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Association between fibrinogen-to-albumin ratio and bone metabolism markers (β-CTX and P1NP) in Chinese individuals with osteoporotic fracture: a cross-sectional investigation

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Abstract

Objective Research on the link between inflammatory indicators and markers of bone metabolism is currently lacking, especially the interaction between Procollagen type 1 N-terminal propeptide (P1NP), the β-C-terminal telopeptide of type 1 collagen (β-CTX), and the fibrinogen-to-albumin ratio (FAR). This study intends to fill that knowledge gap by investigating the possible link between inflammatory indicators and bone metabolism.

Methods This observational study included 718 individuals diagnosed with osteoporotic fractures from Kunshan Hospital Affiliated to Jiangsu University between January 2017 and July 2022. After accounting for several confounders, the independent connection between FAR levels and β-CTX and P1NP was investigated via Generalized Estimating Equations (GEE). On top of that, we used a generalized additive model (GAM) to find any non-linear correlations, and a two-piecewise linear regression model to find the threshold effects in the smoothing curves that came out of it. To ensure the aforementioned result was stable, a subgroup analysis was carried out.

Results The results showed a positive linear correlation between FAR and β-CTX [β = 1.077, 95% confidence interval (CI): 0.24 to 1.92, $P = 0.012$]. The study's findings demonstrated that FAR and P1NP fit curves in an inverted U-shaped pattern, and an inflection point $K = 0.0685$ for FAR was detected. P1NP showed a positive correlation with FAR below the inflection point (β = 306.10, 95% CI: 47.37 to 564.83, $P = 0.021$), and a negative correlation with FAR beyond the inflection point (β = -117.57, 95% CI: -231.34 to -3.80, $P = 0.043$). The subgroup analysis revealed that women had a more significant association between FAR and β-CTX in women than in men.

Conclusions The results provide useful insights into the potential association between FAR and markers of bone metabolism. The study may provide a novel clinical implication by introducing FAR as a potential reference indicator for assessing bone health, offering a cost-effective and conveniently obtainable biomarker to monitor inflammation to improve bone metabolism in the treatment of osteoporosis.

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Keywords Procollagen type 1 N-terminal propeptide (P1NP), Osteoporotic fracture, Fibrinogen-to-albumin ratio (FAR), Inflammatory markers, Bone metabolism markers, β-C-terminal telopeptide of type 1 collagen (β-CTX)

Introduction

Osteoporosis is a prevalent skeletal condition characterized by reduced bone density and degradation of bone structure, resulting in a heightened susceptibility to fractures [1–3]. A recent cross-sectional study conducted on Chinese individuals found that OP prevalence was 5.0% in men aged 40 years and above, while it was 20.6% in women [4]. For bones to remain healthy, the ratio of bone creation to resorption must be balanced [5–7].

To measure bone turnover, researchers rely on biochemical indicators of bone metabolism. In recent years, studying bone metabolism and how it relates to other biomarkers has grown in importance for understanding bone-related disorders including osteoporosis [8]. The biomarkers Procollagen type 1 N-terminal propeptide (P1NP) and β-C-terminal telopeptide of type 1 collagen (β-CTX) are particularly linked to bone metabolism and serve as respective indicators of the extents to which bone formation and bone resorption are occurring [9, 10]. Serum PINP and β-CTX have been suggested as reference bone turnover markers (BTMs) by the International Federation of Clinical Chemistry (IFCC) and the International Osteoporosis Foundation (IOF) [10]. P1NP indicates the activity of osteoblasts, a sign of bone production, while β-CTX, an indicator of bone resorption, reflects the activity of osteoclasts [11]. The equilibrium between bone resorption and formation may be inferred from the levels of β-CTX and P1NP, which in turn represent the overall condition of bone metabolism.

Inflammation is known to have tangible impacts on bone metabolism [12, 13]. Fibrinogen-to-albumin ratio (FAR) is a new type of inflammatory indicator, which has the advantages of being cost-effective, simple, and practical [14]. Evidence shows that FAR is a critical determinant in nutrition, coagulation, and inflammation [15], and it was shown to be positively associated with inflammation [14].

Currently, there are limited investigations on inflammatory and bone metabolism markers [16], and the relationships between FAR and β-CTX and P1NP are even less studied. Therefore, this study attempts to provide insights into the potential association between inflammatory and bone metabolism markers. We hope to provide clinicians with new assessment markers linked to bone health by shedding light on the significance of FAR in bone metabolism and its associations with β-CTX and P1NP, providing more helpful information for evaluating bone health.

Methods

Study subjects

This study collected a cohort of 3558 patients who were diagnosed with osteoporotic fractures and required inpatient surgical treatment at Kunshan Hospital Affiliated to Jiangsu University between January 2017 and July 2022. Patients were excluded if they had missing data for β-CTX or P1NP, if they had missing FAR data, if they had acute infection or were diagnosed with infectious disease [17], or if they were diagnosed with malignant lymphoma [18]. From this criteria, 718 patients were selected and included in the study. The current study received ethical approval from the Institutional Review Board of Affiliated Kunshan Hospital of Jiangsu University (Approval No. 2020-03-046-K01), and was compliant with the Declaration of Helsinki. The researchers examining the data were not provided with patient identifiable data. This investigation was conducted as an observational study, with all patients giving written informed consent and their data being anonymized.

