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Original Article

Risk factors for delayed healing after traumatic limb fractures and a comparative assessment of external versus internal fixation in delayed union

Guichao Guan[1], Zhanli Fu[1], Qi Sun[2]

[1]*Orthopedic Surgery Department II, The Affiliated Hospital of Northwest University Xi'an No. 3 Hospital, No. 10, East Section of Fengcheng 3rd Road, Weiyang District, Xi'an 710018, Shaanxi, China;* [2]*Department of Stomatology, Xi'an Hospital of Traditional Chinese Medicine, No. 69, Fengcheng 8th Road, Weiyang District, Xi'an 710021, Shaanxi, China*

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Abstract: Objective: To identify risk factors for delayed healing after traumatic limb fractures and to compare outcomes between internal and external fixation among patients with delayed union. Methods: We retrospectively reviewed 490 consecutive patients treated between January 2021 and June 2024. Patients were classified into normal healing (n=356) and delayed healing (n=134) groups. Candidate predictors were screened with Least Absolute Shrinkage and Selection Operator (LASSO) regression, followed by univariate and multivariable logistic regression. Receiver operating characteristic (ROC) analysis was used to derive optimal cut-offs. Results: Compared with the normal-healing group, patients with delayed healing were older and had higher BMI, and were more likely to have a history of smoking, diabetes, osteoporosis, or malnutrition; they also differed in fracture types, comminution, operative time, and blood loss (most comparisons P≤0.013). LASSO selected ten variables, including age, BMI, and smoking. ROC-derived thresholds were 62.5 years for age, 24.5 for body mass index (BMI), and 37.5 minutes for operative time. In multivariable analysis, age ≥62.5 years (odds ratio [OR] =2.233; P=0.001), BMI ≥24.5 (OR=5.194; P<0.001), smoking, diabetes, osteoporosis, malnutrition, and greater comminution remained independently associated with delayed healing. Among patients with delayed union, BMI differed by initial fixation method (P=0.027), with a higher BMI in those initially treated with internal fixation (median 24.00 vs. 23.00). Conclusion: Delayed healing after traumatic limb fractures is multifactorial. Older age, higher BMI, smoking, diabetes, osteoporosis, malnutrition, and fracture comminution show independent associations with risk. LASSO aided parsimonious variable selection and may help flag high-risk patients. The influence of initial fixation strategy on subsequent delayed healing requires further study.

Keywords: Traumatic limb fractures, delayed healing, risk factors, penalized regression, internal fixation, external fixation

Introduction

Fractures of the limbs are among the most common trauma injuries seen in an orthopedic practice. Furthermore, fractures may be seen in any age group. For instance, high energy trauma in younger adults and fragility fractures in the elderly [1]. Despite the improvement of surgical techniques and perioperative care, delayed healing and nonunion still represent a major clinical issue. This occurs in 5 to 10% of all fractures and much more in particular anatomical sites and patient subgroups [2, 3]. The resulting complications not only prolong the period of disability and impair the quality of life but also result in significant healthcare costs through prolonged treatment, revision surgery and long rehabilitation [2].

The mechanism of the delayed fracture healing is very complex and depends on too many factors such as patient, injury and treatment. Factors such as patient-level risk, old age, smoking, diabetes mellitus, osteoporosis, malnutrition, and raised BMI have consistently been associated with impaired bone healing in various fractures [4, 5]. Factors related to injury such as the fracture pattern, degree of commi-

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nution, soft-tissue damage and open versus closed injury status further modulate the potential [6, 7]. Awareness of these risk factors allows the identification of high-risk subjects for closer surveillance and management strategies.

Apart from patient and injury characteristics, the choice of fixation method is a significant modifiable treatment factor which directly affects the mechanical environment at the fracture site. Internal fixations like plates and intramedullary nails provide rigid mechanics, which allow early functional rehabilitation but require adequate soft tissue coverage and may be limited in severely comminuted fractures or compromised wound situations [8, 9]. External fixation, particularly in damage-control scenarios, contaminated wounds and extensive soft-tissue injuries, preserves the biology of the fracture zone and provides adequate stability. Still, due to pin-site complications, external fixation may require staged conversion to internal fixation in selected cases.

The usefulness of either internal or external fixation, or perhaps their combination in staged protocols is still unclear, especially with the delayed healing. Evidence on healing course and outcome is lacking for patients who develop delayed union, despite specification of initial fixation choice as per soft-tissue status and contamination [8, 12]. Several studies on fixation methods for specific fracture types have been published. For instance, tibial shaft fracture intramedullary nailing with early weight-bearing has been associated with high union rates [13]. Staged external to internal fixation protocols for severely open fractures have been advocated [14, 15]. Yet few studies directly compare fixation strategies in delayed healing patients, and the role of the host risk factors and fixation selection remains largely unclear.

This knowledge gap has practical implications. When healing is delayed, the surgeon has to decide whether to retain the current fixation or revise to an alternative construct or to augment with biological adjuncts. It is seen that there is little evidence of what would happen if they had undergone some other kind of fix. Moreover, it remains unknown whether patient subgroups, defined by metabolic, nutritional, or injury characteristics, respond differently to internal fixation as compared to external fixation.

In light of this, the current study aimed to identify patient-, injury- and treatment-related risk factors for delayed healing (DH) following traumatic limb fractures, using a combination of Least Absolute Shrinkage and Selection Operator (LASSO) regression and multivariable logistic analysis. The study further aimed to compare clinical and perioperative characteristics between patients who were initially treated with internal fixation (IF) versus IF and external fixation (EF) among those who developed delayed union. Through combining risk factor analysis with fixation strategy comparison, we hope to provide clinically actionable information that can be used for risk stratification and treatment planning in patients at high risk of impaired fracture healing.

Methods and materials

Sample size calculation

Based on the findings of Puccetti et al. [13], we estimated a 28.9% incidence of delayed healing. Utilizing a single-proportion estimate with a two-sided 95% confidence level (Z= 1.96) and an absolute margin of error of 5%, the required sample size was calculated as $N = Z^2 \times P \times (1\text{-}P)/E^2 = 316$. Our final cohort, consisting of 490 participants, exceeds this target and provides a narrower precision for the primary incidence estimate, with an approximate margin of ±4.2%.

