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Elevated levels of β C-terminal telopeptide of type 1 collagen and N-terminal mid-fragment of osteocalcin in patients with non-traumatic osteonecrosis of the femoral head

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Abstract

Objective To investigate the role of serum β C-terminal telopeptide of type 1 collagen (β-CTx) and N-terminal mid-fragment of osteocalcin (N-MID) concentration in non-traumatic osteonecrosis of the femoral head (NONFH).

Materials and methods In this retrospective case-control study, serum β-CTx and N-MID levels were measured in 64 NONFH patients and 64 healthy controls. Propensity score matching (PSM) was used to balance the baseline characteristics of the two groups. The study was conducted at Linyi People's Hospital between January 2023 and February 2024. The primary outcomes included the differences in serum β-CTx and N-MID levels between the two groups, their correlations with clinical parameters, and their diagnostic performance for NONFH.

Results The serum concentration of β-CTx and N-MID was significantly higher in NONFH patients compared to healthy controls (β-CTx: 0.70 ± 0.30 ng/ml vs. 0.36 ± 0.16 ng/ml, $P < 0.001$; N-MID: 21.35 ± 8.24 ng/ml vs. 13.27 ± 3.87 ng/ml, $P < 0.001$). No significant differences were observed in serum β-CTx and N-MID levels among different etiological subgroups or ARCO stages. Pearson analysis revealed a positive correlation between serum β-CTx and N-MID levels, as well as β-CTx and pain duration. The ROC curve analysis showed that β-CTx had an AUC of 0.876 (95% CI 0.815–0.938) with a cut-off value of 0.505 ng/ml, sensitivity of 90.63%, and specificity of 76.56%. N-MID had an AUC of 0.860 (95% CI 0.797–0.924) with a cut-off value of 17.050 ng/ml, sensitivity of 84.38%, and specificity of 78.13%.

Conclusion Serum β-CTx and N-MID levels are significantly elevated in patients with NONFH and may serve as potential biomarkers for the diagnosis of NONFH. Further studies with larger sample sizes are needed to validate these findings and explore their clinical applications.

Keywords Non-traumatic osteonecrosis of the femoral head, Bone turnover, Biomarker, β C-terminal telopeptide of type 1 collagen, N-terminal mid-fragment of osteocalcin

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Introduction

Non-traumatic osteonecrosis of the femoral head (NONFH) is a noteworthy hip joint disease and incurs major healthcare expenditure. It is characterized by bone ischemia and osteocyte necrosis, which ultimately leads to femoral head collapse and osteoarthritis [1, 2]. NONFH affects up to 20 million people and its prevalence is increasing worldwide [3]. It is commonly observed in adults at a productive age with chronic alcohol assumption or long-term corticosteroid use, as well as other less common risk factors [4, 5]. The condition often results in hip pain and progressive loss of joint function, with total hip arthroplasty (THA) being a common treatment in advanced cases [6]. In the United States, it represents the leading cause of THA. Approximately 65–70% of patients with advanced NONFH require THA [7]. Clinical presentation of NONFH is generally asymptomatic in early stages, although occasionally patients could indicate hip or groin pain. Moreover, negative plain radiographs are common at initial stages of NONFH. Thus, a more rapid and precise diagnosis are critical to prevent the progression of NONFH.

Human bone is a continuously remodeled tissue, with approximately 10% of adult bone undergoing remodeling each year [8]. During this process, the activity of osteoblasts and osteoclasts results in the release of bone turnover markers into the circulation. Bone turnover markers are classified into two subtypes: bone formation and bone resorption markers [9]. β-C-terminal telopeptide of type 1 collagen (β-CTx) is a bone resorption marker, while N-MID is a bone formation marker. The measurement of circulating biomarkers may have the potential to detect NONFH in its early or even initial stage, which may be more cost-effective and reproducible than existing methods [10]. It has been reported that both β-CTx and N-MID have the potential to be utilized in clinical practice [11]. Despite these findings, no studies have investigated the synchronous role of β-CTx and N-MID in patients with NONFH.

The present study aimed to analyze the expression, clinical significance, and the synchronous role of β-CTx and N-MID in NONFH, which may help to further clarify the mechanism the NONFH, and contribute to the early detection and diagnosis of NONFH.

