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ORIGINAL RESEARCH

A Retrospective Study of Biological Risk Factors Associated with Primary Knee Osteoarthritis and the Development of a Nomogram Model

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Aim: A high percentage of the elderly suffer from knee osteoarthritis (KOA), which imposes a certain economic burden on them and on society as a whole. The purpose of this study is to examine the risk of KOA and to develop a KOA nomogram model that can timely intervene in this disease to decrease patient psychological burdens.

Methods: Data was collected from patients with KOA and without KOA at our hospital from February 2021 to February 2023. Initially, a comparison was conducted between the variables, identifying statistical differences between the two groups. Subsequently, the risk of KOA was evaluated using the Least Absolute Shrinkage and Selection Operator method and multivariate logistic regression to determine the most effective predictive index and develop a prediction model. The examination of the disease risk prediction model in KOA includes the corresponding nomogram, which encompasses various potential predictors. The assessment of disease risk entails the application of various metrics, including the consistency index (C index), the area under the curve (AUC) of the receiver operating characteristic curve, the calibration chart, the GiViTi calibration band, and the model for predicting KOA. Furthermore, the potential clinical significance of the model is explored through decision curve analysis (DCA) and clinical influence curve analysis.

Results: The study included a total of 582 patients, consisting of 392 patients with KOA and 190 patients without KOA. The nomogram utilized age, haematocrit, platelet count, apolipoprotein a1, potassium, magnesium, hydroxybutyrate dehydrogenase, creatine kinase, and estimated glomerular filtration rate as predictors. The C index, AUC, calibration plot, Giviti calibration band, DCA and clinical influence KOA indicated the ability of nomogram model to differentiate KOA.

Conclusion: Using nomogram based on disease risk, high-risk KOA can be identified directly without imaging.

Keywords: decision support, knee osteoarthritis, nomogram, predictors, risk factors

Introduction

Knee osteoarthritis (KOA) is highly prevalent in clinical practice and is recognized as a profoundly incapacitating form of arthritis, impacting both families and society.[1] It has emerged as the fourth most prevalent cause of disability globally, leading to reduced productivity among the elderly population and imposing a substantial economic burden on society and families.[2] According to findings from the Third National Health and Nutrition Examination Survey in the United States, the prevalence of symptomatic knee osteoarthritis was determined to be 12.1%.[3] Similarly, in Canada, knee osteoarthritis has been reported to have a prevalence of 10.5%.[4] Based on epidemiological survey data conducted in China, the present prevalence of symptomatic knee osteoarthritis is reported to be 8.1%, indicating a substantial population of approximately 110 million individuals affected by this condition.[1] Notably, the prevalence of knee osteoarthritis exhibits an age-dependent pattern, with a prevalence rate of 5.2% observed in individuals below 50 years of age, which escalates to 11%

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among those aged 60 years and above. Additionally, a higher incidence is observed in females compared to males, and there is a discernible trend of increasing prevalence among younger individuals.[5]

Presently, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently employed in the management of KOA, primarily focusing on alleviating joint pain symptoms. Despite their efficacy, these medications can potentially induce adverse effects on the gastrointestinal and cardiovascular systems, thereby giving rise to concerns regarding their safety.[6] In advanced stages of knee osteoarthritis, surgical interventions, such as cartilage transplantation, may be undertaken to address localized cartilage lesions, while total knee replacement surgery becomes necessary for extensive cartilage deterioration.[7,8] Despite the efficacy of surgical interventions, it is important to acknowledge the potential for complications and mortality, as well as the substantial financial burden and limited durability associated with artificial joint replacements. The transitional period between the onset of KOA and the implementation of total knee replacement surgery is characterized by significant pain and functional limitations, leading to considerable distress for patients.[9,10] Consequently, it becomes imperative to ascertain the risk factors for KOA and establish timely diagnoses and clinical interventions to impede disease progression to advanced stages[8]. Such proactive measures hold the potential to enhance patients' quality of life and alleviate the societal burden imposed by this condition.

The diagnostic criteria for KOA have undergone refinement and enhancement by esteemed institutions such as the American College of Rheumatology, the European League Against Rheumatism, and the International Osteoarthritis Research Society, rendering them presently applicable in clinical settings.[11–13] Nevertheless, the identification of KOA in its early stages continues to pose challenges, with existing diagnostic approaches predominantly reliant on X-rays, MRI, and/or arthroscopy.[14] It was difficult to diagnose KOA by indirect risk factors using non-imaging technologies.[15–19] Additionally, X-ray examinations of bone tissue are more cost-effective, but they are not capable of detecting early chronic inflammatory lesions.[20] It is not recommended that MRI be used as a routine examination method by KOA doctors due to the high cost, long procedure time, costly equipment, high demands on doctors, and poor universality of MRI.[21,22] Hence, the present study examined pertinent data obtained from patients diagnosed with KOA at the Department of Joint Surgery in Chengde Medical College Affiliated Hospital, as well as non-KOA patients from the Physical Examination Department. The primary objective was to explore the risk factors associated with KOA and construct a predictive model. The ultimate goal is to effectively identify individuals at a heightened risk of developing KOA, devise tailored intervention approaches, and offer novel perspectives for early detection of this condition.

Patients and Methods

Data Source

This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Chengde Medical University (ethics number: CYFYLL2023222). And the research has obtained the informed consent of the research participants. All human procedures were followed in accordance with the Helsinki Declaration (1964). From February 2021 to February 2023, the participants' information was collected in the Affiliated Hospital of Chengde Medical University. The inclusion criteria of patients are the diagnostic criteria for KOA (ICD10= M17.901) established by American College of Rheumatology (ACR) in 2001.[23] Patients with knee pain have three of the following seven items (a) Age ≥50 years old. (b)morning stiffness <30 min. (c) There is bone noise during joint activity. (d) Knee examination showed bony hypertrophy. (e) There is bone tenderness. (f) There was no obvious synovial warming. (g) Radiological examination showed osteophyte formation. The control group excluded from healthy population outside KOA those who participated voluntarily in the project examination. The exclusion criteria are those who suffer from major diseases (malignant tumor, respiratory failure, inability to walk normally, etc.) that affect the basic clinical information of the examination related to this project, lack of blood biochemical examination and no imaging data to judge whether they have KOA. X-ray photography belongs to Siemens (Ysio), Germany.

