Original Article
Changes in serum inflammatory factors after hip arthroplasty and analysis of risk factors for prosthesis loosening

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Abstract: Objective: To explore the relationship of serum levels of IL-1β, IL-6, and TNF-α with prosthesis loosening after hip arthroplasty, and to establish a predictive model for prosthesis loosening. Methods: We retrospectively analyzed the data of 501 patients who underwent hip arthroplasty in Xi'an International Medical Center Hospital from January 2020 to August 2022. Based on radiological diagnosis, the patients were divided into a prosthesis loosening group and a non-loosening group. Clinical data including postoperative serum levels of inflammatory cytokines were collected. Univariant analysis, Lasso regression, decision tree, and random forest models were used to screen feature variables. Based on the screening results, a nomogram model for predicting the risk of prosthesis loosening was established and then validated using ROC curve, and calibration curve, and other methods. Results: There were 50 cases in the loosening group and 451 cases in the non-loosening group. Postoperative levels of IL-1β, IL-6, and TNF-α were found to be significantly higher in the loosening group (P<0.0001). Univariant analysis showed that osteoporosis and postoperative infection were risk factors for prosthesis loosening (P<0.001). The machine learning algorithm identified osteoporosis, postoperative infection, IL-1β, IL-6, and TNF-α as 5 relevant variables. The predictive model based on these 5 variables exhibited an area under the ROC curve of 0.763. The calibration curve and DCA curve verified the accuracy and practicality of the model. Conclusion: Serum levels of IL-1β, IL-6, and TNF-α were significantly elevated in patients with postoperative prosthesis loosening. Osteoporosis, postoperative infection, and inflammatory cytokines are independent risk factors for prosthesis loosening. The predictive model we established through machine learning can effectively determine the risk of prosthesis loosening. Monitoring inflammatory cytokines and postoperative infections, combined with prevention of osteoporosis, can help reduce the risk of prosthesis loosening.

Keywords: Hip arthroplasty, prosthesis loosening, IL-1β, IL-6, TNF-α

Introduction

Total hip arthroplasty (THA) is considered one of the most significant advancements in orthopedic surgery during the 20th century. It can greatly relieve pain in patients with hip joint diseases, improve hip joint mobility, restore joint function, maintain joint stability, and enhance patients' quality of life [1]. In China, THA was first introduced in the 1960s with the successful use of the Judet-type plastic joint for treating femoral neck fractures. This treatment achieved remarkable therapeutic results and quickly gained recognition in the medical community [2]. In the 1990s, extensive research was conducted on this surgical method, expanding its applications to avascular necrosis of the femoral head, congenital hip disease, hip fractures, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and traumatic arthritis [3].

In clinical practice, it has been observed that hip replacements can fail for various reasons, including prosthesis loosening, recurrent hip dislocations, infections, and periprosthetic fractures [4]. Prosthesis loosening is particularly significant cause of failure in THA [5]. Studies have indicated that the incidence of prosthesis loosening is approximately 10% ten years after THA, and this risk continues to increase over time [6]. Prosthesis loosening not

only affects the stability of the joint prosthesis but also reduces its lifespan, necessitating secondary revision surgeries. These additional surgeries impose psychological, physiological, and economic burdens on patients [7]. Many patients experience symptoms, such as pain and joint movement disorders, when the joint prosthesis becomes loose, often requiring secondary treatment through hip joint revision surgeries [8]. Therefore, early diagnosis of prosthesis loosening after THA is crucial.

Inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, play crucial roles in various physiological and pathological processes in the human body [9]. These cytokines are involved in immune responses, cell proliferation, cell apoptosis, and inflammatory reactions [10]. IL-1β, primarily produced by macrophages, is a multifunctional cytokine that can stimulate bone marrow cell differentiation and promote bone resorption, which may result in a decline in bone density around the prosthesis and increase the risk of prosthesis loosening [11]. Similarly, IL-6 also has a significant impact on bone metabolism. It stimulates the formation of bone marrow cells but simultaneously promotes bone resorption [12]. In the context of prosthesis loosening, elevated levels of IL-6 may accelerate bone resorption, leading to prosthesis instability. TNF-α, mainly produced by activated macrophages, is another cytokine known for promoting bone resorption and inhibiting bone formation. An increase in TNF-α near the prosthesis could cause rapid bone resorption, further increasing the risk of prosthesis loosening [13].

