Association between bone turnover markers and the risk of imminent recurrent osteoporotic fracture

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Abstract. The association between bone turnover markers (BTMs) and the risk of imminent recurrent osteoporotic fracture (ROF) in the elderly remains unclear. The present study thus aimed to explore BTMs in relation to imminent ROF in the elderly with an index OF. For this purpose, data from a prospective cohort study were used for analysis. Elderly patients hospitalized due to an index OF were included and followed-up. The BTMs included bone resorption marker (C-terminal telopeptide of type I collagen) and the bone formation markers, procollagen type I N propeptide, osteocalcin (OC) and total alkaline phosphatase. The outcome was the time to the first ROF following their index fracture. Cox regression analysis was used to assess the association between BTMs and ROF. Model discrimination was calculated to explore whether the BTMs had potential to improve fracture risk prediction. There were 169 eligible patients included in the analysis (median age, 72 years; 87.6% females). During a median follow-up period of 10.5 months, there were seven ROFs (4.1%) observed. Serum OC levels were found to be significantly associated with the risk of ROF [hazard ratio, 0.13; 95% confidence interval (CI) 0.018-0.90; P=0.039] for per-SD increase in OC from multivariable analysis. After incorporating OC into the model, a C-index of 0.83 (95% CI, 0.70-0.96; P<0.001) was observed, which outperformed the model with bone mineral density alone (improvement for C-index, 0.29; 95% CI, 0.028-0.55). On the whole, the present study demonstrates a significant association between serum OC and the decreased risk of imminent ROF in the elderly with index fractures. However, further high-quality evidence is required to further clarify and validate the BTMs in relation to the imminent risk of ROFs among the elderly.

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Introduction

Osteoporotic fracture (OF) is a major public health concern among the aging population worldwide. The risk of recurrent OF (ROF) is substantially high among the elderly; for instance, a previous study found that 26% of elderly community dwellers with an index OF (background OF at baseline) experienced a ROF during the 16-year follow-up period (1). Another study also reported that 15% of elderly post-menopausal women developed an imminent ROF within 2 years following an index OF (2). However, predicting ROF in the elderly, particularly their imminent ROF, remains suboptimal in clinical practice, which poses significant challenges to osteoporosis management and fracture prevention.

Bone turnover markers (BTMs) have been proposed for the risk prediction of OFs. For instance, the International Osteoporosis Foundation suggested the use of BTMs as a potential surrogate for OF risk prediction, independent of bone mineral density (BMD) (3). A recent meta-analysis also demonstrated significant associations between BTMs and future OF risk after adjusting for clinical risk factors and BMD (4). Nevertheless, evidence regarding the role of BTMs in the prediction of imminent ROFs is limited. Therefore, the present prospective cohort study aimed to assess the association between BTMs and risk of ROFs in the elderly who were hospitalized due to an index OF. Clarifying the association between BTMs and the risk of ROFs may help with enhanced risk prediction and management among the elderly with an index fracture.

Patients and methods

Study participants and setting. Details about the study procedures have been published in a previous study (5). In

brief, a cross-sectional study was conducted to explore sleep patterns in relation to BMD by enrolling elderly patients from the Department of Orthopedics in a general hospital in Zhuhai, China from February, 2020 to September, 2021. The consecutive sampling method was used for patient enrollment. Patients were included if they were ≥55 years of age and were hospitalized due to an index OF, where the index OF was defined as all fragility fractures apart from those on toes, the face and fingers. All the elderly patients were admitted to the hospital within 24 h after they developed the index OF. The data were collected through the hospital information system, laboratory measures and the face to face interviews with the research personnel. A total of 100 to 160 patients were estimated to satisfy the sample size requirement (5).

The present study was a post hoc exploratory study aiming to assess the BTMs in relation to imminent ROFs in the elderly. Therefore, follow-up was conducted from December, 2021 to January, 2022 to collect data on ROFs by contacting the participants via telephone calls and searching for their medical records. The Guangdong Second Provincial General Hospital Ethics Committee approved the study. All participants provided written informed consent prior to enrollment.

