



天津医科大学
TIANJIN MEDICAL UNIVERSITY



天津市肿瘤医院 肿瘤研究所
天津医科大学肿瘤医院
TIANJIN MEDICAL UNIVERSITY CANCER INSTITUTE & HOSPITAL

Development and Validation of a Risk Prediction Model for Aromatase Inhibitor - Associated Osteoporosis in Breast Cancer Patients

Osteoporosis in Chinese Breast Cancer Patients: A Retrospective Cohort Study

 Reporters: Yanshan Yi, Gaojing Ren (2024 Ph.D. Candidates in Nursing)

 Supervisor: Professor Wanmin Qiang

 Tianjin Medical University Cancer Institute & Hospital

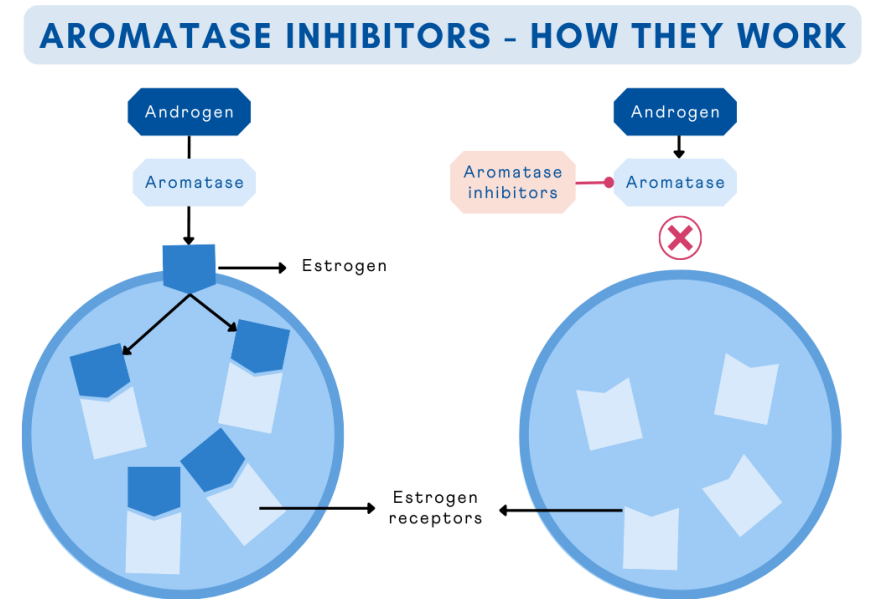


1

Research Background

Research Background

- According to the 2022 Statistical Report from the National Cancer Center of China, breast cancer is the second most common malignant tumor among Chinese women.;
- **Approximately 70% of breast cancer cases are hormone receptor - positive, requiring endocrine therapy.**
- **AI -associated OP** can reduce estrogen levels and the recurrence risk of breast cancer. However, they also cause bone loss. Moreover, the decline in estrogen levels after menopause in women accelerates bone loss.



芳香化酶抑制剂作用机制

Han B, 2024; Waks A G, 2019; 陈茜, 等; Eastell R, 2006

研究背景

➤ **Osteoporosis (OP)** is a systemic bone disease characterized by reduced bone mass and deterioration of bone tissue microstructure. The incidence of AI - related OP in breast cancer patients ranges from approximately 11% to 30%. Osteoporotic fractures are a serious consequence of OP, which can affect patients' treatment compliance and quality of life.

➤ **Risk prediction models** are effective tools for individualized risk prediction and accurate identification of high - risk groups. They use statistical methods to accurately predict the probability of a patient developing a certain disease, classify high - risk groups based on the probability, and implement individualized prevention strategies for high - risk groups.

章振林等, 2023; Kwan M L, 2023; 李文环等, 2017; LeBoff M S, 2022;
Abdel-Razeq H, 2022; Wolff R F; 2019

Research Background

Summary of Existing Studies on Related Risk Prediction Models

Literature	Modeling Method	Study Subjects	Outcome Indicator	Assessment Tool and Diagnostic Criteria	Influencing Factors	Limitations
Li Wenhuan, 2017	Cox Regression	Breast cancer patients taking anastrozole	OP	DXA $T \leq -2.5$	Menopausal duration, duration of anastrozole use, duration of bisphosphonate use, serum bone - specific alkaline phosphatase	When evaluating the predictive value of risk factors, the area under the ROC curve (AUC) is low (0.510 - 0.735), and the final prediction model is not presented, so it cannot be applied clinically.
Lichen Ji 2022	Machine Learning Algorithm	Breast cancer patients	OP	DXA, 2022 AACE Osteoporosis Treatment Guidelines	Age, anti - estrogen therapy, molecular subtype, glucocorticoid therapy, serum bone - specific alkaline phosphatase	When evaluating the predictive value of risk factors, the area under the ROC curve (AUC) is low (0.510 - 0.735), and the final prediction model is not presented, so it cannot be applied clinically.
Meiling Chu 2023	Machine Learning Algorithm	Breast cancer patients taking AI	Bone Loss	DXA $T \leq -1.0$	Duration of breast cancer, duration of oral AI use, hip fracture index, major osteoporotic fracture index, prolactin, osteocalcin	If the bone loss prediction model constructed in this study is used for OP risk prediction, it may overestimate the OP risk in this population.

注：DXA为双能X射线吸收法

李文环等, 2017; Ji L, 2022; Chu M, 2023



2

Research Content and Objectives

Research Content and Objectives

To construct and validate a nomogram model for predicting the risk of AI - related OP in breast cancer patients.



