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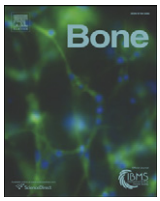

Full Length Article

Bone fracture nonunion rate decreases with increasing age: A prospective inception cohort study

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ABSTRACT

Background: Fracture nonunion risk is related to severity of injury and type of treatment, yet fracture healing is not fully explained by these factors alone. We hypothesize that patient demographic factors assessable by the clinician at fracture presentation can predict nonunion.

Methods: A prospective cohort study design was used to examine ~2.5 million Medicare patients nationwide. Patients making fracture claims in the 5% Medicare Standard Analytic Files in 2011 were analyzed; continuous enrollment for 12 months after fracture was required to capture the ICD-9-CM nonunion diagnosis code (733.82) or any procedure codes for nonunion repair. A stepwise regression analysis was used which dropped variables from analysis if they did not contribute sufficient explanatory power. In-sample predictive accuracy was assessed using a receiver operating characteristic (ROC) curve approach, and an out-of-sample comparison was drawn from the 2012 Medicare 5% SAF files.

Results: Overall, 47,437 Medicare patients had 56,492 fractures and 2.5% of fractures were nonunion. Patients with healed fracture (age 75.0 ± 12.7 SD) were older ($p < 0.0001$) than patients with nonunion (age 69.2 ± 13.4 SD). The death rate among all Medicare beneficiaries was 4.8% per year, but fracture patients had an age- and sex-adjusted death rate of 11.0% ($p < 0.0001$). Patients with fracture in 14 of 18 bones were significantly more likely to die within one year of fracture ($p < 0.0001$). Stepwise regression yielded a predictive nonunion model with 26 significant explanatory variables (all, $p \leq 0.003$). Strength of this model was assessed using an area under the curve (AUC) calculation, and out-of-sample AUC = 0.710.

Conclusions: A logistic model predicted nonunion with reasonable accuracy (AUC = 0.725). Within the Medicare population, nonunion patients were younger than patients who healed normally. Fracture was associated with increased risk of death within 1 year of fracture ($p < 0.0001$) in 14 different bones, confirming that geriatric fracture is a major public health issue. Comorbidities associated with increased risk of nonunion include past or current smoking, alcoholism, obesity or morbid obesity, osteoarthritis, rheumatoid arthritis, type II diabetes, and/or open fracture (all, multivariate $p < 0.001$). Nonunion prediction requires knowledge of 26 patient variables but predictive accuracy is currently comparable to the Framingham cardiovascular risk prediction.

1. Background

Fractures are relatively common among patients older than age 65 [1]. The increase in fracture incidence in the elderly may represent a confluence of trends. The number of falls by the elderly correlates positively with increasing age [2]. There is also a rising age-related incidence of illnesses that increase fall risk, including diabetes [2], Alzheimer's

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disease [3], stroke [4], Parkinson's disease [5], and multiple sclerosis [5,6]. Certain comorbidities which increase in prevalence with age, including diabetes [7,8], osteoporosis [9], osteopenia [10], sarcopenia [11], vitamin D insufficiency [12], and chronic opioid dependency [13] make patients more prone to fracture if they do fall [1]. Finally, certain diseases make elderly patients with fracture more prone to nonunion [14]. People over age 65 are therefore at increased risk for fracture [1] and may also be at increased risk for nonunion.

A better understanding of fracture nonunion in the elderly is important because certain geriatric fractures predispose patients to premature death [15], including fractures of the cervical spine [16], pelvis [17], acetabulum [18,19], hip [1,20,21,22], and distal radius [23]. We seek to develop a predictive algorithm that will alert physicians to elderly patients at risk of fracture nonunion. This may enable clinicians to identify at-risk patients earlier in their course, when intervention could potentially improve clinical outcome.

2. Methods

2.1. Study cohort

The study cohort was derived from the 5% Medicare Standard Analytic Files (SAF) for calendar year 2011, a random sample of the covered lives in Medicare. In 2011, Medicare covered 48.7 million people, including 40.4 million people aged 65 and older, and 8.3 million disabled people. About 25% of all beneficiaries chose to enroll in Part C private health plans, which contract with Medicare to provide Part A and Part B health services. Thus, the traditional fee-for-service Medicare beneficiaries that would have claims in the SAF would be 36.5 million (48.7×0.75). The SAF contains final action claims data submitted by providers for reimbursement. We analyzed all Medicare beneficiaries with ≥1 fracture diagnosis in the 18 bones most frequently fractured.