BTMs. Data on bone resorption marker [C-terminal telopeptide of type I collagen (CTX)] and bone formation markers [procollagen type I N propeptide (P1NP), osteocalcin (OC) and total alkaline phosphatase (TALP)] were collected. The selection of these BTMs was based on the recommendations on the use of BTMs in clinical studies from some consensus and position statements (3,6,7). Fasting blood samples were drawn from all patients on the day or the following morning when they were admitted to hospital and before they received any therapy. All the BTMs were measured using immunoassays on the Roche Cobas e411 analyzer (Roche Diagnostics), where the coefficients of variation (CVs) ranged from 3.4 to 5.7% for the BTM measures. The serum P1NP/CTX ratio was calculated by dividing the P1NP values by the CTX measurements.

Outcome. The outcome in the present study was the time to the first ROF after the index fracture. The index fracture was defined as the OF when the patients were hospitalized at baseline, while a recurrent fracture was defined as the OF that occurred during follow-up. By contacting the patients and searching their medical records, the present study documented whether they developed an imminent ROF, and if so, the time and type of their OF, and whether this fracture required hospitalization. Patients without an imminent ROF during follow-up were categorized into the control group.

Other independent variables. Patient data on sex, age, body mass index (BMI), smoking status and alcohol consumption were collected at baseline. Information on whether they had a prior OF in the previous 5 years, and whether they were administered any anti-osteoporotic drugs before they were hospitalized, was documented. Patient baseline BMD T-scores at lumbar spine L_1 - L_4 were measured using dual-energy X-ray absorptiometry (GE Prodigy, HyClone; Cytiva), where the T-scores were calculated based on the standards for Chinese individuals (8). The CV of spine BMD measures was 1.2%. Data on other independent variables, including circulating 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (PTH) and growth hormone (GH) were also obtained. 25(OH)D levels were measured using the colloidal gold immunochromatography assay with kits from Pro-Med Technology, Ltd. (cat. no. 20142400066). PTH levels were measured using enzyme linked immunosorbent assay (sandwich technique) with kits from Cusabio Technology LLC (cat. no. CSB-E06934h). GH levels were quantified using Siemens IMMULITE platforms (1000) with the standardized assay kits (Siemens Healthcare Diagnostics; cat. no. 20101402367). All the CVs for the three tests were <10%.

Statistical analysis. Frequency and percentage were used to describe categorical variables, and median and interquartile was used for continuous variables due to their violation of normality assumption (all P-values <0.05 from the Shapiro-Wilk test). The Mann-Whitney U test was used to compare whether there was a significant difference in BTMs between patients with and without a ROF during follow-up.

The Cox proportional hazards model was employed to evaluate the association between BTMs and the risk of ROFs, with hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for per-SD (standard deviation) increase in BTMs reported. The results are shown for both the univariate and multivariable models, in which the multivariable model was adjusted for BMD, age, sex and BMI. A global statistical test and a graphical assessment using Schoenfeld residuals were used to test the proportional hazards assumption in the Cox models. Moreover, a post-hoc sensitivity analysis was performed in the model by further adjusting for history of OF, using anti-osteoporotic drugs (bisphosphonates, selective estrogen receptor modulators, calcitonin, parathyroid hormone, calcium and/or vitamin D supplementation, and others), 25(OH)D, PTH and GH, to evaluate whether the results were similar to those from the main analysis.

As an exploratory analysis, the present study assessed whether the BTMs had potential for predicting the risk of an imminent ROF. The BTMs that had a significant association with the risk of OF were entered in the basic model to generate Harrell's C-index, where the basic model included age, sex, BMD and BMI. The C-index from the model with BTMs was also compared to the model only including BMD and the basic model, to examine whether the addition of BMTs can enhance the model discrimination (9). The model only including BMD (BMD-alone) was used as a reference.

All analyses were conducted using STATA Version 17 (StataCorp LLC) and SAS Version 9.4 (SAS Institute, Inc.) software. Unless otherwise specified, all the tests were two-sided and a value of P<0.05 was considered to indicate a statistically significant difference.

Results

A total of 169 eligible patients were enrolled and included in the analyses. They had a median age of 72 years and a median BMI of 22.2 kg/m^2. The majority of the patients were female (87.6%). A small proportion of patients were smokers or consumed alcohol. The median BMD T-score was -3.70

Table I. Description of patient characteristics.

