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Development of prognostic indicators using Classification And Regression Trees (CART) for survival

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Abstract

The development of an accurate prognosis is an integral component of treatment planning in the practice of periodontics. Prior work has evaluated the validity of using various clinical measured parameters for assigning periodontal prognosis as well as for predicting tooth survival and change in clinical conditions over time. We critically review the application of multivariate **C**lassification **A**nd **R**egression **T**rees (CART) for survival in developing evidence-based periodontal prognostic indicators. We focus attention on two distinct methods of multivariate CART for survival: the marginal goodness-of-fit approach, and the multivariate exponential approach. A number of common clinical measures have been found to be significantly associated with tooth loss from periodontal disease, including furcation involvement, probing depth, mobility, crown-to-root ratio, and oral hygiene. However, the inter-relationships among these measures, as well as the relevance of other clinical measures to tooth loss from periodontal disease (such as bruxism, family history of periodontal disease, and overall bone loss), remain less clear. While inferences drawn from any single current study are necessarily limited, the application of new approaches in epidemiologic analyses to periodontal prognosis, such as CART for survival, should yield important insights into our understanding, and treatment, of periodontal diseases.

Prognosis

The 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 to 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

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assigned. Previous studies by McGuire [19.] and McGuire & Nunn [20., 21., 22.] have evaluated the validity of using 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 future condition of a tooth varied by tooth type (i.e., molars vs. non-molars). With respect to the relationship of commonly taught clinical parameters to tooth loss rate, some clinical factors, such as satisfactory crown-to-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 as well as certain immunological and microbiological parameters in 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* were 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.].

While 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 with the IL-1 genotype, tooth mobility, and site-level alveolar bone height at baseline [24.].

One of the underlying premises of our series of papers [19., 20., 21., 22.] is that the traditional method for assignment of prognosis involves a subjective process based on commonly taught clinical parameters and a therapist’s experience and training. There is no established universal set of criteria for assignment of periodontal prognosis, and thus, different practitioners may assign varying prognoses for the same tooth, which can be problematic to the referring dentists, third-party payment plans (e.g., dental insurance companies), and the patients themselves since instead of providing guidance to treatment planning, it creates further uncertainty. In order to remedy this situation, we embarked on a long-term goal 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.

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Classification And Regression Trees (CART)

The idea of regression trees dates back to the automatic interaction detection program by Morgan & Sonquist [23.]. After the 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 provide for 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 to develop meaningful assignment of prognosis in medical research led to the generalization of regression trees to survival analysis. Since survival analysis involves actual failure times in addition to failure status, the 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: (1) The first group, analogous to CART, involves minimizing within-node variability in survival times and is surveyed by Gordon & Olshen [10.], among others [6. 14. 27.]. (2) 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 Ciampi et al. [2.], Segal [25.], and LeBlanc & Crowley [15.]. Notable examples of application of CART for survival in the development of prognosis for cancer include breast cancer where survival trees indicated that lymph node status was the strongest predictor of relapse while the markers cathepsin D and PAI-1 were the strongest predictors of relapse among those without lymph node involvement [11.], thin primary cutaneous malignant melanoma where prognosis based on survival trees was more accurate in predicting metastasis after 10 years than staging 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 occur when either 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 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. Robust inference 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 for multivariate survival analysis to CART for survival. In this paper, we apply this newly developed extension of CART for survival to the data collected for 100 well-maintained periodontal

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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 methodologic approach that we have used successfully to apply CART to patient-based data. As we have reported in our earlier papers, 100 consecutive patients with at least 5 years of maintenance care were selected from one clinician's appointment book over a 2-month period. All subjects included in the study had been 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 their 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 followed for 10 to 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 can be found in our initial reports [19., 20., 21.].

Using the method of <u>C</u>lassification <u>A</u>nd <u>R</u>egression <u>T</u>rees for survival for correlated outcomes, we fit trees using both the marginal goodness-of-split approach and the multivariate exponential model with gamma frailty. A further description of these techniques can be found in our papers in the statistical literature [7., 8., 26.]. Based on trees fit with the marginal approach where the first split occurred on furcation involvement (0 vs. 1, 2, 3), we stratified multivariate exponential survival trees by molars and non-molars. Trees were fit using programs developed in R statistical software.

