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The influence of the interaction between staging, grading and extent on tooth loss due to periodontitis

Andrea Ravidà[1] | Musa Qazi[1] | Maria V. Rodriguez[1] | Matthew Galli[1] | Muhammad H. A. Saleh[2] | Giuseppe Troiano[3] | Hom-Lay Wang[1]

[1]Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA

[2]Department of Periodontics, University of Louisville School of Dentistry, Louisville, KY, USA

[3]Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy

Correspondence
Hom-Lay Wang, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, 1011 North University Avenue, Ann Arbor, MI 48109-1078, USA.
Email: homlay@umich.edu

Funding information
University of Michigan

Abstract

Aim: To assess the ability of two-way interactions between baseline stage, grade and extent to predict tooth loss due to periodontitis (TLP) over a long-term follow-up period.

Materials and Methods: Patients treated for periodontal disease with a complete medical history, baseline periodontal chart, full mouth radiographs and a minimum of ≥10 years follow-up were recruited. Supportive periodontal therapy (SPT) visits were recorded during the entire follow-up period. Patients were categorized according to their stage, grade and extent. The absolute survival at 10-, 20-, and 30-year follow-up was calculated for TLP. Kaplan–Meier survival curves were plotted at the tooth-level and multilevel Cox regression frailty models were constructed in order to assess the association among predictive variables and TLP by taking into account the hierarchical patient-teeth structure.

Results: 442 patients (11,125 teeth) with a mean follow-up of 23 years met the inclusion criteria and were included in this study. The most prevalent diagnosis at baseline was stage III grade B (30.3%), followed by stage II grade B (23.5%). Among the parameters analysed, stage and grade were found to be the best predictors of TLP. Statistically significant differences were observed for extent only in patients with severe disease (stage IV or grade C). The multilevel Cox regression analysis demonstrated that patients with higher concomitant baseline staging and grading developed greater TLP over the follow-up period.

Conclusions: Higher concomitant staging and grading corresponded to greater risk for TLP and generalized extent only became a significant predictor in patients with stage IV or grade C disease.

KEYWORDS
periodontitis, supportive periodontal maintenance therapy, tooth loss

1 | INTRODUCTION

Periodontitis is a chronic inflammatory disease with a multifactorial aetiology associated with dysbiotic microbial biofilms and characterized by progressive destruction of the tooth-supporting apparatus (Hajishengallis & Lamont, 2012). The public health burden associated with periodontal diseases is substantial, as periodontitis is one of the most prevalent chronic diseases and a major cause of tooth loss in adult populations. It has recently been reported that up to 42.2% of US dentate adults aged 30 years and older have

periodontitis, with elderly patients, certain races and smokers exhibiting an increased risk (Eke et al., 2018). Over the last 50 years, as new scientific evidence has emerged surrounding the pathogenesis and aetiology of periodontitis, different classification systems were proposed to provide clinicians with a framework for diagnostic and treatment purposes. A few years after publishing their seminal paper in 1976 describing the pathogenesis of periodontitis, Page and Schroeder developed a preliminary classification system dividing periodontitis into four categories: (1) adult, (2) rapidly progressive, (3) juvenile and (4) pre-pubertal (Page & Schroeder, 1976). In 1989, The World Workshop in Clinical Periodontics (American Academy of Periodontology, 1989) classified periodontitis based on disease progression, although the reasons for variable rates of progression were still unclear at the time (American Academy of Periodontology, 1989). Although this classification system was widely used, drawbacks involving significant overlap between disease categories and the inappropriate emphasis on age of onset necessitated a revised classification. Ten years later, the American Academy of Periodontology (AAP) classification was introduced following a framework proposed by the AAP workshop (Armitage, 1999). In this classification system, the term "adult" was replaced with "chronic", and "early onset periodontitis" was replaced with "aggressive periodontitis". Furthermore, the extent of disease was defined as either localized or generalized based on the number of sites involved using a threshold of 30%. In 2015, a task force was formed to revisit the classification resulting in the introduction of the term "reduced periodontium" and the addition of age as a distinguishing factor between chronic and aggressive periodontitis (more or less than 25 years old; Periodontitis, 2015).

Recently in 2017, the first "World Workshop" combining contributions from international experts around the world was successful in reviewing the literature to make evidence-based conclusions regarding both periodontal and implant-related diseases and conditions. A new classification of periodontal and peri-implant diseases and conditions based on a multidimensional staging and grading system was introduced to overcome some of the limitations related to older classifications. Staging describes the extent and distribution of the disease and is dependent on the severity and complexity of disease management, while grading denotes the rate of periodontitis progression and facilitates risk stratification based upon radiographic bone loss (RBL), clinical attachment loss, case phenotype, smoking status and diabetic status. The new classification system provides clinicians with a solid framework to stratify cases based on disease risk in support of both research and clinical care with the intention of improving both periodontal and systemic health. In one of the main articles of the new classification, Papapanou and coworkers suggested using existing databases as well as developing new databases in order to facilitate the implementation, validation and continuous refinement of the new classification system (Papapanou et al., 2018). In a previous article from our group, we investigated staging, grading and extent as independent variables in a compliant cohort of 292 patients and we found that staging and grading at baseline were significantly associated with risk for tooth loss due to periodontitis (TLP; Ravida et al., 2020). However, the sample size was not large enough to allow for powerful analysis of two-way interactions between prognostic variables. This is because we only included highly compliant patients who attended at least one maintenance visit per year for a minimum of 10-year follow-up. In the present paper, the sample size was increased by including patients with variable maintenance frequencies but still maintaining a minimum of 10-year follow-up to assess the ability of two-way interactions between baseline stage, grade and extent to predict tooth loss due periodontitis over a long-term follow-up period.