Measurements of relevant variables

An observational study design was used to ascertain the levels of fibrinogen and albumin in patients and to apply their ratio, i.e., FAR, as the independent variable. The dependent variables were β-CTX and P1NP, respectively. Fibrinogen level was determined using the automated coagulation analyzer CN-6000, while albumin level was evaluated using the Beckman AU5800 biochemical analyzer pipeline. FAR was calculated by dividing the fibrinogen and albumin levels for each patient. Automated electrochemiluminescence immunoassay (ECLIA) from Roche Diagnostics in Mannheim, Germany was used to assess β-CTX and P1NP in patients with osteoporotic fracture. The patients' age, sex, and body mass index (BMI; overweight: 24–27.9 kg/m^2, obese: ≥ 28 kg/m^2 based on a meta-analysis conducted by the Working Group on Obesity in China [19]) were assessed and documented. The patients' calcium levels were determined using the arsenic azo III method, and their magnesium levels were determined using the xylidyl blue method with the Beckman AU5800 biochemical analyzer pipeline. The patients' activated partial thromboplastin time (APTT) levels were measured using the coagulation method with the automatic coagulation analyzer CN-6000. Hemoglobin and platelet levels were measured using the Sysmex XN-10 (B4) hematology analyzer pipeline. Lastly, patients' serum creatinine levels were

measured using the sarcosine oxidase method with the Beckman AU5800 biochemical analyzer pipeline. All the measurements were obtained from fasting blood samples acquired within 24 h after admission. The samples were collected using identical equipment and by a skilled operator following established protocols.

Covariate analyses

Based on our clinical work experience, relevant studies [14, 18, 20], and clinical guidelines [21], as well as the data available in our database, we select the following variables as covariates for our study: age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin and platelet.

Statistical analyses

The demographic, laboratory, and clinical data were reported as medians (with 25th and 75th percentiles) or means with standard deviations (SDs). Categorical data were provided as frequencies (percentages). For categorical data-based univariate analysis, Fisher's exact tests or Pearson's chi-square tests were used. For continuous data, independent sample t-tests and Mann-Whitney U tests were used when the data were non-normally distributed and regularly distributed, respectively. In addition, univariate analyses were conducted to investigate the associations between patient features of osteoporotic fractures and β-CTX and P1NP levels.

The study used Generalized Estimating Equations (GEE) to investigate the independent association between FAR levels and β-CTX and P1NP in osteoporotic fracture patients, while appropriately controlling for confounders. The models constructed consisted of unadjusted (Model 1), partially adjusted (Model 2), and completely adjusted (Model 3) models. Initially, the variance inflation factor (VIF) was used to identify the presence of co-linearity in the covariance. Subsequently, judgments were taken to correct for these variables based on certain criteria: (1) a significant change in the matched odds ratio (OR) of at least 10% was seen when covariates were included in or excluded from the base or complete models, and (2) covariates either satisfied criteria 1 or demonstrated a P less than 0.1 in the univariate model [22]. Model 2 and Model 3 were built using Criterion 1 and Criterion 2, respectively, for adjusting covariates. Ultimately, three models were created, as outlined below: Model 1 was not adjusted; Model 2 (minimally adjusted model) was adjusted to account for BMI, gender, and age. Model 3 was adjusted to account for age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet.

A generalized additive model (GAM) was employed to identify probable non-linear correlations. A two-piecewise linear regression model was employed to find threshold effects for the generated smoothing curves where such associations were apparent. The inflection point of these curves was automatically calculated using a recursive technique based on a maximum likelihood model, namely when a clear ratio was seen [23]. The studies' robustness and variability among patient subgroups were assessed by conducting subgroup analyses after stratifying patients based on specific variables. Subgroup interactions and modifications were analyzed using the likelihood ratio test (LRT).

The R packages from The R Foundation (www.R-project.org) and EmpowerStats from X&Y Solutions, Inc, MA, USA (www.empowerstats.com) were used for all statistical analyses. A $P < 0.05$ was considered to be statistically significant for a two-sided test.

Results

Patients characteristics

Based on our inclusion/exclusion criteria, a total of 718 hospitalized osteoporotic fracture patients from January 2017 to July 2022 were included in this study (Fig. 1), and the characteristics of these patients are presented in Table 1. Patients included 31.93% males and 68.07% females, with an average age of 68.63 ± 11.27 years, average β-CTX of 0.52 ± 0.25 ng/mL, average P1NP of 55.66 ± 24.87 ng/mL, and average FAR of 0.077 ± 0.0219. Patients were stratified into FAR quartiles (Q1: < 0.06, Q2: 0.06–0.07, Q3: 0.07–0.09, and Q4: 0.09–0.12), and interquartile differences in β-CTX, P1NP, BMI, calcium, magnesium, platelet, lymphocyte, hemoglobin, creatinine, APTT, age, and gender were evident. Particularly, osteoporotic fracture cases with more elevated FAR had higher β-CTX (Q1: 0.47 ± 0.23 ng/mL; Q2: 0.50 ± 0.25 ng/mL; Q3: 0.54 ± 0.27 ng/mL; and Q4: 0.54 ± 0.23 ng/mL), whereas osteoporotic fracture patients with intermediate FAR quartiles had higher P1NP (Q1: 53.38 ± 22.99 ng/mL; Q2: 57.10 ± 26.31 ng/mL; Q3: 56.61 ± 22.62 ng/mL; and Q4: 52.74 ± 21.59 ng/mL).

Factors correlated with β-CTX and P1NP based on univariate analysis

A strong correlation was found in the univariate analysis between β-CTX and P1NP, as well as many other factors such as FAR, BMI, calcium, magnesium, platelet count, lymphocyte count, hemoglobin creatinine, gender, APTT, and age (Table 2).

