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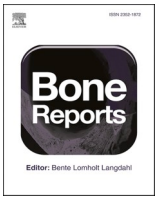

Risk prediction of second hip fracture by bone and muscle density of the hip varies with time after first hip fracture: A prospective cohort study

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ABSTRACT

Purpose: Predictors of 'imminent' risk of second hip fracture are unknown. The aims of the study were to explore strength of hip areal bone mineral density (aBMD), and muscle area and density for predicting second hip fracture at different time intervals.

Methods: Data of the Chinese Second Hip Fracture Evaluation were analyzed, a longitudinal study to evaluate the risk of second hip fracture (of the contralateral hip) by using CT images obtained immediately after first hip fracture. Muscle cross-sectional area and density were measured of the gluteus maximus (G.MaxM) and gluteus medius and minimus (G.Med/MinM) and aBMD of the proximal femur at the contralateral unfractured side. Patients were followed up for a median time of 4.5 years. Separate Cox models were used to predict second hip fracture risk at different time intervals after first event adjusted for age, sex, BMI and diabetes.

Results: The mean age of subjects with imminent (within 1st or 2nd year) second hip fracture was 79.80 ± 5.16 and 81.56 ± 3.64 years. In the 1st year after the first hip fracture, femoral neck (FN) aBMD predicted second hip fracture (HR 5.88; 95 % CI, 1.32–26.09). In the remaining years of follow-up after 2nd year, muscle density predicted second hip fracture (G.MaxM HR 2.13; 95 % CI, 1.25–3.65,G.Med/MinM HR 2.10; 95 % CI, 1.32–3.34).

Conclusions: Our results show that femoral neck aBMD is an important predictor for second hip fracture within the first year and therefore suggest supports the importance concept of early and rapid-acting bone-active drugs to increase hip BMD. In addition, the importance of muscle density predicting second hip fracture after the second year suggest post hip fracture rehabilitation and exercise programs could also be important to reduce muscle fatty infiltration.

Abbreviations: BMD, bone mineral density; IT, intertrochanteric; aBMD, areal BMD; FN, femoral neck; TH, total hip; CSHFE, The Chinese Second Hip Fracture Evaluation; PMS, Parker Mobility Score; CSA, cross-sectional area; HU, Hounsfield Units; G.max, gluteus maximus; G.med/min, gluteus medius and minimus; TR, trochanter; FN CortThick, femoral neck cortical thickness; BMI, body mass index; SD, standard deviation; HR, hazard ratios; MIAF, Medical Image Analysis Framework.

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1. Introduction

It is well known that hip fractures are associated with higher morbidity, mortality and costs than any other osteoporotic fracture. Many hip fracture patients are frail elderly people with a high burden of *co*-morbidities and polypharmacy, and therefore recurrent falls increase the likelihood of subsequent hip fracture. It is also well known that patients with prior osteoporotic fractures are at increased risk of second fractures (Klotzbuecher et al., 2000; Kanis et al., 2004) and that the risk of a second fracture is greatest within the first 1 to 2 years after first fracture (Berry et al., 2007; Johnell and Kanis, 2004; Nymark et al., 2006; Giangregorio et al., 2010). Recently, this recognition of imminent fracture risk and the implication for immediate and effective intervention, has gained increasing interest with the introduction of new anabolic anti-osteoporosis medications (McCloskey et al., 2021). Imminent risk of second hip fracture is in particular high in patients younger than 60 years of age (Kanis et al., 2020), while at age 80 the risk of second hip fracture seems not to be elevated shortly after the first fracture (Kanis et al., 2020). Thus, for an optimization of treatment and prevention strategies, it is very important to identify risk factors of second hip fracture and to understand whether the strength of these factors depend on time after first fracture.

According to international and national osteoporosis and fracture guidelines, all elderly hip fracture patients should be routinely offered anti-osteoporosis medication regardless of bone mineral density (BMD) (Bauer, 2018). However, several studies have shown that in clinical practice, most hip fracture patients do not get anti-osteoporosis medication (Formiga et al., 2005; Desai et al., 2018).

Hip fracture patients also benefit from postoperative rehabilitation (Åkesson et al., 2022). Early mobilization (within 24 h post-surgery) avoids prolonged bed rest and prevents complications (Parker, 2000). However, there is a huge heterogeneity in frequency and duration of physical rehabilitation (Omar et al., 2021).

In a recent prospective analysis with >4.5 years of follow-up of the same data also used for the current study, we have shown that intertrochanteric (IT) areal BMD (aBMD, measured in g/cm^2) was a better predictor of second hip fracture than femoral neck (FN) and total hip (TH) aBMD and that gluteus muscle density was a significant predictor of second hip fracture risk independent of aBMD (Wang et al., 2022). The current study extended the analysis to imminent fracture risk. The power of bone or muscle parameters to predict second hip fracture was determined at different time intervals after first hip fracture. To our knowledge such an analysis has not been reported so far. We hypothesized that both aBMD and muscle density were stronger risk factors for second hip fracture in the first two compared to the years thereafter.

