

Risk factors for nonunion of bone fracture in pediatric patients

An inception cohort study of 237,033 fractures

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Abstract

Adult fracture nonunion risk is related to injury severity and surgical technique, yet nonunion is not fully explained by these risk factors alone; biological risk factors are also important. We test a hypothesis that risk factors associated with pediatric fracture nonunion are similar to adult nonunion risk factors.

Inception cohort study in a large payer database of pediatric fracture patients (0–17 years) in the United States in calendar year 2011. Continuous enrollment in the database was required for 12 months, to allow time to capture a nonunion diagnosis. The final database collated demographic descriptors, treatment procedures as per Current Procedural Terminology (CPT) codes, comorbidities as per International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes, and drug prescriptions as per National Drug Code Directory (Red Book) codes. Logistic regression was used to calculate odds ratios (ORs) for variables associated with nonunion.

Among 237,033 pediatric fractures in 18 bones, the nonunion rate was 0.85%. Increased nonunion risk was associated with increasing age, male gender, high body-mass index, severe fracture (e.g., open fracture, multiple fractures), and tobacco smoking (all, $P < .0001$). Nonunion rate varied with fracture location; scaphoid, neck of femur, and tibia/fibula were most likely to go to nonunion. Nonunion ORs were significantly increased for risk factors including; surgical procedure, cardiovascular disease, Vitamin D deficiency, osteoarthritis, osteoporosis, and opioid prescription (all, multivariable $P < .001$).

Nonunion is rare in pediatric patients, but nonunion risk increases with increasing age. We confirm a hypothesis that risk factors for pediatric nonunion are similar to adult nonunion risk factors. Scaphoid fractures in adolescents have nearly the same risk of nonunion as in adults. Opioids should be used cautiously in pediatric patients, as they are associated with a significant and substantial elevation of nonunion risk.

Level of Evidence: Prognostic study, Retrospective, Level II.

Abbreviations: CPT = Current Procedural Terminology code, EBS = electrical bone stimulation device, ICD-9 = International Statistical Classification of Diseases and Related Health Problems code, LIPUS = low-intensity pulsed ultrasound device, NS = not solvable, OR = odds ratios, pOR = pediatric odds ratio, THERCLS = Red Book therapeutic classification codes.

Keywords: cardiovascular disease, fracture nonunion, opioid use, risk factors, scaphoid fractures, tobacco smoking, vitamin D deficiency

1. Introduction

Bone fractures are commonplace in childhood.^[1] When fracture healing fails, nonunion is one of the most consequential

outcomes.^[2] Nonunion may be rare in long bone fractures in children,^[3,4] though it may be more common than clinicians typically believe.^[5] Risk factors important in predicting adult nonunion are well understood.^[2,6,7] Surgical risk factors for nonunion include location of the fracture site, bone displacement, type of fixation, treatment delay, comminution, inadequate treatment, and wound infection, but these risk factors cannot explain all nonunions.^[2] New evidence suggests that biological risk factors for nonunion are also important, at least in adults, and that fracture nonunion can result from the interplay of surgical and biological risk factors.^[6] In adults, nonunion rate is a function of fracture severity, fracture location, disease comorbidity, and medication use.^[6]

A clear understanding of pediatric nonunion risk factors is important for many reasons. Such an understanding might identify children who are prone to nonunion, help choose between competing therapeutic options, inform the design of clinical trials, and even clarify patient inclusion and exclusion criteria, so that small clinical trials could still yield definitive answers.^[2] Yet risk factors for nonunion in childhood fracture are largely unknown. We hypothesize that the risk factors important in adult nonunion are also important in pediatric nonunion.

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2. Materials and methods

2.1. Database

Truven Health Analytics (Durham, NC) compiled patient-level health claims data for medical and drug expenses, together with laboratory test results, hospital discharge, and death data for 90.1 million patients of all ages.^[6] Here, we analyze the data from the cohort of patients under age 18 at the time of fracture. Patients were primarily children of parents with health insurance provided through their employer. Parents who receive family health insurance as a benefit are preferentially employed in professions, rather than trades, and are likely not to be self-employed.^[6]

This study was exempted from ethical approval because patient data were completely de-identified.^[6] Variables analyzed include patient demographics, treatment procedures as per Current Procedural Terminology (CPT) codes, disease comorbidities as per International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes, and drug prescriptions as per National Drug Code Directory (Red Book) codes.^[6]

2.2. Study design

Study inclusion was limited to patients with a coded bone fracture in calendar year 2011. Patients were excluded if they had <12 months of continuous enrollment following fracture, to capture nonunions not diagnosed immediately. Prior analysis focused on the cohort of patients 18 to 63 years old at fracture.^[6] Our analysis focuses on patients under age 18, in whom skeletal maturity was less likely achieved.^[8] Previous work has shown that nonunion rate as a function of age had a strong inflection point at age 11,^[9] so we here dichotomized young patients as being age ≤ 11 .

