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Research article

Analysis of risk factors and development of a nomogram-based prediction model for defective bony non-union

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ABSTRACT

Objective: To explore risk factors for defective non-union of bone and develop a nomogram-based prediction model for such an outcome.

Methods: This retrospective study analysed the case data of patients with defective bony non-unions who were treated at the authors' hospital between January 2010 and December 2020. Patients were divided into the union and non-union groups according to their Radiographic Union Score for Tibia scores 1 year after surgery. Univariate analysis was performed to assess factors related to demographic characteristics, laboratory investigations, surgery, and trauma in both groups. Subsequently, statistically significant factors were included in the multivariate logistic regression analysis to identify independent risk factors. A nomogram-based prediction model was established using statistically significant variables in the multivariate analysis. The accuracy and stability of the model were evaluated using receiver operating characteristic (ROC) and calibration curves. The clinical applicability of the nomogram model was evaluated using decision curve analysis.

Results: In total, 204 patients (171 male, 33 female; mean [±SD] age, 39.75 ± 13.00 years) were included. The mean body mass index was 22.95 ± 3.64 kg/m^2. Among the included patients, 29 were smokers, 18 were alcohol drinkers, and 21 had a previous comorbid systemic disease (PCSD). Univariate analysis revealed that age, occupation, PCSD, smoking, drinking, interleukin-6, C-reactive protein (CRP), procalcitonin, alkaline phosphatase, glucose, and uric acid levels; blood calcium ion concentration; and bone defect size (BDS) were correlated with defective bone union (all $P < 0.05$). Multivariate logistic regression analysis revealed that PCSD, smoking, interleukin-6, CRP, and glucose levels; and BDS were associated with defective bone union (all $P < 0.05$), and the variables in the multivariate analysis were included in the nomogram-based prediction model. The value of the area under the ROC curve for the predictive model for bone defects was 0.95.

Conclusion: PCSD, smoking, interleukin-6, CRP, and glucose levels; and BDS were independent risk factors for defective bony non-union, and the incidence of such non-union was predicted using the nomogram. These findings are important for clinical interventions and decision-making.

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1. Introduction

The United States Food and Drug Administration defines non-union as a fracture that does not fulfil healing criteria after 9 months or one without signs of healing after 3 months of continuous observation [1]. Non-union is mainly divided into the hypertrophic and atrophic types. Defective bony non-union is a subtype of atrophic non-union, which is caused by infection, trauma, surgery, and tumour resection [2]; it usually cannot heal spontaneously after general repair. Defective bony non-union accounts for 0.4% of all fractures and up to 11.4% of open fractures [3].

Current research into bone defects has focused on therapeutic measures, including reconstruction of the structure, overcoming the defect, and promoting union, and its treatment mainly includes bone grafting, the Masquelet and Illizarov techniques, and others, such as autologous and or allogeneic bone transplantation, artificial bone implantation, and bone transport and or extension. Prognosis has improved significantly, with continuous research being conducted to investigate bone defects and advance contemporary medical treatment. The complex repair process of bone requires the collaborative participation of various cells and tissues, and is easily affected by many factors. However, bone repair remains a challenge for orthopaedic trauma surgeons [4–6]. This retrospective study aimed to analyse patients with bone defects admitted to our hospital between 2010 and 2020 to explore the risk factors affecting the healing of defective bony non-union and to develop a nomogram model to predict the occurrence of this outcome.

2. Materials and methods

2.1. General information

The inclusion criteria for patients with bone defects were as follows: diagnosed between January 2010 and December 2020 and treated surgically at the authors' affiliated hospital; complete information available in the medical record system detailing the results of defect healing; and defective bony non-union in the bones of the extremities. Segmental bone defects are eliminated after shortening fusion or amputation and the Radiographic Union Score for Tibia (RUST) scoring criteria mainly apply to non-union of the long bones [7]; therefore, individuals who underwent treatment with short fusion or amputation, or those with craniofacial, scapular, spinal, or pelvic bone defects, were excluded. All patients included in this study were followed-up 1 year after the last definitive surgery. For example, patients who underwent induced membrane technique (Masquelet technique) would be followed-up 1 year after the second stage of bone graft and internal fixation. X-ray and CT images were collected to determine whether the defective bone non-union was healed 1 year postoperatively. In most cases, standard x-rays of anteroposterior and lateral views were used to diagnose the defects. For complex bone defects, 3D CT was used for evaluation of the defects.

