Development of a Prognostic Naïve Bayesian Classifier for Successful Treatment of Nonunions

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14. ABSTRACT

Background: Predictive models permitting individualized prognostication for patients with fracture nonunion are lacking. The objective of this study was to train, test, and cross-validate a Bayesian classifier for predicting fracture-nonunion healing in a population treated with extracorporeal shock wave therapy. Methods: Prospectively collected data from 349 patients with delayed fracture union or a nonunion were utilized to develop a na?ıve Bayesian belief network model to estimate site-specific fracture-nonunion healing in patients treated with extracorporeal shock wave therapy. Receiver operating characteristic curve analysis and tenfold cross-validation of the model were used to determine the clinical utility of the approach. Results: Predictors of fracture-healing at six months following shock wave treatment were the time between the fracture and the first shock wave treatment, the time between the fracture and the surgery, intramedullary stabilization, the number of bone-grafting procedures, the number of extracorporeal shock wave therapy treatments, work-related injury, and the bone involved (p < 0.05 for all comparisons). These variables were all included in the na?ıve Bayesian belief network model. Conclusions: A clinically relevant Bayesian classifier was developed to predict the outcome after extracorporeal shock wave therapy for fracture nonunions. The time to treatment and the anatomic site of the fracture nonunion significantly impacted healing outcomes. Although this study population was restricted to patients treated with shock wave therapy, Bayesian-derived predictive models may be developed for application to other fracture populations at risk for nonunion.

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Development of a Prognostic Naïve Bayesian Classifier for Successful Treatment of Nonunions

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*Investigation performed at the AUVA-Trauma Center, Meidling, Vienna, Austria; DecisionQ Corporation, Washington, DC;
Walter Reed Army Medical Center, Washington, DC; and National Naval Medical Center, Bethesda, Maryland*

Background: Predictive models permitting individualized prognostication for patients with fracture nonunion are lacking. The objective of this study was to train, test, and cross-validate a Bayesian classifier for predicting fracture-nonunion healing in a population treated with extracorporeal shock wave therapy.

Methods: Prospectively collected data from 349 patients with delayed fracture union or a nonunion were utilized to develop a naïve Bayesian belief network model to estimate site-specific fracture-nonunion healing in patients treated with extracorporeal shock wave therapy. Receiver operating characteristic curve analysis and tenfold cross-validation of the model were used to determine the clinical utility of the approach.

Results: Predictors of fracture-healing at six months following shock wave treatment were the time between the fracture and the first shock wave treatment, the time between the fracture and the surgery, intramedullary stabilization, the number of bone-grafting procedures, the number of extracorporeal shock wave therapy treatments, work-related injury, and the bone involved (p < 0.05 for all comparisons). These variables were all included in the naïve Bayesian belief network model.

Conclusions: A clinically relevant Bayesian classifier was developed to predict the outcome after extracorporeal shock wave therapy for fracture nonunions. The time to treatment and the anatomic site of the fracture nonunion significantly impacted healing outcomes. Although this study population was restricted to patients treated with shock wave therapy, Bayesian-derived predictive models may be developed for application to other fracture populations at risk for nonunion.

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

The majority of the nearly 70 million traumatic injuries occurring annually in the United States involve the musculoskeletal system, amounting to approximately 6 million fractures, which consume a substantial share of the health-care expenditures for trauma[1-6]. The cost of musculoskeletal injuries is considerable in terms of both health-care resources and individual patient morbidity and quality-of-life impairment[1,3,5,6]. In 1995, it was reported that fracture care accounted for $24 billion of the nearly $150 billion per annum spent in the United States on musculoskeletal conditions[2]. Assuming that ∼5% of fractures fail to heal, at an average per-patient cost of ∼$15,000, the estimated annual cost of nonunion treatment in the United States is $4.5 billion. As more emphasis is placed on outcome-based reimbursements, methods

to maximize cost-effective treatment of patients with ununited fractures become essential.

Barriers to fracture-healing include tobacco use, chronic illness, malnutrition, prior radiation, bone loss, comminuted and devascularized bone, impaired blood supply to the fracture site and local soft tissue, instability, and infection[3,7,8]. Advances in the understanding of the pathophysiology of fracture nonunion as well as technical improvements in bone reconstruction have been made in recent years; however, there is a lack of definitive evidence regarding the best treatment method or modality in most instances. Although general principles of nonunion treatment have been established, there is very wide variability in treatment among surgeons. Some surgeons use a particular technique routinely while others never use that

treatment. This treatment variability is partially due to a lack of definitive evidence to guide treatment.