Explorations of the associations between FAR level and β-CTX and P1NP levels

Three models were applied to examine the associations between FAR and β-CTX and P1NP in individuals with osteoporotic fractures (Table 3). The unadjusted model, i.e., Model 1, showed a statistically significant association

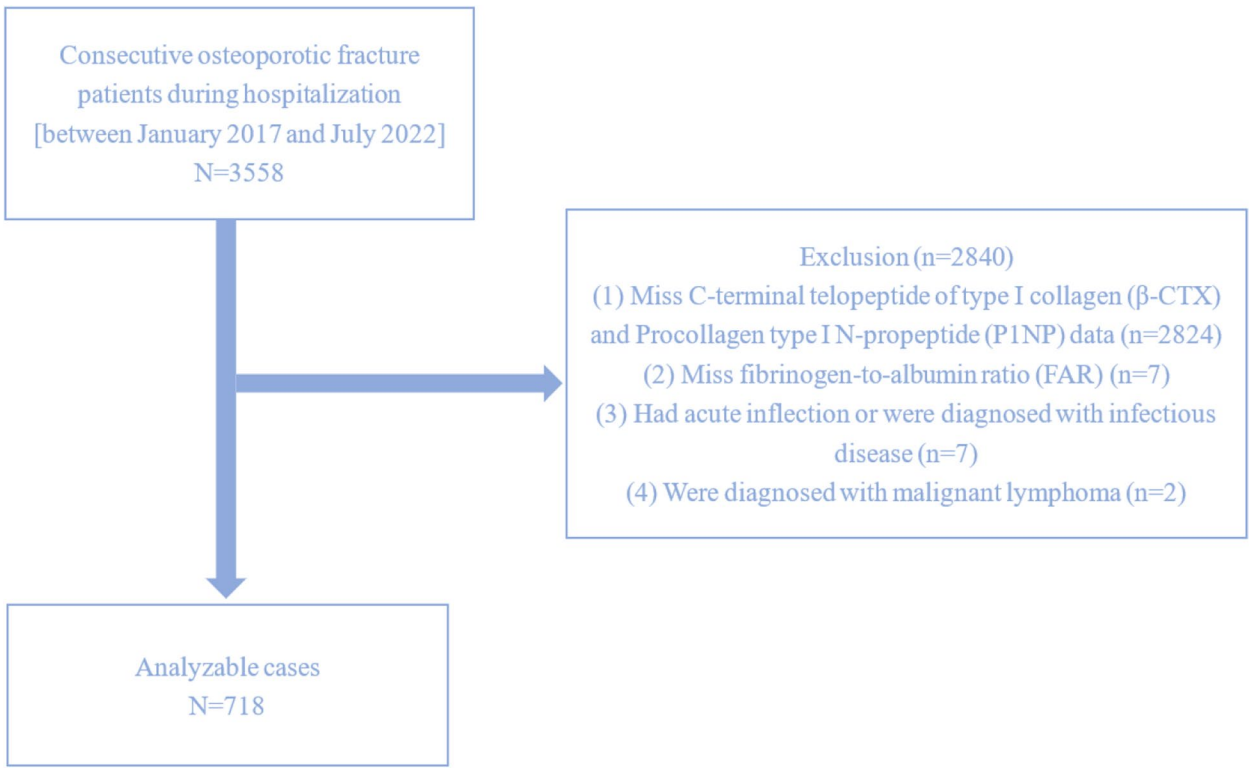

Fig. 1 Study flow chart

Table 1 Patient characteristics based on FAR quartiles

FAR quartile	Total	Q1 (< 0.06)	Q2 (0.06–0.07)	Q3 (0.07–0.09)	Q4 (0.09–0.12)	*P*-value
N	718	180	179	179	180	
β-CTX, ng/mL	0.51 ± 0.24	0.47 ± 0.23	0.50 ± 0.25	0.54 ± 0.27	0.54 ± 0.23	0.011
P1NP, ng/mL	54.95 ± 23.47	53.38 ± 22.99	57.10 ± 26.31	56.61 ± 22.62	52.74 ± 21.59	0.188
BMI, kg/m^2	23.01 ± 3.38	22.70 ± 3.37	23.09 ± 3.66	23.29 ± 3.37	22.96 ± 3.12	0.409
Calcium, mmol/L	2.22 ± 0.12	2.24 ± 0.13	2.22 ± 0.12	2.22 ± 0.12	2.22 ± 0.12	0.440
Magnesium, mmol/L	0.91 ± 0.09	0.90 ± 0.10	0.90 ± 0.09	0.90 ± 0.08	0.93 ± 0.10	0.007
Platelet, ×10^9/L	175.73 ± 59.11	167.65 ± 51.88	169.90 ± 58.38	178.55 ± 56.85	186.80 ± 66.88	0.008
Hemoglobin, g/L	128.32 ± 15.70	129.81 ± 16.75	128.11 ± 16.16	128.92 ± 15.43	126.46 ± 14.30	0.216
Creatinine, μmol/L	62.06 ± 18.67	60.12 ± 16.46	62.60 ± 17.92	59.91 ± 16.15	65.62 ± 22.91	0.011
APTT, s	28.45 ± 3.66	28.21 ± 3.78	28.66 ± 3.83	28.15 ± 3.26	28.80 ± 3.73	0.239
Age, y	68.65 ± 11.31	68.83 ± 11.05	68.69 ± 11.40	68.64 ± 11.11	68.46 ± 11.76	0.992
Gender	N (%)					0.386
Male	473 (65.88%)	127 (70.56%)	116 (64.80%)	111 (62.01%)	119 (66.11%)	
Female	245 (34.12%)	53 (29.44%)	63 (35.20%)	68 (37.99%)	61 (33.89%)	

Abbreviations: *P1NP* procollagen type 1 N-terminal propeptide, *FAR* fibrinogen-to-albumin ratio, *β-CTX* β-C-terminal telopeptide of type 1 collagen, *BMI* body mass index, *APTT* activated partial thromboplastin time

between FAR and β-CTX [β = 1.29, 95% confidence interval (CI): 0.48 to 2.10, $P = 0.002$]. However, no significant association with P1NP as detected ($P = 0.916$). After controlling for age, gender, and BMI, Model 2 revealed a comparable association between FAR and β-CTX (β = 1.30, 95% CI: 0.49 to 2.12, $P = 0.002$), whereas no significant association was observed with P1NP. After controlling for age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet, Model 3 also revealed a statistically significant association

