A prediction model to assign periodontal prognosis based on survival time

Martinez Canut 2018

What is Perioproject?

Perioproject (www.perioproject.com) is a prediction model of tooth loss due to periodontitis in patients following periodontal maintenance. From now on, tooth loss refers to tooth loss due to periodontitis. This tool was introduced to the scientific and clinical community in a study (Martinez-Canut, Alcaraz, Alcaraz Jr. et al. 2018) with the purpose of describing the development of this model and evaluating its performance. A multicentre approach enabled definition of survival times associated with thresholds of probability of tooth loss and the performance of the model was assessed using different tooth loss samples.

The database resulting from an analysis of tooth loss predictors in a sample of 500 carefully documented patients (515 teeth lost) following periodontal maintenance for a mean 20 years (Martinez-Canut 2015) was used to develop this prediction model. The resulting algorithm calculates the probability of tooth loss and associates it with the survival time of periodontally compromised teeth.

As shown in Figure 1, individual prognosis of this 59-year-old male chronic periodontitis patient has been assigned according to the probability of tooth loss (p. value). This probability results from calculating the increase in the risk depending on the following predictors: the patient is a heavy smoker and presents heavy bruxism habit. The age and the number of baseline teeth are also considered. At the tooth level, the extent of attachment loss (probing pocket depth, bone loss and furcation involvement), tooth mobility and the particular type of molar and non-molar teeth are considered. Teeth with higher probability of loss were lost earlier: the actual survival time in years is depicted in yellow.

By analysing different tooth loss samples is possible to associate the probability of tooth loss with the survival time, and associate thresholds of probability of tooth loss with survival times.

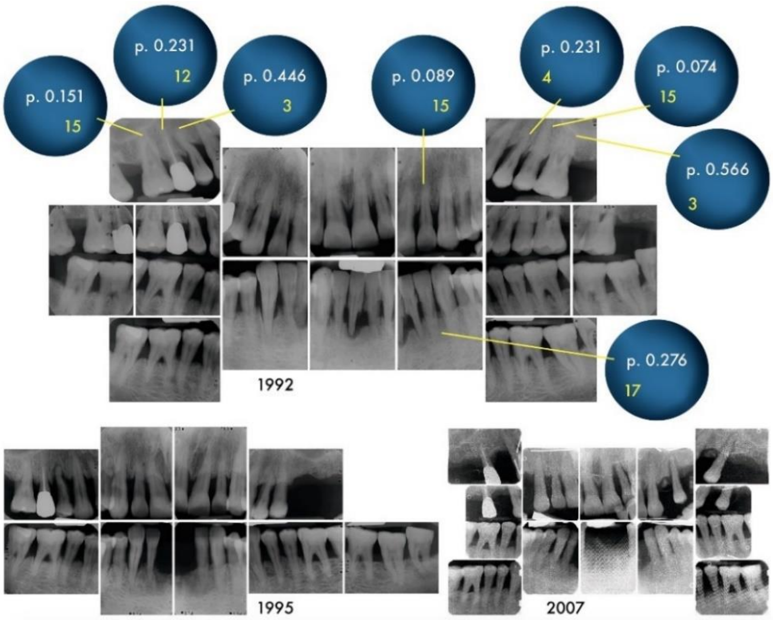


Figure 1

The development of a prediction model to assign periodontal prognosis and estimate survival times of periodontally compromised teeth might seem to be a convoluted approach. However, this prediction model is no more than the result of a statistical analysis of predictors of tooth loss.

If the bowels of this model could be opened up, they would reveal an enormous amount of data that is perfectly arranged under a multilevel analysis, containing the relative risk of tooth loss corresponding to each category of the predictors, which all play their role simultaneously.

This is a very difficult task for a clinician. The calculated probability of tooth loss is not a relative risk, but an absolute one. It is based on objective and measurable parameters, making it possible to estimate the survival times. This considers the fact that tooth loss takes place progressively in time. To our understanding, this approach seems simpler than the subjective interpretation of prognostic factors without clearly defined guidelines.

The group responsible for the development of Perioproject is made up of statisticians (Eratema, Valencia), image designers (Perez Colomer, Valencia) and a group of computer programmers in charge of constructing the prediction model based on the data obtained with the statistical analysis (Instituto Tecnológico de Valencia, ITI, Universidad Politécnica de Valencia).

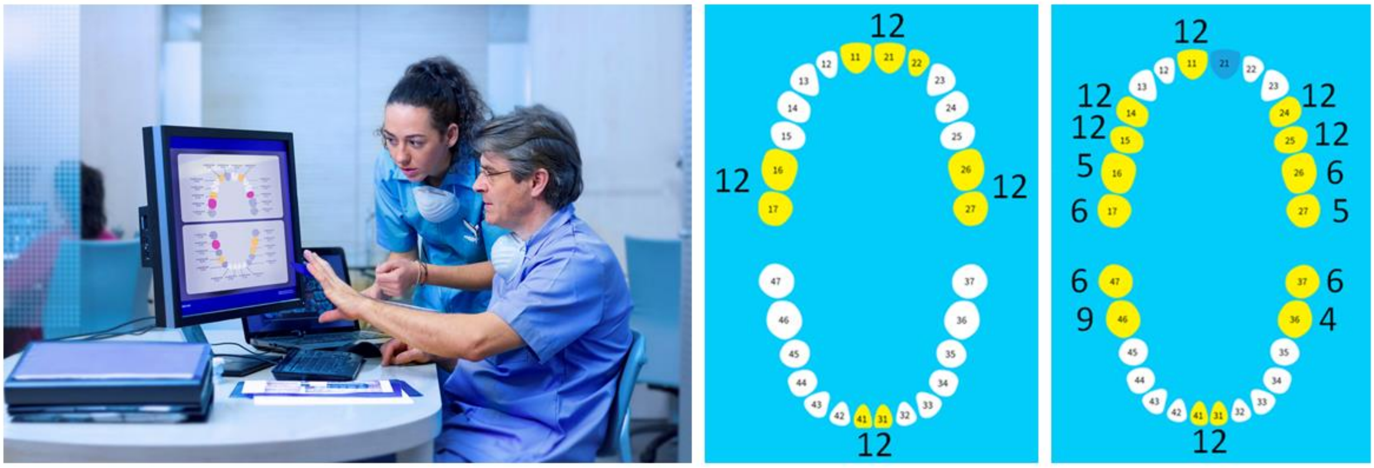
Perioproject as an alternative to conventional periodontal prognostic indexes

The available indexes to assign periodontal prognosis (Becker et al. 1984, McGuire & Nunn 1996, Checchi et al. 2002, Fardall et al. 2004, Kwok & Caton 2007) define each prognostic category with heterogeneous criteria and rather vague terms, as it has been pointed out (Faggion et al. 2007). These indexes were developed to predict tooth loss based on tooth-related factors, without considering the potential impact of patient-related factors.

