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Development of prognostic indicators using classification and regression trees for survival

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Development of an accurate prognosis is an integral component of treatment planning in the practice of periodontics. In addition, assignment of good, long-term prognoses is critical in reliably determining an appropriate restorative treatment plan following periodontal therapy, particularly if major prosthetic reconstruction or placement of dental implants is under consideration. The traditional method of assigning prognosis and predicting tooth survival involves an examiner identifying one or more commonly taught clinical parameters (Table 1) as they uniquely apply to the tooth. These clinical parameters are recorded and weighed according to the past clinical experience of the therapist, and a prognosis is assigned. Previous studies by McGuire (19) and McGuire & Nunn (20–22) have evaluated the validity of use of these clinical parameters for correctly assigning prognosis and predicting tooth survival and change in clinical condition over time. These papers concluded that there was a relationship between many commonly used clinical factors and prediction of change in clinical status over time as well as tooth loss rate, although the ability to predict the future condition of a tooth varied by tooth type (i.e. molars vs. non-molars). With respect to the relationship between commonly taught clinical parameters and tooth loss rate, some clinical factors, such as satisfactory crown / root ratio, mobility status, furcation involvement or heavy smoking, contributed significantly to predicting the rate of tooth loss, while other clinical parameters, such as root form or patient age, demonstrated very little relationship to the probability of tooth loss.

Machtei et al. (17, 18) evaluated both clinical parameters and certain immunological and microbiological parameters for predicting change in clinical status over time as well as tooth loss. Baseline smoking status, cotinine level, mean probing depth, mean attachment loss and crestal bone height were all associated with bone loss over time as well as attachment loss over time, although the relationship to attachment loss was somewhat less than the relationship to bone loss. The presence of *Bacteroides forsythus*, *Prevotella intermedia* and *Porphyromonas gingivalis* was also associated with future periodontal destruction (17). Baseline attachment loss, loss of crestal bone height and various systemic conditions were associated with increased tooth loss over time, while the presence of *B. forsythus* doubled the risk of tooth loss over time (18).

Although our research has focused on the assignment of prognosis based on the relationship of commonly taught clinical factors to tooth loss, other research has investigated the development of criteria for assignment of periodontal prognosis based on radiographic alveolar bone loss. In one study by Horwitz et al. (12), three radiographic measures were found to be predictive of the healing of class II furcation involvement following surgical intervention. In another study by Nieri et al. (24), investigators examined subject-level, tooth-level and site-level variables as predictors of alveolar bone loss over time. The most significant predictors of alveolar bone loss over time were mean alveolar bone loss at baseline, with effect modification by interleukin-1 genotype, tooth mobility and site-level alveolar bone height at baseline (24).

An underlying premise of our previous papers (19–22) is that the traditional method for assignment of prognosis involves a subjective process based on commonly taught clinical parameters and the therapist's experience and training. There is no established universal set of criteria for assignment of periodontal

Table 1. Commonly taught clinical parameters used in assigning prognosis

Individual tooth prognosis	Percentage bone loss
	Probing depth
	Distribution and type of bone loss
	Presence and severity of furcations
	Mobility
	Crown / root ratio
	Root form
	Pulpal involvement
	Caries
	Tooth position and occlusal relationship
	Strategic value
	Therapist knowledge and skill
Overall prognosis	Age
	Medical status
	Individual tooth prognosis
	Rate of progression
	Patient cooperation
	Economic considerations
	Knowledge and ability of dentist
	Etiological factors
	Oral habits and compulsions

prognosis, and thus different practitioners may assign varying prognoses for the same tooth, which may be problematic for referring dentists, third-party payment plans (e.g. dental insurance companies) and the patients themselves, as, rather than providing guidance for treatment planning, it creates further uncertainty. In order to remedy this situation, we embarked on a long-term project to establish objective criteria for assignment of prognosis based on actual outcome. An essential step in pursuing this goal was to extend statistical methods used in development of prognosis in various areas of medicine to the complexities of dental data.

