Am J Transl Res 2026;18(4):3450-3465
www.ajtr.org /ISSN:1943-8141/AJTR0170365

Original Article

A preoperative inflammation-oxidative stress imbalance strongly predicts post-traumatic arthritis after acetabular fracture fixation

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Received November 27, 2025; Accepted February 3, 2026; Epub April 25, 2026; Published April 30, 2026

Abstract: Objective: This study aimed to evaluate the correlation between the development of post-traumatic arthritis (PTA) and a preoperative inflammation and oxidative stress imbalance. Further, the study aimed to evaluate the predictive power of a model based on inflammation and oxidative stress imbalance Index (IOSI). Methods: This retrospective cohort study was conducted from January 2020 to December 2023 and included 258 patients who underwent open reduction and internal fixation of acetabular fractures (training cohort) and 127 patients from another center (external validation cohort). Blood specimens were collected and analyzed for preoperative and discharge levels of IL-6, TNF-α, MDA, SOD, and IOSI. Multivariate logistic regression was applied to identify independent predictors of PTA. Two predictive models were constructed that were a conventional preoperative indicator prediction model (Risk1) and an IOSI-based model (Risk2). Receiver operating characteristic curves, area under the curve AUC, and net reclassification improvement NRI were used to assess model performance. Results: Post-traumatic arthritis (PTA) occurred in 66/258 patients (25.6%) in the training cohort. Compared with the non-PTA group, patients who developed PTA had significantly higher preoperative IL-6, TNF-α, and malondialdehyde (MDA) levels and lower superoxide dismutase (SOD) levels (all P<0.001), resulting in a markedly increased preoperative inflammation-oxidative stress imbalance index (IOSI) (P<0.001). Multivariate logistic regression identified delayed time from injury to surgery (OR=8.463, 95% CI 4.107-18.436; P<0.001), concomitant femoral head fracture (OR=2.832, 95% CI 1.226-6.672; P=0.015), and preoperative IOSI (OR=23.388, 95% CI 10.107-60.825; P<0.001) as independent predictors of PTA. Preoperative IOSI showed the best discriminative performance among individual indicators (AUC 0.813-0.919; cut-off 1.302; sensitivity 84.85%; specificity 78.12%). The IOSI-based model (Risk2) achieved an AUC of 0.911 in the training cohort and 0.821 in the external validation cohort, outperforming the conventional model (Risk1; AUC 0.879 and 0.700, respectively). In the training cohort, the AUC difference between Risk2 and Risk1 was not significant (DeLong P=0.232), whereas Risk2 showed significantly improved discrimination in external validation (P<0.05) and better reclassification (NRI=0.3565). Conclusion: A preoperative inflammation-oxidative stress imbalance could predict PTA after acetabular fracture fixation.

Keywords: Acetabular fracture, post-traumatic arthritis, inflammatory factors, oxidative stress, inflammation-oxidative stress imbalance index, prediction model

Introduction

High-energy trauma usually causes acetabular fractures involving the hip joint's weight-bearing articular surface. Following surgical techniques, open reduction and internal fixation (ORIF) can lead to post-traumatic arthritis (PTA) as a common complication for acetabular fracture surgery [1]. Earlier studies reported that about 13-44% of individuals developed post-traumatic osteoarthritis following ORIF, and many ultimately underwent total hip arthroplasty (THA) for pain relief and functional improvement [2-4]. Research indicates that surgical conversion to THA often occurs within years after PTA thereby indicating an important clini-

https://doi.org/10.62347/DGUG1032

cal burden of PDA. Furthermore, the authors also emphasize the identification of high-risk patients early [5, 6].

The development of PTA from a pathophysiologic perspective is driven by not only the mechanical factors like fracture pattern, quality of articular reduction and accompanying injury to the femoral head but also the joint trauma that initiates complex biological responses. According to some scientific and clinical evidence, acetabular fractures and dislocation of the hip synovial inflammation and cartilage catabolism are activated, which causes an increase in release of pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [7, 8]. Cytokines also stimulate the degradation of the extracellular matrix and suppress the repair capability of chondrocytes, thus accelerating joint degeneration. Simultaneously, traumatic injury leads to the overproduction of reactive oxygen species causing oxidative damage. In cell membranes, malondialdehyde, or MDA, is a product of lipid peroxidation and indicates damage to cell membranes. Also, superoxide dismutase, otherwise known as SOD, denotes the level of endogenous antioxidant defence capacity. A growing body of evidence suggests that chronic inflammation and oxidative stress may positively influence each other and contribute to cartilage degradation and sharpening of osteoarthritis [9, 10].

Several studies have examined whether inflammatory factors and/or oxidative stress markers are involved in osteoarthritis and post-traumatic joint degeneration. However, most studies have looked at the one biomarker in isolation. Notably, the studies often yield different and sometimes contradictory results [11, 12]. Several systematic reviews have observed a large number of candidate biomarkers. They have also reported that single indicators have limited predictive capability. Moreover, there are no clinically applicable predictive tools [12]. Notably, instead, inflammatory and oxidative stress markers have rarely been combined and might only reflect the biological imbalance after joint injury. Additionally, in acetabular fracture patients, there are limited predictive models which have this integrated biological information and external validation [13, 14].

Thus, the present study systematically assessed inflammatory and oxidative stress markers in patients undergoing ORIF for acetabular fractures and devised an inflammation-oxidative stress imbalance index (IOSI) to capture the joint effects of inflammatory activation and antioxidant depletion. Through the construction and external validation of predictive models based on preoperative factors, this work aims to enhance the early risk stratification of PTA. Identifying patients who are at low or high risk may help improve individual follow-up strategies, improve clinical decision-making and create an easy project that improves long-term acetabular fracture surgery outcome.

Materials and methods

Study design and sample size calculation

Through the analysis of clinical characteristics, biomarkers, and follow-up data on patients undergoing ORIF for acetabular fractures, the researchers aimed to develop and validate PTA prediction models in this retrospective cohort study. We estimated required sample size based on previously reported incidence rates of secondary hip osteoarthritis following acetabular fracture surgery. Consequently, the required sample size was 813. According to Rollmann et al., who used data from the German Pelvic Trauma Registry, 25% of patients with acetabular fractures would go on to develop secondary hip osteoarthritis and/or require further joint reconstruction during postoperative follow-up [13]. Thus, we consider the expected incidence P=0.25, and apply the single proportion sample size formula $N = Z^2 \times [P \times (1\text{-}P)]/E^2$. Using Z=1.96 (α=0.05) an allowable error E 0.05, we obtained minimum sample size of 289 cases. This means we need to sample at least 289 cases to make our results sufficiently reliable. A total of 258 cases were actually enrolled in the training cohort (Yan'an People's Hospital, Jan. 2020 to Dec. 2023), and 127 cases in the external validation cohort (Shaanxi Province Nuclear Industry 215 Hospital), for a total of 385 cases, much more than the theoretical minimum. The medical ethics committees of Yan'an People's Hospital approved this study.