Characteristics	Overall patients (n=169)	Patients with ROFs (n=7)	Patients without ROFs (n=162)
Age, median (Q1, Q3), years	72.0 (64.0, 80.0)	73.0 (72.0, 85.0)	71.0 (64.0, 80.0)
Female proportion, n (%)	148 (87.57)	5 (71.43)	143 (88.27)
BMI, median (Q1, Q3), kg/m^2	22.20 (19.50, 24.55)	20.90 (20.21, 23.33)	22.25 (19.20, 24.60)
Use of anti-osteoporotic medication prior to hospitalization, n (%)	26 (15.38)	1 (14.29)	25 (15.43)
History of osteoporotic fracture in the past 5 years, n (%)	71 (42.01)	5 (71.43)	66 (40.74)
Smoking status, n (%)	15 (8.88)	1 (14.29)	14 (8.64)
Alcohol consumption, n (%)	10 (5.92)	0	10 (6.17)
OC, median (Q1, Q3), ng/ml	15.33 (10.13, 20.57)	11.05 (4.41, 14.72)	15.92 (10.86, 20.65)
TALP, median (Q1, Q3), U/l	75.0 (61.0, 95.0)	85.0 (57.0, 96.0)	74.0 (61.0, 95.0)
P1NP, median (Q1, Q3), ng/ml	61.14 (43.44, 89.56)	41.64 (32.74, 70.45)	64.63 (44.70, 91.12)
CTX, median (Q1, Q3), ng/ml	0.54 (0.36, 0.75)	0.42 (0.29, 0.55)	0.55 (0.36, 0.77)
25(OH)D, median (Q1, Q3), ng/ml	23.12 (18.59, 29.72)	22.97 (18.63, 24.60)	23.23 (18.55, 30.30)
PTH, median (Q1, Q3), pg/ml	31.40 (23.21, 43.26)	31.11 (24.29, 44.63)	31.43 (22.76, 43.15)
GH, median (Q1, Q3), ng/ml	0.39 (0.15, 0.90)	0.38 (0.19, 0.91)	0.39 (0.14, 0.90)
BMD T-score, median (Q1, Q3)	-3.70 (-4.30, -2.60)	-3.70 (-4.10, -3.10)	-3.70 (-4.30, -2.60)

ROF, recurrent osteoporotic fracture; Q1, the first quartile; Q3, the third quartile; BMI, body mass index; OC, osteocalcin; TALP, total alkaline phosphatase; CTX, C-terminal telopeptide of type I collagen; P1NP, procollagen type I N propeptide; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; GH, growth hormone; BMD, bone mineral density.

(Q1 to Q3, -4.30 to -2.60). The median measures for OC were 15.33 ng/ml, 75.0 U/l for TALP, and 61.14 and 0.54 ng/ml for P1NP and CTX, respectively (Table I).

During a median follow-up of 10.5 months, there seven ROFs (4.1%) were observed. All the ROFs were vertebral fractures requiring hospital admission. The baseline characteristics of the patients with and without ROFs are presented in Table I. The comparisons of BTMs between the patients with and without ROFs are illustrated in Fig. 1. Patients with ROFs had lower levels of OC (11.05 vs. 15.92 ng/ml), P1NP (41.64 vs. 64.63 ng/ml), CTX (0.42 vs. 0.55 ng/ml) and P1NP/CTX ratio (111.5 vs. 116.6) compared with the controls; however only the difference in OC levels was significant (P=0.035). By contrast, patients with ROFs had a non-significantly higher TALP level when compared with the controls (85.0 vs. 74.0 U/l; P=0.69). The results of the association between BTMs and the risk of recurrent fracture are presented in Table II. OC was found to be significantly associated with the risk of ROFs (HR, 0.13; 95% CI, 0.018-0.90; P=0.039) for per-SD increase in OC from multivariable analysis. There was no significant association between the other BTMs and the risk of ROFs, while a marginally significant association was observed for P1NP (HR, 0.19; 95% CI, 0.034-1.04; P=0.056 for per-SD change in P1NP). Similar results were found from the univariate and sensitivity analyses.