It has been difficult to develop approaches to the management of nonunions on the basis of definitive evidence derived from controlled clinical trials. Practical challenges and study design considerations make the performance of prospective, randomized, placebo-controlled, blinded trials in this setting impractical. In order to improve the evidence for treatment decisions, the best available evidence for evaluating and adopting treatment modalities for the management of nonunions must be obtained from large, well-characterized patient cohorts treated with a consistent therapeutic approach and then assessed for relevant clinical and functional outcomes.

Modalities in the form of applied mechanical energy have been increasingly studied for the treatment of nonunions. One such modality, extracorporeal shock wave therapy, appears to be a promising approach to this complex clinical problem on the basis of its safety and the mechanistic and treatment response data accumulated thus far[9-19]. We showed previously that data from a well-characterized study population consisting of patients with a complex clinical problem (nonunion of the tibial shaft treated with shock wave therapy) can be analyzed to determine factors significantly associated with the healing outcome[18]. The statistical method most commonly utilized to determine independent factors predictive of clinical outcome is logistic regression analysis. Regression models are trained individually for each outcome of interest. This approach allows the regression models to attain goodness of fit with the data, producing generally strong cross-validation statistics. However, logistic regression models are linear (fit to curvilinear space) and are sensitive to outliers and missing data. As a result, when confronted with incomplete and disorganized clinical information, which is common in clinical records, regression approaches can suffer from severely reduced accuracy[20,21].

The Bayesian classification methodology and Bayesian belief network modeling are being utilized with increasing frequency in the field of surgery as they account effectively for data multidimensionality and uncertainty and have the ability to codify complex clinical problems into clear-cut, intuitive, predictive models. We have previously defined proof of principle with this analytical approach, showing how Bayesian belief network models can be used to analyze multifaceted clinical data and present the outcome estimates in a graphical, user-friendly output, enabling the clinician to assimilate complex high-dimensionality data sets into usable and individualized prognostic information[22,23]. The Bayesian belief network methodology incorporates all outcomes and covariates into a single network and, unlike logistic regression, maintains predictive accuracy and robustness in the face of incomplete clinical data. The predictions can then be tested prospectively to confirm their accuracy. In the current study, we assessed the feasibility of developing a clinically relevant probabilistic naïve (e.g., linear) Bayesian belief network model to estimate individualized, site-specific healing in patients with a refractory fracture nonunion treated with extracorporeal shock wave therapy.

Materials and Methods

Clinical Study Inclusion Criteria

Over a ten-year period (December 1998 through December 2008), 349 consecutive patients provided informed consent for, and were entered into, an institutional review board-approved prospective observational study in which they were treated with extracorporeal shock wave therapy for a fracture nonunion at any anatomic site. Patients were excluded if they had a bone defect of >5 mm (the distance between the two fracture fragments on a standardized anteroposterior or lateral radiograph exceeding 5 mm), an open growth plate or a malignant tumor in the treatment area, coagulopathy, or angulation or rotation requiring surgical correction; if they chose surgical intervention; if they were not a suitable candidate for regional or general anesthesia; if they had an active infection in the brain, spinal cord, or lung tissue or in the treatment area; and/or if they were pregnant. "Active or acute infection" was established as an exclusion criterion to avoid bacterial dissemination into the bloodstream. The inclusion criterion was a patient with a fracture nonunion referred after failure of previous therapy on the basis of the practice pattern of the referring orthopaedic surgeon. The study was a retrospective analysis of the data in this study population, which encompassed all patients with a fracture nonunion treated during the ten-year period.

Study Definitions

A fracture was defined as a break or disruption in the continuity of bone. A nonunion was defined, according to the U.S. Department of Health and Human Services criteria, as a fracture that has failed to show continuity of three of four cortices after surgical or nonsurgical treatment for six or more months from the time of the fracture-related injury, or has failed to demonstrate any radiographic change (improvement) for three consecutive months, and is associated with clinical findings consistent with a fracture nonunion (an inability to bear weight on the affected extremity, pain on palpation, or motion at the fracture site for three to six months or more following the incident traumatic event or the last surgical procedure). A treated nonunion in this study was one exposed to therapeutic extracorporeal shock wave therapy.

