

Construction and Validation of a Nomogram for Risk Factors of Nonunion Following Surgical Treatment of Tibial Shaft Fractures

Zhipeng Fan

Shandong First Medical University

Yuhang Jin

Shandong University of Traditional Chinese Medicine

Xuesong Yan

Department of Orthopedics, the 960th Hospital of PLA

Jiawei Li

Department of Orthopedics, the 960th Hospital of PLA

Zhuohang Wu

Shandong Second Medical University

Yongxian Zhang

zhangyongxian513@126.com

Department of Orthopedics, the 960th Hospital of PLA

Research Article

Keywords: Tibial Fracture, Nonunion, Risk Factors, Logistic Regression, Nomogram, Prediction Model

Posted Date: June 24th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9872244/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Tibial nonunion represents a prevalent and severe complication arising after the surgical management of tibial shaft fractures.[1], yet there is a scarcity of individualized, quantitative risk prediction tools in clinical practice, which hinders the early identification of high-risk patients. The primary objective of this investigation is to delineate critical determinants associated with nonunion subsequent to operative management of tibial diaphyseal fractures, thereby facilitating the construction of a prognostic nomogram.

Methods

Over a decade-long span, we conducted a retrospective review of 1,117 individuals who received surgical intervention for tibial fractures at our facility. Patients were categorized into a nonunion group (n = 72) and a union group (n = 1,045) based on follow-up outcomes of at least 6 months postoperatively, and subsequently randomly allocated into training and validation sets. Baseline characteristics of patients in the nonunion and union groups within the training set were compared. Univariate analyses and multivariate logistic regression were performed to identify risk factors associated with nonunion following tibial fracture surgery. A nomogram was constructed. The model's discriminative ability, calibration accuracy, and clinical net benefit were internally validated using receiver operating characteristic (ROC) curves, calibration plots, and decision curve analysis (DCA), respectively.

Results

Univariate analysis and multivariate logistic regression identified age (middle-aged and elderly), sex (male), smoking history, open fractures, postoperative infections, fracture morphology (AO/OTA 42-C), and external fixation as independent risk factors for nonunion after tibial fracture surgery. Based on these variables, the nomogram model yielded a C-index of 0.942 (0.913–0.970) in the training set and 0.840 (0.752–0.929) in the validation set, indicating robust discriminative ability. Calibration curves and decision curve analysis demonstrated that the model exhibited good calibration and significant clinical utility.

Conclusion

Advanced age, male sex, history of smoking, open fracture type, postoperative infection, comminuted fracture morphology, and surgical method (external fixation) are independent risk factors for nonunion after tibial fracture surgery. The constructed nomogram demonstrates robust predictive accuracy, offering a quantitative basis for developing individualized intervention strategies in clinical practice.

Introduction

Bone repair constitutes an intricate physiological cascade encompassing numerous distinct phases, including inflammatory organization, callus formation, and remodeling, regulated by multiple local and systemic factors[2]. The U.S. Food and Drug Administration (FDA) defines fracture nonunion as a fracture that has not healed within 9 months of injury, with no evidence of progressive healing on serial radiographs for at least 3 consecutive months[3]. According to the AO principles, however, clinical studies more frequently recommend adopting a 6-month post-injury timeframe as the diagnostic criterion for nonunion in single-site closed fractures[3, 4]. Owing to the tibia's unique anatomical location and physiological characteristics, it exhibits limited resistance to trauma, resulting in a significantly higher incidence of nonunion compared to other long bones. Clinical evidence suggests that postoperative nonunion rates associated with tibial fractures vary between 5% and 15%[1, 5–7]. The condition is characterized by complex mechanisms, prolonged treatment cycles, and poor prognosis, which severely impair patients' limb function and quality of life while imposing a substantial economic burden and consuming significant medical resources. Schottel and colleagues employed the time trade-off technique to evaluate health-related quality of life metrics in a cohort exceeding 800 individuals suffering from long bone nonunion, revealing that these patients would sacrifice approximately 32% of their remaining lifespan to restore full health[8]. Flores et al. reported that the average direct medical cost of nonunion in patients in Europe and North America was \$30,852, representing 2.6 to 4.3 times that of patients without nonunion.[9]. Tibial nonunion remains a difficult problem to be solved urgently in the field of trauma orthopedics. Current research on nonunion after tibial shaft fracture surgery mostly focuses on single or a few risk factors, lacking systematic integration of key risk factors. There is still a lack of individualized and quantitative risk prediction tools for nonunion after tibial fracture surgery in clinical practice.

This study uses 6 months postoperatively as the diagnostic standard, which conforms to the recommended nonunion diagnosis and adapts to the clinical follow-up characteristics of tibial fractures. By integrating systemic, local, and treatment-related multidimensional factors, this study constructs and validates a nomogram prediction model to achieve an individualized, quantitative assessment of tibial nonunion risk. This methodology overcomes the constraints of prior studies, establishing a robust theoretical framework and offering actionable insights for the early stratification of high-risk cohorts, the development of tailored therapeutic protocols, and the subsequent mitigation of nonunion rates in clinical settings.

Data and Methods

General Data

Case inclusion criteria: (1) Adult patients with tibial fractures admitted to our hospital and receiving surgical treatment from January 2015 to June 2025; (2) Complete postoperative follow-up data, with imaging examination results available at least 6 months postoperatively; (3) Tibial fractures involving the tibial shaft.

Case exclusion criteria: (1) Patients with severe malnutrition, severe osteoporosis, failure of vital organ function, and serious underlying diseases; (2) Isolated tibial plateau fractures and isolated Pilon fractures; (3) Pathological tibial fractures[10]; (4) Isolated avulsion fractures; (5) Tibial fractures with massive bone defects requiring bone grafting[11].

A total of 1117 cases from January 2015 to June 2025 met the above inclusion and exclusion criteria, including 826 males and 291 females; aged 18–87 years, average 47.67 years. The requirement for informed consent was waived for all participants, and the study protocol received formal approval from the Ethics Committee of the 960th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army.

Collection of Clinical Data

Patient clinical data were collected, including fracture healing outcomes, age, gender, BMI, history of diabetes, history of hypertension, history of smoking, history of alcohol consumption, degree of fracture openness, concomitant fibular fracture, occurrence of postoperative infection, fracture morphology, fracture location, time from injury to surgery, surgical fixation method, and simultaneous ipsilateral fibular reduction and fixation.

Surgical Methods

Patients underwent internal fixation with plates, intramedullary nailing, or external fixator fixation according to fracture type, degree of openness, and location. All procedures were performed under general anesthesia. Plate internal fixation: Indicated for closed fractures or open fractures requiring secondary surgery; the procedure involves open exposure and reduction of the fracture site, followed by plate insertion and screw locking. Intramedullary nailing: Used for closed fractures or open fractures undergoing secondary surgery, involving locating the entry point, reaming, and insertion of the intramedullary nail with locking screws. Fixation with an external fixator: Suitable for severe open fractures or cases with high infection risk, involving percutaneous insertion of fixation pins and connection to an external fixator for stable fixation. All surgeries were performed under C-arm fluoroscopic guidance to ensure good fracture reduction and accurate positioning of internal/external fixation devices. For open fracture surgeries, thorough debridement was performed intraoperatively, and targeted anti-infective treatment was administered postoperatively. For surgeries with expected significant postoperative bleeding, drainage tubes were placed; for surgeries with high infection risk, vacuum sealing drainage or continuous irrigation drainage tubes were placed. Follow-up was conducted 6 months postoperatively.

Grading Criteria

Imaging Criteria for Nonunion/Union: Outpatient review combined with telephone follow-up was employed. Imaging examinations were independently reviewed by two senior radiologists in a blinded

manner. Based on the modified Radiographic Union Score for Tibia (mRUST), nonunion was defined as an mRUST score of less than 9 at 6 months postoperatively[12]. Fracture morphology was classified according to the AO-Müller/AO/OTA fracture classification system[13]. Open fractures were categorized according to the Gustilo-Anderson classification (GAC) system[14] (Tables 1–3).