2. Methods

2.1. Study design and participants

The Chinese Second Hip Fracture Evaluation (CSHFE), Clinical Trials.gov Identifier: NCT03461237, is a single-center longitudinal study to assess the risk of second hip fracture. The present analysis used CT images from patients obtained within 48 h after the first fragility hip fracture (baseline visit). Patients were followed up for a median of 4.5 years (from 2015 to 2016 to 2019–2020). At baseline, orthopedists estimated the mobility of patients prior to the first hip fracture using the Parker Mobility Score (PMS). After 4.5 years, patients had a telephone interview regarding the potential incidence of a second hip fracture (of the contralateral side) and/or death. PMS was again determined for the 3 months prior to second hip fracture or prior to death. If the patients had survived without a second hip fracture, PMS was obtained for the 3 months prior to the telephone interview.

A total of 459 patients with acute frailty hip fractures, admitted to the principal investigator's hospital emergency department of orthopaedic trauma between May 2015 and June 2016, were recruited for this study (Fig. 1). All patients underwent surgery after hip fracture. In this institution patients with suspected or already confirmed hip fractures had CT scans routinely. Fully ambulatory Chinese adults with a low-energy injured hip fracture were included. The low energy injury was defined as falls from standing or sitting height. In addition, in order to avoid changes in muscle properties or BMD due to bedrest after surgery, a CT scan had to be taken within 48 h after injury. Patients were excluded due to prior or bilateral hip fractures or inability to stand or walk prior to the first hip fracture. Further exclusion criteria were described in detail recently (Wang et al., 2022; Su et al., 2020), namely stroke, neurologic disorders, rheumatic diseases, heart failure, severe chronic obstructive pulmonary disease and coagulation disorders, and other diseases that limited function. For the final analysis, patients with a Parker Mobility Score ≤ 3 (mobility assessment) after surgery or before death were excluded.

The study was approved by the ethics committee of the principal investigator's hospital. Informed consent was obtained from each participant.

2.2. Muscle density and bone mineral density assessments

Spiral CT scans of the hip were performed for all participants using two 64 slice Toshiba CT scanners (Toshiba Medical Systems Division, Tokyo, Japan) from the top of the acetabulum to 3 cm below the lesser trochanter of both legs. The same CT protocol was used for all participants. Scan parameters for both scanners were 120 kVp, 125 mAs, 500 mm field of view, 512 × 512 matrix, 1 mm reconstructed slice thickness, standard reconstruction.

The muscle measurements were performed by OsiriX software (Lite version 10.0.2, Pixmeo, Geneva, Switzerland) at the unfractured side to avoid acute hemorrhage and hematoma. Precision of this assessment has been reported previously (Wang et al., 2021; Yin et al., 2020). In brief, cross-sectional area (CSA) and density in Hounsfield Units (HU) were measured of the gluteus maximus (G.max) in one CT slice at the level of the greater trochanter and of the gluteus medius and minimus (G.med/min) muscle in one CT slice at the level of the 3rd sacral vertebra (Fig. 2). Muscle segmentation was performed manually using the 'pencil' tool to outline muscle contours. Within the resulting muscle regions of interest, a threshold of −29 HU was used to distinguish muscle tissue from fat.

aBMD of the femoral neck (FN), trochanter (TR), intertrochanter (IT) and total hip (TH) of the unfractured femur was measured using CTXA (version 4.2.3, Mindways Inc), a technique to obtain, two-dimensional projection images from the CT data (Wang et al., 2019). The 3D femoral neck cortical thickness (FN CortThick) was measured by the Medical Image Analysis Framework option Femur (MIAF Femur Version 7.1.0MRH) (Fig. 2). The precision of the bone measurements was reported previously (Yin et al., 2020; Wang et al., 2019).

2.3. Parker mobility score

The Parker Mobility Scores range from 0 to 9. PMS is a validated assessment of mobility (Parker and Palmer, 1993). Parker mobility scores were recorded for the 3 month period prior to first hip fracture (PMS1) and for the 3 month period prior to second hip fracture, the 3 month period prior to death or the three months prior to the telephone interview for those patients surviving without second hip fracture (PMS2). PMS was either obtained directly from the fractured patients of in case of death from relatives having lived with the patient.

2.4. Data collection

Demographic and anthropometric parameters included age, sex and body mass index (BMI). The patients' health related data including blood pressure, hypertension, previous fracture, osteoarthritis, coronary heart disease, and type 2 diabetes were recorded. It was also recorded whether hip arthroplasty surgery was performed after the first hip fracture.

