Establishment and Verification of a Nomogram for Predicting the Risk of Hip Fracture in Osteoporotic Population Based on Blood Biochemical Indicators and Hip Bone Characteristics

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Abstract: **Objective**: It is to identify risk factors for hip fractures in osteoporotic patients, and based on these risk factors, a nomogram for predicting the risk of hip fractures in osteoporotic populations was established and validated**. Methods**: From the Donghua database of the Affiliated Hospital of Chengde Medical College, the general information and data of osteoporosis patients with a clear history of trauma who underwent double hip joint anteroposterior examination and blood biochemical examination from June 2019 to June 2020 were collected and screened. The clinical data were randomly divided into a training group and a verification group by R software. Univariate and multivariate logistic regression were used to determine the independent risk factors of hip fracture risk in the osteoporotic population, and a nomogram was established according to the independent risk factors. Then verification of it was conducted. **Results**: Of the 398 researchers studied, 258 (64.8%) were diagnosed with hip fractures, with the independent risk factors of age, serum calcium concentration, average femoral neck length, femoral shaft average diameter, and femoral average cortical thickness for HF in OP patients. The area under the curve (AUC) of the nomogram for predicting HF in OP patients was 0.998 and 0.990 in the training group and validation group, respectively. The calibration curve reflects the good consistency between the prediction results and the model, and the clinical decision-making. The curve reflects the higher clinical value of the nomogram. **Conclusion**: The nomogram established according to the independent risk factors of patients could accurately predict the risk of HF in OP patients. Clinicians can use this model to provide evidence for individualized diagnosis and treatment of patients and improving treatment plans.

Keywords*:* Nomogram; Osteoporosis; Hip Fracture; Risk Factors

Introduction

The incidence of osteoporosis (OP) is on the rise as the population ages and life expectancy increases [1]. Around the world, the prevalence of OP is approximately 21.7%[2]. Osteoporotic fractures, also known as fragility fractures, are the most common complication of OP. In the United States, about 50% of women and 20% of men with OP will develop fragility fractures [3]. Hip fractures have the highest morbidity, mortality and costs of all osteoporotic fractures [4]. With the development of drugs and the maturity of surgical techniques, the treatment of HF has achieved great progress, and the incidence of HF tends to be stable. [5], However, the high disability rate and high mortality rate of HF are still a major challenge to clinicians and patients. At present, there are as many as 48 tools for fracture prediction in the world [6], and most of them are predicted based on bone density measured by dual-energy X-ray absorptiometry (DXA) or quantitative CT. However, due to the popularity of equipment, primary medical units[7] cannot make accurate and effective predictions. In recent years, more and more studies have shown that bone morphology is closely related to fractures[8, 9]. In addition, blood biochemical indicators have also been confirmed by many scholars to be related to fracture risk[10, 11]. The nomogram is a widely used tool for predicting disease onset and prognosis [12]. With the help of the nomogram, clinicians can obtain accurate evaluation values based on the clinical characteristics of each patient, to assess the risk of clinical events, and to

formulate individualized coping strategies. The purpose of this study is to identify the risk factors of HF by analyzing the hip joint geometry and blood biochemical examination of the patients, and establish a nomogram to evaluate the risk of HF according to the risk factors.

Materials and methods

Selection criteria

From June 2019 to January 2022, the clinical data of the OP population who received double hip alignment examination and blood biochemical examination in the Affiliated Hospital of Chengde Medical College due to trauma were collected retrospectively, and the following variables were recorded: gender, age, mean femoral neck length (MFNL), mean femoral shaft diameter (MFSD), mean femoral cortical thickness (MFCT), cholesterol (CHOL), triglycerides (TG), low-density lipoprotein cholesterol, (LDL), high-density lipoprotein cholesterol (HDL), serum calcium (Ca), serum magnesium (Mg), serum Inorganic phosphorus (IP).