Fractures were identified based on 5-digit ICD-9 codes.^[6] “Rule-out” codes were not counted; such codes are used to order an x-ray in some patients who may not have 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 fracture. Nonunion was determined by the presence of either a nonunion code or a code for prescription use of an electrical bone stimulation (EBS) device. Patients who used low-intensity pulsed ultrasound (LIPUS) devices for fresh fracture were excluded from analysis because this prescription device may increase bone healing rate.

Disease comorbidities were identified using ICD-9 disease codes.^[6] Secondary conditions arising from a chronic disease condition (e.g., 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 diagnosed with diabetes prior to 2011, although subsequent medications used to treat diabetes would be captured. Medications were identified using Red Book therapeutic classification (THERCLS) codes, which are for prescription medications purchased in a retail pharmacy. Such codes can contain a range of medications; the opioid class contains analgesics, but also contains opioid agonists used to treat addiction. Medications were assumed to be chronic, except antibiotics, analgesics, and steroids.

2.3. Analytic strategy

Our overall hypothesis was that fracture nonunion is associated with risk factors coded in CPT, ICD-9, and Red Book codes.

Possible risk factors for nonunion were identified,^[2] 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 etiology, patient demographics, and medication use. We focused specifically on those 18 bones most frequently fractured. We defined an operative treatment variable for patients who received any fracture surgery by CPT code, comparing them to patients without surgery. Statistical analyses used SAS 9.4 (Cary, NC); the critical *P*-value for significance was set at .01.

We did not adjust for multiple comparisons because showing confidence intervals (CIs) for each odds ratio (OR) achieves the same end.^[2] 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 this exploratory context, *P* values are interpreted as a measure of statistical evidence rather than a test of hypothesis.^[2]

3. Results

A total of 237,033 fractures are analyzed (Fig. 1). A demographic summary of pediatric fracture patients demonstrates that, while fracture is common, nonunion is not (Table 1). Nonunion occurred in <1% of fractured bones, with the overall nonunion rate 80% lower than in adults.^[6] The youngest cohort of children (0–6 years old) had a risk of nonunion of only 0.2%, while the cohort aged 12 to 17 years had a nonunion risk roughly 8-fold higher than the youngest children (Table 1). Certain risk factors increased risk of nonunion, including male gender, higher body mass index (BMI), open or multiple fracture, and current tobacco smoking (all, $P < .0001$).

Nonunion rate in individual bones as a function of age is shown (Fig. 2). Results are arrayed left-to-right by increasing nonunion risk in adolescents and nonunion risk in adults is shown for the same patient cohort.^[6] Nonunion risk is generally low until about age 11—roughly the time of puberty—but nonunion risk can rise sharply thereafter. Comparing cohorts revealed a significant increase in nonunion risk for every bone with age ($P < .0001$). The pattern across bones is not simply an increase in nonunion risk with age; instead, some bones in adolescents heal as well as in young children (e.g., femur), while others heal at a rate comparable to adults (e.g., scaphoid). Some bones with nonunion rates $\geq 8\%$ in adults still have rather low nonunion rates in adolescents (e.g., clavicle, femur). Only 3 pediatric fracture sites have more than a 5% nonunion risk in adolescents (e.g., tibia and fibula, femoral neck, scaphoid).