Inclusion and exclusion criteria

Inclusion criteria: Adult patients (≥18 years) with an acetabular fracture whose condition has been confirmed on imaging and underwent

ORIF were included. Only fractures that were closed were included. The surgery was done during the acute phase post-injury. The complete preoperative laboratory data of all patients including IL-6, TNF-α, MDA, and SOD which were sufficient to calculate the inflammation-oxidative stress imbalance system IOSI. Moreover, sufficient clinical and radiographic information along with a minimum follow-up duration of 2 years was required to determine the presence or absence of PTA. Exclusion criteria included: Individuals who had pathologic or open acetabular fractures, pre-existing ipsilateral hip illness i.e. osteoarthritis, femoral head necrosis, hip dysplasia or previous hip surgery, and serious systemic illness that can markedly impact inflammatory or oxidative stress markers. Exclusion was done for patients who had early revision surgery or total hip arthroplasty for other causes than PTA, missing important clinical or laboratory data or insufficient follow up. Those patients judged to meet the above criteria and who developed a PTA during follow up were classified as the PTA group. Those patients who judged to meet the above criteria but did not develop radiographic or clinical evidence of PTA during follow up served as the control (non-PTA) group.

Clinical data collection

All the clinical data were obtained from electronic medical record system and verified by two. Age, gender, height, weight, and body mass index (BMI) were included. Information on injury and disease included the mechanism of injury, fracture type, whether a hip dislocation was present, whether a fracture of the femoral head present, whether an intertrochanteric femoral fracture present, surgical site infection, OTSA index, time from injury to surgery. Biomarkers assessed before and after surgery included interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), superoxide dismutase (SOD), and the imbalance index. IOSI calculation formula: = (IL-6 + TNF-α + MDA)/SOD.

Definition and determination of PTOA

PTOA determination in this study was based on internationally accepted radiologic and symptomatic criteria, with comprehensive assessment using postoperative follow-up data. Final PTOA outcomes relied primarily on radiologic assessment during postoperative outpatient visits, supplemented by telephone follow-up to obtain composite information evaluating joint degeneration occurrence within two years postoperatively. For radiologic assessment, outpatient visits uniformly employed anteroposterior pelvic radiographs and/or hip computed tomography (CT) to evaluate joint structural changes, independently interpreted by two qualified orthopedic surgeons in a blinded manner, with a third senior physician adjudicating discrepancies. PTOA was defined radiologically by any of the following: ① Marked joint space narrowing showing progressive reduction compared to the contralateral side or early postoperative radiographs; ② Increased subchondral sclerosis; ③ New or progressive osteophyte formation; ④ Subchondral cyst formation; ⑤ Irregular articular surfaces, collapse, or bony structural destruction of the acetabulum or femoral head. These diagnostic criteria referenced previous radiological evaluation systems for post-traumatic hip degeneration. Symptomatically, patients presenting with degeneration-related persistent hip pain, stiffness, or limited mobility during follow-up consistent with radiologic findings were also included in the comprehensive PTOA determination [14]. All patients received at least two years of follow-up through outpatient visits and telephone contact, with telephone follow-up supplementing outpatient information and confirming whether patients had received radiologic diagnosis or further surgery at other institutions.

Measurement methods

All laboratory tests were performed in the clinical laboratories of both hospitals according to standardized operating procedures. Blood samples were collected at two predefined time points: within 24 h before surgery after admission (preoperative) and within 24 h before discharge (discharge). The discharge sample typically corresponded to postoperative day 7-14 in our cohort. Serum IL-6 (pg/mL) and TNF-α (pg/mL) levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Enzyme-linked Biotechnology Co., Ltd., Shanghai, China; batch/lot no. ml058097 and ml077385). MDA (mmol/mL) and SOD (mU/mL) were determined using commercial colorimetric assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China; batch/lot no. A003-1-2 and A001-3-2) following the man-

ufacturers' instructions. Absorbance for ELISA was measured using a microplate reader (Bio-Rad iMark/xMark, Bio-Rad Laboratories, Hercules, CA, USA). Colorimetric assays were read using an absorbance microplate reader/spectrophotometer (Epoch 2, Agilent BioTek, Santa Clara, CA, USA). IOSI was calculated at each time point using the following formula: IOSI = (IL-6 + TNF-α + MDA)/SOD. Radiological evaluation included anteroposterior pelvic radiographs and/or hip computed tomography (CT) performed using a CT scanner (SOMATOM Definition AS, Siemens Healthineers, Erlangen, Germany), and images were independently assessed by two blinded orthopedic surgeons.

Outcome measures

The primary outcome was the occurrence of PTA in the postoperative phase as determined by detailed evaluation of clinical symptoms together with radiologic findings. The secondary results of the analysis included changes in inflammatory factors and reactive oxidative stress indices before and after surgery and possible predictive value of the IOSI and its individual indicators. Furthermore, correlation analysis results are mentioned as well as predictive performance of the models (Risk1 vs Risk2).

Statistical analysis

All statistical analyses were performed using R software (version 4.5.1) and SPSS (version 27). Continuous variables underwent normality testing, with independent samples t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed using χ^2 test or Fisher's exact test. Univariate and multivariate logistic regression identified independent factors influencing PTA occurrence. Prediction model discrimination was evaluated using ROC curves and AUC, with a DeLong test comparing AUC differences between models. Cut-off values were obtained from ROC analysis for descriptive purposes only and were not used to dichotomize variables in the regression models. NRI assessed model reclassification performance. Pearson or Spearman correlation analysis examined relationships between inflammatory factors and oxidative stress indicators. Statistical significance was set at P<0.05.

Results

Clinical factors associated with PTA occurrence in acetabular fractures

Univariate analysis of PTA occurrence following acetabular fracture internal fixation revealed that concomitant femoral head fracture (P< 0.001) and time from injury to surgery (P<0.001) were significantly associated with postoperative PTA development. Other general characteristics and injury-related factors, including gender, injury mechanism, fracture classification, hip dislocation, intertrochanteric femoral fracture, surgical site infection, age, BMI, height, weight, and OTSA index, showed no significant differences (P>0.05) (see **Table 1**).

Comparison of inflammatory factors and oxidative stress indicators between patients with and without PTA

Comparison of inflammatory factors and oxidative stress indicators demonstrated that the PTA group exhibited significant abnormalities both preoperatively and at discharge. Preoperative IL-6 (P<0.001), discharge IL-6 (P=0.012), preoperative TNF-α (P<0.001), discharge TNF-α (P<0.001), preoperative MDA (P<0.001), and discharge MDA (P=0.038) were all elevated compared to the non-PTA group. For antioxidant indicators, both preoperative SOD (P<0.001) and discharge SOD (P<0.001) were significantly decreased. IOSI showed significant elevation both preoperatively (P<0.001) and at discharge (P<0.001), suggesting that PTA patients exhibited a more pronounced inflammation and oxidative stress imbalance (see **Table 2**).

