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Prediction of fracture nonunion leading to secondary surgery in patients with distal femur fractures

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Aims

Several previously identified patient-, injury-, and treatment-related factors are associated with the development of nonunion in distal femur fractures. However, the predictive value of these factors is not well defined. We aimed to assess the predictive ability of previously identified risk factors in the development of nonunion leading to secondary surgery in distal femur fractures.

Methods

We conducted a retrospective cohort study of adult patients with traumatic distal femur fracture treated with lateral locking plate between 2009 and 2018. The patients who underwent secondary surgery due to fracture healing problem or plate failure were considered having nonunion. Background knowledge of risk factors of distal femur fracture nonunion based on previous literature was used to form an initial set of variables. A logistic regression model was used with previously identified patient- and injury-related variables (age, sex, BMI, diabetes, smoking, periprosthetic fracture, open fracture, trauma energy, fracture zone length, fracture comminution, medial side comminution) in the first analysis and with treatment-related variables (different surgeon-controlled factors, e.g. plate length, screw placement, and proximal fixation) in the second analysis to predict the nonunion leading to secondary surgery in distal femur fractures.

Results

We were able to include 299 fractures in 291 patients. Altogether, 31/299 fractures (10%) developed nonunion. In the first analysis, pseudo-R^2 was 0.27 and area under the receiver operating characteristic curve (AUC) was 0.81. BMI was the most important variable in the prediction. In the second analysis, pseudo-R^2 was 0.06 and AUC was 0.67. Plate length was the most important variable in the prediction.

Conclusion

The model including patient- and injury-related factors had moderate fit and predictive ability in the prediction of distal femur fracture nonunion leading to secondary surgery. BMI was the most important variable in prediction of nonunion. Surgeon-controlled factors had a minor role in prediction of nonunion.

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Introduction

Distal femur fractures account for 0.4% of all fractures in adults. The majority of these are fragility fractures occurring in women after the age of 60 years.[1,2] The high one-year mortality rate of 25% to 35% in people aged over 60 years with distal femur fractures is comparable to the mortality of proximal femur fractures.[3-7]

Although lateral locking plates are widely used for the treatment of distal femur fractures, there is concern regarding high nonunion risk with associated plate failures.[8-11] Several studies report high

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nonunion rates (10 to 22%) with modern lateral locking plates.[9,10,12-19] In a literature review, 75% of implant failures occurred within three months of operation due to plate fatigue secondary to delayed union and continuous movement of the fracture site.[11]

Development of distal femur fracture nonunion is often multifactorial, involving different patient-, injury-, and treatment-related risk factors. The patient- and injury-related risk factors for distal femur fracture nonunion described in the literature include obesity,[18,20] diabetes,[12] infection,[4,18,20] smoking,[15] open fracture,[9,12,14,18,20-22] fracture comminution,[9,10,17,22] or medial metaphyseal fracture comminution.[9] Additionally, the stiffness of the plate construction impacts the interfragmentary motion in the fracture site, which might affect the healing environment of the bone.[13,23,24] Plate material,[10,11,13,18,25] plate length,[9,12] screw selection,[26] and screw placement[10] have been reported to affect fracture healing.

Despite numerous factors associated with the development of distal femur fracture nonunion, the predictive value of these factors is not well defined in earlier literature. To fill this knowledge gap, we assessed the predictive ability of previously identified patient-, injury-, and treatment-related risk factors in the development of nonunion leading to secondary surgery in patients with distal femur fractures.

Methods

This retrospective cohort study was conducted in a level 1 trauma centre at Helsinki University Hospital with a catchment population of around one million for these fractures. After receiving permission from our institutional review board, we identified all patients with a distal femur fracture treated at our institution between 2009 and 2018.

The detailed inclusion and exclusion criteria are shown in Table I. We included patients aged 16 years or older with traumatic, AO Foundation/Orthopaedic Trauma Association (AO/OTA) classification type 33A2, 33A3, and 33 C distal femur fractures treated with an anatomical lateral locking plate.[27] The surgeries were performed at our institution within one month after injury. Patients with a stress fracture, a pathological fracture, an epicondylar or subchondral fracture, or ligament avulsions (i.e. AO/OTA 33A1 types) were excluded.

All fractures affected the metaphyseal area of the distal femur. The metaphyseal area of the distal femur was defined with a square method as proposed by Urs Heim.[27,28]

We defined a fracture as nonunion only when a patient had a secondary surgical intervention to promote fracture healing. In addition, a reoperation due to plate failure at least three months after the primary operation, and without a new trauma, was considered a fracture nonunion.

Table I. Inclusion and exclusion criteria used in the study.