Several diseases are associated with a greater nonunion risk, including osteoarthritis, rheumatoid arthritis, osteoporosis, and diabetes (Table 2). However, these conditions are rare; osteoporosis affected 300 children in a database of 237,033 patients or <0.13%. Yet for patients with osteoporosis, this condition was a strong predictor of nonunion; osteoporosis is associated with a univariate nonunion OR of 5.34 and a multivariable nonunion OR of 2.75 (Table 2). If the only information that a pediatrician has about a patient is that the patient is diagnosed with osteoporosis, then it is reasonable to conclude that this patient has a 5.34-fold higher risk of nonunion than a patient without osteoporosis.^[6] As other variables become known and can be incorporated into a risk assessment, risk associated specifically with osteoporosis decreases.^[6] In a multivariable analysis, which controls for a host of risk factors,

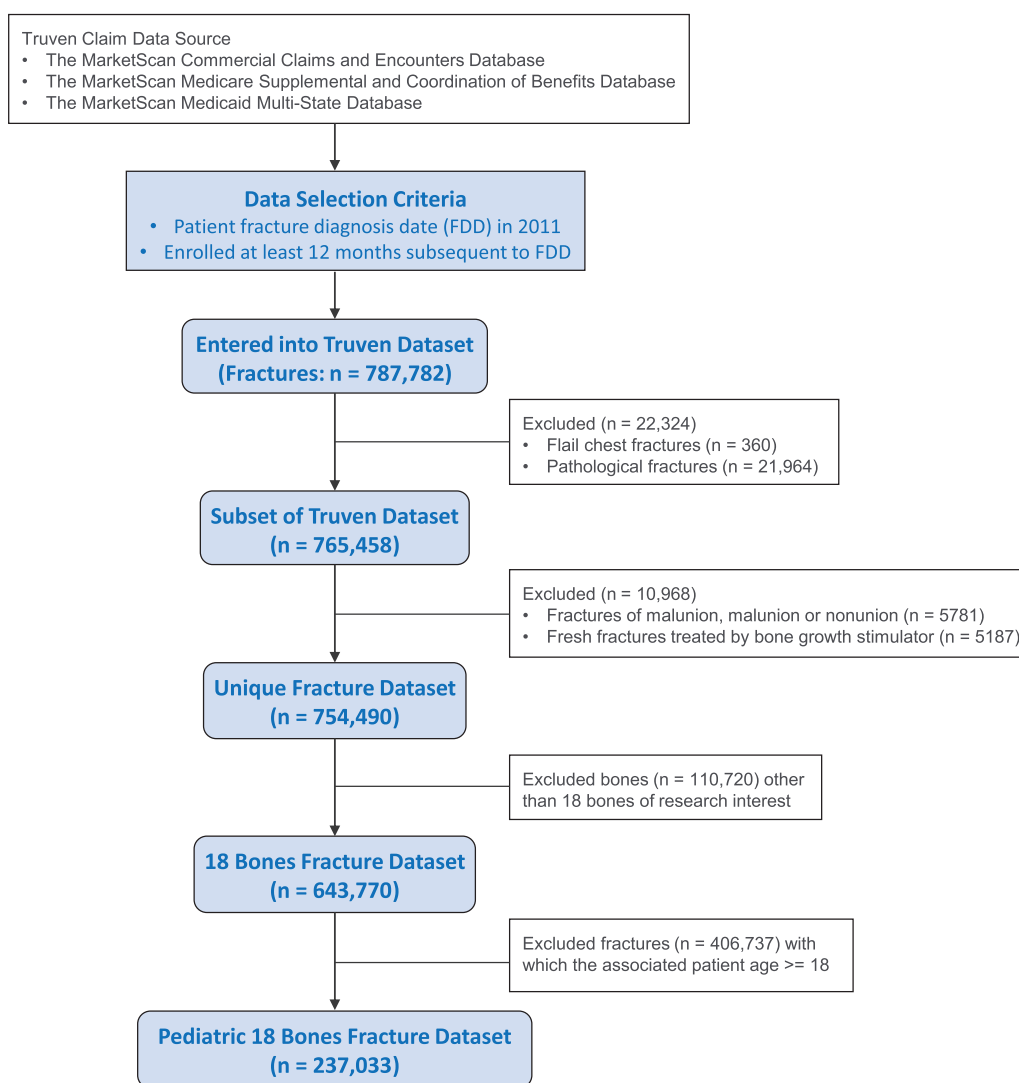


Figure 1. CONSORT diagram. CONSORT=consolidated standards of reporting trials.

the nonunion risk associated specifically with osteoporosis is 2.75-fold times the risk of nonunion in a patient free of osteoporosis (Table 2).

