The Periodontal Risk Score (PRS): Initiation and Model Validation for 6762 teeth.

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Abstract word count: 239
Total word count: 3122
Total number of tables and figures: 1 figure, 3 tables.
Supplemental Material: 2 supplementary tables and 2 supplementary figures
Number of references: 28
Key words (MeSH): [Attachment Loss, Periodontal; Periodontitis; risk factor assessment; tooth loss; validation study]
Running title: Initiation and validation of the Periodontal risk score (PRS).

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All authors gave their final approval and agreed to be accountable for all aspects of the work.
One sentence summary: The Modified-Miller-McEntire prognosis system display excellent predictive capability for tooth loss due to periodontitis.

Conflict of Interest and Source of Funding**:** The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

Data availability: The data that support the findings of this study are available from the corresponding author upon request.

ABSTRACT

Background: Tooth-level prognostic systems are valuable tools for treatment planning and risk assessment of periodontally involved teeth. Recently the Miller-McEntire prognosis index was found to outperform comparable systems. However, it had some limitations. The present study aimed to develop and evaluate the prognostic performance of a modified version that address most limitations of the previous model, called the periodontal Risk Score (PRS).

Methods: Data was retrieved retrospectively from patients who received surgical and non-surgical periodontal treatment at a university setting. Data on medical history and smoking status at baseline and the last maintenance visit were collected. Using both univariate and multivariate Cox proportional hazard regression models to analyze the prognostic capability for predicting tooth loss due to periodontitis (TLP) risk.

Results: A total of 6762 teeth (281 patients) were followed up for a mean period of 22.6 ± 6.34 (10-47.6y) years. The PRS was successfully able to stratify the risk of TLP at baseline when the 3 different classes of association were compared for anterior and/or posterior tooth loss. After controlling for maintenance, age, and gender, the index showed an excellent predictive capacity for TLP with a Harrell's C-index of 0.947.

Conclusion: The updated and simplified Miller-McEntire prognosis index (PRS) displayed excellent predictive capability for anterior as well as posterior tooth loss due to periodontitis. This system was retrospectively able to predict tooth-loss with a very high accuracy even in a population treated by dental students and periodontics residents.

1 | INTRODUCTION

Periodontal risk assessment and prognosis systems are valuable tools to gauge if periodontally compromised teeth are salvageable short- and long-term. When performed accurately, their inclusion helps to customize patient management, provide less invasive treatment plans, reduced long-term costs[1]. Contrary to diagnosis which conveys identifying disease status, risk assessment predicts the likelihood of disease progression. Risk assessment has the potential to adjust the traditional model of care (diagnosis > treatment > maintenance; regardless of the risk for future progression or developing new disease). Instead, a wellness model of care emphasizes prevention, weighing treatment benefit and guided reduction of risk factors in addition to treatment[2, 3].

Although numerous tools exist, there is no single universally accepted system or even set of criteria for periodontal prognosis [4]. As far as we know, only one study attempted to validate these systems prospectively[5], but recently, ten commonly used tooth-level prognostic systems were retrospectively validated and compared and terms of their predictive capacity for tooth loss[6]. All compared systems were able to effectively predict tooth loss. What is more, is that one specific tooth-prognosis system seemed to out-perform all other systems regardless of the nature of analyses, confounders or type of tooth-loss (periodontal versus overall tooth loss) considered[6]. That system was found to be the Miller McEntire Periodontal Prognostic Index (MMPPI) [7].

One main disadvantage of that index is the time required to execute the prognostication is more than most other systems. However, if the clinician thinks the extra time required is not worth the increased predictive value, it is strongly recommended that another system still be used. Currently, several universities like Michigan, Louisville, are using this system to determine the survival of specific teeth in more complex interdisciplinary treatment planning cases, whenever the decision of retaining a tooth is uncertain. This seems particularly useful since it gives a fairly accurate estimation of the 5-10, 10-20 and 20-30y survival. This is hence useful for getting the patient involved in the treatment plan for deciding which teeth can be retained. We are currently studying the possibility of adding the score to patient's EHR (electronic health records), where based on the info entered for each tooth, a PRS score is generated automatically, like what is currently achieved for clinical attachment loss (CAL).