Criteria
Inclusion
Age ≥ 16 years
AO/OTA type 33A2, 33A3, and 33C distal femur fracture
Fracture located in the metaphyseal area of the distal femur (square method)
Operative treatment in Helsinki University Hospital with a distal femur anatomical lateral locking plate from 2009 to 2018
Operative treatment within one month after trauma
Exclusion
Stress fracture
Pathological fracture
Subchondral fracture
Ligament avulsion in distal femur (AO/OTA type 33A1)
Treatment with double-plating or with combined plate and nail method
Non-surgical treatment
Treatment with an unconventional plate (other than distal femur plate)
Patients with insufficient follow-up data to assign fracture healing status

AO/OTA, AO Foundation/Orthopaedic Trauma Association.

The radiological union in the radiograph was defined as a bridging callus consolidation on three of four cortices of the fracture site and disappearance of fracture lines during the follow-up. We excluded patients whose follow-up was too short to determine the final healing status of the fracture. If the radiological follow-up ended before the fracture was radiologically united in radiographs, we assessed the patient records at least 12 months after the injury. If the patient records showed signs of mobilization and no clinical signs of nonunion, such as pain at the fracture site, and these patients did not come back to our institution after 12 months, we assumed that the fracture had been healed, and those patients were included in the study as having fracture union. Helsinki University Hospital is the centre responsible for treating femur fracture nonunions in the Helsinki metropolitan area, so we assumed that distal femur fracture nonunions had not been treated elsewhere. We excluded patients who died before the fracture was healed either according to radiographs or patient records during the first 12 months after the injury.

Surgical treatment. The two plate types used in this study were 4.5 mm stainless steel Variable Angle LCP Curved Condylar Plate System (VA-LCP; DePuy Synthes, USA) and titanium alloy Less Invasive Stabilization System LCP Distal Femur Plate (LISS; DePuy Synthes). The surgeries were performed by senior orthopaedic trauma surgeons or orthopaedic residents with at least three years of surgical experience. Plate type, screw types, and proximal fixation used in the operation were chosen by the treating surgeon. The methods for proximal fixation were 4.5 mm locking and cortical screws, as well as cables and 3.5 mm proximal locking attachment plates for peri-implant fractures. The non-weightbearing period was eight to ten

Table II. Data set used in the study.

Data variables
Patient-related factors (first analysis)
Age at time of injury
Sex
BMI
History of diabetes
Smoking history
Injury-related factors (first analysis)
AO/OTA classification
Periprosthetic fracture*
Open/closed fracture
Trauma energy (high or low)*
Fracture zone length*
Segmental comminution (AO/OTA A3.2, A3.3, C2, C3)
Medial comminution of the fracture*
Treatment-related factors (second analysis)†
Plate length in millimetres
Plate working length
Empty holes adjacent to the fracture site
Plate span ratio
Proximal plate length
Proximal fixation mode
Proximal cortices
Locking screws in the fracture segment

*See text for definition.
†See Figure 1 for definition.
AO/OTA, AO Foundation/Orthopaedic Trauma Association.