Classification and regression trees (CART)

The idea of regression trees dates back to the automatic interaction detection program developed by Morgan & Sonquist (23). After introduction of classification and regression trees (CART) by Breiman et al. (1), tree-based methods attracted wide popularity in a variety of fields because they require few statistical assumptions, handle various data structures readily, and allow meaningful interpretation. Regression trees constitute a data-mining technique that seeks to construct an optimum decision tree based on partitioning a set of variables to accurately predict a dichotomous outcome. The need for meaningful assignment of prognosis in medical research led to generalization of regression trees to survival analysis. As survival analysis involves actual failure times in addition to failure status, use of regression trees with survival analysis enables one to extract more information from data compared with other analytical techniques, such as logistic regression. Existing methods for univariate survival trees generally fall into two groups. The first group, analogous to CART, involves minimizing within-node variability in survival times, and has been reviewed by Gordon & Olshen (10), among others (6, 14, 27). The second group utilizes a goodness-of-split criterion that maximizes the difference in survival between children nodes as measured by a two-sample statistic, such as the log-rank statistic. Research into this second group is exemplified by that by Ciampi et al. (2), Segal (25) and LeBlanc & Crowley (15). Notable examples of application of CART for survival in the development of prognoses for cancer include breast cancer, for which survival trees indicated that lymph node status was the strongest predictor of relapse, while the markers cathepsin D and plasminogen activator inhibitor-1 (PAI-1) were the strongest predictors of relapse among those without lymph node involvement (11), thin primary cutaneous malignant melanoma, for which prognosis based on survival trees was more accurate in predicting metastasis after 10 years than staging methods developed by the American Joint Commission on Cancer (9), and development of prognostic categories based on relapse for head-and-neck squamous cell carcinoma (13).

Multivariate failure time data can arise when a subject experiences multiple failures (recurrent failures, such as restoration failures) or individuals under study are naturally clustered (e.g. tooth loss) with two main approaches (marginal approach and frailty approach) to multivariate survival. For naturally clustered data, the marginal approach advocated by Liang et al. (16) and Wei et al. (28) is useful. In the marginal approach, the marginal distribution of correlated failure times is formulated by a Cox proportional hazards model (5), while the dependence structure is unspecified. A robust approach is made via the technique of estimating equations. The other approach that is particularly applicable to multiple failures is the frailty model first proposed by Clayton (3) and later extended to the regression setting by Clayton & Cuzick (4). In the frailty model approach, dependence is modeled explicitly via a multiplicative random effect term called frailty, which corresponds to some common unobserved characteristics shared by all correlated times.

Recently, we extended the method of classification and regression trees (CART) for survival to accommodate multivariate failure time data (7,8,26), such as tooth loss and restoration failure observed in dental research, by applying techniques used for multivariate survival analysis to CART for survival. In this review, we apply this newly developed extension of CART for survival to data collected for 100 well-maintained periodontal patients who were diagnosed with moderate to severe periodontal disease, in order to determine evidence-based criteria for assignment of prognosis based on commonly taught clinical parameters.

Analytic approaches using CART for identifying prognostic indicators

We present here the methodological approach that we have used successfully to apply CART to patient-based data. As reported previously, 100 consecutive patients with at least 5 years of maintenance care were selected from one clinician's appointment book over a 2-month period (19–22). All subjects included in the study were initially diagnosed with chronic generalized moderate to severe periodontitis and were treated by the same clinician. The inception cohort was established at a fairly uniform point in the disease, and all patients followed a similar course of treatment. Patients in this study were under maintenance regimens of 2- or 3-month intervals, with the majority under a 3-month interval, and were followed for 10–18 years. Most patients were compliant and demonstrated reasonable oral hygiene. Additional information regarding the study population, therapy, limitations of the study and assignment of prognoses is given in our initial reports (19–21).