3

Research Methods and Results

Research Methods

Phase 1: Identification of Potential Influencing Factors for AI - related OP in Breast Cancer Patients

Category	Variables (22 in total)
General Demographic Factors	Age, BMI, Physical Activity
Medical History and Comorbidities	Family History, Fracture History, Fall History, Hypertension, Diabetes, Glucocorticoid Use History
Breast Cancer Disease and Treatment Factors	Molecular Subtype, Chemotherapy, Use of Anthracycline and Cyclophosphamide Chemotherapy Drugs, Radiotherapy, Targeted Drug Therapy, Duration of AI Use
Physiological and Biochemical Indicators	BALP
Lifestyle Factors	Exercise Frequency, Average Exercise Duration, Regular Calcium/Vitamin D Supplementation, Smoking, Carbonated Beverage Consumption, Coffee Consumption

Research Methods

Phase 2: Construction and Validation of the Risk Prediction Model for AI - related OP in Breast Cancer Patients

- **Study Design**: Retrospective cohort study
- **Study Subjects**: Breast cancer patients who completed DXA bone mineral density (BMD) examination and took AI in a tertiary first - class oncology hospital in Tianjin from January 2016 to October 2023.
- **Diagnostic Criteria**: Patients were divided into the osteoporosis group and the non - osteoporosis group according to whether they had OP. Patients diagnosed with OP by DXA were included in the osteoporosis group. According to the WHO diagnostic criteria: OP can be diagnosed if the T - score of any one of the lumbar spine 1 - 4, femoral neck, and total hip is $\leq - 2.5$.

Research Methods

Phase 2: Construction and Validation of the Risk Prediction Model for AI - related OP in Breast Cancer Patients

➤ Inclusion Criteria:

1. Patients with pathologically confirmed primary breast cancer, in accordance with the Breast Cancer Diagnosis and Treatment Guidelines (2022 Edition).;
2. Postmenopausal patients (natural menopause or menopause induced by drugs or surgery) who have taken AI for ≥ 6 months.

➤ Exclusion Criteria:

1. Patients with a previous history of OP or OP detected in the baseline BMD examination.

➤ Exclusion Criteria (for Data):

1. Patients who died or were lost to follow - up after discharge.
2. Patients and/or their family members refused follow - up.
3. Patients with missing data $> 10\%$.

Research Methods

Phase 2: Construction and Validation of the Risk Prediction Model for AI - related OP in Breast Cancer Patients

Sample Size Calculation:

According to the sample size estimation method for Logistic regression analysis, the sample size should be 5 - 10 times the number of independent variables. This study estimated that 22 independent variables would be included. Based on the literature, the incidence of AI - related OP in breast cancer patients is approximately 11% - 30%, and a 10% loss - to - follow - up rate is also considered.

Finally, 1186 patients were included in this study, which met the sample size requirement.

According to the ratio of 7:3, the sample size of the modeling group was 830 cases, and that of the validation group was 356 cases.

Research Methods

Data Collection and Entry:

- The collection and export of data obtained the approval and support of the relevant departments of a tertiary first - class oncology hospital in Tianjin.。
- Data of breast cancer patients who completed DXA examination from January 2016 to October 2023 were exported from the hospital medical record system, and the study subjects were selected according to the inclusion and exclusion criteria. Patients were followed up by telephone according to the Questionnaire on Influencing Factors of AI - related OP in Breast Cancer Patients. Data were entered into Excel spreadsheets on the day of collection.
- Using the patient's name and medical record number as search terms, the patient's BMD test results were viewed through the hospital medical record system and entered into Excel spreadsheets. At the same time, the missing and incomplete contents in the spreadsheets were supplemented and improved.

Research Methods

Phase 2: Construction and Validation of the Risk Prediction Model for AI - related OP in Breast Cancer Patients

SPSS 26.0 and R 4.0.4 software were used for statistical analysis.

Univariate Analysis

- To screen out variables with potential associations with the outcome.

Logistic Regression Analysis

The forward - backward stepwise regression method was used to determine the final variables included in the model, and a nomogram model for predicting the risk of AI - related OP in breast cancer patients was constructed.

Model Evaluation

- Discriminative Ability;
- Classification Performance;
- Calibration;
- Clinical Utility.

Quality Control

➤ Study Design Phase:

- Clinical medical and nursing experts in the fields of breast oncology, bone oncology, breast rehabilitation, and nursing management were invited to revise and improve the potential influencing factor variables, and the potential influencing factor variables and their operational definitions were determined before data collection.
- A pre - experiment was conducted before formal data collection to adjust the content of telephone follow - up and improve the data collection form..

➤ Data Collection and Entry Phase:

- During the telephone follow - up, active communication was conducted with patients, their questions were answered patiently, and their trust and support were obtained.;
- The patients' bone conditions were determined strictly in accordance with the WHO diagnostic criteria. If there were any doubts, BMD diagnosis experts were consulted;
- After the completion of data collection, range and logical verification were conducted on the data collection forms.

➤ Data Analysis Phase:

- Statistical analysis was conducted strictly in accordance with statistical methods, and guidance was sought from professionals in statistical analysis to ensure the reliability and scientificity of statistical analysis.

Ethical Principles

- This study has been approved by the Ethics Committee of Tianjin Cancer Hospital: Approval No. bc2023143.
- The principles of informed consent, voluntariness, confidentiality, impartiality, and non - maleficence were followed

医学伦理委员会快速审评通知书

批件号: bc2023143

项目简况:

临床试验项目名称: 乳腺癌患者芳香化酶抑制剂相关骨质疏松风险预测模型的构建

临床试验主要研究者: 强万敏

临床试验申办者: 天津市肿瘤医院

投票结果:

投票人数 3 人, 同意 3 票, 作必要修改后同意 0 票, 作必要修改后复审 0 票, 不同意 0 票, 终止或暂停先前批准的试验 0 票。

快速审评意见:

医学伦理委员会对上述研究项目有关内容(见附件)进行了认真的快速审评。经审查, 医学伦理委员会同意“乳腺癌患者芳香化酶抑制剂相关骨质疏松风险预测模型的构建”用于发表文章。研究过程中涉及人的样本和数据使用情况, 遵循隐私保护原则, 切实保护个人隐私。如有涉及人类遗传资源相关事宜, 请在人类遗传资源管理办公室审核通过后, 再在我院开展。

主任委员(或授权委员)签字:

主审委员签字:

天津市肿瘤医院医学伦理委员会

2023 年 09 月 08 日

批件有效期: 1 年; 截止日期: 2024 年 09 月 08 日

申办者/研究者在研究期间的注意事项:

