Long term comparison of the Prognostic Performance of PerioRisk, Periodontal Risk Assessment, Periodontal Risk Calculator, and Staging and Grading systems.

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Summary: Periodontal risk assessment tools display a very good predictive capability of tooth loss due to periodontitis.

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Abstract

Background: Clinicians predominantly use personal judgment for risk assessment. Periodontal risk assessment tools (PRATs) provide an effective and logical system to stratify patients based on their individual treatment needs. This retrospective longitudinal study aimed to validate the association of different risk categories of four PRATs (Staging and grading; Periodontal Risk Assessment (PRA); Periodontal Risk Calculator (PRC); and PerioRisk) with periodontal related tooth loss (TLP), and to compare their prognostic performance.

Methods: Data on medical history, smoking status, and clinical periodontal parameters were retrieved from patients who received surgical and non-surgical periodontal treatment. A comparison of the rate of TLP and non-periodontal related tooth loss (TLO) within the risk tool classes were performed by means of Kruskal-Wallis test followed by post-hoc comparison with the Bonferroni test. Both univariate and multivariate Cox Proportional hazard regression models were built to analyze the prognostic significance for each single risk assessment tool class on TLP.

Results: A total of 167 patients with 4321 teeth followed up for a mean period of 26 years were assigned to four PRATs. PerioRisk class 5 had a hazard ratio of 18.43, Stage 4 had a hazard ratio of 7.99, and PRA class 3 had a hazard ratio of 6.13 compared to class/stage I. With respect to prognostic performance, PerioRisk tool demonstrated the best discrimination and model fit followed by PRA.

Conclusion: All PRATs displayed very good predictive capability of TLP. PerioRisk showed the best discrimination and model fit, followed by PRA.

Key words (MeSH): [Attachment Loss, Periodontal; Periodontitis; risk factor assessment; tooth loss; validation study]

Introduction

Nearly 60 years ago, a dominant line of reasoning was that since most adults suffer from periodontal disease, all individuals must be susceptible to it. [1] A later acknowledgment that not all gingivitis lesions progress to periodontitis; and that a small subset of the population is either susceptible to severe periodontitis or on the contrary, resistant to it, changed the mindset toward periodontitis. These newer notions raised plausible questions: 1) Which factors determined an individual's susceptibility to periodontitis? 2) Which determined resistance? A question even more pertinent would be whether a particular individual can be labelled as more susceptible to periodontitis? And how do we identify them?

Numerous longitudinal studies have identified several risk factors for the initiation and progression of periodontitis. [2] It has since been established that periodontitis is a complex multifactorial disease that is influenced by genetic and environmental risk factors, that are critically involved in the initiation and progression of periodontitis. [3] Since the factors correlated with disease progression were not necessarily "causative", the term "risk predictors" seems to be more appropriate when referring to these factors altogether. [4] Risk predictors can be divided into systemic [5], and local predictors. [6, 7] Both of these were found to alter the host response to pathogenic bacterial biofilm.

Persistent efforts were exerted to construct periodontal risk assessment tools (PRATs) for prediction of periodontal disease progression. Most noteworthy, Lang & Tonetti [5] suggested the need for a multilevel risk assessment for disease progression at both the patient and tooth levels. In 1998, Tonetti emphasized the need for a target diagram to handle the multifactorial risk of periodontitis. [8] Later, several tools and risk assessment systems were developed to assess patient-based risk levels for periodontitis progression. [9-15]

Lang and co-workers published a systematic review considering the predictive ability of PRATs and concluded that PRATs do predict periodontitis progression and tooth loss, and recommended that future research should evaluate their utility in risk assessment[16]. The primary objective of this study was to validate the association of different categories of four risk assessment models (Staging and grading; Periodontal Risk Assessment (PRA); Periodontal Risk Calculator (PRC); and PerioRisk) with TLP. A secondary objective was to compare the prognostic performance of these models.

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 approved by the University of Michigan Medical School Institutional Review Board (IRBMED) with the study identifier HUM00157260. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed during the preparation of the manuscript.

Study population

The current data was retrospectively retrieved from chart reviews of patients receiving periodontal treatment between January 1966 and January 2008 at the University of Michigan School of Dentistry, Ann Arbor, Michigan, USA.

Inclusion criteria:

- Patients meeting the case definition of periodontitis as defined by Tonetti et al. [17]

- Patients treated for periodontitis (at least a session of scaling and root planing (SRP)/diseased area with or without additional surgery if needed) and maintained for ≥10 years after active therapy at the University of Michigan School of Dentistry.
- Complete patient charts with clinical attachment level (CAL), Bleeding on Probing (BOP), and full mouth radiographic series of diagnostic quality radiographs (taken within ≤12 months from the baseline/initial periodontal examination).
- Complete medical history recorded at baseline periodontal examination.
- Patients receiving one or more visits of periodontal maintenance therapy (PMT)/year throughout the entire follow-up period.
- Patients whose teeth have been extracted at the University of Michigan School of Dentistry.
- Reason for extraction was identified in patient charts.

