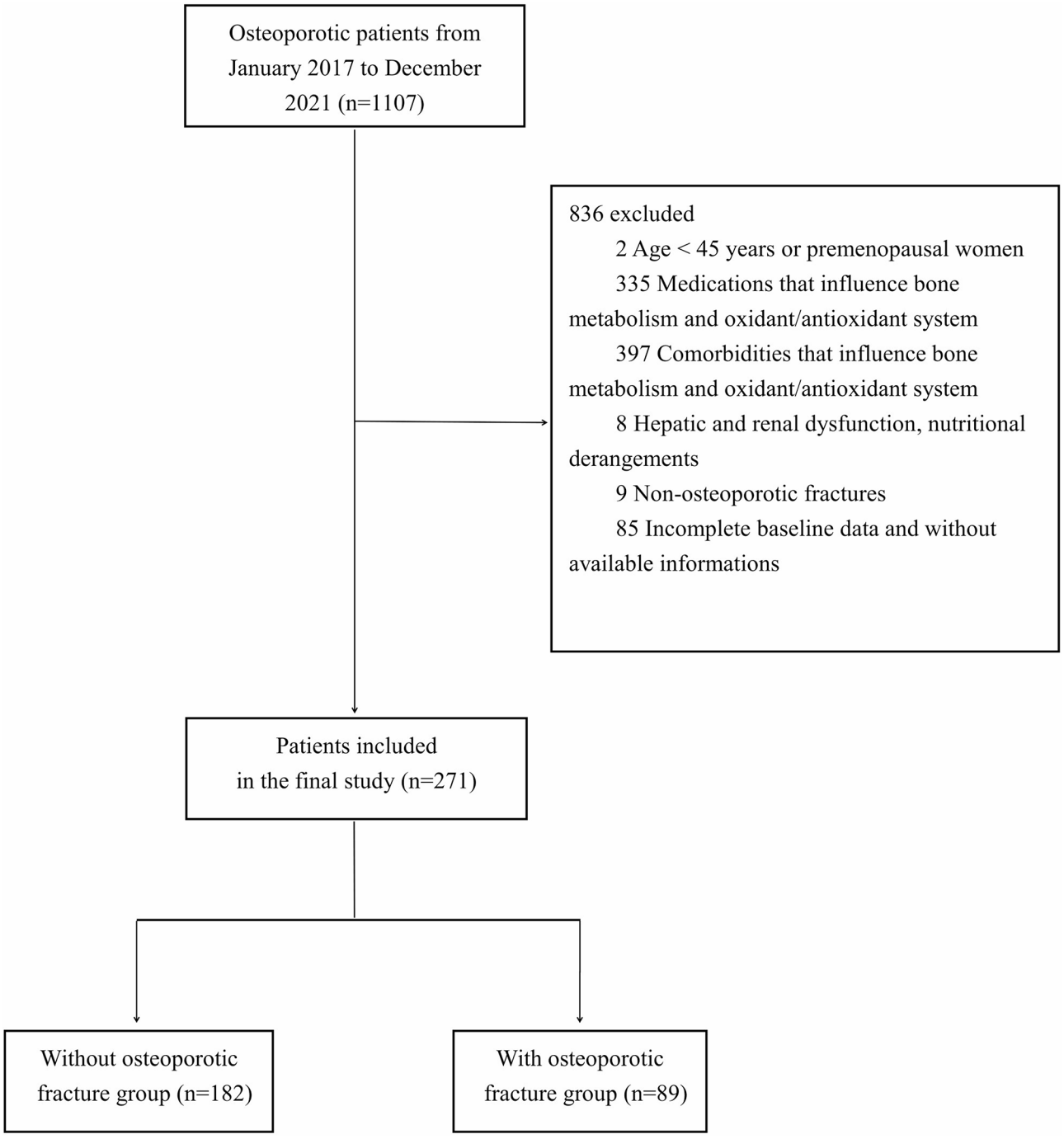

Fig. 1 Flow chart of the study selection

such as serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), uric acid (UA), creatinine (Cr), alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P) were measured on the same day of collection with a full-automatic biochemical analyzer (Jcobas 8000, Roche Diagnostics, Mannheim, Germany). The neutrophil to HDL-C ratio (NHR) was calculated. The concentrations of β-carboxyterminal cross-linked telopeptide of type I collagen (β-CTX), osteocalcin (Osc), amino-terminal propeptide of type-I procollagen (P1NP), 25-hydroxy vitamin D [25-(OH) Vit D], and parathormone (PTH) in serum were determined using an automated electrochemical luminescence immunoassay (Cobas-601, Roche Diagnostics, Mannheim, Germany).

