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Nonunion Risk Assessment in Foot and Ankle Surgery: Proposing a Predictive Risk Assessment Model

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Abstract

Background: Nonunion risk factor identification and modification are subjective. We describe and validate a predictive nonunion risk factor model to identify foot and ankle operative patients at risk for nonunion.

Materials and Methods: One hundred international experts in foot and ankle surgery were surveyed. Nineteen nonunion risk factors were stratified into 3 categories: more significant than, as significant as, and less significant than smoking 1 pack per day. A nonunion risk assessment model was developed by assigning a weighted score to each risk factor, based on its mean score from the survey. A total nonunion risk (TNR) score was calculated for individual patients. It was retrospectively validated in 2 patient cohorts from a single center's prospectively collected end-stage ankle arthritis patient database: 22 cases of ankle and/or hindfoot fusion nonunion and 40 sex- and procedure-matched controls with bony fusion. Analyses included descriptive statistics, logistic regression, and univariate and multivariate linear regression models.

Results: The mean TNR score was 6.6 ± 5.6 in controls and 13.5 ± 8.2 in the nonunion group ($P < .001$). Data showed excellent intraobserver and interobserver correlation coefficients. In a logistic regression model, the risk of nonunion exceeded 9% with a TNR score greater than or equal to 10. Multivariate linear regression analysis, adjusted for age and sex, suggested that lack of fusion site stability and obesity (body mass index greater than 30) were significantly predictive of nonunion.

Conclusion: The nonunion risk assessment model provides a reliable, sensitive, and specific method for predicting nonunion based on objective patient assessment. Orthopaedic patients at risk for nonunion could benefit from targeted intervention.

Level of Evidence: Level IV, retrospective observational study.

Keywords: ankle fusion, nonunion, prediction model, risk assessment

Nonunion is a disabling complication of fusion surgery. Patient morbidity and the burden on health care costs associated with nonunion justify the resources and research focused on improving fusion rates in the settings of elective ankle arthrodesis and fracture surgery.[19] As a result, reducing nonunion rates has been a goal, with recently published rates of nonunion following ankle arthrodesis ranging from 3% to 11%.[7,11,14,23] Determining who is at risk is important to reduce the possibility of nonunion. There is, for example, grade B evidence to support smoking[1,2,5,21] and diabetes[6,8,10,17] as modifiable patient risk factors and grade B evidence to support the use of internal fixation for ankle arthrodesis.[18] Therefore, smoking cessation, control of blood sugar, and surgeon training are appropriate interventions to reduce the risk of nonunion.

A recent international survey of orthopaedic foot and ankle specialists found that active local infection, poor local vascularity, and smoking, alone or in combination, were often considered absolute contraindications for arthrodesis

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surgery.[22] Other risk factors considered by these experts to be important for nonunion included lack of fusion site stability, poor compliance with weightbearing, gaps at the fusion site, poor soft tissue envelope, and poorly controlled diabetes (ie, HbA1c greater than 8%).

Identification of patients at risk for nonunion is difficult, since successful bony union is dependent on a complex interplay of patient, operative, and mechanical factors.[9] A clinical appraisal of an individual patient's nonunion risk profile is influenced by the experience of the assessing clinician and is therefore somewhat subjective. The categorization of patients preoperatively into broad groups of *low risk* and *high risk* for nonunion may result in the underutilization of resources available for risk factor modification and potential failure to identify some high-risk patients.[16] In recent years, there has been an increase in implants and bone graft substitutes available to the orthopaedic surgeon, with the hope that the incidence of nonunion is reduced. These implants and bone graft substitutes may not be cost-effective if used in all patients but may be cost-effective if used in at-risk patients.

Risk assessment models have been developed in various medical subspecialties to facilitate the assignment of individual patients to risk categories. In foot and ankle surgery, quantitative risk assessment for nonunion could be helpful in reducing nonunions in arthrodesis and fracture patients. Risk scoring could assist orthopaedic surgeons in identifying patients with modifiable risk factors who could benefit from focused perioperative education, bone graft substitutes, and newer implant technology.