Statistical Methods

Microsoft Excel was used to summarize and organize the collected data, create original data tables and assign values. Subsequently, SPSS 27.0 software and RStudio 4.5.2 software were used for statistical analysis. After imputing missing values in the database using the 10-fold multiple imputation method, the database was randomly divided into a training set and a validation set in a 7:3 ratio using sampling without replacement. Normality of continuous variables was evaluated using the Kolmogorov-Smirnov test. Variables exhibiting a normal distribution are reported as mean $\pm$ standard deviation (*SD*), with between-group differences analyzed by the independent samples *t*-test. Conversely, non-normally distributed continuous data are summarized as median[P25, P75] (*M*[*Q*₁,*Q*₃]), and intergroup comparisons were made using the Mann-Whitney *U* rank-sum test, reporting the *Z* statistic. Count data were expressed as number of cases, and intergroup comparisons were made using the χ^2 test or Fisher exact probability test. Variables showing statistically significant associations in the univariate analysis of the training cohort were subsequently incorporated into a multivariate logistic regression model to identify independent risk factors for nonunion after surgical treatment of tibial fractures. Variables with statistical significance in the multivariate logistic regression analysis were used to construct the nomogram prediction model. The model was comprehensively evaluated across multiple dimensions, including discrimination, calibration, and clinical utility. Specifically, discrimination was assessed using the receiver operating characteristic (ROC) curve, with an area under the curve (AUC) > 0.7, indicating good discriminatory ability[15]. The accuracy of the prediction model was evaluated using a calibration curve[16, 17]. The clinical applicability of the predictive model was examined through decision curve analysis.[18, 19]. Finally, the model was further validated using the validation set.

Table 1
Modified Radiographic Union Score
for Tibia (mRUST Score)

Score	Callus	Fracture Line
1	-	+
2	+	+
3	+	-

Table 2
Gustilo-Anderson Classification of Open Fractures

Type	Basis for Classification
Type I	A wound < 1 cm, clean, mild soft tissue injury
Type II	A wound 1 to 10 cm, moderate contamination, moderate soft tissue injury
Type III	A wound > 10 cm, extensive contamination, severe soft tissue injury

Table 3
AO/OTA Fracture Classification System for Tibial Shaft

AO/OTA Type	Type Characteristics
42-A	A simple tibial shaft fracture
42-B	A wedge tibial shaft fracture
42-C	A comminuted tibial shaft fracture

Table 4
Comparison of Baseline Characteristics Between Training Set and Validation Set

Influencing Factor	Training Set (N = 782)	Validation Set (N = 335)	Total	P
Outcome Variable, n(%)				0.980
Nonunion	51(6.5)	21(6.3)	72	
Union	731(93.5)	314(93.7)	1045	
Age, mean $\pm$ SD	47.44 $\pm$ 14.60	48.21 $\pm$ 14.22		0.416 ^a
Gender, n(%)				0.282
Male	586(74.9)	240(71.6)	826	
Female	196(25.1)	95(28.4)	291	
BMI ^b (kg/m ²), M[Q ₁ ,Q ₃]	24.73[22.15,27.18]	24.61[22.45,27.34]		0.990 ^c
Diabetes, n(%)				0.151
Yes	47(6.0)	28(8.4)	75	
No	735(94.0)	307(91.6)	1042	
Hypertension, n(%)				0.528
Yes	95(12.1)	46(13.7)	141	
No	687(87.9)	289(86.3)	976	
Smoking History, n(%)				0.639
Yes	291(37.2)	119(35.5)	410	
No	491(62.8)	216(64.5)	707	
Alcohol History, n(%)				0.818
Yes	367(46.9)	154(46.0)	521	
No	415(53.1)	181(54.0)	596	
Fracture Type, n(%)				0.807
Closed Fracture	428(54.7)	176(52.5)	604	
Type $\boxtimes$	101(12.9)	43(12.8)	144	
Type $\boxtimes$	155(19.8)	75(22.4)	230	
Note: ^a) Independent samples t-test; ^c) Mann-Whitney U test; all other comparisons used chi-square tests.				

Influencing Factor	Training Set (N = 782)	Validation Set (N = 335)	Total	P
Type ^a	98(12.5)	41(12.2)	139	
Fibular Fracture, n(%)				0.708
Yes	640(82.1)	271(80.3)	201	
No	142(17.9)	64(19.7)	916	
Postoperative Infection, n(%)				0.312
Yes	36(4.6)	21(6.3)	57	
No	746(95.4)	314(93.7)	1060	
Fracture Morphology, n(%)				0.554
42-A	149(19.1)	72(21.5)	221	
42-B	148(18.9)	66(19.7)	214	
42-C	485(62.0)	197(58.8)	682	
Fracture Location, n(%)				0.019
Proximal Third	130(16.6)	79(23.6)	209	
Middle Third	266(34.0)	111(33.1)	377	
Distal Third	386(49.4)	145(43.3)	531	
Time from Injury to Surgery, n, M[Q ₁ , Q ₃]				
Closed Fracture (n, d)	428, 5[2, 7]	176, 4[1.75, 7]	604	0.509 ^c
Open Fracture (n, h)	354, 6[5, 8]	159, 6[5, 8]	513	0.381 ^c
Surgical Fixation Method ^d , n(%)				0.494
Plate	393(50.3)	177(52.8)	570	
Intramedullary Nail	183(23.4)	81(24.2)	264	
External Fixator	206(26.3)	77(23.0)	283	
Fibular Fracture Reduction and Fixation, n(%)				0.651
Fibula Not Fractured	142(18.2)	61(18.2)	203	
Note: ^a) Independent samples t-test; ^c) Mann-Whitney U test; all other comparisons used chi-square tests.				

Influencing Factor	Training Set (N = 782)	Validation Set (N = 335)	Total	P
Reduction and Fixation Performed	318(40.7)	127(37.9)	445	
Reduction and Fixation Not Performed	322(41.2)	147(43.9)	469	
Note: ^{a)} Independent samples t-test; ^{c)} Mann-Whitney U test; all other comparisons used chi-square tests.				

- ^{b)} BMI data were missing for 278 cases; these missing values were imputed using multiple imputation.
- ^{d)} Some patients who underwent primary fixation with an external fixator received internal fixation with plates or intramedullary nails within 2 months and were included in the internal fixation group for statistical analysis.

Table 5
Univariate Analysis of Tibial Nonunion in the Training Set

Influencing Factor	Nonunion Group (N = 51)	Union Group (N = 731)	Total (N = 782)	t/ χ^2 /Z/ φ	P
Age, n, mean ± SD	57.25 ± 15.54	46.75 ± 14.29	47.44 ± 14.60	-4.792 ^a	< 0.001
Age Group, n				15.506	< 0.001
< 50	15	422	437		
≥ 50	36	309	345		
Gender				6.764	0.009
Male	46	540	586		
Female	5	191	196		
BMI(kg/m ²), M[Q ₁ ,Q ₃]	24.09[20.86,26.71]	24.80[22.19,27.20]	24.73[22.15,27.18]	-1.177 ^b	0.239
BMI Group(kg/m ²), n				0.873	0.832
Underweight (< 18.5)	3	27	30		
Normal weight (18.5– 23.9)	20	271	291		
Overweight (24–27.9)	18	289	307		
Obese (≥ 28)	10	144	154		
Diabetes, n(%)				-0.020 ^c	0.762
Yes	4	43	47		
No	47	688	735		
Hypertension, n(%)				2.007	0.156
Yes	3	92	95		
No	48	639	687		
Note: ^a) Independent samples t-test, ^b) Mann-Whitney U test, ^c) Fisher's exact test. Others are chi-square tests.					

Influencing Factor	Nonunion Group (N = 51)	Union Group (N = 731)	Total (N = 782)	t/ χ^2 /Z/ ϕ	P
Smoking History, n(%)				7.307	0.007
Yes	28	263	291		
No	23	468	491		
Alcohol History, n(%)				0.791	0.374
Yes	27	340	367		
No	24	391	415		
Fracture Type, n(%)				46.739	< 0.001
Closed Fracture	11	417	428		
Type A	4	97	101		
Type B	16	139	155		
Type C	20	78	98		
Fibular Fracture, n(%)				3.906	0.048
Yes	47	593	640		
No	4	138	142		
Postoperative Infection, n(%)				-0.337 ^c	< 0.001
Yes	16	20	36		
No	35	711	746		
Fracture Morphology, n(%)				16.143	< 0.001
42-A	2	147	149		
42-B	4	144	148		
42-C	45	440	485		
Note: ^a) Independent samples t-test, ^b) Mann-Whitney U test, ^c) Fisher's exact test. Others are chi-square tests.					