Clinical Relevance

Scientific Rationale: A recent classification system for periodontal diseases was released; however, scientific validation utilizing pre-existing databases is needed in order to study how staging, grading and extent interact to influence tooth loss due to periodontitis (TLP) over a long-term follow-up.

Principal Findings: Interactions between stage and grade were found to be the strongest predictors of TLP; patients with higher concomitant staging and grading experienced greater TLP over time. Extent played a role only in patients with severe disease (stage IV or grade C).

Practical Implications: Patient stratification based on staging and grading can act as the foundation for the delivery of precision periodontal therapy.

2 | MATERIALS AND METHODS

This investigation was conducted in agreement with the Helsinki Declaration of 1975 (World Medical Association, 1975) as revised in 2013 (World Medical Association, 2013). The protocol was approved by the University of Michigan, School of Dentistry, Institutional Review Board for Human Studies (HUM00157260). This retrospective study involved periodontal patients screened and treated in the time period between January 1966 and January 2008 at the University of Michigan School of Dentistry, Ann Arbor, MI, USA. This study was conducted by obtaining anonymized data; thus, there was no need for informed consent.

2.1 | Study population

Data were retrospectively retrieved from physical and electronic charts for patients who underwent non-surgical and, if indicated, surgical periodontal treatment between January 1966 and January 2008 at the University of Michigan School of Dentistry. Inclusion and exclusion criteria, data collection and patient

allocation according to the 2017 World Workshop case definitions that include stage (I, II, III and IV), grade (A, B and C) and extent (localized, generalized and molar-incisor pattern; Tonetti et al., 2018) are described elsewhere (Ravida et al., 2020). In contrast to our previous article, the inclusion criteria were modified to include erratically maintained patients (<1 supportive periodontal therapy [SPT]/year) in order to increase the sample size and to facilitate more powerful sub-analyses of the interactions between staging, grading and extent on TLP. Briefly, patients treated for periodontal disease (a session of scaling and root planing (SRP) and/or surgical therapy) with a complete medical history, baseline periodontal, full mouth radiographs and a minimum of ≥10-year follow-up at the University of Michigan School of Dentistry were included. Patients receiving care outside the School of Dentistry were excluded. Staging and grading algorithms published by Tonetti and Sanz (2019) were utilized to categorize patients according to their stage and grade based on baseline clinical and radiographic parameters. Extent was calculated after determining stage and was evaluated as the percentage of teeth at the stage-defining severity level (Sanz et al., 2020a). Baseline was defined as T_0: the first SRP appointment of the patient at the periodontal department. The date of the last SPT visit for which data were available was defined as T_1. Staging and grading were conducted by a single investigator (MS) using clinical data collected at the time of initial active periodontal therapy (T_0) after being calibrated by one of the authors of the new classification system (HG; Tonetti et al., 2018). Data on pertinent patient characteristics, the number of SPT visits per year and relevant medical history (history of diabetic status and self-reported smoking history at baseline) were collected. RBL (% of root length) at baseline was measured from periapical radiographs to assess periodontitis stage and grade (Pepelassi et al., 2000). Tooth-specific data on clinical parameters including periodontal probing depth (PPD), clinical attachment level (CAL) calculated as the difference between PPD and the distance from the free gingival margin to the cemento-enamel junction, bleeding on probing and furcation involvement were also collected. Information about masticatory dysfunction, drifting, flaring, bite collapse and plaque accumulation was retrieved from patient records when available. Patient charts were reviewed for TLP and TLO (overall tooth loss) by comparing the number of teeth present at T_0 and T_1. For each non-third molar tooth that was lost, the date and reason for extraction were recorded. The reason for any extraction (TLP, caries, etc.) was always recorded in the patient files as per clinic policy. Teeth extracted during the active treatment phase (teeth deemed as hopeless at or prior to T_0) were not considered in the calculation of TLO and TLP. However, TLP during active therapy was utilized to assess the baseline stage of patients as suggested recently by Sanz et al. (2020). In the cases where teeth were extracted due to a combination of pathologies (i.e. periodontitis, caries, periapical pathology), the overriding reason for tooth loss was evaluated by the specialist who deemed the tooth as hopeless. Also, in the rare case where the cause for tooth loss could not be precisely ascertained (21 teeth total), the tooth loss event was not considered as TLP.