The purpose of this study was to develop an easy-to-use, predictive, clinical risk factor model for nonunion and to validate the model through its application in a retrospective, matched, case-cohort series of patients who have had ankle and/or hindfoot fusion.

Methods

Development of Nonunion Risk Assessment Model

One hundred international orthopaedic foot and ankle surgeons were asked to rate, on a scale of 0 to 10, the relative risk of 18 factors for nonunion, compared to a benchmark risk factor of smoking 1 pack per day, which was assigned a risk significance of 5 of 10. As a result of the survey, the risk factors were divided into 3 categories: more significant than smoking 1 pack per day (ie, with a mean score significantly greater than 5, $P < .001$), no different than smoking 1 pack per day (ie, with a mean score not statistically different from 5, $P > .001$), and less significant than smoking 1 pack per day (ie, with a mean score significantly less than 5, $P < .001$; Table 1).[22] Survey details and results are reported elsewhere.[22]

We developed a nonunion risk assessment model (Table 2) using the mean scores of the individual risk factors as determined in the international survey. In this model, each risk factor was assigned a weighted score. Risk factors that were statistically similar to and therefore equivalent to smoking 1 pack per day were assigned the same neutral score of 5.0. Factors considered to be more or less significant than smoking 1 pack per day were assigned a weighted score equivalent to their mean score, approximated to the closest 0.5 decimal point. Thus, lack of fusion stability, which received a mean score of 8.66 in the international survey (Table 1), was assigned a weighted component score of 8.5 in the nonunion risk assessment model (Table 2). Poorly controlled diabetes (ie, HbA1c greater than 8), with a mean score of 6.76 in the survey, was assigned a component score of 7.0 in the model.

The nonunion risk assessment model calculates a total nonunion risk (TNR) score for a patient, as a sum of the scores of the individual risk components presented by that patient. For example, a morbidly obese (body mass index [BMI] = 45) 65-year-old man with well-controlled diabetes would be assigned a TNR score of 12.5 (ie, 5 [for BMI greater than 40] + 2.5 [for age greater than 60] + 5 [for diabetes with HbA1c of 6 to 8] = 12.5).

Testing and Validity of Nonunion Risk Assessment Model

We investigated the validity and internal consistency of the TNR score, as determined by the nonunion risk assessment model, in 22 consecutive cases of ankle nonunion and 40 control patients with full bony union following ankle and/or hindfoot arthrodesis, matched for sex and procedure, and as identified from the primary study site's prospectively collected patient database. Patients with symptomatic end-stage ankle arthritis of various etiologies were enrolled in this database and underwent arthrodesis between 2002 and 2010. Criteria for inclusion in the database were age over 18, with a primary ankle fusion or primary ankle joint replacement for end-stage ankle arthritis, with or without surrounding joint pathology or deformity. Exclusion criteria were active infection and diabetic neuropathy. The review board of our institution provided ethical approval for data collection and development of the database. All participating patients provided informed consent prior to enrolment in the database and prior to surgery.

A retrospective chart analysis was independently performed on both cohorts by the primary and second authors. Individual risk factors were scored in accordance to the nonunion risk assessment model, and a TNR score was determined for each patient. This exercise was performed twice, 14 to 22 days apart, by both authors to calculate intraobserver reliability.