Data collection and patient classification

Records of patients that were eligible based on our predefined criteria were evaluated by three examiners (MQ, AR, and MS). All data on pertinent patient characteristics (age, gender, social and medical history...etc.) as well as PMT /year, were collected. The baseline visits at which all measurements were recorded was called T0, and last documented date of PMT visit was called T1.

Tooth-specific data on clinical parameters, such as periodontal probing depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), furcation involvement, presence of interproximal restorations or crowns, presence of apical pathology, endodontic root filling, endodontic post, and presence of vertical bone defects, were collected at T0 (baseline) and T1 (last PMT visit). Newer patients' electronic records had CAL calculated automatically. Older charts (prior to 2012) had CAL calculated manually as the difference between PPD and the distance from the free gingival margin (FGM) to the cemental-enamel junction (CEJ). Probing depths and clinical attachment levels were all evaluated at six sites per tooth. Information regarding masticatory dysfunction, drifting, flaring, bite collapse was also collected from patient records. Percentage of radiographic bone loss at T0 was measured from either periapical or bitewing radiographs[18]. Radiographic bone loss was measured as the distance from the CEJ to the most apical extension of the defect. In case of molar teeth, only the root with most radiographic bone loss was assessed.

Tooth loss (TL) data was stratified into tooth loss due to periodontal reasons (TLP) and overall tooth loss (OTL). OTL was calculated by deducting the number of natural teeth present at T1 from the number present at T0. A second level of OTL analysis included logging the date, cause of extraction, and calculating the time the tooth stayed in function till extraction. At this point another group was created, which were teeth extracted only due to periodontal reasons (TLP).

Diabetic control was reported either as A1c or plasma glucose levels. Typically, only patients in late 1980's onwards had HBA_{1C} reports, while those before that had plasma glucose levels (PGL) reported. Since all risk analysis tools evaluated require only HBA_{1C} results, those reporting PGL were converted to HBA_{1C} using an estimated average glucose level (eAG), which has been shown to work with accuracy. [19-21] The conversion process can be done manually, or more conveniently through the American Diabetes Association online conversion calculator.

Cigarette consumption was self-reported. Smokers were stratified into four groups: 1) never-smokers; 2) former smokers (ex-smokers); 3) light current smokers (who smoked <10 cigarettes/day); 4) Heavy current smokers (who smoked ≥10 cigarettes/day). Though, such differentiation was only applied where the risk analysis system allowed it. Otherwise, different smoker categories were grouped to fit every risk analysis tool as will be described in system-by-system patient allocation. Table 1 shows a description of the four tools utilized in comparison.

Patient allocation according to different risk-assessment tools.

Staging and grading systems [17]:

Before staging and grading were determined, the patient had to meet the case definition for periodontitis as defined by the 2017 World Workshop [17, 22]. Patients received a baseline diagnosis always by the same investigators (MS), (HD) after being calibrated by

one of the chief authors of the classification (HG). Recently published clarifications were used to help determine hopeless teeth as well as to elucidate certain cases that fell into a "gray zone" of staging or grading. [23, 24] Only current smokers were considered "smokers". Former smokers were grouped with non-smokers as the stage and grade system does not make such differentiation. Accordingly, patients were classified as each patient received either Stage I-IV or Grade A-C.

Periodontal Risk Assessment (PRA) [5].

The number of residual pockets ≥5mm and the number of lost teeth except third molars were calculated for each patient. As suggested in the tool's website, the percentage of bone loss/age was compared to the distance 1mm apical from the CEJ to the root apex to facilitate calculation. In case bitewing radiographs were used and bone loss was presumed to advance beyond what could be recorded from a bitewing radiograph, the case was excluded.

PRA measures the percentage of BOP as the number of sites with BOP out of a total score of 64, 128, or 192 sites based on whether the 2, 4, or 6 sites were probed. The total number of BOP sites/patient was calculated as such to fulfill this parameter. PRA also includes elements to gauge systemic factors that may affect patient's risk for disease progression. These were defined by the authors as Type I and Type II diabetes mellitus and interleukin-1 (IL-1) polymorphisms. As indicated by the authors, if known,

these were considered as an indicator of risk assessment. If not known or absent, they were not taken into account for the overall evaluation of risk[5].