Assessment of Fracture-Healing

Clinical and radiographic criteria were used to assess healing of the fracture. Clinical criteria of fracture-healing included no pain on weight-bearing, palpation, or attempted manual bending of the fracture site and no movement of the fracture fragment at the fracture site. Imaging assessment included anteroposterior and lateral radiographs made at the time of the initial presentation and at one, three, and six months after the extracorporeal shock wave therapy. Reestablishment of cortical continuity of a minimum of three of four cortices defined fracture-healing. Stress radiography and/or CT scans were obtained if the adequacy of fracture-healing could not be assessed with radiography alone. Magnetic resonance imaging was not utilized in the study.

Fracture-healing was defined as (1) the ability of the patient to bear full weight on the affected limb (for a lower extremity nonunion), (2) the absence of pain or tenderness at the fracture site with manual bending or compression, and (3) reestablishment of cortical continuity on three of four cortices at the fracture site on radiographs and/or CT scans. Failure to meet the aforementioned criteria was considered to represent a persistent nonunion. Patients demonstrating clinical or radiographic improvement, but not complete healing, were categorized as "not healed."

Treatment of the Nonunion

Treatment of all of the nonunions included extracorporeal shock wave therapy. Shock waves were delivered to the nonunion site with the Orthowave 280 device (Tissue Regeneration Technologies, Woodstock, Georgia), with use of the regional or general anesthesia required for focused extracorporeal shock wave therapy as previously described[18]. Following shock wave therapy, the limb was immobilized much like a limb with an acute fracture. Typically, this is done with a plaster cast or customized orthosis. In cases where the nonunion was particularly mobile (>15° of motion apparent on stress fluoroscopy), an external fixator was also placed. Supplementary stabilization was not required in cases of rigidly fixed and internally stabilized fractures without signs of implant loosening. In this study, immobilization was accomplished with an orthosis (n = 36), a plaster cast (n = 187), or external fixation (n = 33).

Previous studies have suggested that initial acute fracture and nonunion healing begins with blood vessel growth into the fracture site[15-17]. Thus, we attempt to minimize micromovement at the nonunion site during the first three to four weeks following shock wave therapy in order to prevent microvessel disruption. Consequently, no weight-bearing on the affected lower extremity is allowed during that period of time. Prior to treatment, the patients were instructed about this postoperative restriction, as the analgesic effect of shock wave therapy immediately following treatment can contribute to a tendency for the patient to resume full weight-bearing on the affected extremity. The duration of immobilization (up to three months) was not standardized in this study, as the length of time that an affected limb was immobilized was an individualized, provider-driven decision based on the location of the fracture, the osseous gap at the fracture site, the stability of the fracture, the mechanical alignment of the extremity, and the presence or absence of infection.

Outcomes

The Bayesian belief network was trained with use of a priori variables to estimate the probability of a persistent nonunion. The primary outcome was the presence or absence of a persistent nonunion at six months from the date of the first treatment with extracorporeal shock wave therapy.

Statistical Methods

The baseline characteristics of the subjects in the various groups were compared by using analysis of variance for continuous variables. Associations between healing outcomes and categorical factors included in the model on the basis of goodness of fit were studied with a contingency table analysis with use of a Fisher exact test (for contingency tables containing any cells with expected values of fewer than five patients) or the Pearson chi-square test as appropriate.

The objective of this study was to evaluate an established methodology, the Bayesian belief network, as a novel approach to aiding orthopaedic surgeons in clinical decision-making. In this instance, we sought to develop a model that could estimate the likelihood of a specific nonunion responding to extracorporeal shock wave therapy. The objective was to provide a statistically derived approach for the selection of patients for treatment with the modality. A Bayesian belief network is a graphical representation of conditional dependence between information features in a domain, which represents the hierarchy by which known factors can be used to estimate clinical outcomes. These outcomes are estimated with use of joint probability distributions, such that knowledge of the existence or likelihood of a given data point (such as the specific bone involved) informs the expected distribution of an outcome (such as the probability of union after treatment). Any amount of available evidence can be input into the network to calculate a specific estimate of outcome.