Table 2 Univariate analyses of factors associated with β-CTX and P1NP

	Mean ± SD/*N* (%)	β-CTX β[a] (95% CI) *P*	P1NP β[b] (95% CI) *P*
FAR	0.0764 ± 0.0219	1.2921 (0.4806, 2.1037) 0.001877	4.2425 (−74.2068, 82.6918) 0.915615
β-CTX, ng/mL	0.5126 ± 0.2444	---	57.1173 (51.4641, 62.7705) < 0.000001
P1NP, ng/mL	54.9513 ± 23.4690	0.0062 (0.0056, 0.0068) < 0.000001	---
BMI, kg/m^2	23.0085 ± 3.3824	0.0012 (−0.0041, 0.0065) 0.653979	−0.0627 (−0.5709, 0.4455) 0.809028
Calcium, mmol/L	2.2231 ± 0.1217	0.1251 (−0.0218, 0.2720) 0.095450	14.4403 (0.3508, 28.5297) 0.044933
Magnesium, mmol/L	0.9063 ± 0.0944	0.0800 (−0.1096, 0.2696) 0.408635	4.4299 (−13.7820, 22.6417) 0.633684
Platelet, ×10^9/L	175.7286 ± 59.1140	0.0004 (0.0001, 0.0007) 0.010878	0.0301 (0.0011, 0.0591) 0.042446
Hemoglobin, g/L	128.3248 ± 15.7036	−0.0011 (−0.0022, 0.0001) 0.070034	−0.1088 (−0.2180, 0.0004) 0.051219
Creatinine, μmol/L	62.0627 ± 18.6696	0.0000 (−0.0009, 0.0010) 0.980699	−0.0712 (−0.1631, 0.0207) 0.129541
Gender			
Male	473 (65.8774%)	Reference	Reference
Female	245 (34.1226%)	−0.0069 (−0.0447, 0.0308) 0.719058	−1.0474 (−4.6699, 2.5750) 0.571070
APTT, s	28.4529 ± 3.6630	0.0017 (−0.0032, 0.0065) 0.507413	0.3040 (−0.1648, 0.7728) 0.204105
Age, y	68.6532 ± 11.3108	0.0006 (−0.0010, 0.0022) 0.460313	0.0440 (−0.1079, 0.1960) 0.570441

Abbreviations: *CI* confidence interval, *P1NP* procollagen type 1 N-terminal propeptide, *FAR* fibrinogen-to-albumin ratio, *β-CTX* β-C-terminal telopeptide of type 1 collagen, *BMI* body mass index, *APTT* activated partial thromboplastin time

[a] Dependent variable is β-CTX

[b] Dependent variable is P1NP

Table 3 Associations between FAR and β-CTX and P1NP in different models based on GEE

	Model 1[a] (*N* = 718) β (95%CI) *P*	Model 1[b] (*N* = 718) β (95%CI) *P*	Model 1[c] (*N* = 718) β (95%CI) *P*
β-CTX	1.29 (0.48, 2.10) 0.002	1.30 (0.49, 2.12) 0.002	1.08 (0.24, 1.92) 0.012
P1NP	4.24 (−74.21, 82.69) 0.916	5.22 (−73.41, 83.85) 0.897	−13.34 (−94.33, 67.66) 0.747

Abbreviations: *GEE* generalized estimating equations, *CI* confidence interval, *P1NP* procollagen type 1 N-terminal propeptide, *FAR* fibrinogen-to-albumin ratio, *β-CTX* β-C-terminal telopeptide of type 1 collagen, *BMI* body mass index, *APTT* activated partial thromboplastin time

[a] No adjustment for confounders

[b] Adjusted for age, gender, and BMI

[c] Adjusted for age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet

between FAR and β-CTX (β = 1.08, 95% CI: 0.24 to 1.92, $P = 0.012$), with no significant association observed with P1NP.

To validate the strength and reliability of Model 3 (i.e., completely adjusted model), additional subgroup analyses were performed. These analyses involved categorizing osteoporotic fracture patients into different strata based on factors such as age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet levels. In these analyses, the remaining covariates that were not used as the stratification variable were adjuste. We detected interactions between different strata when gender was applied as the stratification variable. Further, similar patterns of associations were revealed across different strata when each of the other factors were applied as the stratification variable, such that no significant interactions were detected between different strata for these variables (all $P > 0.05$, Supplementary Table S1). According to the results of the subgroup analyses, the associations between FAR and β-CTX differed in men and women after accounting for age, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet levels.

Spline smoothing plots and threshold analyses

Based on GAM, graphical methods were applied to depict the β-CTX-FAR and P1NP-FAR relationships for the 718 osteoporotic fracture patients to evaluate the linearity or non-linearity of the associations between FAR and β-CTX and P1NP, respectively (Fig. 2). Following that, a threshold effect analysis was performed by with adjustments for age, gender, BMI, creatinine, magnesium, calcium, APTT, hemoglobin, and platelet (Table 4).