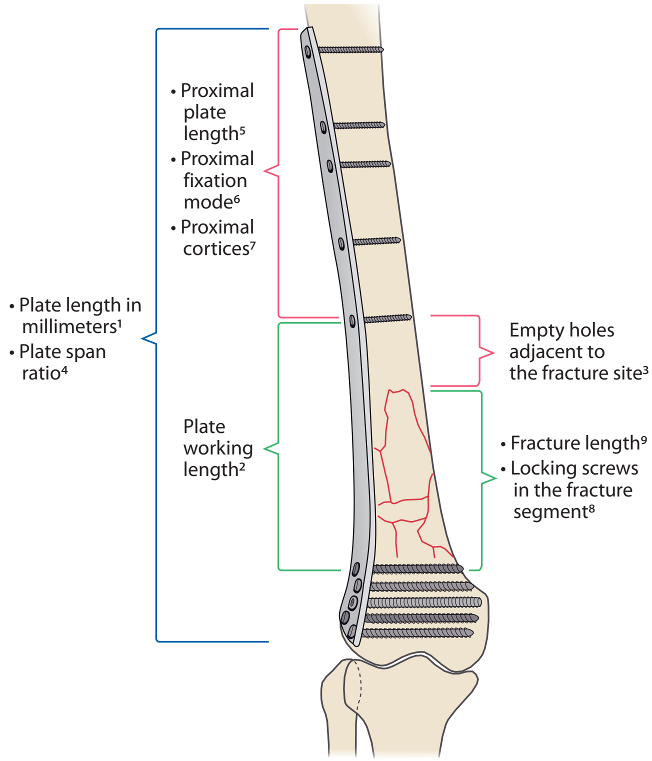

Fig. 1

Treatment-related variables recorded from postoperative radiographs. The known plate length in mm was used to calibrate the radiograph before the measurements. 1) Measured using the number of plate shaft holes first, and then in mm as given by the manufacturer. 2) Defined as distance (mm) from the nearest proximal screw to the nearest distal screw on each side of the fracture. 3) Empty holes in the plate adjacent to the fracture site (i.e. on the intact part of the femur). 4) Plate span ratio: defined as the ratio of the plate length to the fracture length. 5) Defined as the number of plate holes proximal to the fracture lines in radiograph. 6) Proximal fixation modes are: a) locking screws, b) locking + cortical screws (hybrid), c) cortical screws, or d) cables with or without screws. 7) Defined as the number of proximal cortices fixed with screws or cables above the fracture segment. One cable was defined to correspond to a bicortical screw (i.e. purchase of 2 cortices). Sufficient proximal fixation was defined as purchase of 8 or more cortices (e.g. minimum of 4 bicortical screws) and insufficient proximal fixation as purchase of fewer than 8 cortices. 8) Number of locking screws in the plate crossing the fracture segment. 9) Fracture length was measured from the lowest point of fracture line to the highest point of fracture line in radiograph when fracture was reduced.

weeks, followed by half-weightbearing. Weightbearing as tolerated was allowed from week 10 to 12 onwards depending how the fracture had healed. Typically, the follow-up visits were at six and 12 weeks at the outpatient clinic. We had no routine protocol for follow-up visits after 12 weeks, but the follow-up was continued until the patients were mobilized and the fracture showed healing on the radiograph. If patients were discharged already at 12 weeks when the fracture healing was still in progress, they were able to contact our clinic if they had problems with pain or mobilization.

Data collection. Details of the data variables used in this study are shown in Table II. The patient-related factors were age, sex, BMI, history of diabetes, and smoking history.

The details of injury-related factors were as follows: distal femur fractures were classified according to the AO/OTA classification system 2018.[27] High-energy trauma was defined as a motor vehicle accident or a fall from a height of ≥ 1 metre. Low-energy trauma was defined as a fall from a height of < 1 metre. Open fracture was defined as a fracture with a break in the skin near the broken bone. The definition for a periprosthetic fracture was a distal femur fracture above a knee prosthesis. Fractures underneath hip prostheses were included if the fracture line reached the metaphyseal area of the distal femur defined by the square method. However, these fractures were not classified as periprosthetic fractures due to how far the hip prosthesis was positioned from the actual fracture site.

Segmentally comminuted fractures were defined as A3.2, A3.3, C2, and C3 fractures according to the AO/OTA classification. Fracture was defined as medially comminuted when more than one fracture line reached the medial cortex on the radiograph, forming one or more loose bone fragments on the medial side. Fracture zone length was measured from the postoperative radiographs where the fracture was reduced as shown in Figure 1. The known plate length in mm was used to correctly calibrate the radiograph before the measurements were done.

Treatment-related factors were measured from postoperative radiographs. The details of treatment-related factors are shown in Figure 1. The first author (HS) assessed the parameters shown in Figure 1, as well as union status of the fracture from postoperative radiographs, and collected all the other parameters used in the analyses from electronic patient records.

Statistical analysis. Our statistical analysis was based on a predictive approach, and we followed the guidelines of Harrell[29] and Heinze et al.[30] We published our statistical protocol at clinicaltrials.gov before any analyses were carried out.[31] We used logistic regression, since our outcome is binary. Our analysis was three-fold. In the first analysis, we modelled the probability of nonunion using patient- and injury-related variables in logistic regression. In the second analysis, we used treatment-related variables. The third analysis was a combined model that combined the three most important variables from the first analysis with the two most important variables from the second model.

Background knowledge based on previous literature was used to form an initial set of variables potentially predictive for fracture nonunion. Variable missingness was assessed. We assumed Missing Completely at Random (MCAR) for any missing data, and multiple imputation was used. Imputation was based on both predictors and outcome variable. Redundancy analysis was then performed to assess any collinearity between predictors, and data reduction was performed. Binary variables with uneven distribution were critically assessed and excluded from the final variable set if deemed feasible. Model fitting was done with imputed datasets. For fitted models, Nagelkerke's pseudo-R^2 was estimated and used to interpret the applicability of baseline predictors. Variable importance was also assessed using Wald chi-squared test minus degrees of freedom. Multiplicity was not consid-ered since we were not focusing on single regression coefficients, nor did we have specific multiple testing. We performed no univariate screening or stepwise analysis. All models were built a priori based on previous litera-ture, and performance of full models was assessed. When appropriate, associated p- values were calculated. Anal-ysis was done with RStudio (R Foundation for Statistical Computing, Austria) using rms package.