Materials and methods

Study design

In this retrospective case-control study, clinical data were collected from 89 patients diagnosed with non-traumatic osteonecrosis of the femoral head (NONFH) who were hospitalized at Linyi People's Hospital between January 2023 and February 2024. The inclusion criteria were: (1) age ≥ 18 years, and (2) diagnosed with NONFH according to the guideline for clinical diagnosis and treatment of NONFH in adults (2022 version) [12]. The clinical data was collected, including age, gender, body mass index (BMI), comorbidities, Association Research Circulation Osseous (ARCO) stage, Harris Hip Score (HHS), Visual Analogue Scale (VAS), history of trauma or surgery, smoking status, alcohol consumption, corticosteroid use. Additionally, clinical data from 116 healthy individuals who underwent routine health examinations at our hospital during the same period (January 2023 to February 2024) were collected as candidate controls. Exclusion criteria for both groups were as follows: (1) history of hip or femur surgery or trauma, (2) history of malignancies, cardiovascular diseases, and diseases affecting bone metabolism (e.g., thyroid disorders, parathyroid disorders, diabetes mellitus, osteoporosis, or rheumatoid arthritis), (3) participation in other clinical trials within the last 3 months, (4) history of fracture within the past six months. Both groups underwent complete blood count tests, liver and kidney function assessments, coagulation profile analysis, and measurement of β-CTx and N-MID levels. This retrospective case-control study was approved by the Clinical Trial Ethics Committee of Linyi People's Hospital (Approval No. YX200032). The requirement for informed consent was waived due to the retrospective nature of the study.

Propensity score matching method

Propensity score matching (PSM) is a commonly used statistical method that is frequently employed to reduce selection bias and balance the baseline characteristics in retrospective study where randomization is not feasible [13, 14]. Covariates included in the matching process were age, gender, and BMI. In this study, PSM analysis was performed with the MatchIt package with the coarsened exact matching method in R software (version 4.2.1 for Windows). As a result, 64 NONFH and 64 healthy controls were successfully matched by the age, gender, and BMI.

Bone turnover markers measurements

Fasting blood samples were obtained from all NONFH patients and healthy controls at the time of initial diagnosis and routine health examinations, respectively. The blood samples were taken between 6:00 and 10:00 a.m., after overnight fasting for at least 8 h. Serum β-CTx and N-MID levels were measured by electrochemiluminescence immunoassay (ECLI) using a cobas e601 automated immunoassay system (Roche Co., Mannheim, Germany). Inter- and intra-assay coefficients of variation were < 3% and < 5%, respectively.

Radiological progression

The progression of radiographic changes in NONFH was assessed using the four-stage classification system

developed by the Association Research Circulation Osseous (ARCO) [15]. In stage I, the X-ray appears normal, but imaging techniques such as magnetic resonance imaging (MRI) or bone scans reveal abnormalities. Stage II involves X-ray abnormalities, including mild signs of osteosclerosis, localized osteoporosis, or cystic alterations in the femoral head, without any indication of subchondral fractures, fractures in the necrotic area, or femoral head flattening. Stage III is characterized by the presence of fractures in the subchondral or necrotic regions as seen on X-ray. Finally, stage IV shows radiographic evidence of osteoarthritis, including joint space narrowing, changes in the acetabulum, and/or joint destruction.

Pain duration, VAS and HHS

Pain duration was determined by inquiring of the patients "How long have you experienced your hip pain?" Time since onset was recorded in months as a continuous variable. VAS, which ranges from 0 to 10, was employed to assess the pain level in patients with NONFH, where 0 indicates no pain and 10 represents the most intense pain. VAS scores are commonly utilized to gauge pain severity across a variety of conditions, including NONFH. Additionally, the HHS was used to evaluate the symptomatic severity. The HHS is a composite scale with a maximum score of 100 points, where a higher score reflects better hip function and greater patient satisfaction.

