Risk Factors for Nonunion After Nonoperative Treatment of Displaced Midshaft Fractures of the Clavicle

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Background: Identification of patients at higher risk of nonunion after diaphyseal clavicular fractures is desirable to improve patient counseling and enable targeted surgical treatment.

Methods: Seventy-nine percent (941 of 1196) of diaphyseal clavicular fractures were followed to union or nonunion. Demographic, injury, and radiographic characteristics associated with nonunion were determined with use of bivariate and multivariate statistical analyses.

Results: In patients who were eighteen years of age or older, 125 (13.3%) of the fractures had clinical and radiographic evidence of nonunion. Factors significantly associated with nonunion on bivariate analysis were sex, smoking status, overall fracture displacement, overlap, translation, and comminution. The factors that maintained significance on multivariate analysis were smoking (odds ratio, 3.76), comminution (odds ratio, 1.75), and fracture displacement (odds ratio, 1.17). If all displaced midshaft fractures were managed operatively, 7.5 procedures would need to be undertaken to prevent a single nonunion. If only fractures with a predicted probability of ≥40% were managed operatively, the number of patients managed operatively to prevent a single nonunion would fall to 1.7.

Conclusions: Thirteen percent of displaced diaphyseal fractures in patients who were at least eighteen years of age did not heal. Smoking was the strongest risk factor, and smoking cessation should be an integral part of treatment. The probability of nonunion in a particular individual can be estimated with use of a statistical model based on known risk factors. This information can be useful when counseling the patient even though nonunion remains difficult to predict accurately in that individual. The number who would need to be treated to prevent a single nonunion can be reduced by identifying those at higher risk.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Between five and twenty percent of patients[1-4] with midshaft clavicular fractures develop nonunion if treated nonoperatively. Those with displaced fractures are at greater risk[2,4]. Patients undergoing primary fixation have a lower rate of nonunion and report better functional outcomes than those managed nonoperatively. Outcomes following primary fixation are also better than outcomes following secondary fixation in patients who develop nonunion following nonoperative

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A commentary by Andrew H. Schmidt, MD, is linked to the online version of this article at jbjs.org.

TABLE I Logistic Regression Model and Equation to Predict Nonunion of a Displaced Diaphyseal Fracture*

Risk Factor	Regression Coefficient, B	Wald Statistic	P Value of Wald Statistic	Standard Error of B	Odds Ratio Exp(B) (95% CI)
Smoking (1=yes, 0=no)	1.32	33.20	<0.001	0.23	3.76 (2.39 to 5.89)
Comminuted fracture (1=yes, 0=no)	0.56	5.90	0.015	0.23	1.75 (1.11 to 2.76)
Absolute fracture displacement *(mm)*	0.15	81.00	<0.001	0.02	1.17 (1.13 to 1.21)

*Logit(p) = −5.616 + (1.324 × [1 if smoker or 0 if nonsmoker]) + (0.561 × [1 if comminuted fracture or 0 if noncomminuted fracture]) + (0.153 × absolute fracture displacement in millimeters). Percentage probability of nonunion = exp(logit[p])/(1 + exp[logit(p)]) × 100.

management[1]. This has led to growing support for a policy of primary fixation for all displaced midshaft clavicular fractures in active adult patients[1]. However, a blanket surgical approach would expose large numbers of patients who would have healed without surgical intervention to the potential complications of surgery. Identification of patients at higher risk of nonunion is desirable at the time of the initial treatment to improve patient counseling and enable targeted surgical treatment[5].

Previous studies have attempted to estimate the risk of nonunion in individual patients following nonoperative treatment. However, in evaluating the prevalence of nonunion and importance of risk factors, these studies have included fractures in children[6], nondisplaced fractures[3,7,8], and fractures of the medial and lateral ends of the clavicle (whose behaviors differ from that of midshaft fractures). The models generated are therefore limited in their ability to predict nonunion specifically in adults with displaced midshaft fractures[3]. We sought to identify patient-related and injury-related factors that were independently predictive of nonunion in a large cohort of patients with displaced midshaft clavicular fractures. Our secondary aim was to examine the utility of the statistical model generated from these data as a diagnostic "test" by assessing its ability to predict nonunion at different thresholds of predicted nonunion probability.