The accuracy of these indexes is rather low (McGuire & Nunn 1996). For hopeless prognosis, the tooth loss prediction failed, implying a False +, in between 19.6% and 38% of cases (Becker et al. 1984, McGuire & Nunn 1996, Fardal et al. 2004). These percentages were much higher for questionable prognosis: the tooth loss prediction failed in between 37% and 74% of cases (McFall 1982, Becker et al. 1984, McGuire & Nunn, 1996). Thus, it has generally been assumed that the mean probability of accurately predicting tooth loss, excluding good prognosis, is close to being a chance occurrence or comparable to a coin toss (McGuire & Nunn 1996).

It has been generally assumed that there is a paucity of knowledge on periodontal prognosis. This would be in line with the rather low accuracy of tooth loss predictions utilising conventional prognostic indexes. Research on periodontal prognosis has been faced with an interesting paradox. Periodontal treatment and maintenance care is so effective that the resulting tooth loss due to periodontitis is a rare event. This represents the most relevant limitation of research on the subject, since it is difficult to analyse patient- and tooth- related factors in such small tooth loss samples. Despite this difficulty, research on periodontal prognosis has accumulated quite broad knowledge in recent years, and the generally

assumption regarding the paucity of knowledge on the subject might need to be reconsidered.
More recent studies have reported an increase in the risk of tooth loss according to each category of several tooth-related factors in the presence or absence of certain patient-related factors (Miller et al. 2014, Graetz et al. 2015, Martinez-Canut 2015, Dannewitz et al. 2016). Taking the most consistent findings on the impact of the most relevant patient- and tooth-related factors toghether, we have accumulated quite broad knowledge on predictors of tooth loss. The key issue might be how to interpret and apply this knowledg



Perioproject calculates the probability of tooth loss based on 11 patient- and tooth-related factors and assigns survival time to periodontally compromised teeth. The odontograms show a map of individual tooth prognosis to make the results easier interpret. The odontogram on the left presents few teeth assigned longer survival times in a patient with low risk of tooth loss. The opposite occurs on the right.

Reinterpreting the assignation of periodontal prognosis

As clinicians, we can try our best to mentally process the available information to assign the prognosis. But how do we do it? There are no guidelines to handle so many *p*. values and relative risks from so many patient- and tooth-related factors. What does a questionable prognosis, supported by meaningless high p. values, mean?
Insofar as research on periodontal prognosis enlarges the list of regression coefficients and relative risks (O.R and R.R) of predictors of tooth loss, clinicians should interpret the data as practically as possible. However, there are no clearly defined guidelines for doing so, in order to assign a meaningful prognosis in terms of treatment decisions.

The results of the multilevel analysis of predictors of tooth loss performed in our research (Martinez-Canut 2015) provided close to 15 predictors for molars and another 15 predictors for non-molars, with different impact depending on the type of molar and non-molar. Several interactions between certain patient-related factors were also identified. The increase in the risk of tooth loss of all predictors represents an enormous amount of data. How can we mentally process this information to assign a meaningful periodontal prognosis?
It does not seem to be an easy task. This is the rationale for developing a prediction model, that basically is the result of a statistical analysis helping to make a decision. Should researchers try

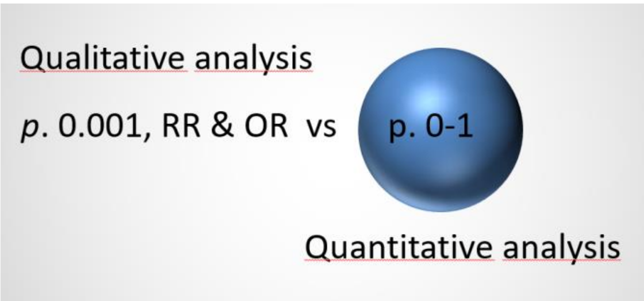
harder with conventional logistic regression or just look at the issue from a different perspective? As is the case with several areas of medicine, the concept of probability is a very different perspective, being the probabilistic prediction of the binary outcome tooth loss. This prediction is an absolute risk, which goes beyond identifying predictors with regression coefficients and the relative risk, odds ratio (OR) and risk ratio (RR) (Pepe et al. 2004, Cerrito 2009, Steyerberg et al. 2010).

The probabilistic prediction of tooth loss is a p value from 0 to 1, supported by measurements of performance of the prediction model. This represents a prognosis in itself, with a defined and objective p value. Interestingly, it might be a meaningful prognosis, and help to make decisions, as long as the probability of tooth loss could be associated to the survival expectancy of the tooth.

The development of the prediction model implies interpreting the analysis of predictors of tooth loss in a completely different way. This means utilising quantitative instead of qualitative analysis. To date, periodontal prognosis has been interpreted through qualitative analysis with conventional logistic regression, by applying the inductive method to the interpretation of results; assigning a suspected weight or value based on how the statistical significance of each predictor is subjectively interpreted. This implies matching words with values. Regardless of how the risk assessment tool or the prognostic tool has been developed, all of them are based on qualitative analysis.

The idea of a prediction model to assign periodontal prognosis was first introduced by Faggion et al (2007), who questioned the actual meaning of certain prognostic categories (e.g. questionable).

It is also interesting to note that a prediction model does not feel fear of failing the prediction. This obvious and apparently trivial observation might be of relevance when realising that the model seems to assign longer survival rates than the subjectively assigned expected survival time to severely compromised teeth. The prediction model confirms the actual efficacy of periodontal treatment while clinicians might still doubt its efficacy.