Discriminative performance of individual indicators for predicting PTA

ROC curve analysis of time from injury to surgery, inflammatory factors, and oxidative stress-related indicators revealed that preoperative IOSI demonstrated optimal overall discriminative ability, with both sensitivity and specificity at high levels, significantly outperforming other single biomarkers in predictive performance. Time from injury to surgery, preoperative IL-6, preoperative TNF-α, preoperative MDA, and preoperative SOD also showed good predictive value. On the other hand, the discharge measurement of the various biomarkers IL-6, TNF-α, MDA, SOD, and IOSI to predict PTA demon-

Table 1. Univariate comparison of baseline characteristics between PTA and non-PTA groups

Factor	Total	PTA Group (n=66)	Non-PTA Group (n=192)	Test Statistic	*P* Value	OR (95% CI)
Gender				0.469	0.493	
Male	173 (67.1%)	42 (63.6%)	131 (68.2%)			1.227 (0.683-2.206)
Female	85 (32.9%)	24 (36.4%)	61 (31.8%)			
Injury Mechanism				0.285	0.867	
Traffic Accident	173 (67.1%)	44 (66.7%)	129 (67.2%)			Reference
Fall	54 (20.9%)	15 (22.7%)	39 (20.3%)			1.128 (0.567-2.241)
Other	31 (12.0%)	7 (10.6%)	24 (12.5%)			0.855 (0.345-2.122)
Fracture Classification				0.088	0.767	
Simple Fracture	78 (30.2%)	19 (28.8%)	59 (30.7%)			1.097 (0.593-2.029)
Complex Fracture	180 (69.8%)	47 (71.2%)	133 (69.3%)			
Hip Dislocation				0.142	0.707	
Yes	83 (32.2%)	20 (30.3%)	63 (32.8%)			1.123 (0.613-2.058)
No	175 (67.8%)	46 (69.7%)	129 (67.2%)			
Femoral Head Fracture				11.969	<0.001	
Yes	55 (21.3%)	24 (36.4%)	31 (16.1%)			0.337 (0.179-0.634)
No	203 (78.7%)	42 (63.6%)	161 (83.9%)			
Intertrochanteric Fracture				<0.001	1.000	
Yes	18 (7.0%)	5 (7.6%)	13 (6.8%)			0.886 (0.303-2.587)
No	240 (93.0%)	61 (92.4%)	179 (93.2%)			
Surgical Site Infection				0.867	0.352	
Yes	9 (3.5%)	4 (6.1%)	5 (2.6%)			0.414 (0.108-1.592)
No	249 (96.5%)	62 (93.9%)	187 (97.4%)			
Age (years)	41.50 (33.00, 53.00)	44.00 (33.25, 52.00)	41.00 (32.75, 53.00)	0.432	0.666	
BMI (kg/m^2)	23.32±2.96	23.25±3.20	23.35±2.88	0.23	0.819	
Height (m)	1.70 (1.65, 1.75)	1.69 (1.65, 1.75)	1.70 (1.65, 1.75)	0.243	0.808	
Weight (kg)	67.44±10.55	67.21±11.71	67.52±10.15	0.203	0.840	
OTSA Index	4.88±3.62	4.77±4.00	4.92±3.49	0.294	0.769	
Time from Injury to Surgery (d)	11.48±3.68	14.55±2.95	10.42±3.30	8.98	<0.001	

Note: BMI, Body Mass Index; OTSA, Osteoarthritis Trauma Score Assessment.

Table 2. Comparison of inflammatory and oxidative stress markers between PTA and non-PTA groups

Factor	Total	PTA Group (n=66)	Non-PTA Group (n=192)	Test Statistic	*P* Value
Preoperative IL-6	32.58±5.57	37.05±4.91	31.05±4.93	8.545	<0.001
IL-6 at Discharge	13.45±4.70	14.70±4.64	13.02±4.66	2.532	0.012
Test/P Statistic		24.67/P<0.001	38.325/P<0.001		
Preoperative TNF-α	47.86±5.61	51.08±5.86	46.75±5.08	5.739	<0.001
TNF-α at Discharge	12.49±5.70	16.42±5.59	11.14±5.08	7.092	<0.001
Test/P Statistic		36.615/P<0.001	67.496/P<0.001		
Preoperative MDA	4.04±0.51	4.31±0.49	3.94±0.49	5.36	<0.001
MDA at Discharge	3.28±0.50	3.39±0.51	3.24±0.50	2.09	0.038
Test/P Statistic		12.346/P<0.001	13.649/P<0.001		
Preoperative SOD	67.80±6.61	64.22±5.99	69.03±6.37	5.367	<0.001
SOD at Discharge	77.92 (73.93, 81.85)	75.38 (72.71, 79.03)	78.64 (74.33, 82.40)	3.595	<0.001
Test/P Statistic		6.612/P<0.001	-15.417/P<0.001		
Preoperative IOSI	1.25 (1.12, 1.37)	1.43 (1.34, 1.56)	1.19 (1.09, 1.30)	8.874	<0.001
IOSI at Discharge	0.38±0.11	0.46±0.10	0.35±0.10	7.593	<0.001
Test/P Statistic		-7.059/P<0.001	-12.015/P<0.001		

Note: IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase; IOSI, Inflammation-Oxidative Stress Imbalance Index.

strated weaker values, with sensitivity and specificity showing a general decline, indicating that the short-term change in the biological status after an operation did not have a significant prognostic value (see **Figure 1**, and Table S1).

Correlation analysis of indicators and multicollinearity assessment

Correlation analysis revealed significant relationships among multiple inflammatory factors and oxidative stress indicators. Strong correlations were observed between discharge TNF-α and discharge IOSI, preoperative SOD and preoperative IOSI, discharge IL-6 and discharge IOSI, and preoperative IL-6 and preoperative IOSI. Additionally, moderate correlation existed between preoperative TNF-α and preoperative IOSI (P<0.05). Some indicators showed only weak correlations, such as discharge SOD with discharge IOSI, time from injury to surgery with preoperative IOSI, and preoperative IL-6 with discharge IOSI. Most other indicator pairs showed weak linear relationships or no significant differences, with no clear correlation trends observed (see **Figure 2**). Further variance inflation factor (VIF) assessment for multicollinearity revealed obvious collinearity when all indicators were entered simultaneously into the model, prompting variable grouping. Results showed: Preoperative indicator model: after including time from injury to surgery, concomitant femoral head fracture, preoperative IL-6, preoperative TNF-α, preoperative MDA, and preoperative SOD, VIF values remained within acceptable ranges without obvious multicollinearity issues. Imbalance index model: preoperative IOSI combined with time from injury to surgery and concomitant femoral head fracture likewise showed no significant collinearity and could be independently entered into analytical models. These results suggest intrinsic coupling relationships among multiple inflammatory and oxidative stress indicators, necessitating stratified prediction model development based on inter-variable correlations and collinearity to improve regression analysis stability and interpretability (see **Figure 2** and **Table 3**).