BMD measurements

All patients underwent a BMD evaluation of the lumbar spine (L1-L4) and femoral neck by dual-energy X-ray absorptiometry (DXA), which was conducted by certified radiology technologists using a Hologic QDR Discovery W instrument (Hologic, Inc., Waltham, MA, USA). Additionally, BMD was then expressed as the T score, calculated on the basis of the normal reference values. The measurements of BMD were not blinded. Based on the total lumbar spine (LS) and femoral neck (FN) BMD, osteoporosis was diagnosed as T-score ≤ -2.5 according to the WHO criteria [22]. The coefficient variation was 0.8% for the lumbar spine and 1.6% for the femur neck.

Fracture assessment and FRAX probabilities

The history of fractures were retrospectively recorded during an interview, including the fracture sites, age at the time of fracture, and cause of fractures. In this analysis, we characterized fragility fractures as low-trauma fractures that occurred at an age ≥ 45 years due to a fall from a standing height or shorter, a trip/slip, or a fall out of bed (fracture of the hip, wrist, spine). We verified the fracture based on the hospital diagnosis or previous radiographic data obtained via radiographs, computed tomography (CT), or magnetic resonance imaging (MRI). Non-fracture fractures that defined as traumatic fractures (due to motor vehicle accident or fall from a place higher than standing height), pathologic fractures (resulted from cancer, bone tuberculosis, etc.), and fractures of the fingers, face, skull, and toes were not taken into account [23, 24].

The 10-year probabilities of hip fracture (without femoral neck BMD) were calculated by using the Chinese (mainland) version of FRAX tool [25]. The FRAX probabilities are based on the clinical risk factors including age, gender, BMI, previous history of fracture, parental history of hip fracture, current smoking, alcohol drinking, glucocorticoids use, rheumatoid arthritis, and secondary osteoporosis.

Statistical analysis

Each continuous variable normality was assessed by the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation (SD) or median (interquartile range) depending on the distribution of variables as appropriate. Categorical variables were described by percentages (%) and frequency. We performed statistical analyses using the independent samples t test for normally distributed continuous variables and Mann-Whitney U test for skewed distributed continuous variables between the baseline characteristics of patients with (at least one fracture) and without fragility fracture. The chi-squared test was given to analyze whether a difference was present between cases and controls for categorical variables. Unadjusted Pearson's or Spearman's correlation analysis were employed to identify the continuous variables that correlated with NHR levels. Point-biserial correlation coefficients were calculated between NHR levels and binary variables. Univariable logistic analysis was first carried out and variables with P values < 0.05 were then entered into a forward stepwise multivariable logistic analysis to identify independent risk factors related to the presence of fragility fracture. Results were presented as odds ratios (OR) with 95% confidence intervals (CI) of the risk factors significantly associated with fragility fracture. The area under the curve (AUC) from receiver operating characteristics (ROC) curve was used to compare the diagnostic accuracy of NLR and FRAX score alone or in combination. The statistical differences between AUCs were evaluated using the MedCalc software (DeLong test). The optimal cut-off value of NHR for identifying fragility fracture was calculated according to Youden's index (sensitivity + specificity − 1). Statistically significant differences were established at two-sided P values < 0.05. The number of patients during the study period determined the sample size. All data analyses and graphics in this study were performed using MedCalc 13.1.2 (MedCalc Software bvba, Ostend, Belgium) and SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of study patients

Of the 271 patients with osteoporosis included in the final analysis, 89 (32.84%) sustained at least one fragility fracture. Of these patients, there were 46 vertebral fractures and 43 nonvertebral fractures. Moreover, the median (IQR) time since the last fragility fracture was 2 (1–4) years. The baseline characteristics of patients according to fragility fracture status are listed in Table 1. The patients with fragility fractures were significantly older than the control subjects. On the other hand, patients had higher BMI, SBP, neutrophil counts, TG, ALP, fracture probability assessed by FRAX, and lower LDL-C levels in the fracture group compared to the control group. The difference in HDL-C between the two groups also trended towards significance (1.36 ± 0.38 vs. 1.45 ± 0.35, $P = 0.089$). In contrast, no heterogeneity was seen in bone turnover markers, T-score, and other clinical parameters. As expected, NHR levels were significantly higher in patients with fragility fracture compared to those without fragility fracture (2.91 ± 1.18 vs. 2.21 ± 0.91, $P < 0.001$).

