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Original Article

Predictive Value of Multiple Clinical and Imaging Parameters for Postmenopausal Osteoporotic Vertebral Refracture after Conservative Treatment

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SUMMARY

Introduction: The risk of osteoporotic vertebral refracture (OVRF) is substantially increased after initial osteoporotic vertebral fracture (OVF). In this study, we comprehensively analyzed risk factors for OVRF in patients undergoing conservative treatment and further evaluated the predictive value of various risk factors.
Methods: Basic information, past medical history and imaging parameters were collected from 151 postmenopausal OVF women treated conservatively. In univariate analysis, chi-square test was used for categorical variables and independent sample t-test was used for continuous variables. Binary logistic regression was used to identify independent risk factors for variables with significant differences in univariate analysis. Then receiver operating characteristic curve analysis (ROC Curve) were drawn for the predictors and area under the curve (AUC) were calculated to evaluate the prediction accuracy.
Results: Univariate analysis and binary logistic regression analysis showed that age ($p < 0.05$) and L3/4 paraspinal muscle fat infiltration ratio (FIR) ($p < 0.05$) were independent risk factors of OVRF. According to the ROC curve, the prediction accuracy of age, FIR and the two parameters together were 0.730, 0.778 and 0.813 respectively. The critical values of age and FIR were 63.5 years and 37.1%, respectively.
Conclusion: OVRF is affected by multiple factors. Age and FIR are independent risk factors of OVRF. The prediction value of integrated two independent risk factors was higher than that of a single risk factor. Postmenopausal women with initial OVF aged over 63.5 years and FIR over 37.1% were more likely to develop OVRF.

1. Introduction

With the aging of society, the incidence of osteoporotic vertebral fracture (OVF) is progressively increasing, predominantly in the elderly and postmenopausal women. OVF leads to disability and dependence on medical care, which is an important factor affecting patients' quality of life.[1–3]

The treatment of OVF includes conservative treatment and vertebral augmentation surgery. Although vertebral augmentation surgery has become an important treatment option, complications including refracture and bone cement leakage have not been well solved,[4] especially osteoporotic vertebral refracture (OVRF),[5,6] which has been concerned by many scholars. Conservative treatment, including bed rest, lumbar brace fixation, anti-osteoporosis drugs and analgesic drugs, is effective for most patients with OVF,[7] but in clinical practice, we frequently encounter OVRF in patients who prefer conservative treatment. Multiple OVRF can lead to kyphosis, or even nerve compression, resulting in limb dysfunction, and even many patients need to stay in bed continuously, severe complications may lead to short-term death.

The risk of OVRF is significantly increased after initial OVF, this phenomenon often referred to as "vertebral fracture cascade".[8,9] Consequently, many scholars are actively exploring the risk factors of OVRF in order to provide new strategies for the prevention and treatment of OVRF. Yet, research on OVRF in patients who prefer conservative treatment are limited. According to the latest literature, the main risk factors for OVRF include BMI, BMD, paraspinal muscle degeneration, severity of vertebral compression, local kyphosis angle, etc. These literatures are mainly single-factor analysis, and there are few comprehensive studies on multiple factors;[10–12] therefore, we designed this study in postmenopausal women for a comprehensive analysis of various risk factors, hoping to provide health guidance and treatment measures to prevent OVRF.

2. Patients and methods

This is a retrospective cross-sectional study approved by the Investigational Ethics Review Board (Jingmen People's Hospital, Clinical Study Ethics Review No. 2021052). According to the information of inpatients registered in our hospital's inpatient case system from January 2019 to December 2021, postmenopausal women with OVF and OVRF were screened out according to inclusion criteria and exclusion criteria.