The results from the exploratory analyses for model discriminatory performance after taking BTMs into account are presented in Table III. The BMD-alone model had a C-index of 0.54, while the basic model yielded a C-index of 0.75. After incorporating OC into the basic model, a C-index of 0.83 (95% CI, 0.70-0.96; P<0.001) was found. This discrimination from the model of OC plus basic model was observed to significantly outperform the BMD-alone model, with an improvement for C-index of 0.29 (95% CI, 0.028-0.55; P=0.030) found.

Discussion

In the present prospective cohort study, the association between BTMs and the risk of imminent ROFs in the elderly hospitalized with an index fracture was investigated. It was found that the per-SD increase in the OC measure was significantly associated with an 87% lower risk of developing ROFs. Exploratory analysis results revealed that incorporating OC into the prediction enhanced the predictive accuracy of recurrent fracture risk when compared with the BMD-alone model.

BTMs have been reported to directly influence some important elements in the development of OFs, including BMD, bone matrix, macro-architecture and micro-architecture (10,11). BTMs reflect the bone turnover process more rapidly than BMD; therefore, they are increasingly used for the assessment of patient responses to treatment (3,12,13). Some observational studies have also revealed an association between baseline BTMs and the risk of index OFs in community dwellers (14-19), with inconclusive results reported. For instance, while BTMs were found to be significantly associated with OFs in elderly women (14,17), a non-significant association was observed in other research on the elderly (19). It has been argued that the use of BTMs as predictors of OFs may be sensitive to be included in a fracture prediction model,