We excluded beneficiaries who did not have both Medicare Part A and Part B eligibility in all of 2011 and 2012, so that a code for nonunion could be captured. Patients were excluded for a malunion claim or if the 2011 claim was for nonunion of a prior fracture.

2.2. Outcome identification

We identified nonunions in the 2011 and 2012 Medicare SAFs using the ICD-9-CM nonunion diagnosis code (733.82) [24] and also using procedure codes for repair of nonunion, including bone graft and various bone growth stimulators, such as electrical stimulation and low-intensity pulsed ultrasound. We identified physician, hospital inpatient, hospital outpatient, and durable medical equipment claims ≤365 days after the fracture index date. Bone graft codes within 6 months of the index date were considered part of the initial fracture treatment and not necessarily evidence of nonunion.

Roughly 84% of patients in the study had only one fracture. The nonunion diagnosis code and some treatment codes are not bone-specific, so we sought to associate nonunion with an individual fracture. We compared the date of nonunion diagnosis or treatment to the dates of fracture care visits. First, we linked patients with a single fracture and a nonunion code on the same day. For patients with multiple fractures and a nonunion, we associated nonunion with the fracture treated within 14 days of the nonunion diagnosis. For the few remaining cases, the fracture that was treated closest to the claim was accepted as a nonunion. We also identified whether death occurred within 365 days of the index date from denominator files for 2011 and 2012.

2.3. Covariate identification

Conditions and comorbidities that could potentially contribute to nonunion were identified through treatment claims up to 1 year prior to, or 30 days after, the index fracture date. A medical condition was considered present when ≥2 claims indicating the condition were found for a patient. Treatments were categorized as surgical or nonsurgical based on procedure codes. Demographic information on age, gender, original reason for Medicare eligibility, and dual eligibility for Medicaid was obtained from the denominator file.

2.4. Analysis

Patient demographics that are binary are presented as percentages and analyzed with a two-tailed χ^2 test. Continuous variables are presented as mean ± standard deviation (SD) and analyzed with a two-tailed Student *t*-test.

Regression analysis used 60 patient characteristics and comorbidities that might contribute to nonunion. Variables included: 6 categories of age; 18 bones of interest (with 1 bone used as a reference); number of concurrent fractures; gender; 23 comorbidity variables (e.g. hypertension); a variable representing whether surgery was performed; open or closed fracture; and 3 variables representing the reason for Medicare eligibility (disabled vs. aged) and whether the patient was dually eligible for Medicaid. Rib fracture was not represented in the model because it was the reference, chosen because it had the lowest risk of nonunion in our cohort.

The dependent variable in the analysis was nonunion (1 = Present, 0 = Absent), and we used a logistic model [25]. For parsimony, the model was estimated using a stepwise procedure, which dropped variables from analysis if they did not contribute sufficient explanatory power. We specified $p = 0.01$ as the significance level to retain a variable in the model. The out-of-sample predictive accuracy of the model was assessed using a receiver operating characteristic (ROC) curve approach [26]. The out-of-sample comparison sample was drawn from the 2012 Medicare 5% SAF files.

2.5. Patient involvement

Patients were not involved in the design of this study, nor were patients recruited for study involvement; this was a payer reimbursement study.

3. Results

A total of 54,269 patients had fracture in the 2011 Medicare 5% SAF database, but 5018 patients were excluded from consideration because they were not Medicare Part A and B eligible in 2011 and 2012 or because they elected to use a health-maintenance organization (HMO) in 2011 or 2012 (Fig. 1). An additional 79 patients had flaws in the demographic file and could not be analyzed, while fewer than 11 patients were under age 18. A total of 1718 patients with 1754 fractures were excluded because there was treatment in 2010 for the same bone treated in 2011, suggesting that the 2011 fracture actually occurred in 2010.