Although the roles of IL-1, IL-6, and TNF-α have been extensively studied in various diseases, their specific mechanisms in prosthesis loosening remain unknown. This research analyzed the changes in serum levels of IL-1, IL-6, and TNF-α after hip arthroplasty and the risk factors affecting patient prosthesis loosening. We aimed to provide a new perspective on the mechanisms of prosthesis loosening and offer better therapeutic and preventative strategies for patients.

Methods and materials

Ethical statement

This study was approved by the Institutional Medical Ethics Committee of Xi'an International Medical Center Hospital.

Sample size calculation

The incidence of hip replacement is usually 5%-15% [5, 7], and we chose 10% as a reference. Assuming that the optimal effective threshold is 10%, α = 0.05, 1-β = 0.95. According to the sample size calculation formula: $n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times p0(1 - p0)}{(p1 - p0)^2}$, about 465 cases are needed. Considering 10% deletion, 516 patients may need to be included. Combined with the actual clinical situation, we collected a total of 501 patients.

Clinical data

A retrospective analysis was conducted on 501 patients who underwent hip arthroplasty in Xi'an International Medical Center Hospital from January 2020 to August 2022. Inclusion criteria: patients with a clear clinical diagnosis who chose to undergo THA in Xi'an International Medical Center Hospital; patients with unilateral disease who only underwent unilateral hip arthroplasty; patients with no history of hip arthroplasty; patients with complete clinical data. Exclusion criteria: patients with bone tumors or other systemic malignant tumors; patients with coagulation abnormalities, hematopoietic disorders, or other hematological diseases; patients with impaired motor function due to other reasons; pregnant and lactating female patients.

Criteria for prosthesis loosening

Acetabular loosening can be classified into four levels. Level I: Intact prosthetic acetabular structure, but with radiolucent areas and sclerotic line changes around the implant and thinning of the acetabular base. Level II: Significant changes in the acetabular base with an enlarged acetabulum. Level III: Obvious displacement of the implant with bone defects in the acetabular roof, superior and medial walls. Level IV: Displacement or protrusion of the implant into the pelvis, with a large area of bone defect and extensive collapse of the acetabulum. The stem loosening can also be divided into four levels. Level I: Minimal loss of intramedullary bone at the prosthesis interface, and reduction of cortical thickness in the proximal part by less than 50%. Level II: Loosening at the interface with the medullary cavity. Level III: Significant bone loss in the medullary cavity, apparent and unstable implant migration, and bone defects in the proximal femur. Level IV:

Significant bone defects around the proximal part of the implant, and large defects in the proximal femoral fracture [14].

Sample selection

Based on the patient inclusion criteria and the criteria for prosthesis loosening, 50 patients who had prosthesis loosening after hip arthroplasty were included in the loosening group, and 451 patients without loosening in the non-loosening group.

Clinical data collection

Clinical data were collected from electronic medical system, including age, sex, type of disease before replacement, osteoporosis, hypertension, diabetes, postoperative secondary infections, operation time, intraoperative bleeding volume, and postoperative drainage. Laboratory indices included serum IL-1β, IL-6, and TNF-α levels 1 d before hip arthroplasty.

Serum inflammatory factors

Peripheral blood (5 mL) was collected from patients before treatment, centrifuged at 1500 rpm for 10 min, and serum was obtained for the detection of IL-1β (ml058059), IL-6 (ml058097), and TNF-α (ml077385) by enzyme-linked immunosorbent assay (ELISA) using kits from mlbio, Shanghai, China [15].

Machine learning feature selection

We utilized decision tree, LASSO, and random forest machine learning models to screen features from the training dataset. The final feature variables were determined using a Venn diagram. A nomogram model predicting the risk of prosthesis loosening was then constructed based on these features [16].

Statistical analysis

Data processing, including deletion and filling, was performed using SPSS 26.0. Decision tree and random forest model analyses were performed on the SPSSAU platform. R software was used for further statistical analyses. The "glmnet" package was used to construct the Lasso model, the "rms" package to construct the nomogram, the "rmda" package to plot the decision curve analysis (DCA), the "rocr" package to plot the receiver operating characteristic (ROC) curve, and the "rms" package to plot the calibration curve and calculate the C-index. A *P*

value of less than 0.05 was considered statistically significant.