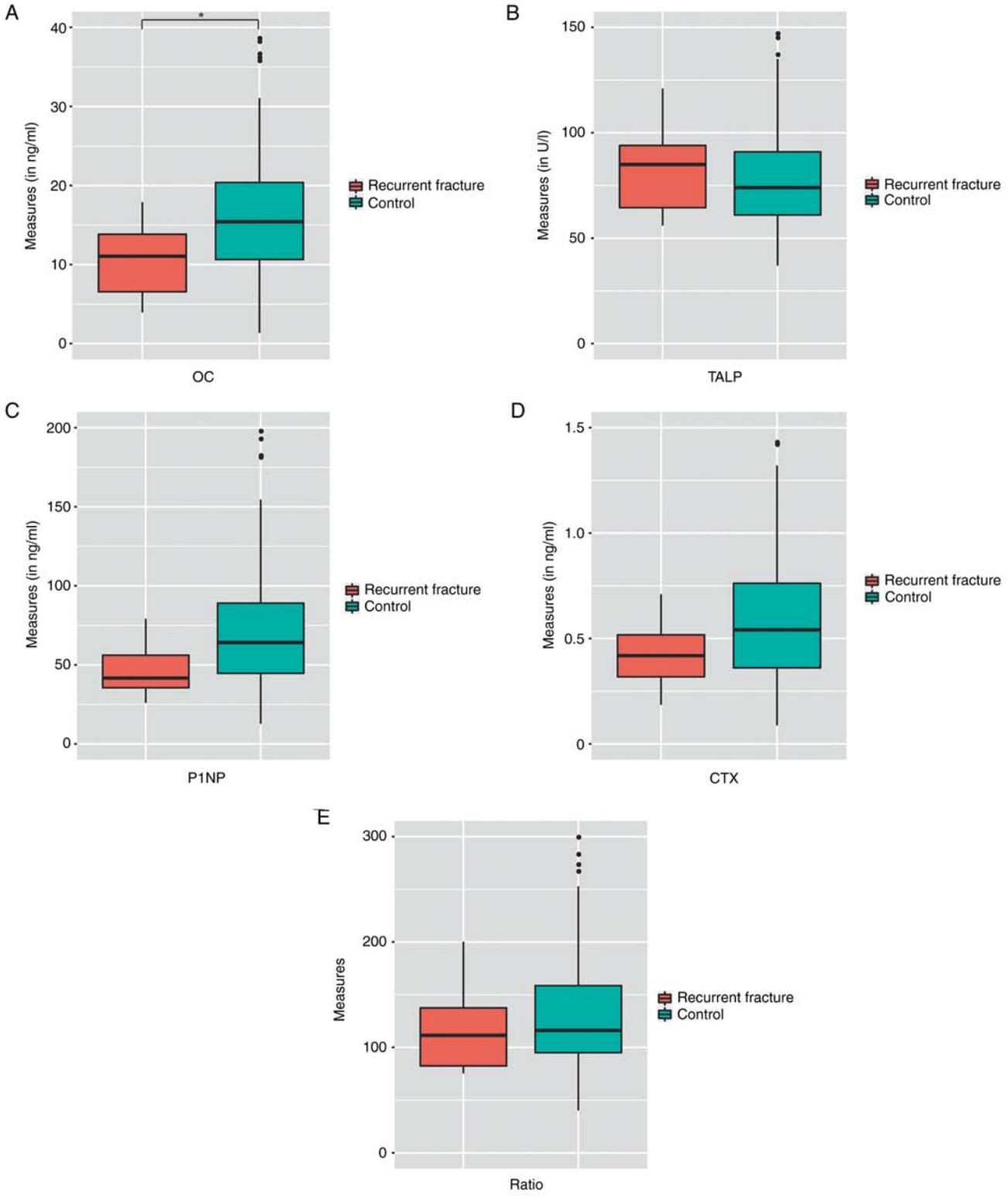

Figure 1. Comparisons of bone turnover marker levels between patients with and without recurrent osteoporotic fractures (A) OC; (B) TALP; (C) P1NP; (D) CTX; (E) P1NP/CTX ratio. *P<0.05, indicates a statistically significant difference. OC, osteocalcin; TALP, total alkaline phosphatase; P1NP, procollagen type I N propeptide; CTX, C-terminal telopeptide of type I collagen.

requiring more exploration for clarifying the potential of BTMs for risk prediction improvement (20).

P1NP and CTX have been suggested as preferred BTMs in bone turnover assessment due to their specificity to bone health, acceptable performance in clinical research and low variability for measurement (13,21). A slight improvement for OF prediction was indicated in models incorporating P1NP and CTX (4). However, they were not significantly associated with the risk of imminent ROFs in the present study. Furthermore, unlike the majority of published results (14,18,19), the present study found that patients with ROFs had lower levels of OC, P1NP and CTX. Likewise, while previous findings reported

Table II. Results for associations between BTMs and risk of ROFs.

	Univariate analysis		Multivariable analysis[a]		Sensitivity analysis[b]	
BTMs	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
OC	0.16 (0.031, 0.86)	**0.032**	0.13 (0.018, 0.90)	**0.039**	0.14 (0.023, 0.88)	**0.036**
TALP	1.07 (0.51, 2.25)	0.86	1.02 (0.49, 2.14)	0.95	1.00 (0.45, 2.22)	0.99
P1NP	0.22 (0.042, 1.16)	0.075	0.19 (0.034, 1.04)	0.056	0.17 (0.026, 1.05)	0.057
CTX	0.44 (0.14, 1.35)	0.15	0.35 (0.10, 1.23)	0.10	0.35 (0.10, 1.25)	0.11
P1NP/CTX ratio	0.54 (0.094, 3.09)	0.49	0.53 (0.081, 3.45)	0.51	0.50 (0.068, 3.60)	0.49

[a]Model adjusted for BMD, age, sex and BMI; [b]model adjusted for BMD, age, sex, BMI, history of OF, anti-osteoporotic drugs, 25(OH)D, PTH and GH. Values in bold font indicate a statistically significant difference (P<0.05). ROF, recurrent osteoporotic fracture; BTMs, bone turnover markers; OC, osteocalcin; TALP, total alkaline phosphatase; CTX, C-terminal telopeptide of type I collagen; P1NP, procollagen type I N propeptide; HR, hazard ratio; CI, confidence interval.

Table III. Results of model discrimination between different models.