Multivariate logistic regression analysis

In the multivariate regression model incorporating preoperative indicators, time from injury to surgery (P<0.001), concomitant femoral head fracture (P=0.015), preoperative IL-6 (P=0.014), preoperative TNF-α (P<0.001), preoperative MDA (P=0.006), and preoperative SOD (P=0.041) were all independent factors for postoperative PTA occurrence, with some inflammatory and oxidative stress-related indicators showing promoting effects while preoperative antioxidant capacity demonstrated protective effects (see **Table 4**). In the model incorporating preoperative IOSI, time from injury to surgery (P<0.001), concomitant femoral head fracture (P=0.022), and preoperative IOSI (P<0.001) all showed significant influence, suggesting that preoperative systemic inflammation and oxidative stress imbalance possess stronger predictive values for PTA occurrence (see **Table 4**).

Comparison of discrimination and reclassification capacity between the two prediction models

When comparing discriminative ability between the two prediction models, the preoperative indicator model (Risk1) achieved an AUC of 0.879, while the preoperative inflammation-oxidative stress imbalance index model (Risk2) achieved an AUC of 0.911. Although Risk2 showed a slightly higher AUC, the difference did not reach statistical significance (DeLong test P=0.232), suggesting limited improvement in overall discrimination after introducing the preoperative imbalance index (see **Figure 3A**). To facilitate practical application of the models, we provided calculation formulas for both prediction models. Risk1 was the traditional preoperative indicator model, with Logit(P) calculated as: Risk1: Logit(P) = -4.055 + 2.136 (Time to Surgery) + 1.041 (Combined Femoral Head Fracture) + 0.930 (IL-6 discharge) + 1.818 (TNF-α discharge) + 1.082 (MDA discharge) - 0.783 (SOD discharge). Risk2 was the model constructed with preoperative inflammation-oxidative stress imbalance index as the core variable, with Logit(P) as: Risk2: Logit(P) = -4.307 + 2.443 (Time to Surgery) + 1.005 (Combined Femoral Head Fracture) + 3.152 (pre-IOSI). Further reclassification analysis showed that Risk2 demonstrated slight improvement over Risk1 in overall reclassification, with overall NRI of 0.1373 (95% CI: -0.0316 to 0.3021), NRI+ of 0.1061 (95% CI: -0.0500 to 0.2616), and NRI- of 0.0312 (95% CI: -0.0269 to 0.0914), but none reached statistical significance, indicating that although the new model showed

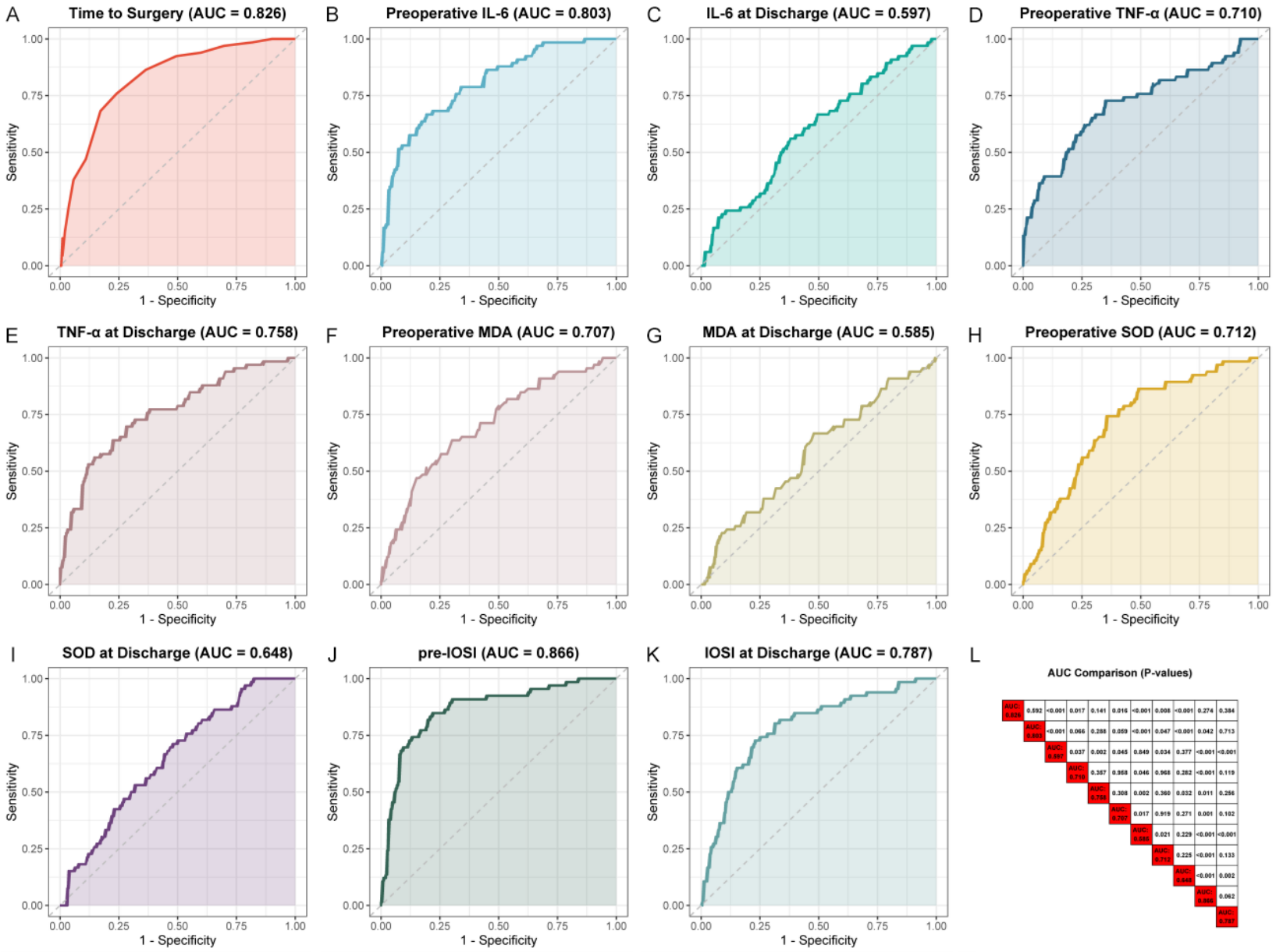
A
Time to Surgery (AUC = 0.826)
B
Preoperative IL-6 (AUC = 0.803)
C
IL-6 at Discharge (AUC = 0.597)
D
Preoperative TNF-α (AUC = 0.710)
E
TNF-α at Discharge (AUC = 0.758)
F
Preoperative MDA (AUC = 0.707)
G
MDA at Discharge (AUC = 0.585)
H
Preoperative SOD (AUC = 0.712)
I
SOD at Discharge (AUC = 0.648)
J
pre-IOSI (AUC = 0.866)
K
IOSI at Discharge (AUC = 0.787)
L
AUC Comparison (P-values)
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00

Figure 1. ROC curve analysis of clinical and biological indicators for PTA prediction. A-K. ROC curves are shown for time from injury to surgery, preoperative IL-6, IL-6 at discharge, preoperative TNF-α, TNF-α at discharge, preoperative MDA, MDA at discharge, preoperative SOD, SOD at discharge, preoperative IOSI, and IOSI at discharge, respectively. L. Matrix presentation of pairwise AUC comparisons among multiple indicators based on DeLong test. Color intensity in the figure reflects significance levels of differences between indicators, visually displaying statistical differences in predictive capacity among different indicators. Note: PTOA, Post-traumatic osteoarthritis; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase; IOSI, Inflammation-Oxidative Stress Imbalance Index.