Correlation analyses of NHR levels with clinical variables

We used the correlation analyses to investigate the association between NHR levels and other fragility fracture related risk factors (Table 2). It was found that there were no correlations between NHR levels and T-score values at any site. However, a significant difference in

Table 1 Baseline clinical characteristics of enrolled patients

Variables	Without fragility fracture (*n* = 182)	With fragility fracture (*n* = 89)	*P*
Age (years)	62.73 ± 7.99	65.73 ± 8.44	**0.005**
Gender, female (%)	156 (85.7%)	80 (89.9%)	0.336
Waistline (cm)	80.13 ± 8.32	80.50 ± 7.31	0.722
BMI (kg/m^2)	22.35 ± 2.88	23.29 ± 3.27	**0.016**
SBP (mmHg)	124.84 ± 16.81	130.88 ± 17.53	**0.007**
DBP (mmHg)	72.83 ± 10.24	73.30 ± 10.31	0.722
Current smokers (%)	7 (3.8%)	2(2.2%)	0.748
Current alcohol use (%)	10 (5.5%)	3(3.4%)	0.648
Neutrophil (×10^9/L)	3.02 ± 1.01	3.66 ± 1.10	**< 0.001**
Lymphocyte (×10^9/L)	1.90 (1.55, 2.30)	1.90 (1.50, 2.40)	0.795
TG (mmol/L)	1.10 (0.82, 1.56)	1.23 (0.95, 1.69)	**0.038**
TC (mmol/L)	4.93 ± 0.97	4.76 ± 1.10	0.205
HDL-C (mmol/L)	1.45 ± 0.35	1.36 ± 0.38	0.089
LDL -C(mmol/L)	3.23 ± 0.91	2.97 ± 0.96	**0.030**
NHR	2.21 ± 0.91	2.91 ± 1.18	**< 0.001**
FPG (mmol/L)	5.32(4.79,6.77)	5.44(4.83,7.28)	0.495
UA (μmol/L)	291.00 (256.50,345.50)	295.00 (248.00, 340.00)	0.920
Cr (μmmol/L)	58.00 (52.00,68.00)	60.00 (52.00, 67.50)	0.836
ALP (IU/L)	66.55 ± 18.48	73.89 ± 24.87	**0.015**
Ca (mmol/L)	2.37 ± 0.10	2.32 ± 0.12	0.351
P (mmol/L)	1.19 ± 0.16	1.16 ± 0.17	0.115
β-CTX (ng/mL)	0.28 (0.15, 0.48)	0.28 (0.16, 0.39)	0.857
Osc (μg/L)	13.40 (9.70,18.00)	13.40 (9.85,17.00)	0.676
PINP (ng/mL)	32.33 (19.14, 50.69)	35.72 (23.86, 47.43)	0.389
PTH (pg/mL)	35.32 (26.08, 44.38)	32.86 (26.68, 41.09)	0.578
25-(OH) Vit D (ng/mL)	28.30 ± 9.15	28.69 ± 8.68	0.736
Total LS BMD (T-score)	-3.12 ± 0.78	-3.17 ± 1.13	0.692
Total FN BMD (T-score)	-2.02 ± 0.76	-2.03 ± 0.72	0.952
FRAX score,%	1.20 (0.55, 1.90)	2.40 (1.50, 3.75)	**< 0.001**
Osteoporosis drug use			
Calcium (%)	106 (58.2%)	57 (64.8%)	0.304
Vitamin D (%)	99 (54.5%)	55 (61.8%)	0.248
Calcitonin	12 (6.6%)	9 (10.1%)	0.309
Bisphosphonates (%)	80 (44.0%)	40 (44.9%)	0.878
Hypertension (%)	65(35.7%)	40 (44.9%)	0.143
Hyperlipidemic (%)	78 (42.9%)	36 (40.4%)	0.706
DM (%)	70 (38.5%)	37 (41.6%)	0.623