1. 充分尊重受试者尊严和自主权, 保证其在充分理解的情况下自愿做出同意的决定。
2. 严格按照临床研究方案进行临床试验。研究期间如发生严重不良事件以及影响研究风险与受益比的非预期不良事件, 应及时报告本伦理委员会。
3. 若临床研究超过一年, 每年度应向本伦理委员会提交临床研究年度报告。试验结束时向本伦理委员会提交临床研究总结报告。

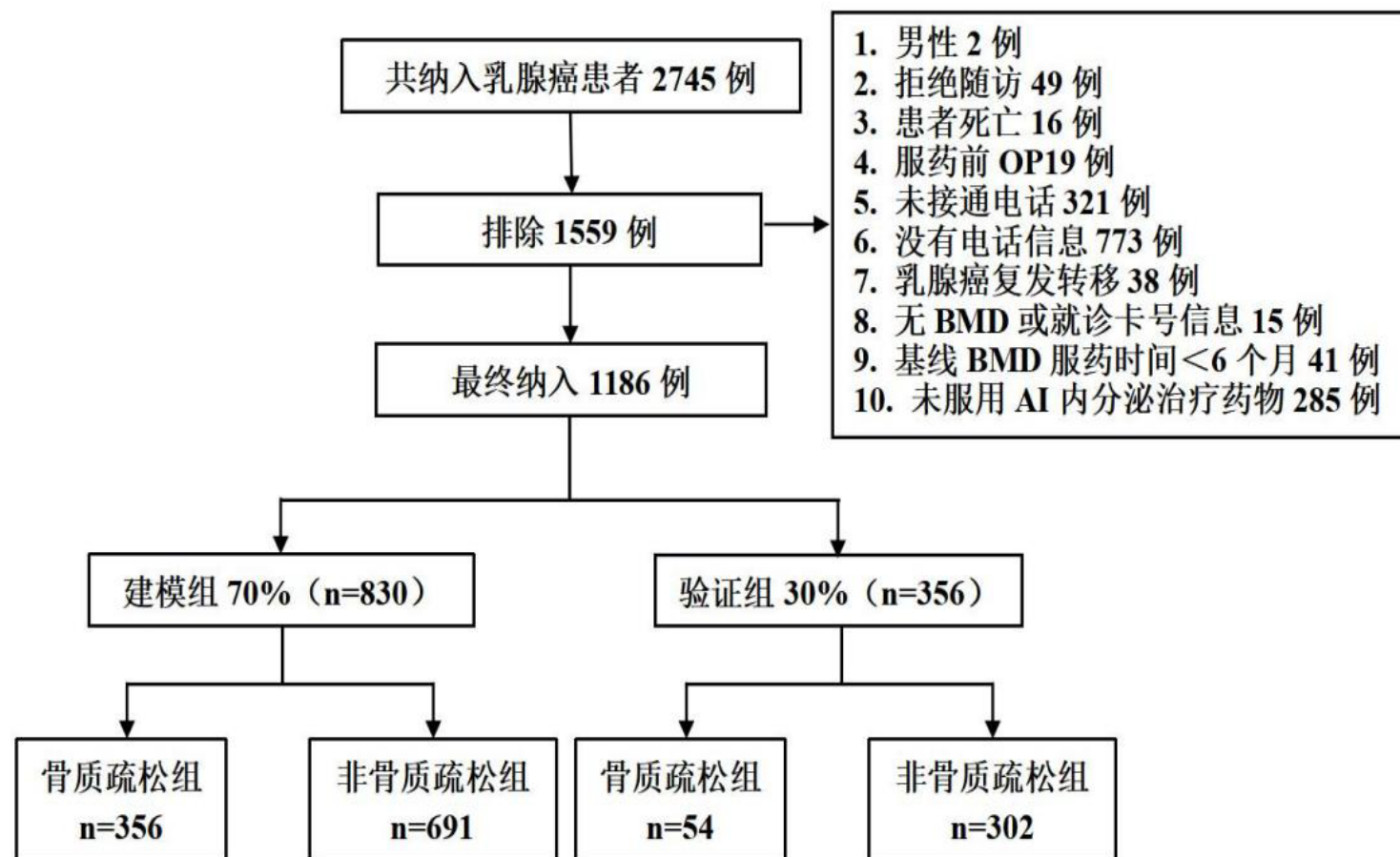
地址: 天津市河西区环湖西路肿瘤医院 D 座负 3 楼(300060)

电话: (022)23340123-6417 传真: (022)23524155

邮箱: ec_tjcih@126.com

Research Results

Baseline Characteristics



- The incidence of OP was approximately 16.27%;
- Except for the variable of carbonated beverage consumption, which showed a statistically significant difference in the baseline data comparison between the modeling group and the validation group ($P < 0.05$), there were no statistically significant differences in other potential risk factors between the modeling group and the validation group ($P \geq 0.05$).

Univariate Analysis

Baseline Characteristics

Variable	Grouping	Osteoporosis	Non - Osteoporosis	t/x ²	P
Age		61.94±6.99	54.53±10.18	-8.095	< 0.001
BMI	Underweight	5(3.70)	12(1.73)	NA	< 0.001
	Normal	63(46.67)	237(34.10)		
	Overweight	58(43.96)	313(45.04)		
	Obese	9(6.67)	133(19.14)		
Physical Activity	Mild	104(77.04)	354(50.94)	38.952	< 0.001
	Moderate	23(17.04)	135(19.42)		
	Severe	8(5.93)	206(29.64)		
Fracture History	No	116(85.9%)	655(94.2%)	11.847	0.001
	Yes	19(14.1%)	40(5.8%)		
Fall History	No	130(96.30)	691(99.42)	7.603	0.006
	Yes	5(3.70)	4(0.58)		
Glucocorticoid History	No	111(82.22)	477(68.63)	10.106	0.001
	Yes	24(17.78)	218(31.37)		
Hypertension	No	93(68.89)	559(80.43)	8.94	0.003
	Yes	42(31.11)	136(19.57)		

Potential influencing factors of AI ↑₈
related OP in breast cancer patients:

- Age
- BMI
- Physical Activity
- Fracture History
- Fall History
- Glucocorticoid Use
- Hypertension
- Diabetes
- Chemotherapy
- Cyclophosphamide and Anthracycline/Taxane Chemotherapy
- Drugs
- Radiotherapy
- Targeted Drug Therapy
- Carbonated Beverage Consumption
- Coffee Consumption

Variable	Grouping	Osteoporosis	Non - Osteoporosis	t/x²	P
Diabetes	No	117(86.67)	639(91.94)	3.875	0.049
	Yes	18(13.33)	56(8.06)		
Chemotherapy	No	42(31.11)	120(17.27)	16.921	0.001
	Adjuvant Chemotherapy	79(58.52)	438(63.02)		
	Neoadjuvant Chemotherapy	10(7.41)	94(13.53)		
	Adjuvant and Neoadjuvant Chemotherapy	4(2.96)	43(6.19)		
Cyclophosphamide and Anthracycline/Taxane Chemotherapy Drugs	No	81(60.00)	348(50.07)	4.462	0.035
	Yes	54(40.00)	347(49.93)		
Radiotherapy	No	89(65.93)	362(52.09)	8.726	0.003
	Yes	46(34.07)	333(47.91)		
Targeted Drug Therapy	No	124(91.85)	581(83.60)	6.021	0.014
	Yes	11(8.15)	114(16.40)		
Carbonated Beverage Consumption	Never	131(97.04)	613(88.20)	NA	0.005
	< 3 bottles/week	4(2.96)	70(10.07)		
	≥ 3 bottles/week	0(0%)	12(1.73)		
Coffee Consumption	Never	124(91.85)	572(82.30)	7.883	0.019
	< 3 cups/week	6(4.44)	80(11.51)		
	≥ 3 cups/week	5(3.71)	43(6.19)		

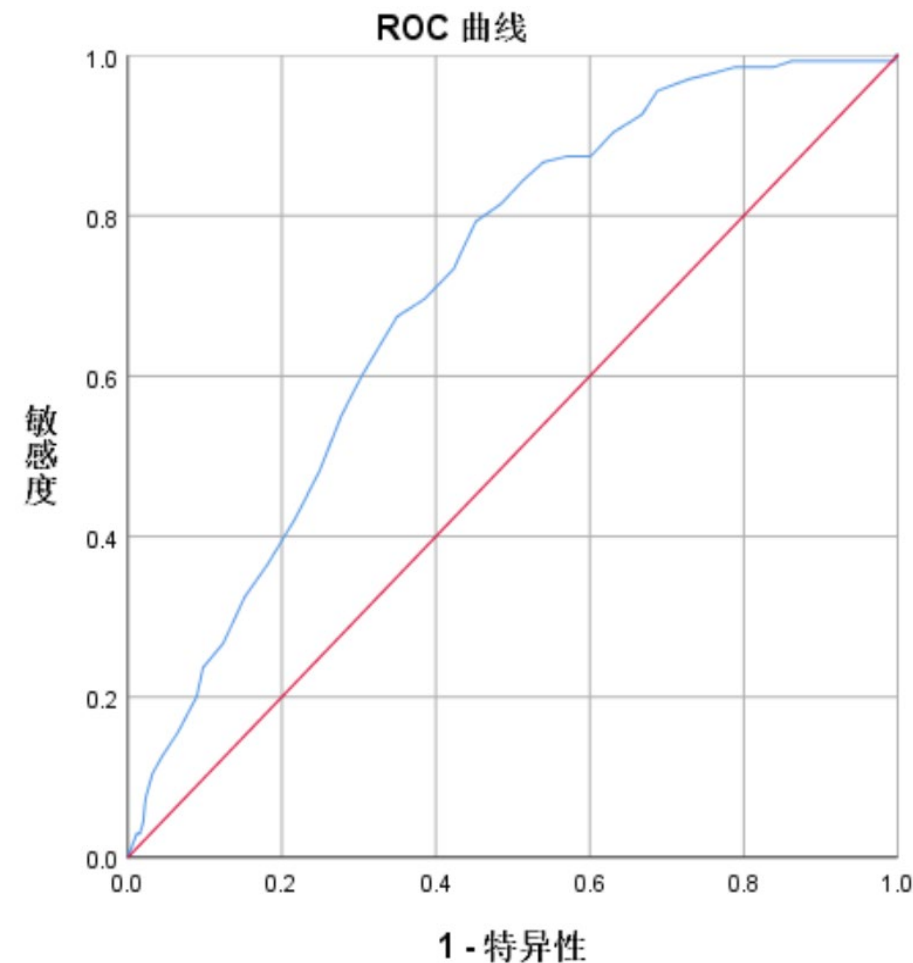


Variables with $P < 0.05$ in the univariate analysis were tested for multicollinearity using tolerance and variance inflation factor.

Variable	Tolerance	VIF
Age	0.678	1.475
BMI	0.959	1.043
Physical Activity	0.885	1.130
Fracture History	0.956	1.046
Fall History	0.967	1.034
Glucocorticoid Use	0.818	1.223
Hypertension	0.829	1.207
Diabetes	0.885	1.130
Chemotherapy	0.757	1.321
Cyclophosphamide and Anthracycline/Taxane Chemotherapy Drugs	0.894	1.119
Radiotherapy	0.818	1.222
Targeted Drug Therapy	0.937	1.068
Coffee Consumption	0.944	1.059

> 0.1

< 10



Age was divided into two groups: < 57 years old and ≥ 57 years old

Univariate Analysis

Binary Logistic Regression Analysis

Finally, 4 independent risk factors were identified, including **age, BMI, physical activity, and fracture history**.