A total of 47,437 Medicare patients with 56,492 fractures were analyzed, and 2.5% of fractures went to nonunion (Table 1). Patients with fracture but without nonunion (age 75.0 ± 12.7 standard deviation, SD), were significantly older ($p < 0.0001$) than patients with nonunion (age 69.2 ± 13.4 SD). Compared to the average Medicare patient, patients were significantly more likely to develop nonunion under age 75, while patients over age 75 were less likely to go to nonunion (Table 1). Among patients ≥85 years, the nonunion rate was 1.3%, whereas the nonunion rate in patients age 55–59 was 5.5% (Table 1).

Nonunion rate varied by bone, from a low of 0.6% in ribs and trunk to a high of 6.4% in scaphoid (Table 2). The estimate of nonunion rate bone-by-bone is likely to be robust as the smallest sample size was scaphoid ($N = 534$), while the largest sample size was neck of femur ($N = 9426$).

Fracture was associated with premature death in many different bones (Table 2). Death rate in the Medicare population overall was 4.8% per year among 50 million patients. Patients with fracture in any

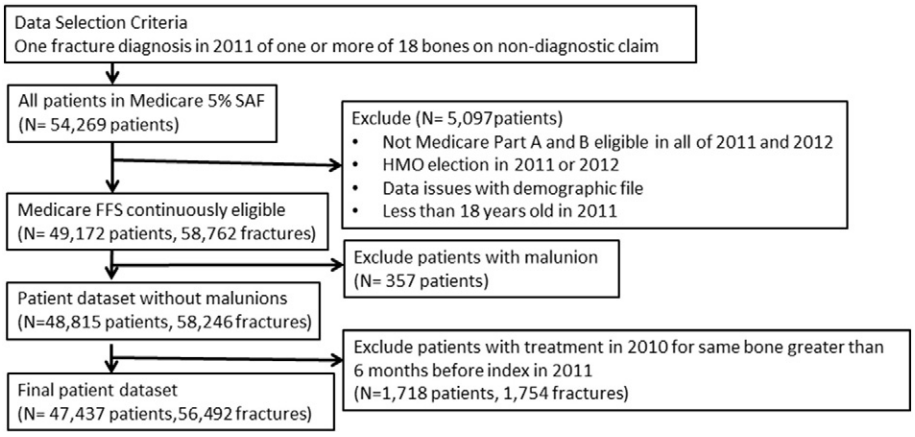

Fig. 1. CONSORT diagram, showing how the analytic sample was assembled.

of 14 bones (Table 2)—or in the pooled category of all bones—were significantly more likely to die within a year of fracture ($p < 0.0001$), after adjusting for age and gender. Risk of death from fracture varied greatly depending on the bone fractured; patients with fractures of the femur had a risk of death 3.7-fold higher than Medicare patients free of fracture, while pelvic fractures increased the risk of death 3.6-fold. Other fractures associated with a high risk of death included tibia + fibula (2.9-fold), humerus (2.7-fold), tibia (2.7-fold) and clavicle (2.6-fold).

Nonunions were more likely to occur in people with various comorbidities (Table 3). Nonunion was significantly more common in patients who were past or current smokers, were obese or morbidly obese, had osteoarthritis, rheumatoid arthritis, type II diabetes (controlled or uncontrolled), or open fracture (all, $p < 0.001$). Nonunions were also more prevalent in patients with alcoholism, osteoporosis, or type I diabetes (controlled or uncontrolled) (all, $p < 0.01$). However, a history of cardiovascular disease or stroke was associated with a reduced risk of nonunion ($p < 0.01$). No significant change in nonunion risk was associated with malnutrition, vitamin deficiency, minor allergy, phlebitis, vascular disease, hypertension, chronic kidney disease, or other renal disorders (Table 3).

The stepwise logistic model for nonunion has 26 significant explanatory variables (Table 4). An odds ratio (OR) > 1 indicates a positive association which increases the risk of nonunion, while OR < 1 indicates a negative association that may be protective from nonunion. Overall, the largest ORs are related to the specific bone fractured, with scaphoid the bone most likely to go to nonunion. The largest OR other than fracture location is rheumatoid arthritis, which is more important than open fracture as a nonunion risk factor. There is a negative association between nonunion and death within one year (Table 4), suggesting that some patients die soon after fracture, before they are diagnosed with nonunion. The only other variable with OR < 1 is age > 75 years (Table 4). Surgery was associated with a nonunion OR > 1, suggesting that surgeons are able to identify patients at risk of nonunion.