Data Collection

All clinical information collected in this study was obtained from patient examination records upon admission or during outpatient visits. The clinical data included two parts: demographic information and laboratory test results. Demographic

information consisted of name, hospitalization number or patient ID, gender, age, height, and weight. Samples were collected within 24 hours of admission. Laboratory test results included: (a) Complete blood count parameters (white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, neutrophil ratio, lymphocyte percentage, monocyte percentage, eosinophil percentage, basophil percentage, neutrophil absolute value, lymphocyte absolute value, monocyte absolute value, eosinophil absolute value, basophil absolute value, mean corpuscular volume, mean corpuscular hemoglobin content, mean corpuscular hemoglobin concentration (MCHC), red cell distribution width coefficient of variation, red cell distribution width -SD value, platelet mean volume, platelet distribution width, large platelet ratio, plateletcrit). (b) Biochemical parameters (total protein, albumin, total bilirubin, prealbumin, aspartate aminotransferase, alanine aminotransferase, glutamate transferase, direct bilirubin, alkaline phosphatase, total cholesterol, triglycerides, high-density lipoprotein cholesterol, apolipoprotein A1, apolipoprotein B, low-density lipoprotein cholesterol, potassium, sodium, chloride, calcium, phosphorus, magnesium, lactate dehydrogenase, creatinine kinase, creatine kinase isoenzyme, blood urea nitrogen (BUN), creatinine, uric acid, bicarbonate, β2-microglobulin, homocysteine measurement, lipoprotein(A), adenosine deaminase, serum total bile acid, glomerular filtration rate). Automatic biochemical analyzer (Beckman AU5800) was used to determine biochemical indexes.

Construction and Estimation of the Nomogram

In order to identify the most effective predictive factors in the training cohort, the researchers employed the Least Absolute Shrinkage and Selection Operator (LASSO) method to screen for risk factors associated with KOA. Subsequently, a predictive model nomogram was constructed by integrating the factors identified through LASSO regression analysis and multivariate logistic regression analysis.[24] Statistical significance was determined by a p-value of less than 0.05. All potential predictors were incorporated into the KOA risk prediction model, and a corresponding nomogram was generated. The Harrell's C statistic, also referred to as the C-index, was employed to assess the discriminative capacity of the nomogram model. The predictive ability of the nomogram model was evaluated by calculating the area under the receiver operating characteristic (ROC) curve (AUC).[25] To demonstrate the discriminative ability of the model, calibration plots utilizing the GiViTi calibration belt were utilized. Additionally, decision curve analysis (DCA) and clinical influence curves were employed to investigate the potential clinical significance of the model,[26–28] with the objective of facilitating early diagnosis of KOA in clinical settings.[29]

Statistical Analysis

All statistical analyses were conducted using R software (version 4.2.2; https://www.r-project.org/). In this study, the comparison of continuous variables between the two groups involved the utilization of mean, standard deviation, and difference. The *t*-test was employed for normally distributed data, while the Wilcoxon rank-sum test was utilized for non-normally distributed data. The LASSO method was implemented using the "glmnet" package in R. The analysis of AUC, C-index, GiViTi calibration belt, and DCA involved the utilization of R packages "pROC", "Hmisc", "givitiR", and "rms", respectively. It is PASS 11.0 that calculates the sample size for this study.[30]

Results

Characteristics of the KOA Patients

Retrospective data were obtained from a cohort of 672 patients who had received a preliminary diagnosis of KOA at the Department of Joint Surgery in the Affiliated Hospital of Chengde Medical University, spanning from February 2021 to February 2023 (Figure 1) Out of these patients, 280 were excluded from the study due to various reasons, including the absence of clinical data (n=138), the presence of other joint osteoarthritis (n=66), a history of knee arthroplasty, bone fixation for KOA, or knee fractures (n=37), active malignant tumors (n=11), renal or hepatic failure (n=11), rheumatic diseases (n=10), and active infections (n=7). In the end, 392 clinical data were collected from KOA patients.

Furthermore, a total of 257 patients who did not receive a diagnosis of KOA were included in the data collection process at the Department of Physical Examination at the same hospital between February 2021 and February 2023 (Figure 1). Out of these patients, 67 were excluded from the study due to various reasons, including the absence of clinical data (n=20), the presence of other joint osteoarthritis (n=18), active malignant tumors (n=9), renal or hepatic