Influencing Factor	Nonunion Group (N = 51)	Union Group (N = 731)	Total (N = 782)	$t/\chi^2/Z/\varphi$	P
Fracture Location, N ^d =1117				2.113	0.347
Proximal Third	9	200	209		
Middle Third	27	350	377		
Distal Third	36	495	531		
Time from Injury to Surgery, n, M[Q ₁ ,Q ₃]					
Closed Fracture (d)	11,5[1.5,6]	417,5[2, 7]	428,5[2, 7]	-0.486 ^b	0.627
Open Fracture (h)	40,6[6,9.75]	314,6[5, 8]	354,6[5, 8]	-0.203 ^b	0.839
Surgical Fixation Method					
Plate	18	375	393	0.530	0.467
Intramedullary Nail	6	177	183		
Internal Fixation (Plate, Intramedullary Nail)	24	552	576	19.893	< 0.001
External Fixator	27	179	206		
Fibular Fracture Reduction and Fixation, N = 640				0.557	0.454
Reduction and Fixation Performed	26	292	318		
Note: ^a) Independent samples t-test, ^b) Mann-Whitney U test, ^c) Fisher's exact test. Others are chi-square tests.					

Influencing Factor	Nonunion Group (N = 51)	Union Group (N = 731)	Total (N = 782)	t/ χ^2 /Z/ φ	P
Reduction and Fixation Not Performed	21	301	322		
Note: ^{a)} Independent samples t-test, ^{b)} Mann-Whitney U test, ^{c)} Fisher's exact test. Others are chi-square tests.					

^{d)} The object of univariate analysis is all data.

Results

The 1117 patients with tibial shaft fractures were divided into a training set (782 cases) and a validation set (335 cases). Comparison between the two groups revealed that, with the exception of fracture location, the P-values for all other variables exceeded 0.05. The univariate analysis of fracture location across the entire sample yielded a P-value of 0.347 (> 0.05), indicating no significant difference in baseline characteristics between the training and validation sets; thus, the grouping criteria were satisfied. Univariate analysis of the clinical data of the two groups of patients showed that age, gender, smoking history, open fracture severity, concomitant fibular fracture, concomitant postoperative infection, fracture morphology, and surgical fixation method were statistically significant ($P < 0.05$) between the two groups, whereas no statistically significant differences ($P > 0.05$) were observed for BMI, alcohol consumption history, comorbid diabetes, comorbid hypertension, time from injury to surgery (for open fractures), or fibular fracture reduction and fixation (Tables 5).

Univariate analysis showed that the incidence of nonunion in patients ≥ 50 years old was significantly higher than that in patients < 50 years old ($\chi^2=15.506$, $P < 0.001$), suggesting that age is a potential risk factor for nonunion. Notably, model evaluation should not rely solely on univariate analysis; greater emphasis must be placed on the discriminative ability of predictors, particularly for continuous variables. In the ROC curve analysis with age as the test variable, the area under the curve (AUC) was 0.725, indicating that age as a single predictor has a moderate level of discriminatory power for the risk of postoperative nonunion and can serve as an important reference indicator for clinical assessment.

Logistic regression analysis is shown in Table 6. Results indicated that older age, male gender, history of smoking, open fracture type, presence of postoperative infection, specific fracture morphology, and external fixation were significant risk factors for nonunion following tibial fracture surgery ($P < 0.05$; 95% CI excluding 1).

Table 6
Logistic Regression Analysis of Risk Factors for Nonunion After Tibial Fracture Surgery

Variable	β	S.E.	Wald	P	OR	95%CI
Age	-0.079	0.012	42.790	< 0.001	0.924	0.902 ~ 0.946
Gender (Male vs. Female)	1.451	0.543	7.149	0.008	4.266	1.473 ~ 12.354
Smoking History (No vs. Yes)	-1.201	0.341	12.419	< 0.001	0.301	0.154 ~ 0.587
Fracture Type (Closed vs. Type I)	-0.788	0.510	2.392	0.122	0.455	0.168 ~ 1.234
Fracture Type (Closed vs. Type II)	-1.221	0.408	8.965	0.003	0.295	0.133 ~ 0.656
Fracture Type (Closed vs. Type III)	-2.659	0.414	41.339	< 0.001	0.070	0.031 ~ 0.157
Fibular Fracture (No vs. Yes)	-0.557	0.493	1.275	0.259	0.573	0.218 ~ 1.506
Postoperative Infection (No vs. Yes)	-2.667	0.414	41.539	< 0.001	0.069	0.031 ~ 0.156
Fracture Morphology (42-A, B vs. 42-C)	-0.548	0.193	8.098	0.004	0.578	0.396 ~ 0.843
Surgical Method (Internal Fixation vs. External Fixation)	-0.503	0.169	8.823	0.003	0.605	0.434 ~ 0.843

Prediction Model Construction and Validation

The seven independent risk factors identified by multivariate analysis served as predictive variables within RStudio (version 4.5.2) to develop a nomogram to estimate the likelihood of nonunion following surgical intervention for tibial fractures. (Fig. 2).

Evaluation of the Prediction Model's Performance

The area under the receiver operating characteristic (ROC) curve (AUC) for the training set model was 0.942 (0.913 ~ 0.970), and the AUC for the validation set model was 0.840 (0.752 ~ 0.929), indicating that the model possesses strong discriminatory ability. After Bootstrap correction, the prediction curve closely followed the Y = X axis, and the predicted probability showed close agreement with the actual observed probability, suggesting that the model has good calibration ability. In terms of clinical utility, relative to the 'treat-all' or 'treat-none' approaches, the predictive model yielded a higher net benefit across nearly the full range of threshold probabilities. (Tables 3–8).

Discussion

Nonunion after tibial shaft fracture surgery results from multiple factors. Common classifications of bone nonunion based on radiographic morphology of the fracture site include hypertrophic, atrophic, sclerotic, and pseudoarthrosis-type nonunions[20]. This study focuses on analyzing risk factors and exclusively includes cases of refractory bone nonunion following surgical treatment of tibial shaft fractures (Fig. 9). This study, through univariate analysis and multivariate logistic regression analysis, identified 7 independent risk factors affecting nonunion after tibial fracture surgery, and constructed and validated a nomogram prediction model, providing robust evidence for early identification of high-risk patients and optimization of intervention strategies in clinical practice.

Clinical Significance of Risk Factors

Age and gender are important host factors for the occurrence of nonunion. People over 50 years old experience decreased bone metabolism due to declining osteoblast function, reduced growth hormone secretion, and decreased local blood supply and repair capacity at the fracture site[21, 22]. Furthermore, elderly patients often have underlying diseases such as osteoporosis and malnutrition, further weakening the fracture healing microenvironment, leading to delayed callus formation and hindering the healing process. For example, vitamin D deficiency can lead to reduced regulation of osteoblast genes by the nuclear receptor VDR (vitamin D receptor), while hypoproteinemia may result in insufficient collagen synthesis. Pignolo highlighted that the RANK-RANKL-OPG and Wnt- β -catenin signaling cascades are pivotal in the pathogenesis of age-associated osteoporosis; moreover, patients exhibiting stable bone mineral density demonstrate a significantly reduced susceptibility to fractures, functional impairment, and all-cause mortality.[22]. The reduced activity of osteoblasts cannot provide an adequate foundation for subsequent bone mineralization. Regarding gender differences, the risk of nonunion after tibial fracture surgery is particularly prominent in males over 50 years old. Males in this age group have relatively higher activity levels, fractures are often accompanied by higher-energy injuries and soft tissue damage, postoperative weight-bearing and stress interference are more pronounced, and the decline in androgen levels in males during middle and old age can directly affect osteoblast proliferation and differentiation. However, controversy persists regarding the effect of age on bone healing[23, 24]. Some studies have failed to demonstrate a statistically significant difference in the ultimate bone healing rates among patients of different ages[25, 26]. As previously noted, middle-aged male patients are more prone to high-energy injuries, thereby rendering them a particularly high-risk group for bone nonunion. This suggests that the impact of age and gender on bone healing may be confounded by other factors, requiring further research to elucidate the underlying mechanisms.