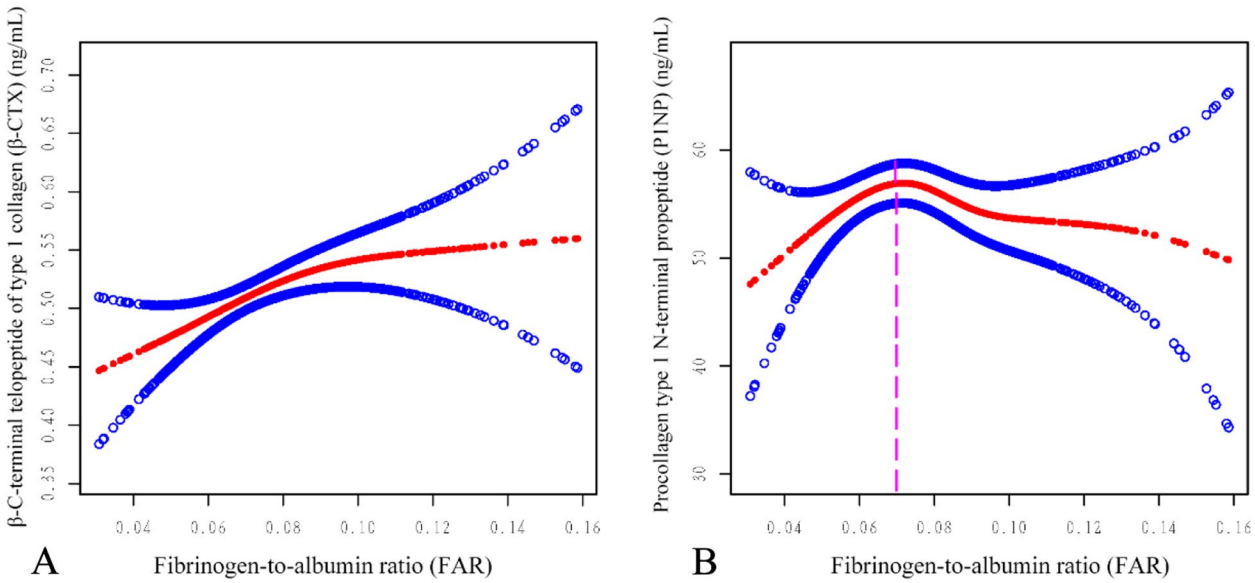

Fig. 2 The associations of FAR with (**A**) β-CTX and (**B**) P1NP based on adjusted smoothing curve fitting. The GAM analyses revealed a linear association between FAR and β-CTX, and a non-linear association between FAR and P1NP with a threshold effect, respectively among individuals with osteoporotic fractures. The top and bottom curves depict the span of the 95% confidence interval, whereas the middle curves show the associations between FAR and β-CTX and P1NP, respectively. age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet count were adjusted in this model. In (**B**), the middle curve showed an inflection point $K = 0.0685$ (vertical dashed line). Abbreviations: GAM, generalized additive model; P1NP, procollagen type 1 N-terminal propeptide; FAR, fibrinogen-to-albumin ratio; β-CTX, β-C-terminal telopeptide of type 1 collagen; BMI, body mass index; APTT, activated partial thromboplastin time

A linear relationship was found between FAR and β-CTX. As shown in Table 3, controlling for age, gender, BMI, creatinine, magnesium, calcium, APTT, hemoglobin, and platelet count revealed an adjusted β (i.e., effect size) of 1.08 (95% CI: 0.24 to 1.92, *P*-value = 0.012).

An inverted U-shaped pattern was revealed between FAR and P1NP, indicating a threshold effect based on smoothing curve fitting. A piecewise linear regression model was applied to detect an FAR inflection point $K = 0.0685$. By contrast, the effect size, 95% CI, and *P* value on the right side of this inflection point were −117.57, −231.34 to −3.80, and 0.043, respectively (Table 4).

Table 4 Threshold analyses examining the relationships between FAR and β-CTX and P1NP based on GEE

	Model 3[a]	
	β-CTX β (95% CI) *P*	**P1NP β (95% CI) *P***
Model A[b]		
One straight line's slope	1.08 (0.24, 1.92) 0.012	−13.34 (−94.33, 67.66) 0.747
Model B[c]		
FAR inflection point (K)	0.088	0.0685
< K (Slope 1)	2.17 (0.75, 3.59) 0.003	306.10 (47.37, 564.83) 0.021
> K (Slope 2)	−0.45 (−2.25, 1.36) 0.627	−117.57 (−231.34, −3.80) 0.043
Slope 2–Slope 1	−2.62 (−5.36, 0.12) 0.062	−423.67 (−749.71, −97.62) 0.011
β-CTX or P1NP value at K, ng/mL	0.55 (0.52, 0.58)	57.60 (54.74, 60.46)
LRT *P*[d]	0.081	0.015

Abbreviations: *GEE* generalized estimating equations, *CI* confidence interval, *P1NP* procollagen type 1 N-terminal propeptide, *FAR* fibrinogen-to-albumin ratio, *β-CTX* β-C-terminal telopeptide of type 1 collagen, *BMI* body mass index, *APTT* activated partial thromboplastin time, *LRT* likelihood ratio test

[a] Adjusted for age, gender, BMI, creatinine, calcium, magnesium, APTT, hemoglobin, and platelet

[b] Linear analysis, $P < 0.05$ indicates a straight line's relationship

[c] Non-linear analysis

[d] $P < 0.05$ means Model B is significantly different from Model A, which indicates a non-linear relationship

Discussion

An imbalance between bone resorption and bone formation is one of essential characteristics of osteoporosis [24], which is affecting a huge number of individuals in China [25]. This research examined 718 osteoporotic fracture patients, which aimed at determining whether there are significant relationships between the new inflammatory biomarker FAR [26] and the BTMs β-CTX and P1NP [11]. To explore the relationships between an inflammatory marker and bone metabolism markers, we measure the level of the readily available and inexpensive biomarker FAR in cohort of osteoporotic fracture patients. A significant linear association between FAR and β-CTX was demonstrated in this study. However, a non-linear association between FAR and P1NP was revealed. Smoothing curve fitting revealed an inverted U-shaped pattern in this relationship, which detected an FAR inflection point $K=0.0685$. To the left of this inflection point, there was a positive relationship between P1NP and FAR, while there was a negative relationship to the right of this inflection point. According to subgroup analyses, women exhibited a more substantial relationship between FAR and β-CTX than men. For the remaining variables applied as the stratification variables, similar patterns of associations were detected between different strata, and no statistically significant interactions were detected cross strata (all $P>0.05$).