Cigarette smoking was categorized into former smokers if smoking cessation was 5 years or more before baseline. Occasional smoker was allocated for patients smoking up to 10 cigarettes per day; smokers/moderate smokers for those smoking up to 20 cigarettes per day; and heavy smoker if more than 20 cigarettes were smoked per day. A risk analysis was run based on the given data. A risk of either low, moderate, or high was assigned to the case based on the logged patient data.

Periodontal Risk Calculator (PRC) [14]

The PRC includes several variables unique to it like presence of calculus, presence of subgingival restorations...etc. (Table 1). Cigarette consumption was recorded as never smoker, current smoker, or former (quit) smoker. For current and former smokers, the duration of smoking in years and the number of cigarettes smoked per day were also considered. In some cases, the data available for former smokers did not include the number of years they were actively smoking before finally quitting. For those patients, the worse possibility was recorded (logged as quit less than 10 years vs quitting more than 10 years ago). PRC had 2 categories, the first calculates the severity of the disease "Gum Disease Score", akin to the stage of disease in the current classification system [17] . The PRC Gum Disease Score (PRC-DS) is comprised of five categories (1=Healthy, 2=Gingivitis, 3=Mild gum disease, 4= Moderate gum disease, 5=Severe gum disease).

The second category of PRC is "Gum Disease Risk Score" (PRC-RS). This describes the likelihood of disease progression, akin to the grading system in the new classification. It also is made up of five categories (1=very low risk, 2=low risk, 3=moderate risk, 4=high risk, 5=very high risk).

PerioRisk (UniFe)[15]*.*

This system, also known as the University of Ferrara (UniFe) risk assessment tool [15] is based on 5 criteria. Each criterion is allocated a score, and a sum of the scores is then calculated and relates to a patient risk score from 1-5 (lowest to highest risk). A simplified version of the PerioRisk known as SmartRisk, was introduced recently, where the score generated from the number of cigarettes per day was combined with the number of sites with PD ≥ 5 mm [25]. The current analysis used the original, more comprehensive version, the PerioRisk. This system also differentiated between never smokers, former smokers, light (1-9 cigarettes/day), regular (10-19 cigarettes/day), and heavy (≥20 cigarettes/day) smokers. The score was then calculated for a 5-level risk score from 1-24 as follows: 1: low risk (score= 1-2); 2: Low-medium risk (score= 3-5); 3: Medium risk (score= 6-8); 4: Medium-high risk (score= 9-14); 5: High risk (score=15-24).

Statistical analysis

Aiming to perform survival analysis the following information was extracted for each patient/tooth: number of teeth at baseline, time occurring from baseline to

tooth-loss, reason for tooth-extraction (TLP versus OTL), time occurring from baseline to patient' last follow-up, number of teeth remaining at last follow-up. Patients were included only when the data extracted gave information of the teeth present at baseline and the time and identifier of the specific teeth lost during the follow-up. Such comparison was performed by means of Kruskal-Wallis test followed by a post-hoc comparison with the Bonferroni test.

Both univariate and multivariate Cox Proportional hazard regression models were built to analyze the prognostic significance for each risk assessment tool class on TLP. Multivariate analysis was performed to take into account the confounding effects of demographic variables (age and gender) and the number of maintenance sessions received by the tooth during the follow-up. At that point, both univariate and multivariate Cox regression models were built to analyze the prognostic significance for each single risk assessment tool class on TLP. Multivariate analysis was performed in order to take into account the confounding effects of demographic variables and the number of maintenance sessions received by the tooth during the follow-up. Subsequently, aiming to keep the hierarchical structure of data with clustering of teeth within patient both univariate and multivariate multilevel Cox regression frailty models were built.

Assessing the predictive performance of the different tools analyzed two measures of model fit, including: Akaike's information criterion (AIC) and Bayesian information criterion (BiC), and prognostic discrimination performance, such as:

Harrell's C-index and Royston's index, for each analyzed model. The higher the Harrell's C-index and Royston's index and the lower the AIC and the BIC, the better the prognostic performance of the periodontal PRATs. In order to assess the intraclass stratification within the PRATs, a post-hoc comparison with Bonferroni test after the multilevel multivariate Cox regression analysis was performed. Visual inspection of survival curves was also performed.

Results

Cohort characteristics and patient allocation

A total of 167 patients with 4321 teeth were included in this study. The mean follow-up for the cohort was 26.1 years, with a follow-up range of 10-48 years. For demographic data of the studied populations see Table S1 in online Journal of Periodontology. All the patients were assigned to specific categories according to the different PRATs. Figure 1 shows a frequency chart depicting the occurrence of each categorical class for the 6 compared PRATs.