Results

In total, 380 distal femur fractures were treated with a lateral locking plate at our institute during the study period. Altogether, 299 fractures in 291 patients fulfilled the inclusion criteria. The flowchart of the study and number of excluded patients are presented in Figure 2. We had to exclude 74 patients due to insufficient follow-up data. Of these, 57 died before the fracture healed during the first 12 months. Additional 17 patients

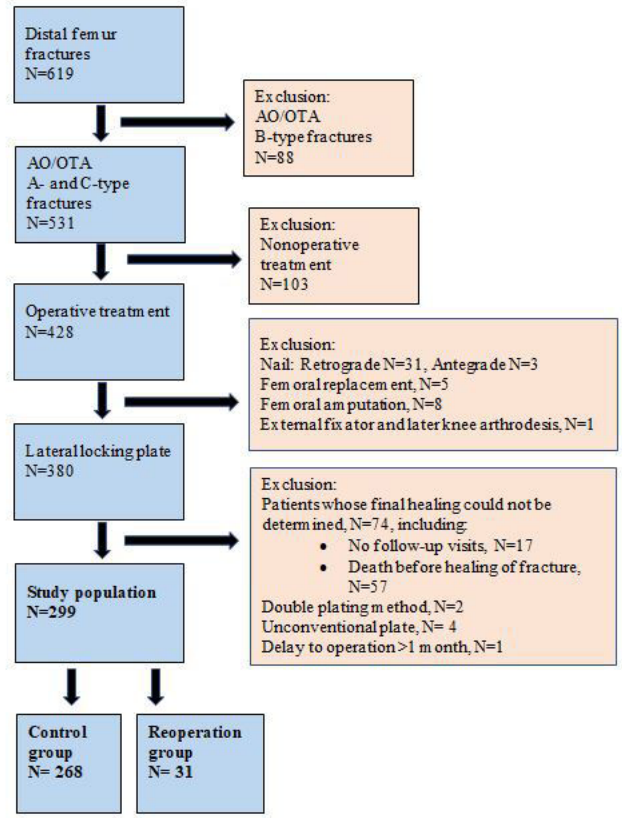

Fig. 2

Flowchart of all distal femur fractures.

had no follow-up data (five lived abroad, two were lost to follow-up after three months for unknown reasons, and they had not used any public medical service after that, and ten lived or had moved to other cities in our country during the follow-up.) Of the 299 fractures, 31 (10%) were reoperated for nonunion. Of these, 68% (21/31) had an associated plate failure, indicating fracture nonunion. The total rate of plate failure was 7% (21/299). One patient had a plate failure 11 days after operation due to a new injury, but this was not included as a nonunion. The follow-up and baseline patient characteristics are shown in Table III.

First analysis. In the first analysis, we modelled the prediction of nonunion using the patient- and injury-related variables shown in Table II. According to the redundancy analysis, the AO classification was reduced from the logistic regression due to collinearity with other variables. Thus, the logistic regression included the following variables: age, sex, BMI, history of diabetes, smoking history, periprosthetic fracture above a knee prosthesis, open/closed fracture, trauma energy, fracture zone length, segmental comminution, and medial comminution of the fracture. Pseudo-R^2 was 0.27 and area under the curve (AUC; i.e. C-index) was 0.81. Elevated BMI and female sex were the most important variables predicting distal

Table III. Follow-up and baseline patient characteristics.