Results

Clinical information

First, we compared the clinical data between the two groups of patients. No significant statistical differences were found in age, sex, type of disease before replacement, hypertension, diabetes, operation time, intraoperative bleeding volume, and postoperative drainage between the loosening group and the non-loosening group (P>0.05, **Table 1**). However, the proportions of patients with osteoporosis and postoperative secondary infections were significantly higher in the loosening group than those in the non-loosening group (P<0.001, **Table 1**).

Expression of inflammatory factors in patients with prosthesis loosening

We compared the serum levels of IL-1β, IL-6, and TNF-α in the two groups of patients one week after surgery. The results showed that serum levels of IL-1β, IL-6, and TNF-α were significantly higher in patients with prosthesis loosening than in those without prosthesis loosening, with a significant statistical difference (P<0.0001, **Figure 1**).

Predictive value of inflammatory factors for prosthesis loosening

We analyzed the predictive value of serum inflammatory factors in patients with prosthesis loosening. Our results showed that the area under the curve (AUC) of IL-1β, IL-6, and TNF-α for predicting prosthesis loosening was 0.811, 0.858, and 0.811, respectively (**Figure 2**; **Table 2**).

Lasso regression feature selection

Lasso regression on 13 factors revealed that age, sex, osteoporosis, postoperative secondary infection, IL-1β, IL-6, and TNF-α were strongly associated with prosthesis loosening (P<0.05, **Figure 3A**, **3B**).

Feature selection using decision tree and random forest models

Features for prosthesis loosening were screened using decision tree and random forest models. The results showed that the factors

Table 1. Analysis of the clinical data

Factors	Loosening Group (n = 50)	Non-loosening Group (n = 451)	χ^2 Value	*P*-value
Age			0.677	0.410
≥40 years	28	335		
<40 years	22	206		
Sex			1.894	0.168
Male	35	325		
Female	15	216		
Type of disease before replacement			1.926	0.587
Femoral head necrosis	10	102		
Femoral neck fracture	22	207		
Rheumatoid arthritis	8	44		
Hip joint developmental abnormality	10	98		
Osteoporosis			12.332	<0.001
Yes	30	189		
No	20	352		
Hypertension			0.188	0.664
Yes	19	189		
No	31	352		
Diabetes			0.997	0.318
Yes	21	189		
No	29	352		
Postoperative secondary infection			14.241	<0.001
Yes	28	162		
No	22	379		
Operation time				
≥2 h	27	257	0.163	0.686
<2 h	23	194		
Intraoperative bleeding volume				
≥200 mL	35	302	0.188	0.664
<200 mL	15	149		
Postoperative drainage				
≥300 mL	31	299	0.369	0.543
<300 mL	19	152		

with weights greater than 0.01 were osteoporosis, sex, age, postoperative secondary infection, hypertension, TNF-α, type of disease before replacement, IL-1β, diabetes, and IL-6 (**Figure 4A**, **4B**).