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Inclusion criteria:

1. Postmenopausal women with single or multiple OVF or OVRF.
2. Anteroposterior and lateral thoracic or lumbar X-ray, thoracic and lumbar MRI examination, BMD examination were all completed, MRI images revealed fresh vertebral fractures.
3. Conservative treatment, including bed rest, lumbar brace fixation, anti-osteoporosis drugs and analgesic drugs, was selected for the first occurrence of OVF.
4. No spinal or hip surgery was performed prior to OVF.
5. All vertebral fracture segments were located from T6 to L5.

Exclusion criteria:

1. OVF or OVRF caused by high energy injury.
2. Pathological fracture caused by spinal tumor, tuberculosis and infection.
3. The following medical history was present: hyperparathyroidism, rheumatic diseases, glucorticoids usage.
4. OVF was treated with vertebral augmentation surgery.

Finally, 151 postmenopausal OVF women treated conservatively were analyzed based on the inclusion criteria and exclusion criteria. OVF is defined as follows: according to Genant's semiquantitative grading system,[13] the vertebral fracture on X-ray shows normal vertebral height or wedge shape change. Meanwhile, MRI shows low signal on T1WI, high signal on T2WI and fat suppression sequence. Patients were divided into non-refracture group and refracture group. Non-refracture group included patients with a history of OVF only once, and the fracture forms included single or multiple segments of fresh OVF; refracture group included patients with more than two times OVF histories, and patients with more than two segmental of fresh or old OVF (A typical cases of OVRF was demonstrated in Figure 1). OVRF can be a refracture of the original fractured vertebral body or a new fracture of an unfractured vertebral body.

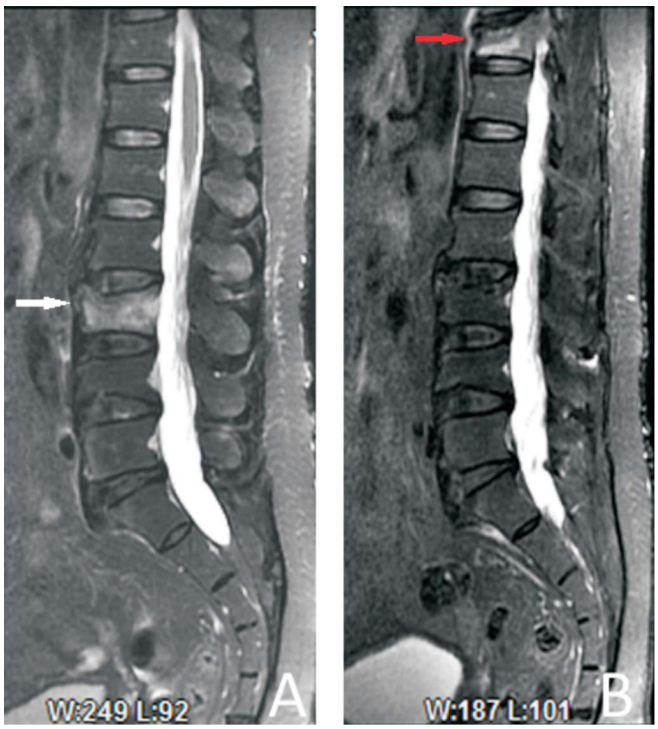

Figure 1. A typical case of OVRF in a 66-year-old woman. A. Fat-suppressed T2-weighted image showing L3 vertebral fracture (white arrow). B. Fat-suppressed T2-weighted image showing a new vertebral fracture (T11) (red arrow) four months after initial vertebral fracture, L3 vertebral fracture healed after conservative treatment.

General information of the two groups was collected, including age, smoking, hypertension, diabetes, weight, height, anti-osteoporosis therapy, lumbar brace fixation, bedridden for more than 4 weeks, body mass index (BMI), bone mineral density (BMD), L3/4 paraspinal muscle fat infiltration ratio (FIR), anterior height of fractured vertebral body (AHF) and adjacent normal vertebral body (AHN) after initial OVF, Cobb's Angle of the fractured vertebral body (CA) (Figure 2). The severity of vertebral compression (SVC) was calculated by the following formula: SVC = (AHN – AHF) / AHN. CA was determined by the angle formed by the perpendiculars of the extension lines of the upper endplate of the upper fractured vertebra and the lower endplate of the lower fractured vertebra. If multilevel OVF exists, SVC and CA were averaged.