We tested a hypothesis that death within one year accounts for the lower nonunion rate among older patients by dropping patients who died within one year from the model. The lower nonunion rate in patients over 65 remained evident, showing that premature death does not fully explain the lower nonunion rate in the elderly. We then tested whether certain variables predict death, using death as a dependent variable. Several variables predicted death in a regression model, including stroke, vascular disease, morbid obesity, phlebitis, alcoholism, malnutrition, and smoking (all, $p < 0.01$), yet only smoking also predicted nonunion in the regression model.

Patients with normal healing had an average of 3.0 comorbidities (±2.2 SD), significantly fewer ($p < 0.0001$) than the 3.3 (±2.4 SD) comorbidities present in nonunion patients. To test a hypothesis that a greater number of comorbidities in Medicare participants <65 years old accounts for the nonunion rate being lower in older patients, we ran a regression model with number of disease comorbidities as an explanatory variable. Having more comorbidities did not significantly increase the risk of nonunion in the regression model.

The strength of the model predicting nonunion was estimated in several ways (Table 4). Area under the curve (AUC) is derived from

Table 1
Demographics of persons in the 5% Medicare Standard Analytic Files (SAF) database in calendar year 2011.

		Count	Healed	Percent of all healed	Nonunion	Percent of nonunion	*P* value
All fractures in Medicare		56,492	55,052	97.5	1440	2.5	–
Age group	<50 years	2726	2599	4.7	127	8.8	<0.0001
	50–54 years	1598	1519	2.8	79	5.5	<0.0001
	55–59 years	1975	1866	3.4	109	7.6	<0.0001
	60–64 years	2182	2100	3.8	82	5.7	0.0003
	65–69 years	8452	8169	14.8	283	19.7	<0.0001
	70–74 years	8329	8085	14.7	244	16.9	0.0170
	75–79 years	8271	8087	14.7	184	12.8	0.0428
	80–84 years	9385	9224	16.8	161	11.2	<0.0001
	≥85 years	13,574	13,403	24.3	171	11.9	<0.0001
Gender	Male	15,211	14,806	26.9	405	28.1	0.2988
	Female	41,281	40,246	73.1	1035	71.9	0.2988
Eligibility basis	Age > 65	43,198	42,307	76.8	891	61.9	<0.0001
	Disability or ESRD	13,294	12,745	23.2	549	38.1	<0.0001
Dual-eligibility for Medicaid		13,810	13,409	24.4	401	27.8	0.0023

Dual-eligibility means that a patient is eligible for Medicare Part A and B. *P* values shown are χ^2 tests of the "Percent of nonunion" versus the "Percent of all healed" for a demographic category. Among patients under age 50 years, 2599 patients (4.7% of 55,052 patients) had "Normal healing", while 127 patients (8.8% of 1440 patients) developed "Nonunion", so there was a significant excess of fracture nonunions among patients under age 50 years (χ^2 analysis, $P < 0.0001$).

Table 2
Count of fractures in study by bone, with nonunion rates.

	Count of fractures	Non-unions	NU%	Died in ≤1 year	Unadjusted death rate (%)	Age-sex adjusted death rate (%)	*P*-value
Total fractures	56,492	1440	2.5	7568	13.4	11.0	<0.0001
Neck of femur	9426	192	2.0	2501	26.5	19.7	<0.0001
Radius	7429	82	1.1	542	7.3	6.9	<0.0001
Ribs and trunk	5726	36	0.6	762	13.3	10.7	<0.0001
Metatarsal	5517	217	3.9	230	4.2	4.5	0.3908
Humerus	5021	218	4.3	746	14.9	12.9	<0.0001
Ankle	4811	157	3.3	379	7.9	7.9	<0.0001
Pelvis	3604	34	0.9	776	21.5	17.2	<0.0001
Radius + ulna	2161	29	1.3	188	8.7	7.6	<0.0001
Femur	2034	122	6.0	416	20.5	17.9	<0.0001
Tibia	1837	80	4.4	228	12.4	12.7	<0.0001
Patella	1833	28	1.5	147	8.0	7.4	<0.0001
Ulna	1354	51	3.8	137	10.1	8.5	<0.0001
Tarsal	1315	44	3.3	66	5.0	5.8	0.0862
Metacarpals	1293	16	1.2	84	6.5	6.2	0.0178
Tibia + fibula	1029	53	5.2	145	14.1	13.7	<0.0001
Clavicle	815	32	3.9	125	15.3	12.3	<0.0001
Fibula	753	15	2.0	73	9.7	9.8	<0.0001
Scaphoid	534	34	6.4	23	4.3	4.0	0.3980