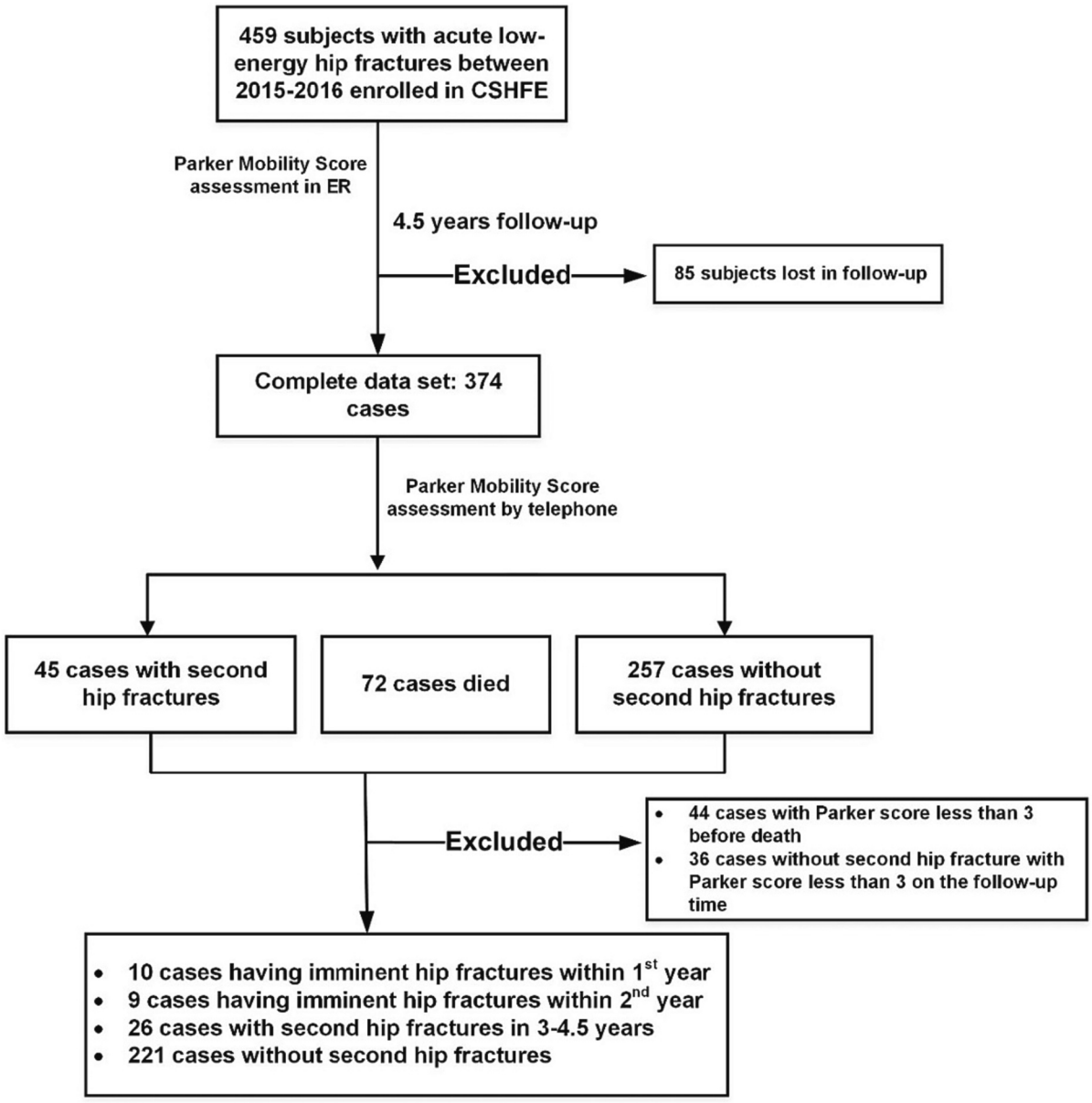

Fig. 1. Flow chart of participant selection for the study.