Use of CART to Identify Periodontal Prognostic Indicators

The analyses that we have reviewed and summarized here have included a total of 2509 teeth from 100 well-maintained 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 provided in Table 2. The first tree shown in Fig. 1 is for the marginal goodness-of-split approach [8.] that 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-to-root-ratio, age at baseline, mobility, and average percent bone loss across the mouth. Table 3 shows how the marginal goodness-of-split tree performed in terms of prediction. While the percent tooth loss for each category increased with worse prognostic category, the lack of sensitivity in terms of 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 conducted with stratification by molars and non-molars. The best performance in terms of prediction was obtained from the multivariate exponential survival trees which are shown in Figs. 2 and 3. Fig. 2 shows the final multivariate exponential survival tree for non-molars. As can be seen in Fig. 2, probing depth, untreated bruxism (i.e., parafunctional habit without a biteguard), oral hygiene, mobility, removable

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abutment, and mean percent bone loss were all significant factors in the multivariate exponential survival tree for predicting tooth loss over time in non-molars. Fig. 3 shows the final multivariate exponential survival tree for molars. Based on Fig. 3, crown-to-root ratio, probing depth, furcation involvement, root form, untreated bruxism, oral hygiene, mobility, biteguard, mean percent 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 depicted in Figs. 2 and 3. Table 5 shows the predictability of the multivariate exponential survival trees by 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. Fig. 4 shows the actual survival for predicted prognostic categories based on the stratified multivariate exponential survival trees. As can be seen from the survival plot in Figure 4, sensitivity and specificity are relatively high for all categories.

Implications for Clinical Research and Practice

Currently, no uniform system for assignment of periodontal prognosis exists. Previous research has demonstrated that many commonly used clinical parameters are associated with the probability of tooth survival [12., 17., 18., 19., 20., 21., 22.]. The purpose of this study was to show the utility of multivariate CART procedures 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 potential proxy for non-molars, we then stratified further CART modeling by molars and non-molars. We then utilized multivariate exponential modeling and grew trees for molars and non-molars separately with much better sensitivity and specificity obtained (Table 5), although results were still not optimal. Based on stratified modeling, unsatisfactory crown-to-root ratio was the most predictive factor in molar failure while probing depth greater than 5 mm was the most predictive factor in 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 unsatisfactory root form. Other factors that were significantly associated with non-molar failure included: increased overall percent bone loss, poor oral hygiene, increased mobility, untreated bruxism, and being a removable abutment. While 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 had better tooth 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 categories with a family history of periodontal disease (Fig. 3). Some of these inconsistencies is likely the result of a relatively small sample size, and some may be the result of selection bias since the sample consisted entirely of well-

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maintained periodontal patients with moderate-to-severe periodontitis in one periodontal practice.

While limited inference can be drawn from the models presented here since the patients were taken from only one periodontal practice, the method applied 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 demonstrate that some common periodontal measures, such as probing depth, mobility, furcation involvement, crown-to-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 percent bone loss, is not so clear. More research in the area of periodontal prognosis, as well as overall dental prognosis, needs to be conducted 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 the 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 for each patient, based on evidence-based prognosis.

