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Epidemiology of Fracture Nonunion in 18 Human Bones

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IMPORTANCE Failure of bone fracture healing occurs in 5% to 10% of all patients. Nonunion risk is associated with the severity of injury and with the surgical treatment technique, yet progression to nonunion is not fully explained by these risk factors.

OBJECTIVE To test a hypothesis that fracture characteristics and patient-related risk factors assessable by the clinician at patient presentation can indicate the probability of fracture nonunion.

DESIGN, SETTING, AND PARTICIPANTS An inception cohort study in a large payer database of patients with fracture in the United States was conducted using patient-level health claims for medical and drug expenses compiled for approximately 90.1 million patients in calendar year 2011. The final database collated demographic descriptors, treatment procedures as per *Current Procedural Terminology* codes; comorbidities as per *International Classification of Diseases, Ninth Revision* codes; and drug prescriptions as per National Drug Code Directory codes. Logistic regression was used to calculate odds ratios (ORs) for variables associated with nonunion. Data analysis was performed from January 1, 2011, to December 31, 2012,

EXPOSURES Continuous enrollment in the database was required for 12 months after fracture to allow sufficient time to capture a nonunion diagnosis.

RESULTS The final analysis of 309 330 fractures in 18 bones included 178 952 women (57.9%); mean (SD) age was 44.48 (13.68) years. The nonunion rate was 4.9%. Elevated nonunion risk was associated with severe fracture (eg, open fracture, multiple fractures), high body mass index, smoking, and alcoholism. Women experienced more fractures, but men were more prone to nonunion. The nonunion rate also varied with fracture location: scaphoid, tibia plus fibula, and femur were most likely to be nonunion. The ORs for nonunion fractures were significantly increased for risk factors, including number of fractures (OR, 2.65; 95% CI, 2.34-2.99), use of nonsteroidal anti-inflammatory drugs plus opioids (OR, 1.84; 95% CI, 1.73-1.95), operative treatment (OR, 1.78; 95% CI, 1.69-1.86), open fracture (OR, 1.66; 95% CI, 1.55-1.77), anticoagulant use (OR, 1.58; 95% CI, 1.51-1.66), osteoarthritis with rheumatoid arthritis (OR, 1.58; 95% CI, 1.38-1.82), anticonvulsant use with benzodiazepines (OR, 1.49; 95% CI, 1.36-1.62), opioid use (OR, 1.43; 95% CI, 1.34-1.52), diabetes (OR, 1.40; 95% CI, 1.21-1.61), high-energy injury (OR, 1.38; 95% CI, 1.27-1.49), anticonvulsant use (OR, 1.37; 95% CI, 1.31-1.43), osteoporosis (OR, 1.24; 95% CI, 1.14-1.34), male gender (OR, 1.21; 95% CI, 1.16-1.25), insulin use (OR, 1.21; 95% CI, 1.10-1.31), smoking (OR, 1.20; 95% CI, 1.14-1.26), benzodiazepine use (OR, 1.20; 95% CI, 1.10-1.31), obesity (OR, 1.19; 95% CI, 1.12-1.25), antibiotic use (OR, 1.17; 95% CI, 1.13-1.21), osteoporosis medication use (OR, 1.17; 95% CI, 1.08-1.26), vitamin D deficiency (OR, 1.14; 95% CI, 1.05-1.22), diuretic use (OR, 1.13; 95% CI, 1.07-1.18), and renal insufficiency (OR, 1.11; 95% CI, 1.04-1.17) (multivariate $P < .001$ for all).

CONCLUSIONS AND RELEVANCE The probability of fracture nonunion can be based on patient-specific risk factors at presentation. Risk of nonunion is a function of fracture severity, fracture location, disease comorbidity, and medication use.

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Supplemental content

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The rate of fracture nonunion is estimated to be between 5%[1] and 10%,[2] and the rate of nonunion may be increasing as the survival rate for patients with severe injuries improves.[3] The risk of nonunion is related to the severity of injury resulting in fracture,[4] and many randomized clinical trials[5] have shown that variations in nonunion rates are associated with different surgical treatments. However, progression to nonunion is not fully explained by these factors alone.[6] Determination of the probability for and potential mitigation of nonunion risk is an important clinical objective because patients with nonunion can expect more long-term pain, physical disability, mental health problems, and medical treatment costs as well as a slower return to normal work productivity.[7] Herein, we describe the epidemiology of fracture nonunion in adults, with a focus on information available to the clinician at patient presentation. We hypothesize that the interplay between a patient's physiologic risk factors and fracture characteristics increases the risk of fracture nonunion.[5] We tested this hypothesis in a large payer database of patients with fracture in the United States.[8]

Key Points

Question Which patient-specific risk factors other than injury severity increase risk of nonunion of fractures?

Findings In an inception cohort study of a payer database in which 309 330 fractures in 18 bones were analyzed, only 5 patient-specific risk factors significantly increased the risk of nonunion more than 50% across all bones: multiple concurrent fractures, prescription nonsteroidal anti-inflammatory drug and opioid use, open fracture, anticoagulant use, and osteoarthritis with rheumatoid arthritis.

Meaning The probability of fracture nonunion can be determined from patient-specific risk factors at presentation.

Methods

Database

Truven Health Analytics (Durham, North Carolina) compiled patient-level health claims data for medical and drug expenses, together with laboratory test results, hospital discharge information, and death data on 90.1 million patients.[9] Data were submitted by hospitals, managed care organizations, Medicare and Medicaid programs, and approximately 300 large corporations in exchange for benchmark reports.[9] This study was approved and exempted from the need for informed consent by the institutional review board of Duke University Medical Center because patient data were deidentified.

The final database contained 1 row per unique fracture, with comma-separated values for patient variables. Variables included patient demographics, treatment procedures as per the *Current Procedural Terminology* codes; disease comorbidities as per the *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes; and drug prescriptions as per National Drug Code Directory (https://www.accessdata.fda.gov/scripts/cder/ndc/) codes.

Study Design

Study inclusion was limited to patients with a coded bone fracture in calendar year 2011. Patients were excluded if they had less than 12 months of continuous enrollment following fracture so as to capture all coded nonunions.

Fractures were identified based on 5-digit *ICD-9* codes. Rule-out codes were not counted; such codes are used to order radiography in some patients who may not have a fracture. In addition, codes with an unspecified character string in the definition were not used because such codes are replaced with a specific code defining the location of the fracture. Nonunion was determined by the presence of either a nonunion code or a code for prescription use of an electrical bone stimulation device since such devices are used to treat nonunion. Patients who used low-intensity pulsed ultrasound devices for a fresh fracture were excluded because this prescription device may increase the healing rate for bone.

Disease comorbidities were identified using *ICD-9* primary disease codes. Secondary conditions arising from a chronic disease condition (eg, diabetic retinopathy) were not used as proxies for the primary disease because of the risk of double counting. Thus, our analysis would not identify patients with diabetes diagnosed before 2011, although medications used to treat diabetes would be captured. Medications were identified using National Drug Code Directory codes, which are for oral medications purchased in a retail pharmacy. Such codes contain a range of medications; the opioid class contains analgesics but can also contain opioid agonists used to treat addiction. Medications were assumed to be part of long-term therapy, with the exception of antibiotics, thrombolytics, analgesics, and corticosteroids.

Analysis focused on the cohort of patients aged 18 to 63 years at the time of the fracture. This age range was chosen because skeletal maturity is achieved by approximately 18 years.[10] Patients younger than 18 years were abundant in the database, but their healing rate was high, so it was less compelling to identify risk factors for those who failed to heal. Patients older than 63 years were excluded because the requirement for 12 months of continuous enrollment created an artifact as patients transitioned to Medicare and no longer appeared in the database. Older individuals were also excluded because only some purchase Medicare supplemental coverage and thus are not representative of other Medicare patients.

Analytic Strategy

Our overall hypothesis was that the probability of fracture nonunion can be determined with the use of risk factors derived from patient demographics, using *Current Procedural Terminology*, *ICD-9*, and National Drug Code Directory codes. Possible risk factors for nonunion were identified in a literature search,[5] with a focus on risk factors likely to be of concern to orthopedic surgeons. We requested information on 257 potential nonunion risk factors, including fracture type, fracture cause, patient demographics, and medication use. We focused on 18 bones most frequently fractured. An operative

treatment variable was defined for patients who received any fracture surgery and we compared them with patients who did not undergo surgery. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc). The critical value for significance was set at $P < .05$.