Using the method of classification and regression trees for survival for correlated outcomes, we fitted trees using both the marginal goodness-of-split approach and the multivariate exponential model with gamma frailty (7, 8, 26). Based on trees fitted using the marginal approach, where the first split occurred on furcation involvement (0 vs. 1, 2 or 3), we stratified multivariate exponential survival trees in terms of molars and non-molars. Trees were fitted using programs developed using R statistical software.

Use of CART to identify periodontal prognostic indicators

The analyses reviewed and summarized here included a total of 2509 teeth from 100 well-maintained

Table 2. Clinical factors for assigning prognosis used in growing survival trees

Clinical factor	Value
Age	Age at entry into study
Probing depth	Deepest probing depth for each tooth
Furcation involvement	Class I, II or III
Root form	Satisfactory vs. unsatisfactory
Crown ⁄ root ratio	Satisfactory vs. unsatisfactory
Mobility	0–3 for each tooth
Smoking status	Smoker vs. non-smoker
Type of bone loss	Horizontal vs. vertical
Root PROXIMITY	Satisfactory vs. unsatisfactory
Hygiene level	Good, fair, poor
Tooth malposition	Normal vs. malposed
Fixed abutment status	No abutment vs. abutment
Removable abutment status	No abutment vs. abutment
Bite guard	No bite guard vs. bite guard
Parafunctional habit	No habit vs. habit
No bite guard with parafunctional habit	Habit and bite guard vs. habit and no bite guard
Percentage bone loss	Mean percentage bone loss across entire mouth
Compliance	Compliant vs. not compliant
Family periodontal history	No history vs. history
Diabetes	No diabetes vs. diabetes
Endodontic involvement	No involvement vs. involvement
Caries involvement	No caries vs. caries

periodontal patients, from a private periodontal practice, with moderate to severe periodontitis. Data were collected using 22 clinical measures, and were considered for inclusion in all survival trees, as shown in Table 2. The first tree shown in Fig. 1 is for the marginal goodness-of-split approach (8), which was applied to all teeth from the dataset. As can be seen from the tree, the significant clinical variables in the tree included furcation involvement, probing depth, crown ⁄ root-ratio, age at baseline, mobility and average percentage bone loss across the mouth. Table 3 shows how the marginal goodness-of-split tree performed in terms of prediction. While the percentage tooth loss for each category increased with worsening prognostic category, the lack of sensitivity in terms of the low tooth loss in the 'questionable' and 'hopeless' categories make this particular tree less than desirable in terms of prediction.

Based on the first split on furcation involvement in the marginal goodness-of-split approach, further survival tree modeling was performed using stratification by molars and non-molars. The best performance in terms of prediction was obtained from the multivariate exponential survival trees shown in Figs 2 and 3. Figure 2 shows the final multivariate exponential survival tree for non-molars. Probing depth, untreated bruxism (i.e. parafunctional habit without a bite guard), oral hygiene, mobility, removable abutments and mean percentage bone loss were all significant factors in the multivariate exponential survival tree for predicting tooth loss over time in non-molars. Figure 3 shows the final multivariate exponential survival tree for molars. Based on Fig. 3, crown ⁄ root ratio, probing depth, furcation involvement, root form, untreated bruxism, oral hygiene, mobility, bite guard, mean percentage bone loss and family history of periodontal disease were all significant factors in the multivariate exponential survival tree. Table 4 summarizes the prognostic categories from the survival trees shown in Figs 2 and 3. Table 5 shows the predictability of the multivariate exponential survival trees for molars vs. non-molars. As can be seen from Table 5, sensitivity increased considerably with stratification by molars vs. non-molars, although optimal sensitivity was still not achieved. Figure 4 shows the actual tooth survival for predicted prognostic categories based on the stratified multivariate exponential survival trees. As can be seen from the survival plot in Fig. 4, sensitivity and specificity are relatively high for all categories.