Certain medications are associated with increased risk of nonunion (Table 2), though univariate ORs for medications are larger than multivariable ORs. For example, tobacco smoking is a significant univariate risk, but not a significant multivariable risk. Cardiovascular disease, osteoarthritis, and vitamin D deficiency increase nonunion risk significantly and substantially (all, $P < .0001$), while risk of nonunion in patients with osteoporosis is less significant ($P = .0018$).

Certain medications increase nonunion risk as a function of age (Fig. 3). Use of bisphosphonates and anticoagulants was associated with a nonunion risk $>2\%$ in the youngest cohort and was important as a correlate of nonunion among adolescents. Using 2% risk of nonunion as a cut-off, several additional medications were important in adolescence, including anticonvulsants, cardiac medications, opioids, oral contraceptives, Non-steroidal Anti-inflammatory Drugs (NSAIDs) + opioids, and reproductive steroids. Nevertheless, the number of children using medications is generally low.

Multivariable ORs for nonunion are shown (Table 3) as a function of fracture type and comorbid illness. The first column pools data for all 18 bones in the calculation of ORs, but risks are also shown separately for the 5 most-frequently fractured bones. Orange highlighting indicates results that are significant ($P \leq .001$), while yellow highlighting shows results less significant ($P \leq .01$) and gray highlighting shows odds ratios that are not solvable (NS). Risk factors significant for “All bones” tend to remain significant for individual bones; age, operative procedure, osteoarthritis, and cardiovascular disease were generally important as nonunion risk factors. Fracture energy is apparently not important in pediatric patients, whereas it is important in adult patients.^[6]

4. Discussion

Fracture nonunion is rare in pediatric patients (Table 1). Nonunion is associated with risk factors such as age, male sex, higher body-mass index, open fracture, multiple fracture, and tobacco use (all, multivariable $P < .0001$; Table 1). Some bones are more likely to go to nonunion in children, especially

Table 1
Demographic summary of pediatric patients (under age 18) with fracture.

Characteristic	Level	Fracture count	Category frequency (%)	Nonunion count	Nonunion frequency (%)	Trend P value
All fractures	Age 0–17	237,033	100	2003	0.85	
Patient age	0–6	54,224	22.88	108	0.20	<.0001
	7–11	79,328	33.47	207	0.26	
	12–17	103,481	43.66	1688	1.63	
	Male	146,243	61.70	1375	0.94	
Gender	Female	90,790	38.30	628	0.69	<.0001
	<25.0	231,180	97.53	1933	0.84	
Body-mass index (BMI)	25.0–29.9	1302	0.55	11	0.84	<.0001
	30.0–39.9	3896	1.64	42	1.08	
	≥40.0	655	0.28	17	2.60	
	Closed	232,852	98.24	1882	0.81	
Open	4,181	1.76	121	2.89		
Fracture type	1	201,930	85.19	1668	0.83	<.0001
	2	29,726	12.54	224	0.75	
	3	4027	1.70	70	1.74	
	4	830	0.35	25	3.01	
	≥5	520	0.22	16	3.08	
	Past/current smoker	No	235,653	99.42	1978	
Yes	1380	0.58	25	1.81		

tibia/fibula, femoral neck, and scaphoid (Fig. 2). In addition, certain medical comorbidities (Table 2) and medications (Fig. 3) are associated with an increased risk of nonunion. Several specific risk factors are broadly associated with nonunion risk (Table 3) including: patient age; operative procedure; osteoarthritis; cardiovascular disease; Vitamin D deficiency (all, multivariable $P < .001$); and osteoporosis ($P < .01$). These findings confirm the hypothesis that risk factors which predispose pediatric patients to nonunion are generally similar to risk factors that predispose adults to nonunion. Nonunion risk in adolescent scaphoid fracture is nearly as high as in adults (Fig. 2), as described.¹¹⁰¹

Certain pediatric nonunion risk factors are similar in magnitude and kind to risk factors in adults.¹⁶¹ In both groups, increased nonunion risk was associated with severe fracture (e.g., open fracture, multiple fractures), high body mass index, and smoking.¹⁶¹ Considering only the “All bones” category, the OR for nonunion was significant ($P < .01$) and similar for certain risk factors in adults¹⁶¹ and pediatric patients (Table 3) including: open fracture (pediatric (p) OR=1.91; adult (a) OR=1.66); operative procedure (pOR=2.58; aOR=1.78); osteoarthritis (pOR=2.45; aOR=1.45); Vitamin D deficiency (pOR=2.91; aOR=1.14); osteoporosis (pOR=2.75; aOR=1.24); antibiotic