From a conceptual stand point, the central idea consists of replacing the subjective interpretation of regression coefficients (p.001 for instance) of qualitative analysis with an objective probability value of tooth loss p from 0 to 1 resulting from quantitative analysis. This is a prognosis in itself.

How Perioproject was develop

Perioproject was developed by taking a systematic approach to model development (Steyerberg & Vergouwe 2014). This prediction model calculates the probability of tooth loss according to the impact of eleven predictors, and this probability can be associated with a certain survival time. This makes it possible to define the prognosis of the whole dentition based on survival expectancy or survival time, but more importantly, to retrospectively assess the accuracy of the prediction with any tooth extracted for periodontal reasons.

The process consists of entering in the model the predictor of a certain tooth extracted after 20 years under periodontal maintenance, for instance, as it was at baseline, i.e. 20 years previously. This makes it possible to assess whether the calculated probability of tooth loss and the associated survival time matched the actual survival time of the extracted tooth.

The database resulting from an analysis of tooth loss predictors in a sample of 500 carefully documented patients (515 teeth lost) following periodontal maintenance for a mean 20 years (Martinez-Canut 2015) was used to develop the prediction model. This analysis (logistic multilevel regression analysis) made it possible to select those variables that are more clearly associated with tooth loss, which are also the ones that are most consistently found to be associated with tooth loss in the literature, with fairly homogeneous relative risks. Thirty-nine studies of predictors of tooth loss in patients following periodontal maintenance for more than 5 years were selected according to previously defined selection criteria (Chambrone et al. 2010, Faggion et al. 2014).

Finally, the number of variables to be analysed was adjusted to the sample size and the number of events per variable analysed (500 patients and 515 teeth lost) so as to avoid over-fitting the model (Peduzzi et al. 1996, Steyerberg & Vergouwe 2014, Wynants et al. 2015).

Based on the above criteria, the following variables were analysed. Five patient-related factors: age, severe periodontitis, heavy smoking, bruxism and baseline number of teeth; and six tooth-related factors: type of tooth, furcation involvement, probing pocket depth, bone loss, mobility and crown-to-root ratio. The statistical analysis of these variables was performed with logistic multilevel analysis.

Due to the low prevalence of tooth loss, the model performed better at rejecting tooth loss. Therefore, it is more appropriate for ascertaining that tooth loss will not occur (Tooth loss −) (higher specificity) while it was less appropriate for ascertaining that tooth loss will occur (Tooth loss +) (moderate sensitivity). The performance of the constructed prediction model was as follows: Calibration measurement R^2 Nagelkerke 0.31 and 0.24 for molars and non-molars respectively. Discrimination measurements (for molars and non-molars respectively) AUC 0.93 and 0.97; sensitivity 39% and 43%; specificity 98% and 99%, PV+ 72% and 60%, and PV- 94% and 98%.

Why assign survival times to periodontally compromised teeth?

According to our database, the percentage distribution of tooth loss through the follow-up period of our research was quite even, 31.6% from baseline to 5 years, 20.2% 5.1 to < 10, 26.5% from 10 to < 15 and 21.6% > 15 years. This otherwise obvious finding was of paramount relevance, revealing that the accuracy of the tooth loss prediction might not be the most relevant issue, since it may depend on the length of the study rather than the prognostic tool or index utilised. The longer the observation period, the higher the probability of tooth loss might be. Therefore, the prediction of the tooth loss event in time seems more useful than the accuracy of the tooth loss prediction. From a clinical perspective, a tooth loss prediction in itself does not help to make any decision other than that regarding the extraction of a periodontally compromised tooth; the question would be when.

Alternatively, the prediction of a certain survival time goes beyond the dichotomous alternative of predicting tooth loss + or tooth loss – and comes closer to the fact that tooth loss occurs progressively in time. This seems more useful for helping the clinician and patient to make a decision.

Thus, the concept of conventional prognostic categories (good, fair, poor, questionable and hopeless) is faced by a more realistic and useful factor, i.e. the estimation of survival time of periodontally compromised teeth. This estimation is possible utilizing a prediction model to calculate the probability of tooth loss, so this probability can be associated with the corresponding survival time of different tooth loss samples in a retrospective manner, as will be addressed in the following section.

The survival times assigned are an objective and measurable language that defines the extent of periodontal involvement. For instance, longer survival times (12 to 22 years) correspond to the intermediate category of tooth-related factors (grade 2 furcation involvement, 30% to 50% bone loss, mobility 2, etc.) in the absence of patient-related prognostic factors (heavy smoking, bruxism, fewer baseline teeth, etc.). The shortest survival times correspond to the poorer category of tooth-related factors in the presence of patient-related prognostic factors.

Multicentre approach to evaluating model performance and defining survival times

Since the prediction model was developed using the database of 515 teeth lost, it should perform well with these teeth but perhaps not with other tooth loss samples. Therefore, three different tooth loss samples with a total of 369 teeth were used to validate the model by associating the intervals of tooth loss probability with the survival time and assessing possible differences between the samples.

These samples were a reference tooth loss sample of 129 teeth (sample 1) that was used to construct the model, a tooth loss sample also composed of 129 teeth that were consecutively extracted by the same clinician (M-C) and which were not used to construct the model (sample 2), and a sample of 111 teeth (sample 3) gathered by the clinicians from four dental practices with more than 25 years of experience in periodontics: Alcaraz, J., Alcaraz, J. Jr., Alvarez-Novoa, P., Alvarez-Novoa, C., Marcos, A., Noguerol, B., Noguerol, F. & Zabalegui, I.

The Perioproject research team gathered at the 2017 SEPA congress held in Malaga, Spain. Two generations of periodontists sharing the feedback of analysing tooth loss with a pioneer prediction model of tooth loss due to periodontitis

Survival times associated with the probability of tooth loss

A moderate negative correlation was found between the probability of tooth loss and the survival time in the whole sample (Pearson -0.502, $p < 0.001$), so that the survival rate increased as the intervals of probability of TLPD decreased (Fig. 1). The initial associations of survival rates and intervals of probability were refined on the basis of the TLPD sample of each association as well as the statistical analysis.

