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An inception cohort analysis to predict nonunion in tibia and 17 other fracture locations

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ABSTRACT

Introduction: The epidemiology of fracture nonunion has been characterized so it is potentially possible to predict nonunion using patient-related risk factors. However, prediction models are currently too cumbersome to be useful. We test a hypothesis that nonunion can be predicted with ≤10 variables, retaining the predictive accuracy of a full model with 42 variables.

Methods: We sought to predict nonunion with prospectively-acquired inception cohort data for 18 different bones, using the smallest possible number of variables that did not substantially decrease prediction accuracy. An American nationwide claims database of ~90.1 million participants was used, which included medical and drug expenses for 2011–2012. Continuous enrollment was required for 12 months after fracture, to allow sufficient time to capture a nonunion diagnosis. Health claims were evaluated for 309,330 fractures. A training dataset used a random subset of 2/3 of these fractures, while the remaining fractures formed a validation dataset. Multivariate logistic regression and stepwise logistic regression were used to identify variables predictive of nonunion. P value and the Akaike Information Criterion (AIC) were used to select variables for reduced models. Area-under-the-curve (AUC) was calculated to characterize the success of prediction.

Results: Nonunion rate in 18 fracture locations averaged 4.93%. Algorithms to predict nonunion in 18 locations in the full-model validation set had average AUC = 0.680 (±0.034). In the reduced models, average validation set AUC = 0.680 (±0.033) and the average number of risk factors required for prediction was 7.6. There was agreement across training set, validation set, and reduced set; in tibia, reduced model validation AUC = 0.703, while the full-model validation AUC = 0.709. Certain risk factors were important for predicting nonunion in ≥10 bones, including open fracture, multiple fracture, osteoarthritis, surgical treatment, and use of certain medications, including anticoagulants, anti-convulsants, or analgesics.

Discussion: Nonunion can be predicted in 18 fracture locations using parsimonious models with <10 patient demography-related risk factors. The model reduction approach used results in simplified models that have nearly the same AUC as the full model. Reduced algorithms can predict nonunion because risk factors important in the full models remain important in the reduced models. This prognostic inception cohort study provides Level I evidence.

Introduction

The lifetime risk of any fracture at age 50 years is 53% among women and 21% among men [1] and roughly 5% of fractures go to nonunion [2]. Given that this nonunion risk is rather high, it would be useful to predict which patients are most at risk of nonunion, so

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treatment could be aimed at preventing this expensive and morbid complication.

However, a bewildering array of risk factors has been identified which could potentially impact fracture healing [3]. Therefore, we characterized which nonunion risk factors were significant by evaluating the epidemiology of 309,330 fractures in a commercially-insured patient population, age 18–63 [2], and in 56,492 fractures in an older Medicare population [4]. These studies show that it is possible to predict nonunion using patient-related biological risk factors assessable by the clinician at fracture presentation, prior to initiating treatment. However, risk prediction models are currently too cumbersome to be useful [4]. Here, we report an effort to derive reduced models able to predict nonunion accurately with fewer risk factors. We test a hypothesis that fracture nonunion is predictable with ≤10 risk factors, while retaining the predictive accuracy of a full model using 42 variables.

Methods

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 roughly 90.1 million patients [2]. This study received exempt approval from the Institutional Review Board of Duke University Medical Center, because patient data were completely de-identified.

Study inclusion was limited to patients with a coded bone fracture in calendar year 2011, provided the patient was continuously enrolled for a period of 12 months after fracture, to allow at least a year to capture a nonunion diagnosis code [2]. Nonunion was determined by 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. Variables of interest included patient demographics, treatment procedures as per Current Procedural Terminology (CPT) codes, co-morbidities as per International Classification of Diseases, Ninth Revision (ICD-9) codes, and drug prescriptions as per National Drug Code Directory (Red Book) codes [2]. The final database contained one row per unique fracture, with values for 257 patient variables, including fracture type, fracture etiology, patient demographics, and medication use. Because 309,330 fractures were assessed, the database contained 79.4 million cells [2].