	Discriminatory performance			
Model	C-index (95% CI)	P-value	Comparison of model discrimination	
BMD-alone model	0.54 (0.35, 0.73)	**<0.001**	Reference	Reference
Basic model[a]	0.75 (0.60, 0.91)	**<0.001**	0.21 (-0.013, 0.44)	0.065
BTM-alone model[b]	0.71 (0.51, 0.90)	**<0.001**	0.17 (-0.18, 0.51)	0.34
BTM + basic model[c]	0.83 (0.70, 0.96)	**<0.001**	0.29 (0.028, 0.55)	**0.030**

[a]The model only included age, sex, BMI and BMD; [b]the BTM refers to osteocalcin; [c]the model included age, sex, BMI, BMD and osteocalcin. Values in bold font indicate a statistically significant difference (P<0.05). BMD, bone mineral density; BTM, bone turnover marker; BMI, body mass index.

that high BTM levels were generally associated with an increased fracture risk, in the present study all the BTMs, apart from TALP, were associated with a decreased risk of OFs (Table II). More specifically, for example, a gradient of risk of ~1.2 per-SD increase in P1NP and CTX was previously reported regarding the fracture risk (4); by contrast, the present study revealed a markedly decreased risk of ROFs with per-SD increase in P1NP (HR, 0.19) and CTX (HR, 0.35), although the association was not significant. While previous studies have focused on fracture-naive patients or those receiving anti-resorptive or anabolic treatment, in the present study, the included patients were among those who were hospitalized within 24 h after they experienced an index fracture and whose BTMs were measured before they received any treatment. Therefore, the BTMs explored in the present study may reflect the acute self-recovery responses of bone turnover after an OF without medication or surgical intervention in the elderly. The pathophysiology of OFs in the elderly remains largely unclear, particularly as regards their substantially high risk of ROFs within a short period of time (22). Thus, the findings of the present study may provide some insight into how BTMs before treatment are associated with an imminent risk of ROFs in the elderly.

The present exploratory analysis found that after incorporating OC in the model including clinical risk factors and BMD, the model yielded an acceptable discrimination (C-index up to 0.83). This result may suggest the potential of adding serum OC measures before treatment to enhance predictive accuracy for ROF risk. OC is produced by osteoblasts only and is excreted by the kidneys; therefore, it has specificity to bone health (23,24). OC had been found to be broadly associated with bone mineralization, body metabolism, cognition and reproduction, thereby being proposed as a bone-derived hormone (23,25). Moreover, OC has been recognized as a specific biomarker of osteoblast function in osteoporosis regarding the assessment of bone formation rate, particularly among elderly women (26). Other potential mechanisms of OC in relation to ROFs have also been reported, which include the improvement of bone microenvironment and mineralization, and the promotion of energy metabolism and hormone down-regulation (27-30). These findings may help interpret why OC could have the potential to improve the model discrimination for risk of ROF. However, evidence of whether increased serum OC levels following an OF and before treatment could react to the acute impaired skeleton homeostasis and may become involved in physiological processes in an endocrine manner, remaining sparse and limited. Subsequently, the serum OC level in relation to an imminent risk of ROFs warrants further research to clarify its potential to improve the prediction of fracture risk in the elderly.

While the trajectory, regulation and function of BTMs in OF remain to be further explored, the present study provided some preliminary evidence on the association between BTM measures following an index fracture and the imminent risk of ROFs in elderly patients. Sound methodology and statistical analysis may strengthen the study findings. There are some limitations to the present study. First, the small sample size prevented the authors from creating further subgroups or performing an exploratory investigation; likewise, the potential insufficient power may lead to model instability and fail to identify a significant association between other BTMs and the risk of ROFs. As an observational study, confounding effects particularly those of unmeasured variables, could not be fully precluded, which may weaken the credibility and strength of the results. For example, little is known about the lifestyle change, treatment and rehabilitation received for the patients after they were discharged from hospital, which would affect the association between BTMs and the imminent risk of ROFs to an unknown extent. All the ROFs were spine fractures demanding a hospital admission, which may underestimate the OF recurrence, particularly when taking the subclinical or undiagnosed fractures into account. Likewise, it may compromise the generalizability of the study findings to other OF sites. Thus, these results should be interpreted with caution and should only be used for hypothesis generation. The included patients were inpatients with an index OF who may be in general, frailer than their peers without a need for hospitalization. Therefore, whether the association between BTMs and imminent ROFs remains robust in outpatients or community dwellers who had an index fracture, remains largely unexplored. The change in or the trajectory of BTMs in relation to ROFs could not be assessed, due to the unavailability of relevant data. Thus, further research is required to evaluate the dynamic role of BTMs in imminent ROF prediction, particularly for the comparisons of BTMs measured before and after treatment for index fractures.