Table 1. Risk Factors for Nonunion Compared to Smoking 1 Pack per Day.[a]

Risk Factor	Mean	SD
More significant than smoking		
Smoker of 2 packs/day	8.69	1.47
Lack of fusion site stability	8.66	1.34
Poor local vascularity	7.66	2.01
Poor compliance with weightbearing	7.45	2.10
Gaps at the fusion site	7.40	2.19
Poor soft tissue envelope	6.78	2.18
Diabetes with HbA1c >8%	6.76	2.18
No different than smoking		
Smokeless tobacco	5.90	2.52
Smoker of half pack/day	5.63	2.07
Obesity with body mass index >40	5.54	2.46
Previous local infection	4.92	2.58
Diabetes with HbA1c between 6% and 8%	4.53	2.03
Obesity with body mass index from 30 to 40 kg/m^2	4.16	2.39
Less significant than smoking		
Nonsteroidal anti-inflammatory drugs	4.05	2.45
Age >80 y	3.80	2.39
Osteoporosis	3.56	2.34
Rheumatoid arthritis	3.05	2.36
Age >60 y	2.54	1.90

[a]Assigned a risk of 5 out of 10, as determined by an international survey of 100 foot and ankle surgeons.[22]

Table 2. Nonunion Risk Assessment Model.

Risk Factor	Score
Smoker of 2 packs/day	8.5
Smoker of 1 pack/day	5
Smoker of half a pack/day	5
Smokeless tobacco	5
Lack of fusion site stability	8.5
Gaps at the fusion site	7.5
Poor local vascularity	7.5
Poor compliance with weightbearing	7.5
Poor soft tissue envelope	7
Diabetes with HBA1c >8	7
Obesity with body mass index >40	5
Previous local infection	5
Diabetes with HBA1c between 6 and 8	5
Obesity with body mass index from 30 to 40	5
Age >60 y	2.5
Rheumatoid arthritis	3
Osteoporosis	3.5
Age >80 y	4
Use of nonsteroidal anti-inflammatory drugs	4

Review of the end-stage ankle arthritis database yielded 22 cases of nonunion affecting either the ankle (n = 13; 59%) or the hindfoot complex (n = 9; 41%). The control group of 40 patients had a similar case mix, with 24 united ankle fusions (60%) and 16 united hindfoot fusions (40%). The nonunion group consisted of 15 men (68%) and 7 women (32%). The control group consisted of 28 men (70%) and 12 women (30%). The mean age was 60.7 ± 9.8 years (range, 41 to 77 years) in the nonunion group and 54.9 ± 12.3 years (range, 22 to 77 years) in the control group.

Data Analysis

Data entered into the prospective end-stage ankle arthritis database include self-reported demographic information and health status questionnaires. Information regarding age, BMI, preoperative smoking behavior, and the use of nonsteroidal anti-inflammatory drugs was obtained from the database. Clinical information pertaining to preoperative examination findings and intraoperative technical details of surgery was obtained from the electronic patient records system.

Patients noted to have abnormal pedal pulses or to demonstrate signs of arterial insufficiency were considered to have poor local vascularity. Patients with previous skin flaps, ulcers, or operative scars at the proposed operative site were deemed to have a poor soft tissue envelope. Poor compliance with weightbearing was ascertained from postoperative consultation notes. Patients were considered positive for nonsteroidal anti-inflammatory drug use if there

Table 3. Risk Factors Selected for Reliability Analysis and for Development of Univariate and Multivariate Linear Regression Models.

Patient Factors	Operative Factors
Age ≥60 y	Intraoperative difficulties
Body mass index >30	
Smoking	
Poor local vascularity	
Poor compliance with weightbearing	
Poor soft tissue envelope	
Diabetes	
Previous local infection	
Rheumatoid arthritis	
Use of nonsteroidal anti-inflammatory drugs	

was documented use in the 6 weeks prior to surgery. Patients were scored positively for osteoporosis if a formal diagnosis had been recorded at any point prior to the ankle surgery in the electronic patient records. Lack of fusion stability was identified in patient charts as revision surgeries and complex fusions, such as tibiotalocalcaneal fusion or ankle-subtalar fusion. Interfragmentary gaps were considered to be present when bony defects requiring additional screws and/or bone graft materials were documented.