2.2 | Statistical analysis

At patient-level, chi-squared independent *t*-test and one-way ANOVA models were used to assess the homogeneity of patient clinical profiles at baseline and compliance of maintenance between stage-grade subgroups. Mann–Whitney and Kruskal–Wallis tests were conducted to assess homogeneity of distributions of absolute loss rates between staging, grading and extent. At the tooth-level, time to event TLP was analysed using Kaplan–Meier survival methodology. Cumulative survival functions were plotted and compared between different categories of stage, grade and extent using log-rank tests. Multilevel Cox regression frailty models were used to assess the association among predictive variables (stage, grade, extent, gender, age and average number of SPT visits per year) for different combinations of classification parameters on TLP. Hazard ratio estimations and corresponding 95% CI were obtained. The significance levels used in analysis were 5% (α = 0.05). Regarding the power analysis, a post hoc estimation was obtained. A sample size of 11,125 independent teeth provided 99.9% power at a 95% confidence to detect a relative risk, RR = 3.0 as significant using a Cox multiple regression model to assess the influence of a two-level factor (e.g. extent) and assuming that 95% of observations were censored. However, teeth were not independent, and this power must be corrected because of the two-level structure of the data. Each patient provided 25 teeth on average and within-subject correlation CCI = 0.5 (moderate) was assumed, leading to a correcting coefficient of D = 13.0. Therefore, 11,125 dependent teeth provided the same power as 855 independent teeth, calculated at 88% power under the aforementioned conditions (RR = 3.0; 95% confidence).

3 | RESULTS

3.1 | Characteristics of patient cohort

A total number of 11,125 teeth in 442 patients (219 males and 223 females) with a follow-up of 275.5 ± 80.7 months (range 124 to 583 months; 10.3–48.6 years) were included in the present retrospective investigation. The profile of each patient group based on all possible two-way combinations of staging and grading is reported in Table 1. There were no significant differences between groups for the average follow-up period, gender and number of teeth at baseline. For patients diagnosed with stage I, II or III, mean age was significantly lower with increasing grade. Only for patients with stage 1 periodontitis, the average number of SPT visits per year was significantly higher for grade A compared with grade B (p = .001).

TABLE 1 Patient-level profile of different groups of included patients subdivided based on periodontitis stage and grade at baseline. Results of chi-squared test, two-sample *t*-test and one-way ANOVA for comparisons between grades within each stage group. Subgroups including less than five cases were excluded from comparisons

Stage	Total	I			II				III				IV			
Grade		A	B	P value	A	B	C	P value	A	B	C	P value	A	B	C	P value
N (Subjects)	442	20	25		11	104	19		8	134	72		3	23	23	
Months Follow-up (Patient-level)	275.5 ± 80.7	271.7 ± 51.1	267.1 ± 78.4	0.823	222.5 ± 53.1	267.9 ± 81.7	265.7 ± 85.1	0.207	295.9 ± 61.1	274.5 ± 77.9	298.9 ± 91.1	0.116	280.0 ± 68.2	268.7 ± 80.0	286.7 ± 88.7	0.473
N (male)	219 (49.5%)	10 (50.0%)	9 (36.0%)	0.345	4 (36.4%)	55 (52.9%)	10 (52.6%)	0.577	6 (75.0%)	62 (46.3%)	40 (55.6%)	0.164	0 (0.0%)	11 (47.8%)	12 (52.2%)	0.768
N (Female)	223 (50.5%)	10 (50.0%)	16 (64.0%)		7 (63.6%)	49 (47.1%)	9 (47.4%)		2 (25.0%)	72 (53.7%)	32 (44.4%)		3 (100%)	12 (52.2%)	11 (47.8%)	
Age (y)	47.5 ± 11.8	44.8 ± 13.5	36.4 ± 10.0	**0.022***	61.1 ± 12.5	47.6 ± 10.6	42.4 ± 12.0	**<0.001*****	57.5 ± 8.9	49.5 ± 10.9	43.8 ± 10.7	**<0.001*****	61.7 ± 11.2	51.7 ± 11.8	48.5 ± 12.1	0.372
Number of teeth at T0	25.2 ± 3.2	26.9 ± 1.7	26.5 ± 1.9	0.452	25.2 ± 2.8	26.0 ± 2.6	25.8 ± 2.0	0.583	24.8 ± 2.0	25.7 ± 2.6	25.7 ± 2.3	0.563	19.7 ± 4.7	20.0 ± 4.7	20.7 ± 4.1	0.598
Average Number of maintenance visits (pat.-level)	40.2 ± 15.9	43.3 ± 13.9	32.4 ± 11.7	**0.007****	27.6 ± 10.2	36.9 ± 18.0	44.0 ± 22.9	0.064	45.6 ± 17.5	40.9 ± 19.5	44.6 ± 25.1	0.465	51.3 ± 21.2	33.7 ± 20.1	36.7 ± 29.2	0.682
Average Number of maintenance visits / Years of follow-up (pat.-level)	1.70 ± 0.68	1.89 ± 0.50	1.45 ± 0.36	**0.001****	1.59 ± 0.77	1.62 ± 0.55	1.99 ± 0.89	0.060	1.89 ± 0.72	1.77 ± 0.69	1.76 ± 0.77	0.898	2.14 ± 0.37	1.49 ± 0.70	1.43 ± 0.79	0.802

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

The bold values are statistically significant.