Sample source

We performed a retrospective review of 490 consecutive patients with traumatic limb fractures treated at our institution from January 2021 to June 2024. All cases met the studyctive review of 490 consecutive patients with traumatic limb fractures treated at our institution from January 2021 to June 2024 strategy comparison, we hopeysis. Thina. Patients received standard in-hospital care and were followed after discharge according to routine clinical practice.

Delayed healing criteria

All patients underwent postoperative radiographic follow-up. Normal healing (n=356) was

defined as the formation of callus during the anticipated healing process, followed by the eventual disappearance of fracture lines without any abnormal findings at the fracture site. Delayed healing (n=134) was diagnosed at four months postoperatively when radiographs revealed minimal callus formation at the fracture ends, mild decalcification, persistent fracture lines, and an absence of sclerosis.

Inclusion and exclusion criteria

Inclusion criteria were: This study focuses on traumatic limb fractures that were treated between January 2021 and June 2024. The inclusion criteria for participants were as follows: individuals aged 18 years and older, a definitive diagnosis based on standard traumatic fracture definitions, complete baseline and follow-up data, and a determinable healing outcome categorized as either normal or delayed. Open injuries included in this study were restricted to Gustilo-Anderson Type I fractures, which are characterized by minimal skin damage, relatively clean wounds without gross contamination, and the absence of major soft-tissue compromise.

Exclusion criteria were: Severe comorbid illnesses, such as active malignancy or severe cardiopulmonary disease, as well as non-traumatic fracture etiologies or severe complications that precluded outcome assessment, incomplete treatment or follow-up records, and concomitant neurologic or vascular injuries that rendered healing evaluation unreliable.

Surgical procedures

All surgeries were performed by experienced orthopedic surgeons under general or regional anesthesia with the patient positioned appropriately based on fracture location. Prophylactic antibiotics were administered 30 minutes before skin incision. Internal fixation: After routine disinfection and draping, the fracture site was exposed through a standard surgical approach appropriate to the anatomical location. The fracture was reduced under direct visualization, with temporary fixation using reduction clamps or Kirschner wires as needed. Definitive fixation was achieved using locking plates and screws for periarticular or metaphyseal fractures, or intramedullary nails for diaphyseal fractures. Intraoperative fluoroscopy was used to confirm fracture reduction and implant positioning. The wound was irrigated thoroughly and closed in layers with placement of a drainage tube when indicated. Internal fixation combined with external fixation: This staged approach was employed in cases with significant soft-tissue swelling or compromise. In the initial stage, the limb was prepared and an external fixator was applied using percutaneous pin placement proximal and distal to the fracture site under fluoroscopic guidance, achieving preliminary fracture reduction and stabilization. After soft-tissue recovery (typically 7-14 days), limited internal fixation was performed through minimally invasive approaches to supplement fracture stability while preserving the periosteal blood supply and minimizing additional soft-tissue disruption. The external fixator was either retained or removed based on fracture stability assessment. Postoperatively, all patients received standardized pain management, thromboprophylaxis, and individualized rehabilitation protocols based on fracture stability, fixation construct, and patient condition.

Clinical data and laboratory testing

Data were extracted from the electronic medical record and follow-up notes. Variables included demographics (e.g., age, sex, BMI), injury characteristics (fracture location and type, degree of comminution), treatment details (initial internal vs. external fixation), operative time, intraoperative blood loss, and length of stay. Laboratory results routinely collected in the perioperative period were also recorded as available. For categorical variables, certain variables were classified into different categories. For example, smoking and alcohol consumption history were categorized as “never” and “other”, with “other” including “former smoker” and “current smoker” for smoking history, and “occasional drinking” and “chronic drinking” for alcohol consumption history. Additionally, fracture location was classified as “upper limb” and “lower limb”, fracture type included “closed fracture” and “open fracture” with open fractures limited to Gustilo Type I; degree of comminution was categorized as “high” and “low” based on radiological assessment. These categorical variable standards were clearly established during data collection and patients were grouped accordingly based on clinical conditions (**Figure 1**). Initial fixation