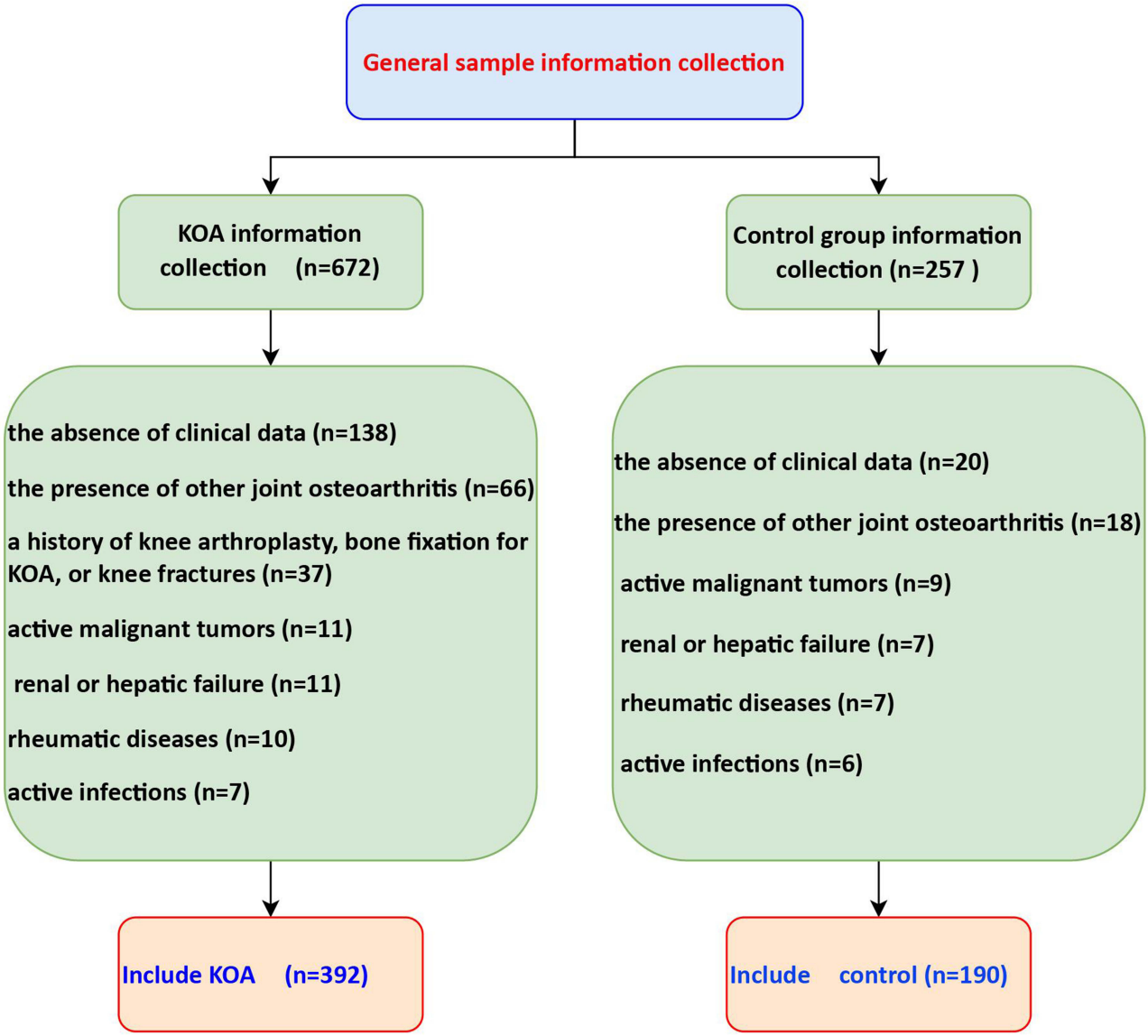

Figure 1 Sample flow diagram for this study.

failure (n=7), rheumatic diseases (n=7), and active infections (n=6). Ultimately, clinical data from a total of 190 non-KOA patients were gathered for analysis.

This study included a cohort of 582 patients, consisting of 203 males and 379 females, with an average age of 61 years (range: 53 to 66.75 years). The patients were categorized into two groups: the KOA group, comprising 392 cases, and the non-KOA group, comprising 190 cases. The sample size required for this study was calculated using PASS 11.0 (setting power=0.9, AUC_0=0.8, AUC_1=0.9). Therefore, 104 samples were necessary for each of the two groups. Table 1 presents the general characteristics and laboratory test results of the KOA group compared to the non-KOA group.

Nomogram Variable Screening and Construction

From Table 1, it was observed that there were 44 factors exhibiting statistical differences that could be included in the LASSO analysis. In the LASSO regression analysis, a total of 582 patients were considered, with 44 initial features. However, after the analysis, these features were reduced to 23 potential nonzero coefficient predictors that were found to be significantly associated with KOA (Figure 2A and B). These 23 factors encompassed variables such as sex, age, height, white blood cell count, haematocrit, platelet count, monocyte percentage, percentage of eosinophils, absolute