Literature has shown that the degeneration of paraspinal muscles is correlated with the occurrence of OVF, and the degeneration of paraspinal muscles at L4 level is representative.[14,15] Therefore, FIR at L3/4 intervertebral disc level was analyzed in this study, which is consistent with previous studies.[14,15] Images were obtained with a 1.5T magnetic resonance scanner (Prisma, Siemens AG, Erlangen, Germany), using a standard spine array coil. Axial T2-weighted images of the lumbar spine were obtained at the intervertebral disc level of L3/4.

Image J software (Image J Version 1.5E, National Institutes of Health, Bethesda, Maryland, USA) was used to outline the boundary of bilateral erector and multifidus muscles and calculate bilateral mean muscle cross-sectional area (MCSA) (Figure 3). The adipose tissue in erector and multifidus muscles was delineated using Threshold segmentation technology[16–18] and the fat cross-sectional area (FCSA) was calculated (Figure 4). Then the FIR was calculated (FIR = FCSA/MCSA). The measurement was performed by two spinal surgeons with more than 10 years of work experience who were blind to the clinical and MRI data. Five patients were randomly selected from each group; L3/4MCSA, L3/4FCSA, and CA were independently measured by two spinal surgeons. Each spinal surgeon measured the parameters twice, and these replicates were performed 10 days apart. BMD at the lumbar spine (L1–L4) was measured by dual-energy X-ray (DXA) (Luna Prodigy Advance, GE, America), the lower value was adopted. Osteoporosis was diagnosed according to World Health Organization criteria: T-score ≤ -2.5 for osteoporosis, between -2.5 and -1.0 for osteopenia, and > -1.0 for normality.[19]

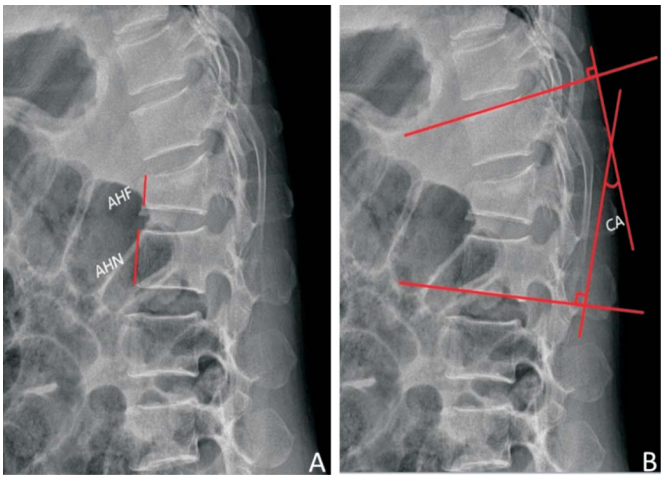

Figure 2. Measurement of vertebral height and Cobb's Angle. A. Anterior height of fractured vertebral body (AHF) and adjacent normal vertebral body (AHN). B. Cobb's Angle (CA).

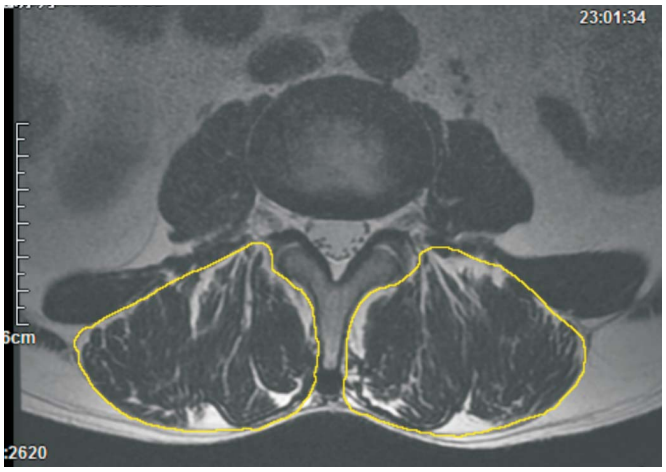

Figure 3. Measurement of paraspinal muscles. L3/4 intervertebral disc level on axial T2-weighted MRI were selected, and the boundary of paraspinal muscles (including erector spinae and multifidus) was depicted by Image J software and cross sectional area (MCSA) was measured.