Significant differences were found between the mean survival rates in the whole sample (ANOVA $p < 0.0001$). Pair-wise comparison of means identified significant differences between the intervals, <0.036 (p = 0.014), 0.081-0.170 (p 0.011), 0.171-0.310 (p < 0.001) and > 0.310 (p < 0.001), so that the means significantly decreased between each pair of increasing intervals (Table 2). TLPD did not occur in the interval < 0.008; while the intervals 0.08-0.035 and 0.036-0.080 were associated with a survival rate of 17 (4.4) and 14.3 (4.7) years respectively, etc. At the opposite extreme, the interval 0.311-0.600 and > 0.600 was associated with a survival rate of 8.3 (4.4) and 6 (3.4) years respectively. Figure 6 depicts the mean survival time (from 0 to 20 years) according to different intervals of probability of tooth loss (>0.018, 0.019-0,035, etc.).

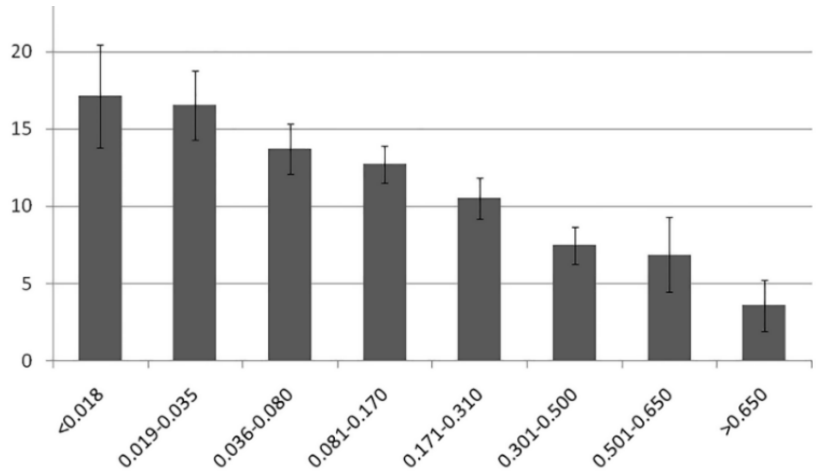


Figure 6

The percentage of cases included within each survival time was calculated according to the standard deviations and the percentiles of each mean. For instance, the interval 0.008-0.036 was associated with a survival time of 12 to 22 years, containing 80% of the cases with this interval. This approach also made it possible to differentiate the lowest and the highest intervals which lacked significant differences according to the Bonferroni corrections: <0.036 and 0.036-0.080, and 0.311-0.600 and > 0.600.

The shorter the amplitude of the survival rates was, the lower the percentage of cases fitting. Survival times between 5 and 10 years included only 55% to 60% of cases, while survival times between 10 and 15 years included the majority of cases. Therefore, the survival times were defined by balancing discrimination (the narrowest feasible survival rate) and accuracy (the highest percentage of cases fitting within the defined survival time). The definitive associations included 80% to 83% of the cases fitting in rates of 5 to 11 years except for two wider rates of 13 and 14 years (Table1). Thus, in between 80% and 83% of cases, the teeth were lost within the expected survival time. The corresponding percentages of 20% and

17% of teeth lost before or after the estimated survival time represent matters for further research that was performed in a fourth study implementing the LTOP system to simultaneously assign overall and individual tooth prognosis. This study also analysed the percentage loss of teeth assigned survival times. These issues are addressed in the limitations of Perioproject.

Table 1. Number of teeth lost and mean survival rates (SD) associated with each interval of probability of tooth loss. Colums means of survival rates A to F were compared (pair-wise comparissons with Bonferroni corrections).

	INTERVALS OF PROBABILITY						
	< 0.008	0.008-0.035	0.036-0.080	0.081-0.170	0.171-0.310	0.311-0.600	> 0.600
n. of teeth lost	0	35	52	111	79	68	24
Mean survival		17	14.3	13.2	10.9	8.3	6
SD		4.4	4.7	5.7	5	4.4	3.4
Colum means		A	B	C	D	E	F
Pair-wise comparisson		C D E F	D E F	D E F	E F		
SURVIVAL RATES		12 to 22	9 to 20	6 to 20	5 to 18	4 to 13	2 to 7
% included		80%	83%	80%	80%	80%	83%

n. teeth lost, number of teeth lost. According to differences between each pair of means (Pair-wise comparisson with Bonferroni corrections), for each significant pair, the key (A to F) of the smaller category appears under the category with larger mean.

Performance of the model using different tooth loss samples

Table 2 and Figure 7 show the mean survival rate (SD) associated with the intervals in samples 1, 2 and 3. Only the four intervals with significant differences (pairwise comparison with the Bonferroni corrections) were included in comparing these samples.

Significant differences were found between the mean survival time in each one of the three samples (ANOVA $p < 0.0001$). In parallel, no significant differences were found between the means in each one of the intervals of the samples (p between 0.184 and 0.544), so the model performed well in the three samples. A similar tendency was found with pair-wise comparison with Bonferroni corrections, despite six of the sub-samples containing less than 30 teeth, thereby limiting the opportunity for a more robust analysis. Only two-thirds of the comparisons revealed no significant differences while in the remaining comparisons the threshold of significance was close to 0.10.

The magnitude of error based on the variation interval (absolute values) was calculated in order to estimate differences in the performance between the samples. It was +5.1%, −13.8%, and −13.3% between samples 1-2, 1-3, and 2-3 respectively.