A total of 305 patients with defective bony non-union were included in this study, of whom 101 were excluded due to partially or completely missing imaging or other data. Thus, 204 patients were ultimately included. The cohort included 171 males and 33 females with a mean age of 39.75 (standard deviation, 13.00) years. The mean body mass index was 22.95 ± 3.64 kg/m^2. Among the included patients, 29 were smokers, 18 were alcohol drinkers, 49 were non-physical labourers, and 21 had a previous comorbid systemic diseases (PCSD) such as hypertension, diabetes, osteoporosis, or syphilis. External fixation was used in 72 cases and internal fixation with, for example, intramedullary nails or plates, was used in 132 cases. The union rate (calculated by dividing the number of union groups by the total number of patients) of defective bony non-union was 51.3% 6 months postoperatively and 85.3% at the 1-year

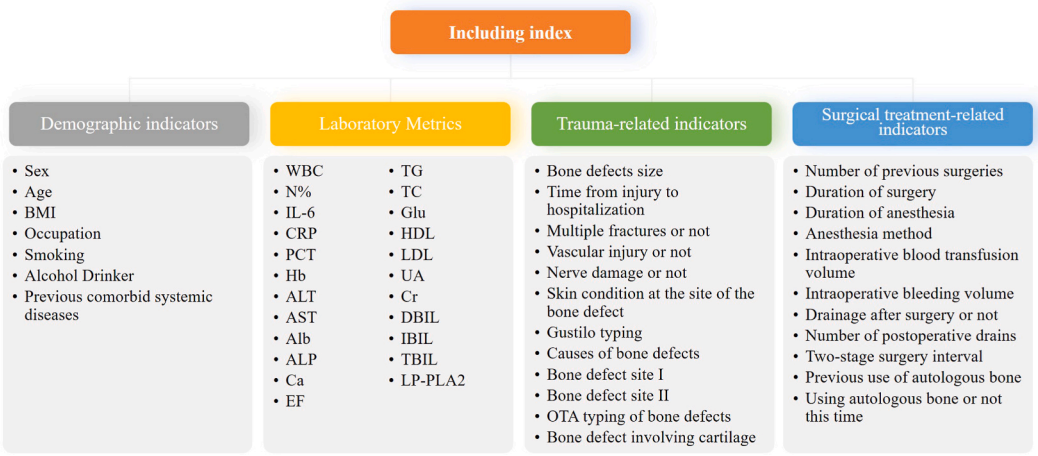

Fig. 1. Main observations. BMI: body mass index; WBC: white blood cell; N%: neutrophil percentage; IL-6: interleukin-6; CRP: C-reactive protein; PCT: procalcitonin; Hb: haemoglobin; ALT: alanine aminotransferase; AST: aspartate transaminase; Alb: albumin; ALP: alkaline phosphatase; Ca: calcium; EF: ejection fraction; TG: triglyceride; TC: total cholesterol; Glu: glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid; Cr: creatinine; DBIL: direct bilirubin; IBIL: indirect bilirubin; TBIL: total bilirubin; LP-PLA2: lipoprotein-associated phospholipase A2. Bone defect site I: mainly divided into upper and lower limbs; bone defect site II: mainly divided into epiphysis and diaphysis.

follow-up. The study strictly adhered to the Declaration of Helsinki and was approved by the Medical Ethics Committee of the authors' affiliated institutions (approval number, XJLL-KY-20222295). Given the retrospective nature of the study and the use of anonymised patient data, the requirement for informed consent was waived. Patients were afforded the opportunity to withdraw unconditionally during the trial.

2.2. Main observed indicators and interpretation

Four main indicator categories were included in this study: basic demographic characteristics, laboratory investigations, trauma-related factors, and surgical treatment-related factors (Fig. 1). According to the postoperative RUST scoring system [8,9] (Table 1), among the anterior, posterior, lateral, and medial regions, each cortex is scored from 1 to 3 as follows: 1 represents callus absent, fracture line visible; 2 represents callus present, fracture line visible; and 3 represents callus present, fracture line invisible. A total of four cases showed definite non-union and 12 showed definite union. Accordingly, patients were divided into two groups: union and non-union.