Acknowledgments

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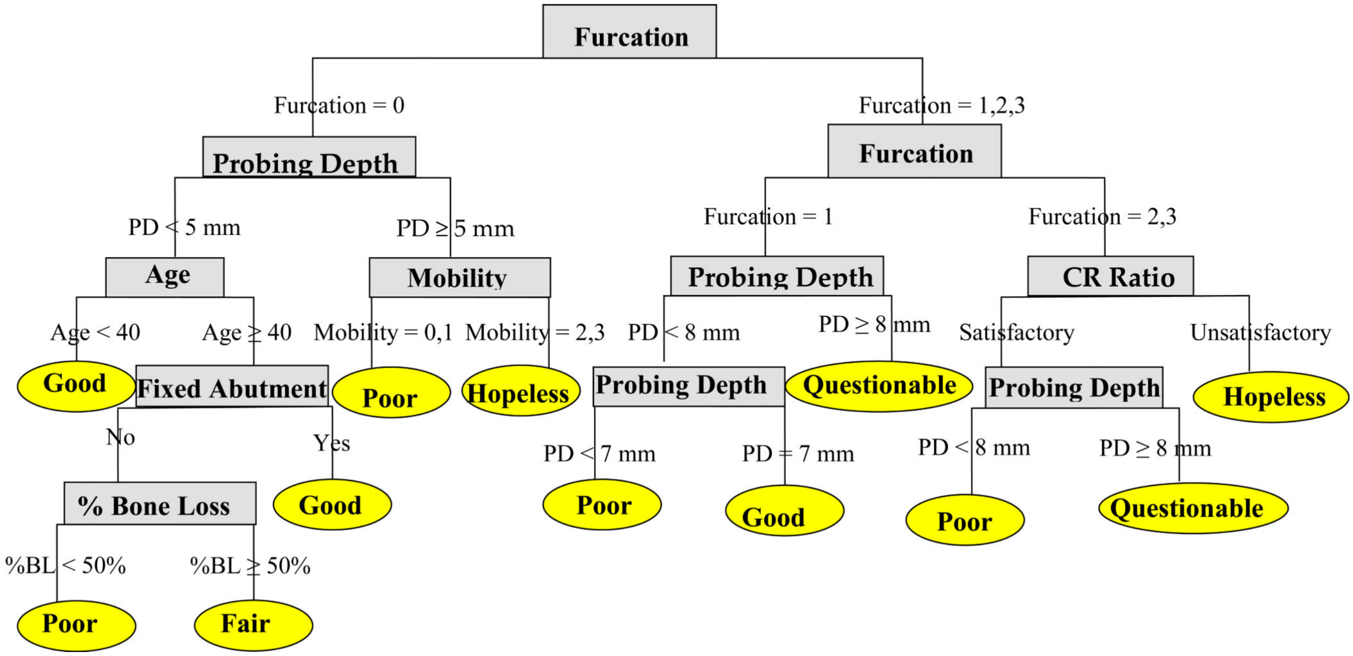

Fig. 1.

Multivariate survival tree for all teeth based on goodness of split method

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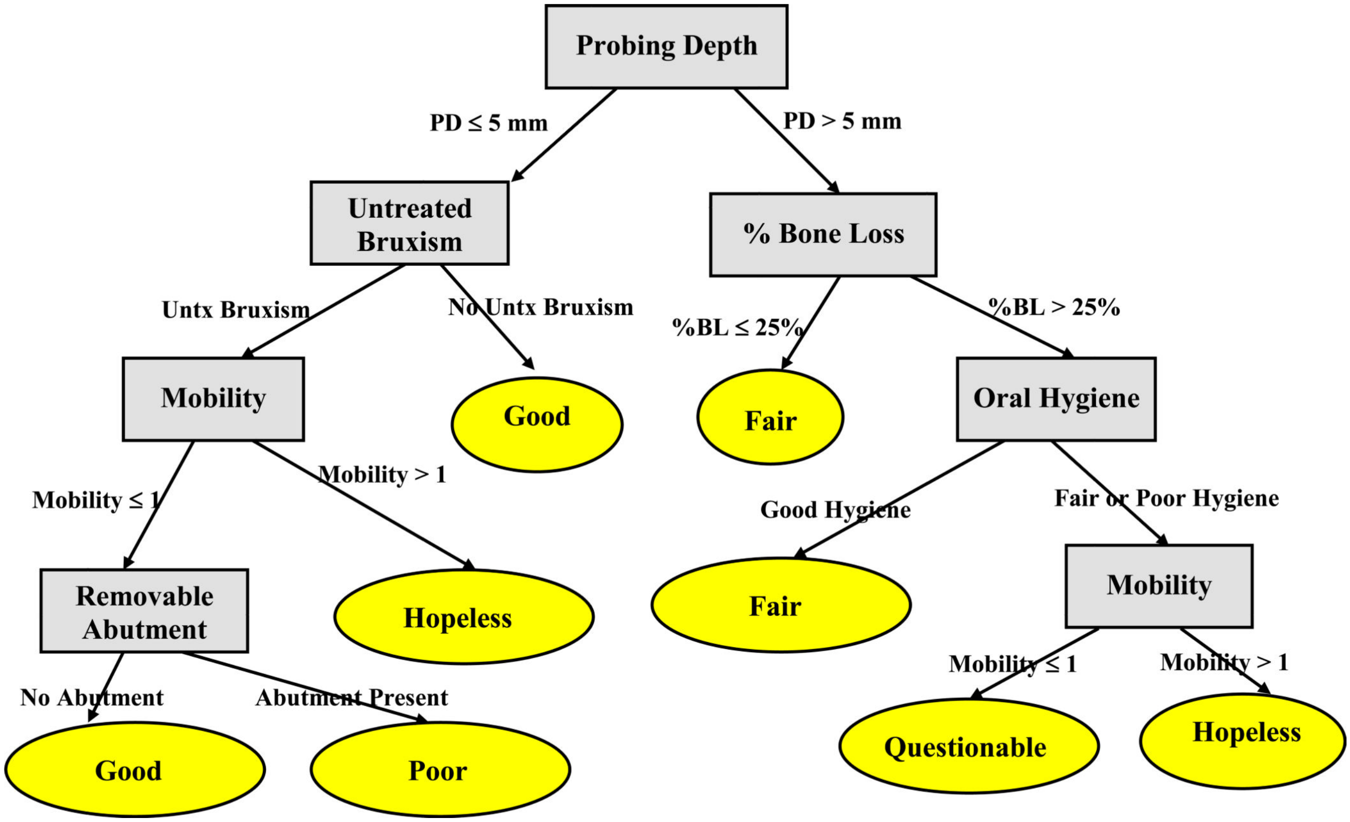