Materials and Methods

Study Design

A database was compiled of patients who were treated nonoperatively in a single trauma unit from January 1994 to December 2007 following a displaced midshaft clavicular fracture. Patients treated from 1997 to 2001 had been the subject of a previous study of outcome and were not included. We performed a retrospective analysis of the data that included only patients who were eighteen years of age or older. Our affiliated Emergency Department provides the only acute musculoskeletal trauma service for the local adult population, and fractures are therefore representative of a cross section of the local population sustaining these injuries.

Inclusion Criteria

Patients who were at least eighteen years of age were included in the study if they had (1) a fracture in the middle three-fifths of the clavicle; (2) complete displacement of the main fragments with no cortical contact; (3) initial nonoperative treatment until either confirmed fracture-healing or the development of nonunion, using criteria stipulated below; and (4) adequate documentation of demographic details and clinical and radiographic follow-up until fracture-healing or the development of nonunion.

Patients Excluded from the Analysis

Of the 1196 adult patients identified as having sustained a displaced diaphyseal clavicular fracture, 941 (78.7%) satisfied the inclusion criteria and were considered further. Fifty-five of the other patients were excluded because documentation of demographic data was missing and we had been unable to gain further information during the follow-up study in 2010. Forty-two patients were excluded because of incomplete documentation of clinical and/or radiographic outcome, and forty-four were excluded because they were lost to follow-up before union status was determined. Eighty-four patients were excluded because they underwent primary operative treatment (within two weeks of injury), which was performed as a result of skin or neurovascular compromise in fourteen; pathological fracture, floating shoulder, or other multifocal shoulder girdle injury in twenty-two; a request by the patient in twenty-three; and a decision of the treating surgeon in twenty-five. Thirty patients were excluded because they underwent early operative treatment from two to twenty-four weeks after injury (at their request or as a result of a decision of the surgeon) before the development of definite nonunion.

Demographics of the Study Population

The mean age of the 941 patients was 36.8 years (range, eighteen to ninety-four years). The study population consisted of 678 men and 263 women. The fracture was caused by a simple fall in 298 patients (31.7%), a fall from a height in sixty-six (7.0%), a bicycle or motorcycle injury in 186 (19.8%), another type of traffic accident in ninety-eight (10.4%), a sport in 201 (21.4%), an assault in forty-five (4.8%), and another cause in forty-seven (5.0%). The dominant arm was affected in 53.8% of the patients. The age, sex, and injury mechanism distributions of the 255 patients who were excluded for the previously stated reasons were similar to those of the patients included in the analysis.

Assessment of Patients, Injury Factors, and Fracture Union

All demographic and outcome data were gathered by two authors (C.J.F., A.E.) and stored anonymously in a database. Demographic information recorded at the time of the original injury included age, sex, mechanism of injury, affected side, injury severity score, other injuries, and handedness. The cognitive score, mobility, alcohol and tobacco usage, medical comorbidities, and medications were recorded from 1997 onward. We also recorded details of the initial treatment: whether a brace or sling was provided, the duration of immobilization, and the timing and duration of physiotherapy. In 2010, we attempted to consolidate the follow-up of patients treated before 1997 by means of either a mailed questionnaire or a telephone consultation. We were able to obtain sufficient information from 382 patients who had initially had incomplete documentation of demographic data.

Patients were reviewed in dedicated trauma clinics and underwent routine clinical and radiographic assessment of fracture union at each visit. A standardized anteroposterior radiograph was used in all cases. Follow-up was continued until clinical and radiographic evidence of union. A fracture was judged to be united when a patient had no or minimal pain, no mobility at the fracture site on clinical examination, and evidence of bridging callus on radiographs. Nonunion was judged to be present if two of these three criteria