Patients included in the study were determined based on the following criteria. Inclusion criteria: 1. Patients diagnosed with osteoporosis (American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 Update[13] was used as its diagnostic criteria). 2. Clarify the history of hip wounds; with clear consciousness, can cooperate for the examination and clinical data collection; 3. In double hip joint position, standard X -ray[14] was used, with the elimination criteria as follows: 1.High energy damage, pathological fracture; 2. Severe liver and kidney dysfunction or long-term use of related drugs affecting bone absorption.

Morphological parameter measurement of femur

The DR digital X-ray photography system (Siemens A032011 in the Netherlands) was used to conduct standard anteroposterior plain film examinations on both hip joints, then imported the qualified plain films into the image processing and measurement softening medical image archiving and transmission system software, and quoted the software that came with it. In the measurement procedures, two experienced observers independently measured FNL, FSD, FCT (In HF patients, the healthy side was measured). Taking the femoral head as a circle, the software's built-in circle tool was used to determine the boundary of the femoral head, arbitrarily determining four points on the circle, then choosing two as a group, connecting these two points respectively, and find out their vertical intersection point of the bisector and the perpendicular bisector is the center of the femoral head. Use the straight line tool of the software to determine the shortest distance of the femoral neck. Half of the shortest distance of the femoral neck is the center of the femoral neck. Draw a line segment connecting the center of the femur and the center of the femoral neck and extend it to the midline of the femoral neck.

FNL: Draw the central axis of the femoral shaft, draw a straight line perpendicular to the central axis of the femur at the place that 2 cm away from the junction of the lower border of the lesser trochanter and the cortex of the femur, and measure the distance between the line and the intersection point of the cortex on both sides of the femoral shaft. This distance is the diameter of the femoral shaft FNL.

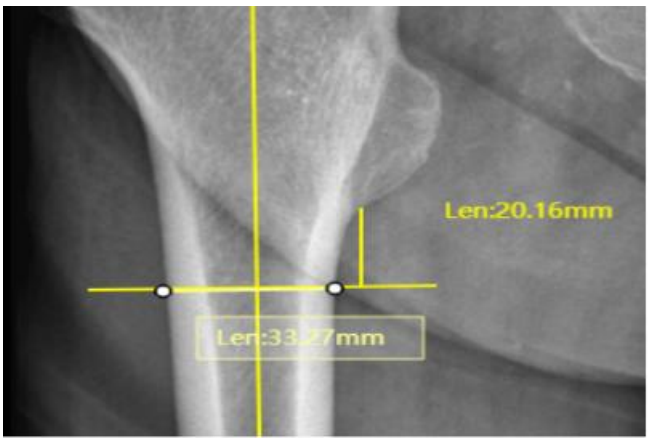

Figure 1: Measuring Femoral Shaft Diameter

FSD: Draw the central axis of the femoral neck, respectively as the central axis of the femoral shaft and the central axis of the femoral neck, and measure the distance from the intersection of the two extension lines to the center of the femoral head.

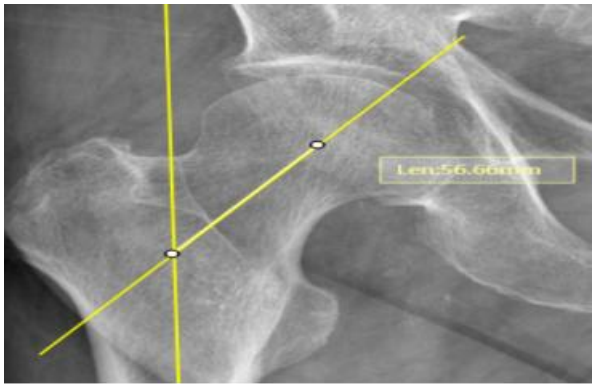

Figure 2: Measuring femoral neck length

FCT：Draw a straight line perpendicular to the central axis of the femoral shaft 5 cm away from the intersection of the lower edge of the lesser trochanter with the cortex of the femur, measure the distance between the line and the intersection point of the lateral cortex on both sides of the femoral shaft, and measure the distance between the straight line and the medial cortex on both sides of the femoral shaft. Combing the distance of the intersecting point, the difference between the above two lengths is the thickness of the femoral cortex.