Risk Stratification of the different PRATs

Risk stratification analysis was performed using both single-level (see Table S2 in online Journal of Periodontology) and multilevel models (Table 2) in the univariate and multivariate analysis. Results of the post-hoc comparison with Bonferroni test are shown in Table S3 in the online Journal of Periodontology. Results of the different models were very similar; however, the multilevel multivariate analysis adjusting for

confounding factors (Table 2) and associated survival curves (Figure 2) were used as final reference for the evaluation of the risk stratification model.

For the PerioRisk model, the hazard ratio increased in the different risk class categories (Table 2), however no statistically significant differences were detected in the comparison of class 1 and class 2 (Bonferroni p-value = 0.70) and between class 3 and class 4 (Bonferroni p-value = 1.00) (Table S3 in the online Journal of Periodontology). Class 5 of the PerioRisk model showed a very high hazard ratio of 18.43 compared to class 1 (Table 2) which is also displayed by the net separation on the resulting survival curve (Figure 2A).

The risk of TLP also showed an increasing trend in the different classes of the PRA tool, with significant differences in the direct comparison among the three different categories (Table 2, Table S3 in the online Journal of Periodontology and Figure 2B). The PRC-RS was less accurate in the prognostic prediction, as shown by the absence of statistically significant differences among the different categories and the absence of a clear separation of survival curves (Table 2, Figure 2C and Table S3). The 2-3-4 PRC-DS categories showed increased hazard ratio compared to the risk class 1 (Table 2), however no significant differences were detected within the classes 2, 3 and 4 (Figure 2D and Table S3 in the online Journal of Periodontology).

A prognostic trend in the risk stratification was noted for the Stage (Table 2 and Figure 2D), however the post-hoc multiple comparison detected an absence of significant differences between Stage 1 and Stage 2 (Bonferroni p-value = 0.618) and between Stage 2 and Stage 3 (Bonferroni p-value = 0.165) (Table S3 in the online Journal of Periodontology). Focusing on the Grade system, although a clear trend was present for Grade C, no differences were detected between Grade A and Grade B (Bonferroni p-value = 0.292) (Figure 2E and Table S3 in the online Journal of Periodontology).

Comparison of the model performance

Indicators of discrimination and model fit were evaluated for the assessment and comparison in the prognostic performance of the different PRATs. As shown in Table 3, the PerioRisk tool showed the best performance of both discrimination (Harrell's C

= 0.687 and Royston's D = 1.209) and model fit (AIC = 3127 and BIC = 3159). The PRA ranked the second in terms of model performance showing good values of discrimination (Harrell's C = 0.670 and Royston's D = 1.39) and model fit (AIC = 3137 and BIC = 3166). The other four predictors showed a weaker performance compared to the PerioRisk and the PRA.

Discussion

The present study consisted of 167 patients, all stratified according to four well known, frequently used, longitudinally or retrospectively validated PRAT systems (a list of studies validating each system is demonstrated in Table 4). Results showed that different risk categories of PRATs were associated with different risk classes. Most significantly, multivariate analysis found that PerioRisk class 5 had a hazard ratio of 18.43 compared to class 1. PRA also showed significant differences between its three different categories, with a class 3 risk having a hazard ratio of 6.13 compared to class1. Similarly, stage 4 had 7.99 hazard ratio compared to stage 1; grade C had 4.97 hazard ratio compared to Grade A; and PAT-DS class 5 had 4.51 hazard ratio compared to class 1. The frequency occurrence of each group category can be appreciated in Figure 1. Multiple studies showed low levels of inter-model categorical agreement when comparing class hierarchy from different PRATs. [33-35] The frequency occurrence of each group category can be appreciated in Figure 1.

These results seem remarkable, but they are far from being perfect. Despite the statistically significant difference between highest and lowest classes in each model in terms of TLP, differences were not always linearly consistent between consecutive classes and the other. For example, for PerioRisk, no significant differences were found between class 1 and 2 and the same was found between class 3 and 4. Likewise, for PRC-DS, no statistically significant differences were detected between the classes 2, 3 and 4, similar findings were encountered for the stage and grade as well. It might be hypothesized that this result might be simply due to the lack of adequate sample size per each class. But this may as well highlight the importance of simplifying the PRATs available by combining some of the classes together. For instance, combining class 1 with 2, and 3 with 4 in PerioRisk. Another way to look at these results is to

reconsider some of the clinical parameters at both ends of contiguous classes and redefining it based on longitudinal studies and reviews defining risk factors which have the most significance [36].