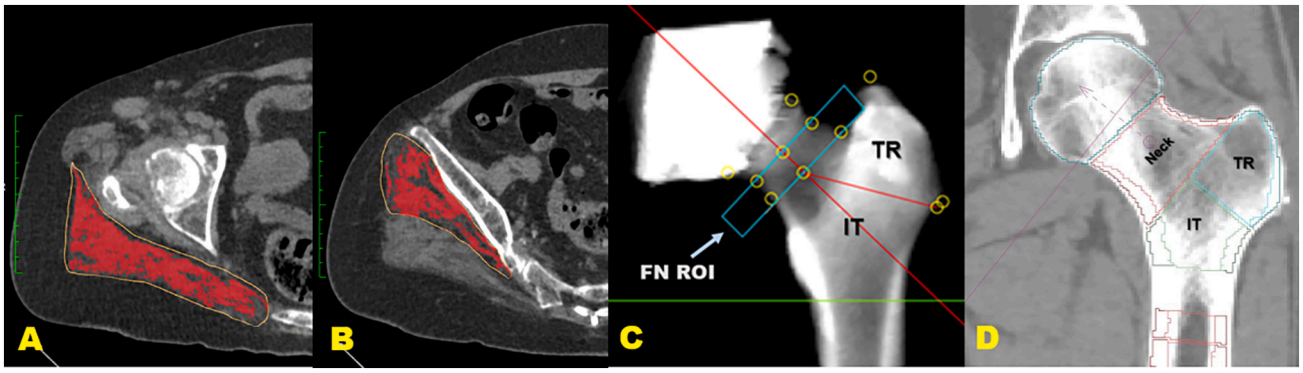

Fig. 2. A representative case with second hip fracture. (A) Measurement of cross-sectional area and mean computed tomography values of the gluteus maximus muscle at the level of the greater trochanter. (B) Measurement of the gluteus medius and minimus muscle at the third sacral level. Muscle region is represented by the area highlighted in red. The gluteus minimus muscle has undergone complete fatty infiltration. (C) Regions of interest (ROIs) analyzed in the proximal femur by QCTPro CTXA. (D) Femoral neck cortical thickness measured by MIAF Femur.

2.5. Statistical analysis

The Statistical Analysis System (SAS 9.4 for Windows; SAS Institute Inc., Cary, NC) was performed for the statistical analyses. Continuous variables were analyzed using two-sample Wilcoxon tests and are reported as mean ± standard deviation (SD). Categorical variables were analyzed using Chi-square tests and are presented as numbers and percentages. Differences were considered significant at $p < 0.025$ to correct for multiple comparisons (Chapurlat et al., 2003) among second hip fracture groups at different time-frames.

Cox proportional hazards models were used to determine the strength of BMD, of muscle density and of muscle area to predict risk of second hip fracture. Separate Cox models were used to predict second hip fracture risk 1) within the first year after surgery ($n = 10$); 2) within the second year after surgery ($n = 9$); 3) after two years till the end of the study ($n = 26$); 4) for the entire study period after surgery ($n = 45$). The following eight muscle and bone parameters that had been identified as significant predictors of fracture risk before (Wang et al., 2022) were again selected as predictors: 1) G.MaxM area; 2) G.MaxM density; 3) G. Med/MinM density; 4) FN CortThick; 5) TH aBMD; 6) FN aBMD; 7) trochanter (TR) aBMD; 8) IT aBMD. In order to compare hazard ratios (HR) across eight muscle and bone parameters, standardized parameters were used in the Cox models by dividing each of the above parameters by their respective sex-specific standard deviation. Age, sex, BMI and diabetes were used as covariates.

3. Results

3.1. Study sample characteristics

The baseline characteristics of the study population are shown in Table 1. Fig. 1 shows the participant selection. The mean age of patients with imminent (within 1st or 2nd year) second hip fracture (79.8 ± 5.2 or 81.6 ± 3.6 years) was higher than that of patients without second hip fracture (72.6 ± 9.8 years).

For patients with second hip fracture, Parker Mobility Scores obtained before the first hip fracture did not differ significantly among time intervals. Prevalence of diabetes was lower in patients with second

Table 1
General characteristics.