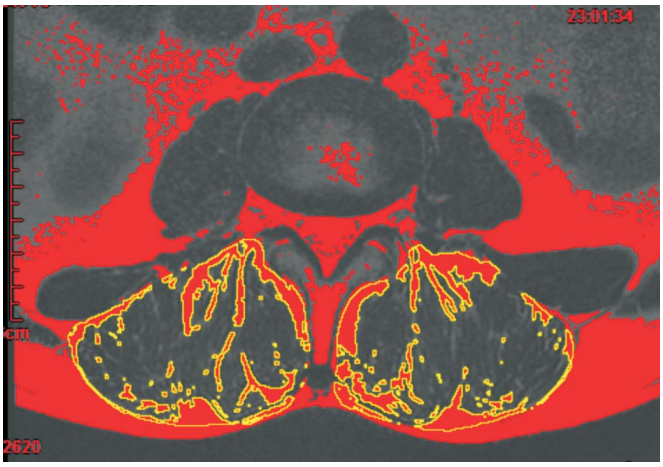

Figure 4. Measurement of fat cross sectional area. L3/4 intervertebral disc level on axial T2-weighted MRI were selected. Threshold segmentation technology was performed to select intraspinal adipose tissue and fat cross-sectional area (FCSA) was measured.

2.1. Statistical analysis

Data statistics and analysis were conducted using SPSS25.0 (IBM Corp., Armonk, NY, USA). Intra-observer reliability and the inter-observer reliability for L3/4MCSA and L3/4FCSA were evaluated by the interclass correlation coefficient (ICC). All statistically significant parameters ($p < 0.05$) were screened out for binary logistic regression analysis to identify independent risk factors. Then receiver operating characteristic curve analysis (ROC Curve) were drawn for the predictors and AUC values were calculated to evaluate the prediction accuracy. All tests were performed with a two-sided significance of 0.05.

3. Results

Intra-observer ICC was excellent for L3/4MCSA, L3/4FCSA and CA [ICC = 0.921 (95% CI = 0.902–0.933); ICC = 0.955 (95% CI = 0.935–0.979); ICC = 0.938 (95% CI = 0.922–0.968)]. The mean inter-observer reliability was also good for L3/4MCSA, L3/4FCSA and CA [ICC = 0.951 (95% CI = 0.932–0.971); ICC = 0.966 (95% CI = 0.942–0.978); ICC = 0.948 (95% CI = 0.933–0.976)].

According to the classification principle, there were 86 cases in non-refracture group and 65 cases in refracture group (Table 1). Univariate analysis showed that there were significant differences in age, weight, height, BMD and FIR between the two groups ($p < 0.05$), but no significant difference in other parameters (Table 1). Binary logistic regression analysis of variables with statistically significant parameters in univariate analysis showed that age ($p < 0.05$) and FIR ($p < 0.05$) were independent risk factors of OVRF (Table 2).

ROC curve was performed to evaluate the predictive value, which shows that the prediction accuracy of age, FIR and the two parameters together are 0.730, 0.778 and 0.813, respectively (Figure 5) (Table 3). Both age and FIR show good prediction accuracy and their

Table 2
Outcome of binary logistic regression analysis.