The biochemical mechanisms by which a history of smoking significantly increases the risk of nonunion are highly complex[27, 28]. Castillo et al. demonstrated that smoking significantly prolongs the time to union of tibial fractures and increases the risk of fracture-related infection[29]. Nicotine in tobacco can cause vasoconstriction by activating $\alpha 7$ nicotinic acetylcholine receptors, reducing local blood perfusion[28, 30, 31]. Tar contains various harmful substances such as polycyclic aromatic

hydrocarbons, phenols, and free radicals, inducing local chronic inflammatory reactions and oxidative stress damage, inhibiting osteoblast proliferation, differentiation, and mineralization ability[28, 32]. At the same time, harmful substances in smoke such as carbon monoxide and hydrogen cyanide can significantly reduce blood oxygen-carrying capacity and interfere with aerobic metabolism in the body. Carbon monoxide has an affinity for hemoglobin about 200 times that of oxygen, and hydrogen cyanide can inhibit the activity of mitochondrial cytochrome C oxidase, collectively causing tissue hypoxia and energy metabolism disorders[28, 30]. In addition, tobacco-related components can downregulate the expression of key factors such as VEGF (vascular endothelial growth factor) and BMP-2 (bone morphogenetic protein-2), inhibiting angiogenesis and osteogenic differentiation, and ultimately impairing fracture union[28, 33–35].

Among local factors, open fractures, comminuted fractures, and postoperative infection are closely related to the occurrence of nonunion. Comminuted fractures, due to their more complex fracture morphology, numerous fracture fragments, and poor stability after reduction and fixation, have a significantly higher risk of postoperative nonunion compared to 42-A and 42-B type fractures, suggesting that for such complex fractures, clinicians need to adopt more robust and precise fixation strategies to reduce the risk of poor healing. Higher Gustilo-Anderson types are often accompanied by more severe soft tissue contusion, extensive periosteal stripping, and wound contamination, not only directly destroying the blood supply at the fracture ends but also significantly increasing the risk of postoperative infection[36–38]. Infection can trigger a persistent inflammatory response, degrading and resorbing newly formed callus, and serves as an important local factor contributing to impaired fracture healing and even nonunion. At the 2021 Orthopaedic Research Society Workshop, Hellwinkel and colleagues provided a systematic synthesis of the mechanistic crosstalk between infection and fracture repair. They underscored a longstanding historical trend wherein bone regeneration and infectious pathology have traditionally been investigated in isolation, effectively treating them as distinct scientific disciplines. They clearly stated that infection is a common cause of fracture nonunion and emphasized that the infection-driven persistent inflammatory response degrades and resorbs newly formed callus[39]. The specific physiological mechanisms by which infection leads to bone nonunion are extremely complex. The core is that bacterial invasion triggers an inflammatory response that destroys the blood supply, cellular microenvironment, and new bone tissue required for fracture healing, ultimately causing the fracture healing process to completely stall. For example, α -toxin secreted by *Staphylococcus aureus* can inhibit osteoblast activity and promote osteoclast differentiation[40]. Enterococci invade the fracture site through wound contamination, forming biofilms, inhibiting osteoblast activity, and destroying local blood supply[41]. At the same time, neutrophil infiltration caused by infection releases oxygen free radicals, damaging the bone matrix and leading to increased bone resorption.

The proliferation, differentiation of osteoblasts, and deposition and mineralization of bone matrix require a static and stable mechanical environment. Micromotion—defined as controlled cyclic axial movement at the fracture site—has been identified as a promising strategy to enhance bone fracture healing[42]. However, excessive and uncontrolled micromotion at the fracture site directly suppresses osteoblast activity while stimulating osteoclast activity, leading to bone resorption exceeding bone formation,

widening of the resorption gap, sclerosis of the bone ends, and impaired bony union. Therefore, regarding treatment-related factors, the use of external fixation is associated with a higher risk of nonunion. While open fractures often necessitate external fixation as a primary intervention due to soft tissue conditions, the elevated risk may also stem from the relatively limited mechanical stability of external fixators, which predisposes the fracture site to excessive micromotion. At the same time, the increased risk of pin tract infection with external fixation can indirectly interfere with the normal fracture healing process[43–45].

Nomogram Model Analysis

The nomogram transforms abstract regression coefficients into an intuitive scoring system. Clinicians can quickly calculate a total score based on patient gender, age, smoking history, and other indicators, and then assess the probability of nonunion occurrence, facilitating early identification of high-risk populations and targeted intervention measures. For example, clinicians can quickly calculate a patient's predicted probability of nonunion using the nomogram. For low-risk patients with a predicted probability $< 10\%$, routine follow-up can be adopted. For medium-risk patients with $10\% \leq \text{predicted probability} < 50\%$, measures such as strengthening smoking cessation education and enhancing nutritional support can be taken. For high-risk patients with predicted probability $\geq 50\%$, infection prevention can be strengthened, individualized rehabilitation interventions can be initiated early, and follow-up frequency can be increased. This study constructed a nomogram prediction model based on the above 7 independent risk factors, achieving individualized quantitative assessment of nonunion risk. The model, validated by ROC curves, showed good discrimination in the validation set (AUC = 0.840, 95% CI: 0.752–0.929, sensitivity 0.712 and specificity 0.783 at the optimal cutoff point), presenting characteristics of "moderate sensitivity, medium to high specificity." These characteristics indicate that the model excels at ruling out nonunion risk and effectively reducing overtreatment; however, the false-negative rate could be further minimized by optimizing the threshold or integrating additional diagnostic examinations. Decision curve analysis suggested that when the threshold probability was within most intervals, the decision guided by the prediction model for nonunion after tibial fracture surgery had a significantly higher net benefit than the strategies of intervening on all patients or on none.

Study Limitations and Future Prospects

Key limitations include the exclusion of hematological indicators such as hemoglobin and albumin, which are closely associated with nutritional status and osteogenic potential; this omission may have prevented the model from achieving optimal predictive performance. This investigation constitutes a single-center retrospective analysis, wherein all enrolled participants received care exclusively at our institution, thereby introducing the possibility of selection bias. The generalizability of the model requires further validation through multi-center studies across diverse geographic regions. There is a lack of prospective studies for validation. The next step will be to conduct multi-center, prospective cohort studies, include blood physiological indicators such as hemoglobin and albumin to construct a more multidimensional combined prediction model; simultaneously, carry out clinical application research of the model to verify its actual effect in guiding clinical interventions and reducing the incidence of nonunion.

Declarations

Author Contributions

This study was designed by Zhipeng Fan and Yongxian Zhang. Research data were collected by Zhipeng Fan, Yuhang Jin, Jiawei Li, and Zhuohang Wu. Zhipeng Fan and Xuesong Yan conducted the statistical analysis. All authors critically reviewed the research results. The initial draft of the paper was primarily written by Zhipeng Fan, with contributions to manuscript revision from Yongxian Zhang and Xuesong Yan. All authors have reviewed and approved the final version of the paper and take full responsibility for the entire content of the work.

Funding

This study did not receive any funding support.

Data Availability

The analytical dataset used in this study contains information that could disclose the privacy of research subjects; therefore, it is not publicly available. Data can be obtained from the corresponding author upon request.

Ethics Approval and Informed Consent

The requirement for informed consent was waived by the Ethics Committee of the 960th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army, which also approved the study protocol. This study complied with the ethical principles of the Declaration of Helsinki.

Clinical Trial Number

Clinical trial number: not applicable.

Consent for Publication

No individual clinical data of patients were published in this article, and thus no related consent for publication was required.

Conflict of Interest

All authors declare that there are no conflicts of interest.

References

1. Saul D, et al. *Bone Healing Gone Wrong: Pathological Fracture Healing and Non-Unions-Overview of Basic and Clinical Aspects and Systematic Review of Risk Factors*, in *Bioengineering (Basel)*. Switzerland; 2023.