Statistical analysis

Statistical software SPSS version 20.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7.0 (GraphPad software Inc., San Diego, CA, USA) were used for statistical analyses and plotting. The *Shapiro-Wilk* test was used to determine whether the variables were normally distributed. The normally distributed variables were expressed as mean ± standard deviation. The non-normally distributed variables were expressed as median (interquartile range). For normally distributed variables, the *t* test was used to compare data between two groups, and one-way analysis of variance (*ANOVA*) test was used for comparison among multiple groups. For non-normally distributed variables, the *Mann-Whitney U* test was used for evaluation between two groups. Frequency and percentage values were used for categorical variables. The *Fisher* exact chi-squared test was used for analysis of categorical variables. Receiver operating characteristic (ROC) curve was used to analyze the predictive value of β-CTx and N-MID levels in serum on NONFH. *Pearson's* correlation is a parametric test applicable for continuous variables, while *Spearman* test is a nonparametric used for analyzing the correlation. A *P*-value < 0.05 was considered statistically significant.

Table 1 Basic characters of NONFH patients and healthy individuals by PSM method

Items	NONFH group (*n* = 64)	Control group (*n* = 64)	*P*-value
Age (years)	52.36 ± 14.76	51.04 ± 10.37	0.562
Gender (n, %)			0.811
Male	54(84.36%)	53(82.81%)	
Female	10(15.64%)	11(17.19%)	
BMI (kg/m^2)	25.05 ± 3.40	25.53 ± 3.14	0.404
ARCO stage (n, %)		\	
Stage I	12(18.75%)	\	
Stage II	15(23.44%)	\	
Stage III	20(31.25%)	\	
Stage IV	17(26.56%)	\	
Etiology (n, %)		\	
steroids	14(21.88%)	\	
alcohol	27(42.18%)	\	
idiopathic	23(35.94%)	\	
Pain duration (months)	57.58 ± 47.23	\	
β-CTx (ng/ml)	0.70 ± 0.30	0.36 ± 0.16	**< 0.001**
N-MID (ng/ml)	21.35 ± 8.24	13.27 ± 3.87	**< 0.001**

Results

Participant characteristics

After PSM analysis, 64 NONFH patients and 64 healthy individuals were matched and included in this study. The basic characters of these 128 individuals are presented in Table 1. No differences were observed in age, gender, and BMI between NONFH patients and controls (all $P > 0.05$), indicating that the levels of β-CTx and N-MID are comparable in both groups.

Comparisons of serum β-CTx and N-MID levels

Both serum β-CTx and N-MID levels were significantly higher in NONFH patients than in control group (β-CTx: NONFH 0.70 ± 0.30 ng/ml vs. Control 0.36 ± 0.16 ng/ml, N-MID: NONFH 21.35 ± 8.24 ng/ml vs. Control 13.27 ± 3.87 ng/ml) (all $P < 0.01$). There were no statistically significant differences in serum β-CTx and N-MID levels among different etiological subgroups (β-CTx: steroids 0.81 ± 0.28 ng/ml, alcohol 0.66 ± 0.24 ng/ml, and idiopathic 0.72 ± 0.36 ng/ml, N-MID: steroids 17.90 ± 5.47 ng/ml, alcohol 21.38 ± 5.25 ng/ml, and idiopathic 22.08 ± 10.96 ng/ml). Also, no differences were observed among different ARCO stages (β-CTx: stage I 0.75 ± 0.43 ng/ml, stage II 0.78 ± 0.22 ng/ml, stage III 0.71 ± 0.36 ng/ml, and stage IV 0.60 ± 0.16 ng/ml, N-MID: stage I 19.58 ± 7.01 ng/ml, stage II 19.78 ± 5.10 ng/ml, stage III 24.47 ± 11.80 ng/ml, and stage IV 20.35 ± 5.25 ng/ml). (Fig. 1)

Correlation analysis of β-CTx and N-MID levels

Pearson analysis revealed a positive correlation between serum β-CTx levels and N-MID ($r = 0.512$, $P < 0.001$). No significant correlations were observed between β-CTx