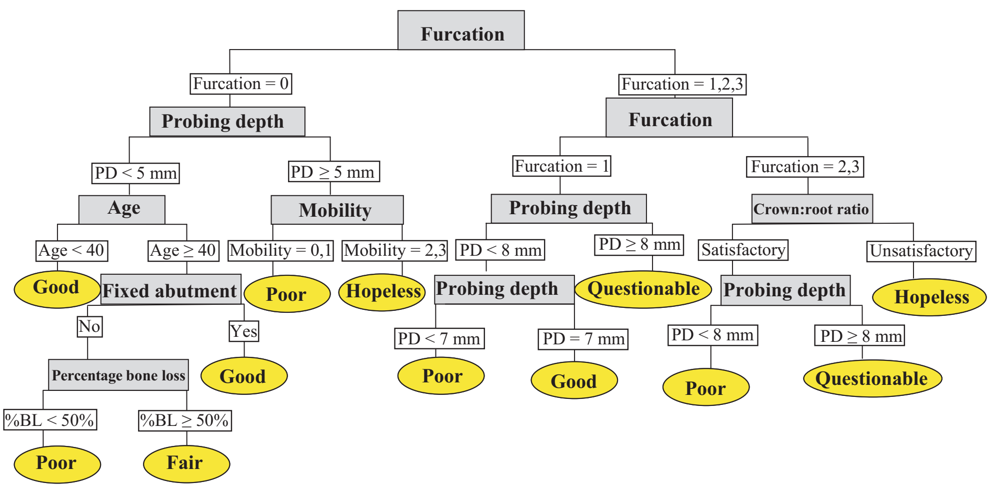

Fig. 1. **Multivariate survival tree for all teeth based on goodness-of-split method. PD, periodontal disease; BL, bone loss.**

Table 3. Predictability of marginal goodness-of-split survival tree

Group	Definition	Number of teeth	Number lost	Percentage lost
I	Good	418	0	0.0
II	Fair	501	2	0.4
III	Poor	1357	66	4.9
IV	Questionable	138	32	23.2
V	Hopeless	95	31	32.6

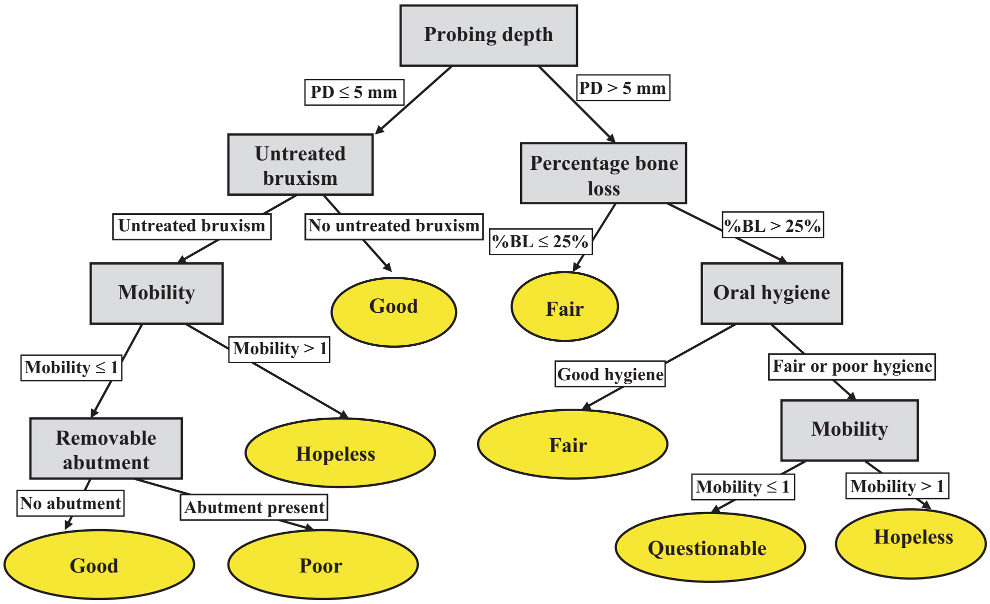

Fig. 2. **Multivariate exponential survival tree for non-molars. PD, periodontal disease; BL, bone loss.**