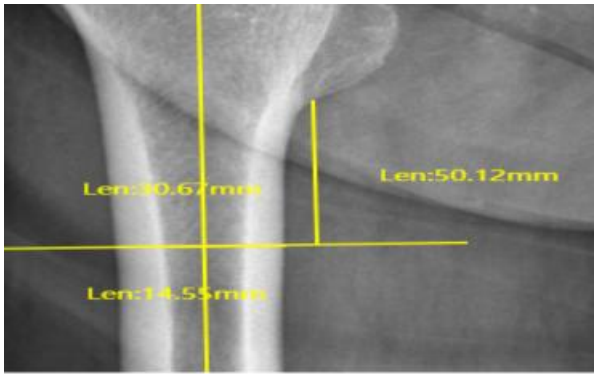

Figure 3: Measurement of Femoral Cortical Thickness

Data analysis and model building

The population included in the study was randomly divided into a training group and a verification group at a ratio of 7:3, and statistical analysis was performed using software IBM SPSS 27.0 and R4.03. Means and standard deviations were used for comparison, and the t-tests on two independent samples were used for comparison, and the difference was considered statistically significant with $p<0.05$. Univariate logistic regression analysis was used to screen risk factors for hip fracture (Enter method), and these risk factors were incorporated into multivariate logistic regression analysis (Enter method) to screen out independent risk factors associated with hip fracture. Use multiple R packages to draw nomograms, calibration plots, ROC curves and DCA plots to evaluate the performance of predictive models.

Result

Baseline characteristics

According to the inclusion and exclusion criteria, a total of 398 patients in the Donghua System of the Affiliated Hospital of Chengde Medical College met the inclusion criteria for this experiment. Results: 172 male patients, 226 female patients; 87 patients under 60 years old; 125 patients between 60-69 years old; 86 patients between 70-79 years old; 80-89 years old were included 86 cases and 14 cases of patients over 90 years old. Using "R" analysis software, according to the ratio of 7:3, they were randomly divided into a training group and a verification group. The training group included 280 patients, 182 of whom had HF, and the verification group included 198 patients, of which 76 had HF. Comparing the general data of the training group and the verification group, there was no statistically significant difference in clinical characteristics ($p>0.05$). See Table 1 for details

Variables		Total (n=398)	group train (n=280)	group validation (n=118)	*p*
Sex ,n(%)	Female	226(56.784)	160(57.143)	66(55.932)	0.824
	Male	172(43.216)	120(42.857)	52(44.068)	
FCT		15.100[13.950,16.360]	15.210[13.960,16.440]	14.860[13.880,16.060]	0.26
FSD		30.140[28.060,32.340]	30.040[27.970,32.080]	30.420[28.340,32.790]	0.149
FNL		49.780[46.230,52.860]	49.890[46.580,53.030]	49.570[46.000,52.250]	0.499
Mg		0.860[0.820,0.920]	0.860[0.820,0.920]	0.860[0.800,0.910]	0.258
Ca		2.230[2.140,2.310]	2.230[2.140,2.310]	2.230[2.140,2.320]	0.699
HDLc		1.140[0.940,1.330]	1.150[0.940,1.330]	1.120[0.960,1.330]	0.549
LDLc		2.410[1.850,2.960]	2.410[1.820,2.920]	2.480[1.930,3.020]	0.239
TG		1.220[0.890,1.700]	1.220[0.870,1.690]	1.320[0.970,1.760]	0.228
CHOL		4.150[3.480,4.840]	4.120[3.420,4.780]	4.210[3.560,4.970]	0.304
Age		68.000[60.000,80.000]	68.000[60.000,79.000]	67.000[60.000,80.000]	0.823

Table 1 Comparison of general data between the training group and the verification group

Risk factors for hip fractures

In the training set (280 patients), there were 182 patients with HF and 98 patients without HF. Through single factor logistic regression, it was found that gender, age, CHOL, TG, LDL, Ca, MFNL, MFSD, and MFCT were compared between the two groups, and the differences were statistically significant ($p<0.05$), which were related to the occurrence of HF in the

osteoporotic population. Risk factors; Multivariate logistic regression analysis showed that gender, age, Ca, MFNL, MFSD, and MFCT were independent risk factors for hip fractures. See Table 2 for details.