In conclusion, in the present prospective study, a significant association was found between serum OC levels and a decreased risk of imminent ROFs in the elderly with index fractures. Serum OC levels may have the potential for prediction of recurrent fractures in the elderly. However, further high-quality evidence is warranted to further clarify and validate the BTMs in relation to the risk of imminent ROFs in the elderly.

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Availability of data and materials

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

Authors' contributions

BZ, LL, MC and GL conceived and designed the study, and acquired the data, performed the statistical analyses and data interpretation, and drafted the manuscript. HZ, XX and RW assisted with the study design and data collection, provided professional support and assisted with the statistical analyses, and made several critical revisions to the manuscript. All authors have read and approved the final manuscript. MC and GL confirm the authenticity of all the raw data. All authors guaranteed the research performed.

Ethics approval and consent to participate

All participants provided written informed consent prior to enrollment in the study. The Guangdong Second Provincial General Hospital Ethics Committee approved the study [appro val no. 20190717-01(2)-YXKXYJ-KT].

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Center JR, Bliuc D, Nguyen TV and Eisman JA: Risk of subsequent fracture after low-trauma fracture in men and women. Jama 297: 387-394, 2007.
2. Iconaru L, Charles A, Baleanu F, Surquin M, Benoit F, Mugisha A, Moreau M, Paesmans M, Karmali R, Rubinstein M, *et al*: Prediction of an imminent fracture after an index fracture-models derived from the frisbee cohort. J Bone Miner Res 37: 59-67, 2022.
3. Vasikaran S, Eastell R, Bruyère O, Foldes AJ, Garnero P, Griesmacher A, McClung M, Morris HA, Silverman S, Trenti T, *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 22: 391-420, 2011.
4. Tian A, Ma J, Feng K, Liu Z, Chen L, Jia H and Ma X: Reference markers of bone turnover for prediction of fracture: A meta-analysis. J Orthop Surg Res 14: 68, 2019.
5. Zeng H, Li L, Zhang B, Xu X, Li G and Chen M: Relationship between sleep pattern and bone mineral density in patients with osteoporotic fracture. Ther Adv Endocrinol Metab 13: 20420188221106884, 2022.
6. Wu CH, Chang YF, Chen CH, Lewiecki EM, Wüster C, Reid I, Tsai KS, Matsumoto T, Mercado-Asis LB, Chan DC, *et al*: Consensus statement on the use of bone turnover markers for short-term monitoring of osteoporosis treatment in the asia-pacific region. J Clin Densitom 24: 3-13, 2021.
7. Park SY, Ahn SH, Yoo JI, Chung YJ, Jeon YK, Yoon BH, Kim HY, Lee SH, Lee J and Hong S: Position statement on the use of bone turnover markers for osteoporosis treatment. J Bone Metab 26: 213-224, 2019.
8. Zhang ZQ, Ho SC, Chen ZQ, Zhang CX and Chen YM: Reference values of bone mineral density and prevalence of osteoporosis in Chinese adults. Osteoporos Int 25: 497-507, 2014.
9. Newson RB: Comparing the predictive powers of survival models using Harrell's C or Somers' D. Stata J 10: 339-358, 2020.