Because so many variables were available for each patient, it was important to group variables into manageable categories. Ultimately, data were pooled to obtain 45 variables of interest (eAppendix in the Supplement). For example, patients had as many as 15 separate fractures, but we binned them into a smaller number of categories for analysis (eg, 1-2 fractures, 3-5 fractures, and ≥6 fractures). Multivariate logistic regression was used to control for correlations among the various risk factors.

We did not adjust for multiple comparisons because showing 95% CIs for each odds ratio (OR) achieves the same end. Furthermore, an OR significant at $P < .001$ is comparable to an OR significant at $P = .05$ that has been Bonferroni corrected for 50 comparisons. Correcting for additional comparisons would be likely to lead to type II (false-negative) errors. In an exploratory context such as this, P values should be interpreted as a measure of statistical evidence rather than a test of hypothesis.

Validation

In parallel to the logistic regression analysis, we also conducted random forest decision tree modeling using the same covariates.[11] The random forest method is invariant to interactions and terms of higher dimension, such as quadratic terms. The random forest method generally performs better than regression methods but, unlike regression analysis, is harder to interpret. We compared the methods using the C statistic (area under the receiver operating characteristic curve) and found that the models were substantially equivalent; the C statistic of the random forest model was only slightly larger than the C statistic of the logistic regression model, differing in the third or fourth decimal place. We elected to report only the main effects logistics regression model herein. Nonunion rates for individual bones were also compared with those in the literature. Data analysis was performed from January 1, 2011, to December 31, 2012.

Table 1. Demographic Summary of Adults With and Without Nonunion Fracture

Characteristic	No. (%)	
	Total	Nonunion
Fractures	309 330 (100)	15 249 (4.9)
Patient age at fracture, y		
18-29	59 451 (19.2)	2704 (4.5)
30-39	44 353 (14.3)	2128 (4.8)
40-49	64 779 (20.9)	3573 (5.5)
50-63	140 747 (45.5)	6844 (4.9)
Sex		
Male	130 378 (42.1)	7010 (5.4)
Female	178 952 (57.9)	8239 (4.6)
BMI		
<25.0	285 611 (92.3)	13 412 (4.7)
25.0-29.9	1570 (0.5)	74 (4.7)
30.0-39.9	13 050 (4.2)	941 (7.2)
≥40.0	9099 (2.9)	822 (9)
Bone type		
Long	166 377 (53.8)	8042 (4.8)
Other	142 953 (46.2)	7207 (5)
Fracture type		
Closed	297 172 (96.1)	13 918 (4.7)
Open	12 158 (3.9)	1331 (10.9)
No. of fractures		
1	256 367 (82.9)	11 389 (4.4)
2	36 818 (11.9)	2069 (5.6)
3	9053 (2.9)	744 (8.2)
4	3411 (1.1)	359 (10.5)
5	1675 (0.5)	237 (14.1)
6	929 (0.3)	192 (20.7)
≥7	1077 (0.3)	259 (24.0)
Past or current smoker		
No	277 720 (89.8)	12 936 (4.7)
Yes	31 610 (10.2)	2313 (7.3)
Diagnosed alcoholism		
No	303 714 (98.2)	14 831 (4.9)
Yes	5616 (1.8)	418 (7.4)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Results

A flowchart (eFigure in the Supplement) shows how the patient sample was assembled. There were 309 330 fractures in patients ranging from 18 to 63 years (mean [SD], 44.48 [13.68]), or approximately 6725 patients in each of the 46 age classes. The overall nonunion rate was 4.9% (**Table 1**), with substantial variation from bone to bone. The metatarsal was the most frequently fractured bone, with a nonunion rate of 5.7%. The lowest nonunion rates were for the metacarpal (1.5%) and radius (2.1%) bones. The highest nonunion rates were for the scaphoid (15.5%), followed by the tibia and fibula (14%) and femur (13.9%). These were the only bones for which the nonunion rate was greater than 10%. If 4.9% of all patients had nonunion fractures (Table 1), then there were approximately 330 nonunion patients per age class. This relatively small number of nonunion fractures per age class could potentially result in uncertainty in estimating nonunion rates as a function of age.

There were clear demographic differences between patients who healed and those who failed to heal (Table 1). Women had more fractures, but men had a higher proportion of nonunions. Open fractures represented 3.9% of all fractures, but 10.9% of open fractures were nonunion and 4.7% of closed fractures were nonunion. Multiple fractures were more likely result in nonunion; nonunion frequency was 4.4% in patients with 1 fracture but 24% among patients with 7 or more fractures.

Multivariate analysis determined the ORs of nonunion with comorbid disease when adjusted for other risk factors (**Table 2**).

Table 2. Demographic Summary of Adults With Fracture and Comorbid Condition

Risk Factor	No. (%)			OR (95% CI)		P Value
	Fractures	Normal Healing	Nonunion Fracture	Univariate	Multivariate	
Male gender	130 378 (42.1)	123 368	7010	1.18 (1.14-1.21)	1.21 (1.16-1.25)	≤.001
Cardiovascular disease[a]	96 209 (31.1)	90 221	5988	1.46 (1.41-1.51)	0.94 (0.90-0.98)	≤.05
Allergy[a]	60 386 (19.5)	57 310	3076	1.04 (1.00-1.08)	0.90 (0.86-0.93)	≤.001
Osteoarthritis only	42 928 (13.9)	39 418	3510	1.96 (1.89-2.04)	1.45 (1.39-1.52)	≤.001
Past or current smoker	31 610 (10.2)	29 297	2313	1.62 (1.54-1.69)	1.20 (1.14-1.26)	≤.001
Obesity	23 719 (7.7)	21 882	1837	1.70 (1.62-1.79)	1.19 (1.12-1.25)	≤.001
Type 2 diabetes	23 681 (7.7)	21 958	1723	1.60 (1.52-1.68)	1.15 (1.07-1.24)	≤.001
Renal insufficiency	19 255 (6.2)	17 678	1577	1.80 (1.71-1.90)	1.11 (1.04-1.17)	≤.001
Vitamin D deficiency	12 661 (4.1)	11 796	865	1.44 (1.34-1.54)	1.14 (1.05-1.22)	≤.001
Osteoporosis	11 683 (3.8)	10 774	909	1.67 (1.55-1.78)	1.24 (1.14-1.34)	≤.001
Nutritional deficiency	7282 (2.4)	6612	670	2.00 (1.84-2.16)	1.09 (1.00-1.19)	.05
Alcoholism	5616 (1.8)	5198	418	1.57 (1.42-1.73)	1.05 (0.94-1.17)	.36
Type 1 diabetes	3194 (1)	2856	338	2.42 (2.16-2.71)	1.40 (1.21-1.61)	≤.001
Phlebitis	3100 (1)	2786	314	2.20 (1.96-2.47)	1.10 (0.97-1.24)	.15
Osteoarthritis and rheumatoid arthritis	2668 (0.9)	2396	272	2.51 (2.21-2.84)	1.58 (1.38-1.82)	≤.001
Rheumatoid arthritis	1920 (0.6)	1804	116	1.42 (1.17-1.71)	1.14 (0.93-1.38)	.20

Abbreviation: OR, odds ratio.

[a] Protective factor.

Multivariate evaluation of fractures associated with comorbidities (Table 2) indicated that 3 risk factors (osteoarthritis [OR, 1.45; 95% CI, 1.39-1.52], osteoarthritis with rheumatoid arthritis [OR, 1.58; 95% CI, 1.38-1.82], and type 1 diabetes [OR, 1.40; 95% CI, 1.21-1.61]) increased the odds of nonunion by at least 40%. Odds ratios for individual nonunion risk factors were generally small, with 13 of 16 multivariate ORs less than 1.40 (Table 2). Two risk factors were inversely associated with nonunion (OR, <1): cardiovascular disease (OR, 0.94; 95% CI, 0.90-0.98) and allergy (OR, 0.90; 95% CI, 0.86-0.93) (Table 2). The number of risk factors and the complex interactions possible between risk factors may explain the absence of multivariate ORs higher than 1.58 (Table 2).