Variable	Healed group (n = 268)	Reoperation group (n = 31)
Follow-up		
Median total follow-up time, mths (IQR)	52 (31 to 87)	61 (39 to 87)
Patients with radiological healing, n (%)	209 (78)	31 (100)
Median radiological follow-up, mths (IQR)	16 (7 to 31)	29 (18 to 53)
Median clinical follow-up, mths (IQR)	55 (32 to 90)	61 (39 to 87)
Patients with clinical healing, n (%)	59 (22)	0
Median radiological follow-up, mths (IQR)	3 (2 to 3)	
Median clinical follow-up, mths (IQR)	46 (25 to 70)	
Median time to reoperation, mths (IQR)		7 (5 to 17)
Plate failure, n (%)	1*	21 (68)
No plate failure, n (%)		10 (32)
Median time to plate failure, mths (IQR)		6 (5 to 9)
Patient-related risk factors		
Median age, yrs (IQR)	71 (56 to 85)	65 (56 to 78)
Sex, n (%)		
Female	192 (72)	25 (81)
Male	76 (28)	6 (19)
BMI		
Median BMI, kg/m^2 (IQR)	25 (21 to 28)	27 (24 to 35)
No data available	8 (3)	0
Diabetes, n (%)		
No, or unknown	228 (85)	21 (68)
Yes	40 (15)	10 (32)
Smoking, n (%)		
No	144 (54)	19 (61)
Yes	84 (31)	10 (32)
No data available	40 (15)	2 (7)
Injury-related risk factors		
AO classification, n (%)		
A2	67 (25)	3 (10)
A3	121 (45)	21 (68)
C1	11 (4)	0 (0)
C2	30 (11)	1 (3)
C3	39 (25)	6 (19)
Knee periprosthetic fracture, n (%)	66 (25)	10 (32)
Open fractures, n (%)	26 (10)	6 (19)
High-energy trauma, n (%)	55 (21)	9 (29)
Median fracture zone length, mm (IQR)	110 (79 to 143)	127 (106 to 145)
Segmental comminution, n (%)	127 (47)	16 (52)
Medial comminution of fracture, n (%)	107 (40)	17 (55)
Treatment-related risk factors		
Median plate length, mm (IQR)	276 (236 to 301)	276 (276 to 316)
Median plate working length, mm (IQR)	99 (62 to 140)	103 (65 to 145)
Median empty holes (IQR)	0 (0 to 1)	0 (0 to 1)
Median plate span ratio (IQR)	2.5 (2 to 3.2)	2.3 (2 to 2.8)
Median proximal plate length, number of proximal holes (IQR)	7 (5 to 8)	7 (5 to 8)
Proximal fixation mode, n (%)		
Locking screws	183 (68)	20 (65)
Locking + cortical screws (hybrid)	64 (24)	9 (29)
Cortical screws	3 (1)	1 (3)
Cables with or without screws	18 (7)	1 (3)
Adequate proximal fixation (i.e. 8 or more cortices), n (%)	212 (80)	24 (77)
Median number of locking screws in fracture segment (IQR)	1 (0 to 2)	0 (0 to 2)

*See the text for details.
IQR, interquartile range.