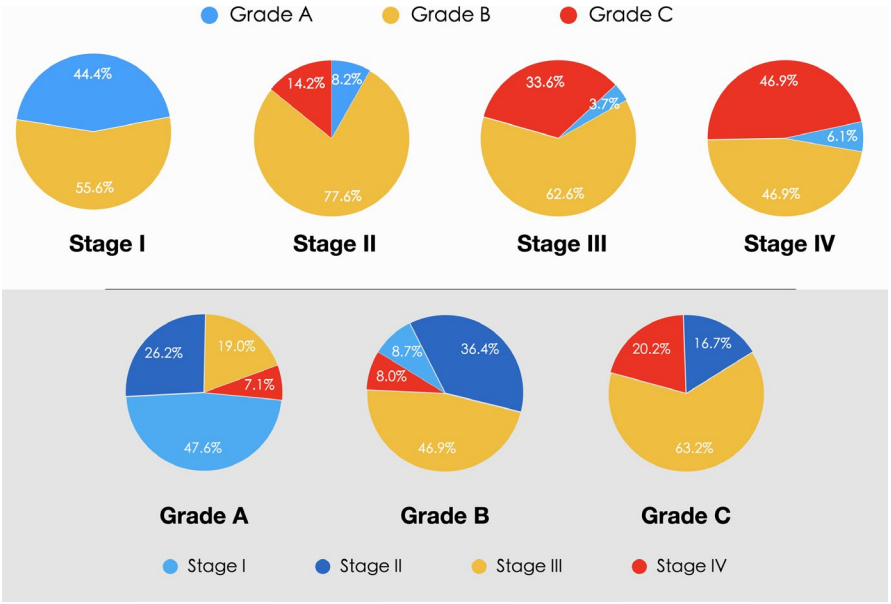

FIGURE 1 Prevalence of various combinations of staging and grading diagnoses at baseline

3.2 | Prevalence of patients according to the 2018 classification

The prevalence of each combination of periodontitis stage and grade in the studied population is shown in Figure 1. The prevalence of grade A disease decreased with increasing stage ranging from 44.44% (stage I) to 6.12% (stage IV), whereas the prevalence of grade C disease increased from 0% (stage I) to 46.94% (stage IV). The prevalence of stage 1 disease decreased with increasing grade from 47.62% (grade A) to 0% (grade C), whereas the prevalence of stage 4 disease increased with increasing grade from 7.14% (grade A) to 20.18% (grade C). The most prevalent diagnosis at baseline was stage III grade B (30.3%; 134/442) followed by stage II grade B (23.5%; 104/442), and stage III grade C (16.3%; 72/442), whereas the least prevalent diagnoses were

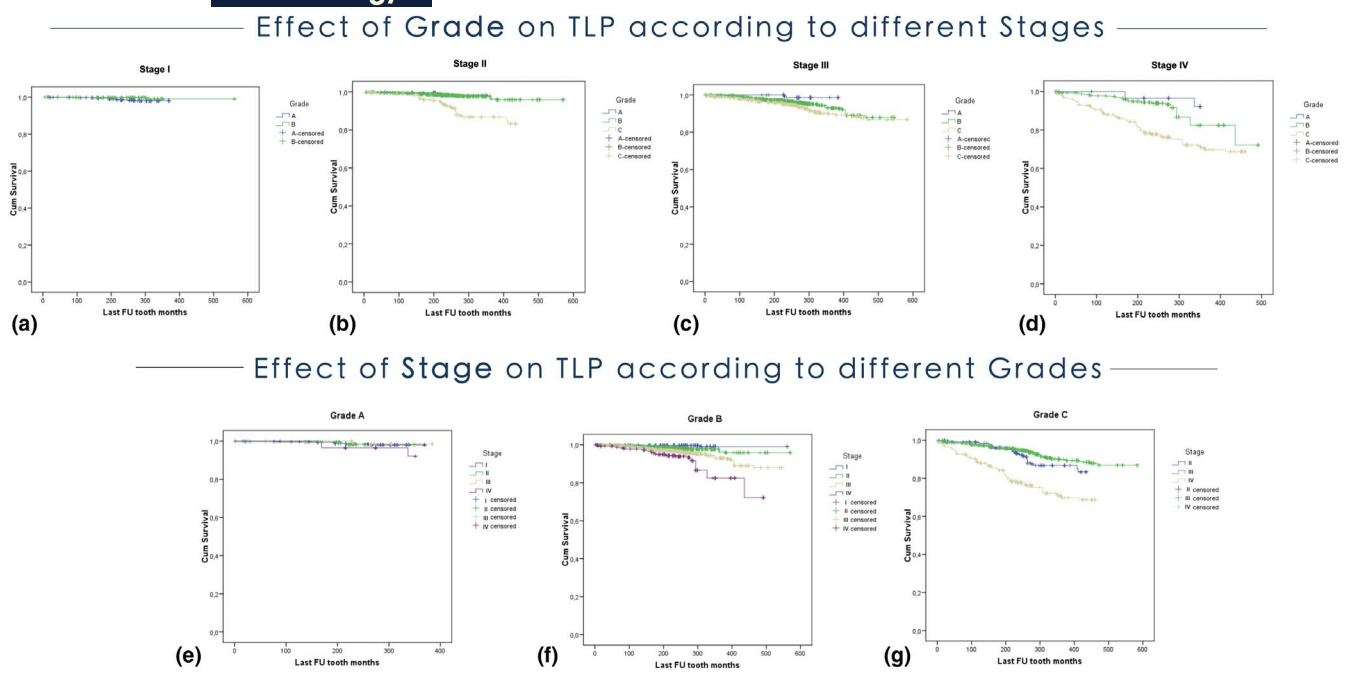

FIGURE 2 Tooth-level univariate analysis of tooth survival demonstrating effect of grade on TLP according to different stages (A–D) and effect of stage on TLP according to different grades (E–G)

stage II grade A (2.5%; 11/442), stage III grade A (1.8%; 8/442), stage IV grade A (0.6%; 3/442) and stage I grade C (0%; 0/442; Figure 1).