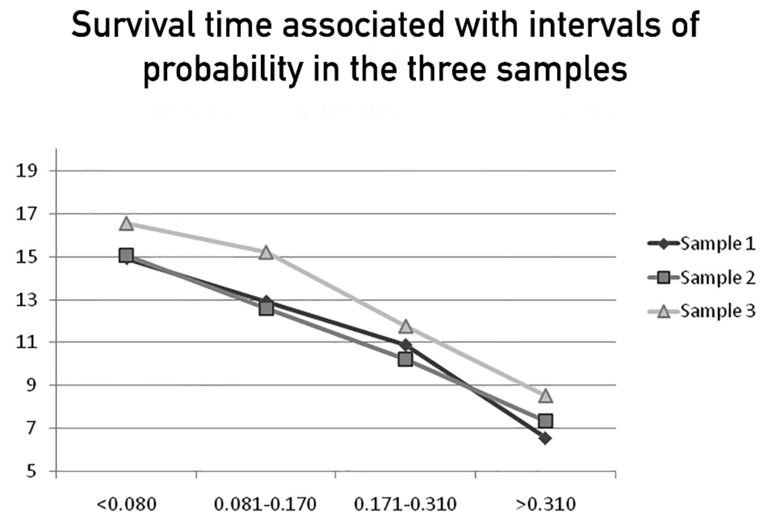
Taking the above findings together, the model was useful for defining intervals of probability of tooth loss associated with survival times in different tooth loss samples.

Table 2. Number of teeth lost and mean survival time (SD) associated with each interval of probability of tooth loss in the three samples

	SAMPLE 1				SAMPLE 2				SAMPLE 3			
	< 0.080	0.081-0.170	0.171-0.310	> 0.310	< 0.080	0.081-0.170	0.171-0.310	> 0.310	< 0.080	0.081-0.170	0.171-0.310	> 0.310
n. of teeth lost	33	48	26	22	32	43	29	25	22	20	24	45
Mean survival	14.9	12.9	10.8	6.5	15	12.5	10.2	7.3	16.5	15.2	11.5	8.5
SD	5.5	5.6	5.2	3	4.4	5.8	4.5	3.7	3.8	5.5	5.3	4.9
SURVIVAL TIME 1	11 to 20	6 to 20	6 to 18	4 to 13	11 to 20	6 to 20	6 to 18	4 to 13	11 to 20	6 to 20	6 to 18	4 to 13
% included	70%	77%	81%	86%	69%	74%	83%	84%	86%	85%	63%	73%
P.p. deviation	-4	-1	5	7	-5	-4	7	5	12	7	-13	-6
SURVIVAL TIME 2	9 to 22	6 to 22	5 to 19	4 to 14	9 to 22	6 to 22	5 to 19	4 to 14	9 to 22	6 to 22	5 to 19	4 to 14
% included	85%	90%	81%	86%	94%	81%	83%	88%	91%	90%	92%	82%
P.p. deviation	-5	6	-4	1	4	-3	-2	3	1	6	7	-3

n. teeth lost, number of teeth lost; P.p., deviation (in Percentage point) respect to the global estimation. Two different survival time 1 and 2 were analysed. The latter, with longer survival intervals, included between 81% to 92% of the cases. Percentage poin deviation ranged from -5 to 7.

Figure 7



The accuracy of the prediction model compared to the accuracy of a conventional subjective periodontal prognosis

The assignment of individual tooth prognosis using conventional periodontal indices should also be addressed. These are the routinely used tools to assign individual tooth prognosis and their accuracy has been assessed by comparing them with the actual event of tooth loss. To complete this approach, the accuracy of the model´s prediction was compared with the conventional periodontal prognosis assigned by the author (M-C) to the whole dentition (12.839 teeth) in the sample (515 teeth lost in 500 patients) used to construct the model.

Based on the relative differences, the prediction model was more accurate than the conventional periodontal prognosis, reducing the percentages of False + between 25% and 75% and False – between 15% and 28% of the times. The results of this indicative assay are presented in Table 3.

Thus, the model performed more accurately, substantially reducing False +. This might be partially due to the fact that the model does not feel but calculates using the database. On the contrary, clinicians feel, among other things, fear of getting the prediction wrong and producing a False –, which could be discouraging and even disappointing for the patient and the clinician. As a result, clinicians tend to assign more prognoses of tooth loss +, as opposed to the model.

Table 3. Accuracy of conventional subjective periodontal prognosis (CPP) and accuracy of prognosis assigned with the prediction model (PM). Relative differences (RD) in the percentage of F+ and F− and F + with each method

	n. teeth (%)	% Tooth loss	CPP	PM	RD
MOLARS					
Total	3.385 (100%)				
Good	2.150 (64%)	4%	4% F−	3.4% F−	− 15%
Questionable	853 (25%)	11%	11% F+ or 89% F−	8.2% F+ or 91.8% F−	− 25.4%
H. Questionable	196 (5.8%)	23.1%	77% F+	22% F+	− 71.5%
Hopeless	156 (4.7%)	50.9%	49% F+	21.5% F+	− 56%
NON-MOLARS					
Total	9.472 (100%)				
Good	8.238 (87%)	0.7%	0.7% F−	0.6% F−	− 28%
Questionable	917 (9.7%)	6.6%	6.6% F+ or 93.4% F−	4% F+ or 96% F−	− 39.3%
H. Questionable	193 (2%)	28.1%	71.9% F+	43.2% F+	− 40%
Hopeless	124 (1.3%)	37.3%	62.7% F+	18.2% F+	− 71%

Teeth which were lost with good and questionable prognosis were considered Fals e −; Teeth retained with highly questionable (H. Questionable) and hopeless prognosis were considered False +; Negative values in RD indicate the extent to which the PM decreased False − and False +

How does Perioproject help to understand the event of tooth loss due to periodontitis?

Understanding tooth loss in patients following periodontal maintenance has capitalised the attention of research on periodontal prognosis. As a matter of fact, it is the key issue in searching for answers.

All the research efforts have been performed utilising conventional logistic regression, accumulating relative risks and regression coefficients for predictors of tooth loss. These values have been subjectively interpreted and matched with words to construct prognostic indexes and risk assessment tools.

The statistical parameter R^2 is a goodness-of-fit parameter that also indicates the extent to which the variance in tooth loss can be explained. It could be interpreted to define how much we know about predictors of tooth loss, as it was discussed in our former publication (Martinez-Canut 2015). While a complete explanation of tooth loss would be $R^2 = 1$ (100%), research with conventional logistic regression has been able to reach a maximum of 0.3% (30%).

Perhaps it is not a question of trying harder with these more conventional approaches, but of introducing different alternatives. This would be the rationale for exploring the usefulness of prediction models.