There were 2,458,783 deaths in the Medicare 100% denominator file leading to an overall death rate of 4.8%. *P*-values shown are for the age-sex adjusted death rate bone-by-bone, in comparison to the overall Medicare death rate.

the Receiver Operator Characteristic (ROC) curve and is used to characterize predictive ability (e.g., AUC = 1.00 is a perfect prediction). The within-sample AUC is 0.725, while the out-of-sample AUC, based on data from 55,696 fractures in 2012, is 0.710, indicating that the model is a good predictor in a sample independent of the sample in which it was derived. The value of Akaike's information criterion (AIC = 12,538.5) was not greatly affected by the number of variables used in the model. Another model designed to minimize AIC by adding 14 additional explanatory variables had a value only slightly lower (AIC = 12,523.8), indicating that the simpler model we present yields an adequate and parsimonious prediction.

AUCs were separately calculated for each bone in the out-of-sample dataset (Table 5). The highest AUC was for metacarpal fracture (AUC = 0.738), while the lowest AUC was for fibula fracture (AUC = 0.547), indicating that the nonunion prediction varies by bone but is always better than a random prediction (AUC = 0.50). However, the lower bound of the 95% confidence interval (CI) is <0.50 for fibula and radius + ulna fractures, indicating that fracture nonunion for these bones is not adequately predicted by the model.

We assessed the predictive ability of the model in another way, independent of AUC. The calculated probability of nonunion was compared to the actual probability of nonunion in the out-of-sample dataset (Table 6). We calculated the average actual probability of nonunion for patients whose predicted probability of nonunion was in the first and the tenth deciles. Patients in the tenth decile for all fractures had an actual probability of nonunion 21-fold higher than patients in the first decile (Table 5). Those bones with the largest differential in risk were pelvis (9.27), patella (9.21), and femoral neck (9.16), while the smallest differential was fibula (1.50). Across all bones, patients in the highest decile were 2.58-fold and 3.68-fold times more likely to have nonunion, compared to patients whose predicted probability was equal to the mean and median, respectively.

Table 3
Comorbidities in study patients.

Comorbidities in patients	Fracture count	% with condition	Normal healing	% normal healing	Nonunion	% nonunion	χ^2 test *P* value
All fractures	56,492	100.0	55,052	97.5	1440	2.5	
Past or current smoker	4584	8.1	4395	8.0	189	13.1	<0.0001
Diagnosed alcoholism	467	0.8	443	0.8	24	1.7	0.0004
Diagnosed obesity	1152	2.0	1097	2.0	55	3.8	<0.0001
Morbid obesity	834	1.5	791	1.4	43	3.0	<0.0001
Malnutrition or vitamin deficiency	4393	7.8	4287	7.8	106	7.4	0.5512
Serious allergy	1478	2.6	1426	2.6	52	3.6	0.0166
Minor allergy	4844	8.6	4732	8.6	112	7.8	0.2739
Cardiovascular disease	27,874	49.3	27,231	49.5	643	44.7	0.0003
Phlebitis	4590	8.1	4454	8.1	136	9.4	0.0634
Vascular disease	7748	13.7	7548	13.7	200	13.9	0.8461
Stroke	8909	15.8	8718	15.8	191	13.3	0.0082
Hypertension	36,571	64.7	35,620	64.7	951	66.0	0.2937
Osteoarthritis (non-spine)	13,940	24.7	13,503	24.5	437	30.3	<0.0001
Osteoarthritis (spine)	3012	5.3	2906	5.3	106	7.4	0.0005
Osteoporosis	7165	12.7	6936	12.6	229	15.9	0.0002
Rheumatoid arthritis	1900	3.4	1805	3.3	95	6.6	<0.0001
Kidney disease (chronic)	6322	11.2	6149	11.2	173	12.0	0.3157
Other kidney and renal disorders	7827	13.9	7608	13.8	219	15.2	0.1321
Diabetes type I controlled	852	1.5	818	1.5	34	2.4	0.0071
Diabetes type I uncontrolled	305	0.5	289	0.5	16	1.1	0.0027
Diabetes type II controlled	15,120	26.8	14,677	26.7	443	30.8	0.0005
Diabetes type II uncontrolled	5323	9.4	5143	9.3	180	12.5	<0.0001
Open fracture	1486	2.6	1422	2.6	64	4.4	<0.0001