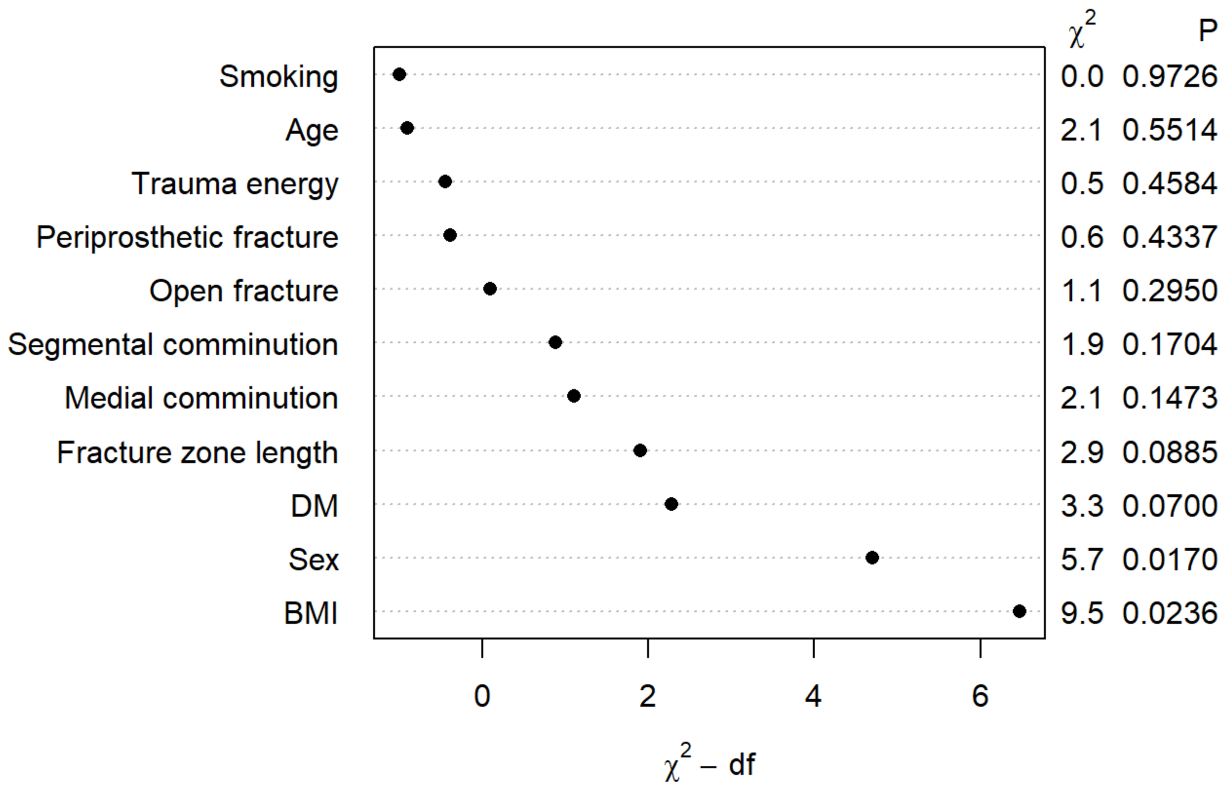

Fig. 3

Importance of the variable (Wald chi-squared test minus degrees of freedom) in the first analysis. Higher values represent higher importance of the variable. DM, diabetes mellitus.

femur fracture nonunion (Figure 3). The effect of BMI on the prediction of nonunion is shown in Figure 4. Odds ratios of the patient- and injury-related variables are shown in Supplementary Table i.

Second analysis. In the second analysis, we modelled the prediction of nonunion using the treatment-related variables shown in Table II. Plate working length and proximal plate length were reduced from the logistic regression after redundancy analysis due to collinearity with other variables. The following variables were thus included in the analysis: plate length in millimetres, empty holes adjacent to the fracture site, plate span ratio, proximal fixation mode, proximal cortices, and locking screws in the fracture segment. Pseudo-R^2 for the treatment-related factors was low (0.06; AUC 0.67). The importance of different treatment-related factors for fracture nonunion prediction are shown in Figure 5. Odds ratios of the treatment-related variables are shown in Supplementary Table ii.

Third analysis. In the third analysis, we combined the five most important variables from the first and second analyses: BMI, sex, and history of diabetes from the first analysis (Figure 3), and plate length and plate span ratio from the second analysis (Figure 5). In this analysis the pseudo-R^2 was 0.19 and AUC 0.78.

Discussion

In this study of patients with a distal femur fracture treated with a lateral locking plate, we analyzed the predictive ability of previously reported patient-, injury-, and treatment-related risk factors for distal femur fracture nonunion. The model including patient- and injury-related factors had moderate fit (AUC 0.81) and predictive ability (pseudo-R^2 0.27) in predicting distal femur fracture nonunion leading to secondary surgery. Surprisingly, treatment-related factors had much less importance in the prediction of nonunion (pseudo-R^2 0.06). The five most important variables from the first and second analyses together had weaker predictive ability (pseudo-R^2 0.19) in the third analysis than patient- and injury-related factors alone in the first analysis. The most important patient- and injury-related variables predicting