Variables		Univariate analysis			Multivariate analysis		
		OR	95%CI	p-value	OR	95%CI	p-value
Sex	Female						
	Male	0.356	0.215, 0.591	<0.01	0.001	0-0.373	0.022
FCT		0.32	0.243-0.420	<0.01	0.095	0.016-0.563	0.01
FSD		2.531	2.021-3.169	<0.01	27.889	2.028-383.526	0.013
FNL		1.089	1.567-2.088	<0.01	1.753	1.049-2.931	0.032
Mg		6.287	0.428-92.304	0.177			
Ca		0.2	0.03-0.150	<0.01	0.005	0-0.997	0.05
HDLc		1.875	0.889-3.952	0.097			
LDLc		0.443	0.316-0.620	<0.01	0.002	0-2.045	0.078
TG		0.625	0.447-0.874	0.05	0.152	0.013-1.796	0.135
CHOL		0.606	0.471-0.781	<0.01	36.894	0.134-10177.986	0.208
Age		1.12	1.207	<0.01	1.314	1.097-1.574	0.03

Table 2: Comparison of univariate and multivariate analyzes of all variables based on HF

Development and validation of nomograms

According to the logistic regression analysis, 6 independent risk factors related to the risk of HF in OP patients were identified, and a nomogram for predicting the risk of HF in patients with osteoporosis was constructed, as shown in Figure 4; at the same time, a forest plot was established according to the risk of HF, as shown in Figure 5; the discriminative power of the prediction model is evaluated by drawing the ROC curve. The AUC values of the training group and the verification group were 0.998 and 0.992, respectively, which proved that the nomogram model had good discriminative power, see Figure 6; the calibration curve showed that the model predicts the OP The risk of hip fractures of patients was in good agreement with the actual risk, as shown in Figure 7; the DCA curve showed that the nomogram provided a good prediction model for assessing the risk of hip fractures, which may have high clinical application significance. See Figure 8.

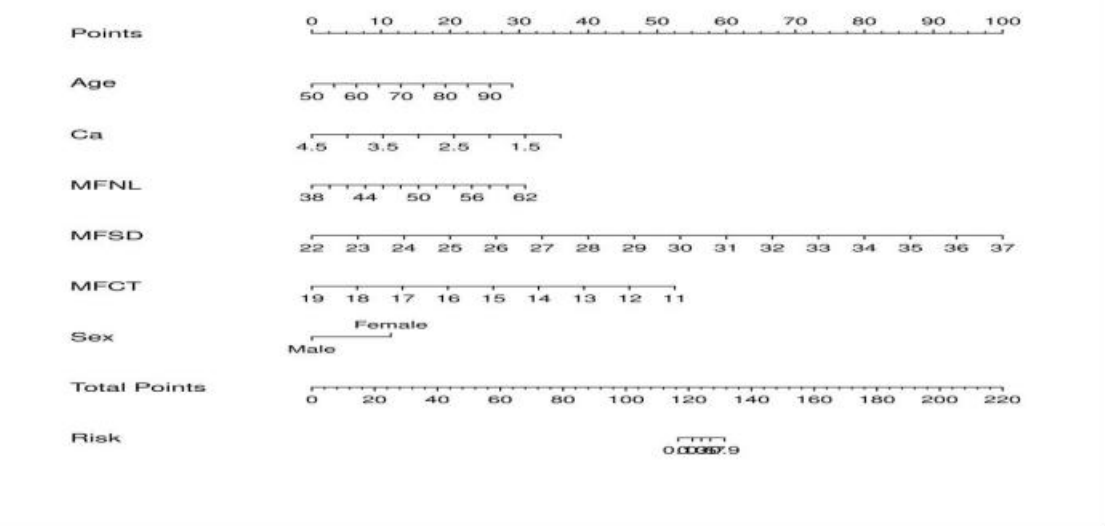

Figure 4: Nomogram developed in this study to predict hip fracture risk in patients with moderate OP ($p<0.05$)