Figure 2. Correlation heatmap and significance comparison of inflammatory factors and oxidative stress markers. Note: IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase. The upper triangle shows significance levels between indicators, while the lower triangle displays correlation coefficients. Deeper colors indicate stronger correlations or greater significance. Significant correlations exist among multiple preoperative and discharge inflammatory and oxidative stress indicators, while some indicator pairs show no obvious linear relationships.

some optimization trend in individual risk redistribution, overall improvement magnitude remained limited (see **Figure 3B**).

Baseline characteristics comparison: external validation cohort versus training cohort

Comparison of baseline characteristics between the external validation cohort and training cohort showed generally similar distributions of demographic and injury-related factors. Gender, injury mechanism, fracture classification, hip dislocation, concomitant femoral head fracture, intertrochanteric femoral fracture, surgical site infection, age, BMI, height, weight, and OTSA index showed no statistical differences between groups (P>0.05), suggesting good comparability of basic characteristics between cohorts (see **Table 5**). Additionally, time from injury to surgery showed no signifi-

Table 3. Multicollinearity assessment of inflammatory and oxidative stress markers (VIF Analysis)

Variable	Combined VIF	Preoperative Indicators VIF	Preoperative IOSI Model VIF	Value content
Time to Surgery	1.52	1.252	1.05	Continuous (days), entered as continuous variable (per 1-day increase)
Combined Femoral Head Fracture	1.16	1.073	1.039	Binary categorical: Yes =1, No =0 (reference)
Preoperative IL-6	7.195	1.181		Continuous (pg/mL), entered as continuous variable
IL-6 at Discharge	133.835			Continuous (pg/mL), entered as continuous variable
Preoperative TNF-α	7.911	1.042		Continuous (pg/mL), entered as continuous variable
TNF-α at Discharge	185.539			Continuous (pg/mL), entered as continuous variable
Preoperative MDA	1.846	1.309		Continuous (mmol/mL), entered as continuous variable
MDA at Discharge	3.451			Continuous (mmol/mL), entered as continuous variable
Preoperative SOD	24.214	1.026		Continuous (mU/mL), entered as continuous variable
SOD at Discharge	30.235			Continuous (mU/mL), entered as continuous variable
pre-IOSI	38.662		1.055	Continuous index, entered as continuous variable
IOSI at Discharge	394.489			Continuous index, entered as continuous variable

Note: IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase; IOSI, Inflammation-Oxidative Stress Imbalance Index. ROC-derived cut-off values were used for discrimination description only and were not applied to dichotomize variables in regression models.

Table 4. Multivariate logistic regression analysis of preoperative indicators and preoperative IOSI

Variable	Preoperative Indicators Multivariate Regression			pre-IOSI Multivariate Regression		
	OR Value	*P* Value	95% CI	OR Value	*P* Value	95% CI
Time to Surgery	8.463	<0.001	4.107-18.436	11.502	<0.001	5.168-27.827
Combined Femoral Head Fracture	2.832	0.015	1.226-6.672	2.731	0.022	1.16-6.546
Preoperative IL-6	2.535	0.014	1.221-5.409			
Preoperative TNF-α	6.158	<0.001	2.981-13.369			
Preoperative MDA	2.952	0.006	1.387-6.585			
Preoperative SOD	0.457	0.041	0.211-0.96			
pre-IOSI				23.388	<0.001	10.107-60.825

Note: IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase; IOSI, Inflammation-Oxidative Stress Imbalance Index.

cant difference between groups (P=0.927), further confirming overall characteristic consistency between the model training cohort and external validation cohort, providing a stable foundation for subsequent model validation (see **Table 6**).

Biomarker comparison between external validation and training cohorts

Comparison of biomarkers between external validation and training cohorts revealed no significant differences in preoperative and discharge indicators including IL-6, TNF-α, MDA, SOD, and IOSI (P>0.05), confirming similarity in baseline biomarker levels between these cohorts. Specifically, preoperative IL-6, preoperative TNF-α, preoperative MDA, preoperative SOD, discharge IL-6, discharge TNF-α, discharge MDA, discharge SOD, and both preoperative and discharge IOSI all failed to reach significance (P>0.05), suggesting minimal differences in these biomarkers between groups that would not affect model reliability. These results indicate that biomarker levels in the external validation cohort aligned with the training cohort, supporting cross-cohort model validation.

Consistency analysis of biomarker levels between external validation and training cohorts

In the analysis of the predictive performance of the two models (Risk1 and Risk2), the performance of the two models were compared in external validation cohort data. An AUC of Risk1 was 0.700 while an AUC of Risk2 was 0.821. Thus, Risk2 with some additional clinical and biological variables significantly improved the discriminative ability for predicting PTA com-