Table 1 Baseline Characteristics of the Study Population

Variables	Total (n = 582)	0 (n = 190)	1 (n = 392)	p-value
Sex, n (%)				< 0.001
Female	379 (65)	95 (50)	284 (72)	
Male	203 (35)	95 (50)	108 (28)	
Age, Median (Q1,Q3)	61 (53, 66.75)	50 (35, 57)	64 (58, 69)	< 0.001
Height, Median (Q1,Q3)	163 (159, 170)	165 (160, 172)	160 (158, 166.25)	< 0.001
Weight, Median (Q1,Q3)	68 (60, 75)	65 (60, 75)	70 (60, 75)	0.073
BMI, Mean ± SD	25.54 ± 3.95	24.48 ± 4.13	26.06±3.76	< 0.001
White_blood_cell_count, Median (Q1,Q3)	5.73 (4.83, 6.84)	6.09 (5.09, 7.53)	5.64 (4.75, 6.49)	< 0.001
Red_blood_cell_count, Median (Q1,Q3)	4.37 (4.11, 4.71)	4.51 (4.18, 4.89)	4.34 (4.09, 4.65)	< 0.001
Haemoglobin, Median (Q1,Q3)	133 (125, 144)	137.5 (126, 150)	132 (123, 142)	< 0.001
Haematocrit, Median (Q1,Q3)	40.3 (37.9, 43.3)	41.2 (37.73, 44.6)	40 (37.9, 42.73)	0.026
Platelet_count, Median (Q1,Q3)	225 (193, 264)	232 (197, 282.5)	223 (191.75, 259)	0.019
Neutrophil_ratio, Mean ± SD	59.25 ± 9.24	61.93 ± 9.26	57.95 ± 8.95	< 0.001
Lymphocyte_percentage, Mean ± SD	30.89 ± 8.18	29.8 ± 8.62	31.42 ± 7.91	0.029
Monocyte_percentage, Median (Q1,Q3)	7 (5.8, 8.3)	6.1 (4.9, 7.18)	7.4 (6.4, 8.62)	< 0.001
Percentage_of_eosinophils, Median (Q1,Q3)	1.8 (1, 2.8)	1.2 (0.7, 2.1)	2.1 (1.2, 3.1)	< 0.001
Percentage_of_basophils, Median (Q1,Q3)	0.5 (0.3, 0.6)	0.3 (0.2, 0.5)	0.5 (0.4, 0.7)	< 0.001
Absolute_value_of_neutrophils, Median (Q1,Q3)	3.34 (2.67, 4.2)	3.67 (2.94, 4.85)	3.16 (2.56, 3.93)	< 0.001
Absolute_value_of_lymphocytes, Median (Q1,Q3)	1.72 (1.38, 2.17)	1.73 (1.36, 2.26)	1.71 (1.38, 2.12)	0.281
Absolute_value_of_monocytes, Median (Q1,Q3)	0.4 (0.33, 0.49)	0.37 (0.29, 0.46)	0.42 (0.34, 0.5)	< 0.001
Absolute_value_of_eosinophils, Median (Q1,Q3)	0.1 (0.06, 0.17)	0.08 (0.04, 0.13)	0.11 (0.07, 0.17)	< 0.001
Absolute_value_of_basophils, Median (Q1,Q3)	0.03 (0.02, 0.04)	0.02 (0.01, 0.03)	0.03 (0.02, 0.04)	< 0.001
Average_volume_of_red_blood_cells, Median (Q1,Q3)	92.45 (89.3, 95.2)	91.4 (88.4, 94.47)	92.9 (89.8, 95.73)	< 0.001
Average_haemoglobin_content, Median (Q1,Q3)	30.6 (29.5, 31.7)	30.5 (29.42, 31.7)	30.6 (29.6, 31.6)	0.735
MCHC, Median (Q1,Q3)	331 (324, 337)	333 (329, 339)	329 (322, 336)	< 0.001
Coefficient_of_the_variation_of_red_blood_cell_distribution_width, Median (Q1,Q3)	12.7 (12.1, 13.7)	40.3 (12.4, 44.2)	12.6 (12.1, 13.1)	< 0.001
Red_blood_cell_distribution_width_SD_value, Median (Q1,Q3)	41.7 (38.82, 44.27)	14.15 (13, 40.88)	42.9 (41.08, 44.92)	< 0.001
Average_volume_of_platelets, Median (Q1,Q3)	10.05 (9.1, 10.8)	0.3 (0.22, 9.8)	10.3 (9.7, 11)	< 0.001
Distribution_width_of_platelets, Median (Q1,Q3)	11.2 (10, 12.7)	10.1 (9.12, 11.1)	11.7 (10.67, 13.43)	< 0.001
Ratio_of_large_platelets, Median (Q1,Q3)	25 (17.92, 31.08)	16.6 (16.1, 22.85)	27.25 (22.48, 33.32)	< 0.001
Thrombocytocrit, Median (Q1,Q3)	0.24 (0.2, 0.3)	13.4 (0.22, 22.7)	0.23 (0.2, 0.26)	< 0.001
Total_protein, Mean ± SD	68.28 ± 5.78	68.37 ± 6.17	68.23 ± 5.59	0.792
Albumin, Median (Q1,Q3)	39.6 (37.5, 42.38)	42.25 (39.6, 44.8)	38.85 (37.08, 40.73)	< 0.001
Total_bilirubin, Median (Q1,Q3)	11.41 (9.21, 14.64)	10.95 (8.66, 14.36)	11.75 (9.45, 14.65)	0.223
Prealbumin, Median (Q1,Q3)	252.75 (214.83, 292.65)	258.55 (223.5, 299.8)	250.8 (213.88, 288.3)	0.109
Alanine_aminotransferase, Median (Q1,Q3)	15.45 (11.22, 22.9)	17.35 (12.7, 26.08)	14.95 (11.1, 21.22)	0.002
Aspartate_aminotransferase, Median (Q1,Q3)	19.6 (16.5, 24.3)	20.85 (17, 26.4)	19.1 (16.28, 23.4)	0.001
Gamma_glutamyltransferase, Median (Q1,Q3)	22.2 (15.9, 35.08)	22.35 (14.87, 37.4)	22 (15.9, 34.2)	0.874
Direct_bilirubin, Median (Q1,Q3)	3 (2.2, 4)	2.4 (1.78, 3.35)	3.3 (2.5, 4.2)	< 0.001
Alkaline_phosphatase, Median (Q1,Q3)	82.25 (69, 99.97)	82.25 (68.23, 103.95)	82.2 (69.65, 98.15)	0.448
Total_cholesterol, Median (Q1,Q3)	4.62 (4.08, 5.4)	4.57 (4, 5.51)	4.63 (4.12, 5.34)	0.955
Triglyceride, Median (Q1,Q3)	1.45 (1.06, 2.13)	1.64 (1.06, 2.44)	1.4 (1.06, 2)	0.071
High_density_lipoprotein_cholesterol, Median (Q1,Q3)	1.2 (1.02, 1.38)	1.19 (0.98, 1.36)	1.2 (1.04, 1.4)	0.202
Apolipoprotein_A1, Median (Q1,Q3)	1.21 (1.09, 1.39)	1.28 (1.11, 1.51)	1.19 (1.08, 1.33)	< 0.001
Apolipoprotein_B, Median (Q1,Q3)	0.89 (0.75, 1.06)	0.89 (0.75, 1.16)	0.88 (0.75, 1.03)	0.234
Low_density_lipoprotein_cholesterol, Median (Q1,Q3)	2.83 (2.46, 3.32)	2.85 (2.49, 3.51)	2.83 (2.46, 3.27)	0.167
Potassium, Median (Q1,Q3)	3.75 (3.52, 3.98)	3.91 (3.72, 4.12)	3.67 (3.44, 3.88)	< 0.001
Sodium, Median (Q1,Q3)	140 (139, 141.19)	139 (138, 141)	141 (139, 142)	< 0.001
Chlorine, Median (Q1,Q3)	106 (105, 108)	106 (104, 107)	106 (105, 108)	< 0.001
Calcium, Median (Q1,Q3)	2.27 (2.2, 2.33)	2.29 (2.21, 2.35)	2.25 (2.2, 2.32)	0.005
Phosphorus, Median (Q1,Q3)	1.13 (1.01, 1.27)	1.16 (1.02, 1.29)	1.11 (1, 1.26)	0.081
Magnesium, Median (Q1,Q3)	0.85 (0.81, 0.9)	0.82 (0.78, 0.86)	0.88 (0.83, 0.91)	< 0.001
Lactic_dehydrogenase, Median (Q1,Q3)	180 (159, 206)	186 (166.25, 213.75)	177.5 (157, 200.25)	< 0.001
Creatine_kinase, Median (Q1,Q3)	69.6 (52.52, 96.9)	88.65 (61.92, 141.78)	63.5 (48.6, 85.15)	< 0.001
Creatine_Kinase_Isoenzyme, Median (Q1,Q3)	12 (9.1, 15)	12.2 (9, 16)	12 (9.57, 15)	0.734
BUN, Median (Q1,Q3)	5.3 (4.33, 6.3)	5.06 (4, 6.14)	5.36 (4.48, 6.42)	0.003
Creatinine, Median (Q1,Q3)	57.05 (50.25, 67.3)	58.8 (50.28, 69.35)	56.65 (50.35, 66.3)	0.468