Another outcome evaluated was comparison of the overall prognostic performance of the four models (Table 3). Although all four models had remarkably similar results, not all PRATs had the same predictive capability, in the present cohort. Again, the PerioRisk tool showed the best performance in terms of discrimination and model fit. The PRA came second in terms of discrimination and model fit. By a narrow margin, the other four predictors showed weaker performance compared to both PerioRisk and the PRA. Few studies showed that PRA and/or PRC risk scores were not associated with tooth loss during PMT, and that PRA Risk level failed to predict PMT outcomes in terms of tooth loss as well [37, 38]

In this context, previous analyses that have been performed based on OTL might have obtained rather misleading results. Main suspected criteria for tooth loss (severity of bone loss, smoking, and compliance) have been found to be inconsistent and non-mutually incident with OTL. [36, 39-42] That basically means that such crucial criteria don't always seem to affect OTL, and if one happens to take an effect, the other criterion does not. [43] This masking effect should be obvious when we consider the fact that OTL includes TLP plus 35%-80% TL due to other reasons (i.e., caries, endodontic failure, fractures and strategic extractions). [39, 44, 45] More relevant to the present viewpoint, Ravidà et al., have shown in a long term follow-up study that PRATs (both the stage and grade systems) are indeed prognostic for TLP, but not OTL. [32]

Generally, PRATs use either baseline or post-treatment parameters to predict risk for tooth loss. Using PRATs at the initial visit allows clinicians to identify individuals with a high risk of disease progression before initiating treatment, thus helping with treatment planning. While the case for using PRATs following treatment proposes that treatment improves the periodontal condition and, in such a way, improves the case prognosis. Extracting teeth with poor/hopeless prognosis at baseline may limit our understanding of patient's potential to respond to anti-infective treatment. It also masks the influence of history of TLP on case prognosis. [17] Finally,

it may affect the accuracy of PRATs that use parameters like bleeding on probing which tends to fluctuate considerably following initial therapy. [46] This study evaded this dilemma by applying PRATs to our patient cohort at baseline, but only assessing teeth that were lost during PMT rather than active periodontal therapy. However, the compared PRATs do not have a homogenous design. Some recommend using pre- and the other recommend post-treatment assessment. Using baseline data for the cohort may have been fairer to PRC and staging and grading systems. Interestingly, both systems had slightly less favorable results compared to PRA and PerioRisk, presuming that PerioRisk and PRA might have even more favorable results if we used post-treatment parameters. Until now, none of the existing PRATs has been consistently validated for application at both phases.

Another limitation of this analysis is that the Stage, not the Grade component of the new classification is supposed to predict tooth loss. However, the authors of this system advocated that Stage and Grade were developed to work mutually, not as independent PRATs [17]. The same is the case for PRC-DS and PRC-RS, which are supposed to be used simultaneously but were considered as independent PRATs in our analysis. This might be one of the reasons that PRC and the Stage and Grade had less favorable results compared to PerioRisk and PRA.

The results showed remarkable similarities between different PRATs, but also showed the inconsistencies within each PRAT classes. It also demonstrated that their predictive capabilities were not ideal, which calls for some refinements of these tools. Maybe criteria other than clinical measurements are needed to improve the PRATs. Current evidence implies that certain salivary biomarkers may add value in the assessment of periodontal therapy. Clinical utility of these and other biomarkers may improve the objective assessments of susceptibility to, or severity of, periodontitis. [47] Lastly, PRATs that performed best in this analysis considered former smokers as higher risk than non-smokers. This has been consistently shown to be true in multiple studies.[48, 49]

Many periodontists tend to gauge periodontal risk based on subjective assessment. This technique seems to dominate clinical practice in spite of the availability of PRATs.[50, 51] Regardless of the clinicians level of experience,

subjective risk assessment could result in incorrect category assignment compared to objective risk assessment tools.[52] Ideally, after risk assessment, PRATs should provide customized recommendations for each individual in terms of further means needed to contain that risk (like extra PMT visits or antimicrobial therapy). However, only PRA provides such customized recommendations for the number of PMT/year based on the risk level. However, the accuracy of such recommendations is yet to be verified.[38]

Risk scores should be used to educate the patients regarding their disease condition and possible progression. A "one size fits all" approach for active and maintenance therapy will rarely meet individual needs of every patient. This would result in under-treatment for some and over-treatment for others, in addition to wasted resources of both the patient and the clinician.[50, 53]

Conclusion

All PRATs displayed very good predictive capability for TLP. PerioRisk showed the best discrimination and model fit, followed by PRA. Association between TLP and PRATs was significant when the highest and the lowest classes were compared. They were not consistent however between successive classes.

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Tables and figures:

Table 1: Comparison of the parameters used in each of the four main categories of periodontal risk assessment tools.