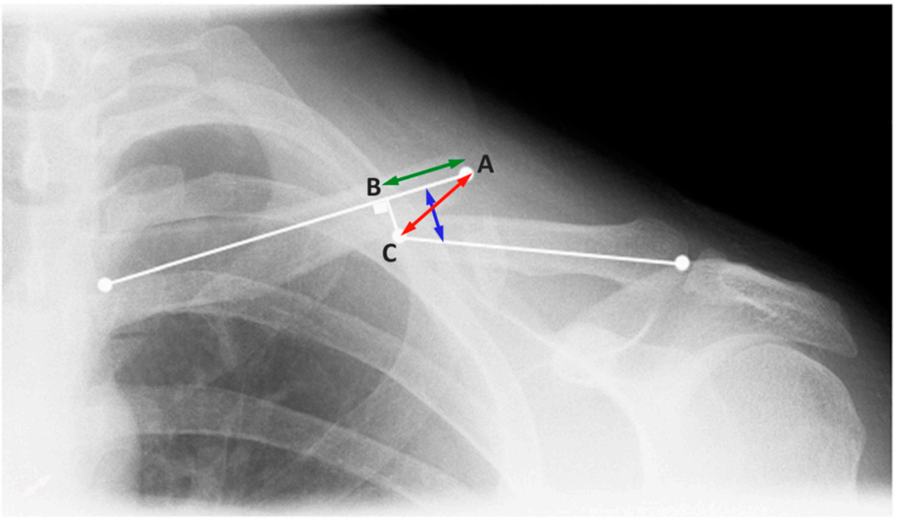

Fig. 1
Anteroposterior radiograph illustrating the methods for determining overlap, translation, and overall displacement. The overlap (green arrow) was the measured distance from the fracture line of the proximal fragment (point A) to the point on the proximal fragment (point B) at which a line perpendicular to the long axis of this fragment would pass through the fracture line of the distal fragment (point C). The translation (blue arrow) was measured where a line at right angles to the midpoint of the overlap crosses the long axis of the distal fragment. The overall displacement (red arrow) was the measured distance between the fracture lines of the proximal (point A) and distal fragments (point C).

remained unsatisfied beyond twenty-four weeks after injury. Patients with suspected nonunion were offered operative open reduction and plate fixation after twenty-four weeks unless they were unfit for surgery. Twelve patients who underwent operative exploration after twenty-four weeks for suspected nonunion had a healed fracture. These fractures were considered to be united in this study.

All initial post-injury radiographs were retrospectively analyzed to assess fracture overlap, translation, overall displacement, and angulation. Measurement of displacement parameters of the main fracture fragments is depicted in Figure 1. The presence of severe wedge or segmental comminution was assessed with use of the Edinburgh clavicular fracture classification. Assessment of the presence or absence of bridging callus on follow-up radiographs was also performed retrospectively.

Statistical Analysis

Binary logistic regression was used to estimate the effect of candidate patient-related and injury-related risk factors (Table I) on the development of nonunion. Bivariate analysis was performed with independent variables classified as either continuous or categorical data. Correlation coefficients were used to assess for multi-collinearity of variables. All variables that were significantly predictive of nonunion ($p < 0.1$) on bivariate analysis were included in a stepwise multivariate model (with use of forward conditional methodology) to identify the factors that were independently predictive of nonunion. Product functions were used to assess for possible interaction of variables in the regression model. To demonstrate that patients with an immature skeleton did not skew the data, a secondary multiple logistic regression analysis incorporating interaction terms between each of these factors and whether or not the patient age was eighteen to twenty-five years was performed. The Hosmer-Lemeshow goodness-of-fit statistic was used to judge the predictive quality of the final model. The Wald chi-square test was used to assess the significance of the independent predictors of nonunion in the final model. A split-sample validation was carried out by dividing the sample at random into equal-sized training and validation sets and confirming that the identified factors were predictors in both sets.

Using this model, the risk factor scores for an individual patient and their regression coefficients (B) can be used to calculate a logit value (logit[p]) for the probability (p) of nonunion at twenty-four weeks. The predicted probability of nonunion can be computed for each patient with use of the equation $p = \exp^{\text{logit}(p)}/(1 + \exp^{\text{logit}(p)})$. We estimated the value of exp(B) (the odds ratio) for each variable to allow estimation of the magnitude of the effect of a one-unit change in the variable on the risk of nonunion when adjusted for the other variables. A p value of ≤ 0.05 was considered significant for type-I error in the multivariate analysis.