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 582)	0 (n = 190)	1 (n = 392)	p-value
Uric_acid, Median (Q1,Q3)	302.6 (251.17, 371.78)	321.15 (262.02, 391.5)	295.95 (249.4, 361.65)	0.005
Bicarbonate, Mean ± SD	25.76 ± 2.36	25.48 ± 2.59	25.89 ± 2.23	0.062
beta2_microglobulin, Median (Q1,Q3)	1.58 (1.39, 1.84)	1.49 (1.32, 1.75)	1.62 (1.43, 1.89)	< 0.001
Homocysteine_determination, Median (Q1,Q3)	12.7 (10.8, 16.5)	12 (9.9, 16.27)	13.15 (11.4, 16.5)	0.002
Lipoprotein_A, Median (Q1,Q3)	12.85 (6.23, 27.8)	12.5 (5.15, 27.78)	13.05 (6.6, 28.02)	0.354
Adenosine_deaminase, Median (Q1,Q3)	9.4 (7.9, 11.47)	8.55 (7.3, 10.17)	9.85 (8.5, 11.9)	< 0.001
Serum_total_bile_acid, Median (Q1,Q3)	3.5 (2.2, 5.9)	3.5 (2.02, 6.47)	3.5 (2.2, 5.7)	0.816
Estimated_glomerular_filtration_rate, Median (Q1,Q3)	101.35 (92.82, 110.46)	109.56 (101.24, 120.84)	98.44 (90.78, 104.63)	< 0.001

value of neutrophils, coefficient of the variation of red blood cell (RBC) distribution width, RBC distribution width SD value, average volume of platelets, albumin, direct bilirubin, apolipoprotein a1, potassium, sodium, magnesium, hydroxybutyrate dehydrogenase, creatine kinase, homocysteine determination, adenosine deaminase and estimated glomerular filtration rate. According to the results of the multivariate logistic regression analysis conducted on the aforementioned 23 factors, it was found that the P values for age, haematocrit, platelet count, apolipoprotein a1, potassium, magnesium, hydroxybutyrate dehydrogenase, creatine kinase, and estimated glomerular filtration rate were all below the significance threshold of 0.05 (Figure 2C). Consequently, these nine factors were incorporated into the nomogram model for the purpose of predicting KOA (Figure 2D).

A Nomogram Evaluation

According to Figure 3A, the nomogram showed good discrimination for KOA risk factors by having a C index and AUC of 0.948. Likewise, the calibration plot (Figure 3B) and GiViTi calibration curve (p=0.441) (Figure 3C) in this study consistently showed a good nomogram.

The Nomogram in Clinical Practice

A DCA of diagnosis KOA was predicted in this study, as shown in the figure below (Figure 3D). As seen by the DCA results, the nomogram used to differentiate KOA in this study population is a better method than all patient interventions and noninterventions because of its threshold probability of 0.03–0.98 (Figure 3D). Furthermore, the clinical impact graph demonstrates a consistent trend wherein the projected count of high-risk patients consistently surpasses the actual count of patients with KOA, a phenomenon that appears to be accompanied by a satisfactory cost-effectiveness ratio as depicted in Figure 3E. These findings suggest that the Nomogram exhibits a heightened clinical capacity for assessing the likelihood of knee osteoarthritis.

Discussion

Osteoarthritis (OA) is a prevalent chronic musculoskeletal ailment, primarily impacting the elderly demographic.[31] In China, there exists a substantial population of individuals afflicted with OA, with a prevalence rate of symptomatic KOA reaching 8.1% among those aged 45 years and above.[1] The manifestation of KOA can result in diminished joint stability and a progressive deterioration of the condition.[32] The projected rise in the incidence of KOA is attributed to the accelerated global aging process, increasing prevalence of obesity, and a growing number of joint injuries. This trend poses a substantial burden on patients in terms of physical function, quality of life, and social participation, as well as on society in terms of economic costs. Consequently, it is imperative to ascertain the risk factors associated with KOA development, facilitate early diagnosis, and offer appropriate clinical interventions.