A naïve Bayesian belief network was trained to estimate the likelihood of fracture-healing six months after extracorporeal shock wave therapy. This model was developed with use of commercially available machine learning algorithms (FasterAnalytics; DecisionQ, Washington, DC), which automatically learn joint probabilities from the prior probabilities in the data[24,25]. For our Bayesian belief network model, we grouped the number of days between the injury and the first administration of extracorporeal shock wave therapy and the number of days between the injury and the surgery into three categories, each using equal probability density binning, a method for converting continuous distributions into normalized parametric distributions. Equal probability density binning creates ranges that segregate the data into groups of similar size. The equal probability ranges used for the number of days between the injury and the first treatment with extracorporeal shock wave therapy were 181 days or less, between 182 and 339 days, and more than 339 days. The equal probability ranges used for the time between the injury and the initial operative treatment were 0 days (the surgery performed on the day of the injury), one to 100 days, and more than 100 days. In order to develop the optimum Bayesian belief network model, a stepwise training process was used. Quantitative as well as qualitative assessments were carried out to optimize variable preparation and variable selection.

Cross-validation was performed on the final naïve Bayesian belief network model with use of a train-and-test cross-validation methodology to produce classification accuracy estimates. Tenfold cross-validation was performed by randomizing the data into ten unique "training" sets containing 90% of the data and ten corresponding "test" sets, each of which contained the remaining 10% of the data. Ten new naïve

Bayesian belief network models were trained with use of the same parameters as those generated by the naïve model from the full data set. Once the test model was created with a training set, the matching test set was entered into the Bayesian belief network model, generating a case-specific prediction for each record for independent variables of interest. After development of the Bayesian belief network model, a receiver operating characteristic curve was plotted for each test to calculate classification accuracy. Receiver operating characteristic curves in this case are a graphical plot of sensitivity versus $(1 - \text{speci-ficity})$ for the Bayesian belief network model at all of the various levels of discrimination threshold. The area under the receiver operating characteristic curve was then calculated, and this served as a metric of overall model quality.

TABLE I Bivariate Analysis of Model Parameters and Nonunion Fracture-Healing Results at Six Months After First Treatment with Extracorporeal Shock Wave Therapy*				
	Healing Result at Six Months After First Treatment with Extracorporeal Shock Wave Therapy			
Parameter	Healed†	Not Healed†	Total‡	P Value
Work-related injury				0.07
Yes	71 (74.0%)	25 (26.0%)	96 (27.5%)	
No	211 (83.4%)	42 (16.6%)	253 (72.5%)	
No. of bone-grafting procedures prior to extracorporeal shock wave therapy				0.04
0	250 (82.8%)	52 (17.2%)	302 (86.5%)	
1	31 (68.9%)	14 (31.1%)	45 (12.9%)	
2	1 (50.0%)	1 (50.0%)	2 (0.6%)	
Anatomic region (affected bone)				<0.01
Tibial shaft	94 (88.7%)	12 (11.3%)	106 (30.4%)	
Femoral shaft	51 (72.9%)	19 (27.1%)	70 (20.1%)	
Foot	28 (100.0%)	0 (0.0%)	28 (8.0%)	
Humerus	25 (65.8%)	13 (34.2%)	38 (10.9%)	
Hand	24 (70.6%)	10 (29.4%)	34 (9.7%)	
Ulna	22 (75.9%)	7 (24.1%)	29 (8.3%)	
Radius	18 (85.7%)	3 (14.3%)	21 (6.0%)	
Patella	9 (81.8%)	2 (18.2%)	11 (3.2%)	
Pelvis	6 (85.7%)	1 (14.3%)	7 (2.0%)	
Fibular shaft	5 (100.0%)	0 (0.0%)	5 (1.4%)	
No. of extracorporeal shock wave therapy treatments				0.01
1	244 (89.4%)	29 (10.6%)	273 (78.2%)	
>1	38 (67.9%)	18 (32.1%)	56 (16.1%)	
Intramedullary stabilization				0.02
No	178 (85.2%)	31 (14.8%)	209 (59.9%)	
Yes	104 (74.3%)	36 (25.7%)	140 (40.1%)	
Time from injury to surgery				0.047
0 days	153 (86.0%)	25 (14.0%)	178 (51.1%)	
1-100 days	67 (78.8%)	18 (21.2%)	85 (24.4%)	
>100 days	61 (71.8%)	24 (28.2%)	85 (24.4%)	
Time from injury to first treatment with extracorporeal shock wave therapy				<0.01
≤181 days	102 (85.0%)	18 (15.0%)	120 (34.4%)	
182-339 days	100 (86.2%)	16 (13.8%)	116 (33.2%)	
>339 days	80 (70.8%)	33 (29.2%)	113 (32.4%)	