Table 3: Results of Logistic Regression Analysis on Influencing Factors of AI - related OP in Breast Cancer Patients

Variable	Regression Coefficient	Standard Error	P	wald	OR	95%CI
Age						
Age < 57 years old						1.000
Age ≥ 57 years old	1.127	0.272	< 0.001	17.217	3.085	1.839~5.347
BMI						
Underweight						1.000
Normal	-0.986	0.606	0.103	2.651	0.373	0.118~1.319
Overweight or Obese	-2.260	0.693	0.001	10.627	0.104	0.027~0.425
Physical Activity						
Mild						1.000
Moderate	0.129	0.278	0.644	0.214	1.137	0.667~1.990
Severe	-1.035	0.448	0.021	5.34	0.355	0.140~0.827
Fracture History						
No						1.000
Yes	0.675	0.327	0.039	4.246	1.963	1.017~3.695
Constant	-1.057	0.635	0.096	2.774	0.347	0.092~1.153

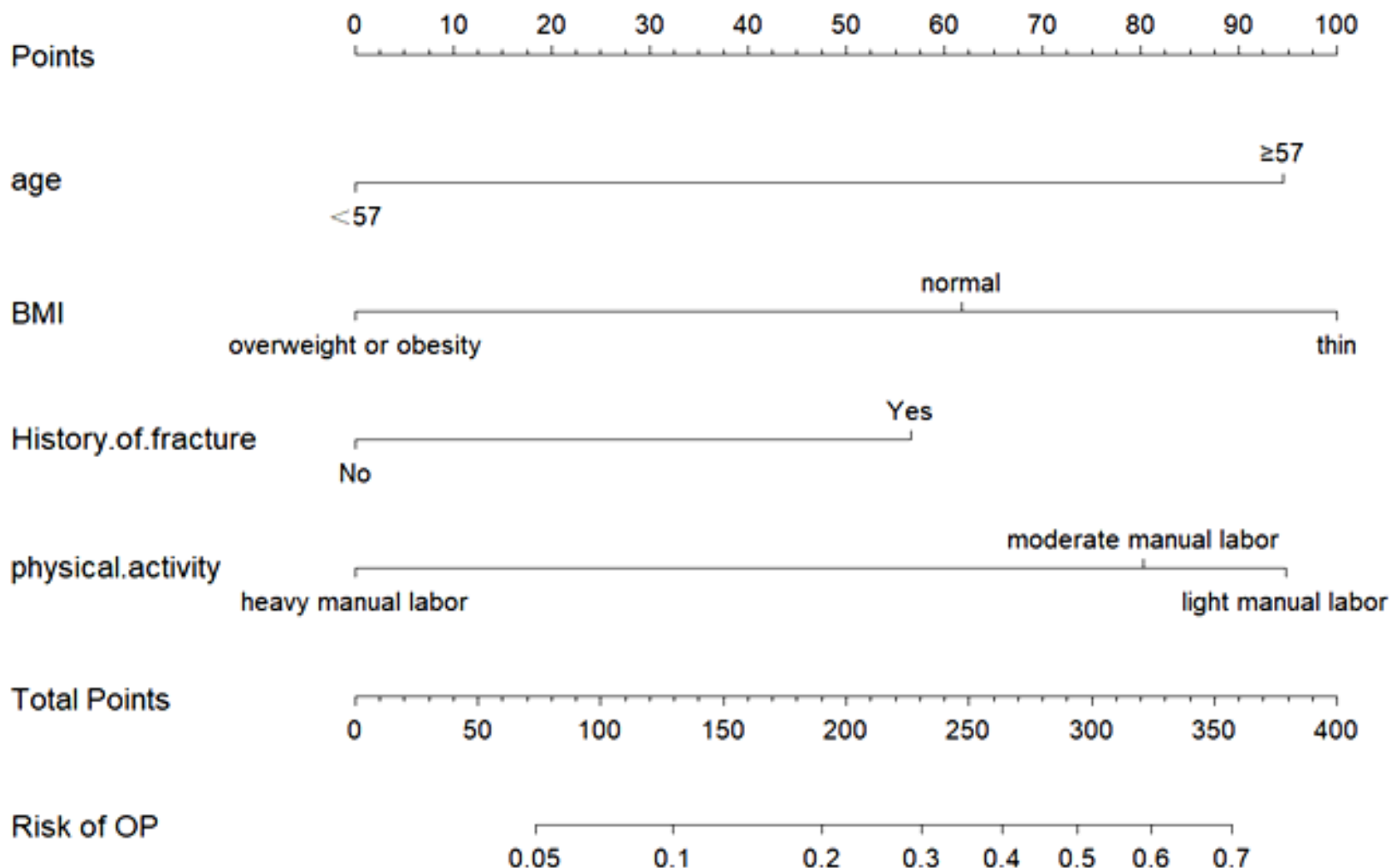
Univariate Analysis

The independent influencing factors

The usage method is as follows:

According to the data of each predictor of the patient, draw a vertical line upward to obtain the score (Points) of a single predictor. The sum of the 4 scores is the total score (Total Points). Draw a vertical line downward to obtain the probability of the patient developing OP (Risk of OP).

Nomogram for Predicting the Risk of AI - related OP in Breast Cancer Patients



Univariate Analysis

Model Validation - Discriminative Ability

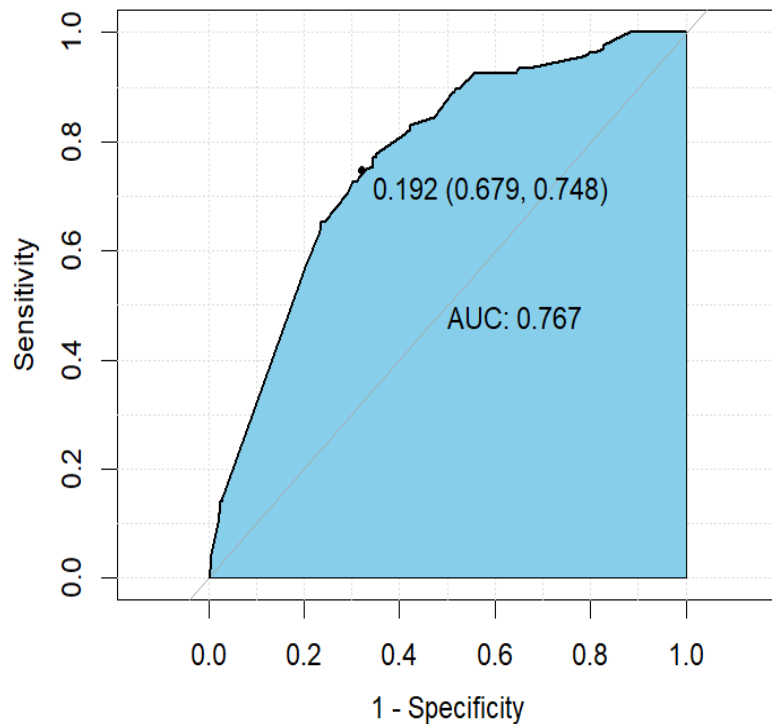


Image: ROC Curve of the Modeling
Group

AUC为0.767 (95%CI: 0.727-0.808)