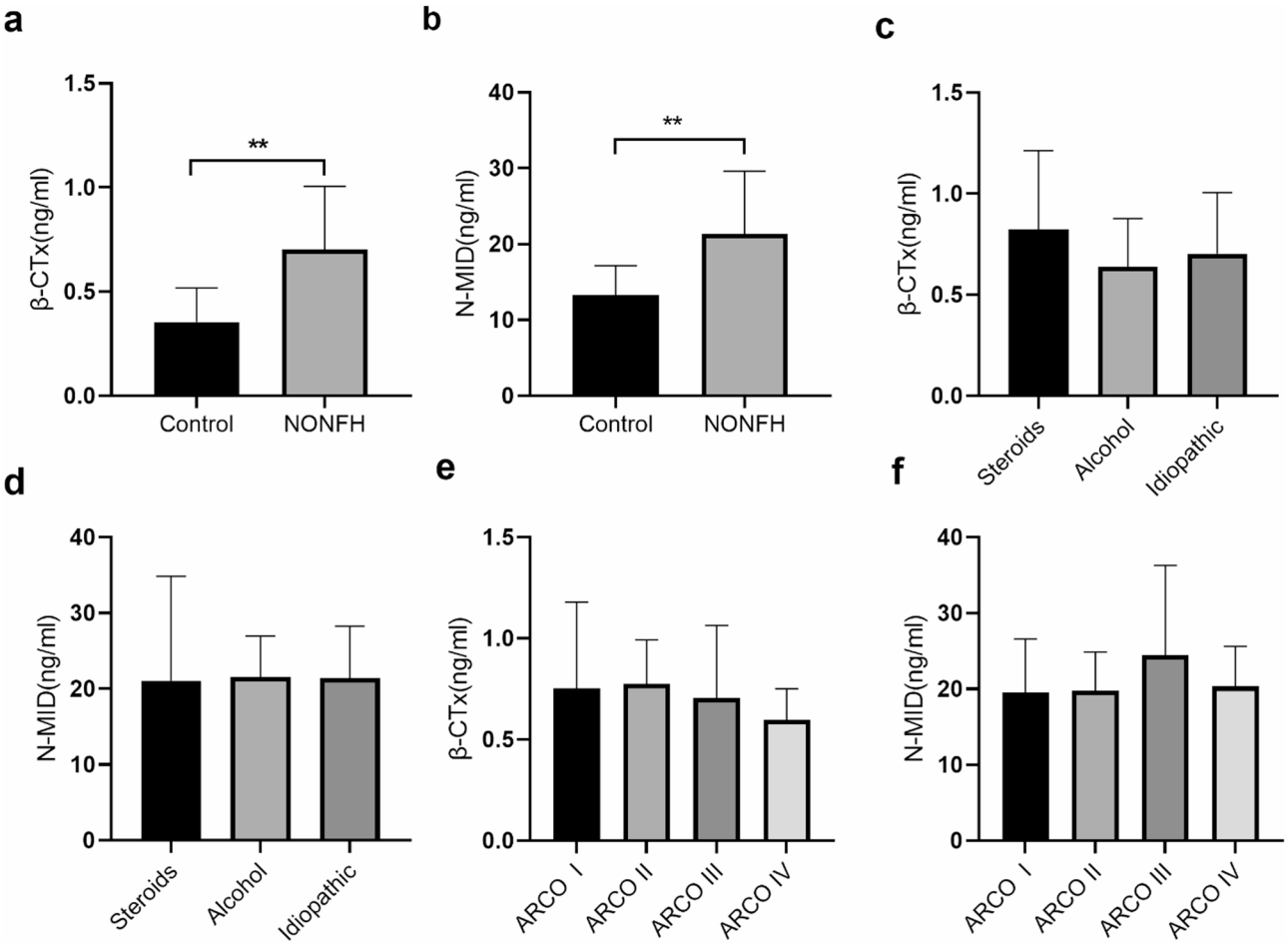

Fig. 1 Comparisons of serum β-CTx and N-MID levels in NONFH patients. ** $P < 0.01$

and HHS *(r*=-0.083, $P = 0.511$), nor between β-CTx and VAS *(r* = 0.086, $P = 0.498$). Likewise, N-MID was not correlated with HHS *(r*=-0.044, $P = 0.732$) or VAS *(r* = 0.126, $P = 0.320$). Additionally, neither β-CTx nor N-MID were correlated with ARCO stages *(*β-CTx: $r = 0.209$, $P = 0.096$, N-MID: $r = 0.084$, $P = 0.509$). Interestingly, β-CTx was significantly correlated with the duration of hip pain ($r = 0.661$, $P < 0.001$), however, nor was N-MID *(r* = 0.229, $P = 0.069$). (Fig. 2)