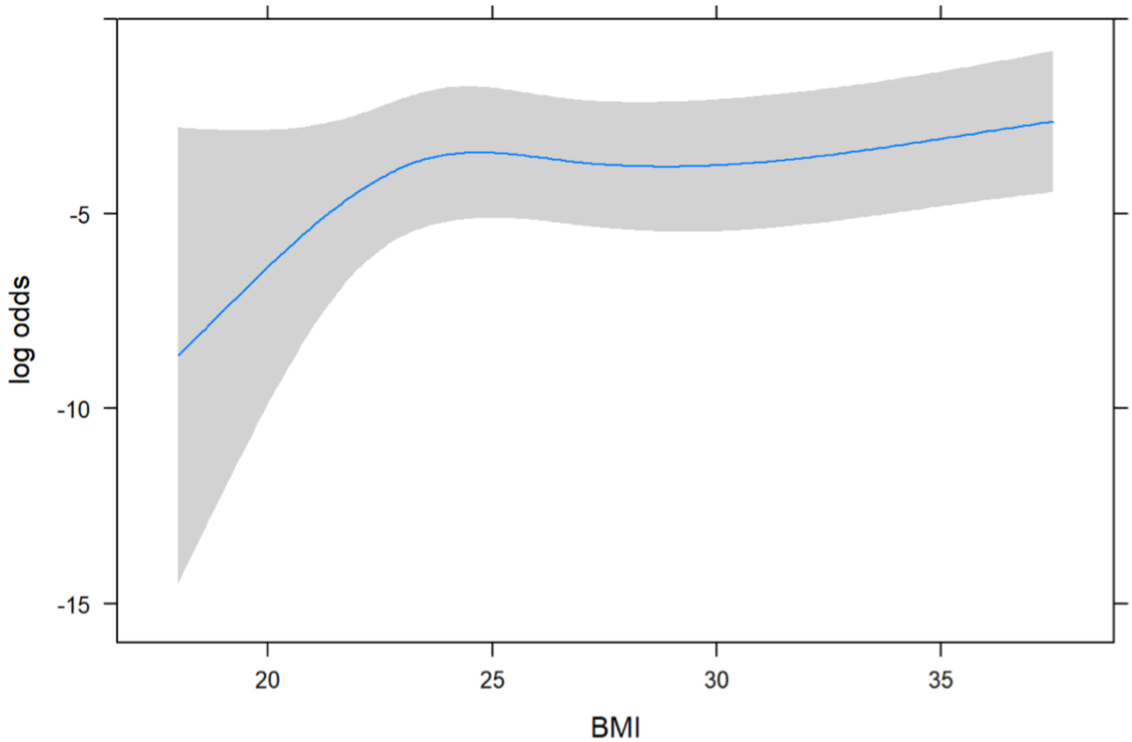

Fig. 4
The effect of BMI on the prediction of nonunion.

nonunion were elevated BMI and female sex. Although these variables were the most important predictors of fracture nonunion, they should not be considered causative factors based on our results.

The distal femur fracture patients in our study represent a typical patient material of distal femur fractures, with a bimodal fracture pattern and a predominance of especially elderly females.[1,2] Our nonunion rate of 10% and plate failure rate of 7% are in line with former literature.[9,10,12-19] We were unable to identify previous studies reporting the predictive ability of risk factors of distal femur fracture nonunion on a wider scale. Rodriquez et al[18] reported their predictive algorithm of four variables (open fracture, infection, obesity, and usage of stainless-steel plate) for distal femur fracture nonunion. Their model was based on a mixture of variables from different categories, i.e. injury-, complication-, patient-, and treatment-related risks. When none of these variables were present (titanium plate used instead of stainless-steel plate), the probability of intervention for fracture nonunion was only 4%, increasing to 96% when all of these variables were present.[18]

Several studies have reported independent patient- and injury-related risk factors for distal femur fracture nonunion, including obesity,[18,20] diabetes,[12] infection,[4,18,20] smoking,[15] open fracture,[9,12,14,18,20-22] fracture comminution,[9,10,17,22] or medial metaphyseal fracture comminution.[9] In this study, we did not evaluate statistical associations of individual risk factors. Instead, our study was designed to evaluate the total predictive ability of the most important patient- and injury-related risk factors. Our model showed a good discrimination between union and nonunion with AUC of 0.81. We excluded deep infection from the variables, as it is more a consequence of the injury or treatment than a patient-, injury-, or surgery-related risk factor.

Our finding that increasing BMI is the most important predictive factor for distal femur fracture nonunion is supported by the previous literature. Rodriquez et al[18] showed that obesity was a significant independent risk factor for secondary surgery after distal femur fracture nonunion. Ricci et al's[12] study revealed that greater BMI was an independent risk factor for lateral locking plate failure. Obesity might be a significant contributing factor for nonunion,[32,33] especially in lower limbs in weight-bearing bones, as there is more stress on the implants, contributing to implant failure.[32]

Surprisingly, in our study the OR for smoking was 0.95 (95% CI 0.51 to 1.76; Supplementary Table i), suggesting that the association of smoking with nonunion in this