Use of certain medications increased the nonunion risk (**Table 3**). After controlling for confounding variables, the most powerful risk factor was use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids (multivariate OR, 1.84; 95% CI, 1.73-1.95). Other pain medications, such as opioids alone, and anticonvulsants, with or without benzodiazepines, were moderately strong positive risk factors, whereas antidiabetics other than insulin (OR, 0.92; 95% CI, 0.86-0.99) and oral contraceptives (OR, 0.88; 95% CI, 0.81-0.95) were inversely associated with nonunion.

Nonunion ORs were significantly increased for many risk factors (**Table 4** and **Table 5**), including number of fractures (OR, 2.65; 95% CI, 2.34-2.99), use of prescription analgesics (NSAIDs and opioids; OR, 1.84; 95% CI, 1.73-1.95), operative treatment (OR, 1.78; 95% CI, 1.69-1.86), open fracture (OR, 1.66; 95% CI, 1.55-1.77), anticoagulant use (OR, 1.58; 95% CI, 1.51-1.66), osteoarthritis with rheumatoid arthritis (OR, 1.58; 95% CI, 1.38-1.82), anticonvulsant use with benzodiazepines (OR, 1.49; 95% CI, 1.36-1.62), opioid use (OR, 1.43; 95% CI, 1.34-1.52), type 1 diabetes (OR, 1.40; 95% CI, 1.21-1.61), high-energy injury (OR, 1.38; 95% CI, 1.27-1.49), osteoporosis (1.24; 95% CI, 1.14-1.34), male gender (OR, 1.21; 95% CI, 1.16-1.25), insulin use (OR, 1.21; 95% CI, 1.10-1.31), diagnosed smoking (OR, 1.20; 95% CI, 1.14-1.26), diagnosed obesity (OR, 1.19; 95% CI, 1.12-1.25), antibiotic use (OR, 1.17; 95% CI, 1.13-1.21), osteoporosis medication use (OR, 1.17; 95% CI, 1.08-1.26), diagnosed vitamin D deficiency (OR, 1.14; 95% CI, 1.05-1.22), diuretic use (OR, 1.13; 95% CI, 1.07-1.18), and renal insufficiency (OR, 1.11; 95% CI, 1.04-1.17) (all, multivariate $P < .001$).

Relatively few risk factors affected multiple bones (Tables 4 and 5). The need for operative treatment was associated with nonunion in 15 bones, anticoagulant use was associated with nonunion in 14 bones, use of analgesics (NSAIDs and opioids) affected 12 bones, and osteoarthritis and use of anticonvulsants each affected 11 bones. Overall, the largest risk factor for nonunion was the number of fractures (OR, 2.65; 95% CI, 2.34-2.99).

A limited number of putative risk factors were inversely correlated with nonunion (Tables 4 and 5), including oral contraceptive use (OR, 0.88; 95% CI, 0.81-0.95), allergy (OR, 0.90; 95% CI, 0.86-0.93), and age (OR, 0.97; 95% CI, 0.95-0.98); each was apparently protective in at least 2 bones. Some bones have several protective factors; both radius and ankle had 3 protective factors. A total of 12 bones had at least 1 protective factor.

Smoking was not identified as a major risk factor in this study (Tables 4 and 5). However, our data included only diagnosed past or current smoking, which most reliably may mean that someone was offered smoking cessation therapy. Thus, our count of smokers is likely an underestimate. Only 10.2% of patients were coded as past or current smokers (Table 1), whereas 18% of the general population is expected to smoke[12] and other nonunion cohort studies have reported a prevalence of smoking higher than the US average.[13] Similarly, we may underestimate obesity prevalence; only diagnosed obesity

Table 3. Medication Use by Adults With Fracture

Risk Factor	No. (%)			OR (95% CI)		P Value
	Fractures	Normal Healing	Nonunion Fracture	Univariate	Multivariate	
Antibiotics	201 728 (65.2)	190 592	11 136	1.47 (1.42-1.52)	1.17 (1.13-1.21)	≤.001
Analgesics (NSAIDs and opioids)	129 213 (41.8)	120 703	8510	2.70 (2.56-2.85)	1.84 (1.73-1.95)	≤.001
Menopausal corticosteroids	102 711 (33.2)	97 001	5710	1.22 (1.18-1.25)	1.02 (0.98-1.05)	.40
Opioids	98 267 (31.8)	93 663	4604	1.88 (1.78-2.00)	1.43 (1.34-1.52)	≤.001
Cardiac medications	91 942 (29.7)	86 415	5527	1.37 (1.32-1.41)	1.04 (0.99-1.08)	.13
Diuretics	38 947 (12.6)	36 257	2690	1.52 (1.46-1.59)	1.13 (1.07-1.18)	≤.001
Anticonvulsants	34 859 (11.3)	31 928	2931	2.04 (1.96-2.12)	1.37 (1.31-1.43)	≤.001
Antidiabetics[a,b]	25 319 (8.2)	23 692	1627	1.36 (1.29-1.43)	0.92 (0.86-0.99)	≤.001
Anticoagulants	24 693 (8)	21 841	2852	2.87 (2.75-2.99)	1.58 (1.51-1.66)	≤.001
NSAIDs	23 847 (7.7)	23 186	661	1.09 (1.00-1.19)	0.98 (0.89-1.07)	.60
Oral contraceptives[b]	19 989 (6.5)	19 227	762	0.75 (0.70-0.81)	0.88 (0.81-0.95)	≤.001
Osteoporosis medications	16 771 (5.4)	15 658	1113	1.40 (1.31-1.49)	1.17 (1.08-1.26)	≤.001
Nonmenopausal corticosteroids	12 765 (4.1)	12 004	761	1.23 (1.15-1.33)	1.07 (0.99-1.15)	.09
Insulin	12 412 (4)	11 347	1065	1.87 (1.75-1.99)	1.21 (1.10-1.31)	≤.001
Benzodiazepines only	9118 (3)	8565	553	1.43 (1.31-1.56)	1.20 (1.10-1.31)	≤.001
Anticonvulsants and benzodiazepines	7154 (2.3)	6509	645	2.20 (2.03-2.39)	1.49 (1.36-1.62)	≤.001
Immunosuppressants	4076 (1.3)	3781	295	1.51 (1.34-1.70)	1.10 (0.97-1.25)	.14
Parathyroid hormone	861 (0.3)	781	80	1.98 (1.57-2.49)	1.27 (0.99-1.62)	.06
Coagulants	318 (0.1)	314	4	0.25 (0.09-0.66)	0.24 (0.09-0.64)	.004

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

[a] Not insulin.

[b] Protective factor.

was analyzed, so many people with nonunion fractures may have been obese but we have no record of it.

Lack of convergence of the model was a rare problem (Tables 4 and 5) except for coagulants, which appear to be rarely used among patients with fractures (Table 3). The number of patients with multiple scaphoid fractures may have been too small to find a solution for nonunion associated with multiple fractures. Only 10 bone-risk factor ORs other than coagulants could not be estimated.

Discussion

There were clear demographic differences between patients whose fractures healed and those whose fractures failed to heal (Table 1). Most risk factors conferred a relatively small increase in multivariate nonunion risk (Table 2), perhaps because there are complex interactions between and among risk factors. Use of certain medications was an important determinant of nonunion (Table 3). Adjusting medication use by patients may enable physicians to improve the odds that a patient will heal. Nonunion rates varied among bones, and the contributions of various risk factors showed a complex interplay (Tables 4 and 5). In general, nonunion rate appears to be a function of fracture severity, fracture location, disease comorbidity, and medication use.

The distinction between univariate and multivariate ORs is important. For example, type 2 diabetes was associated with a univariate OR of 1.60 and a multivariate OR of 1.15 (Table 2). If that diagnosis is the only information that a clinician has about a patient, then it is reasonable to conclude that this patient has a 1.60-fold higher risk of nonunion than does a person without type 2 diabetes. As other variables become known and can be incorporated into a risk assessment, the risk associated specifically with type 2 diabetes decreases. In a multivariate analysis, which controls for many other factors, the nonunion risk associated with type 2 diabetes was 1.15-fold times the risk of nonunion in a person without that disease (Table 2). It is almost certainly the case that type 2 diabetes has not been diagnosed and treatment has not been instituted in some patients; thus, the disease would not have been analyzed in this study. Diabetes medications other than insulin appear to provide protection from nonunion (Tables 4 and 5), although the mechanism of such a protective effect is not known. When working with large patient databases (eg, big data), unanticipated associations are likely to be found. Causality cannot be tested without using an experimental approach; therefore, big data projects should be regarded as an opportunity for hypothesis generation rather than hypothesis testing.