Patients were also grouped according to whether they performed physical or non-physical labour. Work that primarily required muscular activity or prolonged walking was defined as physical labour [10]. The body mass index was calculated as the weight (kg) divided by height squared (m^2) and classified according to the World Health Organization's classification criteria as follows: $\leq$18.49 kg/m^2, underweight; 18.50–24.99 kg/m^2, normal weight; 25.00–29.99 kg/m^2, overweight; and $\geq$30 kg/m^2, obese [11]. PCSD was determined based on the presence of other systemic diseases (such as hypertension, diabetes, and osteoporosis), as documented in the medical records. Patients who smoked $\geq$10 cigarettes per day and had not quit within the 4 weeks prior to surgical treatment were defined as smokers [12,13]. Alcohol drinkers were defined as those who consumed alcohol weekly, in excess of 28 units for males and 14 units for females, without quitting in the 4 weeks prior to surgery [12,13]. The time of pathogenesis was defined as the period from the time of injury to the last definitive procedure. Vascular injury was defined as a major type of vascular injury that required surgical intervention. Nerve injuries were primarily documented at discharge. Interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT) are inflammatory markers and their serum levels become elevated when infection is present. Bone defects were classified into three types based on the fracture classification system of the AO Foundation and or Orthopaedic Trauma Association: grade I, bone defect <50% of the diameter of the long bone; grade II, bone defect >50% of the diameter of the bone; and grade III, complete defect of the bone. Using radiographs, the size of the bone defect was measured in centimetres (cm) using the largest value of the recorded extent of the defect or the largest measurement in the cortical discontinuity on four cortices [7]. Two classifications of bone defect sites were used in this study: upper and lower extremities were classified based on whether the affected bone was weight-bearing; and metaphyseal and diaphysis defects were classified based on the blood supply to the bone tissue. Metaphyseal defects at both ends of the long bone are noted; such defects have a relatively richer blood supply compared with diaphyseal defects [14]. The criteria for union were assessed by two senior orthopaedic surgeons based on a review of the imaging data of patients 1 year after surgery. Union was present when at least three of the four cortices (anterior, posterior, internal, and external) formed a bridging callus and the RUST score was >10; if not, the case was defined as one of non-union [7,15,16].

2.3. Statistical analysis

SPSS Statistics for Windows version 23.0 (IBM Corporation, Armonk, NY, USA) and R-Studio version 4.2.1 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) software was used to conduct the analyses. The Shapiro–Wilk method was used to test the normality of the data. Continuous variables conforming to a normal distribution were expressed as arithmetic mean $\pm$ standard deviation, continuous variables with skewed distribution as median (quartiles), and count data as frequency (percentage). The *t*-test or Welch's *t*-test was used for normally distributed continuous variables and the Wilcoxon rank-sum test for skewed continuous variables. The chi-squared test was used to compare differences in count data between the groups. Statistically significant variables were included in the multivariate logistic regression model to explore the independent risk factors affecting defective unions. A nomogram-based prediction model was simultaneously constructed. The accuracy and stability of the model were assessed using receiver operating characteristic and calibration curves. Decision curve analysis was used to assess clinical applicability. All tests were two-sided, and differences with $P < 0.05$ were considered to be statistically significant, that is, that the included factor effected defective bony non-union. An area under the receiver operating characteristic curve (AUC) of >0.9 was considered to indicate good predictive ability of the model and an AUC of between 0.7 and 0.9 was considered to indicate average predictive ability.

Table 1
Radiographic Union Score for Tibia (RUST) Scoring system.

score	with callus	visible fracture line
1	No	Yes
2	Yes	Yes
3	Yes	No

3. Results

3.1. Univariate analysis of risk factors affecting the healing of defective bony non-unions

Results of the univariate analysis revealed that age, occupation (physical labourers or non-physical labourers), PCSD, smoking status, alcohol consumption, IL-6, CRP, PCT, alkaline phosphatase, blood calcium ion, glucose, and uric acid levels, bone defect size (BDS), and postoperative duration were correlated with healing of defective bony non-unions (all $P < 0.05$). The probability of non-union in patients aged >40 years was 6.5 times higher than that in those aged <40 years. The probability of non-union occurring in patients aged between 40 and 50, 50 and 60, and >60 years was 4.7, 7.3, and 18 times higher, respectively, than that in patients <40 years old. The remaining factors were not statistically significant ($P > 0.05$; Tables 2-6).

3.2. Multivariate analysis of risk factors affecting the healing of defective bony non-unions

Statistically significant variables in the univariate analysis were analysed using multivariate logistic regression, as summarised in Table 7. PCSD (e.g., hypertension, diabetes, and osteoporosis), smoking status, IL-6, CRP, and glucose levels, and BDS were associated with healing of defective bony non-unions ($P < 0.05$). Multivariate logistic analysis revealed that the incidence of defective bony non-union in smokers was 11.7 times greater than that in nonsmokers (odds ratio [OR], 11.723 [95% confidence interval (CI), 2.452–73.654]; $P = 0.004$). The incidence of defective bony non-union was nine times higher in patients with PCSD than in those without (OR, 9.062 [95% CI, 1.409–71.92]; $P = 0.024$). A 1-cm increase in BDS resulted in a 31.5% increased incidence of defective bony non-union (OR, 1.315 [95% CI, 1.044–1.696]; $P = 0.024$).

3.3. Development and assessment of the predictive model

Significant variables in the multivariate analysis were used to develop a predictive model and depicted as a nomogram (Fig. 2). The total score was calculated and the score for each included variable is shown in Fig. 2. The total score was used to assess the incidence of defective bony non-union. The receiver operating characteristic curve was plotted based on the nomogram model (Fig. 3). The value of the AUC of the prediction model was 0.95 (95% CI, 0.894–0.993), which demonstrates that the accuracy of the prediction model was

Table 2
The basic demographic characteristics of patients with defective bony non-union.