Diagnostic performances of β-CTx and N-MID for NONFH

To further explore the diagnostic value of β-CTx and N-MID levels for NONFH, the ROC curves were drawn. As to β-CTx, the area under the curve (AUC) for distinguishing NONFH patients and healthy subjects was 0.876 (95%*CI* 0.815–0.938) and the cut-off value was 0.505 ng/ml, with a sensitivity of 90.63% and a specificity of 76.56% (Fig. 3a). The ROC curve of N-MID level for identifying NONFH patients and healthy controls showed that the AUC was 0.860 (95%*CI* 0.797–0.924) and the cut-off value was 17.050 ng/ml, with a sensitivity of 84.38% and a specificity of 78.13% (Fig. 3b). The above results indicated that β-CTx and N-MID might be biomarkers for NONFH.

Discussion

In adulthood, bone remodeling, or turnover is a lifelong cycle of bone resorption by osteoclasts being followed by bone formation by osteoblasts [16]. The status of bone turnover can be reflected evaluated using a group of proteins and peptides called bone turnover markers. Currently, the pathogenesis and molecular mechanism of NONFH is complex and remains unclear. Recent studies suggest that the disturbance of bone turnover is associated with the pathogenesis of NONFH [17, 18]. However, limited data exist on the bone turnover markers in patients with NONFH. In this study, we have attempt to investigate serum levels of bone turnover markers β-CTx and N-MID in patients with NONFH. Our study revealed that serum levels of β-CTx and N-MID were noticeably higher in patients with NONFH than that of healthy controls.

β-CTx, as a crucial biomarker of bone resorption, is released into the circulation and can be measured in