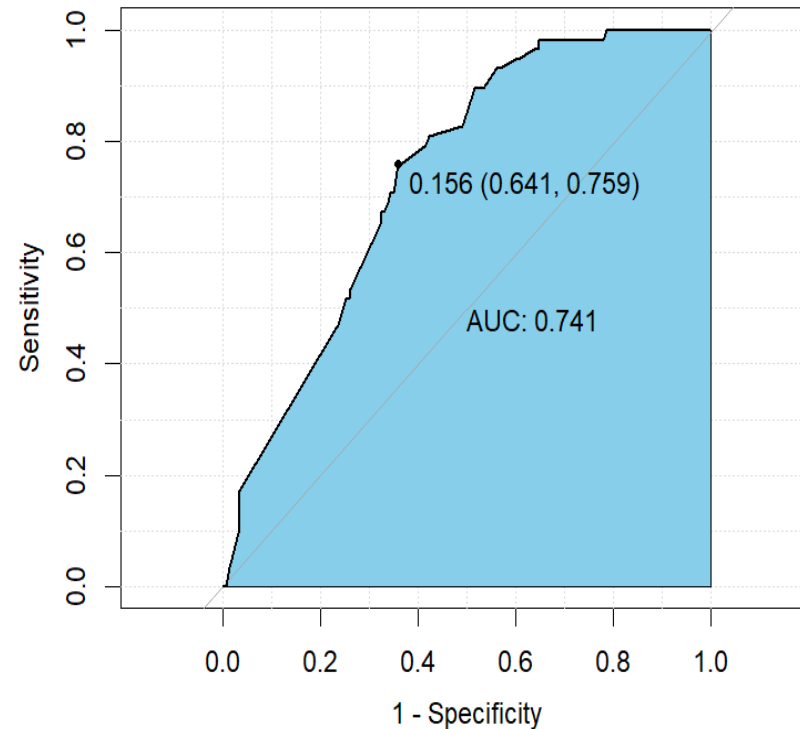


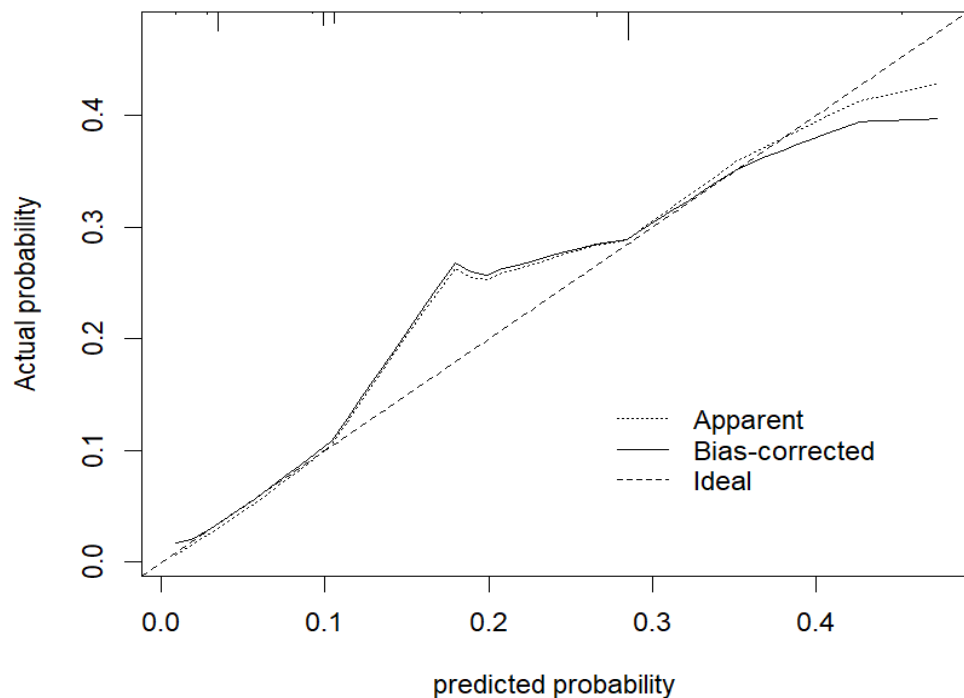
Image: ROC Curve of the Validation
Group

AUC为0.741 (95%CI: 0.683-0.800)