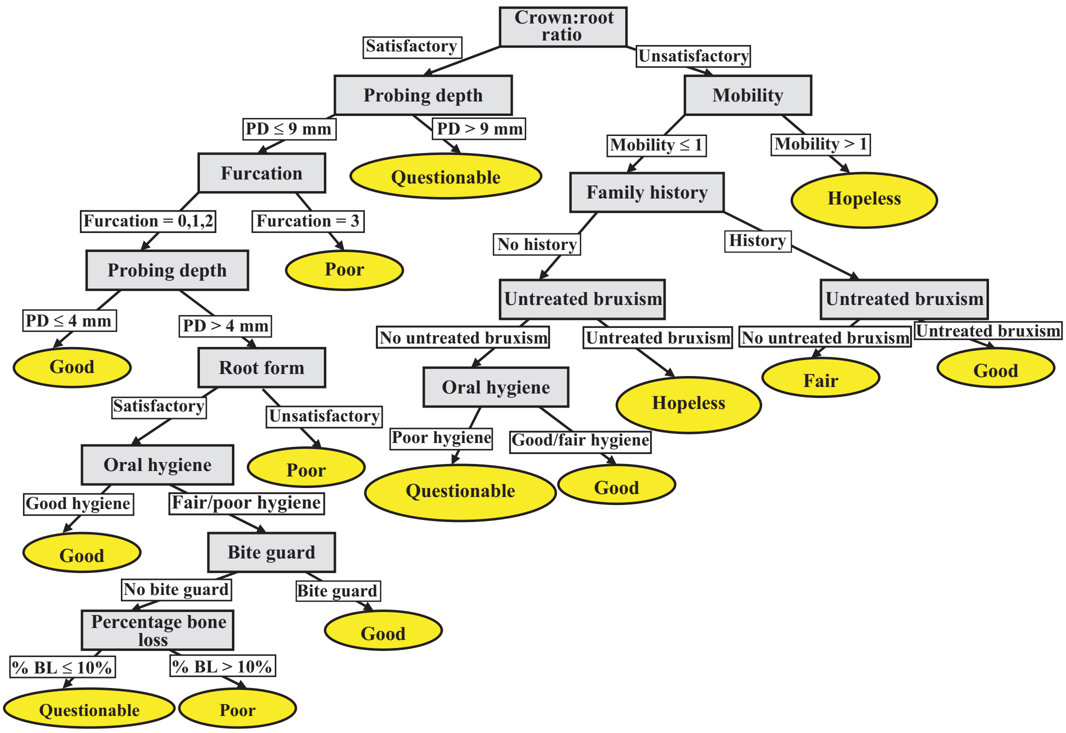

Fig. 3. **Multivariate exponential survival tree for molars. PD, periodontal disease; BL, bone loss.**

Implications for clinical research and practice

Currently, no uniform system for assignment of periodontal prognosis exists. Previous research has shown that many commonly used clinical parameters are associated with the probability of tooth survival (12, 17–22). The purpose of this study was to show the utility of multivariate CART for survival in developing such a system. We first applied multivariate CART for survival using a goodness-of-fit approach to a database consisting of 100 well-maintained patients in one private periodontal practice. However, sensitivity from the final tree was poor, with less than a third of the teeth classified as ‘hopeless’ being lost (Table 3). Based on this initial tree, with the first split on furcation involvement, with furcation of zero being a

Table 4. Classification of prognosis by tooth type (molars vs. non-molars) from multivariate exponential survival trees