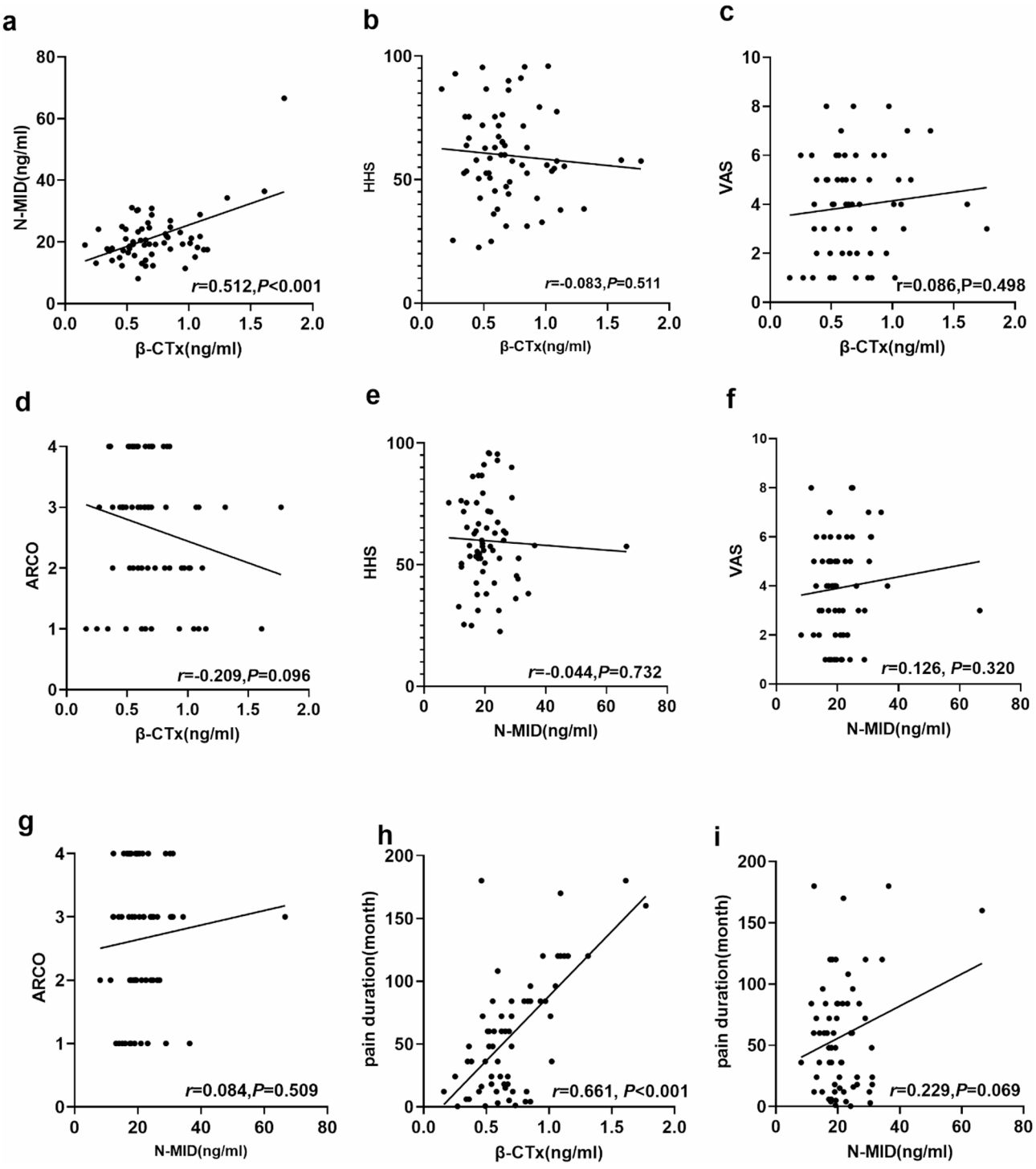

Fig. 2 Correlation analysis of β-CTx and N-MID levels in NONFH patients

serum or urine [11]. Similarly, N-MID is synthesized by osteoblasts and can be measured in the circulation as a biomarker of bone formation [19]. As far as we know, there have been no reports on the measurement of serum N-MID in NONFH patients so far. Our findings of increased serum β-CTx levels are consistent with previous studies. Shi et al. [20] reported that NONFH patients have higher serum concentrations of β-CTx in comparison to controls. All these findings indicate that the elevated levels of β-CTx and N-MID can reflect the high rate of bone remodeling in NONFH. The high remodeling rate in NONFH may be a consequence of