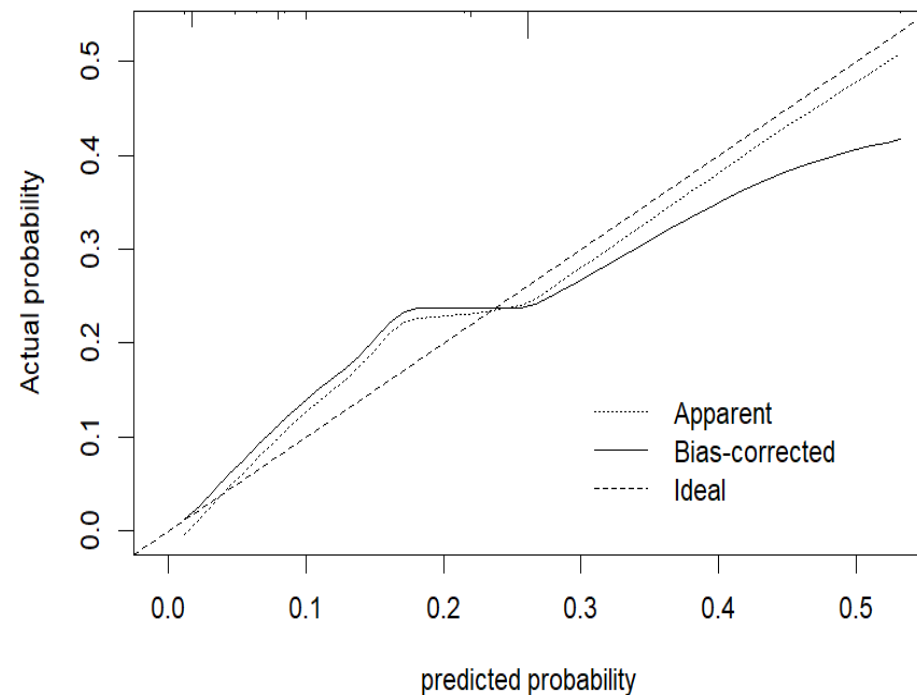


Univariate Analysis

Model Validation - Calibration



Calibration curve of the modeling group: The chi - square value of the H - L test was 1.358, $P = 0.715 > 0.05$

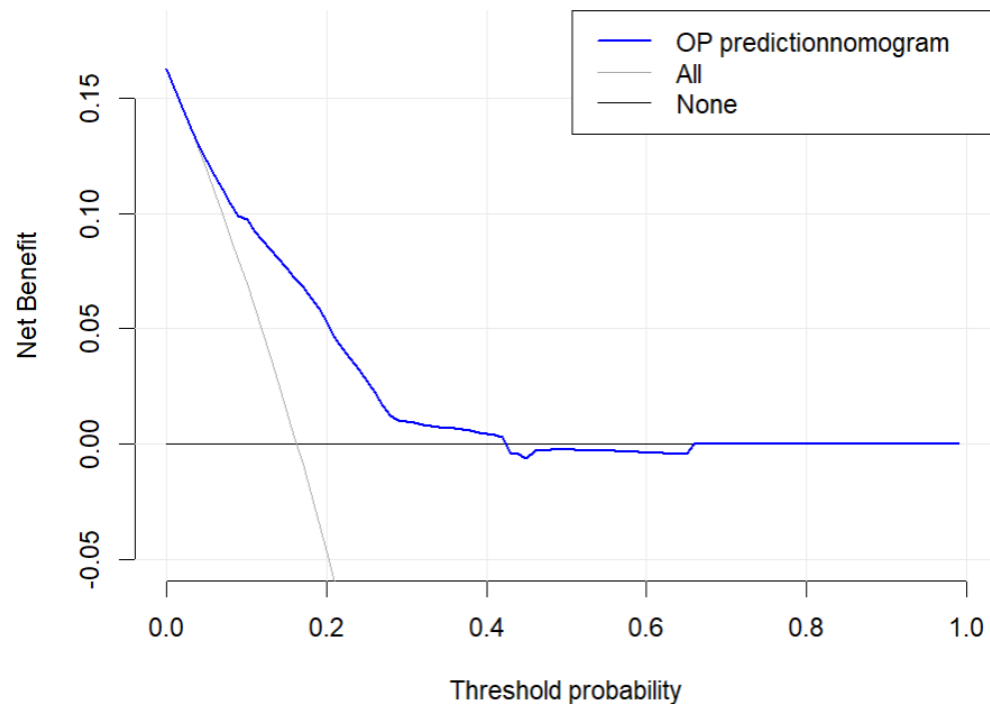


Calibration curve of the validation group: The chi - square value of the H - L test was 3.429, $P = 0.330 > 0.05$

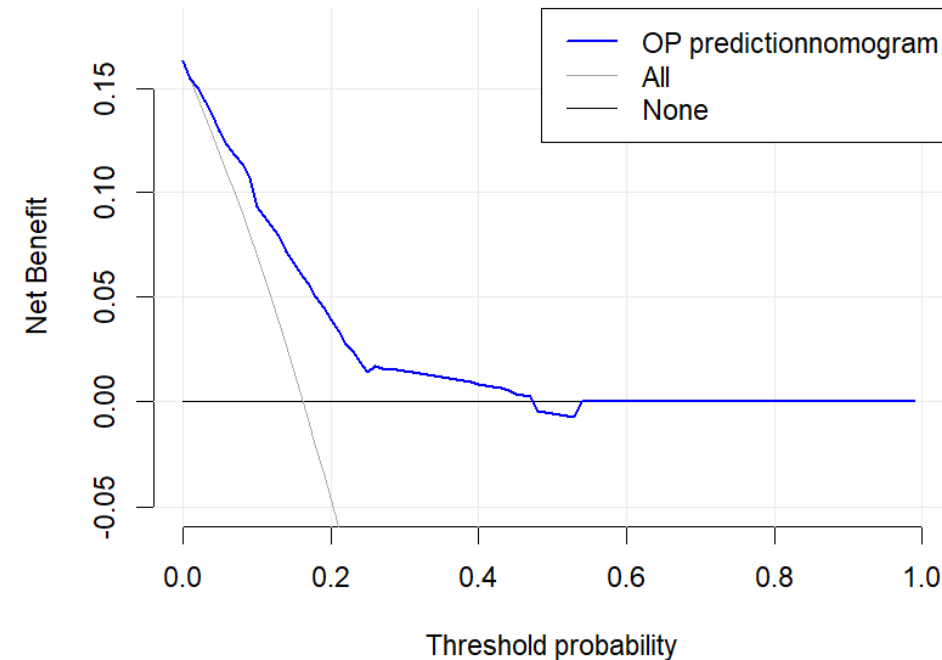


Univariate Analysis

Model Validation - Clinical Utility



DCA curve of the modeling group:
Threshold probability range of 5% - 40%



DCA curve of the validation group:
Threshold probability range of 5% - 45%

4

Research Conclusions

Research Conclusions

- The results of the univariate analysis showed that 14 variables, including age, BMI, physical activity, fracture history, fall history, glucocorticoid use, hypertension, diabetes, chemotherapy, use of cyclophosphamide and anthracycline or taxane chemotherapy drugs, radiotherapy, targeted drug therapy, carbonated beverage consumption, and coffee consumption, were influencing factors of AI - related OP in breast cancer patients.
- Based on the binary Logistic regression analysis, the independent influencing factors of OP were screened out, and the model included age, BMI, physical activity, and fracture history. After validation, the model showed good discriminative ability. The consistency between the predicted probability and the actual probability of OP was good, and the model could effectively identify high - risk groups of OP.