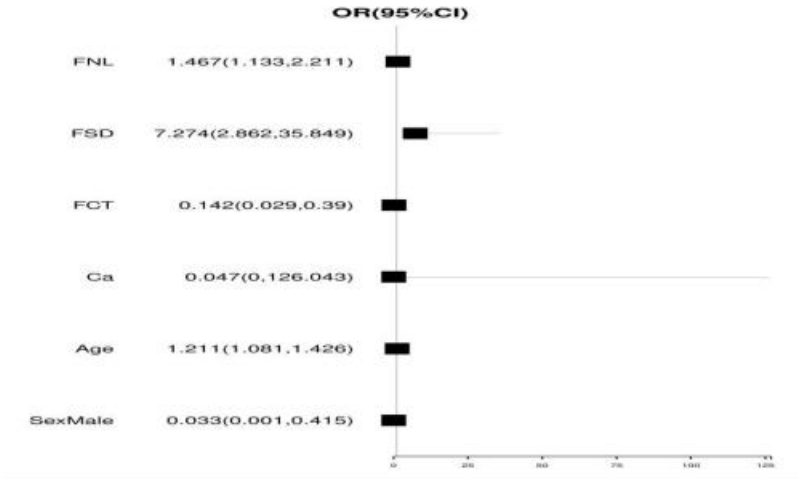

Figure 5: Forest plot. Using multivariate logistic regression analysis to describe the effect of different risk factors in predicting the occurrence of hip fracture

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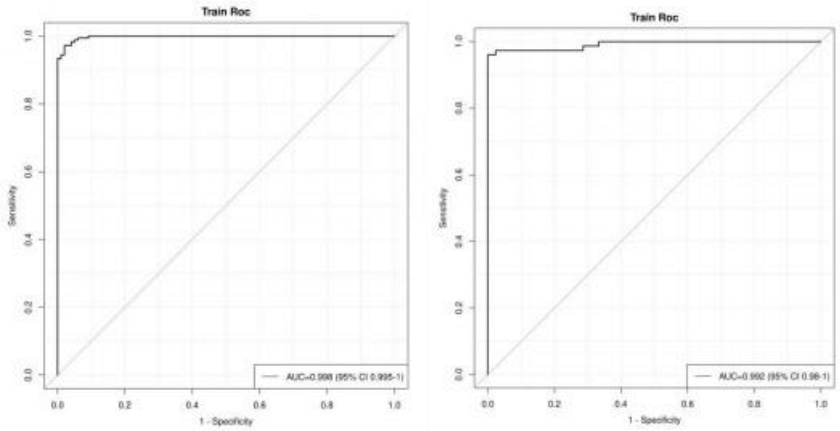

Figure 6: ROC curve in training set a (AUC: 0.998) and validation set b (AUC: 0.992)

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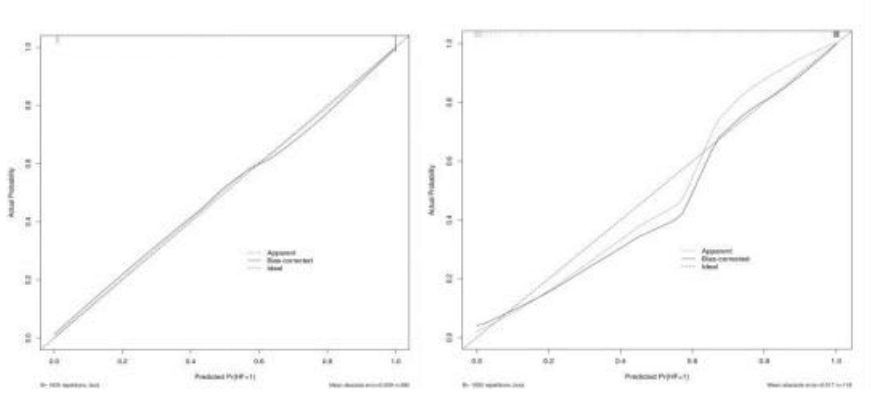

Figure 7: Calibration curves, training set (a) and validation set (b).