Fig. 2.
Multivariate exponential survival tree for non-molars

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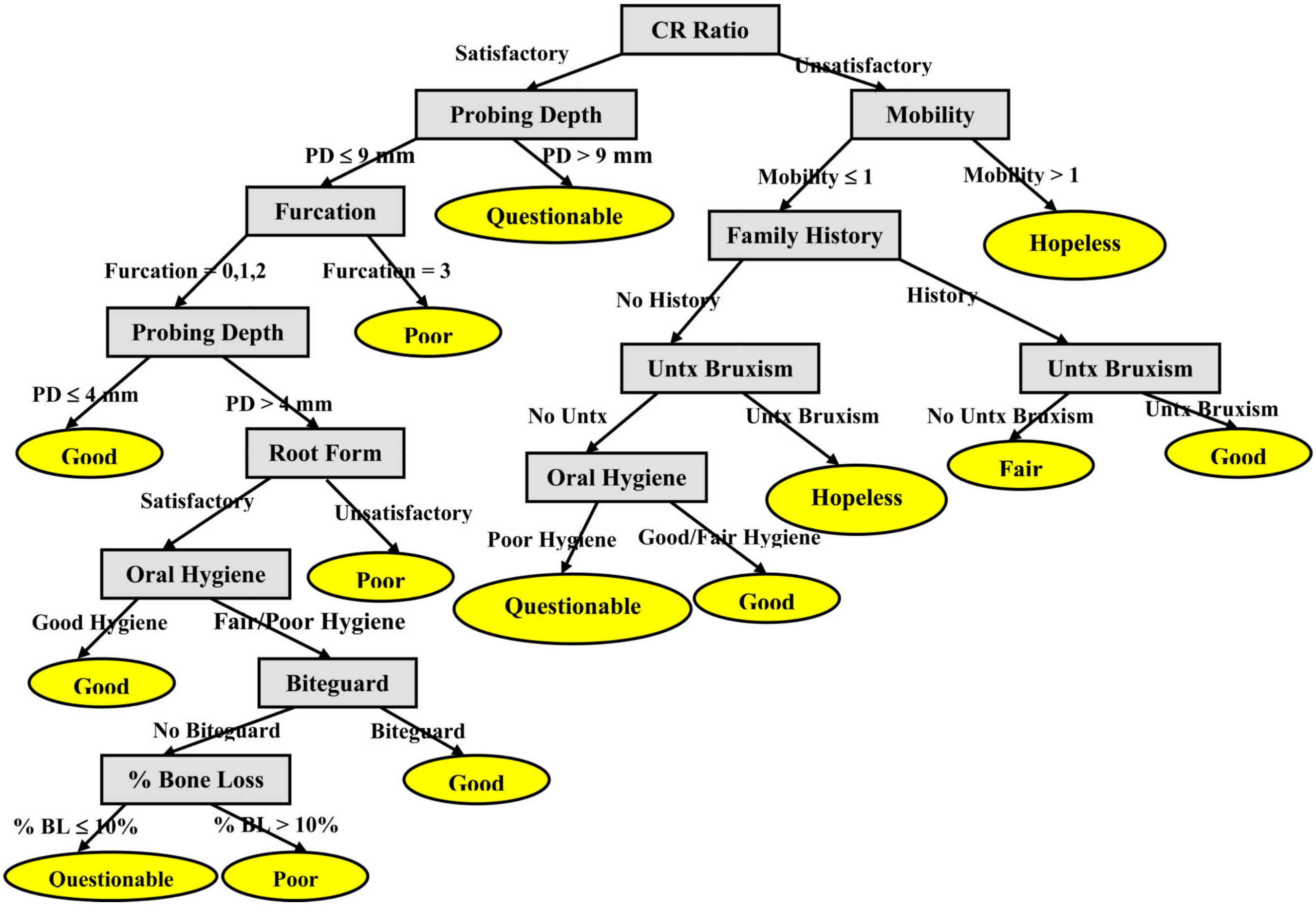