Statistical Methods and Analysis

Eleven risk factors were selected for reliability analysis and for development of a logistic regression model and univariate and multivariate logistic regression models (Table 3). The varying levels of smoking and smokeless tobacco were grouped into a single category of smoking, as were the 2 levels of increased BMI into a single category of BMI greater than 30 and older age into a single category of age greater than or equal to 60. Intraoperative technical difficulties and interfragmentary gaps were combined into a single intraoperative factor for analysis purposes; the remaining factors were considered patient factors (Table 3).

Reliability analysis was performed. Interobserver reliability scores were analyzed to determine the interclass correlation coefficient (ICC) with 2-way randomization and 95% confidence intervals (CIs). Intraobserver reliability scores were similarly analyzed to determine the ICC with a 2-way mixed model and 95% CIs.

A logistic regression model was developed with the TNR score as the predicted variable. To evaluate the ability of the model to distinguish patients with nonunion from those without, receiver operating characteristic curves were generated by varying the TNR score. The area under the receiver operating curve (AUC) was calculated: an AUC less than 0.5 was regarded as having no discrimination ability; an AUC between 0.7 and 0.8 was considered the threshold for acceptable; and an AUC greater than 0.8 was assigned excellent discriminatory performance.[13] The 95% CI of the AUC was also generated, using bootstrap resampling.

Univariate and multivariate linear regression models were developed to evaluate the effect of operative and patient factors on nonunion, using nonunion as the dependent variable. Given the skewed distribution of the dependent variable in the data, a log transformation was then performed for nonunion. Odds ratios (ORs) were used as the measure of association between risk factor and the occurrence of nonunion, and 95% CIs were estimated from the models. Univariate linear regression models were developed, where the risk factor was considered the explanatory variable. Multivariate linear regression models were then developed using the same preselected risk factors as the explanatory variable, with age and sex included as confounding variables to assess the effect of the selected risk factors on nonunion. Given the small number of patients in the nonunion group and, hence, the low prevalence of some risk factors, only the most heavily weighted risk factors (ie, smoking, diabetes, and lack of fusion site stability/intraoperative difficulty) were chosen for prediction analysis. Data reliability was assessed using the Pearson correlation coefficient, with 1.0 indicating exact reproducibility and 0 indicating no reproducibility. All reported P values were 2-sided; $P < .05$ was considered statistically significant.

Results

Risk Factor Analysis

The mean TNR score was 13.5 ± 8.2 (range, 2.5 to 33) in the nonunion group and 6.6 ± 5.6 (range, 0 to 21) in the control group ($P < .001$). Interobserver reliability testing with the TNR score demonstrated ICCs ranging from 0.80 to 0.93. Intraobserver reliability testing demonstrated ICCs ranging from 0.90 to 0.97.

The probability of the presence of nonunion at various TNR scores was obtained from a logistic regression model (Table 4), where the TNR score was the predicted variable included in the model. The model suggested that, with a TNR score of 10 or more, the risk of nonunion exceeds 9%. The estimated AUC of the model was 0.77 with a 95% CI of 0.64 to 0.88 (Figure 1), indicating that the ability of the model to discriminate patients with nonunion from those who achieved fusion reached the acceptable level but was moderate (ie, AUC less than 0.8).

Results of the univariate linear regression model and the multivariate linear regression model adjusted for age and sex are summarized in Table 5. There was strong evidence to support an association between intraoperative difficulty (ie, interfragmentary gaps and/or intraoperative technical difficulty or lack of fusion site stability) and the occurrence

Table 4. Estimated Probability of Nonunion From Logistic Regression Model.