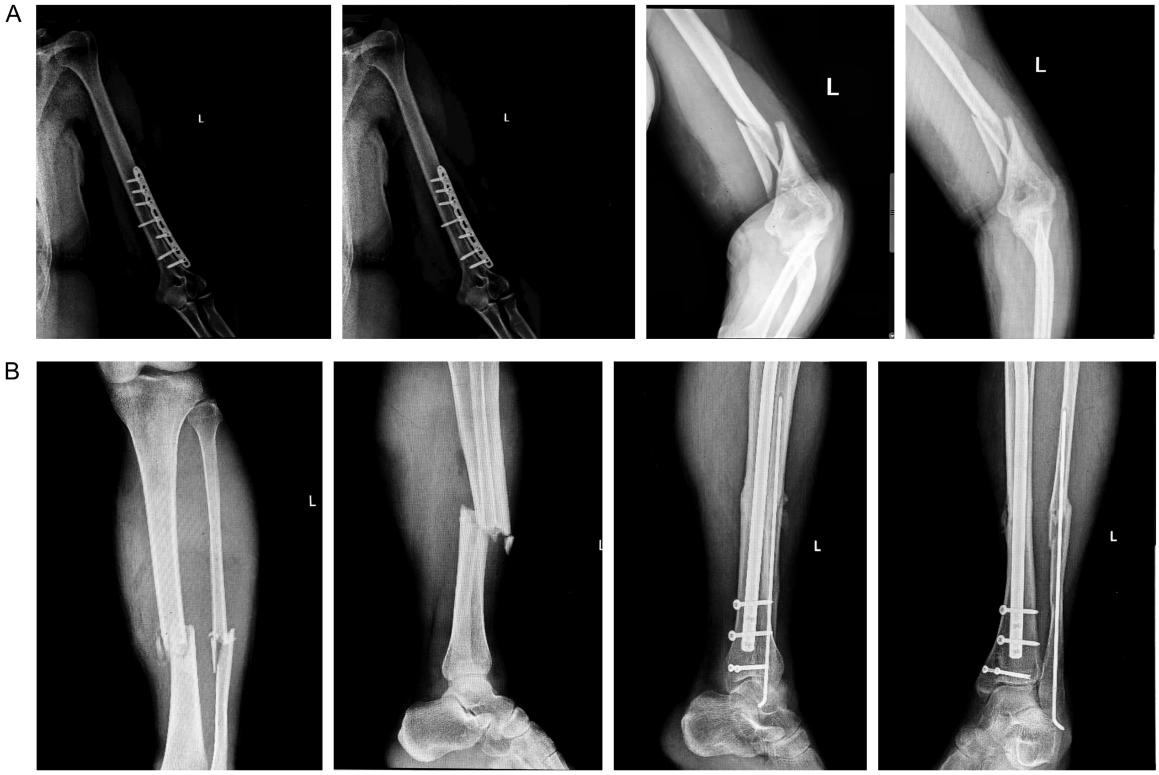

Figure 1. Radiographic follow-up after humeral shaft and tibiofibular fractures. A. A 35-year-old male with a left humeral shaft fracture treated with locking plate fixation. At 1 year postoperatively, radiographs show satisfactory alignment with abundant callus formation and complete fracture healing. B. A 31-year-old male with a left tibiofibular fracture treated with intramedullary nailing of the tibia and fixation of the fibula. At 1 year postoperatively, radiographs demonstrate cortical continuity with bridging callus formation, indicating good fracture healing.

method was categorized as internal fixation alone versus internal fixation plus external fixation (a staged/combined strategy), based on the initial treatment plan recorded in the medical chart.

Outcome measures

The primary outcome was fracture healing status, classified as normal healing or delayed healing based on radiographic criteria described above. The secondary outcome was the comparison of clinical characteristics between different initial fixation methods among patients with delayed healing. Candidate risk factors included demographic, lifestyle, comorbidity, injury, and treatment-related variables as detailed in the clinical data section.

Statistical analysis

The SPSS Software Package Global version 25.0 and R version 4.5.1 were used to analyze all data. Rephrase continuous variables were assessed for normality using the Kolmogorov-Smirnov test and summarized as mean ± standard deviation or median (interquartile range), as appropriate; group comparisons were performed using t-tests or rank-sum tests accordingly. Categorical variables were expressed as frequencies and percentages and compared using chi-square and Fisher's exact tests as appropriate. In order to identify candidate variables for univariable analysis of association with fracture healing status or occurrence of failure, demographic, clinical, injury-related and treatment-related variables were first painstakingly evaluated. A LASSO Regression with Cross-Validation was applied to the predictors to select the most informative predictors and reduce overfitting. The variables that were retained by LASSO were entered into multivariable logistic regression models that determined independent associations with delayed healing, whose results were reported as odds

ratios (ORs) and 95% confidence intervals (CIs). The multicollinearity was assessed using variance inflation factor (VIF) testing. By comparing the fixation strategy distributions of the delayed-healing and normal-healing groups, the relationship between healing outcome and initial fixation strategy was analyzed, followed by inclusion of fixation strategy as a candidate predictor in a univariable analysis and multivariable analysis. We further performed stratified comparisons of baseline and perioperative characteristics within the delayed-healing and normal-healing cohort to explore potential indication-related differences. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Analysis of factors related to delayed healing in traumatic limb fractures and treatment intervention effects

This study investigated the risk factors associated with delayed healing in traumatic limb fractures and examined the differences between external and internal fixation in patients experiencing delayed healing. Compared to the normal-healing group, the delayed-healing group was older, had a higher body mass index (BMI), and reported a greater prevalence of smoking, diabetes, osteoporosis, and malnutrition. Furthermore, significant differences were noted in fracture type and comminution, as well as longer operative times and increased intraoperative blood loss (all $P\leq0.013$). In contrast, factors such as time from injury to admission, alcohol consumption, hypertension, fracture location, injury mechanism, and length of stay showed no significant differences between the groups (all $P\geq0.208$). Additionally, the distribution of the initial fixation method was significantly different ($P=0.002$). Detailed results can be found in **Table 1**.

Feature variable selection for delayed healing in traumatic limb fractures: LASSO regression analysis

Figure 2 summarizes the LASSO feature selection process for delayed healing. **Figure 2A** illustrates the ten-fold cross-validation employed to determine the penalty; the optimal λ (λ=0.0024998) corresponds to the minimum binomial deviance. **Figure 2B** displays the coefficient trajectories across λ, indicating that at the selected penalty, ten predictors are retained: age, BMI, smoking history, diabetes mellitus history, initial fixation method, osteoporosis, malnutrition, fracture type, degree of comminution, and operative time. In contrast, intraoperative blood loss is reduced to zero and is therefore excluded from the LASSO set. This finding suggests that, within the context of the joint penalized model at the chosen λ, blood loss does not provide additional predictive value beyond the selected variables.

Determination of optimal cut-off values for age, BMI, and operative time through ROC curve analysis

Figure 3 illustrates the receiver operating characteristic (ROC) derived thresholds for age, body mass index (BMI), and operative time. In **Figure 3A**, the ROC curve for age demonstrates an area under the curve (AUC) of 0.644, with an optimal cut-off at 62.5 years (Youden index =0.231), corresponding to a sensitivity of 0.679, specificity of 0.656, and an F1 score of 0.475. **Figure 3B** presents the ROC curve for BMI, which has an AUC of 0.704, a cut-off value of 24.5, a Youden index of 0.381, sensitivity of 0.690, specificity of 0.651, and an F1 score of 0.528. **Figure 3C** displays the ROC curve for operative time, yielding an AUC of 0.573, a cut-off value of 37.5, a Youden index of 0.163, sensitivity of 0.470, specificity of 0.667, and an F1 score of 0.433.

Variance inflation factor testing and multicollinearity analysis for feature variables in delayed healing of traumatic limb fractures

Table 2 presents preliminary diagnostics for multicollinearity. The variables 'initial fixation method' and 'operative time' exhibited significant collinearity, with Variance Inflation Factors (VIF) of 25.94 and 25.78, respectively. Consequently, we excluded 'operative time' from the analysis and refitted the models. As indicated in Supplementary Table 1, the VIFs for the remaining predictors ranged from approximately 1.0 to 1.05, suggesting the absence of meaningful multicollinearity.