There were 4584 people in the database who were "Past or current smokers" (8.1% of 56,492 patients). Among smoking patients, 4395 (8.0% of 55,052 patients) had "Normal healing" while 189 (13.1% of 1440 patients) developed nonunion, so there was a significant excess of fracture nonunions among smokers (χ^2 analysis, $P < 0.0001$).

Table 4
Model prediction of nonunion.

Variables	Reference	Odds ratio	Robust SE	*t*-Statistic	*P* value
Constant term		0.009	0.001	-55.89	<0.001
Osteoporosis (OP)	No OP	1.423	0.108	4.64	<0.001
Osteoarthritis (not spine)	No OA	1.337	0.081	4.79	<0.001
Smoker	Not smoker	1.296	0.107	3.12	0.002
Rheumatoid arthritis (RA)	No RA	1.648	0.186	4.43	<0.001
Hypertension	No hypertension	1.214	0.072	3.27	0.001
Disabled	Aged	1.247	0.094	2.94	0.003
Surgery	No surgery	1.329	0.094	4.01	<0.001
Died					
Survived > 365 days	0.623	0.066	-4.48	<0.001	
Open fracture	Closed fracture	1.447	0.195	2.74	0.006
Age ≤ 50	Age 65–69	1.510	0.158	3.94	<0.001
Age 50–54	Age 65–69	1.524	0.192	3.35	0.001
Age 55–59	Age 65–69	1.599	0.177	4.23	<0.001
Age 75–79	Age 65–69	0.697	0.061	-4.13	<0.001
Age 80–84	Age 65–69	0.555	0.051	-6.37	<0.001
Age ≥ 85	Age 65–69	0.430	0.040	-9.02	<0.001
Neck of femur	Not neck of femur	2.119	0.239	6.65	<0.001
Femur	Not femur	5.345	0.648	13.83	<0.001
Scaphoid	Not scaphoid	5.608	1.062	9.11	<0.001
Clavicle	Not clavicle	3.954	0.760	7.15	<0.001
Metatarsal	Not metatarsal	3.391	0.323	12.83	<0.001
Ankle	Not ankle	2.650	0.281	9.19	<0.001
Humerus	Not humerus	4.413	0.423	15.47	<0.001
Tibia + fibula	Not tibia + fibula	4.021	0.641	8.74	<0.001
Ulna	Not ulna	3.409	0.545	7.68	<0.001
Tibia	Not tibia	3.510	0.470	9.38	<0.001
Tarsal	Not tarsal	2.570	0.432	5.61	<0.001
Total observations		56,492			
Within-sample AUC		0.7245			
Out-of-sample AUC		0.7101			
AIC		12,538.50			

All 26 factors are used in prediction of the nonunion risk.

4. Discussion

Nonunion patients are significantly younger than patients who heal normally (Table 1). Fracture in the Medicare population is significantly associated ($p < 0.0001$) with death within 1 year of injury (Table 2), although this observation cannot fully explain the observation that elderly people have a lower nonunion rate than younger people. A wide range of comorbidities is associated with increased risk of nonunion (Table 3), including past or current smoking, obesity or morbid obesity,

Table 5
AUC of the predictive model bone-by-bone.