3.3 | Tooth loss due during specific time intervals

Overall, 1297 (11.7%) teeth were lost during the follow-up period. A total of 554 teeth (4.98%) were lost due to periodontitis throughout the follow-up. From 0–10 years, 10–20 years, and >20-year follow-up, 184 (1.65%), 223 (2.04%) and 147 (1.37%) teeth were extracted for periodontal reasons, respectively. The mean number of TLP for each group throughout the follow-up can be seen in Tables S1–S4.

3.3.1 | Effect of grade on TLP according to different stages

During the first ten years, grade was a significant predictor of TLP for stage IV cases (Table S1). During the first 20 years grade was a significant predictor of TLP for stages I, II and IV, with no significant differences for stage III. From baseline to the last follow-up, grade was a significant predictor of TLP for all stages.

3.3.2 | Effect of stage on TLP according to different grades

Stage was directly associated with increased risk for TLP for grades B and C during all time intervals evaluated throughout the follow-up (0–10, 0–20 and baseline-last follow-up; Table S2). Stage was not a significant predictor of TLP for grade A cases for all the time intervals analysed.

3.3.3 | Effect of extent on TLP according to different stages and grades

Stage IV generalized periodontitis was associated with significantly increased risk for TLP relative to localized for 0–20 years and baseline to last follow-up (Table S3). A strong trend (p = .056) was seen regarding the risk for TLP based on extent for grade C cases when the entire follow-up period was considered (Table S4).

3.4 | Tooth lost due to periodontitis (Kaplan–Meier analysis)

Tooth-level Kaplan–Meier analysis showed significant associations between stage and grade at baseline with TLP throughout the follow-up (Figure 2). As stage and grade increased, the difference in risk for TLP between localized and generalized periodontitis (extent) at baseline increased (Figure 3).

3.4.1 | Effect of grade on TLP according to different stages

Stage I grade A (98%) exhibited significantly lower cumulative survival (p = .048) compared with stage I grade B (99%; Figure 2A). Regarding the stage II subcategory, there was a significant difference (p < .001)

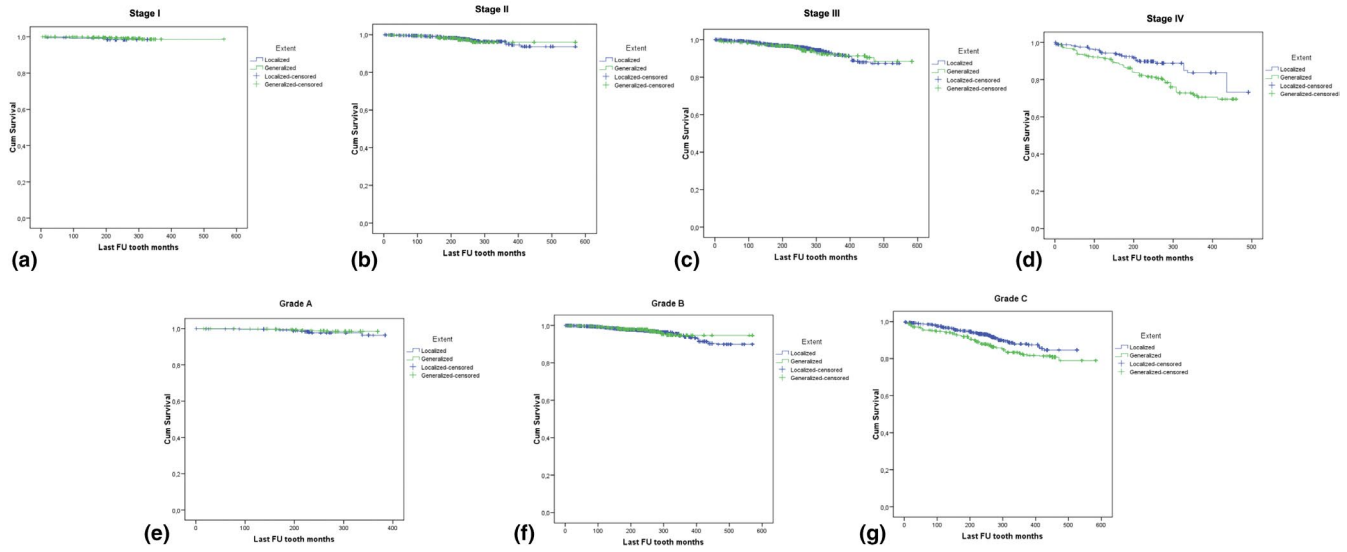

FIGURE 3 Tooth-level univariate analysis of tooth survival demonstrating effect of extent on TLP according to different stages (A–D) and grades (E–G)

in cumulative survival between grade A (98.3%), B (95.9%) and C (83.3%). Grade C exhibited significantly lower survival than grades A and B while no significant difference were found between A and B (Figure 2B). Stage III (Figure 2C) displayed a significant difference ($p < .001$) in cumulative survival between grade A (98.5%), B (88.0%) and C (86.8%) with grades B and C showing a lower survival rate than grade A. For stage IV (Figure 2D), there was a significant difference in cumulative survival rate between patients diagnosed with grade A (92.1%), B (72.1%) and C (68.6%) ($p < .001$) periodontitis at baseline.