	Bone defect union at 12 months postoperatively			
	non-union group	union group	union rate	P value
	n = 30	n = 174	%	
sex, n%				0.07
male	29(96.7)	142(81.6)	83	
female	1(3.3)	32(18.4)	97	
age (y)	49.63 ± 9.34	38.04 ± 12.80	85.3	**<0.01**
age, n%				**<0.01**
<20	0(0.0)	17(9.8)	100	
20-30	1(3.3)	30(17.2)	96.8	
30-40	3(10.0)	40(23.0)	93	
40-50	11(36.7)	51(29.3)	82.3	
50-60	10(33.3)	30(17.2)	75	
≥60	5(16.7)	6(3.4)	54.5	
BMI(kg/m^2)	23.03 ± 2.86	22.94 ± 3.76	85.3	0.9
BMI, n%				0.57
<18.5	1(3.3)	15(8.6)	93.8	
18.5–25.0	21(70.0)	114(65.5)	84.4	
25.0–30.0	8(26.7)	40(23.0)	83.3	
≥30.0	0(0)	5(2.9)	100	
Occupation, n%				**<0.01**
physical labor	16(53.3)	139(79.9)	89.7	
non-physical labor	14(46.7)	35(20.1)	71.4	
PCSD, n%				**<0.01**
no	19(63.3)	164(94.3)	89.7	
yes	11(36.7)	10(5.7)	10.3	
smoking, n%				**<0.01**
no	17(56.7)	158(90.8)	90.3	
yes	13(43.3)	16(9.2)	55.2	
alcohol drinkers, n%				**0.01**
no	23(76.7)	163(93.7)	87.6	
yes	7(23.3)	11(6.3)	61.1	

Note: Normally distributed continuous variables are expressed as mean ± standard deviation and non-normally distributed continuous variables as median (quartiles).BMI: body mass index; PCSD: previous comorbid systemic diseases.

Table 3
Results of laboratory tests for patients with defective bony non-union.

	non-union group	union group	P value
	n = 30	n = 174	
WBC(*10^9/L)	6.26(4.83,7.24)	6.04(5.19,7.11)	0.8
N%	0.62(0.56,0.65)	0.60(0.53,0.65)	0.32
IL-6(pg/ml)	8.54(5.55,18.74)	3.26(2.15,5.32)	**<0.01**
CRP(mg/L)	8.30(4.81,13.29)	2.09(0.91,3.49)	**<0.01**
ESR(mm/h)	8.50(4.75,14.00)	8.00(5.00,14.75)	0.96
PTC(ng/ml)	0.07(0.04,0.09)	0.03(0.02,0.04)	**<0.01**
Hb(g/L)	140(127.25,150.50)	137.50(123.00,149.00)	0.48
AST(IU/L)	20.00(15.75,37.00)	21.00(15.00,30.25)	0.53
ALT(IU/L)	24.50(16.25,45.25)	22.00(15.00,33.00)	0.27
Alb(g/L)	40.90(38.68,44.65)	41.40(38.58,45.20)	0.67
ALP(IU/L)	79.00(68.00,89.25)	86.50(71.75,111.25)	**0.04**
Ca(mmol/L)	2.17(2.05,2.28)	2.26(2.17,2.34)	**0.01**
LP-PLA2(ng/ml)	139.29(109.62,257.89)	140.59(106.83,172.22)	0.61
TG(mmol/L)	1.32(0.68,1.83)	1.30(0.83,2.64)	0.55
TC(mmol/L)	4.68 ± 1.36	4.40 ± 1.01	0.61
Glu(mmol/L)	6.74(5.38,7.70)	4.89(4.53,5.30)	**0.01**
HDL(mmol/L)	1.31 ± 0.41	1.09 ± 0.33	0.22
LDL(mmol/L)	2.37(1.83,3.02)	2.89(2.36,3.35)	0.24
UA(umol/L)	348.76 ± 107.36	309.13 ± 92.06	**0.04**
Cr(umol/L)	74.67 ± 19.24	72.58 ± 16.86	0.08
DBIL(umol/L)	4.00(2.96,5.50)	4.25(2.70,6.00)	0.78
LBIL(umol/L)	5.40(4.35,8.25)	5.90(4.20,8.20)	0.95
TBIL(umol/L)	9.75(7.60,12.63)	10.85(7.43,14.15)	0.65
EF	0.58(0.58,0.60)	0.58(0.57,0.58)	0.4

Note: Normally distributed continuous variables are expressed as mean ± standard deviation and non-normally distributed continuous variables as medians (quartiles).
WBC: white blood cell; N%: neutrophil percentage; IL-6: interleukin-6; CRP: C-reactive protein; PCT: procalcitonin; Hb: haemoglobin; ALT: alanine aminotransferase; AST: aspartate transaminase; Alb: albumin; ALP: alkaline phosphatase; Ca: calcium; EF: ejection fraction; TG: triglyceride; TC: total cholesterol; Glu: glucose; HDL: high-density lipoprotein; LDL: low-density lipoprotein; UA: uric acid; Cr: creatinine; DBIL: direct bilirubin; IBIL: indirect bilirubin; TBIL: total bilirubin; LP-PLA2: lipoprotein-associated phospholipase A2.

very high. The calibration curve (Fig. 4) distributed around the diagonal indicated an excellent predictive ability. Decision curve analysis (Fig. 5) revealed good clinical benefit.