*Only the predictive variables included in the Bayesian belief network model are detailed here. †The percentages in the ''Healed'' and ''Not Healed'' columns are the percentages of the total in the corresponding row that healed or did not heal, respectively. ‡The percentages in the ''Total'' column are the percentages of the total cases in the column for the specific parameter.

Results

The study population consisted of 114 female and 235 male patients. The age at the time of injury ranged from fifteen to ninety-one years, with 50% of the population being between thirty-six and sixty years old at the time of fracture (mean age [and standard deviation], 48 ± 16 years). We could not identify an association between patient age or sex and our primary outcome of persistent nonunion (p = 0.91 and p = 0.99, respectively). The percentage of the patients who sustained a fracture as the result of a work-related injury was 27.5% (Table I). Slightly more than half of the patients in the study had a fracture of the tibial shaft (30.4%) or the femoral shaft (20.1%) (see Appendix). A large majority of the patients underwent a single treatment with extracorporeal shock wave therapy (78.2%), and 86.5% had not had previous bone-grafting of the nonunion. Intramedullary stabilization was performed prior to the shock wave therapy in 59.9%.

Of the 349 nonunions in this study, 282 (80.8%) healed while sixty-seven (19.2%) persisted following treatment. Multiple clinical variables were analyzed to determine if any were significantly associated with nonunion healing. These variables included patient sex, patient age, work-related injury, fracture category (open vs. closed), anatomic fracture location, bone third involved (proximal, middle, or distal)[26], nonunion condition (atrophic/oligotrophic [atrophic and oligotrophic were treated as a single category], hypertrophic, or infected), number of orthopaedic procedures directed at achieving fracture union prior to the extracorporeal shock wave therapy, presence or absence of hardware at the time of the shock wave therapy, number of bone-grafting procedures prior to the shock wave therapy, prior intramedullary stabilization, number of treatments with extracorporeal shock wave therapy, length of time between the injury and the first treatment with extracorporeal shock wave therapy, and length of time between the injury and the first operation. There was a significant relationship between the six-month nonunion-healing result and (1) the number of bone-grafting procedures prior to extracorporeal shock wave therapy (p = 0.037), (2) prior intramedullary stabilization (p = 0.017), (3) the anatomic location of the nonunion (p = 0.002), and (4) the number of shock wave treatments (p = 0.012). There was also a significant relationship between the length of time between the injury and the first treatment with extracorporeal shock wave therapy and nonunion healing (p = 0.004). A significant direct relationship between the length of time between the injury and the surgery and the nonunion healing results was found as well (p = 0.047).

The significant variables ultimately included in the Bayesian belief network model were the number of bone-grafting procedures prior to extracorporeal shock wave therapy, prior intramedullary stabilization, the bone involved, the number of shock wave treatments, the number of days between the injury and the first treatment with extracorporeal shock wave therapy, and the number of days between the injury and the first surgery (Fig. 1). In Bayesian models, predictive variables are not exclusively negative or positive predictors; rather, their effect is manifested in how they interact with other variables in the model. The internal validation receiver operating curve analysis indicated an area under the curve of 0.73 (see Appendix). For all ten cross-validation models, the area under the receiver operating characteristic curve was a mean of 0.66, which represents a predictive, but not strongly predictive, result. Hence, this model should be considered a useful prog-
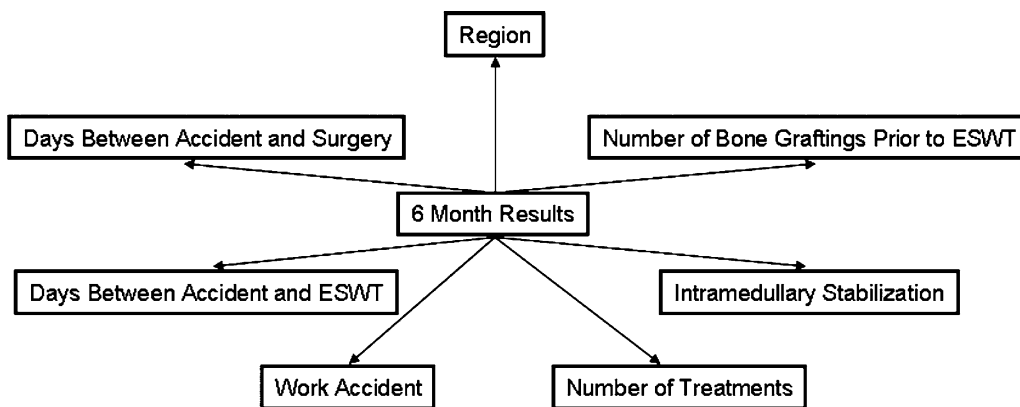