Nomogram models have been shown in previous studies to possess clinical utility in predicting the prognosis of various diseases, such as hepatocellular carcinoma, head and neck melanoma, gliomas, young gastric cancer patients, and the risk of anastomotic leakage after rectal cancer surgery.[19,25–27,33] These models employ logistic regression to visually represent and forecast individual disease risks, thereby facilitating their practical application in clinical settings. In the

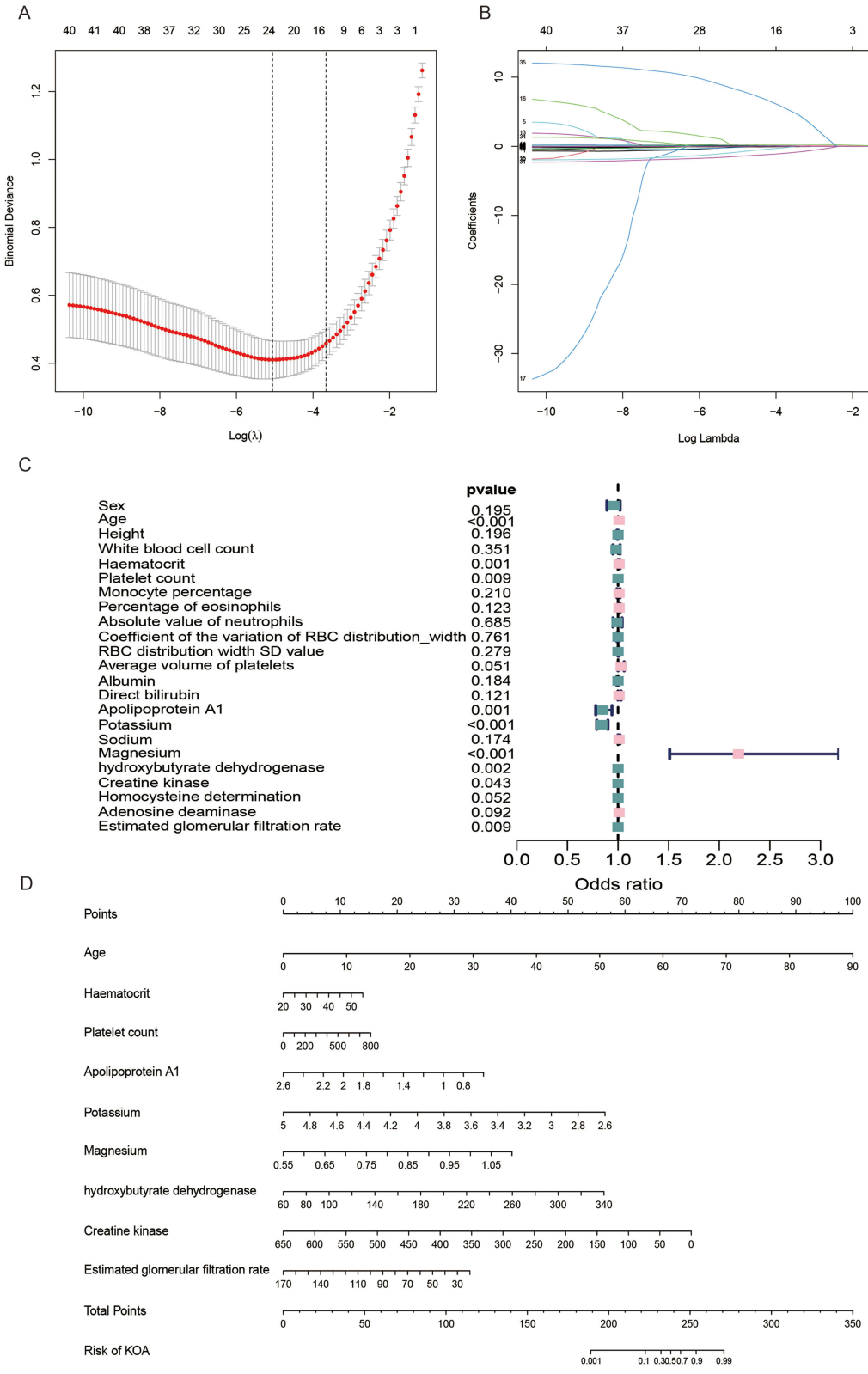

Figure 2 Risk factors for KOA patients included and constructed in a nomogram model. (**A** and **B**) Profiling the coefficients of the 23 prediction factors using the least absolute shrinkage and selection operator (LASSO). (**C**) Analysis of multivariate logistic regression in patients with KOA. (**D**) KOA nomogram prediction.