Univariate logistic regression analysis of risk factors for delayed healing in traumatic limb fractures

Table 3 presents the results of a univariate logistic regression analysis, which identifies

Table 1. Comparison of clinical characteristics between delayed healing and normal healing patients with traumatic limb fractures

Factor	Total	Delayed Healing Group (n=134)	Normal Healing Group (n=356)	Statistical Value	*P* Value
Age	62.30±5.17	64.16±4.60	61.60±5.20	-5.007	<0.001
Gender				0.306	0.58
Male	295 (60.20%)	78 (58.21%)	217 (60.96%)		
Female	195 (39.80%)	56 (41.79%)	139 (39.04%)		
BMI	23.00 [22.00, 24.00]	24.50 [23.00, 26.75]	23.00 [22.00, 24.00]	7.068	<0.001
Time from onset to admission	7.00 [5.00, 9.00]	7.00 [5.00, 9.00]	7.00 [5.00, 9.00]	0.266	0.79
Smoking history				9.163	0.002
Never	153 (31.22%)	28 (20.90%)	125 (35.11%)		
Other	337 (68.78%)	106 (79.10%)	231 (64.89%)		
Alcohol consumption history				0.275	0.6
Never	129 (26.33%)	33 (24.63%)	96 (26.97%)		
Other	361 (73.67%)	101 (75.37%)	260 (73.03%)		
Diabetes mellitus history				11.682	<0.001
Yes	91 (18.57%)	38 (28.36%)	53 (14.89%)		
No	399 (81.43%)	96 (71.64%)	303 (85.11%)		
Hypertension history				0.757	0.384
Yes	146 (29.80%)	36 (26.87%)	110 (30.90%)		
No	344 (70.20%)	98 (73.13%)	246 (69.10%)		
Fracture location				1.526	0.217
Upper limb	263 (53.67%)	78 (58.21%)	185 (51.97%)		
Lower limb	227 (46.33%)	56 (41.79%)	171 (48.03%)		
Injury mechanism				1.589	0.208
High energy	325 (66.33%)	83 (61.94%)	242 (67.98%)		
Low energy	165 (33.67%)	51 (38.06%)	114 (32.02%)		
Initial fixation method				9.969	0.002
Internal fixation	232 (47.35%)	79 (58.96%)	153 (42.98%)		
Internal fixation + External fixation	258 (52.65%)	55 (41.04%)	203 (57.02%)		
Osteoporosis				28.015	<0.001
Yes	192 (39.18%)	78 (58.21%)	114 (32.02%)		
No	298 (60.82%)	56 (41.79%)	242 (67.98%)		
Malnutrition				22.18	<0.001
Yes	168 (34.29%)	68 (50.75%)	100 (28.09%)		
No	322 (65.71%)	66 (49.25%)	256 (71.91%)		
Fracture condition				16.868	<0.001
Gustilo I	95 (19.39%)	42 (31.34%)	53 (14.89%)		
Closed	395 (80.61%)	92 (68.66%)	303 (85.11%)		
Degree of fracture comminution				19.013	<0.001
High	64 (13.06%)	32 (23.88%)	32 (8.99%)		
Low	426 (86.94%)	102 (76.12%)	324 (91.01%)		
Operative time	33.00 [26.00, 49.00]	43.00 [28.00, 50.00]	32.00 [26.00, 49.00]	2.478	0.013
Intraoperative blood loss	72.00 [56.00, 193.75]	175.00 [62.00, 202.00]	68.50 [56.00, 188.00]	3.04	0.002
Length of hospital stay	8.00 [7.00, 11.00]	8.00 [7.00, 10.00]	8.00 [7.00, 11.00]	0.626	0.531

Note: BMI: Body Mass Index.

significant risk factors associated with delayed healing in traumatic limb fractures. Patients aged 62.5 years and older were found to be more susceptible to delayed healing, with an odds ratio (OR) of 2.652 (P<0.001) compared to those younger than 62.5 years. Additionally, patients with a body mass index (BMI) of 24.5 or higher demonstrated a significantly increased risk of delayed healing (OR=5.717, P< 0.001). Conversely, patients with a history of never smoking exhibited a lower risk of delayed healing (OR=0.488, P=0.003). Furthermore,

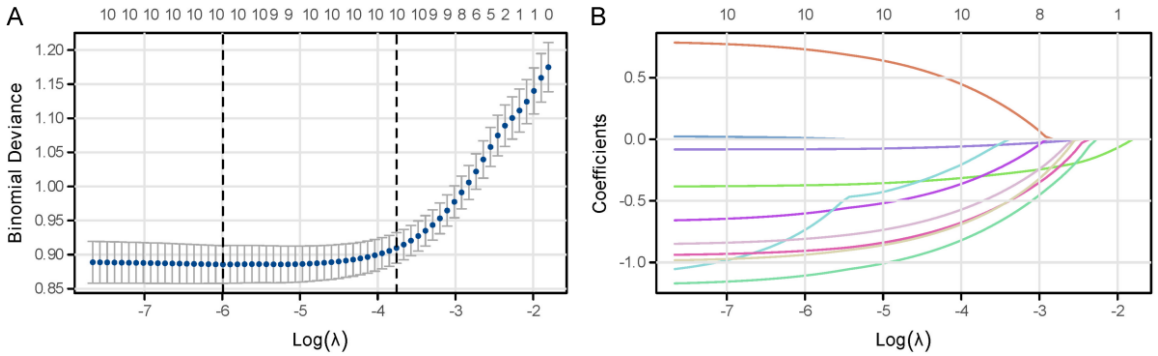

Figure 2. Feature variables for delayed healing in traumatic limb fractures selected by LASSO regression analysis. A. LASSO regression cross-validation results and optimal λ value selection. B. Coefficient paths for each variable. Note: LASSO: Least Absolute Shrinkage and Selection Operator, BMI: Body Mass Index.