Study	Name	Availability	Timing of usage	Description	Parameters implemented	Scoring system
(Page et al. 2002)[14]	Periodontal Risk Calculator **(PRC)/** The Periodontal Assessment Tool **(PAT)**	Free web service (https://secure.previser.com/clinical/login)	Pretreatment	The Oral Health Information Suite® (OHIS®) is an information system that analyses oral health condition and risk. It has been patented by Previser® Inc. (Mount Vernon, WA, USA). The	Age Smoking history Diabetes, Pocket depth Number of teeth Furcation involvements History of periodontal surgery Whether oral hygiene needs	**Risk Score:** 1- Very Low Risk 2- Low Risk 3- Moderate Risk 4- High Risk 5- Very High Risk

				Periodontal Assessment Tool (PAT®) is a modification of a periodontal risk calculator (PRC). previously developed by the same authors.	improvement Whether SRP[1] is done Compliance to maintenance. Subgingival restorations Root calculus Radiographic bone height Vertical bone lesions BOP[2]	**Disease Score:** 1- Healthy 2- Gingivitis 3- Mild Gum disease 4- Moderate Gum disease 5- Severe Gum disease
(Lang and Tonetti 2003)[12]	Periodontal Risk Assessment Model **(PRA)**	Free web service (https://www.perio-tools.com/pra/en/)	Post-treatment	A web-based free service that models a spider web diagram based upon combination	Bone loss/age Cigarette smoking Number of pockets ≥ 5 mm	**Risk Score:** 1- Low Risk 2- Medium

[1] SRP = Scaling & root planning

[2] BOP = Bleeding on Probing

				of various risk predictors that might affect patients' susceptibility to periodontitis.	Number of missing teeth Percentage of sites with BOP Systemic factors (such as diabetes and Il-1 gene polymorphism)	Risk 3- High Risk
(Trombelli et al. 2009)[15]	**(PerioRisk)** or University of Ferrara **(UniFe)**	Manually calculated	Post-treatment	A simplified method for risk assessment based upon various parameters which are allocated according to specific criteria. The sum of the parameter scores is calculated and relates to a risk score.	Bone loss/age Smoking status Diabetes Number of sites with probing depth ≥5 mm Percentage of sites with BOP	**Risk Score:** 1- Low Risk 2- Low-Medium Risk 3- Medium Risk 4- Medium-High Risk 5- High Risk

(Tonetti et al. 2018)[17]	**World workshop 2017** Periodontal disease classification	Readily evaluated	Pretreatment	A new classification for periodontal disease aimed to serve clinical practice and academic premises based on a staging and grading models. **Stages** are simple description of the severity/complexity of an individual case. **Grades** captures the risk of	**Staging Main parameters:** CAL[3] RBL[4] TLP[5] <u>Staging Complexity factors:</u> Sites with PD ≥6 mm[6] Vertical bone loss ≥3mm Class 2 or 3 Furcation involvement Ridge defects Masticatory dysfunction Number of teeth remaining	**Staging**: Stage 1- No risk of TLP Stage 2- No risk of TLP Stage 3- Risk of Tooth (teeth) Loss Stage 4- Risk of Dentition (or Arch) Loss

[3] CAL = Clinical attachment loss

[4] RBL = Radiographic bone loss

[5] TLP = Periodontal tooth loss

[6]PD = Probing depth

disease progression.	Bite collapse, drifting/flaring

Grading Main parameters:	**Grading:**
Monitored progression via CAL or RBL	Grade A- Slow risk of progression
Radiographic bone loss/age	Grade B- Moderate risk of progression
Case phenotype	
<u>Grading Complexity factors:</u>	Grade C- Rapid risk of progression
Smoking status	
Diabetes	

Table 2: Univariate and multivariate risk stratification performed for periodontal-related teeth loss using multi-level cox regression frailty models.

Variables		Multilevel Univariate Analysis		Multilevel Multivariate Analysis	
		HR 95%(CI)	***p-value***	**HR 95%(CI)**	***p-value***
PRA PerioRisk	1 (Ref)	1.00	-	1.00	-
	2	1.70 (0.57-5.06)	0.337	2.05 (0.70-6.05)	0.192
	3	5.52 (1.95-15.66)	0.001*	5.87 (2.09-16.47)	0.001*
	4	5.22 (1.79-15.19)	0.002*	5.90 (2.05-16.97)	0.001*
	5	16.84 (5.02-56.51)	0.000*	18.43 (5.51-61.64)	0.000*
	1 (Ref)	1.00	-	1.00	-
	2	2.29 (1.03-5.12)	0.043*	2.35 (1.06-5.18)	0.034*
	3	6.54 (2.80-15.3)	0.000*	6.13 (2.67-	0.000*