4. Discussion

The mean age of the non-union group was significantly higher than that of the union group at the 1-year postoperative follow-up, and the healing rate tended to decrease with age, especially in patients aged >40 years. Further analysis revealed that patients aged >40 years were 6.5 times more likely to develop defective bony non-union than those aged <40 years. Moreover, patients aged >60 years were 5.6 times more likely to develop defective bony non-union than those aged <60 years and 18 times more likely than those aged <40 years. These findings suggested that age is a risk factor for defective bone healing. This risk may be related to the fact that young patients have significantly higher concentrations of proteins and factors that promote bone formation or mineralisation (including proteases, osteocalcin, osteopontin, and mesenchymal stem cells) than older patients [17–19]. Clark et al. considered that many biological changes in older people—such as immune response, vascularisation and angiogenesis, and osteochondral cells and their progenitors—affect the healing of defective bony non-union [20]. However, through multivariate logistic regression analysis, the current study found that age was not an independent factor for defective bone union. Further analysis revealed that age is related to PCSD: as age increases, so does the probability of having PCSD. Therefore, we prefers to consider age to be a confounding factor. A retrospective matched-pair study conducted by Tanner et al. also found that advanced age alone does not influence the outcome of non-union [21], and Zhang suggested that age does not negatively affect the union of bone defects [22]. However, an age >40 years should be considered a negative influencing factor for non-union and patients who are ≥40 years should be treated with caution [21, 23]. Therefore, the effect of age on bone healing remains controversial.

A total of 21 patients in the study had underlying diseases, including five with hepatitis B, two with syphilis, six with hypertension, five with diabetes mellitus, and three with osteoporosis. The overall union rate in such patients was 10.3%, much lower than that in patients without underlying systemic diseases (Fig. 6). Fracture healing is a complex pathological process involving multiple factors. According to the diamond concept of fracture healing [24], the process of healing requires both a good mechanical environment and a suitable chemical environment. Numerous underlying diseases inhibit the normal physiological function of osteoblasts [25–27] as well as produce or activate osteoclasts [27,28], or result in a poor nutritional supply due to intravascular pathologies [16]. These activities promote bone loss. Moreover, the drugs used to treat these underlying diseases can inhibit callus formation [29].

Xu et al. [13] reported that the incidence of defective bony non-union in patients who stop smoking 4 weeks before surgery was not statistically different from that in nonsmoking patients; therefore, the current study defined smokers as those who continued to smoke

Table 4
Injury factors associated with defective bony non-union.

	non-union group	union group	union rate(%)	P value
	n = 30	n = 174		
bone defects size (cm)	8.0(5.75,10.25)	5.0(4.0,6.25)	85.3	**<0.01**
time from injury to hospitalization (months)	5.5(2.75,15.5)	8(4,15)	85.3	0.37
causes of bone defects, n%				0.50
osteomyelitis	14(46.7)	65(37.4)	82.3	
non-union	1(3.3)	11(6.3)	91.7	
trauma	15(50.0)	90(51.7)	85.7	
occupancy and others	0(0.0)	8(4.6)	100	
multiple fractures, n%				0.78
no	18(60.0)	109(62.6)	85.8	
yes	12(40.0)	65(37.4)	84.4	
vascular injury, n%				0.55
no	21(70.0)	130(75.1)	86.1	
yes	9(30.0)	43(24.9)	82.7	
nerve damage, n%				0.46
no	22(73.3)	138(79.3)	86.3	
yes	8(26.7)	36(20.7)	81.8	
skin condition at the site of the bone defects, n%				0.94
closed	17(56.7)	104(59.8)	86	
sinus tract	2(6.7)	10(5.7)	83.3	
opened	11(36.7)	60(34.5)	84.5	
bone defect site I, n%				0.12
upper extremity	5(16.7)	11(6.4)	68.6	
lower extremity	25(83.3)	161(93.6)	86.6	
bone defect site II, n%				0.24
epiphysis	5(16.7)	46(26.7)	90.2	
diaphysis	25(83.3)	126(73.3)	83.4	
OTA typing of bone defects[a], n%				0.47
II	8(26.7)	58(33.3)	87.9	
III	22(73.3)	116(66.7)	84.1	
bone defect involving cartilage, n%				0.26
no	26(86.7)	163(94.2)	86.2	
yes	4(13.3)	10(5.8)	71.4	

Note: Non-normally distributed continuous variables are expressed as medians (quartiles) and count data are expressed as frequencies (percentages).
[a] Orthopaedic Trauma Association typing of bone defects without type I was included.