Characteristics (mean ± SD)	Total SF	SF at 1st y	SF at 2nd y	SF at > 2 ys	No SF	P value[1]						
	(1)	(2)	(3)	(4)	(5)	(1) vs. (5)	(2) vs. (5)	(3) vs. (5)	(4) vs. (5)	(2) vs. (3)	(2) vs. (4)	(3) vs. (4)
Sample size	*45*	*10*	9	26	*221*							
Covariates												
Age (years)	79.23 ± 7.10	79.80 ± 5.16	81.56 ± 3.64	78.21 ± 8.48	72.60 ± 9.84	**<0.01**	**0.02**	**0.01**	**0.01**	0.41	0.58	0.26
Male sex, % (n)	22.2 (10)	20.0 (2)	0.0 (0)	30.8 (8)	30.8 (68)	0.25	0.47	0.05	1.00	0.16	0.52	0.08
Had diabetes, % (n)	24.4 (11)	40.0 (4)	22.2 (2)	19.2 (5)	48.9 (108)	**<0.01**	0.58	0.12	**<0.01**	0.41	0.20	1.00
Imaging variables												
G.MaxM area (cm^2)	29.16 ± 6.04	30.27 ± 5.26	26.78 ± 6.86	29.55 ± 6.04	33.85 ± 8.46	**<0.01**	0.19	**0.01**	**0.01**	0.57	0.44	1.00
G.MaxM density (HU)	20.50 ± 7.77	20.96 ± 8.02	20.57 ± 7.59	20.29 ± 8.03	25.02 ± 6.95	**<0.01**	0.07	0.06	**<0.01**	0.92	0.83	0.93
G.Med/MinM density (HU)	27.52 ± 5.29	28.61 ± 6.49	26.55 ± 4.41	27.44 ± 5.20	31.97 ± 5.83	**<0.01**	0.08	**0.01**	**<0.01**	0.44	0.58	0.65
FN CortThick (mm)	1.56 ± 0.38	1.34 ± 0.38	1.72 ± 0.15	1.60 ± 0.42	1.55 ± 0.37	0.92	0.10	0.21	0.57	0.03	0.13	0.47
TH aBMD (g/cm^2)	0.53 ± 0.11	0.48 ± 0.08	0.52 ± 0.10	0.54 ± 0.12	0.61 ± 0.13	**<0.01**	**<0.01**	**0.04**	**0.01**	0.41	0.15	0.57
FN aBMD (g/cm^2)	0.47 ± 0.13	0.40 ± 0.05	0.49 ± 0.11	0.49 ± 0.15	0.51 ± 0.11	0.05	**<0.01**	0.71	0.47	**0.03**	0.06	0.95
TR aBMD (g/cm^2)	0.35 ± 0.09	0.31 ± 0.07	0.35 ± 0.09	0.36 ± 0.09	0.41 ± 0.10	**<0.01**	**<0.01**	0.11	**0.03**	0.33	0.14	0.76
IT aBMD (g/cm^2)	0.64 ± 0.13	0.60 ± 0.11	0.64 ± 0.12	0.66 ± 0.14	0.74 ± 0.15	**<0.01**	**<0.01**	**0.04**	**0.01**	0.43	0.20	0.65
Other characteristics												
Height (cm)	160.41 ± 6.47	160.00 ± 5.42	157.50 ± 4.97	161.38 ± 7.11	162.35 ± 9.45	0.25	0.51	0.21	0.65	0.41	0.64	0.22
Weight (kg)	57.35 ± 15.57	59.71 ± 11.90	52.92 ± 5.04	57.83 ± 18.52	61.59 ± 12.83	0.09	0.70	0.10	0.22	0.22	0.80	0.53
BMI (kg/m^2)	22.18 ± 5.50	23.30 ± 4.38	21.34 ± 1.94	22.04 ± 6.53	23.42 ± 5.16	0.20	0.95	0.33	0.26	0.34	0.64	0.80
HA, % (n)	40.0 (18)	10.0 (1)	44.4 (4)	50.0 (13)	36.7 (81)	0.67	0.08	0.63	0.18	0.09	**0.03**	0.77
PMS1	8.49 ± 1.10	8.00 ± 1.41	9.00 ± 0.00	8.50 ± 1.10	8.73 ± 0.80	0.09	**0.01**	0.31	0.19	0.05	0.27	0.19
PMS2	6.57 ± 2.55	4.80 ± 2.70	7.63 ± 1.30	6.96 ± 2.51	7.95 ± 1.37	**<0.01**	**<0.01**	0.51	**<0.01**	**0.02**	**0.03**	0.48
Had hypertension, % (n)	28.9 (13)	40.0 (4)	22.2 (2)	26.9 (7)	20.4 (45)	0.21	0.14	0.89	0.44	0.41	0.45	1.00
Had CHD, % (n)	2.2 (1)	10.0 (1)	0.0 (0)	0.0 (0)	5.0 (11)	0.42	0.48	0.49	0.24	0.33	0.10	NA
Had ever fractures, % (n)	17.8 (8)	20.0 (2)	22.2 (2)	15.4 (4)	21.7 (48)	0.55	0.90	0.97	0.45	0.91	0.74	0.64

Note: SF, second hip fracture (contralateral site); G.MaxM, gluteus maximus muscle; G.Med/MinM, gluteus medius and minimus muscle; HU, Hounsfield unit; CortThick, Cortical thickness; aBMD, areal bone mineral density; TH, total hip; FN, femoral neck; TR, trochanter; IT, intertrochanter; BMI, body mass index; HA, Hip arthroplasty (including total hip arthroplasty and hemiarthroplasty); PMS1, Parker Mobility Score assessed prior to first hip fracture surgery; PMS2, second hip fracture group: Parker Mobility Score assessment within 3 months prior to second hip fracture, group without second fracture: assessment of mobility prior to follow-up visit after first hip fracture; CHD, coronary heart diseases.
1P value obtained from general linear model for continuous variables and from chi-square tests for categorical variable. Significant values are shown in bold font.

hip fractures compared to patients without second fractures except for patients with a second fracture within the first year. All other health related parameters did not show significant differences.

aBMD and muscle area and density at all sites were higher in patients without a second hip fracture than in patients with a second hip fracture.