Classification tables of predicted and actual outcomes were used to estimate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall percentage of correct predictions for the model at different thresholds of the estimated probability of nonunion. We also assessed the number-needed-to-treat value (NNT)—the number of patients who would need to be treated operatively to prevent a single nonunion—at each probability threshold to assess the implications of adopting a policy of primary operative intervention for these fractures.

Source of Funding

No external funding source was used.

Results

Of the 941 patients who were at least eighteen years of age, 125 developed nonunion, representing a risk of 13.3% (95% confidence interval [CI], 11.3% to 15.6%). Sex, smoking status, overall fracture displacement, overlap, translation, and fracture comminution were associated with increased risk of nonunion ($p < 0.1$) on bivariate analysis and were considered in the multivariate model. On multivariate analysis, only the categorical variables of smoking and comminution and the continuous variable of overall fracture displacement remained independently predictive. Examination of these variables revealed no significant interactions or multi-collinearity effects. Further multiple logistic analysis incorporating interaction terms between each of these three factors and whether or not the patient was under twenty-six years of age was performed. Testing these three extra terms simultaneously gave a chi-square

TABLE II "Ready Reckoner" for Estimating the Risk of Nonunion

Overall Displacement *(mm)*	Risk *(%)* Noncomminuted Fracture in Nonsmoker	Comminuted Fracture in Nonsmoker	Noncomminuted Fracture in Smoker	Comminuted Fracture in Smoker
10	2	3	6	10
15	3	6	12	19
20	7	12	23	34
25	14	23	39	52
30	26	39	57	70
40	62	74	86	92

value of 1.34 and p value of 0.72, indicating that there was no strong evidence that the factors that predict nonunion differ between younger and older patients.

The regression coefficient B, odds ratio exp(B), and significance for each variable used for estimating the risk of nonunion in the final model are depicted in Table I. The method of calculating the probability of nonunion in an individual patient is also given in the table. For simplification, a "ready reckoner" for estimating the risk of nonunion at 5-mm intervals of overall fracture displacement is presented in Table II. The Hosmer-Lemeshow chi-square value of the model was 9.48 on eight degrees of freedom ($p = 0.45$). The model, based on the three clinical risk factors, was therefore judged to be of high quality according to the Hosmer-Lemeshow goodness-of-fit statistic. The Wald chi-square statistic for each of the three variables achieved significance in the final model (Table I). When split-sample validation was carried out by dividing the sample at random into equal-sized training and validation sets, the same three factors were found to be independently predictive of nonunion in the training set. The area under the receiver operating characteristic (ROC) curve was 0.848 when the prediction from the training set was used on the patients in the validation set; in comparison, the area under the curve was 0.862 for the analysis of the entire dataset, suggesting that the values in Table III were only slightly overoptimistic.

Eleven (2.1%) of the 518 patients with <15 mm of fracture displacement developed nonunion compared with 114 (27.0%) of the 423 patients with ≥15 mm of displacement. Fifty-two (7.2%) of the 722 nonsmokers developed nonunion compared with seventy-three (33.3%) of the 219 smokers. Only fifty (8.5%) of the 589 fractures with no substantial comminution developed nonunion compared with seventy-five (21.3%) of the 352 with comminution.

The union outcome was cross-tabulated against the outcome predicted by the model in a 2 × 2 table to estimate the model's accuracy as a diagnostic test. PPV and NPV values for

TABLE III Performance of the Multivariate Model at Various Thresholds

Threshold Probability of Nonunion	"At Risk"* *(%)*	Positive Predictive Value *(%)*	Correct:Incorrect Diagnoses in Operative Group†	Negative Predictive Value *(%)*	Surgical Procedures Per Nonunion‡	Total Percentage Correct
100%, nonoperative treatment for all	0	0	No patients managed operatively	86.7	No patients managed operatively	86.7
50%	8.1	55.8	1.3	90.5	1.8	87.6
45%	9.0	55.3	1.2	90.9	1.8	87.6
40%	10.0	58.5	1.4	91.7	1.7	88.4
30%	13.4	54.0	1.2	93.0	1.9	87.8
20%	17.9	48.2	0.9	94.3	2.1	86.1
10%	34.8	31.2	0.5	96.3	3.2	62.9
0%, primary operative treatment for all	100	13.3	0.15	0	7.5	13.3