In brief, when FAR exceeds the threshold, i.e., the inflection point $K=0.0685$, there is a decoupling between the changing trends of β-CTX and P1NP with a rising FAR [27, 28]. Specifically, for individuals with FAR values greater than the inflection point, there is an increasing trend in β-CTX level and a decreasing trend of P1NP level when FAR increases. In addition, the subgroup analysis by using gender as the stratification variable revealed a significant difference in the association between FAR and β-CTX between men and women, women exhibited a more pronounced effect size (β = 2.76, 95% CI: 1.29 to 4.24, $P<0.001$). β-CTX serves as an indicator of bone resorption [29]. Clinical research has shown that individuals with elevated levels of β-CTX are at a heightened risk of experiencing fractures and experiencing a faster rate of bone loss [30]. P1NP is a biomarker of bone formation [31] that reflects the level of osteogenesis activity [11]. FAR is a systemic inflammatory biomarker that measures the ratio of fibrinogen to albumin [26]. A previous study has shown that FAR is correlated with traditional inflammatory biomarkers, confirming that higher FAR levels indicate a more severe inflammatory response [14]. Our study indicates that a high inflammatory state stimulates the breakdown of bone tissue and hinders osteogenesis. Results obtained from subgroup analysis based on gender reveal that inflammation has a greater impact on osteolysis in women with osteoporotic fractures.

Prior research has shown that persistent inflammation plays a significant role in the progression of osteoporosis [32]. Other studies have shown that inflammation hinders the creation of new bone and encourages bone resorption [33–36]. Furthermore, various local and systemic processes related to this phenomenon have previously been clarified [37]. In particular, inflammation is recognized for generating pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1, and interleukin-6 [38]. These cytokines may be generated by various cell types, stimulating several other cell groups via distinct signal transduction pathways. And they can enhance osteoclast activity and suppress osteoblast function [39]. By contrast, our investigation used a unique, economical, and readily available biomarker, FAR [40]. which is a measurement obtained from regular biochemistry and coagulation function testing [41]. Fibrinogen serves as a biomarker for systemic inflammation in the acute phase and plays a vital role in the inflammatory process [42] by stimulating the production of proinflammatory cytokines in the peripheral blood inflammatory environment [43, 44]. Albumin, on the other hand, is a commonly used clinical parameter in blood tests [45]. Systemic inflammation leads to a decrease in albumin levels, irrespective of nutrient intake [46]. Prior research have examined FAR as a possible prognostic indicator for several types of cancer [15, 42, 47], but none have explored its association with biomarkers of bone metabolism.

The findings of this investigation might have a major clinical significance. As our findings indicate, clinicians can first evaluate the inflammatory status of patients aided with the results of routine biochemistry and coagulation function tests to calculate FAR and estimate bone metabolism status in these patients when required to adopt the best management strategies. Moreover, reducing inflammation can help mitigate bone mass loss and decrease the risk of bone metabolism-related disorders [48], our study highlights the importance to monitor inflammatory indicators when treating osteoporosis. According to our findings, clinicians are encouraged to at least ensure that the patient's FAR is less than the threshold of FAR, i.e., $K=0.0685$, to achieve a good level of bone metabolism to diminish bone loss.

The strengths of our study include a nationally representative population and applications of statistical models adjusting for various important confounders. This study has particularly focused on a novel inflammatory indicator, FAR, which is computed based on the measurements of two affordable and easily available biomarkers, i.e., fibrinogen and albumin [49, 50]. Further, the present study is the first Chinese investigation to assess

the relationships between the inflammatory indicator FAR and bone metabolism markers in patients with osteoporotic fracture.

However, this study has limitations. First, due to its cross-sectional design, it was challenging to determine the temporal relationship between FAR and the onset of osteoporotic fracture. Second, our study population includes patients with osteoporotic fracture only, and whether the current findings are applicable to the general population needs further exploration. Furthermore, although we have carefully considered and adjusted for many potential confounding factors, the influence of unknown confounding factors on the measurements cannot be completely ruled out. Subsequently, this calls for more extensive research in the future, involving more detailed investigation.

Conclusions

Our study revealed a linear positive association between FAR and β-CTX, and an inverted U-shaped relationship between FAR and P1NP in patients with osteoporotic fractures. These findings indicate that as inflammation worsened, there was a steady rise in bone resorption. Additionally, bone formation initially rose when FAR increased, but when FAR reached an inflection point $K=0.0685$, it declined as FAR further incremented. Further subgroup analyses revealed that the association between FAR and β-CTX had a greater impact in women than in men. These results have proposed the usage of FAR as a promising inflammatory indicator for assessing bone health in clinical applications. This would give a cost-effective and readily available biomarker to monitor inflammation and enhance bone metabolism in the treatment of osteoporosis. Nevertheless, it is essential to do more comprehensive investigations involving bigger groups of patients to authenticate these findings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08276-w.

Supplementary Material 1.

Supplementary Material 2.

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None.

Authors' contributions
Li-long Feng was responsible for data curation, formal analysis, investigation, project administration, validation, and original draft writing. Ke Lu was involved in data curation, investigation, and writing – review & editing. Chong Li was responsible for data curation and funding acquisition. Min-zhe Xu, Yao-wei Ye, Yi Yin, and Hui-qiang Shan were involved in project administration and writing review and editing.

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Data availability
Data is provided within the manuscript or supplementary information files, and we have de-identified the research data.