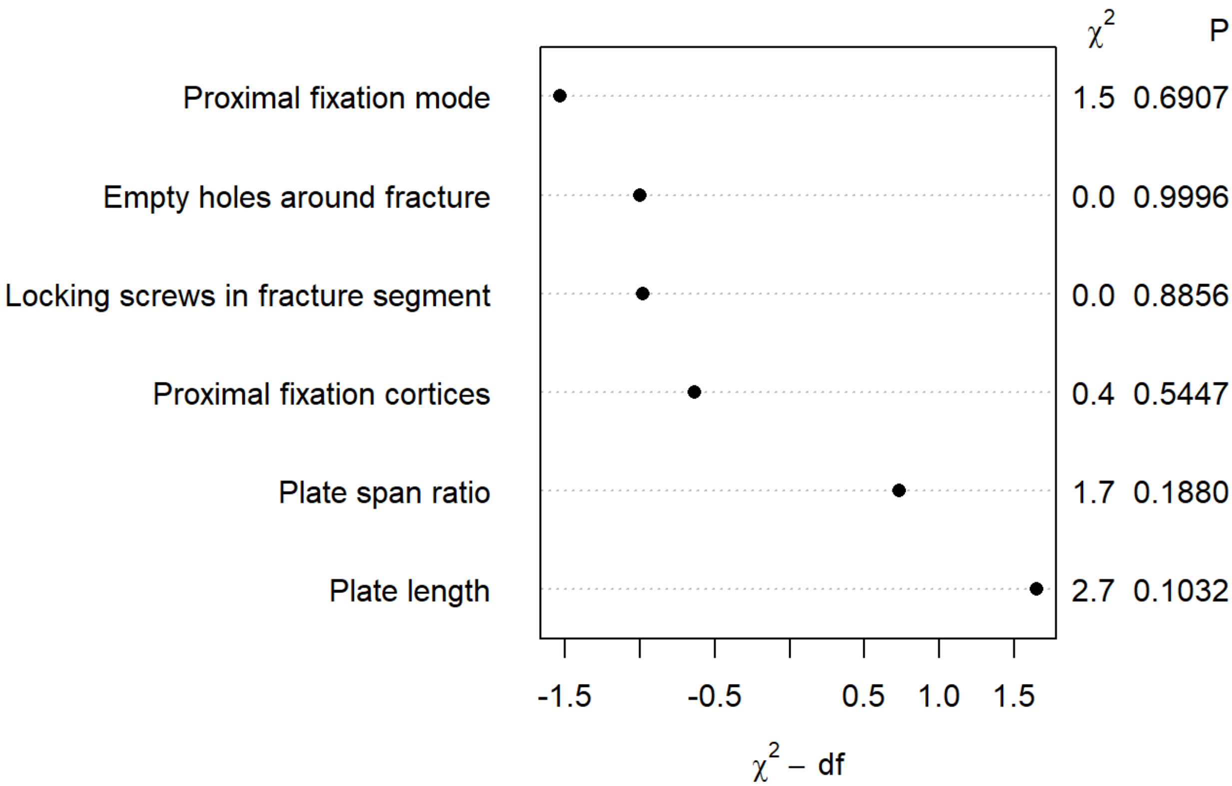

Fig. 5

Importance of the variable (chi-squared test minus degrees of freedom) in the second analysis. Higher values represent higher importance of the variable.

study was insignificant. Moreover, smoking alone was not very predictive for nonunion (Figure 3). However, history of smoking together with other patient- and injury-related variables had moderate predictive ability for distal femur fracture nonunion. In Zura et al's[32] study addressing risk factors for nonunion of bone fractures, smoking was a risk factor for nonunion in numerous retrospective studies. Nonetheless, 36% of recent studies failed to show association of smoking and nonunion, probably because of a small study populations. They suggest smoking as an incremental risk factor, which acquires predictive power only with additional risk factors together.

Several studies have reported treatment-related risk factors for distal femur fracture nonunion. Fracture fixation with locking screws only,[26] fewer empty plate holes adjacent to fracture site,[10] and stainless steel plates instead of titanium plates have been found to be associated with fracture nonunion.[10,13,18,25] Plate fixation with plates with fewer than nine holes has been reported to be more likely to fail than fixation with longer plates.[12] In our study, the treatment-related variables were not good predictors for distal femur fracture nonunion. We were not able to include the plate material as a variable, since our monoaxial plates were titanium and the polyaxial plates were stainless steel, confusing the effect of plate material and design. We argue that even with good surgical principles, it is difficult to overcome the patient- and injury-related risks affecting the healing environment of the bone.

Strengths of our study are the comprehensive dataset with only a few missing data, and a priori defined statistical analysis to avoid selective reporting. However, our study has typical limitations of retrospective studies. We had to exclude 74 patients due to insufficient follow-up data. However, 57 of them died before the fracture healed during the first 12 months, and only 17 had no follow-up data and might have had an intervention for nonunion somewhere else. A national database of patients is not available in our country to confirm what further treatment patients had after they moved their addresses. The exclusion of patients can cause uncertainty in the nonunion rate, but our approach ensured that the study included only fractures with an assigned healing status.

A general problem in nonunion studies is the lack of a universal definition for fracture nonunion.[34] In this study, we decided to avoid uncertainties by determination of nonunion from radiographs. We determined fractures as nonunion only if there was a secondary surgery due to nonunion, or if the osteosynthesis failed at least three months after operation. However, among elderly patients with limited walking ability, a nonunion of the distal femur fracture may not cause any symptoms or plate failure, since there is less stress on the implant in nonambulatory patients.

Our study showed that the model including patient- and injury-related factors had moderate fit and predictive ability in prediction of distal femur fracture nonunion leading to secondary surgery. Increasing BMI was the most important variable in the prediction of nonunion. Surgeon-controlled variables had only a minor role in the prediction. Future research should focus on how to prevent fixation failure in patients most likely to develop a nonunion.

Take home message

- Previously identified patient- and injury-related risk factors seem to have a better predictive ability in predicting a distal femur fracture nonunion than treatment-related factors.
- BMI was the most important variable in prediction of nonunion.
- Patients with elevated BMI might benefit from more robust fixation strategy of their distal femur fracture.

Supplementary material

Odds ratios of the patient-, injury-, and treatment-related variables

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