Although showing promising results when internally and externally validated, this index had several limitations that needed to be addressed first before recommendations are made for using on a wide scale[6]. This index has undergone several modifications to accommodate the significance of

environmental factors.[8] In the modified version of the MMPPI, HbA_{1C} levels instead of binary (Diabetic/Non-Diabetic) records were required. Cigarette consumption was changed into never, former, current light, or current heavy smokers[9]. Finally, instead of 11 classes, the modified version, called the Periodontal Risk Score (PRS) has only 3 classes; (1= Excellent prognosis; 2= Good prognosis; and 3= Guarded Prognosis). Figure 1 shows the modified version of the MMPPI.

If such modified score was proven to be predictable, a prospective study to validate will be the next rationale step before investing in implementing in dental schools and private practices. Hence, the aim of this study was to introduce and validate a new modified version of the MMPPI (PRS) which resolves issues like applicability to front teeth, decreasing the number of classes and emphasizing the role of environmental and systemic factors. Validation of PRS will be in terms of its categorical predictive capability for the risk of periodontal tooth loss (TLP) and prediction of tooth survival over long-term follow-up and contrasting that to the original MMPPI.

2 | METHODS

This study was conducted in agreement with the Helsinki Declaration of 1975 (World Medical Association, 1975) as most recently revised in 2013 (World Medical Association, 2013). The study was also approved by the University of Michigan Medical School Institutional Review Board (IRBMED) (identifier number: HUM00157260). This observational study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines during the preparation of the manuscript. The TRIPOD statement (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) was also taken as a reference for validation of this model.[10]

2.1 | Study population

The present data was extracted from the electronic and paper charts for patients receiving periodontal treatment at the Periodontics and Oral Medicine department between January 1966 and January 2010 at the University of Michigan School of Dentistry, Ann Arbor, Michigan, USA. The complete data of 340 patients with 7924 teeth were included in the analysis.

2.2 | Patient selection criteria

- Patients who have had the active therapy for periodontitis (either surgically or non-surgically) at the University of Michigan School of Dentistry.
- Patients with follow up of 10 or more years (this cut-off point ensured that an effect from TLP could be demonstrated, given the slow pattern of progression of periodontitis)[11].
- Patients receiving at least one visit of supportive periodontal therapy (PMT)/year throughout the entire follow-up period (≥10 years). This was based on the evidence suggesting that patients attending less than 1 PMT visit/year will start losing more teeth regardless of the current severity of periodontitis or the nature treatment provided [12].
    - Complete periodontal charts with Probing Depth (PD), Bleeding on Probing (BOP), Recession (REC), and full-mouth radiographic series of diagnostic quality radiographs (taken ≤12 months from the baseline periodontal examination).
    - Complete medical history recorded at baseline examination.
    - If the reason for tooth extraction was not described in patient charts (in accordance with the University of Michigan School of Dentistry's policies) or could not be established with a high degree of confidence, the tooth was excluded.
    - If a smoker did not report the number of cigarettes/day or time since they started smoking, the whole case was excluded. Smoking in this cohort was self-reported.
    - Diabetic patients not reporting hemoglobin A1c (HbA1c) and/or plasma glucose levels at the baseline visits. If a patient only reported plasma glucose levels, their scores were converted to HbA_{1C} percentage using estimated average glucose levels (eAG) [13, 14].

2.3 | Data collection and patient classification

Records of the patients were screened and evaluated by two examiners (HD and MS). If patient data was acceptable for the pre-set inclusion criteria, all patient-level factors (age, gender, history of smoking, systemic conditions...etc.), as well as frequency of PMT (number of visits/year), were collected. Tooth- and site-level information such as PD, clinical attachment level (CAL), BOP, tooth mobility, furcation involvement, number of furcations involved[7], and keratinized tissue width (KTW) were collected from patient charts at T0 (time of active periodontal therapy) and T1 (last PMT visit). PD, CAL, and BOP were evaluated at six sites per tooth (mesio-, mid- and disto-buccal; mesio-, mid- and disto-lingual). Radiographic bone loss was calculated from either periapical or bitewing radiographs.