2. Du H et al. *LncRNA GABARAPL2 promotes non-union long bone fractures by suppressing bone mesenchymal stromal cell osteogenesis*, in *J Orthop Surg Res*. 2025: England. p. 741.
3. Buckley RE, Moran CG, Apivatthakakul T, editors. *AO Principles of Fracture Management*. Stuttgart,Germany,ISBN9783132423091: Georg Thieme; 2018.
4. Ozkan S et al. *Diagnosis and management of long-bone nonunions: a nationwide survey*, in *Eur J Trauma Emerg Surg*. 2019: Germany. pp. 3–11.
5. Nicolaides M, et al. *The Effect of Delayed Surgical Debridement in the Management of Open Tibial Fractures: A Systematic Review and Meta-Analysis*. Diagnostics (Basel). Switzerland; 2021.
6. Puccetti V, et al. *Risk Factors at Non-Union of Tibial Fracture Treated with Intramedullary Nail*. *Acta Ortop Bras*. 2024;32(2):e278581.
7. Zura R, et al. *Epidemiology of Fracture Nonunion in 18 Human Bones*, in *JAMA Surg*. United States; 2016. p. e162775.
8. Schottel PC, O'Connor DP, Brinker MR. *Time Trade-Off as a Measure of Health-Related Quality of Life: Long Bone Nonunions Have a Devastating Impact*, in *J Bone Joint Surg Am*. 2015: United States. pp. 1406–10.
9. Flores MJ, et al. *The economic impact of infection and/or nonunion on long-bone shaft fractures: a systematic review*. *OTA Int*. United States; 2024. p. e337.
10. Sanders PTJ et al. *Long-Term Clinical Outcomes of Intercalary Allograft Reconstruction for Lower-Extremity Bone Tumors*, in *J Bone Joint Surg Am*. 2020: United States. pp. 1042–1049.
11. Lasanianos NG, Giannoudis KN. *Current management of long bone large segmental defects*. *Orthop Trauma*. 2010;24(2):149–63.
12. Wu K-J et al. *The risk factors of nonunion after intramedullary nailing fixation of femur shaft fracture in middle age patients*. *Medicine*, 2019. 98(29).
13. Park JW, et al. *Reliability of the 2018 Revised Version of AO/OTA Classification for Femoral Shaft Fractures*. *Clin Orthop Surg*. 2024;16(5):688–93.
14. Axelrod D, et al. *Change in Gustilo-Anderson classification at time of surgery does not increase risk for surgical site infection in patients with open fractures: A secondary analysis of a multicenter, prospective randomized controlled trial*. *OTA Int*. United States; 2023. p. e231.
15. (PhD) KH-T. *Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation*. *Casp J Intern Med*. 2013;4(2):627–35.
16. Van Calster B et al. *Calibration: the Achilles heel of predictive analytics*, in *BMC Med*. 2019: England. p. 230.
17. Austin PC, Steyerberg EW. *The Integrated Calibration Index (ICI) and related metrics for quantifying the calibration of logistic regression models*, in *Stat Med*. England; 2019. pp. 4051–65.
18. Vickers AJ, Elkin EB. *Decision curve analysis: a novel method for evaluating prediction models*, in *Med Decis Making*. 2006: United States. pp. 565–74.

19. Vickers AJ, Van Calster B, Steyerberg EW. *Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests*, in *BMJ*. 2016: England. p. i6.
20. Wu KT et al. *Prognostic factors of extracorporeal shockwave therapy in the treatment of nonunion in long bones: a retrospective study*, in *Int J Surg*. 2024: United States. pp. 6426–6431.
21. Fang H et al. *The Mechanism of Bone Remodeling After Bone Aging*, in *Clin Interv Aging*. 2022: New Zealand. pp. 405–415.
22. Pignolo RJ. Aging and Bone Metabolism. *Compr Physiol*. 2023;13(1):4355–86.
23. Taormina DP et al. *Older age does not affect healing time and functional outcomes after fracture nonunion surgery*, in *Geriatr Orthop Surg Rehabil*. 2014: United States. pp. 116–21.
24. Tanner M, et al. *Does Age Influence the Outcome of Lower Limb Non-Union Treatment? A Matched Pair Analysis*, in *J Clin Med*. Switzerland; 2019.
25. Hernandez RK, et al. *Patient-related risk factors for fracture-healing complications in the United Kingdom General Practice Research Database*, in *Acta Orthop*. Sweden; 2012. pp. 653–60.
26. Saul D, Khosla S. *Fracture Healing in the Setting of Endocrine Diseases, Aging, and Cellular Senescence*, in *Endocr Rev*. 2022: United States. pp. 984–1002.
27. Patel RA, Palmer RFWRM. The effect Smok bone healin Source Bone Joint Res SO Bone Joint Res. 2013;2:11.
28. Xie W, et al. Analysis of the toxicity and mechanisms of osteoporosis caused by cigarette toxicants using network toxicology and molecular docking techniques. *Sci Total Environ*. 2025;1000:180414.
29. Renan C, Castillo M, Bosse MJ, Ellen MD, MacKenzie J, PhD, and, Brendan M, Patterson M, the LEAP Study Group. Impact of Smoking on Fracture Healing and Risk of Complications in Limb-Threatening Open Tibia Fractures. *J Orthop Trauma*. 2005;19:151–7.
30. Xu B, et al. The influence of smoking and alcohol on bone healing: Systematic review and meta-analysis of non-pathological fractures. *EClinicalMedicine*. England; 2021. p. 101179.
31. Alijevic O, et al. *Differentiating the Neuropharmacological Properties of Nicotinic Acetylcholine Receptor-Activating Alkaloids*, in *Front Pharmacol*. Switzerland; 2022. p. 668065.
32. Zhao C, et al. The effect of different tobacco tar levels on DNA damage in cigarette smoking subjects. *Toxicol Res (Camb)*. England; 2020. pp. 302–7.
33. Gruber MD et al. *The Effects of Nicotine- and Cigarette-Related Products on Osteogenesis, Bone Formation, and Bone Mineralization: A Systematic Review*, in *Neurosurgery*. 2023: United States. pp. 247–256.
34. Tan Q, et al. A variability in response of osteoclasts to zoledronic acid is mediated by smoking-associated modification in the DNA methylome. *Clin Epigenetics*. Germany; 2023. p. 42.
35. Jaleel Z, et al. Association of vaping with decreased vascular endothelial growth factor expression and decreased microvessel density in cutaneous wound healing tissue in rats. *Wound Repair Regen*. 2021;29(6):1024–34.

36. Kharbanda H et al. *Complications and Functional Outcomes in Open Tibia-Fibula Fractures: A Retrospective Analysis from a Tertiary Care Centre*, in *J Orthop Case Rep*. 2025; India. pp. 365–373.
37. Singh A, et al. The Effect of Timing of Debridement and Surgical Intervention in Open Fractures on the Rate of Infection and Surgical Outcomes: A Prospective Study in a Tertiary Care Setup. *Cureus*. 2023;15(4):e37204.
38. Bakshi AS, et al. Association of Surgical Debridement Timings With Infection and Non-union Rates in Open Fractures of Lower Limb Long Bones. *Cureus*. 2025;17(1):e77392.
39. Hellwinkel JE, et al. The intersection of fracture healing and infection: Orthopaedics research society workshop 2021. *J Orthop Res*. 2022;40(3):541–52.
40. Liu G, et al. alpha-Hemolysin suppresses osteogenesis by inducing lipid rafts accumulation in bone marrow stromal cells. *Food Chem Toxicol*. 2020;145:111689.
41. Gok SM, et al. [Investigation of Antibiotic Resistance and Virulence Factors of *Enterococcus faecium* and *Enterococcus faecalis* Strains Isolated from Clinical Samples]. *Mikrobiyol Bul*. 2020;54(1):26–39.
42. Lv J, Qi W, Leung FKL. Advancements in micromotion-based fixation systems for fracture healing. *J Orthop Surg (Hong Kong)*. 2025;33(2):10225536251352559.
43. Drakou A, Spyridon Sioutis IZ. *Sucralfate Prevents Pin Site Infection Source J Long Term Eff Med Implants SO 2024*. *Injury*, 2024. 34(1):1 – 7 (2024).
44. Frank FA et al. A practical definition of pin site infection. *Injury*, 2024. 55(2).
45. Hlad LM, et al. Treatment of External Fixator Pin Tract Deep Infections With an Antibiotic Sparkler. *Foot Ankle Spec*. 2026;19(1):53–7.