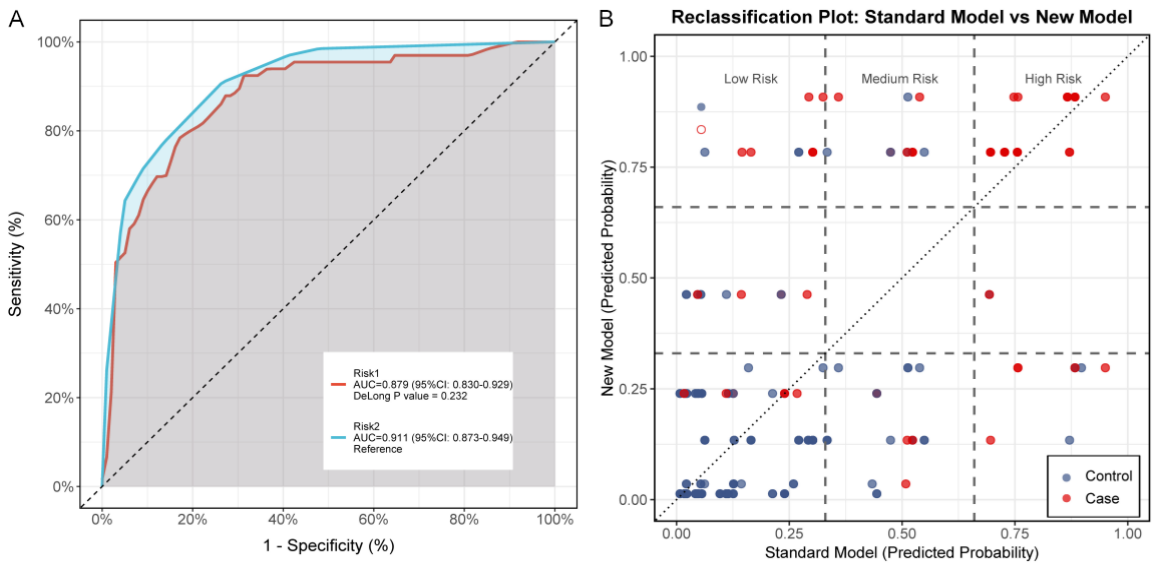

Figure 3. Comparison of discrimination and reclassification performance between preoperative indicator model (Risk1) and preoperative inflammation-oxidative stress imbalance index model (Risk2). A. ROC curve comparison of the two models. The Risk2 curve sits slightly higher than Risk1, but the difference did not reach statistical significance. B. Reclassification scatter plot. The vertical axis represents predicted probability from the new model (Risk2), while the horizontal axis represents predicted probability from the old model (Risk1).

Table 5. Comparison of baseline characteristics between external validation and training cohorts

Factor	Total	External Validation (n=127)	Training Cohort (n=258)	Test Statistic	*P* Value	OR (95% CI)
Gender				0.110	0.740	
Male	256 (66.5%)	83 (65.4%)	173 (67.1%)			1.079 (0.689-1.689)
Female	129 (33.5%)	44 (34.6%)	85 (32.9%)			
Injury Mechanism				0.608	0.738	
Traffic Accident	254 (66.0%)	81 (63.8%)	173 (67.1%)			Reference
Fall	85 (22.1%)	31 (24.4%)	54 (20.9%)			1.226 (0.733-2.051)
Other	46 (11.9%)	15 (11.8%)	31 (12.0%)			1.033 (0.529-2.021)
Fracture Classification				0.145	0.703	
Simple Fracture	114 (29.6%)	36 (28.3%)	78 (30.2%)			1.095 (0.686-1.750)
Complex Fracture	271 (70.4%)	91 (71.7%)	180 (69.8%)			
Hip Dislocation				0.200	0.655	
Yes	121 (31.4%)	38 (29.9%)	83 (32.2%)			1.111 (0.701-1.761)
No	264 (68.6%)	89 (70.1%)	175 (67.8%)			
Femoral Head Fracture				0.027	0.870	
Yes	83 (21.6%)	28 (22.0%)	55 (21.3%)			0.958 (0.573-1.603)
No	302 (78.4%)	99 (78.0%)	203 (78.7%)			
Intertrochanteric Fracture				0.102	0.750	
Yes	28 (7.3%)	10 (7.9%)	18 (7.0%)			0.877 (0.393-1.961)
No	357 (92.7%)	117 (92.1%)	240 (93.0%)			
Surgical Site Infection				<0.001	1.000	
Yes	14 (3.6%)	5 (3.9%)	9 (3.5%)			0.882 (0.289-2.688)
No	371 (96.4%)	122 (96.1%)	249 (96.5%)			
Age (years)	43.00 (33.00, 53.00)	45.00 (35.00, 53.00)	41.50 (33.00, 53.00)	0.778	0.437	
BMI (kg/m^2)	23.18±3.12	22.89±3.43	23.32±2.96	1.286	0.199	
Height (m)	1.70 (1.65, 1.75)	1.70 (1.65, 1.75)	1.70 (1.65, 1.75)	<0.001	0.917	
Weight (kg)	66.99±10.57	66.08±10.61	67.44±10.55	1.187	0.236	
OTSA Index	4.75±3.59	4.47±3.53	4.88±3.62	1.068	0.286	
Time from Injury to Surgery (d)	11.46±3.60	11.44±3.44	11.48±3.68	0.092	0.927	

Note: BMI, Body Mass Index; OTSA, Osteoarthritis Trauma Score Assessment.

Table 6. Comparison of biomarker levels between external validation and training cohorts

Factor	Total	External Validation (n=127)	Training Cohort (n=258)	Test Statistic	*P* Value
Preoperative IL-6	32.44±5.43	32.14±5.15	32.58±5.57	0.777	0.438
IL-6 at Discharge	13.24±4.73	12.83±4.79	13.45±4.70	1.197	0.232
Test/P Statistic		-5.295/P<0.001	27.381/P<0.001		
Preoperative TNF-α	48.01±5.62	48.33±5.63	47.86±5.61	0.780	0.436
TNF-α at Discharge	12.52±5.66	12.58±5.62	12.49±5.70	0.156	0.876
Test/P Statistic		26.499/P<0.001	53.434/P<0.001		
Preoperative MDA	4.06±0.53	4.10±0.55	4.04±0.51	1.129	0.26
MDA at Discharge	3.28±0.50	3.28±0.49	3.28±0.50	0.002	0.999
Test/P Statistic		9.503/P<0.001	9.155/P<0.001		
Preoperative SOD	67.93±6.46	68.21±6.16	67.80±6.61	0.609	0.543
SOD at Discharge	77.79±5.46	77.82±5.03	77.78±5.67	0.067	0.947
Test/P Statistic		-6.686/P<0.001	-12.329/P<0.001		
Preoperative IOSI	1.24(1.12, 1.36)	1.23(1.12, 1.35)	1.25(1.12, 1.37)	0.508	0.611
IOSI at Discharge	0.38±0.11	0.37±0.11	0.38±0.11	0.640	0.523
Test/P Statistic		27.941/P<0.001	-8.236/P<0.001		

Note: IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase; IOSI, Inflammation-Oxidative Stress Imbalance Index.

pared to Risk1. The difference between these was significant (P<0.05) indicating better overall prediction power of the Risk2 Model (**Figure 4A**). Further NRI analysis demonstrated that Risk2 exhibited a global NRI of 0.3565 (95% CI: 0.1762 to 0.5264), with NRI+ of -0.4324 (95% CI: -0.5953 to -0.2856) and NRI- of 0.7889 (95% CI: 0.6941 to 0.8706). The global metric of the NRI revealed a poorer reclassification performance of the Risk2 model in cases (NRI+) with a lower intensity of the standard model (negative NRI value). Nevertheless, in the control group (NRI-), Risk2 significantly outperformed Risk1 in reclassifying low-risk patients, thus showing its advantage for identifying low-risk patients (**Figure 4B**). This analysis bolsters the capacity of the Risk2 model, particularly for enhancing predictive power among low-risk individuals.