Fig. 3.
Multivariate exponential survival tree for molars

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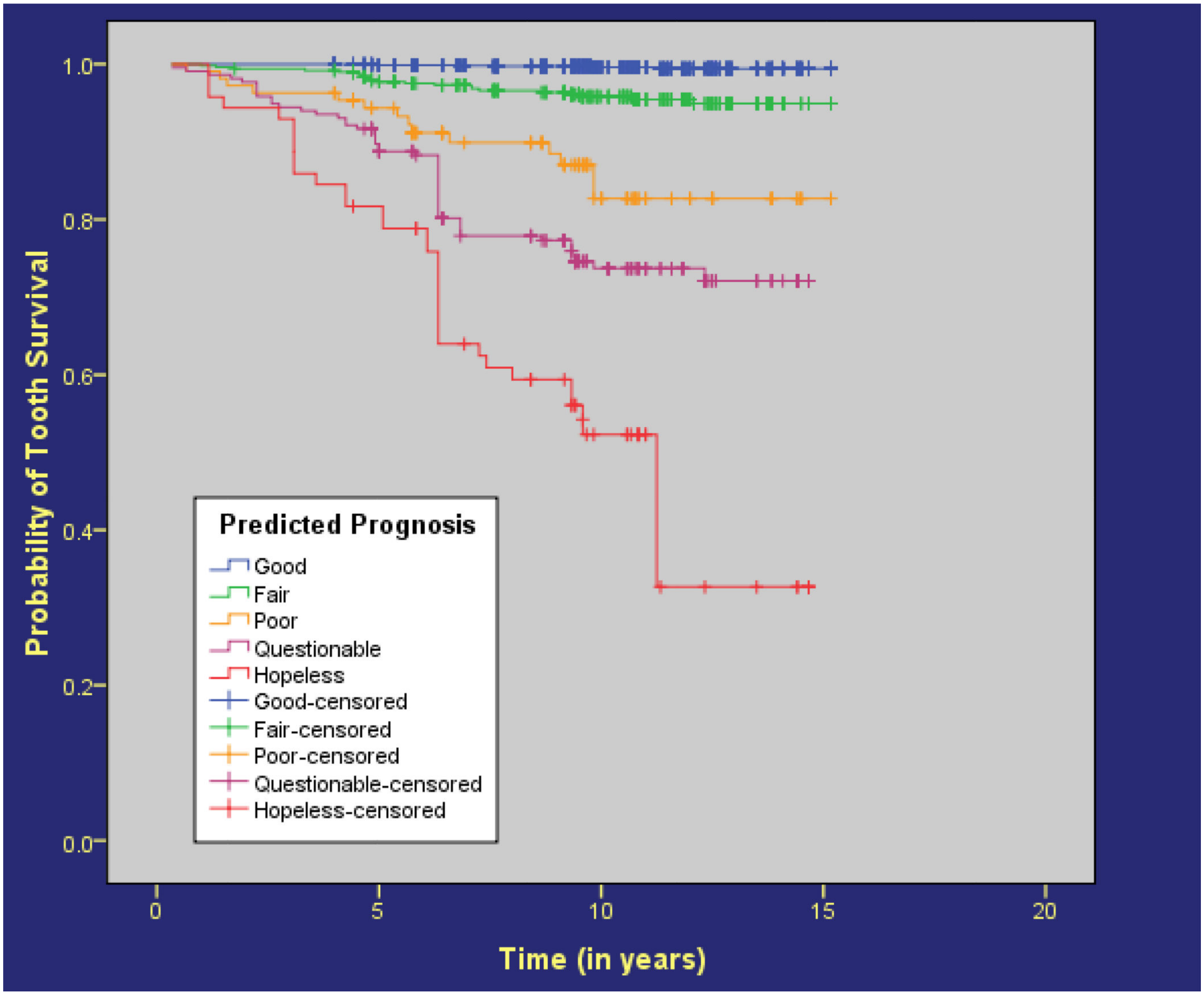