Fig. 1

Bayesian belief network model to estimate nonunion healing at six months after the first treatment with extracorporeal shock wave therapy. The significant variables ultimately included in the Bayesian belief network model were the number of bone-grafting procedures prior to the first treatment with extracorporeal shock wave therapy (ESWT), prior intramedullary stabilization, the anatomic region of the nonunion (the bone involved), the number of shock wave treatments, the number of days between the injury and the extracorporeal shock wave therapy, and the number of days between the injury and the surgery.

TABLE II Inference Table of Likelihood of Fracture-Nonunion Healing by Anatomic Region and Days Between Injury and First Treatment with Extracorporeal Shock Wave Therapy

Anatomic Region (Affected Bone)	Probability Estimate of Fracture-Nonunion Healing at Six Months After First Treatment with Extracorporeal Shock Wave Therapy (%)		
	≤181 Days Between Injury and Therapy	182-339 Days Between Injury and Therapy	>339 Days Between Injury and Therapy
Femoral shaft	79.2	80.6	62.5
Fibular shaft	89.8	90.6	79.4
Foot	97.7	97.9	94.9
Hand	76.9	78.4	59.3
Humerus	73.1	74.8	54.4
Patella	83.0	84.2	68.2
Pelvis	83.6	84.9	69.2
Radius	87.4	88.4	75.3
Tibial shaft	91.4	92.1	82.4
Ulna	80.8	82.2	64.9

nostic tool. Cross-validation analysis produced an 86% positive predictive value for "healed" and a 29% negative predictive value for "not healed," when the threshold was set at a ≥80% likelihood of resulting in a positive healing outcome, as predicted by the model. With only 349 total records, and only sixty-seven "not-healed" outcomes, there was a high degree of variance between the results in the cross-validation exercises.

As all variables in the model are at some level conditionally dependent with six-month follow-up, and all of the features are available at the time of the extracorporeal shock wave therapy, they can be used to predict the likelihood of a successful healing outcome. Using only a priori features, we generated an inference table that can be used to quickly estimate the six-month nonunion-healing outcome for all known combinations of the selected features (see Appendix). These a priori features are the number of bone-grafting procedures prior to extracorporeal shock wave therapy, prior intramedullary stabilization, the bone involved, the number of days between the injury and the first treatment with extracorporeal shock wave therapy, and the number of days between the injury and the first surgery. They were used to predict the likelihood of a positive six-month healing result. These predictions can also be used prospectively in future studies.

The probabilities of site-specific fracture-healing at ≤181, 182 to 339, and >339 days between the time of the fracture and the extracorporeal shock wave therapy were 0.73, 0.75, and 0.54, respectively, for the humerus; 0.77, 0.78, and 0.59 for the hand; 0.79, 0.81, and 0.63 for the femoral shaft; 0.81, 0.82, and 0.65 for the ulna; 0.83, 0.84, and 0.68 for the patella; 0.84, 0.85, and 0.69 for the pelvis; 0.87, 0.88, and 0.75 for the radius; 0.90, 0.91, and 0.79 for the fibular shaft; 0.91, 0.92, and 0.82 for the tibial shaft; and 0.98, 0.98, and 0.95 for the foot (Table II). Under the most favorable circumstances, healing occurs >97% of the time. Under the least favorable circumstances, healing occurs between 37% and 63% of the time.