10. Devogelaer JP, Boutsen Y, Gruson D and Manicourt D: Is there a place for bone turnover markers in the assessment of osteoporosis and its treatment? Rheum Dis Clin North Am 37: 365-386, v-vi, 2011.
11. Shetty S, Kapoor N, Bondu JD, Thomas N and Paul TV: Bone turnover markers: Emerging tool in the management of osteoporosis. Indian J Endocrinol Metab 20: 846-852, 2016.
12. Naylor KE, Jacques RM, Paggiosi M, Gossiel F, Peel NF, McCloskey EV, Walsh JS and Eastell R: Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study. Osteoporos Int 27: 21-31, 2016.
13. Lorentzon M, Branco J, Brandi ML, Bruyère O, Chapurlat R, Cooper C, Cortet B, Diez-Perez A, Ferrari S, Gasparik A, *et al*: Algorithm for the use of biochemical markers of bone turnover in the diagnosis, assessment and follow-up of treatment for osteoporosis. Adv Ther 36: 2811-2824, 2019.
14. Ivaska KK, Gerdhem P, Väänänen HK, Akesson K and Obrant KJ: Bone turnover markers and prediction of fracture: A prospective follow-up study of 1040 elderly women for a mean of 9 years. J Bone Miner Res 25: 393-403, 2010.
15. Crandall CJ, Vasan S, LaCroix A, LeBoff MS, Cauley JA, Robbins JA, Jackson RD and Bauer DC: Bone turnover markers are not associated with hip fracture risk: A case-control study in the women's health initiative. J Bone Miner Res 33: 1199-1208, 2018.
16. Yao S, Laurent CA, Roh JM, Lo J, Tang L, Hahn T, Ambrosone CB, Kushi LH and Kwan ML: Serum bone markers and risk of osteoporosis and fragility fractures in women who received endocrine therapy for breast cancer: A prospective study. Breast Cancer Res Treat 180: 187-195, 2020.
17. Qu XL, Zheng B, Chen TY, Cao ZR, Qu B and Jiang T: Bone turnover markers and bone mineral density to predict osteoporotic fractures in older women: A retrospective comparative study. Orthop Surg 12: 116-123, 2020.
18. Dai Z, Wang R, Ang LW, Yuan JM and Koh WP: Bone turnover biomarkers and risk of osteoporotic hip fracture in an Asian population. Bone 83: 171-177, 2016.
19. Bauer DC, Garnero P, Harrison SL, Cauley JA, Eastell R, Ensrud KE and Orwoll E; Osteoporotic Fractures in Men (MrOS) Research Group: Biochemical markers of bone turnover, hip bone loss, and fracture in older men: The MrOS study. J Bone Miner Res 24: 2032-2038, 2009.
20. Vilaca T, Gossiel F and Eastell R: Bone turnover markers: Use in fracture prediction. J Clin Densitom 20: 346-352, 2017.
21. Eastell R, Pigott T, Gossiel F, Naylor KE, Walsh JS and Peel NFA: DIAGNOSIS OF ENDOCRINE DISEASE: Bone turnover markers: Are they clinically useful? Eur J Endocrinol 178: R19-R31, 2018.
22. Migliorini F, Giorgino R, Hildebrand F, Spiezia F, Peretti GM, Alessandri-Bonetti M, Eschweiler J and Maffulli N: Fragility fractures: Risk factors and management in the elderly. Medicina (Kaunas) 57: 1119, 2021.
23. Moser SC and van der Eerden BCJ: Osteocalcin-A versatile bone-derived hormone. Front Endocrinol (Lausanne) 9: 794, 2018.
24. Zoch ML, Clemens TL and Riddle RC: New insights into the biology of osteocalcin. Bone 82: 42-49, 2016.
25. Wei J and Karsenty G: An overview of the metabolic functions of osteocalcin. Curr Osteoporos Rep 13: 180-185, 2015.
26. Kuo TR and Chen CH: Bone biomarker for the clinical assessment of osteoporosis: Recent developments and future perspectives. Biomark Res 5: 18, 2017.
27. Manolagas SC: Osteocalcin promotes bone mineralization but is not a hormone. PLoS Genet 16: e1008714, 2020.
28. Dumitru N, Carsote M, Cocolos A, Petrova E, Olaru M, Dumitrache C and Ghemigian A: The link between bone osteocalcin and energy metabolism in a group of postmenopausal women. Curr Health Sci J 45: 47-51, 2019.
29. Razzaque MS: Osteocalcin: A pivotal mediator or an innocent bystander in energy metabolism? Nephrol Dial Transplant 26: 42-45, 2011.
30. Patti A, Gennari L, Merlotti D, Dotta F and Nuti R: Endocrine actions of osteocalcin. Int J Endocrinol 2013: 846480, 2013.