Table 5
Factors associated with surgery for defective bony non-union.

	non-union group	union group	union rate	P value
	n = 30	n = 174	(%)	
number of previous surgeries(times)	2.0(1.0,3.0)	2.0(1.0,3.0)	85.3	0.97
duration of surgery(min)	155.0(123.75,178.00)	160.00(125.00,205.00)	85.3	0.55
duration of anesthesia(min)	205.00(166.25,230.25)	210.00(170.00,260.00)	85.3	0.55
two-stage surgery interval(weeks)	11.50(8.00,16.00)	12.00(8.00,20.00)	85.3	0.35
intraoperative bleeding volume(ml)	300(137.50,400)	300(200,600)	85.3	0.19
number of postoperative drains	1(1,2)	1(1,2)	85.3	0.76
anesthesia method, n%				0.48
non-general anesthesia	10(33.3)	47(27.0)	82.5	
general anesthesia	20(66.7)	127(73.0)	86.4	
previous use of autologous bone, n%				0.88
no	28(93.3)	161(92.5)	85.2	
yes	2(6.7)	13(7.5)	86.7	
using autologous bone or not this time, n%				0.29
no	7(23.3)	24(13.8)	77.4	
yes	23(76.7)	150(86.2)	86.7	
drainage after surgery or not, n%				0.87
no	2(6.7)	7(4.0)	77.8	
yes	28(93.3)	167(96.0)	85.6	

Note: Non-normally distributed continuous variables are expressed as medians (quartiles); count data are expressed as frequency (percentage).

within 4 weeks of their surgery. Patients who smoked had a significantly higher risk of developing defective bony non-union than those who did not ($P < 0.01$; OR, 7.55). This finding is consistent with those of previous studies [13,30,31], and can be attributed to several factors. First, tobacco contains nicotine, which causes vasoconstriction and reduces blood supply [13]. Second, nicotine can directly

Table 6
Union rate for patients with defective bone discontinuity at different periods.

	total	non-union group	union group	union rate (%)	*P* value
6 months	199	97	102	51.3	<0.01
12 months	204	30	174	85.3	

Table 7
Results of the multivariate logistic regression at 12-months postoperatively.

	B	S.E.	Wald	Sig.	Exp(B)	95%CI for Exp(B)	
						Lower	Upper
PCSD	2.204	0.98	5.06	0.024	9.062	1.328	61.835
smoking	2.462	0.845	8.494	0.004	11.723	2.239	61.374
IL-6	0.131	0.049	7.08	0.008	1.141	1.035	1.257
CRP	0.232	0.083	7.922	0.005	1.261	1.073	1.483
PCT	2.974	1.636	3.306	0.069	19.575	0.793	483.089
Glu	0.652	0.262	6.184	0.013	1.919	1.148	3.207
BDS	0.274	0.122	5.076	0.024	1.315	1.034	1.669

Note: IL-6: interleukin-6; CRP: C-reactive protein; PCT: procalcitonin; Glu: glucose; BDS: bone defect size; PCSD: previous comorbid systemic diseases.

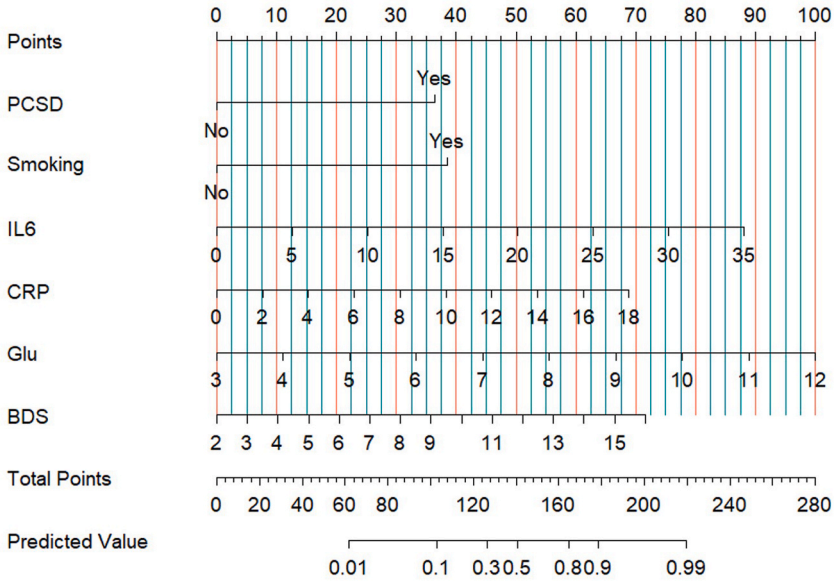

Fig. 2. The nomogram-based prediction model for defective bony non-union. IL-6: interleukin-6(pg/ml); CRP: C-reactive protein(mg/L); PCT: procalcitonin(ng/ml); Glu: glucose(mmol/L); BDS: bone defect size(cm); PCSD: previous comorbid systemic disease; predicted value: the rate of incidence of defective bony non-union.