	B	p value	OR	95% confidence interval of OR	
				Lower bound	Upper bound
BMD	-0.15	0.44	0.859	0.58	1.27
Age	0.07	< 0.05	1.073	1.01	1.14
Weight (kg)	-0.67	0.07	0.514	0.25	1.06
Height (cm)	0.45	0.07	1.568	0.96	2.56
L3/4FIR (%)	0.12	< 0.01	1.123	1.06	1.19
Constant	-77.32	0.05	0.000		

BMD, bone mineral density; BMI, body mass index; FIR, fat infiltration ratio; OR, odds ratio; SD, standard deviation.

Table 1
Outcome of independent sample t-test between the two groups.

Parameters	No-refracture group (n = 86)	Refracture group (n = 65)	p value
Smoking, n	9	7	0.723
Anti-osteoporosis therapy, n	72	59	0.206
Lumbar brace fixation, n	59	45	0.815
Diabetes, n	12	10	0.805
Hypertension, n	46	35	0.922
Bedridden for more than 4 weeks, n	33	26	0.519
BMD	-3.45 ± 1.18	-4.14 ± 1.15	< 0.01
BMI (kg/m^2)	23.17 ± 2.68	22.24 ± 3.27	0.06
Age	65.90 ± 8.30	72.91 ± 6.67	< 0.01
Weight (kg)	57.42 ± 9.11	52.97 ± 9.05	< 0.01
Height (cm)	157.12 ± 5.74	152.65 ± 14.23	< 0.05
L3/4FIR (%)	29.95 ± 7.51	39.72 ± 9.32	< 0.01
SVC (%)	21.10 ± 1.13	23.12 ± 1.44	0.26
CA	11.51 ± 0.84	14.04 ± 1.12	0.06

BMD, bone mineral density; BMI, body mass index; CA, Cobb's Angle; FIR, fat infiltration ratio; n, number of subjects; SD, standard deviation; SVC, severity of vertebral compression.

comprehensive prediction accuracy is higher. Through further calculation to determine the critical values of age and FIR, the results demonstrated that patients aged over 63.5 years (sensitivity 0.969, specificity 0.453) and FIR over 37.1% (sensitivity 0.615, specificity 0.849) were more likely to develop OVRF. The incidence of OVRF increased by 7.3% with the increase of age by one year and the incidence of OVRF increased by 12.3% for every 1% increase in FIR.

Although BMD was not an independent risk factor of OVRF, BMD showed significant differences in univariate analysis between the two groups. ROC curve analysis of BMD showed that the prediction accuracy of BMD was 0.639, slightly worse than that of age and FIR. Patients with OVF who prefer conservative treatment are more likely to develop OVRF when BMD T-scores is less than -2.85 (sensitivity 0.954, specificity 0.337). The comprehensive prediction accuracy of age, FIR and BMD was 0.821 (Figure 6) (Table 3), which showed better prediction effect.

4. Discussion

Postmenopausal OVF is an important complication of postmenopausal osteoporosis.[20] An in-depth understanding of the risk factors of OVRF will provide positive guidance for its prevention and treatment. OVRF has attracted the attention of many scholars, but most of the current studies mainly focus on OVRF after vertebral augmentation.[21,22] As far as we know, there is no comprehensive prediction study on the risk factors of OVRF for conservative treatment. After initial OVF, many patients prefer conservative treatment, including bed rest, thoracolumbar brace fixation, anti-osteoporosis drugs and analgesic drugs, due to missed diagnosis, misdiagnosis, lack of medical funds and other reasons. Clinically, we frequently encounter OVRF within a short period of time in patients who choose conservative treatment after initial OVF. Consequently, exploring the risk factors of OVRF in such patients will help to provide more active and effective prevention strategies. Therefore, the purpose of this study is to synthesize risk factors and further analyze their predictive value.