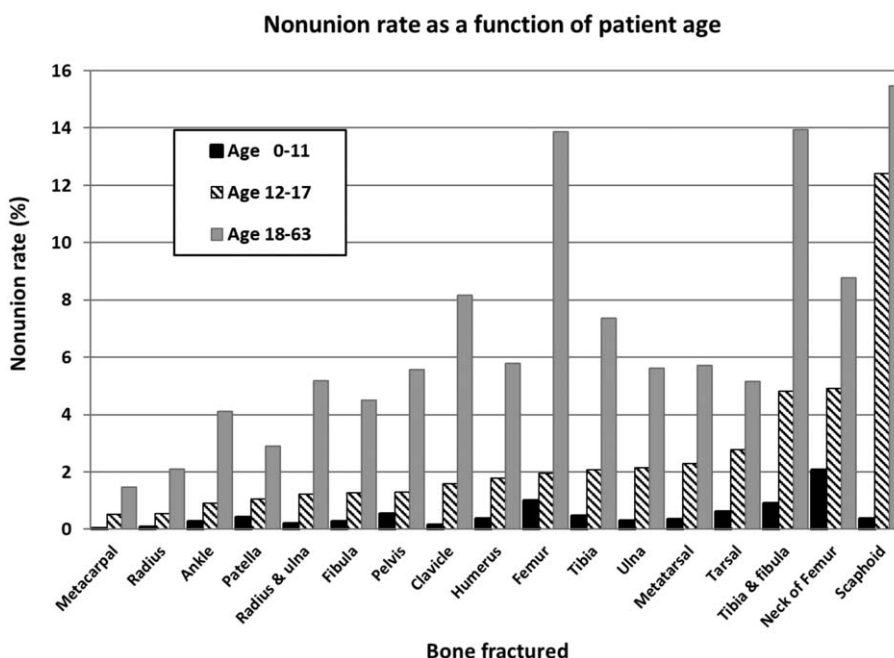


Figure 2. The impact of age on risk of nonunion, for 3 different age classes of patients. Data on patients age 18-63 is taken from reference 9. For every bone, there was a significant effect of age nonunion rate across the 3 cohorts ($P < .0001$).

Table 2
Demographic summary of pediatric patients (under age 18) with fracture and a diagnosed comorbid condition.

Risk factor	Fracture count	Risk prevalence	Healed	Nonunion	Univariate OR	Multivariate OR	Univariate P value
Male	146,243	61.70%	144,868	1375	1.36 (1.24, 1.49)	0.93 (0.83, 1.03)	.1617
Allergy diagnosis	59,995	25.31%	59,589	406	0.75 (0.67, 0.83)	0.85 (0.76, 0.95)	.0077
Cardiovascular disease	6976	2.94%	6816	160	2.91 (2.47, 3.42)	1.82 (1.52, 2.17)	<.0001
Obesity diagnosis	5853	2.47%	5783	70	1.44 (1.13, 1.82)	1.28 (0.99, 1.64)	.0565
Renal insufficiency	1690	0.71%	1667	23	1.63 (1.08, 2.45)	0.97 (0.63, 1.48)	.8765
Past/Current smoker	1380	0.58%	1355	25	2.18 (1.47, 3.25)	0.64 (0.42, 0.96)	.0323
Osteoarthritis	906	0.38%	863	43	5.95 (4.37, 8.11)	2.45 (1.78, 3.38)	<.0001
Vitamin D deficiency	832	0.35%	805	27	3.98 (2.70, 5.84)	2.91 (1.91, 4.42)	<.0001
Diabetes type II only	667	0.28%	656	11	1.97 (1.09, 3.58)	1.38 (0.68, 2.78)	.3677
Osteoporosis	300	0.13%	287	13	5.34 (3.06, 9.33)	2.75 (1.46, 5.18)	.0018
Rheumatoid arthritis	280	0.12%	277	3	1.29 (0.41, 4.04)	1.16 (0.36, 3.71)	.8069
Diabetes type I/II	220	0.09%	219	1	0.54 (0.08, 3.83)	0.39 (0.05, 3.27)	.3886
Alcoholism diagnosis	191	0.08%	189	2	1.24 (0.31, 5.00)	0.41 (0.10, 1.67)	.2130

treatment (pOR=1.18; aOR=1.17); anticoagulant treatment (pOR=2.45; aOR=1.58); prescription opioid use (pOR=2.47; aOR=1.43); and use of prescription NSAIDs and opioids (pOR=2.52; aOR=1.84).

