

Construction and Validation of Predictive Model for Decreased Bone Density in Premature Ovarian Insufficiency

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Abstract: Premature ovarian insufficiency (POI) is an endocrine disorder that affects women of childbearing age. It is characterized by premature ovarian failure, leading to decreased estrogen levels and increased gonadotropin levels. POI not only impacts reproductive health but is also associated with various long-term health issues, particularly osteoporosis due to decreased estrogen protection, making individuals more susceptible to developing osteoporosis. This study utilized a retrospective cohort study design, including patients diagnosed with POI at the First Affiliated Hospital of Henan Polytechnic University during a certain period. Through detailed medical history collection, bone density measurements, and assessment of other relevant factors, we analyzed potential risk factors associated with decreased bone density caused by POI. Multivariable logistic regression analysis was used to identify independent risk factors, upon which a predictive model was constructed. The results showed that a total of 198 POI patients were included in the study, among whom 54 (34.8%) had decreased bone density. Multivariable analysis revealed that age, parity, family history of osteoporosis, BMI, and regular physical exercise were significantly associated with decreased bone density. Based on these factors, we developed a predictive model and evaluated its predictive performance using the receiver operating characteristic (ROC) curve, with an area under the ROC curve of 0.953 (95% CI: 0.924–0.983), indicating good predictive accuracy.

Keywords: Premature ovarian insufficiency, decreased bone density, predictive model, risk factors

1. Introduction

Premature ovarian insufficiency is a serious endocrine disorder that significantly impacts women's health. It typically occurs in women under 40 years old, with an incidence rate of about 1%. Premature ovarian insufficiency not only leads to reduced fertility but also presents a range of clinical symptoms such as hot flashes, night sweats, and challenges in the psychological and social aspects, which are closely related to sudden changes in hormone levels. Apart from directly affecting reproductive health, premature ovarian insufficiency also increases the risk of developing osteoporosis due to long-term estrogen deficiency, a silent disease that can result in severe health complications. Osteoporosis is a common disease affecting the elderly globally, characterized by decreased bone mass and degeneration of bone microstructure, thereby increasing the risk of fractures. It is estimated that over 200 million women worldwide are affected by osteoporosis, leading to significant healthcare burdens and impacting patients' quality of life. Particularly for women with premature ovarian insufficiency, early estrogen deficiency exacerbates bone loss, making them more susceptible to osteoporosis at an earlier stage than the general population.

Although the association between premature ovarian insufficiency and osteoporosis is well recognized, the understanding of specific risk factors for premature ovarian insufficiency patients developing osteoporosis remains limited. Early identification of these risk factors and interventions are crucial in preventing the progression of osteoporosis in women with premature ovarian insufficiency. This study aims to identify risk factors associated with secondary osteoporosis in premature ovarian insufficiency through retrospective analysis and construct a predictive model to evaluate the risk of osteoporosis development in clinical practice, thereby providing a basis for personalized prevention strategies. Through this research, we hope to enhance long-term bone health for women with premature ovarian insufficiency and alleviate the social and healthcare burdens associated with it.

2. Materials and Methods

2.1 General Information

A total of 213 patients with premature ovarian insufficiency, aged below 40, admitted to the First Affiliated Hospital of Henan Polytechnic University from January 2019 to September 2023 were selected. Inclusion criteria: Age: Females under 40 years old. Outpatients or inpatients with a history of menstrual cessation (amenorrhea) lasting at least 4 months. Serum follicle-stimulating hormone (FSH) levels consistently above 40 mIU/mL in two measurements taken at least one month apart. Exclusion of other potential causes of amenorrhea, such as pregnancy, lactation, contraceptive use, severe stress, chronic diseases, pituitary or hypothalamic disorders, etc. Medical history and physical examination: Patients must have complete medical history records and physical examination data. Additional assessments: Additional biochemical tests and clinical evaluations may be required to exclude other endocrine or metabolic abnormalities related to osteoporosis. Exclusion criteria: Exclusion of patients using any medications that may affect bone metabolism (such as long-term use of glucocorticoids) or known bone diseases (such as primary osteoporosis, multiple myeloma, etc.). All participants in this study were informed of the study details and voluntarily agreed to participate by signing an informed consent form.

2.2 Methods

2.2.1 The Diagnostic Criteria for Osteoporosis

Using the dual-energy X-ray bone densitometer/EXCELLUS device from Osteosys company, this study conducted DXA scans of the participants' lumbar spine and hip bone density. Radiologists evaluated the measured bone mineral density (in g/cm²) without knowledge of the participants' grouping. Bone density diagnostic criteria: Referring to the 'Diagnostic criteria for primary osteoporosis: year 2012 revision.'^[1], a T-score at or above -1.0 standard deviation indicates normal bone density; a T-score between -1.0 and -2.5 standard deviations indicates mild bone loss; while a T-score at or below -2.5 standard deviations indicates osteoporosis. In this study, the categories of $-2.5SD < T < -1.0SD$ and $T \leq -2.5SD$ were combined as reduced bone mass.