Total Nonunion Risk Score	Risk of Nonunion	95% Confidence Intervals	
		Lower	Upper
0	0.021	0.021	0.014
5	0.045	0.045	0.038
10	0.092	0.092	0.077
15	0.178	0.178	0.122
20	0.319	0.319	0.185
25	0.502	0.502	0.270
30	0.684	0.684	0.375
35	0.824	0.824	0.495
40	0.910	0.910	0.614
45	0.956	0.956	0.722

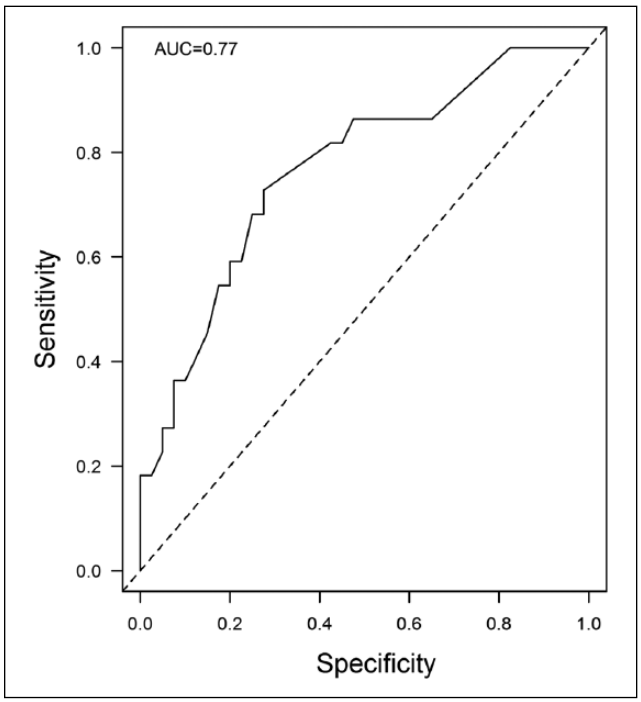

Figure 1. Receiver operating characteristic curve of total nonunion risk score in the nonunion risk assessment model for 22 nonunion cases and 40 controls. The estimated area under the curve (AUC) was 0.77, with a 95% confidence interval of 0.64 to 0.88.

of nonunion, with an OR of 4.35 (95% CI: 1.14, 16.59; $P = .03$) in the multivariate regression model. There was also strong evidence of association between obesity (BMI greater than 30) and the occurrence of nonunion in the multivariate regression model. The OR was 4.15 (95% CI: 1.29, 13.30; $P = .02$), suggesting that nonunion is 4 times as likely to occur in patients with BMI greater than 30 compared to patients with BMI less than or equal to 30. There was a trend toward a positive correlation between increasing age and nonunion. For each decade of increasing age, the univariate regression model demonstrated an OR of 1.63 ($P = .07$). The multivariate model demonstrated positive correlations for diabetes (OR, 2.26) and for smoking (OR, 1.59) as risk factors for the occurrence of nonunion, but these associations were not statistically significant.

Discussion

The nonunion risk assessment model that we developed assigned the test cohort of patients with a nonunion a mean TNR score of 13.47, compared to 6.6 for the control group, and a TNR score of 10 or more was modeled to yield a risk of nonunion exceeding 9%. This threshold is likely to be considered unacceptable for most joints in foot and ankle fusion surgery today. The nonunion risk assessment model demonstrated excellent interobserver and intraobserver reliability.

Previous nonunion scoring systems have been largely based on radiographic appraisal with a view to guiding operative technique and mode of reconstruction.[3] To our knowledge, there has been no previous attempt to recognize the multitude of both patient and operative factors within an objective scoring system that reliably confers prognosis prior to foot and ankle arthrodesis surgery.

The aim of this study was to quantify risk factors for nonunion and attempt validation of the risk assessment tool in a pilot study of 60 patients. We carefully selected a control group that was sex and procedure matched. The results of this pilot study suggest that this risk factor model is highly reliable and is an easily applicable scoring tool. The results from the receiver operating characteristic curve suggest that this scoring tool has a reasonably high degree of sensitivity and specificity, with good discriminatory potential between the nonunion and union cases.