Several significant ($P < .01$) nonunion risk factors in adults^[6] were not significant in pediatric patients (Table 3), including ≥ 6 fractures (pOR=0.85; aOR=2.65); use of anticonvulsant medications alone (pOR=1.09; aOR=1.37); use of benzodiazepine alone (pOR=0.52; aOR=1.21); use of benzodiazepine and anticonvulsants together (pOR=0.78; aOR=1.49); type I diabetes (pOR=0.39; aOR=1.40); high-energy fracture (pOR=1.05; aOR=1.38); male sex (pOR=0.93; aOR=1.21); insulin use (pOR=1.04; aOR=1.21); diuretic use (pOR=0.54; aOR=1.13); and renal insufficiency (pOR=0.97; aOR=1.11). In children, there was only 1 significant ($P < .01$) risk factor not also important in adult patients; patient age (pOR=2.49; aOR=0.97).

Most pediatric nonunion risk factors identified have prior support in the literature. For example, bisphosphonate use was associated with nonunion risk in both children and adolescents (Fig. 3). Bisphosphonates are used in pediatric patients to treat a growing number of disorders including generalized or localized deficits in bone mineralization, genetic and acquired metabolic bone diseases, heterotopic calcification, and hypercalcemia.^[11,12] Bisphosphonates are used most commonly for osteogenesis imperfecta and can mediate increased bone mineral density and decreased long bone fracture.^[13] But bisphosphonates have also been linked to an increased risk of atypical femoral fracture,^[14–16] with a 70% risk increase in one meta-analysis.^[17]

Bisphosphonate therapy may be associated with delayed healing of fractures.^[18] A recent meta-analysis did not find evidence that use of bisphosphonates after surgery interfered with fracture healing,^[19] but a cohort study of 19,731 adult patients found that bisphosphonates in the post-fracture period were

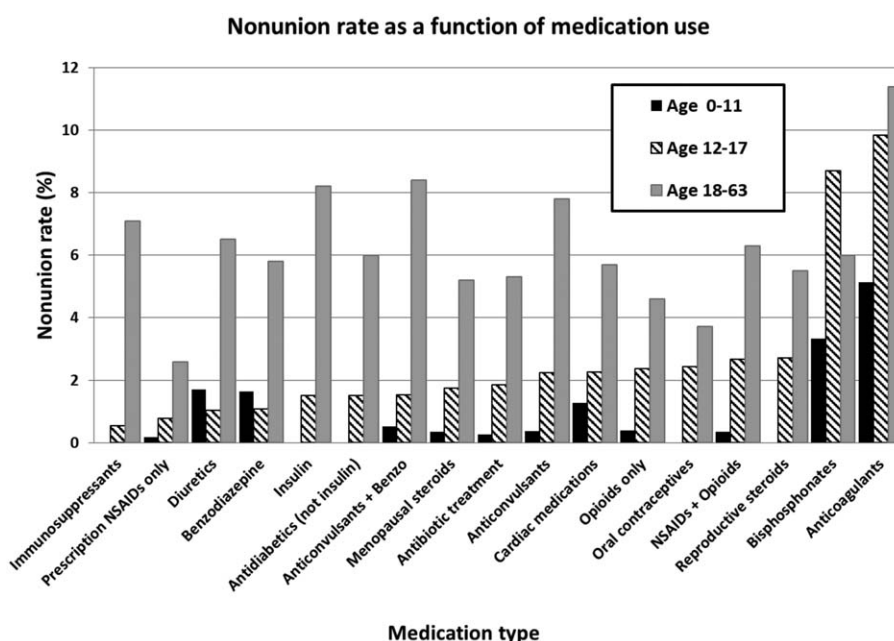


Figure 3. The impact of medication use on risk of nonunion, for 3 different age classes of patients. Data on patients age 18–63 is taken from reference 9.