Fig. 4.
Survival plot for prognostic categories generated by stratified multivariate exponential survival trees

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Table 1

Commonly taught clinical parameters used in assigning prognosis

Individual Tooth Prognosis
Percentage of bone loss
Probing depth
Distribution and type of bone loss
Presence and severity of furcations
Mobility
Crown-to-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 consideration
Knowledge and ability of dentist
Etiological factors
Oral habits and compulsions

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Table 2

Clinical factors in 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, III
Root Form	Satisfactory vs. Unsatisfactory
Crown-to-Root Ratio	Satisfactory vs. Unsatisfactory
Mobility	0 to 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	Not Abutment vs. Abutment
Removable Abutment Status	Not Abutment vs. Abutment
Biteguard	No Biteguard vs. Biteguard
Parafunctional Habit	No Habit vs. Habit
No Biteguard with parafunctional habit	Habit and Biteguard vs. Habit and No Biteguard
% Bone Loss	Mean percent bone loss across entire mouth
Compliance	Comliant 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

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Table 3

Predictability of marginal goodness-of-split survival tree

Group	Definition	Teeth	# Lost	% 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%

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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	**Good** Unsatisfactory Crown-to-Root Ratio Mobility of 0 or 1 Family History of Periodontal Disease Untreated Bruxism *or* Satisfactory Crown-to-Root Ratio Furcation Involvement of 0, 1, or 2 Probing Depth ≤ 4 mm *or* Satisfactory Crown-to-Root Ratio Furcation Involvement of 0, 1, or 2 Probing Depth > 4 mm and ≤ 9 mm Satisfactory Root Form Good Oral Hygiene *or* Satisfactory Crown-to-Root Ratio Furcation Involvement of 0, 1, or 2 Probing Depth > 4 mm and ≤ 9 mm Satisfactory Root Form Fair or Poor Oral Hygiene Uses Biteguard *or* Unsatisfactory Crown-to-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 % Bone Loss ≤ 25% *or* Probing Depth > 5 mm % Bone Loss > 25% Good Oral Hygiene	**Fair** Unsatisfactory Crown-to-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	**Poor** Satisfactory Crown-to-Root Ratio Probing Depth ≤ 9 mm Furcation Involvement of 3 *or* Satisfactory Crown-to-Root Ratio Furcation Involvement of 0, 1, or 2 Probing Depth > 4 mm and ≤ 9 mm Satisfactory Root Form Fair or Poor Oral Hygiene No Biteguard % Bone Loss >10% *or* Satisfactory Crown-to-Root Ratio Furcation Involvement of 0, 1, or 2 Probing Depth > 4 mm and ≤ 9 mm Unsatisfactory Root Form
Questionable Probing Depth > 5 mm % Bone Loss > 25% Fair or Poor Oral Hygiene Mobility of 0 or 1	**Questionable** Satisfactory Crown-to-Root Ratio Probing Depth > 9 mm *or* Satisfactory Crown-to-Root Ratio Furcation Involvement of 0, 1, or 2 Probing Depth > 4 mm and ≤ 9 mm Satisfactory Root Form Fair or Poor Oral Hygiene No Biteguard % Bone Loss >10% *or* Unsatisfactory Crown-to-Root Ratio Mobility of 0 or 1

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Non-Molars	**Molars**
	No Family History of Periodontal Disease No Untreated Bruxism Poor Oral Hygiene
Hopeless Probing Depth > 5 mm % 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	**Hopeless** Unsatisfactory Crown-to-Root Ratio Mobility of 2 or 3

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Table 5

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

Group	Definition	Non-Molars			Molars		
		Teeth	# Lost	% Lost	Teeth	# Lost	% 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%