The manner in which these risk factors act in combination is open to debate. Indeed, a risk factor identified as an "independent" potential predictor of nonunion is clearly dependent on the other risk factors taken into account in the multivariate model. Risk factors that are characterized as "independent" cannot necessarily be freely combined. A risk-scoring system is generally developed from the logistic regression coefficients derived from a large-scale epidemiologic study, whereby a multivariate model is constructed on the basis of a large cohort of hospitalized medical patients and then applied to an independent cohort to assess its performance. However, adequately powered studies using multiple logistic regression analyses to determine the independent predictors of nonunion have yet to be conducted.

More recently, risk assessment models have been introduced across various operative and medical specialties to facilitate the assignment of individual patients to risk categories.[4,20] With current technology and specific software

Table 5. Results of Univariate and Multivariate Logistic Regression Models to Assess the Association Between Patient Characteristics and the Occurrence of Nonunion.

	Univariate Analysis			Multivariate Analysis		
Factor: Effect	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age: per 10 y	1.63	0.96, 2.76	.07			
Sex: male vs female	0.81	0.26, 2.53	.72			
Body mass index: >30 vs ≤30	3.64	1.22, 10.83	.02	4.15	1.29, 13.30	.02
Intraoperative difficulty: yes vs no	2.77	0.88, 8.75	.08	4.39	1.15, 16.69	.03
Diabetes mellitus: yes vs no	3.00	0.46, 19.49	.25	2.26	0.33, 15.60	.41
Smoking: yes vs no	1.23	0.19, 8.00	.83	1.59	0.23, 11.24	.64

Abbreviations: CI, confidence interval; OR, odds ratio.

programs, hospitals with electronic patient records have the capacity to systematically evaluate the risk of an adverse event and generate an electronic alert. For example, this is available in practice for the detection and treatment of venous thromboembolism[15] and falls.[12] The advent of a quantitative nonunion risk assessment model and the implementation of a computer alert program would allow orthopaedic surgeons to screen each patient's nonunion risk in a time-economic fashion and to institute a focused risk modification program in a timely manner.

Intraoperative difficulty (ie, interfragmentary gaps and/or technical difficulty), obesity, and possibly age were associated with an increased risk for nonunion. Intervention strategies—preoperative patient measures (eg, weight loss recommendations) and intraoperative measures (eg, use of bone graft in the presence of large interfragmentary gaps)—could be considered to reduce the risk of nonunion in high-risk patients. Larger-scale studies are needed to confirm the increased risk for nonunion of these factors and to evaluate other, less frequently observed risk factors.

This study was intended as a pilot assessment; nevertheless, it has limitations. First, the case numbers were small. Given the low prevalence of all risk factors in the cohort, conducting multiple regression analysis on this data set to establish the "independent predictability" of all 11 preselected risk factors proved difficult and resulted in imprecise predictions with wide CIs. A multicenter trial with a larger data set and multiple independent cohorts of patients is likely necessary to overcome this problem. Second, the composite TNR score was assumed to be an aggregate of all individual weighted risk scores for a given patient. Although this appears to have been a sensible approach following our retrospective validation, a well-designed prospective case-cohort study is warranted to establish the clinical utility of this scoring tool.

Summary

This pilot study suggested that the nonunion risk assessment model (Table 2) provides a reliable, sensitive, and specific method for predicting nonunion based on objective patient assessment. It is a simple tool that can be inserted into existing documentation with related interventions targeted to reduce risk for nonunion. It could also form part of an electronic record where risk analysis and automated calculations are performed routinely with alerts. A number of orthopaedic patients, while relatively few overall, are anticipated to be at risk for nonunion in the setting of elective foot and ankle arthrodesis and fracture surgery and could benefit from targeted intervention. This evidence-based tool is intended to conserve physician time and hospital resources, identify and stratify patients at risk, and thereby improve clinical outcome. Future studies should focus on (1) validating this risk assessment model in the setting of multiple, large, independent cohorts of preoperative foot and ankle arthrodesis patients; (2) further exploring the lack of fusion site stability, obesity, and patient age as increased risks for nonunion; and (3) developing physician and patient interventions for these risk factors to reduce an individual's risk for nonunion.

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