5

Limitations and Prospects

Limitations and Prospects

Limitations

- This is a retrospective study.
- It is a single - center study.

Prospects

- In the future, multi - center and prospective studies can be carried out to validate and optimize the predictive performance of the model, so as to promote its popularization and application.

Main References

30



- [1] Han B, Zheng R, Zeng H, et al . Cancer incidence and mortality in china, 2022 [J]. Journal of the National Cancer Center, 2024, 10: 27.
- [2] Waks A G, Winer E P. Breast cancer treatment: A review [J]. 2019, 321(3): 316.
- [3] National Health Commission of the People's Republic of China. Breast Cancer Diagnosis and Treatment Guidelines (2022 Edition) [J]. Chinese Journal of Rational Drug Use, 2022, 19(10): 1 - 26.
- [4] National Comprehensive Cancer Network. Nccn guidelines:Breast cancer version 4.2022[EB/OL]. [2024-1-10]. <https://nccn.medlive.cn/guide/detail/149>.
- [5] E B C T C G. Aromatase inhibitors versus tamoxifen in early breast cancer: Patient-level meta-analysis of the randomised trials [J]. Lancet , 2015, 386(10001): 1341-1352.
- [6] Chen Xi, Sun Jing, Wang Qin, et al. Long - term follow - up results of bone loss during aromatase inhibitor treatment for breast cancer [J]. Chinese Journal of Osteoporosis, 2023, 29(07): 992 - 997.
- [7] Eastell R, Hannon R A, Cuzick J, et al . Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the anastrozole, tamoxifen, alone or in combination (atac) trial (18233230) [J]. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 2006, 21(8): 1215-1223.
- [8] Chinese Society of Osteoporosis and Bone Mineral Disease, Zhang Zhenlin. Guidelines for the Diagnosis and Treatment of Primary Osteoporosis (2022) [J]. Chinese General Practice, 2023, 26(14): 1671 - 1691.
- [9] Kwan M L, Lo J C, Laurent C A, et al . A prospective study of lifestyle factors and bone health in breast cancer patients who received aromatase inhibitors in an integrated healthcare setting [J]. Journal of cancer survivorship : research and practice, 2023, 17(1): 139-149.
- [10] Li Wenhuan, Zhou Zhuohui. Prediction model and application analysis of osteoporosis in postmenopausal breast cancer patients treated with anastrozole [J]. Electronic Journal of Tumor Metabolism and Nutrition, 2017, 4(03): 327 - 332.
- [11]LeBoff M S, Greenspan S L, Insogna K L, et al . The clinician's guide to prevention and treatment of osteoporosis [J]. Osteoporosis international, 2022, 33(10): 2049-2102.
- [12]Abdel-Razeq H, Al-Rasheed U, Mashhadani N, et al . The efficacy of a comprehensive bone health program in maintaining bone mineral density in postmenopausal women with early-stage breast cancer treated with endocrine therapy: Real-world data [J]. Irish journal of medical science, 2022, 191(6): 2511-2515.
- [13]Wolff R F, Moons K G M, Riley R D, et al . Probast: A tool to assess the risk of bias and applicability of prediction model studies [J]. Annals of internal medicine, 2019, 170(1): 51-58.
- [14]Moons K G, Royston P, Vergouwe Y, et al . Prognosis and prognostic research: What, why, and how? [J]. BMJ (Clinical research ed), 2009, 338: b375.
- [15]Arksey H, O'Malley L. Scoping studies: Towards a methodological framework [J]. Int J Soc Res Methodol, 2005, 8(1): 19-32.
- [16]Daudt H M L, van Mossel C, Scott S J. Enhancing the scoping study methodology: A large, inter-professional team's experience with arksey and o'malley's framework [J]. BMC medical research methodology, 2013, 13(1): 48.
- [17]Wells G A, Shea B, Oconnell D, et al . The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses [J]. Appl Eng Agric, 2000, 18(6): 727-734.
- [18]Rostom A, Dubé C, Cranney A, et al. Celiac Disease. Rockville (md): Agency for healthcare research and quality (us)[EB/OL]. (2004). [2023-04-18].
<https://www.ncbi.nlm.nih.gov/books/NBK35156/>
- [19]Ji L, Zhang W, Zhong X, et al . Osteoporosis, fracture and survival: Application of machine learning in breast cancer prediction models [J]. Frontiers in oncology, 2022, 12: 973307.
- [20]Chu M, Zhou Y, Yin Y, et al . Construction and validation of a risk prediction model for aromatase inhibitor-associated bone loss [J]. Frontiers in oncology, 2023, 13: 1182792.
- [21] Wang Chunzhi, Siqin. Research on Data Statistical Processing Methods and Their Application in the Delphi Method [J]. Journal of Inner Mongolia University of Finance and Economics (Comprehensive Edition), 2011, 9(04): 92 - 96.
- [22]Kanis J A, Glüer C C. An update on the diagnosis and assessment of osteoporosis with densitometry. Committee of scientific advisors, international osteoporosis foundation [J]. Osteoporosis international, 2000, 11(3): 192-202.



天津医科大学
TIANJIN MEDICAL UNIVERSITY



天津市肿瘤医院 肿瘤研究所
天津医科大学肿瘤医院
TIANJIN MEDICAL UNIVERSITY CANCER INSTITUTE & HOSPITAL

**We sincerely invite all experts
to criticize and guide us**

Reporters: Yanshan Yi, Gaojing Ren

Supervisor: Wanmin Qiang

2024 Ph.D. Candidates in Nursing