2.2.2 Clinical Information Collection

A self-designed questionnaire was used to collect clinical information, including patient age, body mass index (BMI), duration of premature ovarian insufficiency (whether >10 years), family history of osteoporosis, smoking history, alcohol consumption history, age at menarche, parity, etc. A total of 209 questionnaires were distributed in this study, with 189 valid responses received (90.43%).

2.2.3 Statistical Methods

Data analysis was performed using SPSS 25.0 software. Categorical data were presented as [n (%)], and the chi-square test was used. The Kolmogorov-Smirnov (K-S) test was used to assess the normal distribution of continuous data, with a $P > 0.05$ indicating a normal distribution, presented as ($\bar{x} \pm s$), and independent sample t-tests were used for intergroup comparisons. When the data did not follow a normal distribution, it was presented as M (Q1, Q3), and the Mann-Whitney U test was used. Logistic regression analysis was conducted to identify factors influencing bone density reduction in patients with premature ovarian insufficiency. Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1 Comparison of General Data between Normal Bone Group and Reduced Bone Mass Group

Compared to the non-occurrence group, the occurrence group had a higher average age ($P < 0.05$), a lower proportion of individuals with regular physical exercise ($P < 0.05$), an increased proportion of individuals with a family history of osteoporosis ($P < 0.05$), and a higher number of childbirths ($P < 0.05$). Refer to Table 1

Table 1: Comparison of General Data between the Two Groups

The general information	Occurrence group(n=54)	Non-occurrence group(n=135)	Z/ χ^2	P
Age[M(Q1,Q3),]	37(36,38)	35(33,36)	7.964	<0.001*
BMI[M(Q1,Q3),kg/m ²]	21.34(19.82,23.17)	22.21(20.70,24.39)	2.12	0.034*

Family history of OP [n(%)]	12(22.22)	15(11.11)	3.89	0.049*
Smoking [n(%)]	4(7.41)	5(3.70)	1.17	0.280
Alcohol consumption[n(%)]	7(12.96)	10(7.41)	1.45	0.228
Age at menarche [M(Q1,Q3)]	12(11,13)	12(11,13)	0.42	0.672
Number of childbirths [M(Q1,Q3)]	3(2,4)	1(1,3)	7.09	<0.001*
Regular physical exercise [n(%)]	20(37.04)	79(58.52)	7.14	0.008*
Take calcium supplements[n(%)]	26(48.15)	80(59.26)	1.93	0.164
Duration of premature ovarian failure > 10 years [n(%)]	5(9.26)	8(5.93)	0.67	0.413
Drinking milk [n(%)]	12(22.22)	43(31.85)	1.73	0.188
The consumption of meat in diet[n(%)]	20(37.04)	63(46.67)	1.45	0.228
The consumption of a vegan diet[n(%)]	5(9.26)	10(7.41)	0.18	0.670
Living alone[n(%)]	10(18.52)	14(10.37)	2.31	0.129

3.2 Multifactorial Analysis of Factors Influencing Bone Density Reduction in Patients with Premature Ovarian Insufficiency

A logistic regression analysis was conducted with bone density reduction (No=0, Yes=1) as the dependent variable and age (actual value), BMI (actual value), number of childbirths (actual value), regular physical exercise (Yes=0, No=1), and family history of osteoporosis (No=0, Yes=1) as independent variables. The results showed that age, number of childbirths, and family history of osteoporosis are risk factors for bone density reduction in patients with premature ovarian insufficiency, while BMI and regular physical exercise are protective factors ($P < 0.05$). Refer to Table 2. The predictive model formula obtained is: $P = -40.347 + 1.311 \times \text{age} + (-0.408) \times \text{BMI} + 2.147 \times \text{family history of osteoporosis} + 1.454 \times \text{number of childbirths} + (-1.810) \times \text{regular physical exercise}$

Table 2: Multifactorial Analysis of Factors Influencing Bone Density Reduction in Patients with Premature Ovarian Insufficiency

Independent variable	B	SE	Wald χ^2	P	OR	95% CI
Age	1.311	0.274	22.825	<0.001	3.709	2.166~6.351
BMI	-0.408	0.141	8.430	0.004	0.665	0.505~0.876
Family history of OP	2.147	1.054	4.148	0.042	8.560	1.084~67.588
Number of childbirths	1.454	0.338	18.472	<0.001	4.282	2.206~8.312
Regular physical exercise	-1.810	0.835	4.700	0.030	0.164	0.032~0.841
Constant term	-40.347	9.193	19.261	<0.001	0.000	-

3.3 Model Construction and Validation

Using normal bone density as the negative sample and reduced bone density as the positive sample, a ROC curve was established. The results showed that the area under the ROC curve (AUC) for predicting reduced bone density was 0.953 (95% CI: 0.924-0.983), with the optimal cutoff value being 0.319. At this cutoff value, the sensitivity for diagnosing reduced bone density was 90.7%, specificity was 88.9%, positive predictive value was 86.5%, negative predictive value was 55.8%, and accuracy was 92.0% ($P < 0.001$). This indicates that the model demonstrates good predictive ability and can provide valuable assistance in clinical practice. The results are shown in Figure 1 and Table 3.