The percentage of cases in which a certain probability of tooth loss coincides with a defined survival time would be very usefull; an objective, evidence-based criterion to decide whether to extract or maintain a compromised tooth. Let´s consider the following hypothetical scenario: an upper second molar with a p 090 could be lost in 10 to 20 years in 80% of the cases, according to the particular database of the prediction model. This would explain tooth loss to a higher extent than any R^2 value of conventional regression analysis. Going a step further, the issue would be exploring the reason why the remaining 20% of tooth loss is not explained. Our further research found some answers.

To our understanding, before searching for unsuspected, exotic or unknown additional prognostic factors outside the prediction model, a more precise definition should be made for the predictors included into the model. This is because we have relatively well-defined categories for each tooth-related factor but there is no enough data to differentiate categories for most patient-related factors. Tooth related factors are graded numerically (grade I, II and III furcation involvement, etc.) and the increase in the risk for each category is known. However, the relevant patient-related factors are subjective and qualitatively described. For instance: “this patient grindes their teeth a lot” or “is a heavy smoker”. These categories do not allow definition of possible differences between smoking two packs per day for 25 years or smoking one pack per day for 10 years. Regarding bruxism, it seems posible to grade the certainty with which bruxism is identified: Possible, probable and definite bruxism (Lobezzo et al. 2012) but we are still far from categorising its intensity and duration. In parallel, we are still discussing whether occlusal trauma associated with bruxism causes any deleterious effect on the periodontium.
From a perspective of the risk of developing periodontal disease, the whole predisposing, etiological and pathological factors represent a complex scenario. From the perspective of periodontal prognosis for patients under periodontal may not be so complex, since we know relatively well what predictors are involved. This is so as long as we do not try to understand this tooth loss by analysing it for reasons other than periodontal ones or erroneously equating risk with prognosis.

What is the actual usefulness of prediction models of tooth loss?

Although a prediction model does not feel, it certainly listens and talks. Furthermore, it is a master model that provides us with invaluable information and later on I will explain the most relevant lesson that Perioproject taught me.
Each tooth lost after years of periodontal maintenance contains valuable information on periodontal prognosis, according to the peculiarities of the tooth and the patient. This long story about predictors is well worth writing into a prediction model. By feeding the model with the most extensive and reliable data, the model might return some highly relevant information, as feedback. Thus, Perioproject is actually a master model.
The probability of tooth loss can be manipulated by including or excluding certain predictors, as well as modifying their categories. This enables definition of practical rules to understand and apply periodontal prognosis. For instance, it is possible to estimate the survival time of teeth presenting the intermediate category of tooth-related factors (bone loss 30-50%, mobility 2, etc.) depending on the participation of one, two or more patient-related factors. The progressive incorporation of predictors helps to understand what is actually observed in daily practice. For instance, the behavior of a long root (C/R 1/2) with bone loss > 50% in the absence of any patient-related factor; in the presence of smoking; in the presence of bruxism; or a short root (C/R 1/1) in the presence of bruxism and fewer baseline teeth. The latter situation plus fewer baseline teeth, etc.
The lowest threshold of probability of tooth loss was 0.008. No tooth with lower values was lost. This threshold corresponded to the presence of only one of the following tooth-related factors: grade III furcation involvement, bone loss >50%, mobility 2 and probing pocket depth > 6 mm, in the absence of bruxism and smoking. This threshold also corresponded to the presence of smoking and bruxism in the absence of any tooth-related factor. The interval 0.09 to 0.036 resulted

from the above described tooth-scenario of related factors but in the presence of smoking. This interval predicts that if tooth loss occurs, it would do so in between 12 and 22 years in 80% of cases. Rather than relying on extreme p values ensuring a good prognosis (p 0.001) or a hopeless one (p 0.999), it seems to be an exciting challenge to understand the meaning of the intermediate *p*. values, those formerly interpreted as questionable prognosis.
Utilising the retrospective approach with any tooth extracted for periodontal reasons, the accuracy of the model is assessed. This might help when assigning prognosis at baseline to a comparable tooth in a similar patient.
As other authors have suggested with respect to the assessment of risk (Lang et al. 2015), we could use a prediction model as a complimentary tool to improve our knowledge on periodontal disease, identify the actual impact of each predictor or estimate rates of survival expectancy according to the probability of tooth loss. The increase in knowledge acquired this way would allow us to formulate practical clinical guidelines to assign more accurate periodontal prognosis. Neither the assignation of survival times to periodontally compromised teeth nor the LTO index to assess the risk of tooth loss, are definitive tools. These tools represent a language to communicate and develop further research on periodontal prognosis.
As I mentioned earlier, I will now explain the most relevant lesson that Perioproject taught to me: periodontal prognosis is not an issue of accuracy but an issue of probability. I thought that conventional individual tooth prognosis was as inaccurate as a coin toss because it considered only one side of the coin: tooth-related factors. So I expected that if we were to include the other side, that is, patient-related factors determining overall prognosis, it might be possible to substantially increase the accuracy of periodontal prognosis. That is to say, increase the accuracy of the tooth loss prediction well above 50% or a chance occurrence.
But again, I was wrong. According to our further research, this accuracy could be 0% in some cases and close to 100% in others. It was an issue of mere probability: the probability of tooth loss that is associated with a survival time; the probability of tooth loss occurring; the probability of tooth loss occurring within the estimated survival time, and the probability of tooth loss occurring in accordance with the particular risk of tooth loss of the patient.
This is a fascinating lesson that I had the chance to learn with the use of a prediction model, together with the use of the LTO index (Long-term outcome) to assess the risk of the patient experiencing tooth loss. The integration of the LTO index and the tooth loss prediction assigned with Perioproject simultaneously made it possible to develop of the LTOP system to assign comprehensive periodontal prognosis.
The reader might like to take a look to the document that introduced this approach: “Integrating overall and individual tooth prognosis. The LTOP system”. This document summarises the textbook of the same title.

The limitations of Perioproject and a shared strength

Perioproject obviously presents certain relevant limitations. Fortunately, it is possible to overcome some of these constraints by integrating overall and individual tooth prognosis. This means interpreting the results of Perioproject from the perspective of the patient´s proclivity to lose their teeth (LTO index).