3.4.2 | Effect of stage on TLP according to different grades

There was no significant difference ($p = .317$) in cumulative survival rates for grade A (Figure 2E) between patients diagnosed with stage I (98.0%), II (98.3%), III (98.5%) or IV (92.1%) periodontitis at baseline. Grade B showed significant differences ($p < .001$) in cumulative survival rate between stage I (99.0%), stage II (95.9%), stage III (88.0%) and stage IV (72.1%), with survival rate decreasing as stage increased (Figure 2F). For grade C, there were also significant differences ($p < .001$) in cumulative survival rates between stage II (83.3%), stage III (86.8%) and stage IV (68.8%), with survival rate significantly decreasing as stage increased (Figure 2G).

3.4.3 | Effect of extent on TLP according to different stages and grades

No significant differences in cumulative survival rates were found for stages I, II and III between localized and generalized periodontitis at baseline (Figure 3A–C). However, statistically significant differences ($p < .001$) were found for stage IV in cumulative survival between localized (73.2%) and generalized (69.5%) periodontitis at baseline (Figure 3D). In terms of grading, only C displayed a significant ($p < .001$) difference (84.6% vs.79.0%; Figure 3E–G).

3.5 | Multilevel Cox regression survival analysis

3.5.1 | Effects of grade on tooth loss by Stage

Stepwise multilevel multivariate Cox regression analysis controlling for gender, age and number of maintenance visits per year using grade A as a reference revealed that the hazard ratio for TLP increased with higher stage and grade (Table 2). Stage I grade B demonstrated a significantly lower risk for TLP relative to grade A (HR 0.17; 0.05–0.56; $p = .003$). For stage II, there was no significant difference in risk for TLP between grades A and B, but grade C demonstrated a significantly increased risk relative to grade A (HR 6.50; 1.78–23.7; $p = .005$). Stage III displayed a significant difference in risk for TLP between grades A and B (HR 5.00; 1.43–17.5; $p = .011$), as well as between grades A and C (HR 8.29; 2.35–29.2; $p = .001$). Finally, stage IV showed a significant difference in risk for TLP between grades A and C (HR 6.08; 1.12–33.1; $p = .037$), but not between grades A and B ($p = .396$).

3.5.2 | Effect of stage on tooth loss by grade

Using stage I as a reference, the hazard ratio for TLP increased with higher stage and grade (Table 3). For grade A, there were no significant differences in risk of TLP among groups. Patients with grade B displayed significantly higher risk of TLP for stage III (HR 6.47; 2.18–19.3; $p < .001$) and IV (HR 11.9; 3.67–38.9; $p < .001$) relative

TABLE 2 Results from stepwise multilevel Cox regression using grade A and female gender as reference for vertical comparisons. Hazard ratio (HR) and 95% confidence interval were reported

Periodontal-Related Survival									
		Stage							
		I		II		III		IV	
		HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*
Grade	A	1.00		1.00		1.00		1.00	
	B	0.17 (0.05-0.56)	**0.003****	1.09 (0.32-3.72)	0.892	5.00 (1.43-17.5)	**0.011***	2.13 (0.37-12.2)	0.396
	C	---		6.50 (1.78-23.7)	**0.005****	8.29 (2.35-29.2)	**0.001****	6.08 (1.12-33.1)	**0.037***
Gender	Female	1.00		1.00		1.00		1.00	
	Male	0.42 (0.14-1.30)	0.132	1.29 (0.71-2.37)	0.406	1.13 (0.76-1.69)	0.553	0.91 (0.44-1.89)	0.793
Age		1.02 (0.98-1.06)	0.216	1.00 (0.97-1.03)	0.933	1.03 (1.01-1.05)	**0.011***	1.01 (0.96-1.06)	0.719
N° of Maintenances per year		0.22 (0.04-1.22)	0.084	0.55 (0.32-0.97)	**0.039***	0.74 (0.43-1.28)	0.278	0.95 (0.49-1.86)	0.884

Abbreviation: HR, hazard ratio

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.01$.

The bold values are statistically significant.

to stage I. For grade C, stage II was used as a reference due to the limited prevalence of detectable stage I grade C disease ($n = 0$). No significant difference in risk of TLP between stages II and III was recorded, but there was a significant difference between stages II and IV (HR 2.39; 1.14–5.00; $p = .020$).

3.5.3 | Effect of extent on tooth loss by stage and grade

Only generalized stage IV (HR 1.87; 1.01–3.46; $p = .046$) and generalized grade C (HR 1.73; 1.07–2.82; $p = .027$) exhibited a significantly higher risk for TLP relative to localized disease (Table 4; Table S5).