Figures

ROC Curve of Age for predicting in the training set

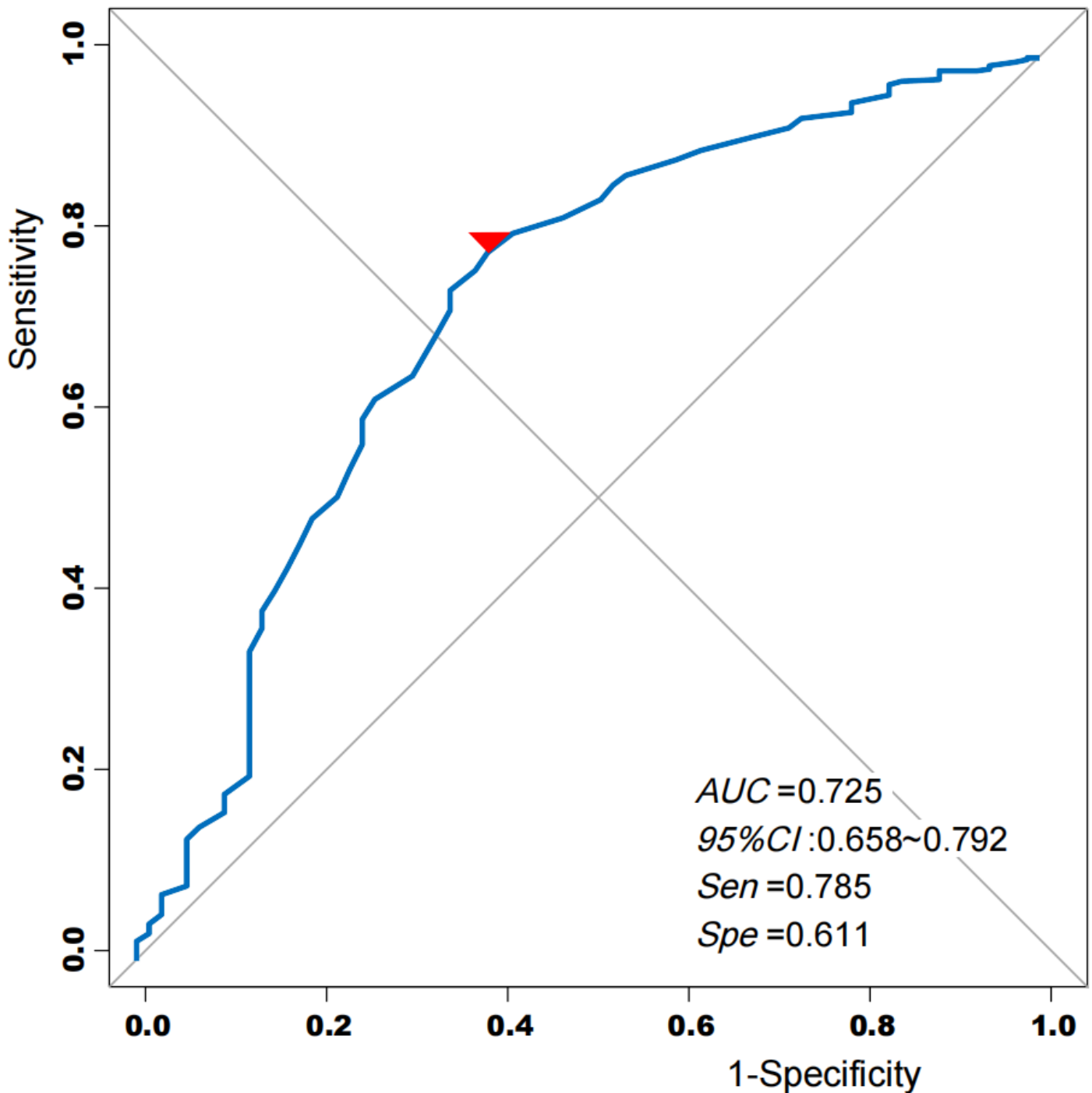


Figure 1

ROC curve illustrating the predictive ability of age for nonunion. In the training set, the AUC of the ROC curve was 0.725 (95% CI 0.658 to 0.792), yielding a sensitivity of 0.785 and a specificity of 0.611 at the optimal cutoff point, indicating that age, as a standalone predictor, demonstrates moderate discriminative ability regarding the risk of nonunion following tibial shaft fracture surgery.

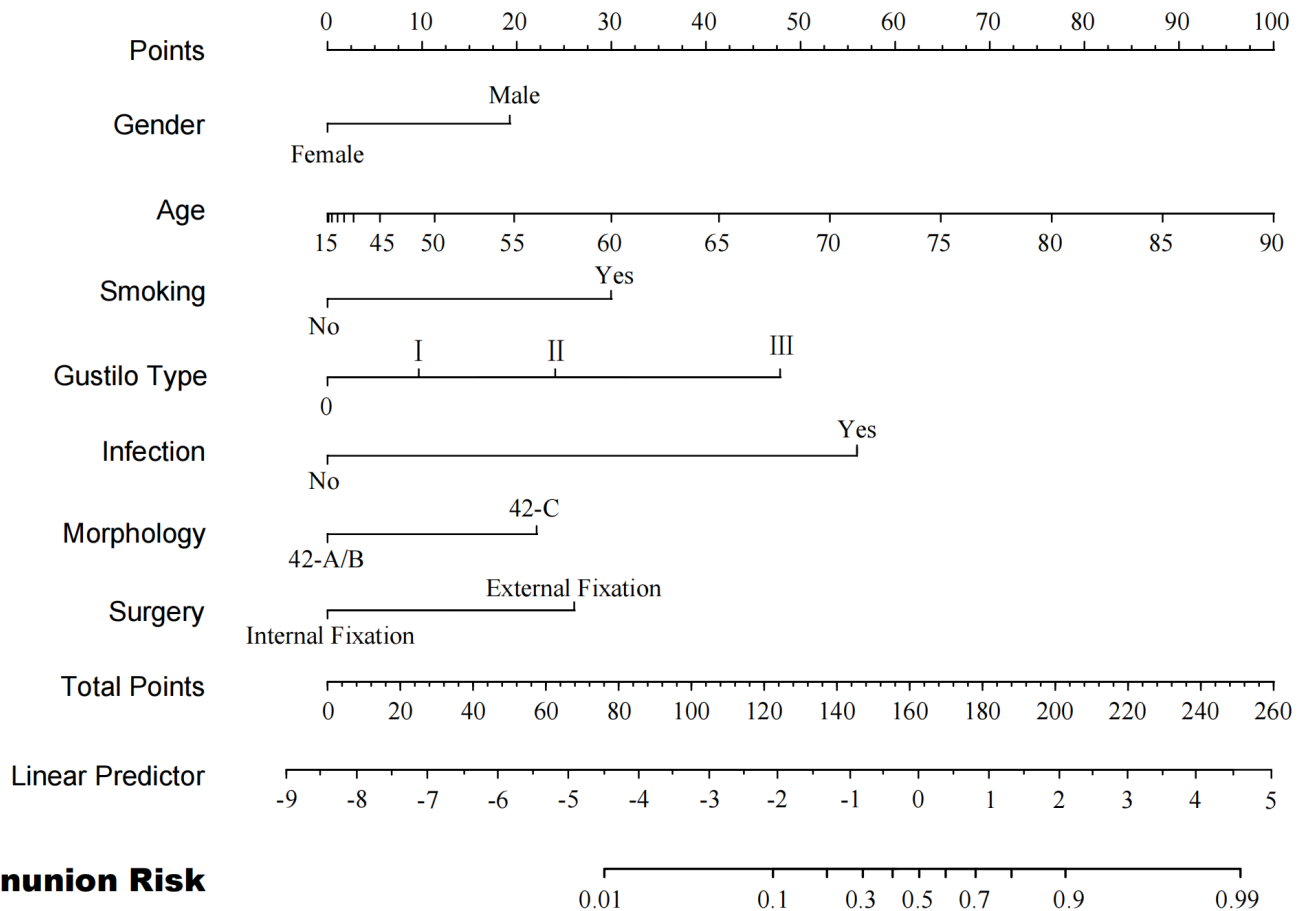


Figure 2

Nomogram model for factors influencing nonunion after tibial shaft fracture surgery. The "Points" scale represents the score assigned to each variable, aligned with the seven statistically significant variables listed in the rows below. For example, a patient with a Type III open fracture according to the Gustilo-Anderson classification is assigned a score of 24 points for this item. The "Total Points" value represents the cumulative sum of the scores derived from the seven variables listed above. The "Nonunion Risk" axis indicates the predicted probability of nonunion following tibial shaft fracture surgery, calculated by projecting downward from the "Total Points" and "Linear Predictor" scales.