3.2. Muscle and bone: prediction of imminent second hip fracture

Areal BMD of the FN (adj. HR 5.88; 95 % CI, 1.32–26.09) predicted second hip fracture within the 1st but not within the 2nd year after first hip fracture. Within the 1st year after first hip fracture, associations of areal BMD of TH (adj. HR 3.23; 95 % CI, 0.95–10.97) and IT (adj. HR 3.17; 95 % CI, 0.99–10.16) with second hip fracture were borderline significant. Muscle parameters and FN cortical thickness were not significant predictors of imminent second hip fracture (Figs. 3 and 4).

3.3. Muscle and bone: prediction of second hip fracture >2 years after first hip fracture and for total follow-up period

None of the aBMD measurements predicted second hip fracture after the 2nd year of first hip fracture (Fig. 3). Muscle density of G.MaxM (adj. HR 2.13; 95 % CI, 1.25–3.65) and G.Med/MinM (adj. HR 2.10; 95 % CI, 1.32–3.34) predicted second hip fracture after the 2nd year of first hip fracture (Fig. 4).

Over the total follow-up period of 4.5 years, muscle density but not muscle area significantly predicted second hip fracture. Also, none of the aBMD parameters did predict second hip fracture during this period (Figs. 3 and 4).

4. Discussion

As shown previously (Wang et al., 2022) aBMD of the hip and muscle density of the gluteus maximus are independent risk factors for second hip fracture within 4.5 years after fist hip fracture. Here we extended the analysis of aBMD and muscle parameters to specifically predict the short term or 'imminent' risk of second hip fracture.

In our study with a mean patient age of 79 years we did not observe an increased imminent risk of second hip fracture. Approximately 10 patients suffered a second hip fracture in each of the 4.5 years after first hip fracture. This is consistent with the recent analysis for elderly (80 years of age) patients by McCloskey et al. (McCloskey et al., 2021) and the findings from The Study of Osteoporotic Fractures (Chapurlat et al., 2003). Notably, in these studies the relative risk (compared to an age- and sex-matched population) for second hip fracture was highest at younger age and then decreased progressively with age. However, the age dependence of absolute risk, as observed in the current study, is different. Patients, who fractured their contralateral hip during the follow-up, were older than those who survived without second hip fracture. This observation is in line with the literature. Advancing age remains an independent risk factor for imminent subsequent fracture (Banefelt et al., 2019) . A second hip fracture incidence per person year of 0.038 in our study compared well with the range of 0.033–0.035 reported in other studies of Asian (Lee et al., 2013; Hagino et al., 2012; Lee et al., 2016) and the Framingham (Kanis et al., 2004) populations.

In the current analysis, 10 second hip fractures per year is a relatively small number and therefore lower CIs of several HR were just below or above significance. Nevertheless, FN aBMD was a strong and significant predictor (HR > 2.5) of second hip fracture in the 1st year. TH and IT aBMD were borderline significant predictors of second hip fracture within the 1st year after first hip fracture. After the 1st year, aBMD HRs decreased by >50 %. Apparently, second hip fracture during the 1st year after first hip fracture is not a random event. Affected patients seem to be especially frail with low bone mineral density, low cortical thickness, low Parker Mobility Scores and numerically higher prevalence of hypertension. These patients are predisposed to increased complication rates and increased sensitivity to the deleterious effects of postoperative immobilization and the ensuing bone loss after the first hip fracture. Those patients suffering a second hip fracture after the 2nd year were not characterized by lower bone mineral density, but had lower muscle density compared to the patients without second hip fracture, possibly