The overall nonunion rate that we report was 4.9% (Table 1). This rate is somewhat lower than others reported in the literature,[1,2] although the healing rate for individual bones aligns well with previously published information. For example, the tibial nonunion rate we report was 7.4% for 12 808 fractures. The literature suggests that the expected nonunion rate for tibial fractures is 7.6%, a value derived by collating the reported healing rate in 46 publications spanning the period from 1976 to 2014 and including 5920 fractures treated

Table 4. Multivariate ORs for Nonunion Among Adults With Fracture: First Set

Risk Factor	OR (95% CI)									
	All 18 Bones (N = 309 330)	Metatarsal (n = 58 377)	Radius (n = 50 998)	Ankle (n = 45 861)	Metacarpals (n = 20 370)	Trunk (n = 19 364)	Tarsal (n = 19 306)	Humerus (n = 15 062)	Tibia (n = 12 808)	Radius and Ulna (n = 9380)
≥6 vs 1-2 Fractures per patient	2.65 (2.34-2.99)[a]	2.39 (1.08-5.26)	3.87 (2.42-6.18)[a]	4.57 (3.05-6.84)[a]	1.43 (0.44-4.71)	3.17 (1.93-5.20)[a]	3.88 (2.39-6.29)[a]	2.75 (1.75-4.33)[a]	3.16 (2.10-4.73)[a]	1.81 (1.02-3.20)
NSAID with opioid use vs no analgesics	1.84 (1.73-1.95)[a]	1.61 (1.44-1.80)[a]	2.58 (2.01-3.30)[a]	1.68 (1.40-2.01)[a]	2.91 (1.79-4.73)[a]	1.80 (1.15-2.81)[b]	2.25 (1.77-2.84)[a]	1.27 (0.95-1.68)	1.93 (1.45-2.57)[a]	1.78 (1.20-2.63)[c]
Requires operative vs conservative procedure	1.78 (1.69-1.86)[a]	4.02 (3.60-4.49)[a]	1.51 (1.30-1.76)[a]	1.01 (0.89-1.14)	1.60 (1.19-2.15)[c]	4.89 (3.08-7.75)[a]	1.48 (1.18-1.86)[a]	3.07 (2.52-3.73)[a]	2.46 (1.92-3.15)[a]	1.41 (1.09-1.83)[b]
Open vs closed fracture	1.66 (1.55-1.77)[a]	0.98 (0.74-1.30)	1.91 (1.46-2.48)[a]	1.38 (1.16-1.65)[a]	2.16 (1.44-3.25)[a]	1.00 (0.44-2.29)	1.13 (0.85-1.48)	1.66 (1.28-2.16)[a]	2.34 (1.94-2.82)[a]	2.07 (1.57-2.71)[a]
Anticoagulant use vs none	1.58 (1.51-1.66)[a]	1.28 (1.11-1.47)[a]	1.89 (1.51-2.36)[a]	1.75 (1.54-1.99)[a]	3.60 (2.32-5.60)[a]	2.41 (1.86-3.12)[a]	1.52 (1.24-1.86)[a]	1.17 (0.90-1.52)	1.56 (1.33-1.83)[a]	2.05 (1.47-2.86)[a]
Osteoarthritis with rheumatoid arthritis vs no diagnosis	1.58 (1.38-1.82)[a]	1.48 (1.14-1.92)[c]	1.87 (1.15-3.03)	1.94 (1.32-2.87)[a]	4.23 (1.60-11.16)[c]	1.32 (0.56-3.09)	1.98 (1.20-3.28)[b]	1.49 (0.85-2.61)	1.89 (1.08-3.32)	1.45 (0.57-3.72)
Anticonvulsants with benzodiazepines vs none	1.49 (1.36-1.62)[a]	1.06 (0.85-1.32)	2.06 (1.52-2.78)[a]	1.72 (1.36-2.17)[a]	1.62 (0.86-3.05)	2.32 (1.55-3.47)[a]	1.56 (1.13-2.14)[b]	1.60 (1.15-2.22)[c]	1.17 (0.78-1.76)	3.21 (2.02-5.08)[a]
Unknown energy vs low-energy accident	1.48 (1.39-1.57)[a]	1.37 (1.17-1.59)[a]	1.18 (0.98-1.42)	1.52 (1.31-1.77)[a]	1.52 (1.00-2.32)	1.12 (0.81-1.54)	2.58 (1.84-3.63)[a]	1.00 (0.83-1.20)	1.66 (1.26-2.17)[a]	1.15 (0.87-1.51)
Osteoarthritis only vs no diagnosis	1.45 (1.39-1.52)[a]	1.38 (1.26-1.52)[a]	1.66 (1.40-1.97)[a]	1.52 (1.34-1.72)[a]	1.31 (0.88-1.94)	1.27 (1.00-1.62)	1.92 (1.62-2.27)[a]	1.37 (1.12-1.65)[c]	1.19 (0.98-1.43)	1.73 (1.31-2.28)[a]
Opioids only vs no opioids	1.43 (1.34-1.52)[a]	1.30 (1.15-1.47)[a]	1.91 (1.48-2.45)[a]	1.12 (0.93-1.35)	2.80 (1.73-4.53)[a]	1.25 (0.79-1.97)	1.72 (1.34-2.20)[a]	1.00 (0.75-1.33)	1.52 (1.14-2.02)[c]	1.35 (0.92-2.00)
Type 1 diabetes vs no diagnosis	1.40 (1.21-1.61)[a]	1.34 (1.01-1.75)	0.60 (0.28-1.28)	2.29 (1.63-3.22)[a]	1.13 (0.22-5.77)	1.22 (0.48-3.08)	2.16 (1.24-3.74)[b]	1.02 (0.56-1.84)	1.47 (0.80-2.68)	0.98 (0.37-2.57)
High-energy vs low-energy accident	1.38 (1.27-1.49)[a]	1.20 (0.90-1.59)	1.24 (0.94-1.63)	1.76 (1.41-2.19)[a]	2.93 (1.68-5.10)[a]	1.26 (0.87-1.82)	1.83 (1.19-2.80)[b]	1.20 (0.90-1.60)	1.46 (1.06-2.00)	1.15 (0.79-1.66)
Anticonvulsants only vs none	1.37 (1.31-1.43)[a]	1.25 (1.13-1.38)[a]	1.53 (1.28-1.82)[a]	1.49 (1.31-1.70)[a]	2.26 (1.63-3.12)[a]	1.69 (1.33-2.14)[a]	1.34 (1.12-1.59)[c]	1.35 (1.12-1.63)[c]	1.13 (0.93-1.36)	1.78 (1.37-2.32)[a]
3-5 vs 1-2 Fractures per patient	1.32 (1.23-1.40)[a]	0.90 (0.62-1.30)	1.94 (1.54-2.44)[a]	1.59 (1.31-1.92)[a]	2.14 (1.25-3.67)[b]	2.69 (2.07-3.48)[a]	1.28 (0.96-1.71)	0.99 (0.76-1.29)	1.42 (1.14-1.77)	1.42 (1.07-1.87)
Osteoporosis vs no diagnosis	1.24 (1.14-1.34)[a]	1.34 (1.13-1.58)[a]	1.57 (1.19-2.07)[a]	1.31 (1.02-1.67)	2.25 (0.94-5.36)	1.04 (0.58-1.86)	1.13 (0.78-1.63)	1.40 (1.03-1.89)	0.83 (0.55-1.24)	1.23 (0.78-1.96)
Male vs female gender	1.21 (1.16-1.25)[a]	1.08 (0.99-1.17)	1.45 (1.26-1.66)[a]	1.24 (1.12-1.38)[a]	0.82 (0.62-1.09)	1.06 (0.86-1.32)	0.96 (0.82-1.11)	1.11 (0.94-1.30)	1.33 (1.14-1.55)[a]	1.57 (1.26-1.96)[a]
Insulin use vs none	1.21 (1.10-1.31)[a]	1.56 (1.31-1.85)[a]	1.43 (1.00-2.06)	1.24 (1.00-1.55)	1.14 (0.54-2.40)	0.91 (0.56-1.48)	1.14 (0.77-1.67)	1.45 (1.06-1.99)	0.69 (0.47-1.00)	1.28 (0.77-2.13)
Past/current smoker vs never smoked	1.20 (1.14-1.26)[a]	1.03 (0.90-1.17)	1.24 (1.02-1.50)	1.18 (1.03-1.36)	1.22 (0.88-1.69)	1.07 (0.82-1.39)	1.17 (0.95-1.43)	1.22 (0.99-1.50)	1.29 (1.06-1.57)	1.33 (0.99-1.76)
Benzodiazepine only vs no anticonvulsants	1.20 (1.10-1.31)[a]	0.97 (0.79-1.18)	1.23 (0.89-1.69)	1.38 (1.08-1.76)[b]	0.87 (0.42-1.82)	1.05 (0.62-1.76)	1.22 (0.86-1.72)	1.85 (1.34-2.54)[a]	1.19 (0.81-1.73)	1.33 (0.80-2.23)
Obesity vs no diagnosis	1.19 (1.12-1.25)[a]	1.10 (0.97-1.23)	1.04 (0.82-1.30)	1.38 (1.20-1.58)[a]	0.94 (0.55-1.59)	1.02 (0.72-1.43)	1.16 (0.93-1.44)	1.03 (0.81-1.30)	1.21 (0.97-1.51)	1.38 (0.99-1.92)