Discussion

The present study was conducted to determine the feasibility of developing a clinically useful probabilistic naïve Bayesian belief network model to estimate individualized, site-specific fracture-healing in a selected patient study population—one that had undergone extracorporeal shock wave therapy for a nonunion that had been refractory to surgical treatment and immobilization. Successful nonunion healing in this consecutive cohort encompassing all patients with a nonunion treated at a single center with the same shock wave device occurred 80% of the time within six months after the first treatment with the shock wave therapy. While healing outcome results have a significant relationship with all of the variables in our Bayesian belief network model, including the anatomic location of the nonunion, the number of bone-grafting procedures and/or intramedullary stabilization prior to extracorporeal shock wave therapy, and the number of shock wave treatments, the Bayesian belief network identified two covariates within the model that appear most predictive of fracture-healing. These covariates—the time to the first treatment with extracorporeal shock wave therapy following the fracture and the specific bone involved—dominate the model and appear to provide the bulk of the predictive power.

The probability of a positive healing result deteriorates significantly with the time to the shock wave therapy following the injury[12,14,18,27]. When more than eleven months (339 days) have elapsed between the injury and the extracorporeal shock wave therapy, nonunion healing rates are significantly lower than those observed when extracorporeal shock wave therapy is administered earlier in the course of the fracture nonunion. The anatomic region (specifically, the affected bone) is also an independent predictor of healing following extracorporeal shock wave therapy. However, there is an important interaction between these two clinical variables in terms of their effect on the six-month healing results. The inference table (Table II)

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demonstrates the likelihood of fracture-healing at six months and underscores this conditional dependence of these two a priori variables, anatomic region and days between the injury and the extracorporeal shock wave therapy. Although healing is the most likely outcome in all cases, the effect time (from the time of injury to the extracorporeal shock wave therapy) differs according to the specific bone affected. Unlike the case in linear models, in Bayesian models predictive variables are not exclusively positive or negative predictors. In particular, nonunions of the foot tend to heal at a very high rate regardless of the time between the injury and the shock wave therapy. In the study population, all twenty-eight foot fracture nonunions healed, including five with lag times of 1995 days (five and a half years), 1131 days, 801 days, 752 days, and 728 days between the injury and the first treatment with extracorporeal shock wave therapy. Conversely, the time between the fracture and the shock wave therapy has a pronounced effect on the Bayesian belief network model estimate of healing of a femoral shaft nonunion. The estimated likelihood of a femoral shaft nonunion healing at six months drops from 79% to 63% when the time between the injury and the first treatment with extracorporeal shock wave therapy increases from ≤181 to >339 days. A similar pattern emerges for nonunion of the hand, with a 77% healing estimate when shock waves are administered within 181 days after the injury but a healing rate of only 59% when the first treatment with extracorporeal shock wave therapy is delayed for >339 days. The effect of a time lag between the injury and the first treatment with extracorporeal shock wave therapy on nonunion healing retains significance even when the data are restricted to patient subsets with femoral shaft and hand fractures (at a 90% significance level). Because of sample-size limitations, we were unable to conduct statistical testing on the relationship between the number of days until the first treatment with extracorporeal shock wave therapy and the healing outcome for the humerus or ulna. Another potential limitation is the bias associated with the stringent definition of fracture-healing used in this study, which required that all of three criteria be met: (1) an ability to bear full weight on the affected limb (for lower-extremity nonunions), (2) the absence of pain or tenderness at the fracture site, and (3) reestablishment of cortical continuity of three of four cortices at the fracture site as seen radiographically.

We believe that our study demonstrates the potential utility of Bayesian belief network classification models not only for selecting patients for extracorporeal shock wave therapy, but, perhaps more importantly, also to identify candidates for other novel or established therapeutic modalities. The Bayesian classification methodology is designed to be inherently robust and tolerant of heterogeneous and incomplete data sets, while presenting graphical feedback to the user, which allows the clinician not only to receive a case-specific estimate of outcome, but also to understand how the estimate is derived[28]. We believe that this is a superior paradigm for support of clinical decision-making as it allows the clinician to interact with the system in an intuitive manner and also to make informed decisions with statistical guidance, rather than making decisions on the basis of black-box algorithms.

Appendix

_eA_ Tables presenting the results for tibial and femoral shaft nonunion healing, the validation statistics for the naïve Bayesian belief network, and an inference table of the ten nonunions most likely and the ten least likely to heal are available with the electronic version of this article on our web site at jbjs.org (go to the article citation and click on "Supporting Data"). ∎

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