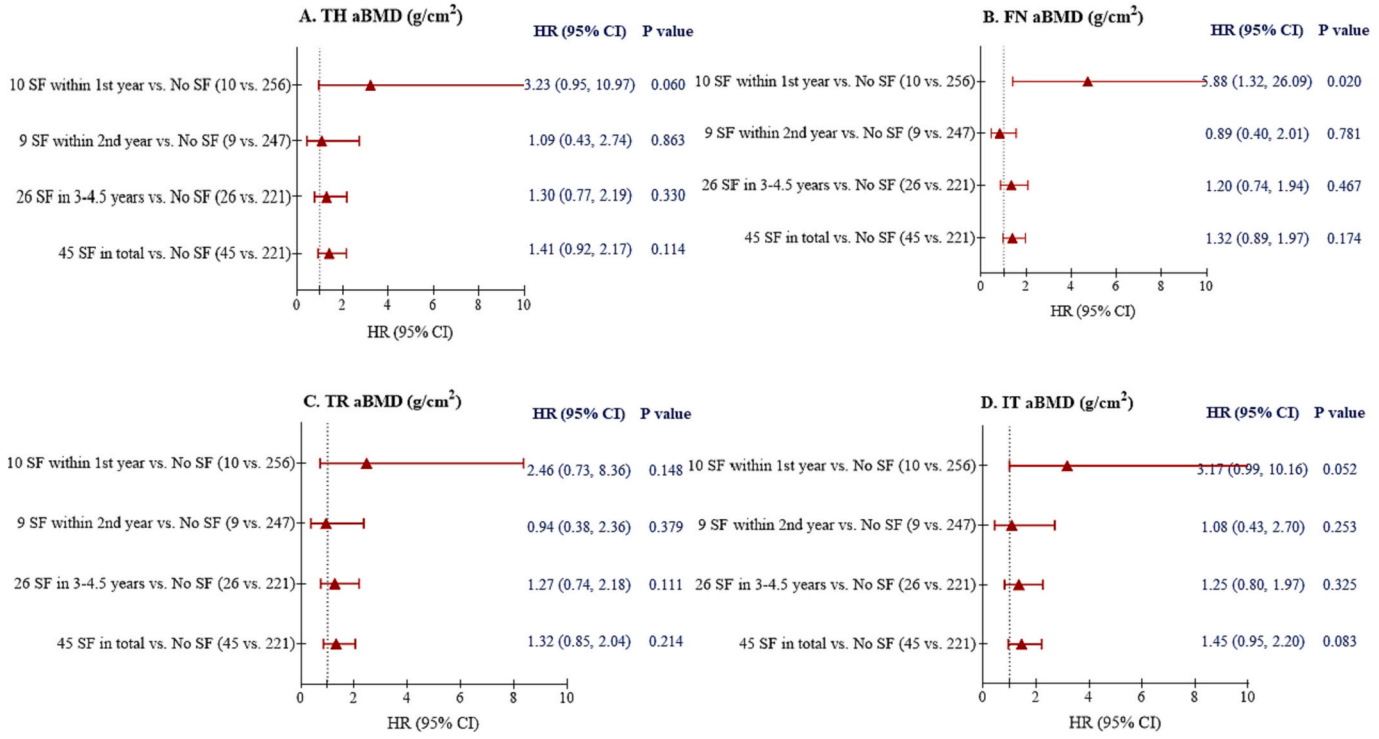

Fig. 3. Hazard ratios (HR) of second hip fracture per one SD decrease of TH aBMD(A), FN aBMD (B), TR aBMD (C), and IT aBMD (D). All HR were adjusted for age, sex, BMI and diabetes. Note: SD, standard deviation; TH, total hip; FN, femoral neck; TR, trochanter; IT, intertrochanter; aBMD, areal bone mineral density.