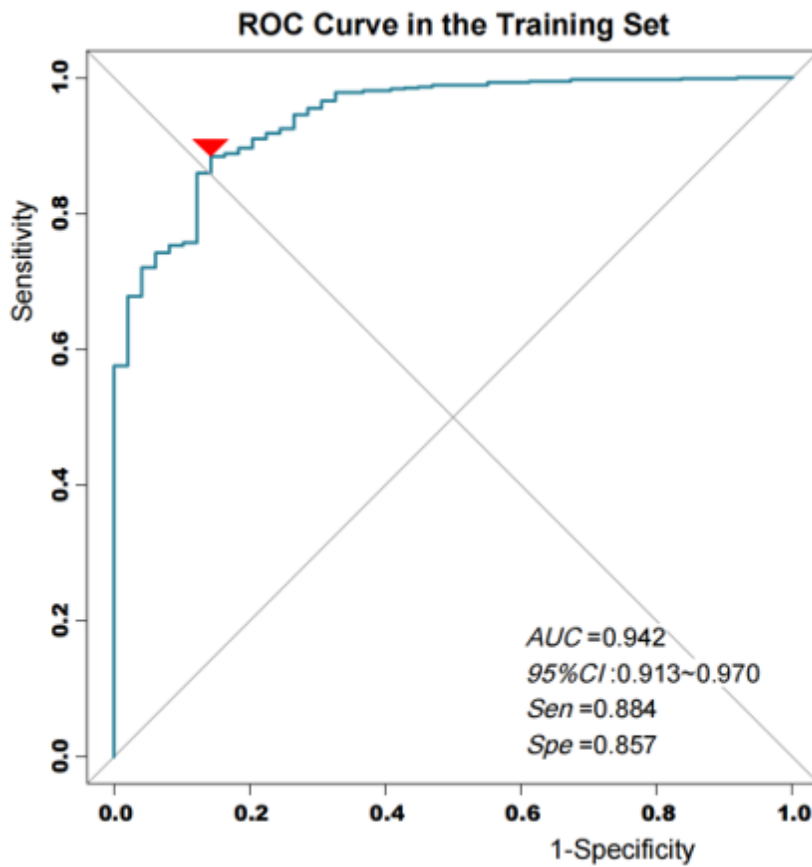


Figure 3

display the ROC curves for the training and validation sets. The Youden index method was used to determine the optimal diagnostic threshold based on the ROC analysis. In the validation set, the AUC of the model's ROC curve was 0.840 (95% CI 0.725 to 0.929), demonstrating good sensitivity and specificity at the optimal cutoff, which indicates strong discriminatory ability of the model.

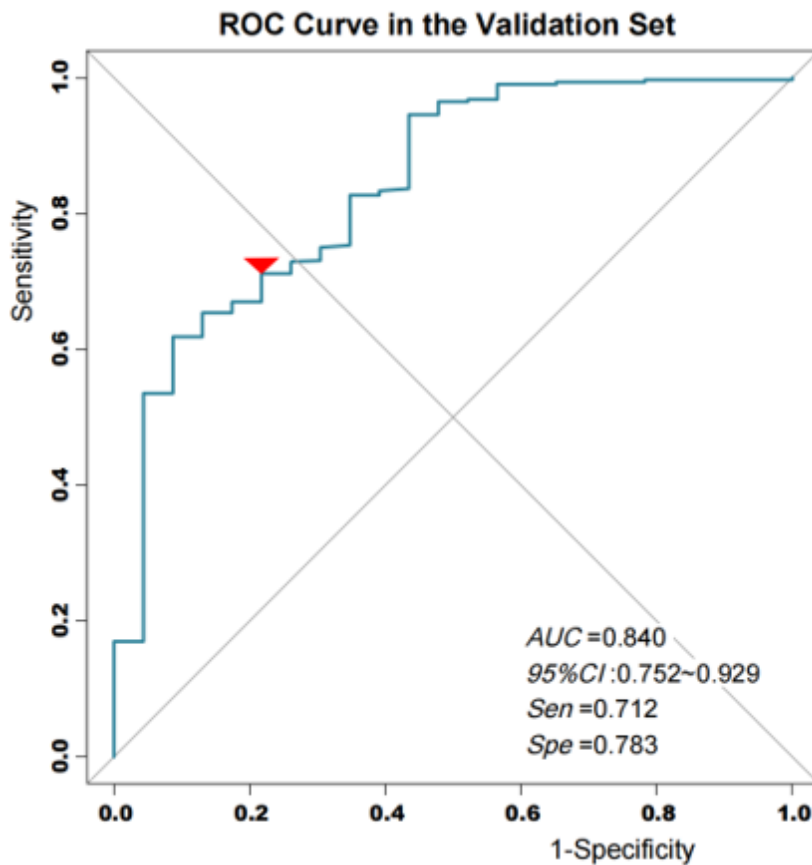


Figure 4

display the ROC curves for the training and validation sets. The Youden index method was used to determine the optimal diagnostic threshold based on the ROC analysis. In the validation set, the AUC of the model's ROC curve was 0.840 (95% CI 0.725 to 0.929), demonstrating good sensitivity and specificity at the optimal cutoff, which indicates strong discriminatory ability of the model.

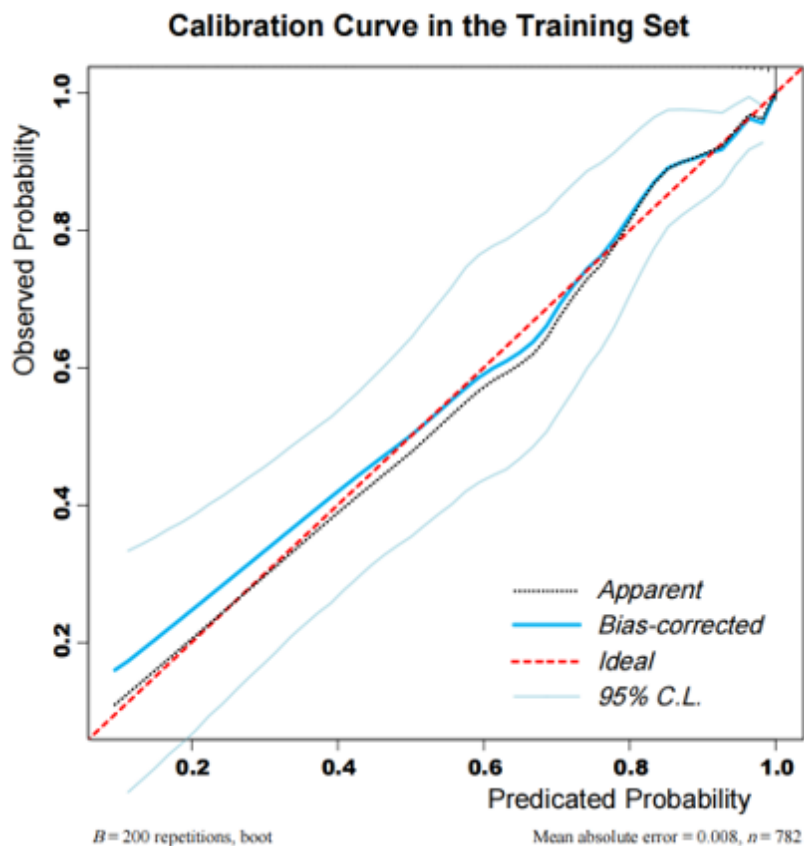


Figure 5

display the calibration curves for the training and validation sets. After Bootstrap resampling ($B=200$) and bias correction, the model aligned closely with the ideal curve. The mean absolute error (MAE) was 0.008 for the training set and 0.009 for the validation set, indicating the model's high predictive accuracy. In the range of lower predicted probabilities (<0.6), likely attributable to the relatively small sample size in this region, the confidence interval may become wider, and even the 95% confidence interval may exhibit discontinuities.