Notes: Continuous data were reported as mean ± standard deviation or median (25th and 75th quartile), and categorical data were expressed as frequencies (percentages). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHR, neutrophil to high-density lipoprotein cholesterol ratio; FBG, fasting blood glucose; UA, uric acid; Cr, creatinine; ALP, alkaline phosphatase; Ca, calcium; P, phosphorus; β-CTX, β-isomerized carboxy-telopeptide of type I collagen; Osc, Osteocalcin; PINP, amino-terminal propeptide of type I collagen; PTH, parathyroid hormone; 25-(OH) Vit D, 25-hydroxyvitamin D; LS, lumbar spine; FN, Femur neck; FRAX score, Fracture Risk Assessment Tool score for hip fracture; BMD, bone mineral density; DM, type 2 diabetes mellitus

Table 2 Correlation of NHR levels with clinical variables in osteoporotic patients

Variables	*r*	*P*
Total LS BMD (T-score)	-0.015	0.800
Total FN BMD (T-score)	0.050	0.410
ALP	0.222	**< 0.001**
Ca	-0.106	0.082
P	-0.060	0.323
β-CTX	-0.014	0.814
Osc	-0.152	**0.012**
PINP	-0.063	0.302
PTH	-0.032	0.594
25-(OH) Vit D	-0.253	**< 0.001**
fragility fracture	0.310	**< 0.001**

Abbreviations: NHR, neutrophil to high-density lipoprotein cholesterol ratio; BMD, bone mineral density; ALP, alkaline phosphatase; Ca, calcium; P, phosphorus; β-CTX, β-isomerized carboxy-telopeptide of type I collagen; Osc, Osteocalcin; PINP, amino-terminal propeptide of type I collagen; PTH, parathyroid hormone; 25-(OH) Vit D, 25-hydroxyvitamin D; LS, lumbar spine; FN, Femur neck

NHR levels was observed between patients with vs. without fragility fracture ($r = 0.310$; $P < 0.001$). Particularly, NHR levels were significantly negatively associated with osteocalcin (r = -0.152; $P = 0.012$) and 25-(OH) Vit D (r = -0.253; $P < 0.001$), while a positive associated with ALP ($r = 0.222$; $P < 0.001$) were noted.

Additive value of NHR in the detection of fragility fracture

The discriminatory ability of NHR to identify patients with fragility fractures was assessed. According to Youden's Index, the optimal cut-off value of NHR levels for diagnosing fragility fracture was 2.42. The AUC of NHR for predicting the risk of fragility fracture prevalence was calculated as 0.681 (95% CI: 0.611–0.751, $P < 0.001$). The AUC for FRAX score was 0.763 (95% CI: 0.705–0.821, $P < 0.001$). However, there was no difference between the AUC of NHR and the AUC of FRAX score ($P = 0.089$). Furthermore, combining the two ratios resulted in an AUC of 0.805 (95% CI: 0.752–0.857, $P < 0.001$), suggesting that the combination was a powerful marker for predicting fragility fracture (Fig. 2).

Multivariable logistic regression analysis of risk factors of fragility fracture

In order to further explore the underlying risk factors for fragility fracture, binomial logistic regression analysis was performed (Table 3). Univariable logistic regression analysis revealed that age, BMI, SBP, neutrophil counts, LDL-C, ALP, FRAX score, and NHR levels (all $P < 0.05$) were risk factors associated with fragility fracture. Higher NLR (per unit) as a continuous variable was independently associated with a greater risk of prevalent fragility fracture both in the univariable (OR: 1.898, 95% CI: 1.463–2.462; $P < 0.001$) and the multivariable logistic regression analysis (OR: 1.924, 95% CI: 1.443–2.564; $P < 0.001$) after