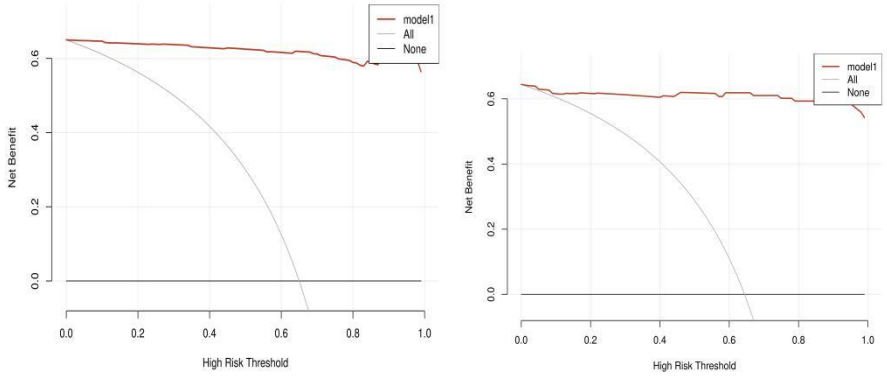

Figure 8: DCA curve. In training set (a) and validation set (b)

Discussion

With the ageing of the global population, OP has become a common disease, and HF is its most common and serious complication, which will significantly increase the social cost [15] and seriously affect the function and life of patients. The study by Olalla Guzon-Illescas et al. showed that the overall survival rate decreased after the diagnosis of HF[16]. At present, studies in many countries have shown that preventive drug therapy can effectively reduce the incidence of HF[17]. Therefore, early prevention has become the consensus of researchers and clinical workers, so it is very meaningful to establish an effective risk prediction model. In our study, we analyzed the data of 398 patients with HF and identified age, gender, MFSD, MFNL, MFCT, as risk factors independently associated with HF, on this basis, we constructed A nomogram of HF risk in the elderly population, validated by related models. Through this nomogram, clinicians can identify the risk of HF in patients, which provide guidance for preventive measures for fractures.

Fragility fractures occur in people over 50 years old. In our study, age is an independent risk factor for HF, which is consistent with the conclusions of most researchers[18]. Decreased intensity, while we considered increased underlying disease and decreased physical activity, also made age a risk factor for developing HF. In addition, the gender (female) is an independent risk factor for HF, and estrogen plays an important role in the balance of bone metabolism. It can stimulate the proliferation and differentiation of osteoblasts, promote the apoptosis of osteoclasts, and maintain the balance in the bone microenvironment, to protect bone tissues, and the decline of estrogen levels after women enter menopause leads to the destruction of the balance of bone microenvironment, which leads to an increased risk of fractures[19]. We believe that women can use estrogen supplements in real time after menopause, which can effectively reduce fractures risk[20]; Ca is an independent risk factor for HF, Ca is an important substance to maintain bone remodeling and promote bone formation, and is an important nutrient for bones. In this study, the decrease in Ca leads to an increased risk of HF. Calcium

supplementation may be needed in due course, but high-dose calcium supplementation may lead to increased cardiovascular risk[21]. Therefore, regular and systematic use of calcium supplementation is the safest and most effective way to reduce the risk of HF.