Declarations

Ethics approval and consent to participate
The current study received ethical approval from the Institutional Review Board of Affiliated Kunshan Hospital of Jiangsu University (Approval No. 2020-03-046-K01) and was compliant with the Declaration of Helsinki. All participants included in the study provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Ichikawa S, Koller DL, Padgett LR, Lai D, Hui SL, Peacock M, et al. Replication of previous genome-wide association studies of bone mineral density in premenopausal american women. J Bone Min Res. 2010;25:1821–9.
2. Abar O, Dharmar S, Tang SY. The effect of aminoguanidine (AG) and pyridoxamine (PM) on ageing human cortical bone. Bone Jt Res. 2018;7:105–10.
3. Li JY, Chassaing B, Tyagi AM, Vaccaro C, Luo T, Adams J, et al. Sex steroid deficiency–associated bone loss is microbiota dependent and prevented by probiotics. J Clin Invest. 2016;126:2049–63.
4. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, et al. Prevalence of osteoporosis and fracture in China: the China osteoporosis prevalence study. JAMA Netw Open. 2021;4:e2121106.
5. Jiang C, Ma Q, Wang S, Shen Y, Qin A, Fan S, et al. Oxymatrine attenuates osteoclastogenesis via modulation of ROS-Mediated SREBP2 signaling and counteracts Ovariectomy-Induced osteoporosis. Front Cell Dev Biol. 2021;9:684007.
6. Wilson C, Gossiel F, Leonard R, Anderson RA, Adamson DJA, Thomas G, et al. Goserelin, as an ovarian protector during (neo)adjuvant breast cancer chemotherapy, prevents long term altered bone turnover. J Bone Oncol. 2016;5:43–9.
7. Zakłos-Szyda M, Nowak A, Pietrzyk N, Podsędek A. Viburnum opulus L. juice phenolic compounds influence osteogenic differentiation in human osteosarcoma Saos-2 cells. Int J Mol Sci. 2020;21:4909.
8. Chen Y, Zhang W, Chen C, Wang Y, Wang N, Lu Y. Thyroid and bone turnover markers in type 2 diabetes: results from the METAL study. Endocr Connect. 2022;11:e210484.
9. Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2011;22:391–420.
10. Szulc P, Naylor K, Hoyle NR, Eastell R, Leary ET, National Bone Health Alliance Bone Turnover Marker Project. Use of CTX-I and PINP as bone