Construction of prosthesis loosening nomogram

Using univariate analysis, LASSO, random forests, and decision trees, we identified five feature variables: osteoporosis, postoperative secondary infection, IL-1β, IL-6, and TNF-α (**Figure 5A**). In the risk prediction nomogram visualization, 'Points' represent the score corresponding to each variable, with different variable values having different 'Points' (**Figure 5B**). By summing up the scores for each variable, we obtain the 'TotalPoints'. Consequently, the risk of prosthesis loosening for each patient could be determined from the 'Risk of Prosthesis Loosening' section below. This facilitated individualized prediction of clinical prosthesis loosening. The effectiveness of the risk prediction model was evaluated using the AUC, C-index, DCA, and calibration curve. The AUC was 0.763, indicating a good discriminatory ability of the prediction model
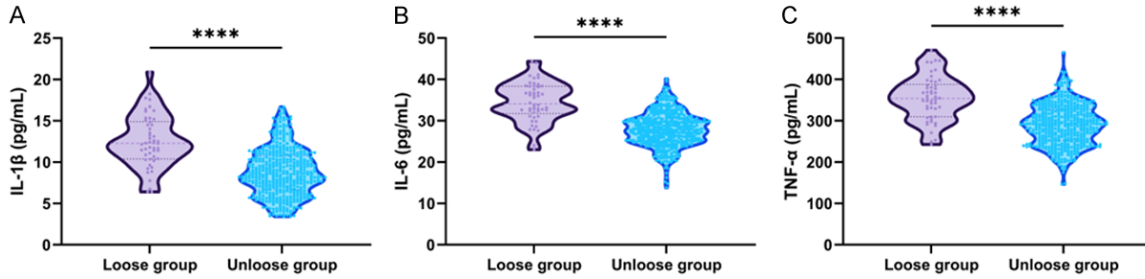
Figure 1. Comparison of expression levels of inflammatory factors in the serum of patients. A. Comparison of IL-1β expression levels. B. Comparison of IL-6 expression levels. C. Comparison of TNF-α expression levels. Note: ****P<0.0001; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α.
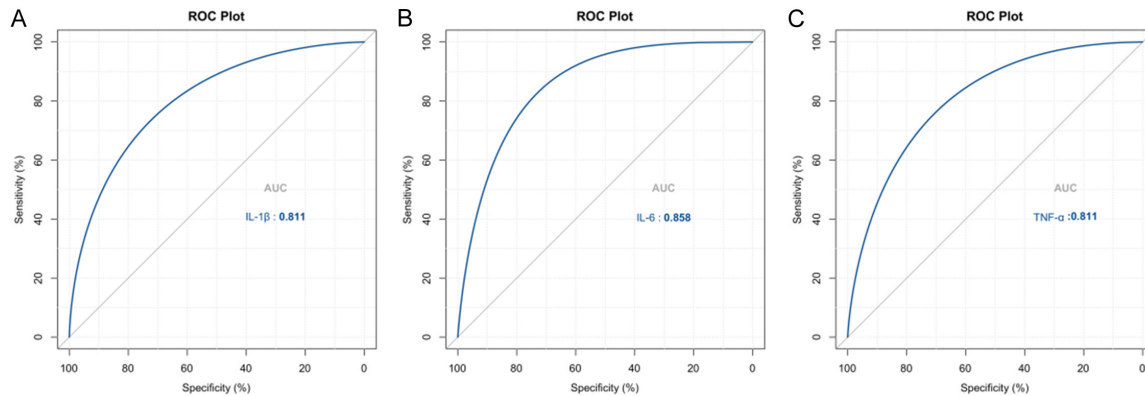

Figure 2. ROC curves of inflammatory factors in predicting prosthesis loosening. A. ROC curve of IL-1β. B. ROC curve of IL-6. C. ROC curve of TNF-α. Note: ROC, Receiver Operating Characteristic; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α.

(**Figure 5C**). The calibration curve demonstrated that the predicted probability of prosthesis loosening aligned well with the actual situation, highlighting the accuracy of the prediction model (**Figure 5D**). The C-index was 0.952 (0.927-0.977), indicating a strong consistency between the actual and predicted probabilities of prosthesis loosening. The DCA showed that the prediction model provided a favorable clinical net benefit across various threshold probabilities (0%-97%), confirming its practicality (**Figure 5E**).

Discussion

Artificial hip joint replacement surgery is an established and effective clinical treatment for hip joint diseases. This surgery can alleviate joint pain and restore patients' mobility, so its clinical application has been widely recognized for over 30 years [17, 18]. However, despite its success, some patients who have undergone this surgery experience prosthesis loosening,

which greatly diminishes the effectiveness of the treatment.

In this study, we utilized machine learning techniques to investigate various potential factors that may contribute to prosthesis loosening in patients undergoing hip joint replacement. Through comprehensive data analysis, we identified several key factors, including osteoporosis, postoperative secondary infections, IL-1β, IL-6, and TNF-α. Osteoporosis is a bone disease characterized by a significant reduction in bone mass and disruption of bone microstructure [20]. This condition increases the risk of bone resorption and fractures around the prosthesis, thereby elevating the risk of prosthesis loosening. According to Xu et al. [18], osteoporosis primarily manifests in two types. The first type is associated with long-term medication use, particularly corticosteroids, which can result in avascular necrosis of the femoral head and necessitate hip replacement. The second type of osteoporosis is linked to age and sex, par-

Table 2. ROC curve parameters of inflammatory factors for predicting prosthetic loosening

Predictive Variables	AUC	95% CI	Cut-off Value	Sensitivity	Specificity	Youden's Index
IL-1β	0.811	0.751-0.872	10.155	0.69401	0.82	0.51401
IL-6	0.858	0.799-0.918	31.98	0.84257	0.76	0.60257
TNF-α	0.811	0.746-0.875	329.16	0.76497	0.74	0.50497