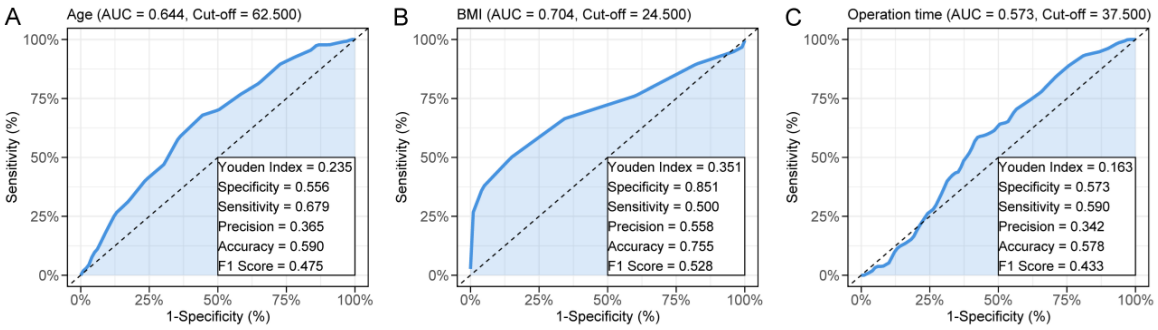

Figure 3. ROC curve analysis for determining cut-off values of age, BMI, and operative time. A. ROC curve and cut-off value for age. B. ROC curve and cut-off value for BMI. C. ROC curve and cut-off value for operative time. Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, BMI: Body Mass Index.

Table 2. Preliminary VIF testing results and multicollinearity analysis

Variable Name	Variable Type	Assignment Content	VIF	Interpretation
Age	(X)	≥62.5=1, <62.5=0	1.01830087	Low multicollinearity
BMI	(X)	≥24.5=1, <24.5=0	1.020867302	Low multicollinearity
Smoking history	(X)	Never =1, Other =0	1.056266068	Low multicollinearity
Diabetes mellitus history	(X)	Yes =1, No =0	1.049225882	Low multicollinearity
Initial fixation method	(X)	Internal fixation =1, Internal fixation + External fixation =0	25.94257549	High multicollinearity
Osteoporosis	(X)	Yes =1, No =0	1.052608053	Low multicollinearity
Malnutrition	(X)	Yes =1, No =0	1.016660544	Low multicollinearity
Fracture condition	(X)	Gustilo I =1, Closed =0	1.017085705	Low multicollinearity
Degree of fracture comminution	(X)	High =1, Low =0	1.030266882	Low multicollinearity
Operative time	(X)	≥37.5=1, <37.5=0	25.78171222	High multicollinearity
Healing status	(Y)	Delayed healing =1, Normal healing =0		

Note: VIF: Variance Inflation Factor, BMI: Body Mass Index.

individuals with a history of diabetes mellitus were found to be more prone to delayed healing (OR=2.263, P=0.001). Patients who received internal fixation as their initial fixation method had a higher risk of delayed healing (OR=1.906, P=0.002) compared to those who underwent a combination of internal and external fixation. Other identified risk factors for delayed healing included osteoporosis (OR=2.957, P<0.001), malnutrition (OR=2.638, P<0.001), Gustilo

Table 3. Univariate logistic regression analysis of risk factors for delayed healing in traumatic limb fractures

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
Age	0.975	0.214	<0.001	2.652	1.745	4.031
BMI	1.743	0.228	<0.001	5.717	3.656	8.939
Smoking history	-0.717	0.24	0.003	0.488	0.305	0.781
Diabetes mellitus history	0.817	0.243	0.001	2.263	1.406	3.641
Initial fixation method	0.645	0.206	0.002	1.906	1.273	2.852
Osteoporosis	1.084	0.209	<0.001	2.957	1.964	4.452
Malnutrition	0.97	0.209	<0.001	2.638	1.75	3.974
Fracture condition	0.959	0.238	<0.001	2.61	1.636	4.165
Degree of fracture comminution	1.156	0.275	<0.001	3.176	1.855	5.441

Note: OR: Odds Ratio, BMI: Body Mass Index.

Table 4. Multivariate logistic regression analysis of independent risk factors for delayed healing in traumatic limb fractures

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
Age	0.803	0.25	0.001	2.233	1.374	3.671
BMI	1.648	0.262	<0.001	5.194	3.127	8.739
Smoking history	-0.797	0.292	0.006	0.451	0.25	0.789
Diabetes mellitus history	0.683	0.305	0.025	1.98	1.085	3.601
Initial fixation method	0.596	0.249	0.017	1.815	1.117	2.975
Osteoporosis	1.167	0.251	<0.001	3.212	1.977	5.29
Malnutrition	0.883	0.248	<0.001	2.419	1.491	3.944
Fracture condition	0.756	0.291	0.009	2.129	1.2	3.766
Degree of fracture comminution	1.045	0.335	0.002	2.842	1.471	5.504

Note: OR: Odds Ratio, BMI: Body Mass Index.

Type I fracture condition (OR=2.610, P<0.001), and a high degree of fracture comminution (OR=3.176, P<0.001).

Multivariate logistic regression analysis of independent risk factors for delayed healing in traumatic limb fractures

Table 4 presents the results of a multivariate logistic regression analysis, which further confirms the independent risk factors associated with delayed healing in traumatic limb fractures. Compared to patients aged less than 62.5 years, those aged 62.5 years or older (OR=2.233, P=0.001) represent an independent risk factor for delayed healing. Patients with a body mass index (BMI) of 24.5 or higher (OR=5.194, P<0.001) continue to demonstrate a higher risk of delayed healing. In contrast, patients with a 'never' smoking history (OR= 0.451, P=0.006) exhibit a lower risk of delayed healing, while those with a history of diabetes mellitus (OR=1.980, P=0.025) are more susceptible to delayed healing. Patients who received internal fixation as the initial fixation method (OR=1.815, P=0.017) had a higher risk of delayed healing compared to those who underwent both internal and external fixation. Additionally, osteoporosis (OR=3.212, P<0.001), malnutrition (OR=2.419, P<0.001), Gustilo Type I fracture condition (OR=2.129, P=0.009), and a high degree of fracture comminution (OR=2.842, P=0.002) were identified as independent risk factors for delayed healing.