Due to the reduction of bone mass and bone quality in the human body, the bone strength is reduced. Among them, the bone quality is mainly affected by the geometric properties and material properties of the bone. Some studies have shown that[22], the geometric changes of the hip joint can be a decisive factor for whether the fracture occurs or not, and the reason is consistent with the mechanics. The femoral neck is an important anatomical tissue connecting the femoral head and the femoral shaft. According to geometric mechanics, if the moment arm is too long, it is easy to break when it is subjected to a small force (such as a low-energy injury such as a fall). Therefore, the shape of the femoral neck that is too long may lead to HF, the direction of the trabecular bone in the femoral neck is different[23], and the high shear force is also an important internal cause of HF. Cortical bone is an important supporting tissue for bone. During the aging process, the pores in the cortex increase, while the bone quality decreases, the bone strength decreases, which makes fractures prone to occur. Therefore, with the decrease of FCT, the risk of HF increases; the transition zone, as an important connection between the femoral head and the femoral shaft, is prone to fracture, and the diameter of the femoral shaft measured at this site is related to the risk of fracture, which may be related to the cortical changes in the transition zone. Osteogenesis, FSD increases with aging in compensation[24]. Due to the presence of osteoporosis in patients, the femoral medullary cavity expands, which leads to the cortex in this area gets thinner, then the load capacity of the bone is reduced and is prone to fractures. In addition, whether different blood lipid levels can affect fractures is controversial. Wang Yanmao[25]and some other scientists believed that different blood lipid levels had a strong correlation with fractures, but in this study, it was found that CHOL, TG, LDL, HDL and other indicators were not independent risk factors for HF. It is consistent with the research results of M Tohidi et al.[26] This still requires further research on the understanding of physiology, pathways, etc.

Insufficiency of this study: first, this study is a retrospective study, and there is a certain selection bias; second, in addition, the sample size was small and the case source was single, and large samples from other databases are still needed for research verification; third, in this study, the research item included was not sufficient, where it only included some morphological indicators and biochemical indicators, and other parameters such as material science should be further added. However, this study still provides help for primary hospitals to predict and prevent HF.

Conclusion

Age, gender, FSD, FNL, and FCT are risk factors independently associated with HF. A nomogram model was constructed based on these risk factors. This model can be used to predict the risk of HF in OP patients. Based on this nomogram, it can used as references by clinicians in helping patients make wiser prevention and treatment options.

References

[1] Clynes MA, Harvey NC, Curtis EM, Fuggle NR, Dennison EM, Cooper C, The epidemiology of osteoporosis. British medical bulletin 2020, 133(1):105-117.

[2] Salari N, Darvishi N, Bartina Y, Larti M, Kiaei A, Hemmati M, Shohaimi S, Mohammadi M, Global prevalence of osteoporosis among the world older adults: a comprehensive systematic review and meta-analysis. Journal of orthopaedic surgery and research 2021, 16(1):669.

[3] Porter JL, Varacallo M, Osteoporosis. In: StatPearls. edn. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.

[4] Wáng YXJ, Fragility fracture prevalence among elderly Chinese is no more than half of that of elderly Caucasians. Quantitative imaging in medicine and surgery 2022, 12(2):874-881.

[5] Curtis EM, Moon RJ, Harvey NC, Cooper C: The impact of fragility fracture and approaches to osteoporosis risk assessment worldwide. Bone 2017, 104:29-38.

[6] El-Hajj Fuleihan G, Chakhtoura M, Cauley JA, Chamoun N: Worldwide Fracture Prediction. Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry 2017, 20(3):397-424.

[7] Perry L, Malkin R: Effectiveness of medical equipment donations to improve health systems: how much medical equipment is broken in the developing world? Medical & biological engineering & computing 2011, 49(7):719-722.

[8] Aldieri A, Terzini M, Audenino AL, Bignardi C, Morbiducci U: Combining shape and intensity dxa-based statistical approaches for osteoporotic HIP fracture risk assessment. Computers in biology and medicine 2020, 127:104093.

[9] Senra AR, Carvalho DR, da Silva MR, Sousa AN, Torres J: Proximal femur geometry: a major predictor of proximal femur fracture subtypes. Hip international: the journal of clinical and experimental research on hip pathology and therapy 2022: 11207000221129785.

[10] Barzilay JI, Buzkova P, Kuller LH, Cauley JA, Fink HA, Sheets K, Robbins JA, Carbone LD, Elam RE, Mukamal KJ: The Association of Lipids and Lipoproteins with Hip Fracture Risk: The Cardiovascular Health Study. The American journal of medicine 2022, 135(9):1101-1108.e1101.