(continued)

Table 4. Multivariate ORs for Nonunion Among Adults With Fracture: First Set (continued)

Risk Factor	OR (95% CI)									
	All 18 Bones (N = 309 330)	Metatarsal (n = 58 377)	Radius (n = 50 998)	Ankle (n = 45 861)	Metacarpals (n = 20 370)	Trunk (n = 19 364)	Tarsal (n = 19 306)	Humerus (n = 15 062)	Tibia (n = 12 808)	Radius and Ulna (n = 9380)
Antibiotic use vs none	1.17 (1.13-1.21)[a]	1.12 (1.02-1.22)	1.07 (0.93-1.23)	1.26 (1.12-1.41)[a]	1.45 (1.09-1.94)	1.33 (1.06-1.67)	1.08 (0.92-1.26)	1.11 (0.94-1.30)	1.30 (1.11-1.52)[a]	1.22 (0.98-1.51)
Osteoporosis medication use vs none	1.17 (1.08-1.26)[a]	1.26 (1.09-1.45)[c]	1.00 (0.76-1.31)	1.05 (0.83-1.34)	0.57 (0.20-1.64)	0.88 (0.51-1.52)	1.39 (1.01-1.92)	1.15 (0.86-1.52)	1.56 (1.11-2.18)[b]	0.81 (0.51-1.28)
Type 2 diabetes only vs no diagnosis	1.15 (1.07-1.24)[a]	1.08 (0.93-1.26)	1.38 (1.05-1.80)	1.32 (1.09-1.59)[c]	1.22 (0.64-2.33)	1.67 (1.15-2.41)[b]	1.01 (0.73-1.37)	1.00 (0.75-1.33)	1.27 (0.95-1.70)	1.09 (0.71-1.69)
Vitamin D deficiency vs no diagnosis	1.14 (1.05-1.22)[a]	1.11 (0.96-1.28)	0.88 (0.64-1.19)	1.06 (0.86-1.30)	0.56 (0.23-1.41)	1.18 (0.76-1.83)	1.13 (0.84-1.52)	0.95 (0.69-1.30)	1.34 (0.97-1.83)	0.82 (0.47-1.44)
Diuretic use vs none	1.13 (1.07-1.18)[a]	1.10 (1.00-1.21)	1.16 (0.97-1.39)	1.06 (0.92-1.20)	0.81 (0.51-1.30)	1.00 (0.77-1.31)	1.39 (1.14-1.68)[a]	1.26 (1.04-1.52)	1.26 (1.03-1.55)	1.09 (0.81-1.47)
Renal insufficiency vs no diagnosis	1.11 (1.04-1.17)[a]	1.03 (0.90-1.18)	1.25 (1.00-1.57)	1.16 (0.98-1.36)	1.29 (0.79-2.11)	1.14 (0.84-1.55)	0.71 (0.53-0.93)[d,e]	1.38 (1.08-1.76)[b]	1.38 (1.07-1.76)	1.18 (0.82-1.70)
Immunosuppressant use vs none	1.10 (0.97-1.25)	1.17 (0.92-1.47)	1.38 (0.89-2.12)	0.67 (0.44-1.03)	0.86 (0.27-2.67)	0.28 (0.07-1.18)	1.19 (0.69-2.05)	1.51 (0.93-2.46)	2.07 (1.28-3.36)[c]	0.97 (0.44-2.15)
Alcoholism vs no diagnosis	1.05 (0.94-1.17)	1.23 (0.91-1.67)	1.11 (0.73-1.68)	1.55 (1.19-2.02)[a]	1.51 (0.83-2.74)	0.80 (0.50-1.29)	0.85 (0.49-1.46)	1.30 (0.91-1.85)	0.67 (0.42-1.09)	1.39 (0.77-2.50)
Phlebitis vs no diagnosis	1.10 (0.97-1.24)	1.25 (0.92-1.69)	1.20 (0.68-2.10)	1.11 (0.80-1.52)	2.04 (0.85-4.92)	0.55 (0.26-1.12)	1.36 (0.81-2.26)	0.71 (0.37-1.38)	0.62 (0.38-1.02)	0.66 (0.24-1.79)
Parathyroid hormone use vs no hormones	1.27 (0.99-1.62)	1.08 (0.63-1.84)	2.72 (1.43-5.18)[c]	0.95 (0.41-2.21)	NC	3.23 (1.01-10.27)	0.60 (0.18-2.05)	1.20 (0.49-2.95)	1.51 (0.55-4.18)	2.65 (0.96-7.27)
Rheumatoid arthritis only vs no diagnosis	1.14 (0.93-1.38)	0.90 (0.60-1.33)	0.79 (0.34-1.82)	1.72 (1.07-2.78)	NC	0.54 (0.07-4.04)	1.41 (0.68-2.91)	1.16 (0.54-2.47)	0.94 (0.38-2.29)	1.59 (0.59-4.27)
Nonmenopausal corticosteroid use vs none	1.07 (0.99-1.15)	1.19 (1.03-1.38)	1.30 (0.97-1.73)	0.95 (0.75-1.18)	0.89 (0.45-1.76)	0.71 (0.42-1.19)	0.98 (0.73-1.33)	0.82 (0.57-1.18)	1.33 (0.99-1.78)	1.06 (0.66-1.69)
Cardiac medication use vs none	1.04 (0.99-1.08)	1.05 (0.96-1.15)	1.04 (0.88-1.22)	1.04 (0.92-1.17)	1.22 (0.85-1.74)	0.86 (0.67-1.08)	1.01 (0.85-1.21)	0.93 (0.77-1.11)	0.99 (0.82-1.18)	1.18 (0.91-1.53)
Nutritional deficiency vs no diagnosis	1.09 (1.00-1.19)	1.20 (0.97-1.48)	0.97 (0.67-1.42)	1.35 (1.07-1.71)	1.49 (0.73-3.05)	1.45 (1.00-2.11)	1.30 (0.89-1.89)	1.00 (0.73-1.36)	1.18 (0.83-1.66)	0.54 (0.27-1.05)
Menopausal corticosteroid use vs none	1.02 (0.98-1.05)	1.10 (1.02-1.19)	1.02 (0.88-1.17)	0.91 (0.82-1.01)	1.13 (0.86-1.47)	1.18 (0.95-1.45)	1.12 (0.97-1.29)	1.01 (0.86-1.17)	0.94 (0.80-1.10)	1.03 (0.82-1.28)
NSAIDs only vs no analgesics	0.98 (0.89-1.07)	1.04 (0.90-1.20)	0.92 (0.59-1.43)	1.03 (0.78-1.37)	1.42 (0.65-3.13)	0.81 (0.38-1.72)	1.05 (0.75-1.47)	0.50 (0.28-0.91)	0.34 (0.17-0.69)[d,e]	0.89 (0.42-1.88)
Coagulant use vs no coagulants	0.24 (0.09-0.64)[d,e]	0.52 (0.16-1.66)	NC	NC	NC	NC	NC	2.24 (0.28-18.07)	NC	NC
Medicare vs commercial payer	0.69 (0.55-0.86)[a,e]	0.81 (0.49-1.33)	0.63 (0.25-1.55)	0.51 (0.27-0.94)[d,e]	0.61 (0.07-5.27)	NC	1.11 (0.46-2.64)	0.42 (0.15-1.15)	1.50 (0.70-3.23)	0.93 (0.27-3.19)
Oral contraceptive use vs no contraceptives	0.88 (0.81-0.95)[a,e]	0.91 (0.78-1.05)	0.72 (0.52-1.00)	0.77 (0.60-0.98)[d,e]	0.45 (0.22-0.92)[d,e]	0.89 (0.47-1.65)	1.13 (0.87-1.45)	1.00 (0.67-1.48)	0.99 (0.70-1.40)	1.13 (0.72-1.79)
Allergy vs no diagnosis	0.90 (0.86-0.93)[a,e]	0.99 (0.90-1.07)	0.75 (0.63-0.88)[a,e]	0.96 (0.85-1.08)	0.95 (0.70-1.30)	0.64 (0.49-0.84)[a,e]	0.87 (0.73-1.02)	1.09 (0.91-1.30)	0.74 (0.61-0.89)[d,e]	0.75 (0.57-0.98)
Treatment information unknown vs conservative	0.92 (0.88-0.96)[a,e]	0.77 (0.71-0.83)	1.35 (1.15-1.58)[a]	0.65 (0.58-0.72)[a,e]	1.81 (1.36-2.41)[a]	1.67 (1.21-2.30)[c]	0.67 (0.58-0.76)[a,e]	1.07 (0.87-1.32)	1.35 (1.07-1.71)	1.69 (1.25-2.28)[a]