Non-molars	Molars
Good	
Probing depth ≤5 mm No untreated bruxism OR Probing depth ≤5 mm Untreated bruxism Mobility of 0 or 1 Not a removable abutment	Unsatisfactory crown ⁄ root ratio Mobility of 0 or 1 Family history of periodontal disease Untreated bruxism OR Satisfactory crown ⁄ root ratio Furcation involvement of 0, 1, or 2 Probing depth ≤4 mm OR Satisfactory crown ⁄ root ratio Furcation involvement of 0, 1, or 2 Probing depth > 4 and ≤9 mm Satisfactory root form Good oral hygiene OR Satisfactory crown ⁄ root ratio Furcation involvement of 0, 1, or 2 Probing depth > 4 and ≤9 mm Satisfactory root form Fair or poor oral hygiene Uses bite guard OR Unsatisfactory crown ⁄ root ratio Mobility of 0 or 1 No family history of periodontal disease No untreated bruxism Good or fair oral hygiene
Fair	
Probing depth > 5 mm Percentage bone loss ≤25% OR Probing depth > 5 mm Percentage bone loss > 25% Good oral hygiene	Unsatisfactory crown ⁄ root ratio Mobility of 0 or 1 Family history of periodontal disease No untreated bruxism
Poor	
Probing depth ≤5 mm Untreated bruxism Mobility of 0 or 1 Removable abutment	Satisfactory crown ⁄ root ratio Probing depth ≤9 mm Furcation involvement of 3 OR Satisfactory crown ⁄ root ratio Furcation involvement of 0, 1, or 2 Probing depth > 4 and ≤9 mm Satisfactory root form Fair or poor oral hygiene No bite guard Percentage bone loss > 10% OR Satisfactory crown ⁄ root ratio Furcation involvement of 0, 1, or 2 Probing depth > 4 and ≤9 mm Unsatisfactory root form
Questionable	
Probing depth > 5 mm Percentage bone loss > 25% Fair or poor oral hygiene Mobility of 0 or 1	Satisfactory crown ⁄ root ratio Probing depth > 9 mm OR Satisfactory crown ⁄ root ratio Furcation involvement of 0, 1, or 2 Probing depth > 4 and ≤9 mm Satisfactory root form Fair or poor oral hygiene No bite guard Percentage bone loss > 10% OR Unsatisfactory crown ⁄ root ratio Mobility of 0 or 1 No family history of periodontal disease No untreated bruxism Poor oral hygiene
Hopeless	
Probing depth > 5 mm Percentage bone loss > 25% Fair or poor oral hygiene Mobility of 2 or 3 OR Probing depth ≤5 mm Untreated bruxism Mobility of 2 or 3	Unsatisfactory crown ⁄ root ratio Mobility of 2 or 3

potential proxy for non-molars, we further stratified CART modeling by molars and non-molars. We then utilized multivariate exponential modeling and produced trees for molars and non-molars separately, obtaining with much better sensitivity and specificity (Table 5), although the results were still not optimal. Based on stratified modeling, unsatisfactory crown ⁄ root ratio was the most predictive factor for molar failure, while probing depth > 5 mm was the most predictive factor for non-molar failure. Other factors that were significantly associated with molar failure included increased probing depth, increased mobility, increased furcation involvement, no family history of periodontal disease, poor oral hygiene, and

Table 5. Predictability of multivariate exponential survival trees by tooth type (non-molars vs. molars)

Group	Definition	Non-molars			Molars		
		Number of teeth	Number lost	Percentage Lost	Number of teeth	Number lost	Percentage lost
I	Good	1402	4	0.3	220	2	0.9
II	Fair	241	5	2.1	251	16	6.4
III	Poor	19	1	5.3	89	13	14.6
IV	Questionable	142	31	21.8	74	21	28.4
V	Hopeless	31	14	45.2	40	24	60.0