				14.09)	
W2017 Stage	1 (Ref)	1.00	-	1.00	-
	2	1.46 (0.18-11.66)	0.718	1.32 (0.18-10.1)	0.784
	3	1.28 (0.17-9.59)	0.812	1.08 (0.15-7.84)	0.935
	4	1.92 (0.26-14.24)	0.521	1.98 (0.48-8.14)	0.479
	5	4.36 (0.60-31.93)	0.147	4.51 (0.64-31.96)	0.131
PRC-DS	1 (Ref)	1.00	-	1.00	-
	2	2.28 (1.03-5.04)	0.041*	2.29 (1.06-4.94)	0.034*
	3	3.07 (1.54-6.15)	0.002*	3.22 (1.64-6.32)	0.001*
	4	3.73 (1.92-7.23)	0.000*	3.51 (1.84-6.69)	0.000*
PRC-RS	1 (Ref)	1.00	-	1.00	-
	2	1.94 (0.63-6.02)	0.250	2.00 (0.66-6.05)	0.217
	3	2.72 (0.92-8.03)	0.070	2.95 (1.02-8.51)	0.045*
	4	7.95 (2.36-26.74)	0.001*	7.99 (2.46-26.06)	0.001*

	A (Ref)	1.00	-	1.00	-
Grade	B	1.51 (0.61-3.74)	0.371	1.73 (0.70-4.28)	0.232
	C	3.84 (1.44-10.22)	0.007*	4.97 (1.81-13.60)	0.002*

W2017

Table 3: Comparison of model risk stratification performance using measurements of model fit (Akaike's information criterion and Bayesian information criterion); and prognostic discrimination (Harrell's C-index and Royston's index). The higher Harrell's C-index and Royston's index and the lower the AIC and the BIC, the better the prognostic performance of the periodontal PRATs analyzed.

PRAT	Multilevel Univariate Cox Regression Frailty models				Multilevel Multivariate Cox Regression Frailty models			
	Harrell's c-index	Royston's D-index	Akaike's Information Criterion	Bayesian Information Criterion	Harrell's c-index	Royston's D-index	Akaike's Information Criterion	Bayesian Information Criterion
PerioRisk	0.671	1.259	3129	3154	0.687	1.209	3127	3159
PRA	0.655	1.149	3138	3151	0.670	1.039	3137	3156

PRC-RS	0.624	0.819	3150	3176	0.648	0.990	3144	3176
PRC-DS	0.636	1.024	3145	3164	0.653	0.986	3141	3167
W2017 Stage	0.623	0.859	3147	3166	0.653	0.923	3143	3169
W2017 Grade	0.620	0.812	3149	3162	0.656	0.878	3144	3163

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Table 4: A list of studies validating each of the four compared PRATs accompanied with the main findings of the validation study.

Name	System validation
Periodontal Risk Calculator **(PRC)**	**(Page et al. 2002; Page et al. 2003)** [14, 26]: Risk scores is associated with tooth loss and/or bone loss in a non-treated patient population. **(Martin et al. 2010)**[27] (maintained patient population): Risk scores were associated with higher tooth loss rate.
Periodontal Risk Assessment Model **(PRA)**	**(Costa et al. 2021; Eickholz et al 2008; Matuliene et al. 2010; Leininger et al. 2010)**[28-31] Risk level significantly predicted outcomes in terms of tooth loss and/or periodontitis progression in maintained patients.
(PerioRisk) or University of Ferrara (**UniFe**)	**(Trombelli et al. 2009)** [25]**:** Risk scores were associated with tooth loss. **(Trombelli et al. 2017)**[25]**:** Risk scores were associated with tooth loss in maintained patients.
World workshop 2017 Periodontal disease classification	**(Ravidà et al. 2020)**[32]**:** Both Stage ang Grade were associated with periodontal tooth loss in maintained patients.

Figure 1: A frequency chart portraying the frequency of occurrence of each categorical class for the 6 compared PRATs in the same cohort.