Note: ROC, Receiver Operating Characteristic; AUC, Area Under Curve; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α.
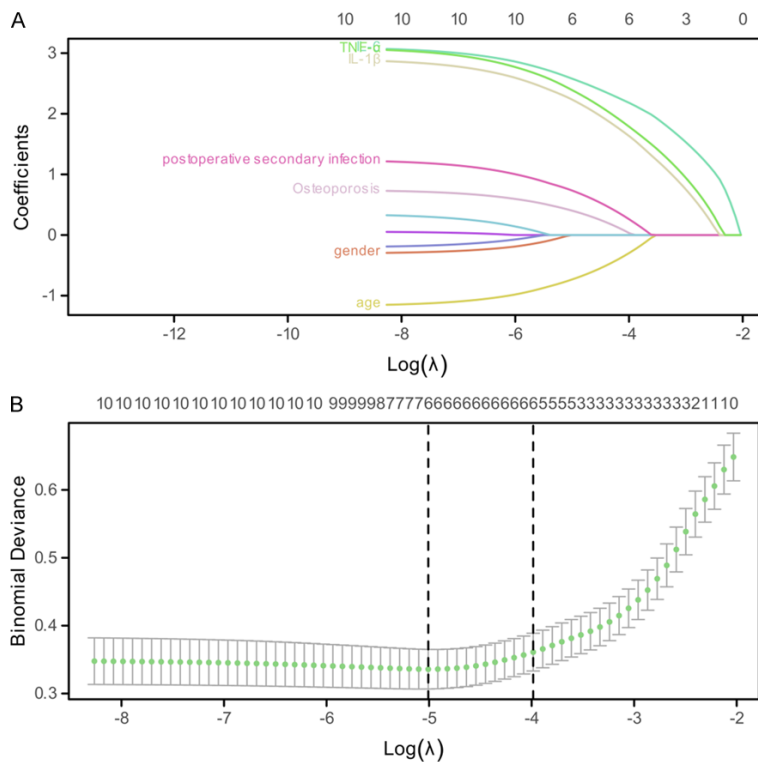

Figure 3. Lasso regression screening for factors related to prosthesis loosening. A, B. The minimum criteria were used to perform LASSO regression, and CVFIT and lambda curves were shown, demonstrating the regression. Note: LASSO, least absolute shrinkage and selection operator; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α.

ticularly common in elderly women [21]. Imbalances in bone metabolism and bone loss are the primary causes of this type of osteoporosis. To effectively prevent osteoporosis and minimize the risk of prosthesis loosening, we recommend that patients to adopt appropriate post-surgery immobilization measures and engage in moderate physical activities under the guidance of a physician [22]. Furthermore, patients with severe osteoporosis can use anti-osteoporosis medications, such as teriparatide or bisphosphonates, which have demonstrated efficacy. Additionally, cemented fixation techniques have shown superior effects in reducing the risk of prosthesis loosening.