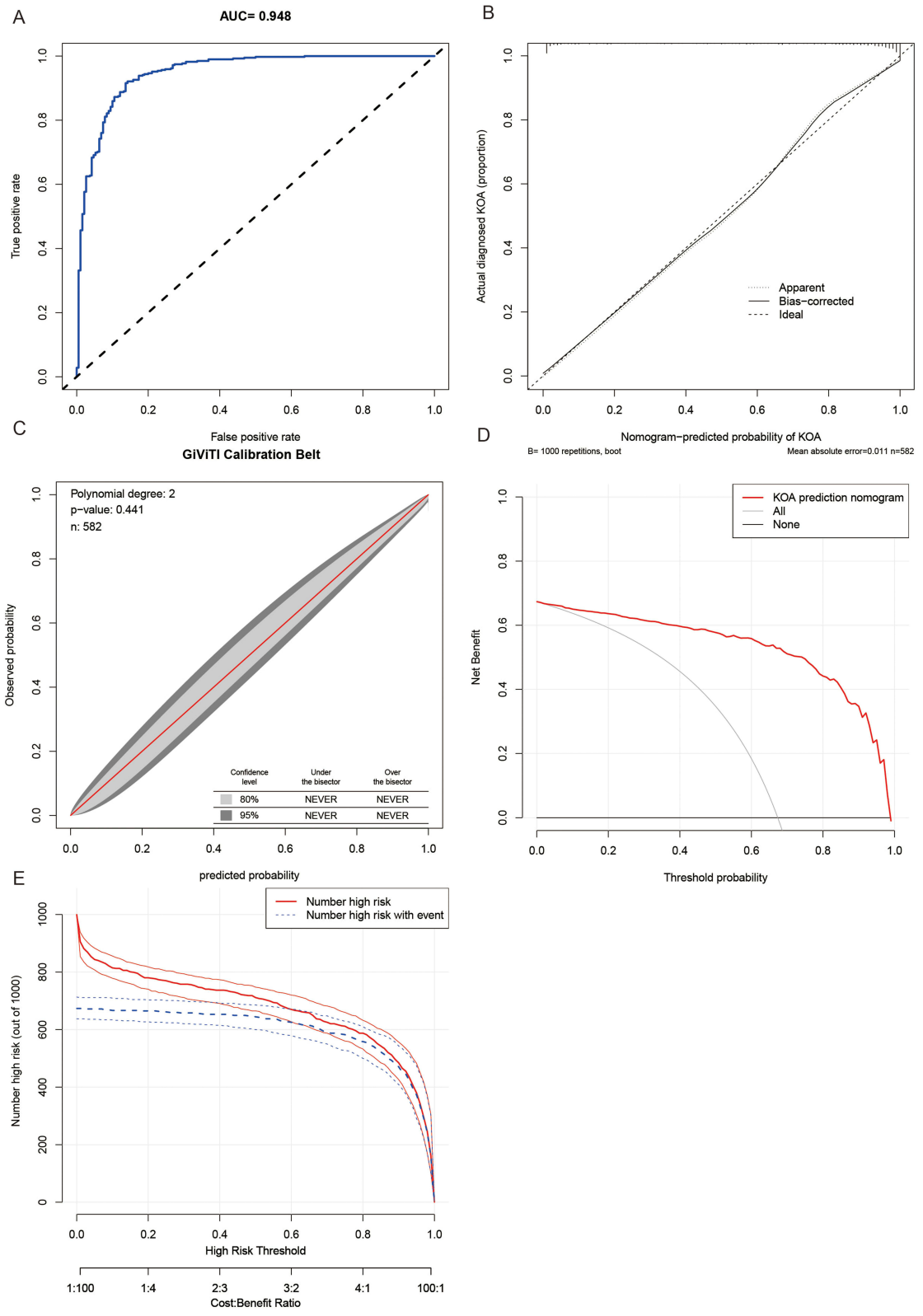

Figure 3 Nomogram model evaluation and clinical application in KOA patients. (**A**) A ROC curve based on a predictive nomogram for KOA. (**B**) Calibration plots for predicting KOA. (**C**) GiViTi calibration curve for predicting KOA. (**D**) Decision curve analysis for predicting KOA. (**E**) Clinical impact plot for predicting KOA.

realm of KOA, the efficacy and practical significance of nomogram models have been substantiated, enabling the anticipation of the likelihood of advanced KOA necessitating surgical replacement and the manifestation of post-replacement complications.[34,35] Nevertheless, there exists a dearth of scholarly literature concerning the construction of nomogram models for forecasting the susceptibility to developing KOA, potentially attributable to the prevalent utilization of ancillary examinations in clinical settings to evaluate its existence. In the present study, we have successfully developed a nomogram model that utilizes easily accessible demographic and laboratory data to accurately predict the likelihood of developing KOA. This innovative model offers a visualized and personalized approach to forecasting the risk of KOA, thus facilitating the formulation of preventive strategies. Furthermore, it supplements the probability of the incidence of KOA through non-imaging methods, thus overcoming the limitations of imaging technology. This nomogram model can be applied in primary healthcare settings, such as community health service stations, where imaging equipment is not available. It is particularly useful for patients who are unwilling or unable to undergo radiation exposure, such as pregnant women, as well as for patients who face challenges in undergoing X-ray examinations due to long-term bed rest, among other circumstances. Therefore, a reduction in examination costs can be achieved, as well as a reduction in radiation damage caused by patients' exposure to X-rays.

Multiple studies have examined the correlation between age and KOA. Calce et al determined that age accounts for a significant portion of the observed changes in KOA patients.[36] Deng et al proposed that the aging process plays a pivotal role in the pathogenesis of osteoarthritis.[37] Zhang et al concluded that osteoarthritis is a type of arthritis that is closely linked to age and is a leading cause of chronic disability among older individuals.[38] Our study aligns with these aforementioned findings, as we discovered that age independently contributes to the risk of KOA, with the likelihood of developing the condition increasing as one ages. Age is significantly associated with two additional independent risk factors that were identified in our study, namely blood potassium levels and estimated glomerular filtration rate. As individuals age, their appetite gradually diminishes, leading to insufficient intake of potassium. Moreover, the likelihood of developing KOA increases with advancing age, further exacerbating the decline in appetite and potassium intake. Similarly, the formula used to calculate estimated glomerular filtration rate demonstrates a gradual decrease with age, accompanied by an increased risk of developing KOA. It follows, then, that the risk of developing KOA increases as the estimated glomerular filtration rate decreases.

The term "Mean corpuscular hemoglobin concentration (MCHC)" pertains to the mean concentration of hemoglobin per liter of blood. Previous research has substantiated that, within a specific range, MCHC exhibits a gradual decline in conjunction with the severity of KOA. MCHC is determined by dividing the quantity of hemoglobin per liter of blood by the hematocrit (HCT).[39] This rationalizes the outcomes of our study, indicating that an escalation in HCT corresponds to an augmented likelihood of developing KOA.

Previous studies have established a significant correlation between platelet count and hip and knee osteoarthritis, a finding that aligns with our own research.[40] Platelet-rich plasma (PRP) currently stands as the prevailing biological therapy in the realm of osteoarthritis.[41] PRP is favored for its minimal invasiveness, favorable safety profile, ease of administration, and cost-effectiveness. The release of growth factors from platelets in PRP is hypothesized to enhance the joint pathology of patients with OA by facilitating chondrogenesis, stimulating the proliferation of cartilage cells, and augmenting the secretion of hyaluronic acid by synovial cells.[42] Currently, PRP is being employed in clinical settings for the management of OA and cartilage injuries. This phenomenon may elucidate the rationale behind the observed elevation in platelet count among individuals with KOA, as an adaptive response to the development of KOA.