*Percentage of whole cohort identified as being at risk of nonunion. †Ratio of correct to incorrect diagnoses in the operative group if all patients with a probability greater than the threshold are managed operatively. ‡Number of surgical procedures undertaken per nonunion if all patients with a probability greater than the threshold are managed operatively.

different thresholds of predicted probability are depicted in Table III. The sensitivity of the model is the proportion of nonunions correctly identified at a particular threshold value, whereas the PPV is the proportion of patients with nonunion who are correctly diagnosed at a particular threshold. The specificity and NPV provide similar estimates for fracture union. Decreasing the threshold for diagnosis of nonunion from 50% increases the sensitivity of the model to detect a higher proportion of nonunions, but it decreases the PPV of the model at that particular threshold. In contrast, decreasing the threshold for diagnosis decreases the specificity of the model to predict union while increasing the NPV. The overall percentage of correct diagnoses is lower at lower threshold values than at higher thresholds.

If all displaced midshaft fractures were managed operatively in patients eighteen years of age or older, the calculated NNT to prevent a single nonunion was 7.5. If only those fractures with a predicted nonunion probability of ≥40% were managed operatively, the NNT fell to 1.7.

Discussion

Although historical estimates of the nonunion rate following displaced midshaft clavicular fractures are low, our findings support the increased prevalence of nonunion reported in contemporary studies[1]. Nonunion occurred in 125 (13.3%) of the 941 patients who were at least eighteen years of age. Within the same database, no nonunions occurred in 184 patients who were less than eighteen years of age, yielding an upper 95% confidence limit of 2% for the prevalence of nonunion in this group. On stepwise multiple logistic regression analysis of patients who were at least eighteen years of age, age no longer represented an independently significant predictor of nonunion. In this group, only smoking, comminution, and overall displacement were independently predictive of nonunion. Thus, the risk was close to zero in children but then leveled out at an appreciable value in adults. Using a multivariate model that takes the three identified risk factors into account, estimates of the risk of nonunion after nonoperative management can be produced. Previous studies have included children[6], nondisplaced fractures[3,7,8], and fractures of the lateral and medial ends of the clavicle, which behave differently. To reduce the confounding effects of age, displacement, and anatomical location, only displaced midshaft fractures in adults were considered in the present study.

The majority of the fractures in our study cohort occurred in young men, often during participation in sports or cycling. Smoking was independently predictive of nonunion but we did not determine the strength of the association to establish whether heavier smokers were at greater risk. The deleterious effects of smoking on fracture-healing have been demonstrated in both experimental[9] and clinical studies[10]. However, previous studies in which smoking was explored as a risk factor for clavicular nonunion revealed no association[2,8].

Both displacement and comminution were associated with an increased rate of nonunion, confirming the importance of fracture morphology on healing. Displacement and comminution are associated with higher-energy trauma and likely reflect the severity of underlying osseous and soft-tissue injuries[11]. Previous studies have demonstrated a correlation between fracture comminution and poorer outcome[2-4,11].

The association between initial displacement and poor functional outcome has been extensively described. High nonunion rates (up to 29%) have been observed in displaced fractures[2,3,6,12-16], and a direct relationship exists between increased displacement and worse functional outcome scores[1]. A significant association ($p < 0.0001$) between initial shortening and the development of nonunion has been reported[2]. It has also been reported that displaced midshaft fractures were 18.5 times more likely to result in delayed union or nonunion compared with nondisplaced fractures[3]. Within our model, the odds ratio associated with displacement appears low because it is expressed as the value per millimeter. However, most displaced fractures are displaced at least 10 mm.