2.4 | Statistical analysis

The following variables were analyzed: age, gender, tooth identifier, position (anterior/posterior), jaw (maxilla/mandible), time from T0 to T1, tooth status at T1 (periodontal-related loss, loss for a non-periodontal cause, present), number of PMT visits from baseline to the last follow-up, tooth-level membership class.

Survival analyses were performed, after checking for the presence of proportional hazard assumption (estat phtest in STATA), for TLP using both univariate and multivariate Cox regression frailty models that were built for each classifier. In the multivariate model, the tooth classifier memberships were included with potential confounding factors (age, gender and number of maintenance visits underwent by the tooth during the whole follow-up). To analyze the prognostic performance, the modified PRS, overall performance (Harrell's C-index and Royston's index) and model fit (Akaike and Bayesian information criterion) were measured for each Cox regression model [15]. In addition, a post-hoc comparison was conducted using the Bonferroni test to evaluate intraclass stratification in both systems. Ratios of Restricted Mean Survival Time (RMST) in the univariate analysis, for the comparison with the reference class were also assessed.

3 | RESULTS

3.1 | Baseline sample characteristics and descriptive statistics

A total of 281 patients (132 females and 149 males; mean age of 47.58 ± 12.01 years old) accounting for 6762 teeth were included in the analysis. Excluded patients had missing information (mostly systemic conditions) at baseline that precluded usage of the PRS. At baseline, 3391 maxillary and 3371 mandibular teeth were present. Of these, 3784 teeth were located posteriorly (molar and premolar regions), and 2978 were located anteriorly. Characteristics of the patient cohort is reported in more detail in Table 1.

The follow-up ranged from 10-47.6 years, with the mean follow-up of teeth included in the analysis being 270.9 ± 76.08 months (22.6 ± 6.34).

3.2 | General prognostic performance of the original and simplified index

The two most frequent categories based on the MMPPI index were Score 1 (40.96%) and 2 (15.13%), respectively, and the least were Score 10 (0.15%) and 9 (0.38%), respectively. Similarly, for the PRS, the most frequent category was Score 1 (69.23%), followed by Scores 2 (25.72%) and 3 (5.06%), in

an ascending order. The original Miller & McEntire model comprising 11 classes of risk yielded a prognostic performance of Harrell's c-index equal to 0.7410 at the multilevel univariate Cox regression frailty model. On the other hand, the PRS including 3 risk classes yielded a prognostic performance of 0.7157. The prognostic performance of both predictive models still resulted in a significant result at the multivariate analysis when included in a Cox model with other covariates (namely, age, gender and maintenance visits). This yielded a prognostic performance of Harrel's c-index equal to 0.9469 for the PRS.

Regarding differentiation in prognostic capability between molar and molar teeth, the PRS showed a slightly better prognostic performance for non-molar (C-index = 0.6869) compared to molar teeth (0.6662) in the multilevel univariate analysis.

3.3 | Stratified prognostic performance of the original and modified index

For the 5-year follow up, using a logistic regression model, teeth lost for other reasons before the 5-year threshold have been excluded. An odds ratio of 5.75 ± 2.33 (95% CI: 2.59 – 12.74) for Class 2 and 20.68 ± 9.04 (95% CI: 8.77 – 48.73) for Class 3 for tooth loss compared to Class 1. The AUC (Area Under the Curve) of the ROC (Receiver-operating characteristics) showed a moderate accuracy of 0.76. AUC was calculated at the univariate analysis.

The PRS stratified teeth accurately into each of its 3 categories ($p<0.05$), while the MMPPI index did not (see Figure S1 in online Journal of Periodontology). The univariate analysis showed a hazard ratio (HR) of 3.48 ± 0.47 (95% CI: 2.67 - 4.53) for Class 2 and 13.09 ± 2.00 (95% CI: 9.70 - 17.68) for Class 3 in the PRS (Table 3). These remained statistically significant in the multivariate analysis with HRs of 3.66 ± 0.67 (95% CI: 2.55 - 5.25) and 10.93 ± 2.59 (95% CI: 6.87 - 17.40), respectively. Incisors and premolars had significantly less HR to be lost due to periodontitis compared to molar teeth (HR: 3.3 vs 10; P=0.000). Supplementary table 1 (see Table T1 in online Journal of Periodontology) shows risk stratification by tooth type.