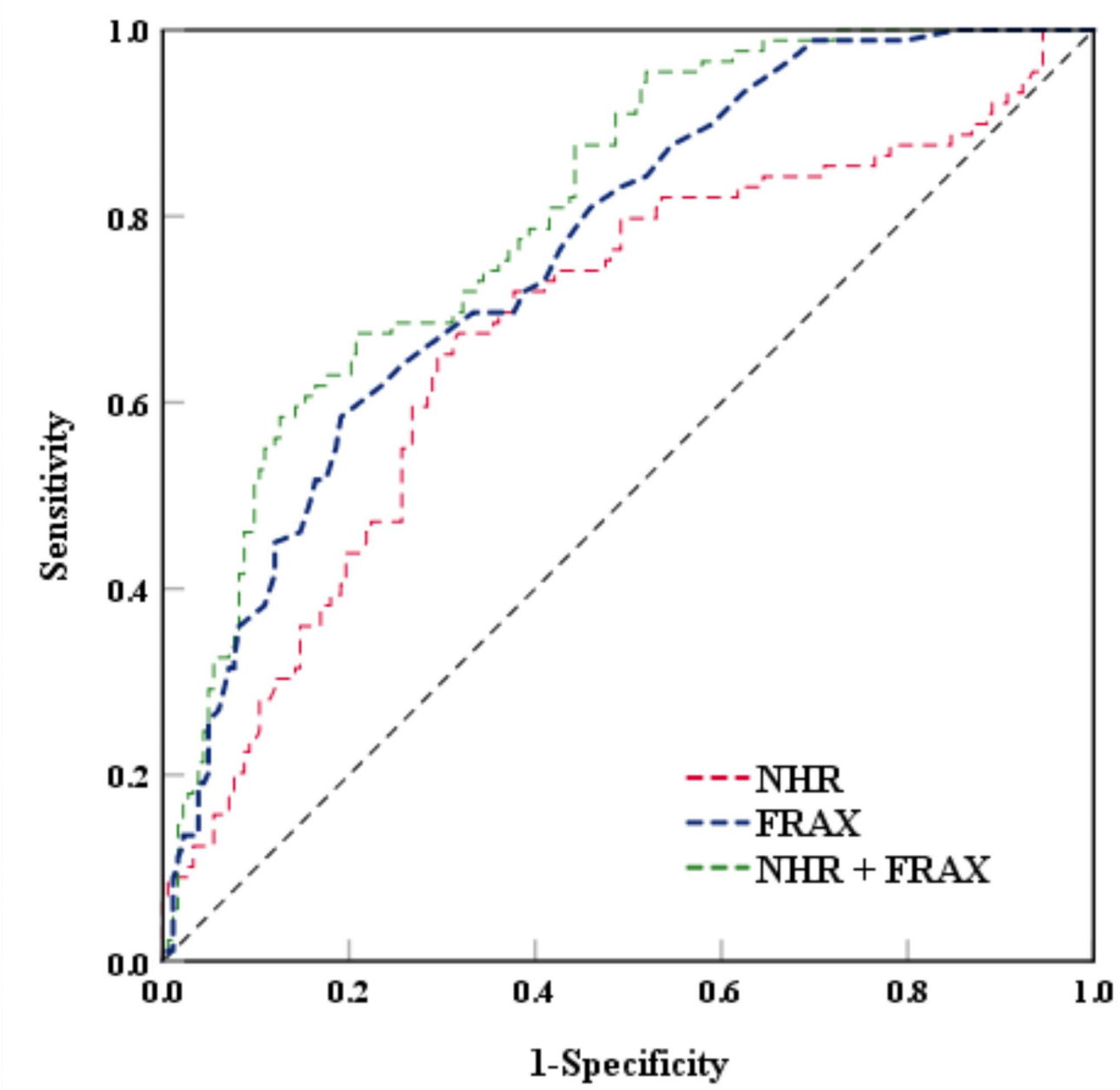

Fig. 2 Comparison of the ROC curves of NHR, FRAX score, and their combination for detecting the presence of fragility fracture

adjusting for ALP and FRAX score. Consequently, NHR was an independent predictor of fragility fracture.

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Discussion

The present retrospective study, conducted in osteoporotic patients, demonstrated a positive association between NHR level and risk of fragility fracture. Furthermore, NHR levels were found to be negatively correlated with osteocalcin and 25-(OH) Vit D levels, but not with BMD. As was expected, we also found that levels of NLR were significantly higher in patients with fragility fracture than in those without fragility fracture. Importantly, a high level of NHR was an independent and additive risk factor for fragility fracture even after adjustment for FRAX score. This study appears to be novel to report a relationship between NHR and fragility fracture, suggesting that NHR may improve the predictive capacity of current fracture risk assessment tools.