Analytic strategy

Our overall hypothesis was that fracture nonunion can be predicted by risk factors derived from CPT, ICD-9, and Red Book codes. Because so many variables were available for each patient, we coalesced variables into manageable categories [2]. For example, patients had as many as 15 concurrent fractures, but we binned fractures into a smaller number of categories for analysis (*e.g.*, 1–2 fractures, 3–5 fractures, ≥6 fractures). Multivariate logistic regression was used to control for correlations among risk factors, and data were pooled to obtain 42 variables of interest [2].

Variables were then organized into 6 domains: patient demographic characteristics; fracture characteristics; reimbursement source; treatment procedures; disease comorbidities; and prescription medications. For example, data about medication use was pooled into 7 broad categories, as defined by Red Book codes (antibiotics, opiates, prescription NSAIDs, steroids, cardiac medications, anticonvulsants, and anticoagulants). The odds ratio (OR) for all variables of interest for nonunion was then calculated for all bones pooled and for each of the 18 fracture locations separately. Statistical analyses used SAS 9.4 (Cary, NC).

Algorithm derivation

We sought to use the smallest number of predictor variables possible in a "reduced model" that did not substantially decrease prediction accuracy, relative to the full model using all 42 variables. A training dataset used a random selection of 2/3 of patients in the full dataset; the remaining 1/3 were reserved as a validation dataset. Success of the parsimonious models was characterized with an area-under-the-curve (AUC) statistic derived from the receiver operating characteristic (ROC) curve. The order of importance was determined by the order that variables entered a stepwise multivariate logistic regression, and the Akaike Information Criterion (AIC) was used to select which variables to retain in the model.

Treatment information was unknown in roughly 50% of cases, so we could not discern whether treatment was operative or conservative; all such cases were combined into a single category ("Treatment information unknown"). We then fitted both a multivariate logistic regression model and a stepwise logistic regression model over the training dataset and let them grow to incorporate all variables. ORs and p-values were obtained for each of the variables from the multivariate model and the AIC was obtained for each step of the stepwise model. Important variables to retain in the reduced model were identified by two methods; P-value variable (PVV) selection and AIC selection. The PVV criterion initially retained variables in the multivariate model if the risk factor for nonunion had p-value <0.1. The AIC criterion retained variables in the stepwise model as a series of models was built, starting from a null model with no variables and adding variables to attain the full model with all variables. AIC was calculated, and variables were retained in the reduced model if they provided explanatory power. For data visualization, we transformed AIC to McFadden's adjusted pseudo-R^2 and plotted this against the number of risk factors to form an AIC "lift" curve. This was a linear transformation, so minimizing AIC was equivalent to maximizing pseudo-R^2 [2].

After building the initial multivariate and stepwise models, new multivariate logistic regression models were fitted respectively, using retained variables from each of the initial models. Both new models provided ORs and p-values and they were compared side by side. A variable was retained if it had a p-value <0.05 in either of the two models. In the last round, a new multivariate logistic regression model was fitted over retained variables from the previous round. If one or more risk factors had OR-associated P > 0.01, we dropped the risk factor with the larger P-value and refitted the logistic regression model. This process was repeated until all risk factors had P < 0.01. If a variable contained more than 2 categories but some had nonsignificant P-values, categories were combined or pulled into the reference group.

Results

The distribution of fractures as a function of patient age showed a notch at age 64 (Fig. 1), which may result from the requirement for continuous insurance coverage for 12 months; as patients retire, they transition to Medicare and are lost to the commercial coverage database. Some patients purchase Medicare advantage and are retained in the database, but these patients are not necessarily representative of the pre-retirement cohort (Fig. 1). Therefore, we chose not to analyze data for patients older than age 63.

A plot of nonunion rate for "All bones" as a function of age shows that nonunion rate for pre-pubertal children is negligible (Fig. 2). Patients under age 18 have a nonunion rate substantially less than that of adults, so we chose not to analyze data for patients younger than age 18. A violin plot of the probability density

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