Discussion

This study aimed to evaluate the role of inflammatory factors and oxidative stress in the development of PTA post-ORIF of acetabular fractures and the predictive value of IOSI. The results revealed that the patients who developed PTA had significantly higher concentrations of pre-operative IL-6, TNF-α, and MDA. Furthermore, their SOD was markedly lower indicating more prominent inflammatory activation and antioxidant depletion. The IOSI was significantly raised both preoperatively and at discharge, showing greater sensitivity than single indicators. On the other hand, prolonged time from injury to surgery and concomitant fracture of the femoral head were subject to defy risks for PTA. Through a model comparison study, external validation showed that Risk2, incorporating IOSI as the main feature, had better discriminatory performance than Risk1. This suggested that infusing inflammation and oxidative stress information may meaningfully enhance capacity for PTA early identification of risk. The development of such a validated predictive tool addresses a critical need in orthopedic trauma for robust, clinically actionable evidence. This need is underscored by the fact that even for common perioperative management strategies, such as the use of single-dose intra-articular morphine for post-arthroscopy pain, systematic reviews have concluded that the evidence base is often limited by small sample sizes and an unclear risk of bias, making definitive recommendations challenging [15]. Our study, by employing external validation and focusing on a composite biological index, aimed to contribute higher-quality evidence to the field, bridging the gap between biological understanding and reliable clinical prognostication.

Acute damage due to acetabular fractures not only damages the cartilage surface and struc-

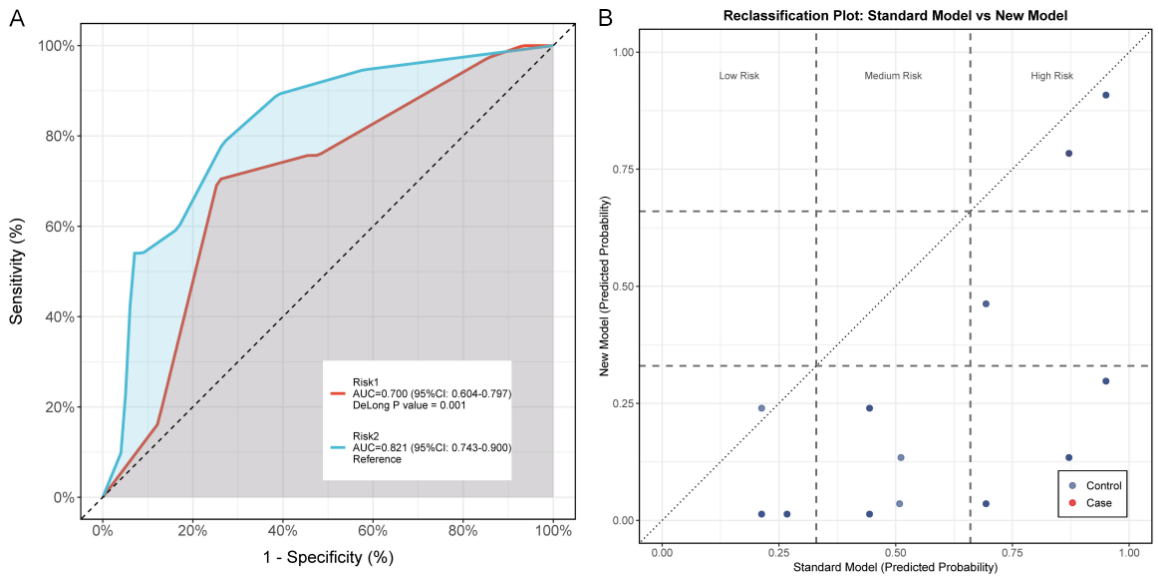

Figure 4. ROC Curve and NRI analysis comparison between Risk1 and Risk2. A. ROC curves of both models (Risk1 and Risk2). Risk2 demonstrates significantly higher discriminative performance. B. Reclassification analysis (NRI) showing that the Risk2 model achieved significant reclassification improvement in low-risk populations, but demonstrated poorer reclassification performance for high-risk populations.

ture of the joint, it also evokes local and systemic cascade of inflammation reactions [16]. In a recent study conducted by Nakamura et al. [7] on a rodent hip dislocation model, it was established that the reduced dynamic load activates IL-6 and MMP3 expression through the STAT3/periostin/NF-κB signaling axis, thus leading to acetabular cartilage degeneration. The post-trauma inflammatory network mainly uses IL-6 and TNF-α as mediator. Both substances can prompt synovial cells and chondrocytes to release matrix metalloproteinases. This accelerates damage to the cartilage matrix and inhibits repair and regeneration of the chondrocytes. Consequently, there is progressive joint deterioration [17, 18]. Research evidence indicates that unstimulated OA chondrocytes release IL-6, PGE2 and MMP1 at significantly higher levels than non-OA chondrocytes along with lower glycosaminoglycan production which indicates OA induces long-lasting metabolic changes [19]. Eitner et al. [8] found that IL-6 trans-signaling and high autocrine IL-6 production play critical roles in human OA chondrocyte metabolism. The production of inflammatory mediators was significantly increased and cartilage matrix proteins significantly decreased when complexed with IL-6/sIL-6R. Conversely, neutralizing antibodies against IL-6 signaling did not significantly affect the metabolism of OA chondrocytes. Oxidative stress levels rise when inflammatory responses become chronic. Excessive accumulation of ROS harms lipid membranes, proteins, and even DNA. High MDA is a common indicator of increased lipid peroxidation.

Under continuous inflammatory conditions, not only do the mega-antioxidants levels drop but also the body's antioxidant system is depleted, which is demonstrated by lower SOD levels. The weakening of the defense capacity would cause further ROS accumulation. Liu et al., [9] displayed that the physiological metabolite α-ketoglutarate can ameliorate osteoarthritis by inducing mitophagy and inhibiting the generation of ROS. Mechanisms include upregulation of ACAN and COL2A1 while downregulating MMP13, ADAMTS5, IL-6, and TNF-α. Studies have shown that oxidative stress is a crucial regulator of cells' fate in osteoarthritis, where the increased generation of the radical leads to aberrant cell fate decisions including senescence, misdifferentiation, cell death, and mitochondrial dysfunction [20]. Inflammation and oxidative stress mutually reinforce each other, forming a vicious cycle that accelerates PTA progression. This interplay is also evident in rheumatoid arthritis, where inhibition of the IL-6 receptor with tocilizumab significantly improves clinical responses but at the expense

of increased adverse events, highlighting the need to balance therapeutic benefit against biological risk [21]. According to Cao et al. [22], OA progression can be improved through the alteration of oxidative microenvironment via SOD3-enriched exosome-loaded bio-nanoparticles. Exosomes enriched with SOD3 significantly improved antioxidant capacity chondrocytes and EC matrix metabolic stability. Huang et al. [23] developed IgG-conjugated bilirubin/JPH203 nanoparticles that achieved M1 to M2 macrophage polarization by scavenging ROS, inhibiting the NF-κB pathway, and suppressing the mTOR pathway, thereby inhibiting the inflammatory environment and promoting cartilage protection. Research shows that gastrodin improves inflammation, oxidative stress, and extracellular matrix degradation in IL-1β-mediated human OA synoviocytes by inhibiting Gremlin-1 expression and reducing NF-κB pathway activity [24]. Inflammation and oxidative stress mutually reinforce each other, forming a vicious cycle that accelerates PTA occurrence and progression. Compared to single factors, IOSI can simultaneously capture both inflammatory enhancement and antioxidant capacity reduction, thus better reflecting overall homeostatic disruption before PTA occurrence. The significantly elevated IOSI in PTA patients in this study aligns closely with this pathologic mechanism, supporting the biological rationale for IOSI as a comprehensive mechanistic predictor.