(continued)

Table 4. Multivariate ORs for Nonunion Among Adults With Fracture: First Set (continued)

Risk Factor	OR (95% CI)									
	All 18 Bones (N = 309 330)	Metatarsal (n = 58 377)	Radius (n = 50 998)	Ankle (n = 45 861)	Metacarpals (n = 20 370)	Trunk (n = 19 364)	Tarsal (n = 19 306)	Humerus (n = 15 062)	Tibia (n = 12 808)	Radius and Ulna (n = 9380)
Antidiabetics, not insulin vs no antidiabetics	0.92 (0.86-0.99)[d,e]	1.02 (0.88-1.18)	0.66 (0.50-0.89)[d,e]	0.92 (0.77-1.10)	0.89 (0.47-1.68)	0.81 (0.55-1.18)	0.76 (0.56-1.02)	0.84 (0.64-1.10)	1.08 (0.81-1.43)	1.27 (0.84-1.93)
Medicaid vs commercial payer	0.94 (0.88-0.99)[d,e]	0.79 (0.66-0.95)	0.95 (0.74-1.21)	1.03 (0.87-1.21)	0.66 (0.44-1.00)	0.78 (0.58-1.06)	0.92 (0.71-1.19)	1.47 (1.17-1.84)[a]	0.99 (0.78-1.24)	0.56 (0.37-0.83)[d,e]
Cardiovascular disease vs no diagnosis	0.94 (0.90-0.98)[d,e]	1.01 (0.91-1.10)	1.00 (0.84-1.18)	0.92 (0.81-1.05)	0.81 (0.56-1.16)	1.08 (0.85-1.38)	0.88 (0.73-1.05)	0.83 (0.68-1.00)	1.06 (0.88-1.27)	0.84 (0.64-1.09)
Patient age increase by 10 y	0.97 (0.95-0.98[a,e]	1.06 (1.02-1.09)[b]	0.93 (0.88-0.98)[d,e]	1.04 (0.99-1.08)	0.87 (0.78-0.96)[d,e]	1.03 (0.93-1.13)	0.96 (0.90-1.01)	1.04 (0.97-1.11)	0.93 (0.87-0.98)	0.87 (0.80-0.94)[a,e]

Abbreviations: NC, nonconvergence of the model; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

[a] $P \leq .001$.

[b] $P \leq .01$.

[c] $P \leq .005$.

[d] $P \leq .05$.

[e] Protective factor.

with a variety of conservative and operative methods.[14-58] The agreement between our database and the literature is striking since both samples include many patients who received a wide range of treatments.

Similarly, the nonunion rate we report for clavicle fractures is 8.2% for 7414 fractures. Collation of literature on clavicle fractures suggests that the expected nonunion rate is 8.6%. This percentage was derived from the reported healing rate in 12 separate publications[59-70] spanning the period from 2004 to 2013 and including 3168 patients treated with a range of conservative and operative methods. Both samples are large, and the nonunion rate in our database again differs by less than a percentage point from the literature values.

The overall nonunion rate we report (4.9%) is slightly lower than the 5% to 10% that reviews suggest,[1,2] which may reflect reporting bias. Clinicians generally report more often on fractures that heal poorly.[71] Metacarpal fractures heal with a nonunion rate of just 1.5% and have been reported only 226 times in the literature (per PubMed search, December 21, 2015: search terms, *bone fracture healing* and *metacarpal*). Conversely, tibia fractures have a nonunion rate of 7.4% and have been reported 2578 times in the literature (per PubMed search, December 21, 2015: search terms, *bone fracture healing* and *tibia*). Similarly, femur fractures have a nonunion rate of 13.9% and have been reported 2791 times in the literature (per PubMed search, December 21, 2015, search terms, *bone fracture healing* and *femur*).

This research has several limitations. First, Truven Health Analytics is a payer database that excludes unemployed or indigent patients who might have had a higher rate of nonunion. Second, some diagnoses may have been coded incorrectly as fracture if coding was performed before radiographic imaging. However, this error is unlikely because rule-out codes were not counted; such codes are used to order imaging if a fracture is suspected. Third, some fractures that received treatment in 2011 could have occurred earlier. Fourth, uncoded patient data cannot contribute to conclusions. Data were more likely to be missing from the database if information was not crucial to reimbursement; smokers not receiving medication for smoking cessation would likely not be coded as smokers. Nevertheless, missing data are a problem in every study, including randomized clinical trials. Therefore, we used statistical methods, including random forest analysis, that are robust and resilient despite missing data.[11] Additional limitations are characteristic of claims databases in general; there is imprecision in *ICD-9* coding schemes,[72] and coding errors are common but are assumed to distribute randomly and to be minimized by the need for accurate reporting for claims reimbursement and by legal penalties for fraudulent reporting.[73] Limitations do not appear to be a substantial issue because the nonunion rates we report are similar to others in the literature.

An important strength of this research is that it has contributed novel insights into the cause of fracture nonunion. For example, use of certain medications is a key risk factor for fracture nonunion (Table 3). Because medication use is a modifiable risk factor, our findings suggest that clinicians could counsel patients about use of medications. Other strengths of this research are that all data were collected prospectively, the 12-month follow-up time represents a longer follow-up interval