Comparison of risk factors among delayed healing patients with different initial fixation methods

Table 5 presents the analysis results after grouping delayed healing patients by their ini-

Table 5. Comparison of risk factors among delayed healing patients with different initial fixation methods

Variable	Total	Internal Fixation (n=79)	Internal Fixation + External Fixation (n=55)	Statistical Value	*P* Value
Smoking history				2.295	0.13
Never	28 (20.90%)	13 (16.46%)	15 (27.27%)		
Other	106 (79.10%)	66 (83.54%)	40 (72.73%)		
Diabetes mellitus history				0.299	0.585
Yes	38 (28.36%)	21 (26.58%)	17 (30.91%)		
No	96 (71.64%)	58 (73.42%)	38 (69.09%)		
Osteoporosis				0	0.996
Yes	78 (58.21%)	46 (58.23%)	32 (58.18%)		
No	56 (41.79%)	33 (41.77%)	23 (41.82%)		
Malnutrition				0.146	0.702
Yes	68 (50.75%)	39 (49.37%)	29 (52.73%)		
No	66 (49.25%)	40 (50.63%)	26 (47.27%)		
Fracture condition				3.249	0.071
Gustilo I	42 (31.34%)	20 (25.32%)	22 (40.00%)		
Closed	92 (68.66%)	59 (74.68%)	33 (60.00%)		
Degree of fracture comminution				0.218	0.64
High	32 (23.88%)	20 (25.32%)	12 (21.82%)		
Low	102 (76.12%)	59 (74.68%)	43 (78.18%)		
Age	64.16±4.60	64.04±5.04	64.35±3.93	0.379	0.705
BMI	24.50 [23.00, 26.75]	25.00 [22.50, 27.00]	24.00 [23.00, 26.00]	0.098	0.922
Operative time	39.90±11.58	48.63±5.75	27.35±3.22	-24.85	<0.001
Intraoperative blood loss	140.55±72.27	198.30±24.82	57.60±9.32	-40.085	<0.001

Note: BMI: Body Mass Index.

tial fixation method based on healing status. Patients with varying initial fixation methods were compared across multiple variables. No significant differences were observed in smoking history (P=0.130), history of diabetes mellitus (P=0.585), osteoporosis (P=0.996), malnutrition (P=0.702), degree of fracture comminution (P=0.640), age (P=0.705), and BMI (P=0.922). However, fracture condition (P=0.071) approached significance among patients with different initial fixation methods, with the internal fixation group exhibiting a higher proportion of Gustilo Type I fractures (25.32% vs. 40%). In addition, the internal fixation group demonstrated significantly longer operative time (P<0.001) and greater intraoperative blood loss (P<0.001) compared to the internal fixation + external fixation group.

Comparison of risk factors among normally healing patients with different initial fixation methods

Table 6 compares patients with normal healing, stratified by the initial fixation strategy. The body mass index (BMI) differed significantly between the groups (P=0.027), with higher values observed in the internal fixation group (median 24.00 vs. 23.00). The history of smoking approached significance (P=0.050), as the internal fixation group exhibited a lower proportion of never-smokers (29.41% vs. 39.41%). No significant differences were noted in diabetes, osteoporosis, malnutrition, fracture type, and comminution (*P* values ranging from 0.333 to 0.947). Furthermore, both operative time and intraoperative blood loss were significantly greater in the internal fixation group compared to the internal fixation plus external fixation group (both P<0.001).

Discussion

Delayed healing after traumatic limb fractures worsens function and drives costs, so recognizing high-risk patients early and tailoring treatment is clinically important. Puccetti et al. reported a 28.9% delayed-healing rate in traumatic tibial fractures and highlighted high-energy trauma, open injury, and staged external fix-

Table 6. Comparison of risk factors among normally healing patients with different initial fixation methods

Variable	Total	Internal Fixation (n=153)	Internal Fixation + External Fixation (n=203)	Statistical Value	*P* Value
Smoking history				3.827	0.05
Never	125 (35.11%)	45 (29.41%)	80 (39.41%)		
Other	231 (64.89%)	108 (70.59%)	123 (60.59%)		
Diabetes mellitus history				0.004	0.947
Yes	53 (14.89%)	23 (15.03%)	30 (14.78%)		
No	303 (85.11%)	130 (84.97%)	173 (85.22%)		
Osteoporosis				0.052	0.82
Yes	114 (32.02%)	48 (31.37%)	66 (32.51%)		
No	242 (67.98%)	105 (68.63%)	137 (67.49%)		
Malnutrition				0.222	0.638
Yes	100 (28.09%)	41 (26.80%)	59 (29.06%)		
No	256 (71.91%)	112 (73.20%)	144 (70.94%)		
Fracture condition				0.939	0.333
Gustilo I	53 (14.89%)	26 (16.99%)	27 (13.30%)		
Closed	303 (85.11%)	127 (83.01%)	176 (86.70%)		
Degree of fracture comminution				0.218	0.641
High	32 (8.99%)	15 (9.80%)	17 (8.37%)		
Low	324 (91.01%)	138 (90.20%)	186 (91.63%)		
Age	61.60±5.20	61.69±5.01	61.54±5.35	-0.28	0.78
BMI	23.00 [22.00, 24.00]	23.00 [22.00, 24.00]	23.00 [22.00, 24.00]	2.217	0.027
Operative time	36.94±13.29	50.65±7.34	26.60±4.44	-38.306	<0.001
Intraoperative blood loss	116.42±70.81	194.98±26.73	57.22±8.81	-68.678	<0.001

Note: BMI: Body Mass Index.

ation as key predictors [13]. Prior work also points to patient bone health and injury severity as central drivers: for example, Wnt-pathway activity modulates callus formation [3], complex or comminuted patterns and open injuries carry higher risk [4, 9], and weight-bearing strategy interacts with fixation stability to influence time to union [10, 11]. In this single-center retrospective cohort study, we combined univariable and multivariable logistic regression with LASSO to identify determinants of delayed healing and compared perioperative profiles across initial fixation strategies in patients with delayed union. The findings fit clinical experience: risk is additive and multifactorial - host metabolic and skeletal status, lifestyle exposures, and fracture morphology all matter - and perioperative management (including fixation choice and loading) likely shapes the mechanical milieu that ultimately affects healing.