Table 3

Multivariate odds ratio (OR) for nonunion among pediatric patients (under age 18) with 95% confidence intervals.

Age increases by 4 years	Age does not change	2.49 (2.33, 2.66)	2.24 (1.81, 2.76)	2.53 (1.99, 3.20)	1.84 (1.53, 2.20)	2.49 (2.04, 3.02)	1.67 (1.22, 2.29)
Male	Female	0.93 (0.83, 1.03)	1.16 (0.81, 1.65)	0.47 (0.32, 0.69)	0.84 (0.58, 1.21)	0.76 (0.59, 0.98)	0.98 (0.64, 1.48)
High-energy accident	Low-energy accident	1.05 (0.82, 1.34)	1.50 (0.67, 3.36)	1.02 (0.53, 1.95)	0.86 (0.37, 1.96)	0.62 (0.20, 1.86)	1.07 (0.30, 3.85)
Unknown energy accident	Low-energy accident	1.63 (1.41, 1.88)	2.36 (1.40, 3.96)	1.09 (0.72, 1.66)	1.26 (0.81, 1.95)	1.54 (0.98, 2.42)	1.51 (0.82, 2.80)
Open fracture	Closed fracture	1.91 (1.56, 2.32)	1.88 (0.75, 4.73)	1.77 (1.02, 3.08)	2.07 (1.08, 3.99)	0.39 (0.12, 1.31)	1.79 (0.76, 4.21)
Medicaid coverage	Commercial coverage	0.67 (0.60, 0.76)	0.50 (0.32, 0.76)	0.79 (0.51, 1.22)	1.16 (0.79, 1.70)	0.59 (0.41, 0.86)	0.51 (0.29, 0.89)
Operative procedure	Conservative treatment	2.58 (2.29, 2.89)	3.89 (2.68, 5.64)	3.45 (2.32, 5.12)	4.85 (2.97, 7.93)	5.25 (3.63, 7.60)	2.13 (1.26, 3.60)
Treatment info unknown	Conservative treatment	1.25 (1.12, 1.39)	2.04 (1.43, 2.90)	2.07 (1.21, 3.52)	3.09 (1.87, 5.12)	0.88 (0.68, 1.14)	0.85 (0.54, 1.32)
Past / Current smoker	Non-smoker	0.64 (0.42, 0.96)	0.82 (0.19, 3.50)	0.87 (0.11, 6.78)	0.96 (0.20, 4.61)	0.27 (0.04, 2.01)	0.00 (0.00, Inf)
Diagnosis of allergy	No allergy diagnosis	0.85 (0.76, 0.95)	0.77 (0.63, 1.12)	0.66 (0.41, 1.05)	0.88 (0.58, 1.32)	1.10 (0.83, 1.46)	0.78 (0.47, 1.27)
Osteoarthritis only	No arthritis	2.45 (1.78, 3.38)	4.02 (1.43, 11.30)	3.15 (0.64, 15.52)	3.15 (0.69, 14.41)	3.96 (2.01, 7.80)	1.89 (0.44, 8.01)
Cardiovascular disease	No cardiovascular disease	1.82 (1.52, 2.17)	2.52 (1.43, 4.44)	3.56 (1.96, 6.49)	1.17 (0.47, 2.91)	0.82 (0.44, 1.53)	2.67 (1.35, 5.28)
Vitamin D deficiency	No Vitamin D deficiency	2.91 (1.91, 4.42)	5.50 (1.74, 17.33)	5.87 (1.44, 24.01)	0.00 (0.00, Inf)	3.14 (1.37, 7.22)	0.00 (0.00, Inf)
Diagnosis of obesity	No obesity	1.28 (0.99, 1.64)	0.19 (0.03, 1.40)	0.77 (0.63, 1.12)	2.04 (0.80, 5.22)	2.31 (1.37, 3.92)	2.30 (1.12, 4.73)
Osteoporosis	No osteoporosis	2.75 (1.46, 5.18)	8.08 (1.04, 62.82)	6.11 (0.42, 87.90)	0.00 (0.00, Inf)	2.18 (0.27, 17.36)	0.00 (0.00, Inf)
Prescription NSAIDs only	No analgesics	1.05 (0.81, 1.35)	0.48 (0.12, 2.01)	2.15 (0.61, 7.63)	1.03 (0.35, 2.99)	1.34 (0.83, 2.15)	1.28 (0.48, 3.40)
Opioids only	No analgesics	2.47 (2.18, 2.78)	3.57 (2.43, 5.24)	3.73 (2.14, 6.50)	1.87 (1.17, 3.01)	2.43 (1.79, 3.30)	2.37 (1.41, 3.98)
NSAIDs + Opioids	No analgesics	2.52 (2.18, 2.91)	4.30 (2.69, 6.86)	3.35 (1.68, 6.68)	1.95 (1.07, 3.54)	1.88 (1.30, 2.71)	2.35 (1.28, 4.31)
3-5 fractures / Patient	1-2 fractures / Patient	1.31 (1.05, 1.63)	2.01 (1.09, 3.67)	1.82 (1.07, 3.09)	0.87 (0.33, 2.28)	0.98 (0.20, 4.73)	1.45 (0.42, 5.03)
		P ≤ 0.001	P ≤ 0.01	NS			