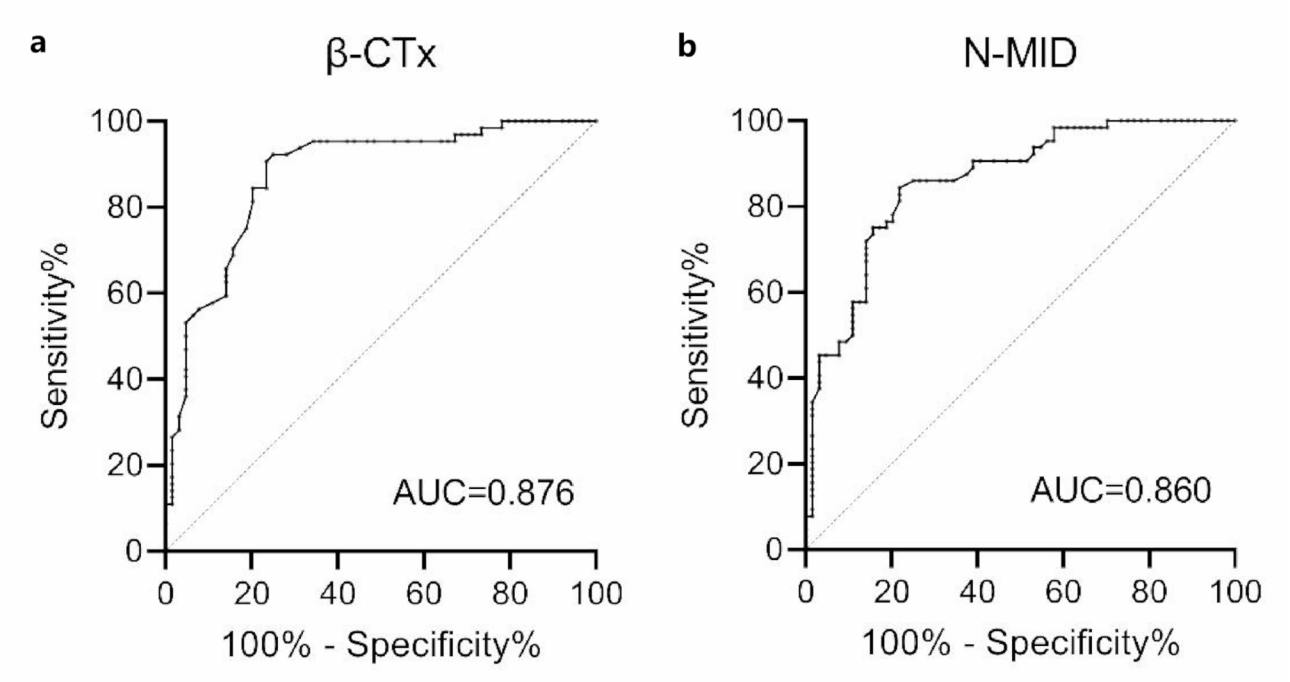

Fig. 3 Diagnostic values of serum β-CTx and N-MID levels for NONFH

the increased number and activitiy of osteoclasts as well as osteoblasts in necrotic and sclerotic regions of femoral head, respectively [21]. However, excessive activity of bone turnover eventually leads to femoral head collapse [22]. Moreover, the high rate of bone turnover was reported in other bone disorders, such as osteoarthritis [23], osteoporosis [24], and bone metastases [25, 26]. We also compared serum β-CTx and N-MID levels among different etiological subgroups without statistical significance. This suggests that increased bone turnover may be a common pathological feature of NONFH, regardless of the specific etiology.

The results of correlation analysis demonstrated that serum β-CTx levels were positively correlated with N-MID. We speculate that the higher rate of bone resorption may be followed by the more active process of bone formation. In addition, serum β-CTx and N-MID levels were not associated with clinical parameters such as HHS or VAS. Notably, our study highlighted an association between serum β-CTx levels and the duration of hip pain. In general, hip pain is the most frequently reported symptom of NONFH patients. Pain in the groin is the most common, followed by pain referred into the thigh and buttock [27]. Due to pain presented with joint motion or weight-bearing, patients generally reduce weight-bearing and activity to avoid pain. However, under the lack of load and mechanical stress stimulation, bone resorption process is accelerated. We speculate that the lack of mechanical stress stimulation on the bone may be the potential mechanism underlying the positive correlation between serum beta-CTx levels and pain duration. Furthermore, He et al. [28] reported that hip pain was a risk factor for femoral head collapse. These findings imply that pain relief is critical in the treatment of NONFH [6, 29].

Early detection of NONFH is critical for initiating appropriate treatment and preventing disease progression. Current diagnostic methods, such as radiography and MRI, have limitations in detecting early-stage NONFH. The use of serum biomarkers may provide a more sensitive and cost-effective approach for early diagnosis. ROC curve analysis demonstrated that both β-CTx and N-MID have significant diagnostic value for NONFH. The AUC values for β-CTx and N-MID were 0.876 and 0.860, respectively, indicating a good diagnostic performance. These results suggest that serum β-CTx and N-MID levels may serve as potential biomarkers for the diagnosis of NONFH.

This is the first study to investigate the synchronous role of β-CTx and N-MID in patients with NONFH. However, there are a number of potential limitations to this study. First, this was a single-center, retrospective study, so the results should be validated in multi-centers. Second, this study only provides a snapshot of the serum levels of β-CTx and N-MID at a single time point. Longitudinal studies are needed to assess the changes in these markers over time. Multi-center studies with more diverse patient populations are needed to validate our results.

Conclusion

In conclusion, serum β-CTx and N-MID levels are significantly elevated in patients with NONFH compared to healthy controls. Serum β-CTx and N-MID may serve as potential biomarkers for the diagnosis of NONFH.

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Author contributions
BXZ and SYW: clinical design; experiment work; and writing of the manuscript. QS: data analysis. ZQW: research design. ZF: clinical work, manuscript review, and project administration. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by Linyi People's Hospital Ethics Committee (No. YX200342).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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