The survival curves based on the multi-level multivariate Cox regression analysis are depicted in Supplementary Figure 2 (see Figure S2 in online Journal of Periodontology). Supplementary Figure 2 shows survival curves comparing MMPPI to the PRS; and molar versus non-molar and maxillary versus mandibular teeth, respectively (see Figure S2 in online Journal of Periodontology).

3.4 | Probability of tooth loss.

The PRS showed moderate Sensitivity (78.05%) and Specificity (69.60%). Sensitivity and specificity have been calculated at the univariate analysis. A total of 700 teeth (10.35%) were lost throughout the follow-up period; of these, 303 (4.48%) were TLP. Survival analysis of PRS in 5-year increments up to 30 years follow-up is shown in supplementary table 2(see Table T2 in online Journal of Periodontology).

4 | DISCUSSION

The present observational study validated a modified version of the Miller-McEntire prognosis system that was designed for only posterior teeth and lacked significance between categories when evaluating the prognostic performance.[6] Excellent prognostic performance was demonstrated by both the modified indices (c-index of 0.947), with prognostic assessment of non-molar teeth being superior to that of molar teeth by the modified index.

External validation utilizing a different patient cohort is a key component in demonstrating the applicability of any diagnostic or prognostic prediction model.[16] A recent investigation by our group compared through external validation the prognostic performance of 10 different prognostic systems.[6] In that study, the original Miller-McEntire demonstrated the best model fit after a univariate and multivariate analysis as it relates to prognostic performance with TLP as an endpoint. The external validation of this proposed, modified model uses a new and distinct patient cohort compared to the previous investigation. Due to overall tooth loss not being an accurate endpoint of specifically periodontal risk assessment[17-19] and significantly impairing all prognostic systems in our previous investigations,[6, 20] TLP was the single endpoint used in the analyses of this study.

Few of the previous concerns using the MMPPI were A) It was originally developed and validated for use only for posterior teeth[7]. B) When the original index was externally validated, it was noted that not all class severities showed statistically significant inter-class differences. This was attributed to the index having 11 classes, which made the number of teeth assigned to each class less considerably[6]. C) Another problem with such a big number of classes is that it makes its use clinically less practical and difficult to explain to the patient. D) Finally, few modifications were made to the MMPPI, like adding stipulations for the number of cigarettes smoked[21] and the level of diabetic control.

One aspect of prognostic performance that makes a prognostic system ideal is clear inter-category distinction.[22] As aforementioned, the MMPPI was among prognostic systems that showed a lack of significance between disease severity.[6] This was demonstrated once again in the current multi-level, multivariate analysis of the present investigation. In contrast, with only 3 classes, the PRS demonstrated significant differences between disease categories with an HR of 3.7 and 10.9 for class 2 and 3, respectively. This means that merging classes of severity with the goal of reducing the number of categories provides pragmatism to the overall index and lays out distinct groups that can be confidently expected to clinically behave differently over time. It is noteworthy that the standard errors and 95% confidence intervals of the MMPPI categories of severity are quite wide, and particularly in relation to those of the PRS. This is most likely a function of decreased number of statistical units per category, especially that this effect increases with ascending categories (e.g., n = 79 for Score 7, n = 32 for Score 8, n = 26 for Score 9, n = 10 for Score 10). This also indirectly contributes to the resultant ambiguous stratification between categories, which is counteracted by the PRS providing clearer inter-category distinction.

The PRS exhibited better prognostic performance for single-rooted versus multi-rooted teeth. Molar teeth have been historically documented to be more commonly lost as a result of periodontal disease.[19, 23-25] This is primarily attributed to the presence of furcation involvement which, in its moderately to severely advanced form, is an evidenced risk factor for tooth loss.[24, 26] In the PRS, single-rooted teeth are automatically assigned a score of 0 for two of the seven categories. This allows for single-rooted teeth to only acquire a greater score when other factors (e.g., smoking, diabetes, probing depth) are in more advanced stages, which is clinically when single-rooted teeth are most observed to be lost to periodontal disease.