The diagnosis of infection mainly relies on clinical symptoms, routine blood tests, C-reactive protein, erythrocyte sedimentation rate, and pathogenic tests. Bacterial infection can not only cause bone defects and tissue necrosis but is also a leading cause of prosthesis loosening [23]. For an infection to occur, several conditions must be met: the presence of an infection source, a suitable environment for bacterial survival, and a lack of immune resistance in the patient. Previous studies have shown that open wounds in hip joint replacement surgery are ideal environment for bacterial survival [24]. Coupled with reduced immunity in the patient, the risk of bacterial infection can increase greatly. Additionally, the prolonged duration of surgery is also considered a significant risk factor for infection. Currently, the widely adopted international treatment strategy for prosthesis loosening caused by joint prosthesis infection is staged treatment. While this strategy is effective in many cases, it has a long treatment cycle and places a substantial physical, psychological, and financial burden on patients, with a failure rate of about 10% [25]. Therefore, further research and exploration are needed for the prevention and treatment of prosthetic joint infections. Artificial hip joint replacement surgery has significantly improved the quality of life for patients with hip joint diseases. However, prosthesis loosening remains to be a challeng-
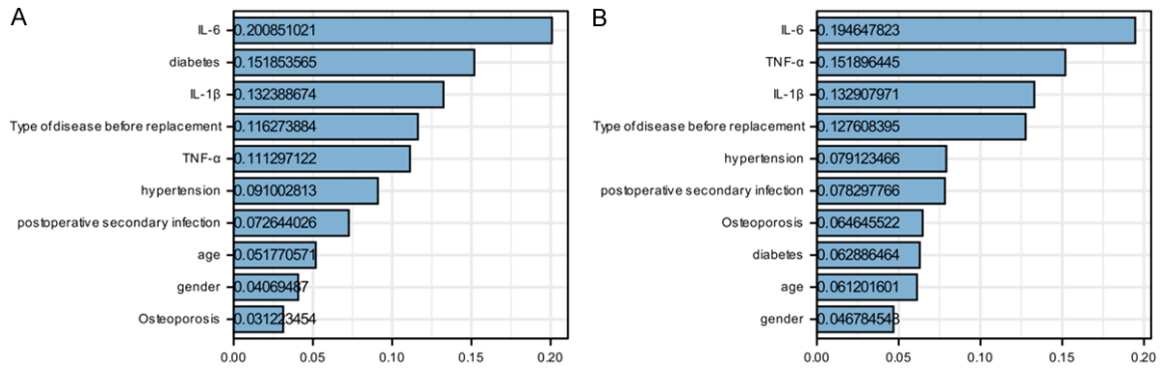
Figure 4. Display of feature variables from decision tree and random forest models. A. Feature variables selected by decision tree. B. Feature variables selected by the forest model. Note: IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α.
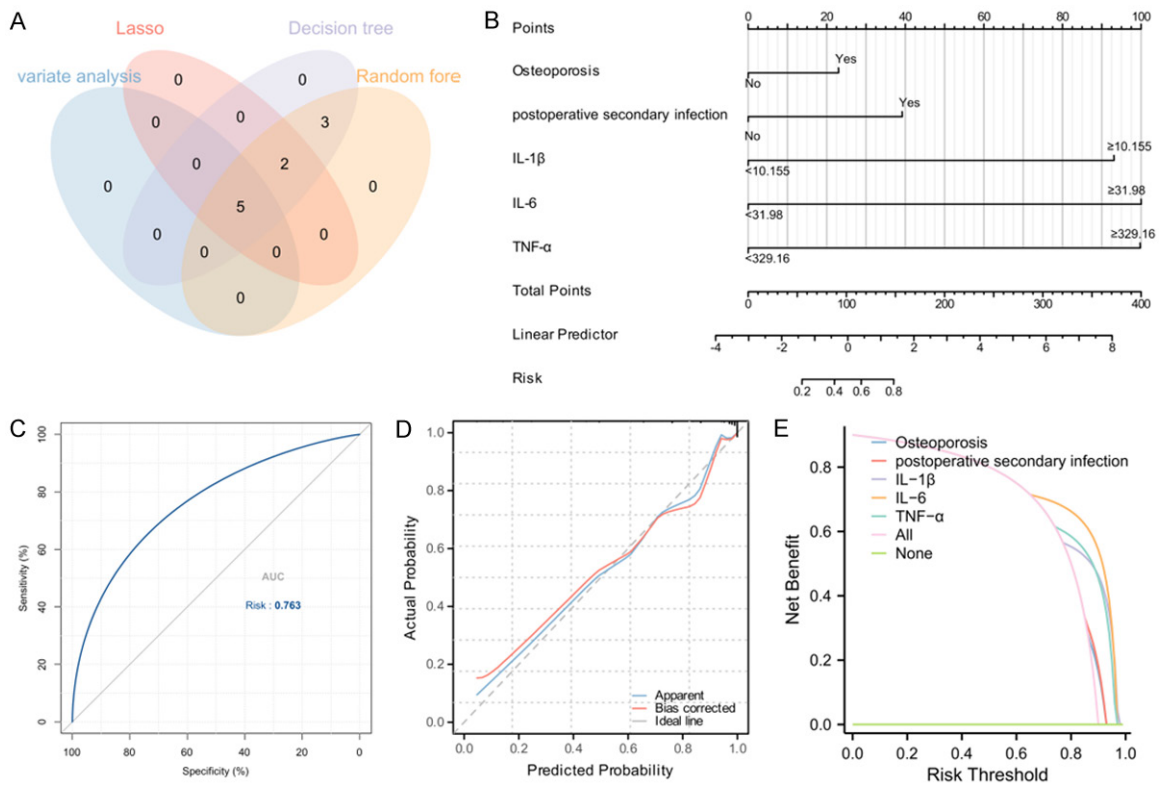

Figure 5. Construction and validation of the prosthesis loosening nomogram. A. Feature variables screened by Venn diagram. B. Risk prediction nomogram for prosthesis loosening. C. ROC curve analysis of the nomogram's efficacy in predicting prosthesis loosening. D. Calibration curve of the nomogram model predicting prosthesis loosening. E. DCA of the nomogram model predicting prosthesis loosening. Note: ROC, Receiver Operating Characteristic; IL-1β, Interleukin-1β; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; DCA, Decision Curve Analysis.

ing postoperative complication that affects patient outcomes. Understanding the underlying factors contributing to this complication is crucial for enhancing patient care.