Regarding risk factors, multivariate regression demonstrated that age ≥62.5 years (OR=2.233) and BMI ≥24.5 (OR=5.194) maintained stable associations with delayed healing. Age-related effects can be explained biologically: with increasing age, periosteal blood supply, osteoblast activity, and bone turnover rates decline, slowing repair processes; simultaneously, comorbidity burden and rehabilitation compliance differences may have additive effects [16]. He et al. [17] reported that younger age predicted delayed healing in extra-articular mid- to distal-tibial fractures, whereas in our broader limb-fracture cohort, older age (≥62.5 years) was associated with higher risk. This discrepancy likely reflects differences in anatomical focus, injury mechanism and soft-tissue status, and treatment pathways across the studies. By contrast, BMI showed a clearer and stronger signal in our data, with higher BMI associated with delayed healing; external reports also link obesity to protracted healing (e.g., BMI ≥30 kg/m^2 predicting longer time to union in refractory long-bone nonunion [18]). Notably, in fixation-stratified analyses within the delayed-healing subgroup, BMI did not differ between fixation methods, supporting in-

terpretation of BMI as a host factor rather than a surrogate for surgical complexity. As we established in our work, we feel that the BMI cut-off value of 24.5 has particular clinical relevance in Asia as it is the WHO Asian-specific overweight cut-off value. Based on what we see in our work, having a high body mass index can slow down and even prevent the body from healing. Furthermore, it raises the chances of complications that affect the skin and connective tissues. Accordingly, patients with BMI ≥24.5 should receive preoperative nutritional counselling and weight control advice, if possible, and surgeons should expect delayed healing in this group.

According to our cohort's findings, being a none smoker was associated with a lower risk of delayed healing (OR=0.451). Evidence shows that exposure to tobacco impairs early repair by disrupting the organization of the hematoma, process of angiogenesis, and development of osteogenesis. Moreover, it is associated with higher rates of delayed union or nonunion; the time to union is prolonged in long-bone fractures [19, 20]. Diabetes is also associated with delayed healing (OR=1.980), reflecting the negative impact of glycemic variability and microvascular disease on the healing environment; stress hyperglycemia scores have been predictive of delayed healing following surgery for fracture of the tibia [21]. According to evidence from fractures at other sites, smoking, diabetes and obesity are associated with a higher risk of postoperative complications. In analyses stratified by fixation, the delayed-healing subgroup's BMI wasn't different between fixation strategies, supporting its interpretation as a host factor rather than a surrogate of surgical complexity. We feel that smoking and diabetes are modifiable risk factors that need aggressive intervention perioperatively. We suggest initiating smoking cessation programs at admission for all smoking fracture patients, even if complete cessation is not attainable prior to surgery [22]. We recommend strict perioperative glycemic control for diabetic patients with target blood glucose levels <10 mmol/L as this may improve the environment for callus formation. The interventions are low cost and feasible in most clinical settings and may result in substantial improvements in healing outcomes.

Osteoporosis (OR=3.212) and malnutrition (OR=2.419) were associated with higher risk of delayed healing, consistent with the idea that impaired bone quality and inadequate substrates for callus formation can slow repair. Clinically, both conditions can be screened and addressed perioperatively (e.g., nutritional assessment and bone-health optimization), although effects likely vary by baseline status and timing. In line with this, Russo and colleagues linked vitamin D deficiency to delayed healing after foot and ankle fractures and arthrodesis, with obesity and diabetes emerging as additional risk factors [23]. Broader syntheses likewise note that clustered comorbidities can compromise bone healing and increase the likelihood of delayed union or nonunion, underscoring the need for routine risk assessment in practice [24]. Osteoporosis and malnutrition are often underdiagnosed but are very common in fracture patients, especially in the acute trauma setting focusing on managing the injury. As per our recommendations, we advocate screening for osteoporosis (heel ultrasound/when possible a DEXA) and nutritional status (serum albumin, prealbumin and hemoglobin) in all patients over the age of 60 years presenting with limb fracture. Supplementation of calcium and vitamin D in the early stage along with optimizing dietary protein should be considered standard of care not adjuvants.

Regarding injury pattern, a higher degree of comminution was associated with delayed healing (OR=2.842), and Gustilo type I open injuries carried greater risk than closed fractures (OR=2.129). These associations are clinically plausible: comminution compromises construct stability and alters load sharing at the fracture gap, while even low-grade open injuries reflect soft-tissue compromise and reduced local perfusion, with some contamination risk. Notably, our cohort included only Gustilo Type I open fractures, so the observed effect pertains to low-grade open injuries and should not be extrapolated to higher-grade wounds. Research by Bauwens et al. found that active smoking, fracture gap >5 mm, and initial open trauma were risk factors for complications and nonunion following intramedullary nailing of tibial shaft fractures. This study also observed distributional differences in these variables through inter-group comparisons, supporting

their inclusion as robust initial screening indicators for risk stratification. In our opinion, the presence of even a Gustilo Type I open fracture can increase the odds of delayed healing by over twice the factor. Any violation of the soft-tissue envelope, no matter how insignificant, changes the whole healing process. It is therefore recommended that clinicians not underestimate the significance of low-grade open injuries and that they consider more frequent radiographic follow-up and lower intervention thresholds in these patients. Moreover, we propose that the index procedure for comminuted fractures should include biological augmentation strategies (e.g., an autologous bone graft) rather than a wait-and-see policy.

Interpretation of surgery-related variables proves more complex. On the one hand, intergroup comparisons showed obvious differences in operative time and intraoperative blood loss between delayed healing and normal healing groups, suggesting that longer operations and greater blood loss may associate with higher delayed healing risk; on the other hand, LASSO feature selection included operative time in the candidate set, but Variance Inflation Factor (VIF) testing revealed high multicollinearity with initial fixation method. After removing operative time, model multicollinearity significantly improved, with remaining variable VIF values approaching 1, and the final multivariate model retained independent effects of "initial fixation method" (internal fixation relative to internal fixation + external fixation: OR=1.815). Research by Liu et al. [25] demonstrated that dual plate fixation showed better healing outcomes and lower reoperation rates compared to single lateral locking plates in comminuted distal femur fractures, suggesting that fixation method selection significantly impacts healing outcomes. Interpreting from both statistical and clinical perspectives, this suggests that fixation method and operative time/blood loss may lie within the same "causal pathway" or reflect the same underlying construct (surgical complexity and soft tissue disruption). Our findings suggest that operative time and blood loss are not independent risk factors as such. Rather, they are indicators of surgical invasiveness and soft-tissue handling. In our clinical practice we feel that optimizing surgical time and blood loss by smart implant choice and preoperative planning and sequencing may enhance healing. We thus highlight the importance of surgical efficiency not as volume but as a surrogate for minimizing tissue trauma.