Previous studies have reported that chronic inflammation is associated with osteoporosis and fractures [26, 27]. Over the past decade, a growing body of studies has paid more attention to the linkage between novel inflammatory markers and fragility fracture [10–12]. The NHR

Table 3 Logistic regression analysis for risk factors associated with fragility fracture

Variables	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.046 (1.013–1.079)	0.005	——	0.361
BMI (kg/m^2)	1.107 (1.017–1.205)	0.019	——	0.082
SBP (mmHg)	1.021 (1.005–1.036)	0.007	——	0.249
Neutrophil (×10^9/L)	1.756 (1.367–2.256)	< 0.001	——	0.187
LDL-C (mmo/L)	0.734 (0.553–0.973)	0.032	——	0.828
ALP (IU/L)	1.017 (1.004–1.029)	0.009	1.018 (1.004–1.032)	**0.012**
FRAX score	6.250 (3.157–12.375)	< 0.001	8.618 (4.075–18.225)	**< 0.001**
NHR	1.898 (1.463–2.462)	< 0.001	1.924 (1.443–2.564)	**< 0.001**

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; LDL-C, low-density lipoprotein cholesterol; ALP, alkaline phosphatase; FRAX score, Fracture Risk Assessment Tool score for hip fracture; NHR, neutrophil to high-density lipoprotein cholesterol ratio

is a relatively emerging marker to reflect systemic inflammation and is found valuable for predicting the outcomes of many diseases [28–30]. Nevertheless, whether NHR could also help to determine fragility fracture risk has not been fully explored.

The possible role of neutrophils in bone resorption and remodeling was supported by several basic sciences and even clinical data. Present studies revealed that activated neutrophils up-regulate the expression of RANKL resulting in osteoporosis through activation of osteoclasts [20, 28]. On the other hand, neutrophils could affect fracture healing outcomes [29]. Noteworthily, we found that patients with fragility fractures exhibited higher levels of neutrophils. Nowadays, much less is known about the pathophysiological links between HDL-C level and fragility fracture. However, the reported associations between HDL-C levels and fragility fracture are controversial [21, 30–31]. A recent meta-analysis including 11 studies (seven prospective, three cross-sectional, and one case-control study) indicated that decreased levels of HDL-C were associated with an increased risk of fragility fracture. Similarly, we also observed that patients with fragility fractures were associated with lower HDL-C levels. Therefore, we speculated that the elevated NHR attributed to both the increased neutrophils and decreased HDL-C levels may be possible to aid the fragility fracture risk stratification in osteoporotic patients.

At present, FRAX is widely used in fracture risk estimate. Given this scenario, the results of this study showed that FRAX score in patients with fragility fracture was apparently higher than in patients without fragility fracture. More than that, the present study further identified that the combination of NHR and FRAX score was a stronger predictive performance for fragility fracture. If confirmed in larger series, our results could suggest integrating FRAX algorithm with NHR in osteoporotic patients.

Limitations

Inevitably, the interpretation of this study also had some potential limitations which should be noted. First, this study was retrospective. A causal relationship between NHR levels and the risk of fragility fracture could not be clearly elucidated due to its case-control design. Second, approximately three-quarters of patients were excluded. The number of our target patients was still not abundant. Moreover, all subjects were recruited from the same geographic region. Therefore, the findings must be interpreted with caution taking into account these selection biases. To confirm the validity of our results, further multicenter and prospective studies with larger sample sizes should be performed. Third, unfortunately, we could not identify the exact period lapsed from fracture to measurement. Its analyses were dependent on the baseline measurements of NHR at admission instead of serial measurements. Lastly, residual confounding variables might still exist, for instance, other inflammatory cytokines, or physical activity levels. In addition, the results of this study should not be over-generalized, since high external validity is not likely with just one study. However, our preliminary study is intriguing for clinics in this field.

Conclusions

Our findings newly demonstrated that a higher NHR was associated with the presence of fragility fracture. In this light, osteoporotic patients with a high level of NHR should be aware of the potential risk of fragility fracture. Because NHR is economical and easily measurable, in future clinical practice, it could be easily performed in fragility fracture screening and prevention. However, owing to the inherent limitations of this study, additional large-scale studies are required to confirm our results.

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Author contributions
Liman Wang designed the study, performed the data analyses, and wrote the manuscript. Liman Wang, Dan Xu, and Meijiao Chen undertook data collection. Liman Wang prepared Figs. 1 and 2; Tables 1, 2 and 3. Liman Wang and Dan Xu provided funding supports. Xuhui Huang supervised the study and critically revised the manuscript. All authors approved the final manuscript.

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Data availability
Our study only collected the clinical data of patients and did not interfere with the treatment plan of patients. The datasets related to this study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles of Helsinki Declaration. The study approval was obtained from the Ethics Committee of Fujian Provincial Hospital (K2022-01-010).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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