	Number of cases	Out-of-sample AUC	Bootstrapped SE	Lower limit 95% CI	Upper limit 95% CI
All bones model	55,696	0.7101	0.0067	0.6970	0.7232
Weighted average AUC of bone specific models		0.6479			
Ankle	4591	0.6004	0.0236	0.5541	0.6467
Clavicle	909	0.6810	0.0435	0.5958	0.7662
Fibula	722	0.5471	0.0923	0.3662	0.7280
Humerus	5032	0.6166	0.0217	0.5742	0.6591
Metacarpal bone(s)	1250	0.7380	0.0913	0.5590	0.9170
Metatarsal	5515	0.5863	0.0200	0.5472	0.6255
Neck of femur	9121	0.6579	0.0189	0.6209	0.6949
Other/unspecified parts of femur	2073	0.6356	0.0248	0.5870	0.6841
Patella	1783	0.6421	0.0403	0.5631	0.7210
Pelvis	3708	0.6987	0.0423	0.6159	0.7816
Radius	7261	0.6265	0.0316	0.5646	0.6884
Radius and ulna	2049	0.6023	0.0575	0.4896	0.7150
Rib(s), sternum, larynx, and trachea	5537	0.6189	0.0507	0.5194	0.7183
Scaphoid	548	0.7351	0.0381	0.6604	0.8098
Tarsal	1353	0.6335	0.0419	0.5514	0.7156
Tibia	1841	0.6399	0.0361	0.5692	0.7107
Tibia and fibula	1029	0.5735	0.0368	0.5013	0.6457
Ulna	1374	0.6139	0.0406	0.5343	0.6934

Table 6
Probability of fracture nonunion.

	Probability of nonunion per decile				Risk ratios		
Bone type	First decile	Tenth decile	Mean	Median	Tenth vs. first	Tenth vs. median	Tenth vs. mean
All fractures	0.00321	0.06839	0.02654	0.01857	21.32	3.68	2.58
Ankle	0.01717	0.06034	0.03367	0.02953	3.52	2.04	1.79
Clavicle	0.00000	0.13187	0.04182	0.03604	NM	3.66	3.15
Neck of femur	0.00426	0.03903	0.02116	0.01763	9.16	2.21	1.84
Femur	0.02400	0.10577	0.06138	0.05117	4.41	2.07	1.72
Fibula	0.02703	0.04054	0.01278	0.01135	1.50	3.57	3.17
Humerus	0.01417	0.09055	0.04470	0.03993	6.39	2.27	2.03
Metacarpals	0.00719	0.02400	0.01262	0.01135	3.34	2.11	1.90
Metatarsal	0.01449	0.06679	0.04041	0.03748	4.61	1.78	1.65
Patella	0.00485	0.04469	0.01202	0.01069	9.21	4.18	3.72
Pelvis	0.00224	0.02079	0.00890	0.00698	9.27	2.98	2.34
Radius	0.00353	0.02653	0.01111	0.00937	7.51	2.83	2.39
Radius and ulna	0.00000	0.01463	0.01206	0.01052	NM	1.39	1.21
Ribs and trunk	0.00212	0.01261	0.01064	0.00937	5.94	1.35	1.19
Scaphoid	0.00000	0.08929	0.06488	0.06050	NM	1.48	1.38
Tarsal	0.00735	0.05000	0.03461	0.03052	6.80	1.64	1.44
Tibia and fibula	0.03738	0.06604	0.05258	0.04452	1.77	1.48	1.26
Tibia	0.02591	0.09730	0.04579	0.03874	3.76	2.51	2.12
Ulna	0.01220	0.05036	0.03878	0.03500	4.13	1.44	1.30

Probability of a nonunion expressed for patients in the first and tenth decile of the sample, in terms of the OSS predicted probability of nonunion. NM - not meaningful.

osteoarthritis, rheumatoid arthritis, type II diabetes, and open fracture (all, $p < 0.001$). A logistic model (Table 4) predicted nonunion with reasonable accuracy (AUC = 0.725), suggesting that patients at risk of nonunion can be identified. Although patients who die in less than a year may not have had time to be diagnosed with nonunion prior to death (Table 2), age and death are both in the predictive model (Table 4), suggesting that premature death cannot fully explain the reduced rate of nonunion in the elderly.

Increasing patient age is associated with decreased risk of nonunion (Table 2). It is possible that nonunion patients are not seeking care or are not being diagnosed with the same sensitivity as younger patients. However, few patients who survive to an advanced age may have risk factors for nonunion, since many risk factors for nonunion (Table 4) are also risk factors for premature death. For example, risk of premature death or disability is increased for patients who smoke [27,28], are physically disabled [29], have hypertension [28,30], osteoporosis [31,32], osteoarthritis [33], or rheumatoid arthritis [34], and all of these are risk factors for nonunion (Table 4).