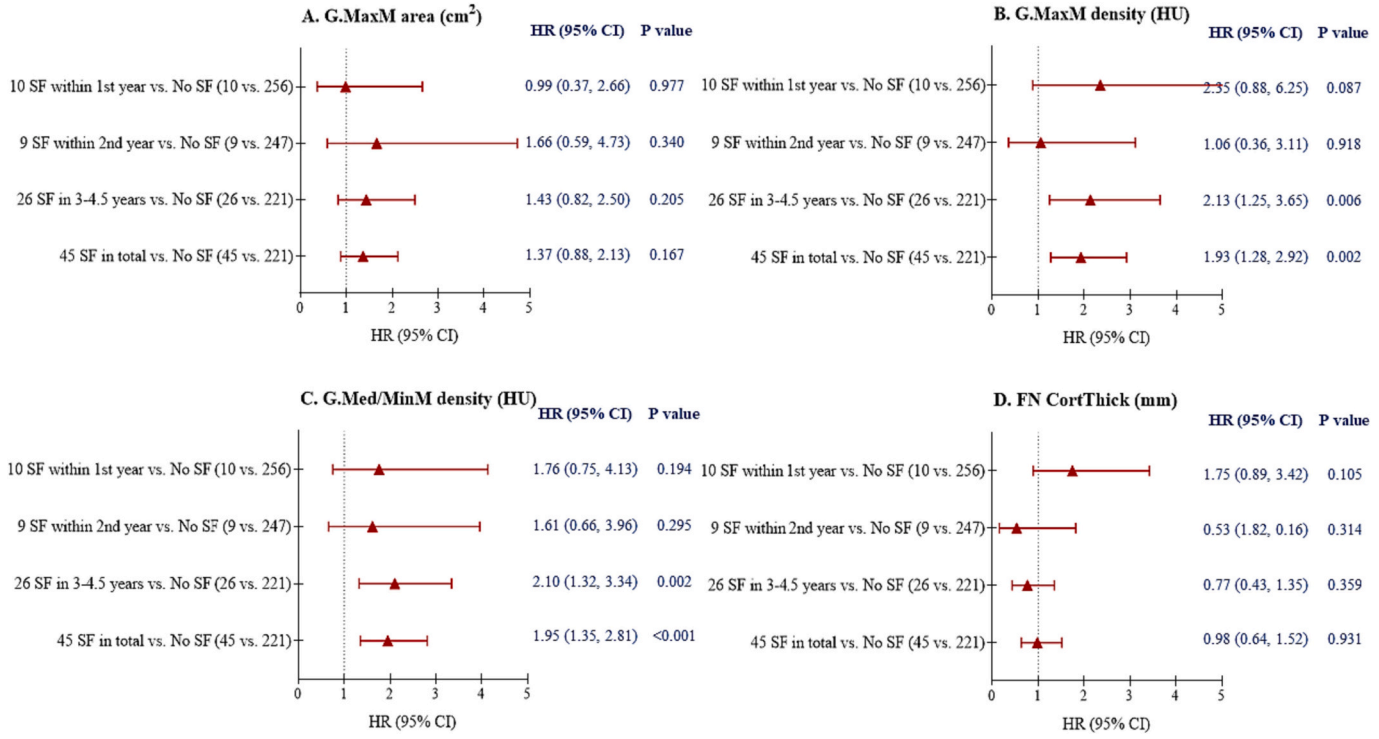

Fig. 4. Hazard ratios (HR) of second hip fracture per one SD decrease of G.MaxM area (A), G. MaxM density (B), G.Med/MinM density (C),and FN CortThick (D) with time-frame. All HR for muscle parameters were adjusted for age, sex, BMI and Parker Mobility Score before first hip fracture and the HR for FN CortThick was adjusted for age, sex, BMI and diabetes.

predisposing them to an increased risk of falls. Based on these data we speculate that the risk of second hip fracture in the first year is determined mostly by the low bone mineral density and therefore suggests the use of early and rapid-acting anti-osteoporosis medication whereas the second hip fracture risk after the second year is also depending on lower muscle function and could be improved with physical rehabilitation.

Most studies on imminent hip fracture risk (Kanis et al., 2020; Lee et al., 2016; Barron et al., 2020; Toth et al., 2020) did not include aBMD or muscle parameters as risk factors, therefore our results cannot be readily compared to published data. Barron et al. (Barron et al., 2020) reported that low total hip aBMD was a significant risk factor for imminent (1 year) second hip fracture risk but 2nd year data or HR were not reported. Hip fracture patients are notoriously undertreated with anti-osteoporosis medications and in agreement with our discussion above the effect of bisphosphonates on BMD may not be strong nor quick enough in the first year after fracture in particular in those with low BMD (Toth et al., 2020; Lyles et al., 2007). There is little standardization of rehabilitation programs after hip fracture, which typically concentrate on functional recovery and fall prevention (Chudyk et al., 2009; De et al., 2021) but effectiveness on BMD and muscle density or composition has not been evaluated. Even prevention of late (> 1st year) second hip fractures seems to require a combined action with anti-osteoporotic medication and enhanced rehabilitation of mobility and muscle function.

This study has several limitations. First, it was a single-center study with limited sample size. Second, study results cannot be extrapolated to other ethnicities. Third, CT scans of the hip were performed at baseline and were not repeated, so data on changes of bone and muscle parameters after first hip fracture are lacking. Fourth, we did not perform a detailed assessment of physical function and fall risk, which may have added to a better understanding of the causes of second hip fracture, in particular relating to falls. However, we did use the Parker Mobility Score to exclude patients with poor mobility.

In conclusion, our study shows that both bone mineral density and hip muscle density are important and independent predictors of second hip fracture. Although we did not find an increased 'imminent' second hip fracture risk in this elderly Chinese population, we did show that bone mineral density is the most important predictor for recurrent hip fracture in the first year after hip fracture whereas in the following years, also density of the hip muscles becomes an important predictor. From a clinical perspective, this result stresses the importance of early and fast-acting use of bone-active medication, and of post-fracture physical rehabilitation and exercise to prevent the fatty infiltration and atrophy of the hip musculature as well as falls in the prevention of second hip fractures with its devastating effect on patient survival and well-being.

CRediT authorship contribution statement

Ling Wang: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Minghui Yang:** Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. **Yufeng Ge:** Writing – original draft, Visualization, Validation, Resources, Formal analysis, Conceptualization. **Yandong Liu:** Writing – original draft, Visualization, Software, Resources, Methodology, Conceptualization. **Gang Wang:** Visualization, Validation, Methodology, Investigation, Data curation. **Yongbin Su:** Visualization, Validation, Software, Data curation. **Zhe Guo:** Visualization, Methodology, Data curation. **Lu Yin:** Writing – review & editing, Visualization, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Pengju Huang:** Visualization, Data curation, Conceptualization. **Jian Geng:** Validation, Data curation, Conceptualization. **Glen M. Blake:** Writing – review & editing, Visualization, Validation. **Bo He:** Writing – review & editing, Data curation, Conceptualization. **Shiwen Zhu:** Writing – review & editing, Resources, Formal analysis, Data curation. **Xiaoguang**

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Declaration of competing interest

KE is a part time employee of Clario, Inc.. Other authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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