Apolipoprotein A1 (ApoA1), a protein weighing 28-kDa, assumes a critical function in lipoprotein metabolism as the principal protein constituent of high-density lipoprotein. By activating lecithin cholesterol acyltransferase, ApoA1 facilitates the transportation and metabolism of cholesterol in the liver, thereby impeding the onset of hypercholesterolemia.[43] Given that hypercholesterolemia represents a risk factor for OA,[44] the likelihood of developing KOA escalates as the levels of ApoA1 decrease.

The relationship between dietary magnesium and OA has been proposed by Kuang et al.[45] In addition to its ability to slow down chondrocyte apoptosis, magnesium supplementation has been shown to promote chondrocyte proliferation and differentiation. Veronese et al conducted a cross-sectional study which demonstrated that a 100 mg increase in daily magnesium intake significantly enhanced the cartilage volume and thickness of knee joint surfaces, indicating the

potential role of magnesium in the prevention and treatment of KOA.[46] Yao et al discovered that the action of Mg^{2+} on OA involves the facilitation of hypoxia-inducible factor-1α (HIF-1α)-mediated synthesis of chondrocyte matrix.[47] Additionally, they substantiated that the intra-articular administration of Mg^{2+} and vitamin C can mitigate joint degradation and pain in a mouse model of OA by impeding osteophyte development and the expression of pain-associated neuropeptides. This finding presents a potential alternative therapeutic approach for managing OA. According to our study, blood magnesium levels increase with the risk of developing KOA, suggesting that blood magnesium levels may play a protective role in the knees in the aftermath of KOA development.

Lactate dehydrogenase (LDH) is ubiquitously distributed in the cytoplasm and mitochondria of diverse tissues and cells, encompassing the liver, heart, skeletal muscle, lung, spleen, brain, red blood cells, and platelets.[48] LDH exists as a tetramer with a molecular weight of 135 kDa, comprising M and H subunits that assemble to generate five distinct isoenzymes: H4 (LD1), MH3 (LD2), M2H2 (LD3), M3H (LD4), and M4 (LD5). Alpha-hydroxybutyrate dehydrogenase, an isoenzyme of LDH, encompasses the combined activities of LDH1 and LDH2. Patients with KOA frequently exhibit muscular impairment surrounding the joints,[48] resulting in heightened levels of LDH and alpha-hydroxybutyrate dehydrogenase. Consequently, elevated alpha-hydroxybutyrate dehydrogenase serves as a predisposing factor for the development of KOA.

The manifestation and progression of osteoarthritis frequently lead to muscle atrophy, which has a detrimental impact on joint mobility, while muscle weakness expedites the advancement of osteoarthritis.[49–52] Diminished skeletal muscle mass is a prevalent attribute among individuals diagnosed with osteoarthritis.[52] In comparison to individuals in good health, patients with knee osteoarthritis (KOA) exhibit a lower proportion of overall body muscle mass, particularly in the lower extremities. The quadriceps femoris and hamstring muscles demonstrate both muscle weakness and atrophy, potentially serving as direct risk factors for the manifestation and progression of KOA.[53] Research has demonstrated that individuals with hip and knee osteoarthritis experience a reduction in the cross-sectional area of their muscles by 12–19%.[54] In a study conducted by Jeon et al,[55] it was observed that skeletal muscle mass in patients with knee osteoarthritis is significantly lower compared to that of healthy individuals. While the precise mechanisms responsible for muscle atrophy in osteoarthritis remain a topic of debate, the atrophy of muscles surrounding the affected joints plays a crucial role in the onset and progression of osteoarthritis, highlighting its distinctive significance. Creatine kinase is predominantly present in muscles, and a decline in its levels is an inevitable consequence of muscle atrophy. Consequently, the gradual decrease in creatine kinase levels corresponds to an increased susceptibility to KOA development.

It has been reported in other studies that osteoarthritis incidence varies by gender.[23,56,57] Women account for 72% of KOA cases in this study. Studies have reported that women are more seriously affected by knee osteoarthritis. Especially after the age of 50, the proportion of women suffering from osteoarthritis is higher than that of men.[58] In addition to sex hormones, reproductive factors, and hormone supplements, osteoarthritis is affected by these factors. There is evidence that endogenous hormones and reproductive factors contribute to osteoarthritis, especially KOA.[59] It is therefore essential to understand how and why these gender differences occur in order to formulate an effective strategy for battling KOA in the future.

The C-index of our KOA diagnostic and prediction nomogram model was determined to be 0.948, signifying a commendable concordance between the anticipated risk of KOA development and the observed outcomes during internal validation. The calibration curve additionally substantiated the model's predictions by demonstrating exceptional discriminatory power and precision. Furthermore, our study not only showcased its remarkable predictive accuracy but also substantiated the efficiency of the nomogram model in forecasting the risk of KOA, as evidenced by the ROC curve. Moreover, by evaluating the clinical decision curves and clinical impact curves, we further validated the model's robust clinical utility and effectiveness, thereby reinforcing its superiority or inferiority in statistical inference outcomes.

The study is subject to several limitations, namely a small sample size, the fact that it was conducted at a single center, and the necessity for additional validation of the nomogram model in predicting the risk of developing KOA through multicenter and large-scale case studies. Additionally, this study does not include all biochemical detection indicators, which may result in some deviations in the selection of indicators, thus affecting the results. Lastly, the results of this study may be influenced by the living habits of the population, race and age, as well as certain limitations of the detection indicators.

Conclusions

In summary, this research has successfully developed a nomogram model that utilizes nine independent biological risk factors to predict the likelihood of developing KOA. The utilization of this nomogram model enables personalized and visual predictions, facilitating the identification of individuals at high risk for KOA and assisting in the formulation of preventive strategies. Furthermore, it opens up new avenues for indirectly diagnosing KOA with non-imaging methods, which contribute towards addressing the limitations of imaging techniques.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available because of restricted access to our hospital database but are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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