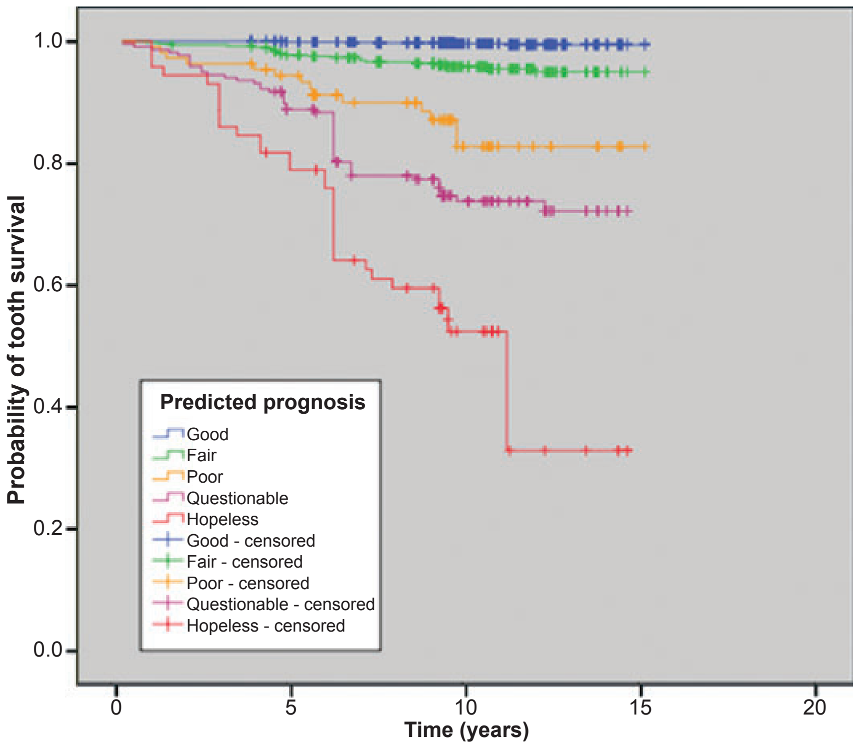

Fig. 4. Survival plot for prognostic categories generated by stratified multivariate exponential survival trees.

unsatisfactory root form. Other factors that were significantly associated with non-molar failure included increased overall percentage bone loss, poor oral hygiene, increased mobility, untreated bruxism, and the presence of a removable abutment. Although many of these factors make intuitive sense as predictors of tooth loss and are consistent across trees, other factors are inconsistent, such as the effect of untreated bruxism on the survival of molars. For instance, molars in patients with a family history of periodontal disease and untreated bruxism showed better survival than molars in patients with a family history of periodontal disease and no untreated bruxism (Fig. 3). Conversely, molars in patients without a family history of periodontal disease and untreated bruxism had worse tooth survival than either category of bruxism with a family history of periodontal disease (Fig. 3). Some of these inconsistencies are probably the result of a relatively small sample size, and some may be the result of selection bias, as the sample consisted entirely of well-maintained periodontal patients with moderate to severe periodontitis from one periodontal practice.

While limited inference can be drawn from the models presented here, as the patients were taken from only one periodontal practice, the method used demonstrates the utility of this new statistical methodology in developing evidence-based periodontal prognosis. In the future, periodontal prognostic indicators based on survival trees built from data collected from a large, heterogeneous population of patients from multiple practitioners may provide a better basis for assignment of prognosis, and thus treatment planning. The models presented also show that some common periodontal measures, such as probing depth, mobility, furcation involvement, crown ⁄ root ratio and oral hygiene, are significant predictors of tooth survival. In contrast, the role of some of common periodontal measures, such as untreated bruxism, family history of periodontal disease and overall percentage bone loss, is not so clear. More research in the area of periodontal prognosis, as well as overall dental prognosis, is required in order for practitioners to better assess the condition of a tooth at any point in time and develop treatment plans that are better guided by evidence-based assignment of prognosis.

This study demonstrates the utility of multivariate CART for survival in development of evidence-based prognostic indicators. Eventually, with accumulation of longitudinal data from many practices, we should be able to develop evidence-based prognostic indicators that can be utilized by periodontists, dentists, third-party payment plans and patients to determine the optimum treatment plan in each case, based on evidence-based prognosis.

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