The sensitivity of the tooth loss prediction depends on the risk

Although the teeth lost matched the estimated survival time in close to 80% of cases, not all teeth assigned survival times were lost during the observational period. The percentage of teeth predicted to be lost that were still retained (False +) varied to a moderate extent, although some of these teeth were non-functional and/or presented extreme mobility. This finding is consistent with the characteristics of the prediction model, it being more appropriate for ascertaining that tooth loss will not occur (Tooth loss −) (higher specificity) but less appropriate for ascertaining that tooth loss will occur (Tooth loss +) (moderate sensitivity).

This is also in line with the actual event of tooth loss in periodontal patients, which can be defined according to the following two items of scientific evidence in patients following periodontal maintenance:

1. Close to 60% of patients following periodontal maintenance do not lose teeth and close to 30% lose very few teeth. Higher tooth loss rates are concentrated in a smaller percentage of patients (3% to 8.9%) as already mentioned. Therefore, research efforts to improve the accuracy of periodontal prognosis should focus on these patients, attempting to improve the sensitivity of the tooth loss prediction. Conversely, the specificity of the prediction that tooth loss will not occur has been shown to be high, especially in the remaining percentage of patients that will not experience tooth loss. Therefore, periodontal prognosis in terms of predicting tooth loss would actually be more accurate in the reduced percentage of patients losing more teeth and much more inaccurate in patients with a low risk. The key issue would be the baseline identification of both groups of patients.

2. Teeth with the same extent of periodontal involvement might be lost or retained depending on the risk of the patient experiencing tooth loss.

Thus, the risk of tooth loss of each periodontal patient seems to be the other side of the coin of the complex reality of tooth loss. Our research went a step further in focusing on the risk of tooth loss by developing a research study of predictors of long-term outcomes in patients following periodontal maintenance (Martinez-Canut, Llobell & Romero 2018). The main results enabled development of the Long-term Outcome Index (LTO index) to assess the risk of the patient experiencing worse long-term outcomes in terms of tooth loss. By doing so, the goal of identifying, at baseline, the group of patients that do not lose teeth (60%) and the group of patients with a higher risk of tooth loss (3% to 8.9%) was achieved.

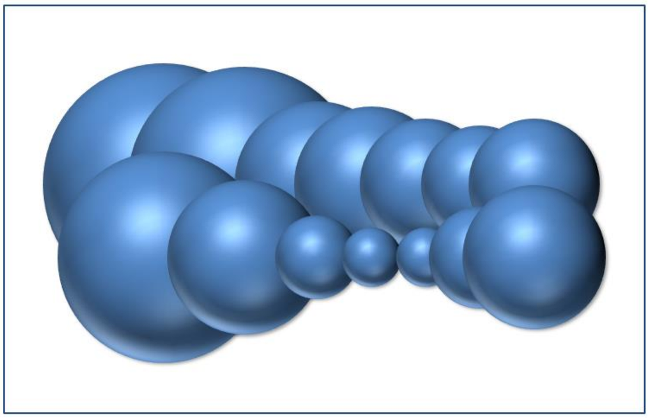
When the accuracy of the Perioproject prediction is interpreted considering the type of patient, according to the LTO index, the results demonstrate that the accuracy was much higher for patients with a higher risk of tooth loss (LTO index 4 and 5) in comparison with patients that are more resistant to losing their teeth (LTO index 0, 1 and 2).

Matching the estimated survival time depends on the root anatomy

At percentages of around 20%, the actual survival time of teeth lost did not fit within the estimated survival time. This represents an interesting observation that requires answers. This is the benefit of investigating with tangible, measurable data. Since we have defined survival times, it was possible to identify the teeth that did not match the estimated survival time, and search to find what characterises these teeth. By doing so, this limitation gave us the chance to gain a better understanding of individual tooth prognosis.

The results of this complementary research were quite interesting: crown-to-root ratio and more importantly root length were the prognostic factors that were most clearly associated with deviations of the expected survival time.
A long root would be responsible for a longer survival time even with the poorest categories of tooth-related factors (grade III furcation involvement, mobility III, etc.) while a short root and especially a short convergent root in second molars could justify the earlier loss of the tooth, especially in the presence of bruxism and smoking.
An additional finding was that the lack of an antagonist increased the assigned survival time.

This situation occurred most frequently in the lower first molars in the absence of upper molars and corresponds to the most common tooth loss pattern and sequence found in our sample. The teeth with the highest loss rates were the upper molars and the lower second molars. Once these teeth are lost and not replaced, the lower first molar can be retained even with extreme attachment loss. The loss of the upper premolars would be the following expected outcome. However, the survival time of these teeth would depend on the root length and the participation of bruxism. Lower premolars and lower canines are rarely lost or are the last teeth lost.



A more accurate individual tooth prognosis requires consideration of the percentage of loss of each tooth. The size of the spheres illustrates the actual percentage for each tooth and makes comparison easier. The accuracy of the tooth loss prediction for the upper molars and lower second molar would be much higher in comparison with the lower canines and premolars

The paucity of knowledge to categorise patient-related factors and the long span of the survival times

The long span of certain survival rates, some of 13 and 14 years, is a main limitation. It is acknowledged that shorter survival times would be desirable. This limitation might be partially attributed to the paucity of knowledge to categorise patient-related factors and the tooth loss sample size.
It has already been mentioned that we have relatively well-defined categories of tooth-related factors, while we have not been able to categorise patient-related factors (severity and duration of smoking and bruxism). Smoking and bruxism might have quite different impacts depending on the intensity and the length of the habits (Martinez-Canut 2015). The simultaneous impact of smoking and bruxism might be much more relevant than previously suspected (Martinez-Canut, Llobell & Romero 2017) but we do not know how to categorise this.