turnover markers: National Bone Health Alliance recommendations to standardize sample handling and patient preparation to reduce pre-analytical variability. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2017;28:2541–56.
11. Cho SW. New biological markers of bone metabolism in osteoporosis treatment. Endocrinol Metab. 2016;31:400–1.
12. Huang S, Xu L, Sun Y, Lin S, Gu W, Liu Y, et al. Systemic administration of allogeneic mesenchymal stem cells does not halt osteoporotic bone loss in ovariectomized rats. PLoS ONE. 2016;11:e0163131.
13. Mace ML, Gravesen E, Nordholm A, Egstrand S, Morevati M, Olgaard K, et al. The calcified vasculature in chronic kidney disease secretes factors that inhibit bone mineralization. JBMR Plus. 2022;6: e10610.
14. Ding Y, Xue L. The potential value of fibrinogen to albumin ratio (FAR) in the assessment of inflammation in spondyloarthritis. BMC Musculoskelet Disord. 2022;23:864.
15. Mai R-Y, Bai T, Luo X-L, Wu G-B. Preoperative fibrinogen-to-albumin ratio predicts the prognosis of patients with hepatocellular carcinoma subjected to hepatectomy. BMC Gastroenterol. 2022;22:261.
16. Cimaz R, Gattorno M, Sormani MP, Falcini F, Zulian F, Lepore L, et al. Changes in markers of bone turnover and inflammatory variables during alendronate therapy in pediatric patients with rheumatic diseases. J Rheumatol. 2002;29:1786–92.
17. Deng C, Zhang S, Ling J, Chen Z, Feng Y, Xie Y, et al. Prognostic value of the fibrinogen albumin ratio index (FARI) in nasopharyngeal carcinoma patients undergoing radiotherapy. Sci Rep. 2023;13:20630.
18. Wang X, Hu Y, Luan H, Luo C, Kamili K, Zheng T, et al. Predictive impact of fibrinogen-to-albumin ratio (FAR) for left ventricular dysfunction in acute coronary syndrome: a cross-sectional study. Eur J Med Res. 2023;28:68.
19. Zhou B-F, Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off points of body mass index and waist circumference in Chinese adults. Biomed Environ Sci BES. 2002;15:83–96.
20. Vasikaran S, Thambiah SC, Tan RZ, Loh TP. The use of bone-turnover markers in Asia-Pacific populations. Ann Lab Med. 2024;44:126–34.
21. Watts NB, Camacho PM, Lewiecki EM, Petak SM, AACE/ACE Postmenopausal Osteoporosis Guidelines Task Force. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal Osteoporosis-2020 Update. Endocr Pract off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2021;27:379–80.
22. Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med. 2000;343:1826–32.
23. Liu S, Wang X, Lu Y, Li T, Gong Z, Sheng T, et al. The effects of intraoperative cryoprecipitate transfusion on acute renal failure following orthotropic liver transplantation. Hepatol Int. 2013;7:901–9.
24. Aibar-Almazán A, Voltes-Martínez A, Castellote-Caballero Y, Afanador-Restrepo DF, Carcelén-Fraile M, del López-Ruiz C. Current status of the diagnosis and management of osteoporosis. Int J Mol Sci. 2022;23:9465.
25. Wang Y, Tao Y, Hyman ME, Li J, Chen Y. Osteoporosis in China. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2009;20:1651–62.
26. Fang L, Yan F-H, Liu C, Chen J, Wang D, Zhang C-H, et al. Systemic inflammatory biomarkers, especially fibrinogen to albumin ratio, predict prognosis in patients with pancreatic cancer. Cancer Res Treat off J Korean Cancer Assoc. 2021;53:131–9.
27. Hou J, He C, He W, Yang M, Luo X, Li C. Obesity and bone health: a complex link. Front Cell Dev Biol. 2020;8: 600181.
28. Zheng Y, Li J, Wu J, Yu Y, Yao W, Zhou M, et al. Tetrahydroxystilbene glucoside isolated from polygonum multiflorum Thunb. Demonstrates osteoblast differentiation promoting activity. Exp Ther Med. 2017;14:2845–52.
29. Liu Z, Liu H, Li Y, Wang Y, Xing R, Mi F, et al. Adiponectin inhibits the differentiation and maturation of osteoclasts via the mTOR pathway in multiple myeloma. Int J Mol Med. 2020;45:1112–20.
30. Eastell R, Vrijens B, Cahall DL, Ringe JD, Garnero P, Watts NB. Bone turnover markers and bone mineral density response with risedronate therapy: relationship with fracture risk and patient adherence. J Bone Min Res. 2011;26:1662–9.
31. Ho RC, Chua AN, Husain SF, Tan W, Hao F, Vu GT, et al. Premenopausal Singaporean women suffering from major depressive disorder treated with selective serotonin reuptake inhibitors had similar bone mineral density as compared with healthy controls. Diagnostics. 2022;12: 96.
32. Jiang N, An J, Yang K, Liu J, Guan C, Ma C, et al. NLRP3 inflammasome: a new target for prevention and control of osteoporosis? Front Endocrinol. 2021;12: 752546.
33. Tanaka Y, Nakayamada S, Okada Y. Osteoblasts and osteoclasts in bone remodeling and inflammation. Curr Drug Target Inflamm Allergy. 2005;4:325–8.
34. Boyce BE, Li P, Yao Z, Zhang Q, Badell IR, Schwarz EM, et al. TNFα and pathologic bone resorption. Keio J Med. 2005;54:127–31.
35. Hardy R, Cooper MS. Bone loss in inflammatory disorders. J Endocrinol. 2009;201:309–20.
36. Epsley S, Tadros S, Farid A, Kargilis D, Mehta S, Rajapakse CS. The effect of inflammation on bone. Front Physiol. 2021;11: 511799.
37. Adamopoulos IE. Inflammation in bone physiology and pathology. Curr Opin Rheumatol. 2018;30:59–64.
38. Yan J, Yang S, Han L, Ba X, Shen P, Lin W, et al. Dyslipidemia in rheumatoid arthritis: the possible mechanisms. Front Immunol. 2023;14: 1254753.
39. Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. Nat Rev Drug Discov. 2012;11:234–50.
40. Ma K, Li J, Shen G, Zheng D, Xuan Y, Lu Y, et al. Development and validation of a risk nomogram model for predicting contrast-Induced Acute kidney Injury in patients with Non-ST-Elevation acute coronary syndrome undergoing primary percutaneous coronary intervention. Clin Interv Aging. 2022;17:65–77.
41. Ren H, Liu W, Niu A, Zhao X. Fibrinogen to albumin ratio, a novel serum indicator for evaluating the severity of preeclampsia: a single-center retrospective study. Med (Baltim). 2023;102:e33419.
42. Tan Z, Zhang M, Han Q, Wen J, Luo K, Lin P, et al. A novel blood tool of cancer prognosis in esophageal squamous cell carcinoma: the Fibrinogen/Albumin ratio. J Cancer. 2017;8:1025–9.
43. Jensen T, Kierulf P, Sandset PM, Klingenberg O, Joø GB, Godal HC, et al. Fibrinogen and fibrin induce synthesis of proinflammatory cytokines from isolated peripheral blood mononuclear cells. Thromb Haemost. 2007;97:822–9.
44. Yakovlev S, Zhang L, Ugarova T, Medved L. Interaction of fibrin(ogen) with leukocyte receptor alpha M beta 2 (Mac-1): further characterization and identification of a novel binding region within the central domain of the fibrinogen gamma-module. Biochemistry. 2005;44:617–26.
45. Tang X, Cao Y, Liu J, Wang S, Yang Y, Du P. Diagnostic value of inflammatory factors in pathology of bladder cancer patients. Front Mol Biosci. 2020;7:575483.
46. Almasaudi AS, Dolan RD, Edwards CA, McMillan DC. Hypoalbuminemia reflects nutritional risk, body composition and systemic inflammation and is independently associated with Survival in patients with colorectal Cancer. Cancers. 2020;12:1986.
47. Sun H, Ma J, Lu J, Yao Z-H, Ran H-L, Zhou H, et al. Fibrinogen-to-albumin ratio predicts overall survival of hepatocellular carcinoma. World J Gastrointest Oncol. 2023;15:1662–72.
48. Liu J, Zhao L, Yang X, Liu C, Kong N, Yu Y, et al. Bone mineral density, bone metabolism-related factors, and microRNA-218 are correlated with disease activities in Chinese ankylosing spondylitis patients. J Clin Lab Anal. 2022;36:e24223.
49. Bekos C, Grimm C, Brodowicz T, Petru E, Hefler L, Reimer D, et al. Prognostic role of plasma fibrinogen in patients with uterine leiomyosarcoma – a multicenter study. Sci Rep. 2017;7:14474.
50. Agarwal C, Bansal K, Pujani M, Singh K, Chauhan V, Rana D, et al. Association of coagulation profile with microvascular complications and glycemic control in type 2 diabetes mellitus – a study at a tertiary care center in Delhi. Hematol Transfus Cell Ther. 2019;41:31–6.

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