In this study, we found significant differences between the two groups in age, weight, height, FIR, and BMD. Patients in the refracture group had higher paraspinal muscle FIR, lower BMD and higher age. Regression analysis showed that age and FIR were independent risk factors of OVRF. At the same time, age and FIR showed good prediction accuracy of OVRF, which was higher than BMD. The prediction value of integrated two independent risk factors was higher than that of a single risk factor. Based on this study, patients at high risk of OVRF should be given more targeted prevention and treatment programs. If OVF patients are older than 63.5 years and L3/4 FIR is more than 37.1%, they should not be recommended for conservative treatment. Meanwhile, they should be advised to actively carry out exercise during rehabilitation treatment to improve muscle strength, balance and fear of falling,[23] and standard anti-osteoporosis treatment is essential.[24]

In the typical case we provided, this was a 66-year-old patient who preferred conservative treatment after the initial onset of OVF. After four months the patient developed OVRF. According to the results of this research by our team, this patient was older than 63.5 years at the time of initial OVF, and the risk of OVRF was significant if conservative treatment was selected. Therefore, conservative management should not be recommended for the patient at the time of initial OVF. The results of our research will provide some guidance for selecting conservative treatment or surgical treatment for patients with initial OVF.

Fat infiltration of paraspinal muscle is an important feature of paraspinal muscle degeneration,[25] but there is no significant correlation between the changes of body composition of paraspinal

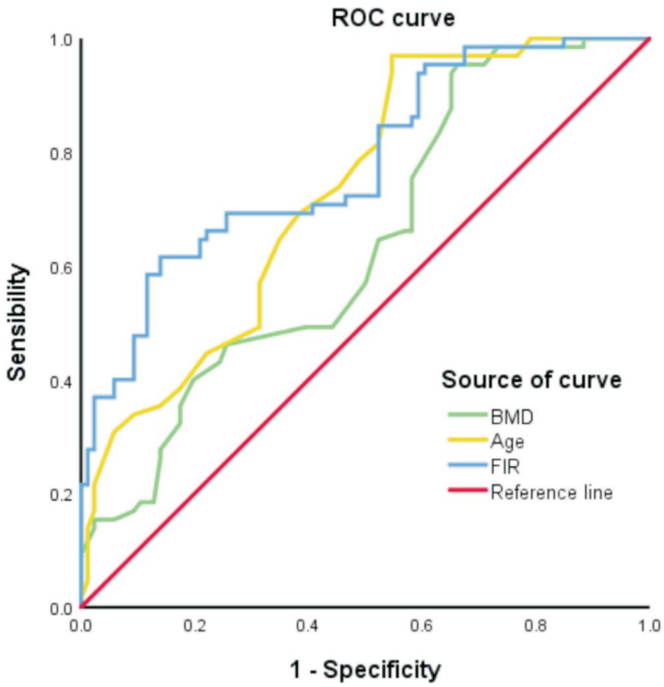

Figure 5. ROC curve.

Table 3
Area under the curve (AUC).

Parameter	AUC	Standard deviation	p value	95% confidence interval	
				Lower bound	Upper bound
Age	0.730	0.04	< 0.01	0.65	0.81
L3/4FIR(%)	0.778	0.04	< 0.01	0.70	0.85
BMD	0.639	0.05	< 0.01	0.55	0.73
Age + L3/4FIR	0.813	0.03	< 0.01	0.75	0.88
Age + L3/4FIR + BMD	0.821	0.03	< 0.01	0.76	0.89

BMD, bone mineral density; FIR, fat infiltration ratio.