The present investigation is characterized by some key merits. Firstly, the MMPPI is based on a tooth survival model which showed a 38% increase in the risk of tooth loss with each unit increase in the index[7] and it was confirmed as possibly the best predictive prognostic tool present[9]. Its strength comes from the weight of systemic factors in the overall prognostic assessment compared to other prognostic tools;[6] factors which are well-evidenced in influencing periodontal disease and specifically TLP.[9, 22, 27] This lays the fundamental clinical value of the succeeding, modified index. Secondly, while the MMPPI was developed to exclusively evaluate the prognosis of multi-rooted teeth, the modified index has demonstrated increased applicability in its successful use for single-rooted teeth as well. Thirdly, the data in this study are based on a large sample size that is associated with a nearly 23-year observational period. Prognostic tools are devised to provide an effective prediction method for both

clinicians and patients, and oftentimes patients are concerned with the expected timeline of their oral health and therapeutic outcomes.

This model showed a moderate Sensitivity (78.05%) and Specificity (69.60%). A very low Sensitivity has been the hallmark of tooth loss predictive models reported previously (ranging between 0-21%) [5, 28]. That said, the presented model also appears to have less specificity than other models that reach almost 100%. We presume that the higher Sensitivity attained in this study is due to considering periodontal tooth loss rather than overall tooth loss as an outcome[17]; and that the lower Specificity is due to the very long follow-up period of patient follow-up, meaning our exposures may have significantly changed over time (for instance smoking, systemic conditions, etc.), which also means a wider window for periodontal breakdown.

A long-term follow-up such as that demonstrated in this investigation provides greater confidence in the predictability of the index's quantitative prognostic assessment. Nonetheless, it may also be limitations to this study. The understanding of available evidence, clinical practice, and decision-making regarding extraction versus implant placement changes over years. Moreover, since we excluded any data from patients who were non-maintenance-compliant, and those who had a follow-up of ≤ 10 years, we may have inadvertently fell into selection bias. Finally, we used complete cases analysis to fulfill each category of the PRS prognostic system, which have led to exclusion of more patients.

A predictive model that is built on retrospective data like the one presented in this study should be validated prospectively. However, using periodontal tooth loss as an outcome in such case might be challenging. Periodontitis Progression can be defined in different ways, where tooth loss due to periodontitis (as compared to overall tooth loss) seems to be the most definitive. Such incident (periodontal tooth loss) happens over long years in maintained populations[11]. The authors of the longitudinal studies acknowledged that early on and chose CAL as a surrogate of periodontitis progression instead of periodontal tooth loss.

In the future, it will be ideal for this model to be validated prospectively by a different group of investigators as a continuation to the validation of our model development studies.

5 | CONCLUSION

The PRS have demonstrated better prognostic performance to the original MMPPI. It was also able to exhibit better prognostic performance for non-molar compared to molar teeth. The PRS more effectively and accurately stratified teeth into categories of severity, while being more pragmatic due to the reduced number of overall categories.

Tables and figures:

Table 1: Patient characteristics and patient-related parameters of the included sample.

Table 2: A logistic regression model performed for periodontal-related tooth loss over 5-year follow-up period.

Table 3: Univariate and multivariate risk stratification performed for periodontal-related tooth loss using multi-level Cox regression frailty models performed for the overall follow-up time.