[11] Song Y, Xu L, Jin X, Chen D, Jin X, Xu G: Effect of calcium and magnesium on inflammatory cytokines in accidentally multiple fracture adults: A short-term follow-up. Medicine 2022, 101(1):e28538.

[12] Balachandran VP, Gonen M, Smith JJ, DeMatteo RP: Nomograms in oncology: more than meets the eye. The Lancet Oncology 2015, 16(4):e173-180.

[13] Watts NB, Camacho PM, Lewiecki EM, Petak SM: American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis-2020 Update. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2021, 27(4):379-380.

[14] Fajar JK, Taufan T, Syarif M, Azharuddin A: Hip geometry and femoral neck fractures: A meta-analysis. Journal of orthopaedic translation 2018, 13:1-6.

[15] Rinonapoli G, Ruggiero C, Meccariello L, Bisaccia M, Ceccarini P, Caraffa A: Osteoporosis in Men: A Review of an Underestimated Bone Condition. International journal of molecular sciences 2021, 22(4).

[16] Guzon-Illescas O, Perez Fernandez E, Crespí Villarias N, Quirós Donate FJ, Peña M, Alonso-Blas C, García-Vadillo A, Mazzucchelli R: Mortality after osteoporotic hip fracture: incidence, trends, and associated factors. Journal of orthopaedic surgery and research 2019, 14(1):203.

[17] LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, Siris ES: The clinician's guide to prevention and treatment of osteoporosis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2022, 33(10):2049-2102.

[18] Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, Debeer J, Bhandari M: Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. CMAJ : Canadian Medical Association journal, 2010, 182(15):1609-1616.

[19] Li L, Zhao X, Yang X, Tang X, Liu M: Dynamic hip screws versus cannulated screws for femoral neck fractures: a systematic review and meta-analysis. Journal of orthopaedic surgery and research 2020, 15(1):352.

[20] Fracture fixation in the operative management of hip fractures (FAITH): an international, multicentre, randomised controlled trial. Lancet (London, England) 2017, 389(10078):1519-1527.

[21] Bartels S, Kristensen TB, Gjertsen JE, Frihagen F, Rogmark C, Dolatowski FC, Figved W, Benth J, Utvåg SE, Total Hip Arthroplasty Leads to Better Results After Low-Energy Displaced Femoral Neck Fracture in Patients Aged 55 to 70 Years: A Randomized Controlled Multicenter Trial Comparing Internal Fixation and Total Hip Arthroplasty. The Journal of bone and joint surgery American volume 2022, 104(15):1341-1351.

[22] Rotem G, Sharfman ZT, Rath E, Gold A, Rachevsky G, Steinberg E, Drexler M, Haviv B, Amar E, Does hip morphology correlate with proximal femoral fracture type? Hip international: the journal of clinical and experimental research on hip pathology and therapy 2020, 30(5):629-634.

[23] Zhu X, Mei J, Ni M, Jia G, Liu S, Dai Y, Zhang Y, [General anatomy and image reconstruction analysis of the proximal femoral trabecular structures]. Chinese journal of reparative and reconstructive surgery 2019, 33(10):1254-1259.

[24] Hu ZS, Liu XL, Zhang YZ, Comparison of Proximal Femoral Geometry and Risk Factors between Femoral Neck Fractures and Femoral Intertrochanteric Fractures in an Elderly Chinese Population. Chinese medical journal 2018, 131(21): 2524-2530.

[25] Wang Y, Dai J, Zhong W, Hu C, Lu S, Chai Y, Association between Serum Cholesterol Level and Osteoporotic Fractures. Frontiers in endocrinology 2018, 9:30.

[26] Tohidi M, Barzegar N, Hasheminia M, Azizi F, Hadaegh F, Association of different lipid measures with incident bone fractures: Tehran lipid and glucose study. Postgraduate medicine 2022, 134(3):326-332.