The need for a definitive validation of the model with other tooth loss samples

The prediction model was developed utilising a sample of 515 teeth lost in the original database (Martinez-Canut 2015). The tooth loss samples utilised to perform the multicentre study consisted of 369 teeth lost (129 of these teeth belonging to the original sample of 515 teeth lost). Therefore, a total sample of 755 teeth lost,

in patients following periodontal maintenance for a mean 20 years, was analysed in our research. However, despite this sample being relatively large, it is still too small for a more detailed analysis. The prevalence of teeth presenting the worst category of tooth-related factors is usually low. In parallel, differences depending on the type of tooth, which is a variable implemented in the model, seems to be relevant. Upper and lower second molars accumulated 54% of the total loss in our study, enabling a more precise distribution of the associations between probability of tooth loss and survival intervals. However, this was not possible for teeth with lower loss rates.

It is important to note that our model was developed by analysing a particular sample of patients and therefore further research with other populations and other independent clinicians is necessary for definitive validation. However, prospective long-term follow-ups to 20 years, as were performed retrospectively in the present study, do not seem feasible. Prospective medium-term studies at around 10 years could easily be performed, despite the lack of information on longer survival rates of 10 to 20 years.

The rather low variation interval between the samples gathered by different clinicians in our research may partially depend on its inclusion criteria; implying strict compliance with periodontal maintenance.

On the other hand, this model has been conceived as a dynamic tool that is capable of progressively incorporating additional and reliable data in order to overcome its current limitations. Thus, being realistic, it is not the intention of the authors to validate this tool with long-term prospective studies. This approach takes too long while the accuracy and usefulness of the model can be perfectly assessed in a retrospective manner, not by a single research team, but by any clinician with reliable long-term records.

References

Becker, W., Berg, L. & Becker, B.E. (1984) The long term evaluation of periodontal treatment and maintenance in 95 patients. *International Journal of Periodontics and Restorative Dentistry* **4**, 54-71

Chambrone, L., Chambrone, D., Lima, L.A. & Chambrone; L.A. (2010) Predictors of tooth loss during long-term periodontal maintenance: a systemic review of observational studies. *Journal of Clinical Periodontology* **37**, 675-684

Checchi, L., Montevecchi, M., Gatto, M.R.A. & Trombelli, L. (2002) Retrospective study of tooth loss in 92 treated periodontal patients. *Journal of Clinical Periodontology* **29**, 651-656

Cerrito, P. B. (2009) The problem of regression assumption and the use of predictive modeling. SAS Global Forum. Data mining and predictive modeling. Paper 106-2009

Dannewitz, B., Zeidler, A., Hüsing, J., Saure, D., Pfefferle, T., Eickholz, P. & Pretzl, B. (2016) Loss of molars in periodontally treated patients: results 10 years and more after active periodontal therapy. *Journal of Clinical periodontology* **43**, 53-62

Faggion, C.M. Jr., Petersilka, G., Lange, D.E., Gerss, J. & Fleming, T.F. (2007) Prognostic model for tooth survival in patients treated for periodontitis. *Journal of Clinical Periodontology* **34**, 226-231

Faggion, C.M. Jr., Chambrone, L. & Tu, Y-K. (2014) Quality of logistic regression reporting in studies of tooth survival after periodontal treatment. *Journal of Clinical Periodontology* **41**, 1184-1192

Fardal O., Johannessen, A.C. & Linden, G.J., (2004) Tooth loss during maintenance following periodontal practice in Norway. *Journal of Clinical Periodontology*, **31**, 550-555

Graetz, C., Dörfer, C.E., Kahl, T., El-Sayed, K., Wiebe, J.-F., Gomer, K. & Ruhling, A. (2011) Retention of questionable and hopeless teeth in compliant patients treated for aggressive periodontitis. *Journal of Clinical Periodontology* **38**, 707-714

Kwok, V. & Caton. J.G. (2007) Prognosis revisited: a system for assigning periodontal prognosis. *Journal of Periodontology* **78**, 2063-2071

Martinez-Canut, P. (2015) Predictors for tooth loss due to periodontal disease in patients following long-term periodontal maintenance. *Journal of Clinical Periodontology* (JCPE 12475)

Martinez-Canut, P., Llobell, A. & Romero, A. (2017) Predictors of long-term outcomes in patients undergoing periodontal maintenance. *Journal of Clinical Periodontology* **44**, 620-631

Martinez-Canut, P., Alcaraz, Jr., Alcaraz, J. Jr., Alvarez-Novoa, P., Alvarez-Novoa, C., Marcos, A., Noguerol, B., Noguerol, F. & Zabalegui, I. (1998) Introduction of a prediction model to assigning periodontal prognosis based on survival time. *Journal of Clinical periodontology* **45**, 46-55

Martinez-Canut & Llobell (2018) A comprehensive approach to assigning periodontal prognosis. *Journal of Clinical Periodontology* **45**, 431-439

McGuire, M.K. & Nunn, M.E. (1996) Prognosis versus actual outcome. III. The effectiveness of clinical parameters in accurately predicting tooth survival. *Journal of Periodontology* **67**, 666-674

Miller, P.D., McEntire, M.L., Marlow, N.M. & Gellin, R.G. (2014) An evidence based score system to determine periodontal prognosis on molars. *Journal of Periodontology* **2**, 214-225

Peduzzi, P., Concato, J., Kemper, E. Holford, T.R., Feistein, A.R. (1996) A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology* **49**, 1373-1379

Pepe, M.S., Janes, H., Logton, G., Leisenring, W., Newcomb, P. (2004) Limitations of the odds ratio in gauging the performance of a diagnosis, prognostic, or screening marker. *American Journal of Epidemiology* **159**, 882-890

Steyerberg, E.W., Vickers, A.J., Cook, N.R., Gerds, T., Gonen, M., Obuchowski, N., Pencina, M. & Kattam, M.W. (2010) Assessing the performance of a prediction model: a framework for some traditional and novel measures. *Epidemiology* **21**, 129-138

Steyerberg, E. W. & Vergouwe, Y. (2014) Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*; **35**, 1925-1931

Wynants, L., Bouwmeester, W., Moons, K.G., Moerbeek, M., Timmerman, D., Van Huffel, S., Van Calster, B., Vergouwe, Y. (2015) A simulation study of simple size demostrated the importance of the number of events per variable to develop prediction models in clustered data. *Journal of Clinical Epidemiology* Feb 14. pii: S0895-4356(15)00088-8. doi: 10.1016/j.jclinepi.2015.02.002. [Epub ahead of print]