3.6 | Overall tooth loss analysis

The impact of the staging and grading on TLO is shown utilizing both Kaplan–Meier survival analysis (Figures S1 and S2) and multilevel Cox regression analysis (Table S6A–D). Grade exhibited a significant effect on overall tooth loss for stages II, III and IV. In contrast to TLP, no significant effects were found for either stage on tooth loss by grade, or extent on tooth loss by stage and grade.

4 | DISCUSSION

In the present study, we found that higher concomitant staging and grading corresponded to a greater risk for TLP. Generalized extent only became a significant predictor of TLP in patients with stage IV or grade C disease. To the best of our knowledge, no study has previously explored this interaction before. Furthermore, it is difficult to find another article studying TLP with a similar follow-up time and sample size. Indeed, although numerous studies have investigated TLO (Axelsson & Lindhe, 1981; McGuire & Nunn, 1996; Papantonopoulos, 2004; Eickholz et al., 2008; Jansson & Lagervall, 2008; Pretzl et al., 2008; Graetz et al., 2019), studies specifically investigating TLP over a long-term follow-up with large sample

TABLE 3 Results from stepwise multilevel Cox regression using stage 1 and female gender as reference for vertical comparisons. Hazard ratio (HR) and 95% confidence interval were reported

Periodontal-Related Survival							
		Grade					
		A		B		C	
		HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*
Stage	I	1.00		1.00		---	
	II	0.74 (0.11-4.89)	0.755	2.83 (0.90-8.90)	0.075	1.00	
	III	0.62 (0.13-2.98)	0.553	6.47 (2.18-19.3)	**<0.001*** **	0.65 (0.34-1.26)	0.204
	IV	2.45 (0.43-14.0)	0.314	11.9 (3.67-38.9)	**<0.001*** **	2.39 (1.14-5.00)	**0.020***
Gender	Female	1.00		1.00		1.00	
	Male	0.79 (0.30-2.09)	0.633	1.14 (0.75-1.71)	0.543	0.99 (0.62-1.58)	0.967
Age		1.01 (0.96-1.06)	0.783	1.03 (1.01-1.05)	**0.005****	1.01 (0.98-1.03)	0.665
N° Maintenances per year		0.77 (0.31-1.89)	0.563	0.76 (0.49-1.19)	0.231	0.79 (0.46-1.36)	0.396

Abbreviation: HR, hazard ratio.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.01$.

The bold values are statistically significant.

sizes are scarce in the literature (Fardal et al., 2004; Chambrone & Chambrone, 2006; Martinez-Canut, 2015). The present manuscript also shed light on the importance of analysing TLP at the time of validating a diagnostic system as opposed to TLO. The impact of increased disease severity (effect of stage on tooth loss by grade) and the effect of extent on tooth loss according to stage and grade were better captured when TLP was analysed.

Since Hirschfeld and Wasserman (1978), the present article is the second largest in terms of sample size and has the longest follow-up. These authors investigated TLP in a population of 600 patients followed over a mean period of 22 years and found that 83.2% of the population lost 0–3 teeth, whereas 12.6% lost 4–9 teeth, and 4.2% lost 10–23 teeth. Analyses rested on dividing patients based on three different responses to treatment according to the tooth loss pattern (well-maintained, downhill and extreme downhill), whereas our study focused on evaluating the risk for TLP based on baseline diagnosis according to the 2018 classification system. Studies such as this are essential in order to increase understanding of the different possible trajectories for disease progression after an initial diagnosis according to the recent classification system (Ravida et al., 2020).

In the present study, the most prevalent diagnoses in a population of periodontal patients treated in an academic setting were stage III grade B, followed by stage II grade B, and stage III grade C. The least prevalent diagnoses were stages II grade A, stage III grade A, stage IV grade A and stage I grade C. Indeed, no stage I grade C patients were found making this the least prevalent diagnosis. This is perhaps due to the difficulty of detecting disease at an early stage in rapidly progressing cases using current diagnostic tools. Indeed, current gold standard diagnostics (periodontal charting and radiographic analysis) are limited in their ability to detect early breakdown, predict future progression and conduct real-time assessments of disease activity (Ortman et al., 1982; Goodson et al., 1984). Our results are in agreement with Graetz et al. (2019) where most patients were diagnosed as generalized stage III grade C, stage IV grade C or stage III grade B. In both studies which involved

TABLE 4 Results from stepwise multilevel Cox regression using localized disease and female gender as reference for vertical comparisons. Hazard ratio (HR) and 95% confidence interval were reported

Periodontal-Related Survival									
		Stage							
		I		II		III		IV	
		HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*	HR 95%(CI)	*P-Value*
Extent	Localized	1.00		1.00		1.00		1.00	
	Generalized	0.53 (0.12-2.33)	0.397	1.04 (0.40-2.68)	0.933	1.16 (0.70-1.92)	0.561	1.87 (1.01-3.46)	**0.047***
Gender	Female	1.00		1.00		1.00		1.00	
	Male	0.76 (0.20-2.87)	0.685	1.25 (0.68-2.31)	0.468	1.14 (0.75-1.73)	0.548	1.09 (0.55-2.16)	0.798
Age		1.05 (1.01-1.09)	**0.021***	0.99 (0.96-1.02)	0.424	1.02 (0.99-1.05)	0.084	0.99 (0.95-1.04)	0.728
N° of Maintenances per year		0.76 (0.16-3.59)	0.732	0.74 (0.40-1.36)	0.337	0.69 (0.39-1.23)	0.208	0.84 (0.43-1.65)	0.622

Abbreviation: HR, hazard ratio.