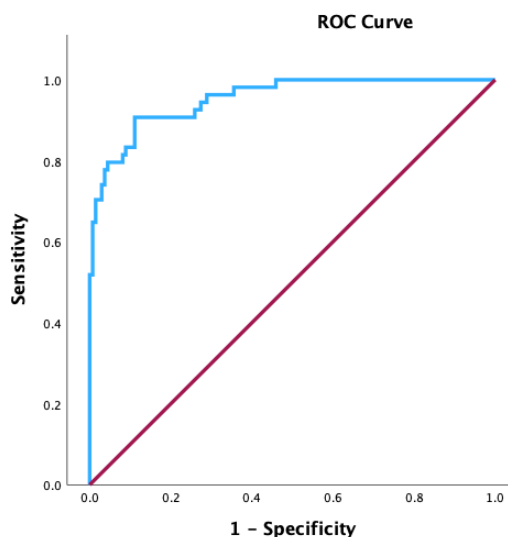


Figure 1: ROC curve of bone mineral density reduction prediction model for patients with premature ovarian insufficiency

Table 3: ROC Curve Area and Related Statistics (%) of the Bone Density Reduction Prediction Model for Patients with Premature Ovarian Insufficiency

Model	AUC (95% CI)	Cut-off value	Sensitivity	Specificity	Accuracy
Logistic (P)	0.953 (0.924-0.983)	0.319	90.7	88.9	92

4. Discussion

Osteoporosis has a subtle onset, and high detection costs, and poses a significant threat to the bone health of women with premature ovarian insufficiency. Clinical prediction models have shown great potential in the diagnosis and prediction of various diseases. Therefore, this study aimed to explore the bone density and clinical characteristics of women with premature ovarian insufficiency to construct a clinical prediction model in the form of a probability column chart to achieve early prediction of osteoporosis and subsequent personalized early treatment, thus promoting the development of women's public health.

In this study, we conducted an in-depth logistic regression analysis to explore the independent influencing factors of secondary bone density reduction in patients with premature ovarian insufficiency (POI). BMI was identified as a protective factor, a finding consistent with previous research. Studies by Fan J and others have suggested that higher BMI may be related to the presence of adipose tissue, which can promote estrogen production and increase free hormone levels, potentially protecting bone density^[2]. Yun Zhan and colleagues, in a study of 11,075 adults from the National Health and Nutrition Examination Survey (NHANES), suggested that BMI may be a potential factor affecting the mechanism of bone density due to socioeconomic status^[3]. Previous research has shown a close relationship between the development of osteoporosis in perimenopausal women and factors such as age^[4] ^[5], number of childbirths^[6], family history of osteoporosis^[7], BMI^[8] ^[9], and regular physical exercise^[10]. By including 14 factors in the logistic regression model, the results of this study align with trends observed in previous research conclusions.

Most studies on osteoporosis in women have focused on perimenopausal or type 2 diabetes patients in recent years. However, women with premature ovarian insufficiency are at a higher risk of bone density reduction due to the early loss of estrogen protection. The model for predicting bone density reduction in patients with premature ovarian insufficiency established in this study was validated by the receiver operating characteristic (ROC) curve, with an area under the curve of 0.953, demonstrating good predictive ability and providing a convenient and practical method for predicting bone health in this often overlooked patient group.

In this study, we delved into the risk factors for secondary bone density reduction in patients with

premature ovarian failure (POF) and successfully constructed a predictive model aimed at identifying high-risk individuals early to implement preventive measures. Our analysis indicates that age, BMI, family history of osteoporosis, number of childbirths, and regular physical exercise are important indicators for predicting the development of bone density reduction in POF patients. The predictive model constructed in this study, validated by statistical methods, exhibits good sensitivity and specificity, serving as a practical tool for clinicians to assess and manage the risk of bone density reduction in patients with premature ovarian insufficiency.

However, despite the good performance of this model on the current dataset, it still has certain limitations. Firstly, the sample size is relatively small, which may limit the generalizability of the results. Secondly, our data primarily come from a specific population, which may not fully represent other racial and cultural backgrounds. Future research should involve larger and more diverse populations to enhance the model's generalizability.

In conclusion, this study not only provides new insights into the risk factors for secondary bone density reduction in premature ovarian insufficiency but also offers a valuable tool for clinical practice through the construction of a predictive model. We hope that these findings will contribute to improving prevention and management strategies for osteoporosis resulting from bone density reduction triggered by premature ovarian insufficiency.

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