The present study has a number of shortcomings. The complex three-dimensional configurations of fractures are not fully appreciated on radiographs, limiting the accuracy of measurements of displacement, translation, and angulation. In addition, subtle inconsistencies in patient positioning and radiographic projection make standardization challenging. Although radiography allows a qualitative assessment of callus formation and cortical bridging, doubt has been cast over its reliability for the assessment of fracture-healing[17]. This may have contributed to misdiagnosis of nonunion in the twelve patients who underwent operative exploration after twenty-four weeks for suspected nonunion but were found to have a healed fracture. This 10% false-positive rate may affect the interpretation of the results of this study, as sixteen patients diagnosed with nonunion did not have surgery and some of these may have had a united fracture. Three-dimensional computed tomography would improve the interpretation of fracture morphology and provide a more accurate assessment of healing in future studies[18], but its use was limited in the present study by its cost and higher radiation dosage. Patients who underwent operative treatment before twenty-four weeks for reasons including skin compromise, patient request, or a decision of the surgeon were excluded. It is almost certain that some of these patients were at high risk of nonunion, affecting the external validity of the study. In view of these shortcomings, it is important that the results of this study be validated in independent samples.

By applying our multivariate model, we produced estimates of the risk of nonunion after nonoperative management. We created a probability calculator that stratifies the risk, taking into account the three independently predictive risk factors. From the "ready reckoner" (Table II), it can be seen that nonunion in nonsmokers with noncomminuted fractures is approximately thirty times more likely in fractures with 40 mm of overall displacement compared with those with 10 mm of displacement. Our results confirm the need for consideration of all three variables when identifying patients at greatest risk.

Our statistical model enables estimation of the risk of nonunion in patients with displaced midshaft clavicular fractures undergoing nonoperative management. However, because of the relatively low prevalence of nonunion, the ability of the model to accurately predict nonunion in individual patients is poor. Although it is possible to select a particular threshold of estimated risk below which we can be fairly certain that patients will not develop nonunion, it is less certain that patients above this threshold will develop this complication. This is a common problem with statistical models that evaluate outcomes of low prevalence. Lowering the threshold for the predicted probability increases the sensitivity of the model to identify those who will develop nonunion, but at the expense of reducing the overall accuracy of the model to correctly identify those who will achieve union (i.e., the PPV value) and reducing the overall percentage of correct diagnoses.

Many patients at high predicted risk of nonunion will heal without this complication, and a number of patients with few risk factors will nevertheless develop nonunion. Unfortunately, it is the latter patients (young, nonsmokers) in whom the consequences of nonunion and the potential benefits of surgery are greatest. There are likely to be additional risk factors for nonunion that we did not identify despite the large numbers of patients included. These factors might include interposition of soft tissue between fragments and genetic predisposition. It is also conceivable that factors of low prevalence may influence the development of nonunion in individual cases. In particular, comorbidities that may increase the risk of nonunion include rheumatoid disease, immunocompromise, renal failure, epilepsy, and use of drugs such as corticosteroids and those interfering with vitamin-D metabolism. Because these comorbidities do not occur with sufficient frequency to permit their identification as statistically significant risk factors, they cannot be incorporated into the diagnostic test even though they may be important in individual cases.

We believe that the predicted probability of nonunion should be used to guide clinicians in counseling patients, rather than to apply an arbitrary threshold of risk to determine the management strategy. Furthermore, the ability of the model to predict a higher risk of nonunion in certain patients does not imply that their outcome would always be improved by primary operative intervention, especially if they are heavy smokers. Primary fixation of all displaced midshaft clavicular fractures has been advocated in recognition of the increased rate of nonunion and inferior functional outcomes associated with nonoperative treatment of fractures of this type[1]. However, with this approach, more than seven procedures would need to be undertaken to prevent a single nonunion (Table III). By providing estimates of the probability of nonunion, we hope to improve awareness of which patients are at greatest risk of nonunion while minimizing the number of patients undergoing unnecessary surgery. We believe that treatment of patients should be individualized, with consideration of each patient's activity level and expectations of treatment. Where appropriate, smoking cessation should form an integral part of treatment. ■

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