*$p < 0.05$.

The bold values are statistically significant.

long-term follow-up of maintenance patients after an active treatment phase, an imbalance in relative prevalence was found favouring severe and rapidly progressing disease (Graetz et al., 2019).

Overall the results demonstrate that the risk for TLP increases with higher staging and grading. A trend for increased TLP for higher staging and grading was noted based on the slopes of the Kaplan–Meier survival curves which increased for higher stages and grades. In addition, the spread between the Kaplan–Meier survival curves increased with higher staging and grading indicating that as stage increases, the difference in the risk for TLP between various grades increases. Likewise, as grade increases, the difference in risk for TLP between various stages increases. Although patients diagnosed with stage I grade B at baseline exhibited significantly lower risk for TLP relative to stage I grade A patients, overall TLP was relatively low for stage 1 patients throughout the follow-up meaning the clinical significance of this result is limited. There were no significant differences in the risk for TLP between grade A groups when comparing stages I-IV reflecting that tooth extraction is rare in treatment of grade A disease. Interestingly, in the first 10 years stage III grade C patients exhibited higher TLP than stage II grade C patients, but after 10 years and from baseline to last follow-up, the reverse was seen. This is likely due to an increased tendency to treat stage III grade C patients with extractions at an earlier time point coupled with the fact that stage II patients have no previous history of TLP, whereas stage III patients have usually lost I–IV teeth (Tonetti et al., 2018). Although the univariate analysis demonstrated a significantly increased risk for TLP for stage II grade C relative to stage III grade C, no significant difference was found for the stepwise multilevel Cox regression when controlling for gender, age, and number of SPT visits per year. In addition, the prevalence of stage II grade C was relatively limited which may have impacted our analysis. In our previous study, we found no significant difference in risk for TLP between localized and generalized periodontitis at baseline when extent was analysed as an independent variable (Ravida et al., 2020). The present study found significant differences due to consideration of the interaction between staging, grading and extent. Since the present study only found an increased risk for TLP for generalized periodontitis relative to localized for stage IV and grade C disease, this suggests that the difference in risk for TLP between localized and generalized disease patterns only becomes significant at higher-level staging and grading.

The present study is not free from limitations. Indeed, we analysed the various two-way interactions between staging, grading and extent. Although conducting a three-way analysis would likely yield more accurate results, doing so was not possible due to limitations in the sample size of subgroups. In addition, the variable of SPT was controlled using a yearly rate which did not take into account the variability which may exist in maintenance patterns where patients may become more and less compliant on an annual basis. Additionally, analysis of smoking habits did not consider the impact of the event of smoking cessation during the follow-up. However, past research has shown that a wash-out period of 11 years is required after successfully quitting for a former smoker to return to the baseline periodontal disease risk of a non-smoker (Tomar & Asma, 2000). In addition, the wash-out period for TLP has been

estimated at 15 years (Ravidà et al., 2020). For diabetes, changes in glycaemic control have been shown to influence periodontal disease risk with poorly controlled diabetics (Hba1c >9%) having a 2.9-fold higher risk for severe disease (Tsai et al., 2002). The present study did not consider dynamic changes in glycaemic control throughout the follow-up, but instead utilized a baseline HbA1c value to assess diabetic status. Finally, the goal of this paper was to study tooth loss which is the end outcome of periodontitis. For patients diagnosed with initial/early disease (lower staging and grading), perhaps the variable of TLP may not be able to accurately capture the true risk for disease progression as sensitively as changes in CAL and RBL, as these patients may still experience appreciable attachment loss and periodontal destruction without requiring tooth extractions. Whereas when disease is advanced, TLP likely becomes a much more significant indicator of disease progression.

5 | CONCLUSION

Stage III grade B was the most prevalent diagnosis, whereas diagnosis with stage II, III or IV coupled with grade A, as well as stage I grade C were the least prevalent. Overall, risk for TLP increased significantly at higher stage and grade combinations. Extent only had a significant impact on risk for TLP for stage IV and grade C subgroups indicating that the difference in risk for TLP between localized and generalized disease is most appreciable in advanced cases. Analysis of TLP better captured the impact of increased disease severity and extent compared with TLO.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Andrea Ravidà contributed to the conception and design of the study, acquisition of the data and drafting of the article; Maria Vera, Muhammad H. A. Saleh and Musa Qazi contributed to the acquisition of data; Matthew Galli contributed to the acquisition of data and drafting of the article; Giuseppe Troiano contributed to the conception and design of the study, data analysis and interpretation; Hom-Lay Wang contributed to the conception, critical revision of the article and final approval of the version to be published.

DATA AVAILABILITY STATEMENT

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

ORCID

Andrea Ravidà https://orcid.org/0000-0002-3029-8130
Giuseppe Troiano https://orcid.org/0000-0001-5647-4414
Hom-Lay Wang https://orcid.org/0000-0003-4238-1799

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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