The generally superior predictive performance of preoperative indicators over discharge indicators in this study may relate to preoperative inflammation and oxidative stress status better reflecting injury severity itself, while early postoperative indicators are influenced by surgical trauma, anesthetic stress, and postoperative fluctuations, leading to decreased predictive stability. The IOSI index is a composite index which reflects simultaneous multi-pathway disease signals. Such as inflammatory activation, oxidative damage and depletion of antioxidant reserve. Hence IOSI index is more sensitive than single biomarker index for disease. The research is the first to compare IOSI (intraocular optical strength index) before and after surgery (discharge). They find that IOSI before surgery has a better predictive value than on discharge. The incorporation of IOSI into a PTA predictive model framework represents an important first that was developed here. In addition, after using multivariate regression some biomarkers becoming no longer significant may be due to the fact that their effects were taken up by IOSI as a composite, which also reflects coupling between different pathologic processes.

In addition to biological factors, the established risk factors concerning time from injury to surgery and simultaneous femoral head fracture still had stable predictive power. A meta-analysis revealed that older age, female sex, posterior wall fracture, acetabular impaction, femoral impaction, and femoral head dislocation are significant risk factors for conversion to THA [3]. According to the multivariate logistic regression analysis conducted by Kavak et al. [11], dislocation, wound complications, quality of reduction, and diabetes are linked with poor outcomes. The longer the period for which the cartilage is kept under compression and instability after injury till surgery, the longer the inflammatory response lasts and the faster the joint will degenerate. According to Chen et al. [4], if the operation is delayed by one day, the risk of THA does increase by 36%. Concomitant femoral head fracture represents damage to an important weight-bearing surface with more apparent injuries to the blood supply and thus significantly increases the risk of PTA. According to the evidence, the Kocher-Langenbeck approach is associated with almost a twelve-fold INCREASE in excess risk of THA compared to the ilioinguinal approach with INCREASE occurred and significantly related the surgical waiting time for THA [25]. The results collectively show that the emergence of PTA is driven by structural injury and biological response mechanisms.

Analysing Risk1 (traditional indicator model) and Risk2 (IOSI model), their AUC differences in the training set were not statistically significant, whereas the performance differences in the external validation set were obvious. Risk2 modeling based on biological information characterized by inflammation-oxidative stress imbalance was found to have a better AUC. In a meta-analysis involving 1,284 patients, Yuan et al. [5] found that THA in patients with PTOA can lead to significant symptomatic and functional improvements. Furthermore, the 15-year survival rates still reached 83%. This finding underscores the importance of early identification of high-risk patients to improve prognosis.

Studies using mid-term follow-up by Ramanath et al. [26] showed that the ORIF group had better functional scores (dorsiflexion and palmarflexion) than the non-ORIF group. This justifies the emphasis on surgery. The suitability of the model's performance was further supported by the consistency of demographic and biological baseline characteristics of the training and validation cohorts. NRI analysis of Risk2 showed that it has better reclassification performance at a lower risk, which indicates its use as an early exclusion tool for PTA in low-risk patients who do not need close monitoring. Clinical workflows can include stratified management strategies alongside model output probabilities, such as close structural imaging monitoring or proactive anti-inflammatory intervention for high-risk patients, close follow-up plans for medium-risk patients, and reduced unnecessary examination for low-risk patients to improve medical efficiency. This model can also be used in research settings such as screening of high-risk populations in a prospective study to improve the efficiency and success rate of intervention trial. Our prediction model is clearly clinically useful and has statistical significance.

This study has one key strength, being multicenter external validation. The findings showed that Risk2 exhibited considerable predictive performance even in different hospitals and has strong generalization potential for incorporating IOSI into prediction models. A systematic review [27] of 29 studies involving 1,220 THA patients reported high complication rates after ORIF and conservative treatment, with infection rates as high as 3.6%, highlighting the need for early risk assessment. Notwithstanding that, this study had limitations, including its retrospective design (with potential selection bias), the limited sample size for some fracture subtypes, and the inability to capture dynamic biomarker changes because measurements were available at only two time points. Postoperative biomarkers were obtained at discharge rather than at a fixed postoperative day; although discharge occurred mostly within postoperative day 7-14, residual timing heterogeneity may have introduced noise and attenuated the prognostic value of discharge measurements. In addition, quantitative imaging parameters were not included, and the cross-disease stability of IOSI was not systematically validated. Future multicenter studies with larger samples and standardized postoperative sampling windows should further investigate the association between dynamic IOSI changes and PTA progression, and integrate multidimensional features (e.g., radiomics and metabolomics) to enhance model performance.

Conclusion

This study systematically evaluated preoperative and discharge levels of IL-6, TNF-α, MDA, SOD, and IOSI, comparing differences between patients who did and did not develop PTA, and clarifying the predictive performance of individual indicators and IOSI. We constructed both a traditional preoperative indicator model (Risk1) and a model incorporating preoperative IOSI (Risk2), assessing their discrimination and reclassification capacity through ROC curves and NRI, and testing model robustness and generalization value using an independent external validation cohort.

Disclosure of conflict of interest

None.

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Table S1. Comparison of discriminative performance of different predictive indicators for PTA recognition

Marker	95% CI	Specificity	Sensitivity	Youden Index	Cut-off	Accuracy
Time from Injury to Surgery (d)	0.770-0.882	76.04%	75.76%	51.80%	12.5	75.97%
Preoperative IL-6	0.742-0.865	80.73%	66.67%	47.40%	35.245	77.13%
IL-6 at Discharge	0.518-0.676	61.98%	56.06%	18.04%	14.605	60.47%
Preoperative TNF-α	0.632-0.789	65.10%	72.73%	37.83%	48.905	67.05%
TNF-α at Discharge	0.688-0.828	71.88%	69.70%	41.57%	13.57	71.32%
Preoperative MDA	0.634-0.781	69.79%	63.64%	33.43%	4.195	68.22%
MDA at Discharge	0.505-0.666	52.08%	66.67%	18.75%	3.255	55.81%
Preoperative SOD	0.643-0.782	64.58%	74.24%	38.83%	67.04	32.95%
SOD at Discharge	0.575-0.721	52.08%	71.21%	23.30%	78.42	43.02%
Preoperative IOSI	0.813-0.919	78.12%	84.85%	62.97%	1.302	79.84%
IOSI at Discharge	0.722-0.852	77.08%	72.73%	49.81%	0.416	75.97%

Note: PTOA, Post-traumatic osteoarthritis; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; MDA, Malondialdehyde; SOD, Superoxide Dismutase; IOSI, Inflammation-Oxidative Stress Imbalance Index.