Table 5. Multivariate ORs for Nonunion Among Adults With Fracture: Second Set

Risk Factor	OR (95% CI)								
	Ulna (n = 8605)	Clavicle (n = 7414)	Scaphoid (n = 7149)	Patella (n = 6710)	Pelvis (n = 6356)	Fibula (n = 5978)	Neck of Femur (n = 5321)	Tibia and Fibula (n = 5249)	Femur (n = 5022)
≥6 vs 1-2 Fractures per patient	1.22 (0.62-2.39)	0.21 (0.03-1.58)	NC	0.90 (0.33-2.41)	3.94 (2.61-5.96)[a]	1.92 (0.78-4.73)	2.59 (1.43-4.69)[b]	2.33 (1.41-3.85)[a]	2.11 (1.45-3.07)[a]
NSAID with opioid use vs no analgesics	2.47 (1.68-3.63)[a]	1.95 (1.39-2.75)[a]	2.59 (2.09-3.22)[a]	1.94 (1.00-3.78)	1.30 (0.82-2.07)	1.40 (0.88-2.25)	1.54 (1.03-2.29)	1.41 (1.01-1.96)	1.61 (1.14-2.26)[c]
Requires operative vs conservative procedure	1.66 (1.31-2.12)[a]	2.17 (1.71-2.74)[a]	1.40 (1.15-1.69)[a]	4.20 (2.44-7.21)[a]	1.95 (1.31-2.89)[a]	2.05 (1.41-2.97)[a]	1.32 (0.58-2.95)	1.39 (1.05-1.85)	4.61 (2.30-9.22)[a]
Open vs closed fracture	1.16 (0.85-1.59)	1.23 (0.70-2.16)	1.61 (1.05-2.46)	1.34 (0.85-2.09)	0.99 (0.55-1.76)	1.83 (1.16-2.88)[c]	1.31 (0.88-1.94)	2.04 (1.69-2.46)[a]	1.79 (1.43-2.24)[a]
Anticoagulant use vs none	1.77 (1.24-2.52)[b]	0.85 (0.54-1.35)	1.29 (0.80-2.10)	2.04 (1.42-2.92)[a]	1.35 (1.05-1.74)	2.50 (1.81-3.43)[a]	1.62 (1.32-2.00)[a]	1.69 (1.41-2.02)[a]	1.43 (1.19-1.72)[a]
Osteoarthritis with rheumatoid arthritis vs no diagnosis	1.38 (0.52-3.66)	0.70 (0.15-3.20)	2.48 (0.90-6.84)	1.90 (0.73-4.96)	1.80 (0.73-4.43)	0.51 (0.11-2.38)	2.00 (1.12-3.56)	1.11 (0.38-3.26)	0.57 (0.30-1.09)
Anticonvulsants with benzodiazepines vs none	1.10 (0.63-1.91)	0.86 (0.46-1.60)	1.02 (0.59-1.74)	3.32 (1.82-6.04)[a]	1.86 (1.15-3.01)	1.31 (0.66-2.62)	1.49 (0.98-2.26)	0.62 (0.33-1.14)	1.93 (1.27-2.92)[b]
Unknown energy vs low-energy accident	1.31 (0.97-1.75)	1.24 (0.90-1.69)	2.37 (1.73-3.24)[a]	1.62 (0.98-2.67)	2.57 (1.43-4.60)[b]	1.07 (0.73-1.56)	1.50 (1.11-2.01)[c]	1.43 (1.08-1.87)	1.26 (0.90-1.76)
Osteoarthritis only vs no diagnosis	1.52 (1.15-2.00)[b]	0.99 (0.74-1.31)	2.20 (1.74-2.78)[a]	2.44 (1.68-3.54)[a]	1.53 (1.15-2.02)[b]	1.36 (0.96-1.92)	1.56 (1.22-1.99)[a]	1.02 (0.79-1.30)	0.91 (0.73-1.13)
Opioids only vs no opioids	2.00 (1.36-2.94)[a]	1.47 (1.04-2.06)	3.14 (2.56-3.85)[a]	1.03 (0.51-2.06)	1.06 (0.66-1.69)	1.10 (0.69-1.77)	0.89 (0.59-1.33)	1.02 (0.73-1.41)	0.99 (0.70-1.40)
Type 1 diabetes vs no diagnosis	0.46 (0.13-1.70)	1.76 (0.56-5.48)	1.43 (0.44-4.65)	0.20 (0.02-1.67)	0.59 (0.16-2.11)	0.85 (0.21-3.47)	2.01 (1.03-3.92)	2.47 (1.27-4.80)[c]	1.17 (0.59-2.30)
High-energy vs low-energy accident	1.12 (0.73-1.69)	0.83 (0.57-1.21)	0.85 (0.51-1.41)	2.18 (1.10-4.32)	1.73 (0.93-3.19)	1.42 (0.83-2.42)	1.62 (1.07-2.44)	1.34 (0.97-1.85)	1.38 (0.94-2.03)
Anticonvulsants only vs none	1.28 (0.96-1.69)	1.39 (1.06-1.82)	0.99 (0.74-1.31)	1.41 (0.94-2.10)	1.68 (1.29-2.19)[a]	1.69 (1.20-2.37)[b]	0.98 (0.76-1.26)	1.20 (0.97-1.49)	1.51 (1.22-1.86)[a]
3-5 vs 1-2 Fractures per patient	1.00 (0.72-1.39)	0.99 (0.65-1.50)	0.36 (0.18-0.73)[d,e]	1.78 (1.01-3.12)	1.66 (1.24-2.22)[a]	1.25 (0.80-1.94)	1.25 (0.91-1.72)	0.90 (0.71-1.13)	1.40 (1.09-1.78)[c]
Osteoporosis vs no diagnosis	0.78 (0.44-1.39)	1.30 (0.73-2.29)	2.45 (1.31-4.58)[b]	2.82 (1.53-5.17)[a]	1.44 (0.86-2.41)	0.32 (0.11-0.96)	1.09 (0.78-1.50)	0.60 (0.36-1.01)	1.58 (1.13-2.20)[c]
Male vs female gender	1.12 (0.90-1.38)	0.61 (0.50-0.74)[a,e]	2.55 (2.09-3.11)[a]	1.56 (1.11-2.20)	1.09 (0.85-1.40)	0.95 (0.72-1.26)	1.21 (0.96-1.50)	1.22 (1.02-1.46)	0.97 (0.81-1.17)
Insulin use vs none	1.38 (0.76-2.50)	0.82 (0.39-1.72)	0.76 (0.35-1.62)	1.30 (0.64-2.63)	1.13 (0.63-2.03)	1.17 (0.59-2.33)	0.92 (0.59-1.42)	0.87 (0.55-1.35)	1.20 (0.80-1.80)
Past/current smoker vs never smoked	1.36 (1.02-1.81)	1.36 (1.05-1.77)	1.11 (0.86-1.43)	1.22 (0.79-1.86)	1.38 (1.02-1.87)	1.67 (1.17-2.37)[b]	1.01 (0.75-1.35)	1.33 (1.06-1.68)	1.45 (1.14-1.84)[b]
Benzodiazepine only vs no anticonvulsants	1.18 (0.71-1.95)	1.48 (0.95-2.30)	0.98 (0.62-1.53)	2.42 (1.23-4.77)	1.89 (1.11-3.22)	0.87 (0.39-1.91)	0.62 (0.32-1.21)	1.28 (0.78-2.09)	1.41 (0.88-2.25)
Obesity vs no diagnosis	1.66 (1.18-2.31)[b]	1.57 (1.05-2.34)	0.98 (0.68-1.41)	1.20 (0.75-1.92)	1.34 (0.93-1.94)	0.85 (0.56-1.30)	1.61 (1.18-2.21)[b]	1.20 (0.90-1.60)	1.11 (0.85-1.45)
Antibiotic use vs none	1.22 (0.97-1.51)	1.07 (0.88-1.28)	1.04 (0.89-1.20)	1.15 (0.79-1.67)	1.18 (0.91-1.52)	1.02 (0.76-1.37)	1.25 (0.98-1.58)	1.34 (1.11-1.61)[b]	1.32 (1.08-1.60)[c]
Osteoporosis medication use vs none	1.43 (0.90-2.26)	0.66 (0.38-1.15)	0.66 (0.30-1.45)	0.68 (0.33-1.37)	1.12 (0.68-1.83)	1.16 (0.57-2.39)	1.23 (0.90-1.66)	1.36 (0.85-2.14)	0.91 (0.65-1.28)
Type 2 diabetes only vs no diagnosis	0.65 (0.39-1.08)	0.83 (0.49-1.41)	0.61 (0.35-1.08)	1.22 (0.65-2.29)	1.02 (0.64-1.61)	1.08 (0.62-1.86)	1.14 (0.78-1.66)	1.38 (0.97-1.96)	1.30 (0.91-1.85)
Vitamin D deficiency vs no diagnosis	1.03 (0.64-1.66)	1.29 (0.82-2.01)	0.94 (0.54-1.65)	1.49 (0.82-2.70)	0.98 (0.60-1.60)	1.00 (0.54-1.86)	1.32 (0.91-1.91)	1.09 (0.73-1.65)	2.15 (1.56-2.96)[a]
Diuretic use vs none	0.88 (0.64-1.20)	0.98 (0.70-1.36)	0.89 (0.63-1.27)	1.26 (0.82-1.93)	1.18 (0.85-1.63)	1.40 (0.98-2.00)	1.06 (0.82-1.37)	1.14 (0.88-1.48)	1.20 (0.94-1.52)
Renal insufficiency vs no diagnosis	1.59 (1.13-2.24)	1.20 (0.81-1.78)	0.90 (0.62-1.30)	1.28 (0.78-2.11)	1.25 (0.90-1.75)	0.98 (0.59-1.63)	0.74 (0.53-1.01)	1.13 (0.82-1.53)	1.00 (0.76-1.31)
Immunosuppressant use vs none	1.50 (0.72-3.09)	0.43 (0.13-1.43)	0.57 (0.19-1.66)	4.83 (2.11-11.08)[a]	1.10 (0.44-2.74)	2.07 (0.81-5.32)	0.84 (0.42-1.66)	1.25 (0.64-2.47)	1.08 (0.52-2.24)
Alcoholism vs no diagnosis	1.43 (0.87-2.34)	0.99 (0.58-1.66)	0.93 (0.47-1.83)	1.36 (0.57-3.25)	0.84 (0.47-1.50)	0.73 (0.30-1.75)	0.85 (0.51-1.40)	0.63 (0.37-1.04)	0.60 (0.35-1.03)