Inflammation is considered a primary driver for prosthesis loosening, particularly when trig-

gered by infections or peri-prosthetic osteolysis. Infections can cause the formation of a biofilm on the implant's surface, which further promotes inflammation and damages bone tissue [13]. Inflammatory cytokines like TNF-α, IL-6, and IL-1β can directly or indirectly affect osteoclasts and their precursors, leading to osteo-

clast differentiation, maturation, and bone resorption activities. For example, TNF-α inhibits bone formation and stimulates osteoclast activation through multiple mechanisms [26]. While IL-6 has a relatively weak direct impact on bone resorption, it can enhance the pro-resorptive effect of other factors [27]. On the other hand, IL-1β suppresses osteoclast apoptosis by activating the NF-κB signaling pathway and further stimulates the proliferation and differentiation of osteoclast precursors [28]. We believe that the association between these inflammatory cytokines and prosthesis loosening in patients undergoing hip replacement is due to their direct or indirect modulation of osteoclast activity, which affects the structure and stability of bone tissue. Particularly in the presence of infections, these factors may intensify the inflammatory response, leading to bone tissue damage and an increased risk of prosthesis loosening. Therefore, effective management and control of the inflammatory response are crucial to ensure the stability of the implant.

Nomograms serve as a graphical representation tool, providing clinicians with an easy and intuitive way to predict the likelihood of an event or disease occurrence. In this study, we successfully identified 5 key features closely associated with prosthesis loosening: osteoporosis, postoperative secondary infections, IL-1β, IL-6, and TNF-α, by integrating univariate analysis and machine learning techniques such as LASSO, random forests, and decision trees. Each of these variables has a score in the nomogram, allowing us to calculate a total score for each patient, which in turn estimates their risk of prosthesis loosening. To validate the effectiveness of our model, we employed the ROC curve, DCA, and calibration curve. The AUC was 0.763, demonstrating the model's strong discriminative ability. The calibration curve showed a high level of agreement between predicted and actual outcomes, further confirming the accuracy of the model. The DCA confirmed the model's significant clinical net benefit across various probability thresholds. Overall, our study provides a powerful predictive tool for hip replacement patients, assisting physicians in making informed treatment decisions, which help formulate personalized treatment plans.

Incorporating 501 patients as subjects in this study ensured the reliability of our statistical analysis due to the sizable sample. We enhanced the depth and breadth of our research by utilizing both univariate analysis and machine learning methods. The introduction of machine learning enabled us to develop a clinically reliable prediction model of prosthesis loosening, which we have successfully internally validated. Furthermore, this study carried out a novel exploration of the potential relationship of IL-1β, IL-6, and TNF-α with prosthesis loosening, providing valuable insights for future related studies. However, we acknowledge certain limitations in our study. As a retrospective study, our design inherently faces constraints and challenges in establishing clear causative relationships. The absence of long-term follow-ups limited observation of long-term variations in inflammatory cytokine levels. Additionally, not directly comparing our predictive model with other models leaves the superiority or inferiority of our model undetermined. To address these challenges, our future research plans include adopting a prospective study design, conducting long-term follow-ups, and comparing our model with other models and functional validations. Furthermore, we aim to further validate the model on an even larger patient population to enhance its reliability.

Patients with postoperative prosthesis loosening showed significantly increased serum levels of IL-1β, IL-6, and TNF-α. Independent risk factors for prosthesis loosening include osteoporosis, postoperative infections, and increased inflammatory cytokines. Machine learning-based prediction models can effectively assess the risk of prosthesis loosening. Therefore, monitoring inflammatory factors and postoperative infections, along with implementing osteoporosis prevention measures, can help reduce the risk of prosthesis loosening.

Disclosure of conflict of interest

None.

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