Comparing the delayed healing subgroups further revealed that the patients in the internal fixation group or the internal fixation plus external fixation group had no differences in baseline risk characteristics, including smoking, diabetes mellitus, osteoporosis, malnutrition, degree of comminution, age, and BMI. The differences were evident only in operative time and blood loss: the internal fixation group had an average operative time of approximately 48.6 minutes and blood loss of 198 ml, while the internal fixation plus external fixation group had an average of approximately 27.4 minutes and 58 ml, respectively. Based on the findings, the relationship between fixation strategy and delay in healing may exert its effects through surgical exposure with its impact on any soft tissue and local perfusion rather than reflecting any baseline differences between the patients. Put differently, fixation choice may function more as a response to fracture complexity and soft-tissue status than as an independent cause of delayed healing, with the extent of exposure and soft-tissue disruption playing a more direct role in subsequent repair. Taking these observations into account, we would like to put forth that the choice between internal fixation alone and combined methods should not be construed as a dichotomy whereby either option is superior to the other, but in fact a choice influenced by soft-tissue status only. Our proposal is a "soft-tissue first approach". When soft-tissue conditions are not optimal, the staged approach using initial external stabilization allows for soft-tissue healing before definitive fixation. Thus, despite two procedures, overall surgical trauma is reduced to only one procedure. This method coincides with the principles of damage-control orthopedics. This may explain why the operative time and blood loss are lower in the combined fixation group.

Within the normally healing cohort, the internal-fixation group had a slightly higher mean BMI than the internal-plus external-fixation group (23.14 vs. 22.75). Although this difference is small, it may reflect routine surgical decision-making - surgeons sometimes favor internal

fixation when greater initial stability or quicker functional recovery is desired - or that satisfactory healing can still be achieved at modestly higher body mass under careful soft-tissue handling and rehabilitation. This pattern does not conflict with the cohort-level finding that BMI ≥24.5 marks higher risk: above that threshold, adverse metabolic and mechanical effects appear to dominate, consistent with reports linking higher BMI to nonunion and prolonged healing after distal femur and femoral shaft fractures [26, 27]. Minor differences in BMI (for example 23.14 compared to 22.75) below the threshold are unlikely to affect the outcome when the appropriate constructs and perioperative management are used to achieve normal healing. Essentially, there appears to be a threshold-like effect wherein a BMI of 24.5 and above will alert us to pay closer attention to nutrition/metabolic control/load environment. Below that, a careful fixation strategy and technique will counter small differences related to weight. This finding should reassure the clinicians in daily practice as when surgery is performed properly on a patient with a body mass index below the risk threshold it will heal normally irrespective of the fixation used. We warn against applying this to patients with high BMI. In our opinion, BMI 24.5 should be viewed as a clinical alert point which prompts intensification of monitoring, together with potential earlier intervention if healing milestones are not met.

These findings suggest several practical avenues for care. Both the blood biomarkers able to predict fracture healing are promising but current evidence suggests they may not be accurate enough yet for personal decision making [28]. At admission, we need a simple risk screen that takes into account age, BMI, diabetes, smoking, osteoporosis, nutrition, and injury pattern (comminution, Gustilo grade). This could identify patients who will benefit from closer early postoperative review and imaging. It allows us to identify stalled healing earlier and to implement second-line intervention on time. While biological augmentation continues to attract interest, Nicholson and colleagues emphasized that most nonunions remain manageable with standard surgical techniques when indications and execution are sound [29]. Perioperatively, routine measures - smoking cessation, glucose control, nutritional support, and bone-health optimization - should be organized systematically, with expectations set that effects depend on baseline status and timing [30]. Surgical planning can then align with soft-tissue conditions and contamination risk: when envelopes are tenuous or comminution is severe, external fixation or staged approaches help limit operative time and blood loss; when soft tissues are acceptable and early stability is essential, internal fixation supports earlier mobilization, provided soft-tissue protection principles are respected. For high-risk patients, postoperative loading cadence and adherence deserve the same attention as the index operation, so that mechanical and biological conditions work in concert to support callus maturation.

This study has several limitations. First, its single-center retrospective design limits external generalizability and precludes strong causal inference; although LASSO and multivariable adjustment were applied, residual selection and information bias cannot be completely excluded. Second, some potentially relevant biological and functional variables - such as vitamin D status, nutritional biomarkers, systemic inflammatory markers, rehabilitation compliance, and detailed weight-bearing protocols - were not systematically collected, which may have led to underestimation of their influence on fracture healing. Third, open fractures were intentionally restricted to Gustilo-Anderson Type I injuries to reduce heterogeneity related to severe soft-tissue damage, contamination, and vascular compromise; however, because external fixation is more commonly indicated in higher-grade open fractures, this restriction limits the generalizability of our findings regarding fixation strategies, which should therefore be interpreted as applicable mainly to closed fractures and low-grade open injuries. Finally, fixation strategy comparisons were not adjusted using propensity score methods, and external validation or decision curve analysis was not performed; thus, the clinical applicability and net benefit of the predictive model warrant further evaluation in prospective, multicenter studies.

Conclusion

This study confirms that age, BMI, smoking, diabetes mellitus, osteoporosis, malnutrition, and

injury complexity are closely related to delayed healing, with BMI ≥24.5 serving as a high-risk threshold; fixation method effects may be mediated through surgical exposure. Among normally healing patients, internal fixation groups had higher BMI, suggesting that reasonable strategies and management can counteract mild weight difference impacts.

Disclosure of conflict of interest

None.

Address correspondence to: Qi Sun, Department of Stomatology, Xi'an Hospital of Traditional Chinese Medicine, No. 69, Fengcheng 8th Road, Weiyang District, Xi'an 710021, Shaanxi, China. E-mail: 18165265386@163.com

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Supplementary Table 1. VIF testing results for remaining variables after excluding operative time

Variable	VIF	Interpretation
Age	1.017303367	Low multicollinearity
BMI	1.020707925	Low multicollinearity
Smoking history	1.053798049	Low multicollinearity
Diabetes mellitus history	1.049023179	Low multicollinearity
Initial fixation method	1.036542829	Low multicollinearity
Osteoporosis	1.051809879	Low multicollinearity
Malnutrition	1.014266525	Low multicollinearity
Fracture condition	1.009858033	Low multicollinearity
Degree of fracture comminution	1.03017085	Low multicollinearity

Note: VIF: Variance Inflation Factor, BMI: Body Mass Index.