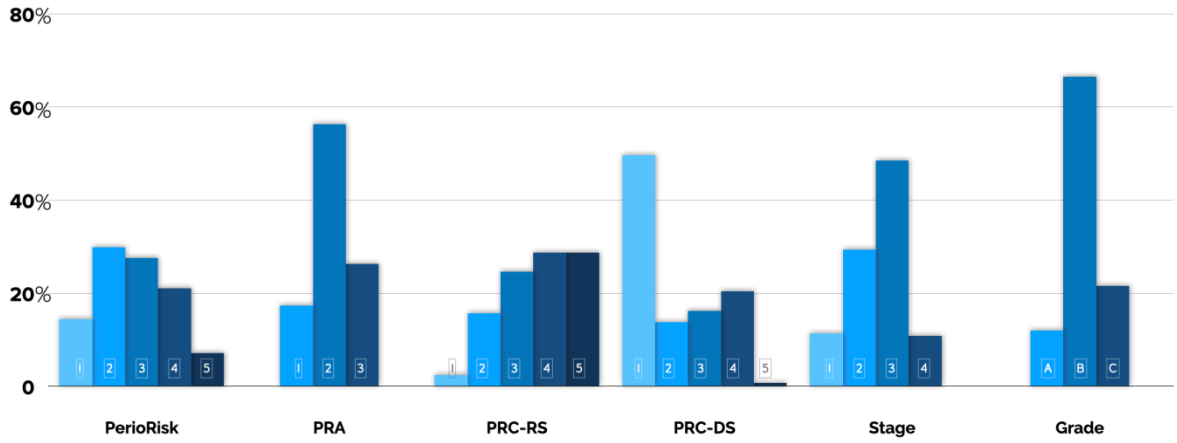
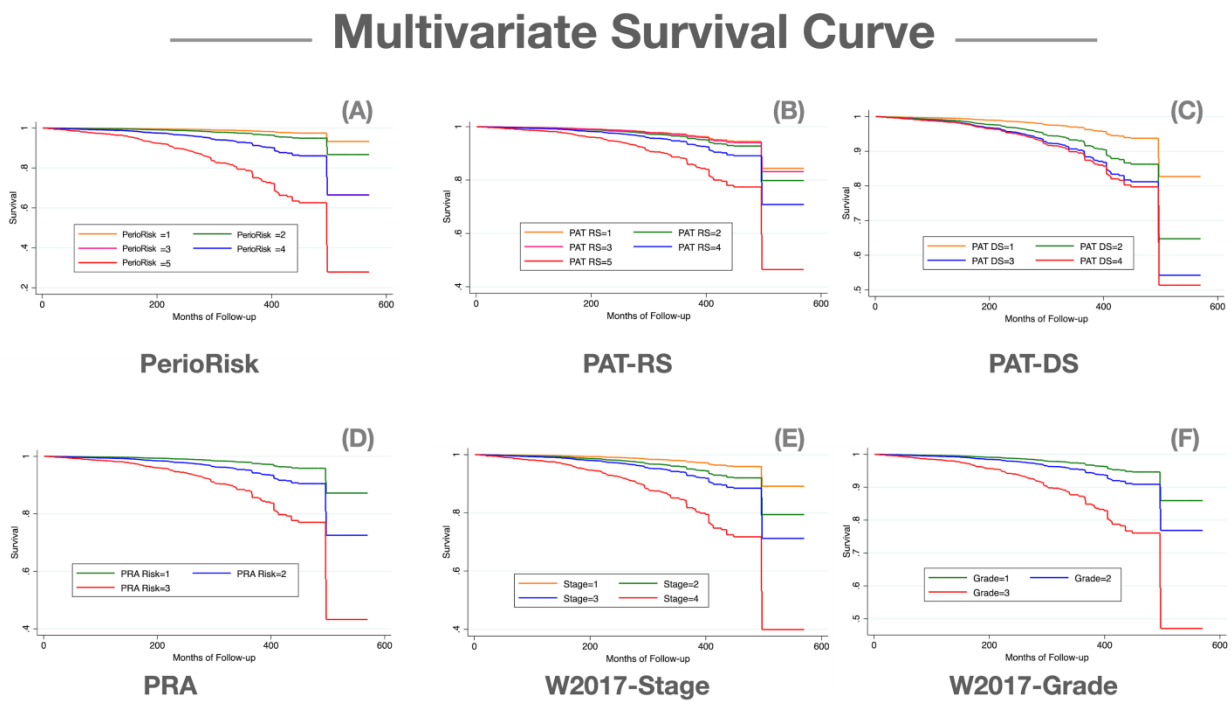


Figure 2: Survival curves built on multilevel multivariate Cox Regression analysis adjusting for confounding factors such as: Age, Gender and number of maintenance visits.



Supplementary Tables and figures:

Supplementary Figure 1: Survival curves based on the multilevel univariate Cox Regression analysis.

Supplementary Table 1: Demographics and characteristics of patients included in the cohort.

Supplementary Table 2: Univariate and multivariate risk stratification performed using single-level Cox Regression Models.

Supplementary Table 3: Assessing the intraclass stratification in PRATs using Bonferroni multiple comparison test after the multilevel multivariate Cox regression analysis was performed.

Supplementary Table 4: A list of studies validating each of the four compared PRATs accompanied with the main findings of the validation study.