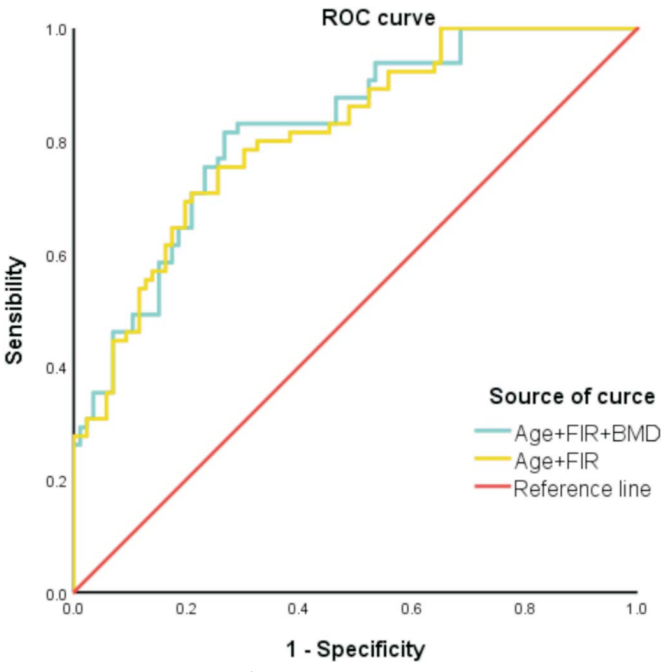

Figure 6. ROC curve.

muscle and BMI, which may be related to the fact that local muscle degeneration is not synchronized with the changes of body composition.[26] Li et al. have shown BMI is a risk factor of OVF,[27] which is inconsistent with the conclusion of this study. The reason may be that we did not include BMI of patients without osteoporotic fractures in the study. Degenerative forms of paraspinal muscle include reduced functional muscle volume and increased muscle fat infiltration, while reduced muscle function may lead to loss of balance and coordination, resulting in an increased risk of falls in patients with osteoporosis,[28] which increases the risk of OVF. Previous studies have demonstrated that BMD is closely related to FIR,[26,29] because there are a variety of common endocrine and molecular signaling pathways between bone and muscle,[30] so the degeneration may affect each other. With age, degeneration of both bone and muscle may occur simultaneously. Relevant studies have demonstrated that osteoporosis and sarcopenia often coexist,[31,32] our previous studies confirmed that the degree of paravertebral muscle degeneration was correlated with the severity of vertebral compression in OVF,[33] so the overall degeneration of bone and muscle should be paid close attention in considering the risk factors of OVRF. At the same time, comprehensive prevention, rehabilitation and treatment measures for bone and muscle should be provided in the process of OVRF prevention. Although BMD was not found to be an independent risk factor in our research model, Liisa et al.[34] demonstrated that the importance of bone mineral density in predicting the risk of osteoporotic fractures decreases with age, BMD as an critical risk factor for OVF has been confirmed,[35] and its correlation with OVF cannot be denied. Many patients in our model had obvious vertebral hyperosteoplasia and acute vascular calcification, which may affect the accuracy of BMD in dual-energy X-ray examinations. Therefore, the conclusions of this study are inconsistent with previous studies, and more accurate conclusions can be drawn by further QCT determination of BMD.

In this study, multiple risk factors of OVRF were comprehensively analyzed and independent risk factors were found. In the meantime, the independent and comprehensive predictive values of various high risk factors were further discussed, providing preventive measures and treatment guidance for clinical prevention of OVRF. Nevertheless, there are certain limitations in this study: The number of cases in this study is small, and the predicted critical values of each independent risk factor need to be further investigated with a larger sample size and multi-center research. OVRF is affected by multiple factors, such as whether standardized anti-osteoporosis treatment is carried out during conservative treatment, whether braces are worn, and whether patients have cognitive dysfunction, etc., which have not been included in this research. These factors need to be further analyzed.

5. Conclusions

In conclusion, age and L3/4FIR are independent risk factors for OVRF in postmenopausal women. The prediction value of integrated two independent risk factors was higher than that of a single risk factor. Postmenopausal women with initial OVF are more likely to develop OVRF if they are over 63.5 years old and L3/4FIR over 37.1%, more targeted prevention and treatment programs should be provided for these patients.

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Conflict of interest

The authors declare no conflict of interest concerning this manuscript.

Ethics approval

This study was approved by the Investigational Ethics Review Board (Jingmen People's Hospital, Jingmen, Hubei, China), and an exemption from informed consent was obtained from the board.

Data availability

All data are available upon reasonable request.

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