(continued)

Table 5. Multivariate ORs for Nonunion Among Adults With Fracture: Second Set (continued)

Risk Factor	OR (95% CI)								
	Ulna (n = 8605)	Clavicle (n = 7414)	Scaphoid (n = 7149)	Patella (n = 6710)	Pelvis (n = 6356)	Fibula (n = 5978)	Neck of Femur (n = 5321)	Tibia and Fibula (n = 5249)	Femur (n = 5022)
Phlebitis vs no diagnosis	1.69 (0.76-3.73)	0.67 (0.25-1.80)	0.67 (0.22-1.99)	0.32 (0.07-1.38)	0.77 (0.39-1.54)	0.93 (0.43-2.01)	1.78 (1.08-2.92)	1.12 (0.68-1.84)	2.22 (1.41-3.49)[a]
Parathyroid hormone use vs no hormones	NC	2.59 (0.63-10.66)	NC	NC	0.42 (0.09-1.86)	10.1 (2.10-48.43)[b]	0.34 (0.08-1.47)	1.42 (0.39-5.21)	2.17 (0.81-5.86)
Rheumatoid arthritis only vs no diagnosis	0.80 (0.23-2.75)	3.89 (1.59-9.51)[b]	0.80 (0.18-3.62)	NC	0.63 (0.08-4.75)	0.35 (0.04-2.87)	1.11 (0.33-3.75)	1.78 (0.73-4.37)	1.24 (0.46-3.31)
Nonmenopausal corticosteroid use vs none	0.98 (0.62-1.55)	0.68 (0.40-1.13)	1.07 (0.72-1.59)	0.45 (0.18-1.11)	1.40 (0.90-2.18)	1.25 (0.70-2.23)	1.63 (1.06-2.50)	1.02 (0.68-1.54)	1.30 (0.88-1.92)
Cardiac medication use vs none	1.04 (0.80-1.35)	1.03 (0.81-1.32)	0.97 (0.74-1.25)	1.20 (0.82-1.77)	1.07 (0.81-1.43)	1.05 (0.76-1.46)	1.12 (0.88-1.42)	1.00 (0.80-1.23)	1.10 (0.88-1.36)
Nutritional deficiency vs no diagnosis	1.33 (0.77-2.27)	0.72 (0.37-1.39)	0.55 (0.25-1.24)	0.82 (0.35-1.92)	1.39 (0.93-2.05)	0.86 (0.39-1.90)	1.10 (0.76-1.60)	0.85 (0.56-1.30)	0.81 (0.56-1.17)
Menopausal corticosteroid use vs none	1.03 (0.83-1.27)	1.22 (1.00-1.48)	0.89 (0.75-1.05)	0.94 (0.67-1.31)	0.89 (0.69-1.15)	1.13 (0.85-1.51)	0.90 (0.73-1.12)	1.01 (0.83-1.22)	0.82 (0.67-0.99)
NSAIDs only vs no analgesics	1.00 (0.51-1.95)	0.75 (0.36-1.57)	1.09 (0.76-1.57)	0.92 (0.31-2.71)	0.66 (0.29-1.49)	1.15 (0.56-2.34)	0.55 (0.27-1.13)	0.96 (0.54-1.70)	0.98 (0.55-1.72)
Coagulant use vs none	NC	NC	NC	NC	NC	NC	NC	NC	NC
Medicare vs commercial payer	0.73 (0.17-3.19)	NC	1.23 (0.27-5.61)	NC	0.88 (0.19-3.96)	0.56 (0.07-4.37)	0.61 (0.24-1.54)	1.52 (0.61-3.78)	0.53 (0.22-1.29)
Oral contraceptive use vs none	1.04 (0.69-1.58)	1.29 (0.85-1.94)	0.80 (0.54-1.19)	1.16 (0.54-2.47)	0.83 (0.47-1.45)	0.97 (0.52-1.80)	1.27 (0.74-2.16)	1.19 (0.80-1.77)	0.67 (0.41-1.11)
Allergy vs no diagnosis	0.83 (0.64-1.06)	0.94 (0.75-1.18)	0.97 (0.80-1.17)	0.83 (0.56-1.23)	1.00 (0.74-1.35)	0.94 (0.67-1.30)	0.84 (0.64-1.10)	0.70 (0.55-0.89)[d]	0.69 (0.54-0.87)[d,e]
Treatment information unknown vs conservative	0.96 (0.75-1.21)	1.25 (0.97-1.59)	0.85 (0.73-0.99)	1.24 (0.74-2.07)	1.37 (0.96-1.96)	1.51 (1.10-2.06)[c]	1.01 (0.45-2.28)	0.87 (0.65-1.16)	3.52 (1.77-7.01)[a]
Antidiabetics, not insulin vs no antidiabetics	0.90 (0.56-1.44)	0.97 (0.58-1.63)	1.25 (0.76-2.05)	0.86 (0.46-1.61)	1.09 (0.68-1.77)	0.68 (0.39-1.18)	0.94 (0.65-1.36)	0.90 (0.63-1.27)	0.76 (0.53-1.08)
Medicaid vs commercial payer	0.82 (0.58-1.16)	1.01 (0.71-1.43)	0.86 (0.63-1.19)	1.35 (0.86-2.11)	1.15 (0.84-1.58)	0.91 (0.58-1.41)	0.84 (0.61-1.15)	1.16 (0.90-1.50)	0.77 (0.60-0.99)
Cardiovascular disease vs no diagnosis	1.06 (0.82-1.38)	1.06 (0.83-1.34)	0.80 (0.62-1.02)	0.79 (0.52-1.18)	0.78 (0.58-1.05)	1.22 (0.87-1.71)	0.78 (0.60-1.02)	1.00 (0.80-1.24)	0.88 (0.70-1.10)
Patient age increase by 10 y	0.89 (0.82-0.96)[d,e]	1.23 (1.15-1.32)[a]	0.80 (0.75-0.85)[a,e]	0.85 (0.74-0.97)	1.05 (0.95-1.15)	0.96 (0.86-1.08)	0.94 (0.85-1.03)	1.02 (0.95-1.09)	1.01 (0.94-1.08)

Abbreviations: NC, nonconvergence; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

[a] $P \leq .001$.

[b] $P \leq .005$.

[c] $P \leq .01$.

[d] $P \leq .05$.

[e] Protective factor.

than used in most other published studies,[5] and the outcomes reported reflect real-world outcomes.

Conclusions

Fracture nonunion can result from the interplay of many risk factors. Key risk factors include features of the fracture, such as severity and location, as well as issues such as comorbidities and use of certain medications. Fracture severity, fracture location, comorbidity, and medication use could be incorporated into an algorithm that would help clinicians determine which fractures are at greatest risk of nonunion. Medications have a significant effect on fracture healing and can potentially be altered after fracture to improve healing.

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