alter various cytokine genes (e.g., the vascular endothelial growth factor and bone morphogenetic protein genes) associated with angiogenesis or osteoblast differentiation, thereby inhibiting skeletal angiogenesis and callus formation [32]. In addition, smoking produces carbon monoxide and hydrogen cyanide: the former reduces the oxygen-carrying capacity of red blood cells and the latter prevents aerobic metabolism by inhibiting cytochrome *c* oxidase [13].

Univariate analysis revealed that the median blood levels of IL-6, CRP, PCT, glucose, and uric acid were higher in the non-union group than in the union group. Conversely, the median calcium ion concentration and alkaline phosphatase level in the blood were lower in the non-union group than in the union group. Multivariate analysis revealed statistically significant differences in the IL-6 and CRP levels between the two groups. Further analysis revealed that the groups with up-regulated IL-6, CRP, and PCT levels (beyond the upper limit of the normal range) had 12.8, 16.4, and 21.18 times higher risks, respectively, for defective bony non-union than that of the normal group (95% CI, 5.15–31.99, 8.32–53.87, and 6.45–41.45, respectively; Fig. 7). This observation may be related to the fact that infection inhibits neovascularisation around the bone defect [33] and thus affects the delivery of cytokines and nutrients that promote bone formation, thereby altering the local microenvironment. Moreover, many inflammatory factors, such as IL-6, can activate and enhance the function of osteoclasts while inhibiting their function [34–36].

BDS was identified as an independent risk factor for defective bony non-union, with larger defects associated with a greater risk of

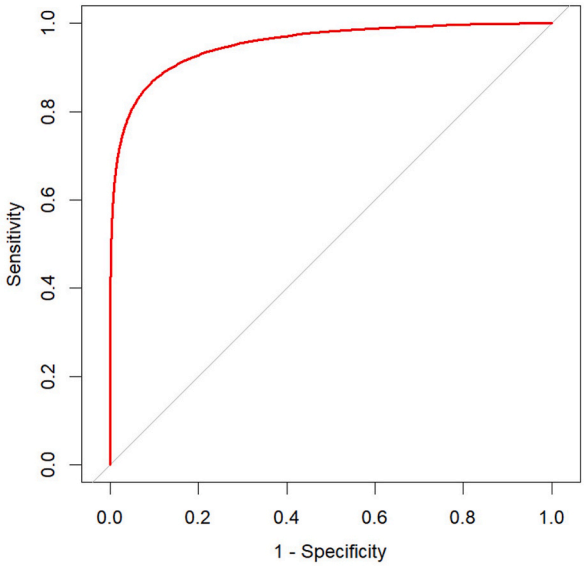

Fig. 3. Receiver operating characteristic curve for the nomogram-based prediction model.

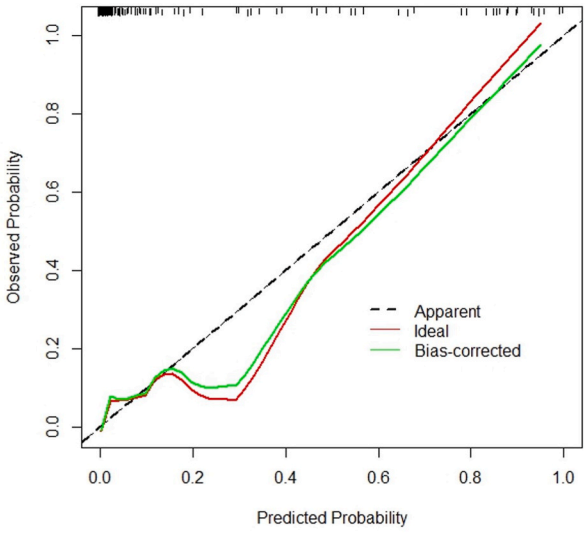

Fig. 4. Calibration curves for the nomogram-based prediction model.

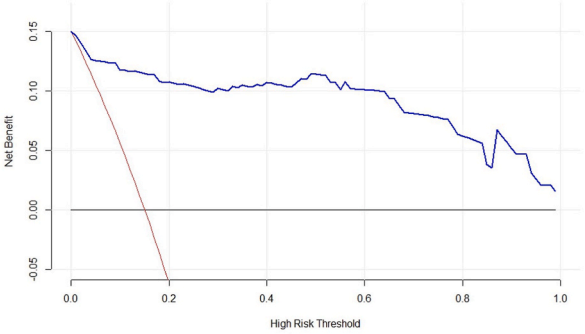

Fig. 5. Decision curve analysis for the nomogram-based prediction model.