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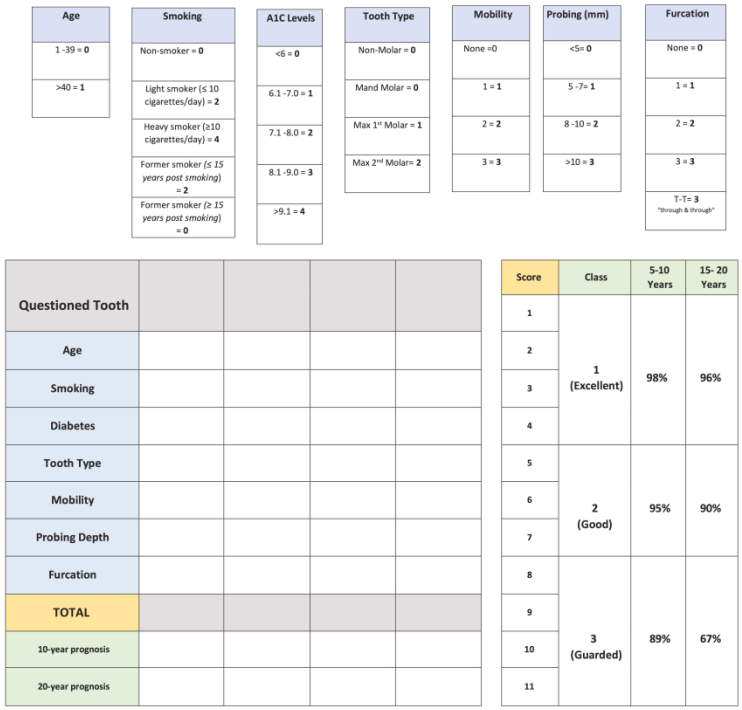

Figure 1: The PRS card with the updated classes and survival predictability.

Table 1: Patient characteristics and patient-related parameters of the included sample.

Characteristics		**Enrolled**
Sex		
Teeth in Female	n (%)	3478 (51.43%)
Teeth in Males	n (%)	3284 (48.57%)
Age	Years	47.58 ± 12.01
Follow-up	Months	270.9 ± 76.08
Total Teeth T0	n	6762

Mandibular Teeth T0	n (%)	3371 (49.85%)
Maxillary Teeth T0	n (%)	3391 (50.15%)
Posterior Teeth at T0	n (%)	3784 (55.96%)
Anterior Teeth at T0	n (%)	2978 (44.04%)
Status at the end of Follow-up		
Survived	n (%)	6062 (89.65%)
Lost for Periodontal Disease	n (%)	303 (5.87%)
Lost for Other Reasons	n (%)	397 (5.87%)

Table 2: A logistic regression model performed for periodontal-related tooth loss over 5-year follow-up period.

		OR 95%(CI)	***p-value***	**Coeff 95%(CI)**	***p-value***
A (Ref)	Excellent	1.00	-	1.00	-
B	Good	5.75 (2.59 - 12.74)	0.000	1.74 (0.95 - 2.54)	0.000
C	Guarded	20.68 (8.77 - 48.73)	0.000	3.02 (2.17 - 3.88)	0.000

Table 3: Univariate and multivariate risk stratification performed for periodontal-related tooth loss using multi-level Cox regression frailty models performed for the overall follow-up time.

Factors	**Multilevel Univariate**	**Multilevel Multivariate**
	HR (95% CI), p-value	**HR (95% CI), p-value**
Age	1.01 (0.99 - 1.03), 0.297	
Maintenance	0.82 (0.81- 0.84), (0.001)	0.83 (0.81- 0.85), (0.001)
Sex		
Male	Ref.	
Female	0.936 (0.58 -1.50), (0.783)	
Position		
Anterior	Ref.	Ref.
Posterior	2.51 (1-94 – 3.26), (0.001)	1.14 (0.76 – 1.71), 0.531
Jaws		
Mandibular	Ref.	Ref.
Maxillary	1.57 (1.24 – 1.98), (0.001)	0.79 (0.55 – 1.14) 0.207
Modified Score		
Excellent	Ref.	Ref.
Good	4.16 (3.06 – 5.69), (0.001)	3.65 (2.02 – 5.18), (0.001)
Guarded	17.54 (11.7 – 29.3), (0.001)	10.9 (3.85 – 15.9), (0.001)
Tooth Type		
Incisor	Ref.	Ref.
Canine	0.30 (0.16 – 0.55), (0.001)	0.42 (0.19 – 0.93), (0.032)
Premolar	0.99 (070 - 1.39), (0.955)	0.94 (0.65 – 1.47), (0.967)
Molar	2.99 (2.23 – 4.01), (0.001)	2.82 (1.66 – 4.78), (0.001)