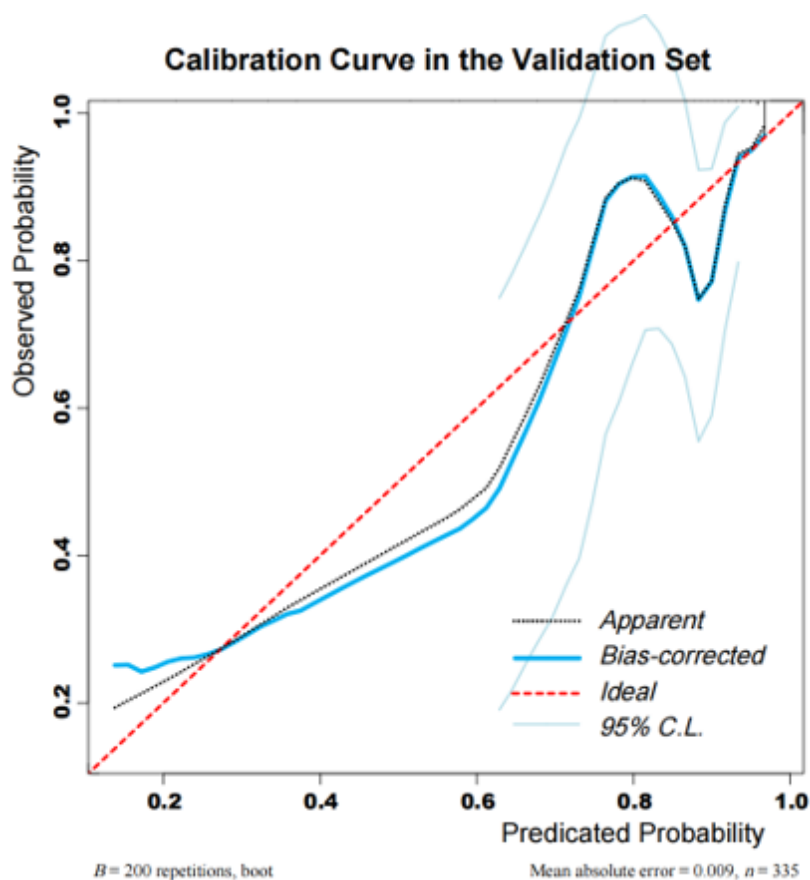


Figure 6

display the calibration curves for the training and validation sets. After Bootstrap resampling ($B=200$) and bias correction, the model aligned closely with the ideal curve. The mean absolute error (MAE) was 0.008 for the training set and 0.009 for the validation set, indicating the model's high predictive accuracy. In the range of lower predicted probabilities (<0.6), likely attributable to the relatively small sample size in this region, the confidence interval may become wider, and even the 95% confidence interval may exhibit discontinuities.

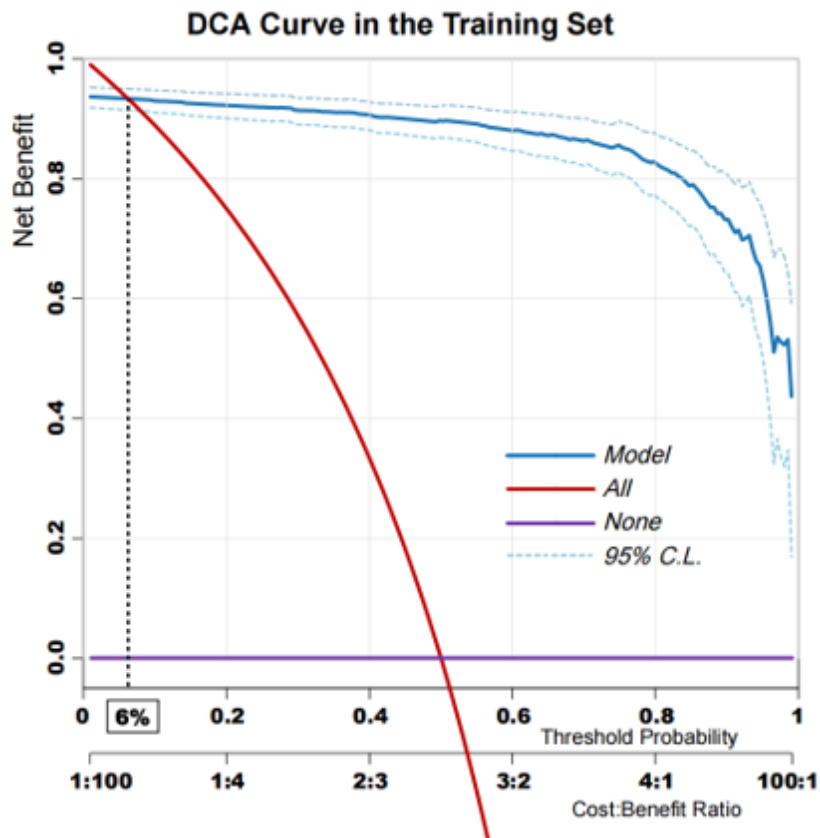


Figure 7

display the decision curve analyses for the training and validation sets. In the training set, the prediction model for nonunion after tibial shaft fracture surgery demonstrated a significantly higher net benefit than the "intervene all" or "intervene none" strategies when the threshold probability ranged from 6% to more than 99%. In the validation set, this beneficial range was maintained between 7% and 97%. Within the clinically commonly used risk threshold range, using the prediction model to guide intervention can yield a substantial net benefit for patients, markedly superior to the strategies of universal intervention or no intervention. The 95% confidence intervals overall were narrow and closely aligned with the model curve, indicating stable estimation of the model's net benefit and reliable results.

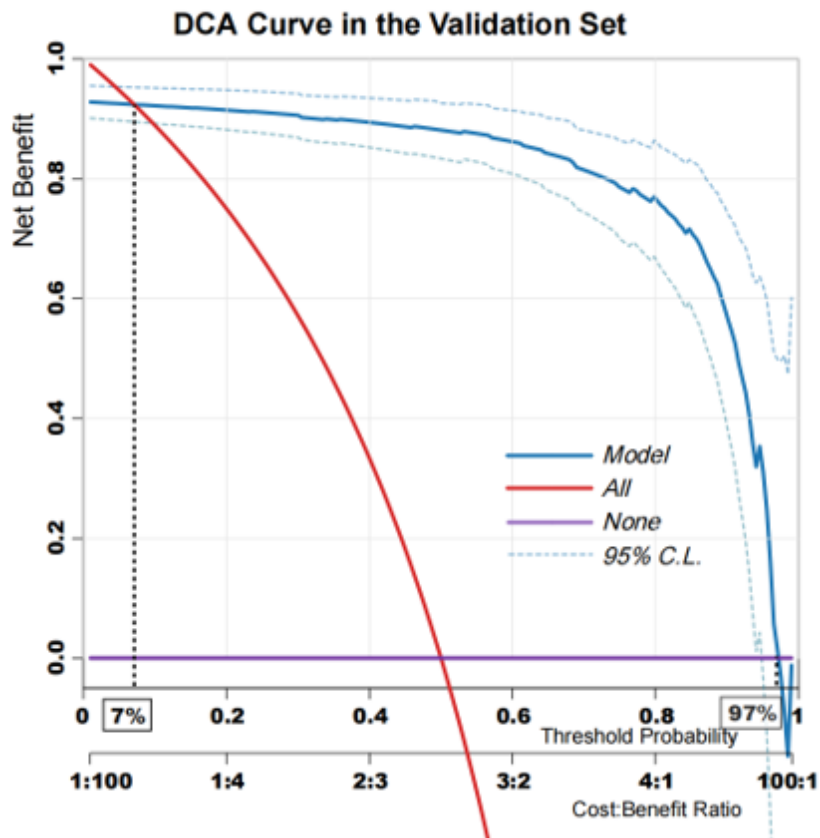


Figure 8

display the decision curve analyses for the training and validation sets. In the training set, the prediction model for nonunion after tibial shaft fracture surgery demonstrated a significantly higher net benefit than the "intervene all" or "intervene none" strategies when the threshold probability ranged from 6% to more than 99%. In the validation set, this beneficial range was maintained between 7% and 97%. Within the clinically commonly used risk threshold range, using the prediction model to guide intervention can yield a substantial net benefit for patients, markedly superior to the strategies of universal intervention or no intervention. The 95% confidence intervals overall were narrow and closely aligned with the model curve, indicating stable estimation of the model's net benefit and reliable results.



Figure 9
illustrates imaging findings from several cases of bone nonunion.