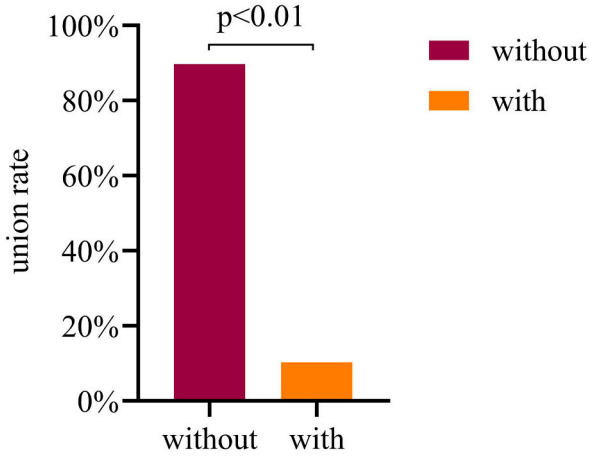

Fig. 6. The healing rate for patients with or without previous comorbid systemic disease (PCSD).

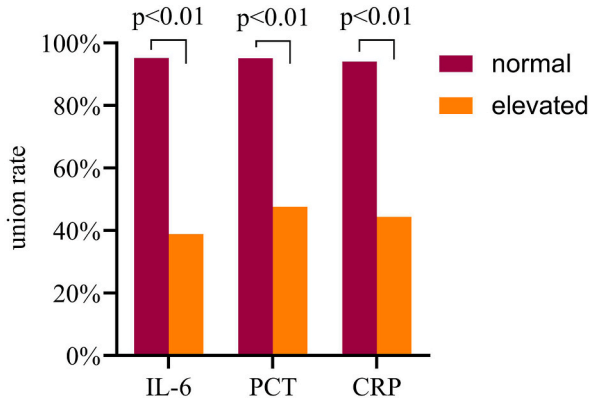

Fig. 7. The healing rate for patients with and without elevated levels of interleukin-6(IL-6), C-reactive protein (CRP), and procalcitonin(PCT).

non-union. In the present study, the mean defect lengths of the union and non-union groups were found to be 5.57 ± 2.34 cm and 8.43 ± 3.40 cm, respectively. An increase in the BDS of 1 cm resulted in a 31.5% increase in the incidence of defective bony non-union (OR, 1.315 [95% CI, 1.044–1.696]; P = 0.024). However, some researchers have found that BDS does not influence the incidence of defective bony non-union [37]; this discrepancy may be explained by the different treatment modalities used(e.g., the Masquelet and Illizarov techniques), which account for the different percentages in each group. The healing time of bone defects treated using the Ilizarov technique is positively correlated with the length of the bone defect [38], whereas the healing time of bone defects treated using the Masquelet technique is not [39]. Mineralisation and haematomas are likely to occur in extensive bone defects, thereby preventing healing. Therefore, this conclusion must be interpreted with caution, and real-world studies using larger sample sizes are needed for continued development. In addition, due to the limited data information in this retrospective study, some important factors, such as vascular and nerve injury, have not been found to affect the healing of defective bony non-union.

5. Limitations

Several limitations must be mentioned. First, data compilation was incomplete because of the retrospective study, and some factors could not be analysed. Second, the incidence of defective bony non-union is relatively low, the current single-centre study included a small number of cases, factors such as defect site and treatment modality could not be investigated further. In a follow-up study, a multicentre, real-world study with a large sample size will be conducted in conjunction with other trauma centres. Simultaneously, we will focus on the mechanisms of PCSD and BDS that are related to the healing of defective bony non-union.

6. Conclusion

This retrospective study revealed that PCSD, smoking, IL-6 and CRP levels, and BDS were independent risk factors that affected the healing of defective bony non-union. The nomogram-based prediction model we developed may provide excellent guidance for the development of treatment protocols and help reduce the incidence of defective bony non-union.

Declaration

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Data availability statement

The data used in this study will be made available on request.

CRediT authorship contribution statement

Jingdi Chen: Writing – review & editing, Writing – original draft, Software, Data curation, Conceptualization. **Wei Wu:** Writing – original draft. **Chunxing Xian:** Methodology, Investigation. **Taoran Wang:** Investigation, Formal analysis. **Xiaotian Hao:** Formal analysis. **Na Chai:** Resources, Formal analysis. **Tao Liu:** Methodology, Conceptualization. **Lei Shang:** Software, Methodology. **Bo Wang:** Software, Formal analysis. **Jiakai Gao:** Resources. **Long Bi:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Long Bi reports financial support was provided byFoundation for Innovative Research Groups of the National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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