Multivariate odds ratio (OR) for nonunion. All 18 bones are pooled are shown, together with the 5 most frequently fractured bones. Data for the remaining 13 bones are available upon request. NSAIDs=Non-steroidal Anti-inflammatory Drugs.

associated with a significant doubling of nonunion risk.^[20] Bisphosphonates have also been shown to prolong healing times of distal radius fractures,^[21] and can delay hard callus remodeling during fracture healing in rats.^[22] Differences in union time between users and nonusers of bisphosphonates were not judged severe enough to change current practice recommendations in adults,^[23] but our data may provide motivation to revisit this recommendation in children.

Contraceptive and reproductive steroid use was associated with increased nonunion risk in adolescents (Fig. 3). Chronic exposure of children to supraphysiologic glucocorticoids was associated with reduced bone mineral density, an increase in fracture rate, and compromised linear growth.^[24] Rheumatic diseases are also associated with increased fracture risk, which may result from chronic glucocorticoid exposure, and greater glucocorticoid exposure is correlated with greater bone mineralization.^[25] Vertebral fractures are common in children taking glucocorticoid medications for rheumatic disorder^[26]; glucocorticoid use can result in osteoporosis in children with chronic inflammatory diseases^[27]; and inhaled corticosteroids for asthma can result in osteoporosis and increased fracture risk in children.^[28] Corticosteroids affect bone mineral density and increase fracture risk, and growth suppression can occur at high steroid doses.^[29,30]

Nonunion risk associated with opioid use in adults is well documented.^[6,31,32] Opioids roughly double the risk of nonunion ($P < .0001$) of 18 bones pooled (Table 3), as well as radius, radius/ulna, ulna, metatarsal, tarsal, and scaphoid (Table 3). Opioids are widely prescribed for fracture pain in children; up to 85% of pediatric emergency physicians surveyed in North America reported using oral opioids for pediatric musculoskeletal pain.^[33] Inadequate treatment of painful conditions in children is a common problem^[34] and opioids are used increasingly for pediatric orthopedic pain.^[35] Yet recent clinical trial results on post-fracture pain show ibuprofen is as effective as opioids for pain relief in pediatric patients, with fewer adverse events.^[36] Post-fracture pain can be adequately managed with ibuprofen,^[37] and our results suggest opioids should be used sparingly in pediatric patients.

A major limitation of this study is that these patients may not be typical of American children, given that they were mostly children of people employed in professions, rather than trades. For example, many clinicians might find that their practice is not comprised of 97.3% of children with a BMI ≤ 25 (Table 1). Another limitation is that we cannot separate fracture subtypes of interest. For example, humerus fractures are grouped, although supracondylar humerus fractures may heal differently than lateral condylar fractures.

Pediatric fracture management may be altered by a better awareness of which patients—and which bones—are most at risk of nonunion. Nonunion is rare in pediatric patients but occurs in predictable patterns. There is an increasing risk of nonunion with age, especially after age 11, for unknown reasons. Important pediatric nonunion risk factors—obesity, open fracture, and smoking—are familiar from adult fracture. However, some risk factors appear to be stronger in children, including Vitamin D deficiency, osteoarthritis, osteoporosis, bisphosphonate use, anticoagulant treatment, and prescription opioid use. Finally, our results suggest it may be wise to consider alternatives to opiates for pain control.

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