The CMS nonunion model presented (Table 4) predicts nonunion with reasonable accuracy; the in-sample AUC for the model was 0.725, while the out-of-sample AUC was 0.710. This compares favorably with the AUC for the Framingham risk score, which has been used to predict cardiovascular event risk among patients with no known cardiovascular disease [35]. A meta-analysis of 16 studies showed that, among men, the Framingham AUC was 0.708 (±0.060 SD) while, in 10 studies in women, the Framingham AUC was 0.773 (±0.033 SD) [35]. Prediction of type II diabetes risk based on age, sex, and body mass index achieved an AUC of 0.63, yet adding an additional 18 established genetic risk factors only increased the AUC to 0.66 [36]. The accuracy of osteoporotic fracture risk prediction using the fragility fracture (FRAX) tool is comparable to our nonunion prediction; the AUC for osteoporotic fracture prediction averaged 0.71 across 2 studies in men and 0.74 across 9 studies in women [37].

It is not known why fracture is associated with premature death (Table 2). Relatively little is known about mortality associated with trauma in the elderly [1,38], yet there have been many studies which document that loss of mobility is associated with increased morbidity and mortality [39]. Elderly adults lose muscle mass and lean body tissue more rapidly than young adults during prolonged physical inactivity [40]. Ten days of experimental bed rest in otherwise-healthy 67-year-old adults resulted in 14% loss of power, 13% loss of strength, and 12% loss of aerobic capacity [41]. Elderly patients hospitalized with acute illness experience a rapid decline in function; two-thirds of patients aged ≥74 years suffered a functional decline by the second day in hospital [42]. A recent study of 2293 patients (age ≥ 70) showed that in one-third of patients activities of daily living declined between hospitalization and discharge [43]. The frequency of functional decline increased markedly with age; only 23% of patients aged 70–74 experienced a decline in function with hospitalization, but fully 63% of patients > 90 years old declined in function [43]. Hence, one might expect physical performance to be dramatically diminished in elderly adults with fracture.

Caution is warranted in interpreting these results; the study is based on claims data, so a patient must seek and receive care for a nonunion diagnosis to be present in the data. Unlike patients in a randomized clinical trial (RCT), patients in Medicare are not followed prospectively, nor are they uniformly evaluated for specific outcomes. It is perhaps possible that physicians of elderly patients are less likely to observe a nonunion or to submit a nonunion claim. Further study is needed to determine whether the observed decrease in risk of nonunion is due to under-treatment of existing nonunions or to a lower incidence of nonunions. A second weakness of this study is that the encrypted version of the Medicare database does not contain medication records, so we were unable to assess the impact of medication usage on nonunion risk.

A strength of this analysis is that results are informative at a bone-specific level. For example, risk of nonunion for patella is 9-fold higher for patients in the 10th decile of predicted probabilities, relative to the first decile (Table 5). Based on these findings, patients with a higher predicted probability of a nonunion (e.g. predicted probability in the tenth decile) could be monitored more closely so as to treat delayed union aggressively, and thereby potentially prevent nonunion.

5. Conclusion

We have shown that fracture nonunion can be predicted with reasonable accuracy and that geriatric fracture is associated with an increased risk of premature death. We also demonstrate that fracture is less likely to produce nonunion in the elderly. More research is needed to investigate the relationship between fracture, nonunion, and death. We postulate that people who survive long enough to fracture a bone late in life have relatively few impediments to healing; such patients may be better able to heal than people who fracture at a younger age.

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All authors of this manuscript have potential financial competing interests. R. Zura, M. J. Braid-Forbes, K. Jeray, S. Mehta, T. A. Einhorn, J. T. Watson, G. J. Della Rocca, and K. Forbes are all consultants for Bioventus, which makes a bone-healing device, and everyone except M. J. Braid-Forbes and K. Forbes have received speaker fees and travel reimbursement. M. J. Braid-Forbes and K. Forbes received payment as consultants specifically for this project. R.G. Steen is an employee of Bioventus. None of the authors has any non-financial competing interests.

The processed data that support the findings of this study are available from M. J. Braid-Forbes, but restrictions apply to the availability of the raw data, which were used under license for the current study, and so raw data are not publicly available. Processed data are however available from the authors upon request.

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