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The correlation between history of periodontitis according to staging and grading and the prevalence/severity of peri-implantitis in patients enrolled in maintenance therapy

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Abstract

Background: The aim of this study was to determine if a previous history of periodontitis according to the preset definitions of the 2017 World Workshop is correlated with increased implant failure, and occurrence and severity of peri-implantitis (PI).

Methods: A retrospective analysis of patients with a history of periodontitis who received nonsurgical and, if indicated, surgical corrective therapy prior to implant placement was performed. Periodontitis stage and grade were determined for each included patient based on data from the time of initiation of active periodontal therapy. Cox Proportional Hazard Frailty models were built to analyze the correlation between stage and grade of periodontitis at baseline with implant failure, as well as occurrence and severity of PI.

Results: Ninety-nine patients with a history of periodontitis receiving 221 implants were followed for a mean duration of 10.6 ± 4.5 years after implant placement. Six implants (2.7%) failed and a higher rate of implant failure due to PI was found for grade C patients ($P < 0.05$), whereas only an increased trend was seen for stages III and IV compared with I and II. Grading significantly influenced the risk of marginal bone loss (MBL) >25% of the implant length ($P = 0.022$) in PI-affected implants. However, a direct correlation between higher-level stage and grade and PI prevalence was not recorded.

Conclusion: No statistically significant association between periodontitis stage or grade and the prevalence of PI was found. However, when PI was diagnosed, there was a relationship between periodontitis grade and severity of PI or the occurrence of implant failure.

KEYWORDS
dental implants, periodontal diseases, periodontitis

1 | INTRODUCTION

Peri-implantitis (PI) is a highly prevalent and asymptomatic complex chronic inflammatory disease culminating in progressive loss of supporting bone around dental implants.[1-3] The etiologies of both PI and periodontitis (PR) are believed to be microbially-mediated.[4] One of the principal articles of the recent 2017 World Workshop indicated that there is a strong level of evidence that patients with a previous history of PR, inadequate biofilm control, and a lack of regular maintenance care are at an increased risk for developing PI.[1] PI etiology, risk factors, and management are less well-understood compared to PR.

PR, much like PI, is a chronic inflammatory disease caused by a biologically destructive interaction between the host immunoinflammatory response and subgingival microbial biofilm which may lead to both oral (e.g., tooth loss) and systemic sequelae.[5-8] Several studies included in a recent narrative review showed a greater risk (in between 2.2 and 19 times) of PI in patients with a history of treated PR.[9] A meta-analysis demonstrated that PR patients had a 2.3-fold greater risk of developing PI compared to periodontally healthy patients.[10] In addition, implants placed in patients with prior tooth loss because of PR were significantly more likely to develop PI and exhibited 0.5 mm more marginal bone loss (MBL) on average after 5 years.[11] Possible theories for a linkage between PR and PI include that PR patients might harbor more pathogenic bacterial species, a higher bacterial load, or an impaired host immune response.[12]

Aoki and co-workers demonstrated that periodontal pathogens that reside in deeper pockets such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* can be transmitted from affected teeth to adjacent implants.[13] Pjetursson and co-workers also illustrated that PR patients with residual periodontal probing depths (PPDs) ≥5 mm had a significant higher risk for the development of PI and implant loss.[14] Residual PPD≥ 6 mm involving >10% of sites after treatment in severe periodontitis patients was shown to be a significant risk indicator for development of PI.[15] Daubert et al.[16] reported that severe PR was the strongest risk indicator for PI of all examined variables. In addition, Ong et al.[17] found that PR patients had an overall higher percentage of biologic complications, including implant failures, than non-PR patients.

However, it should be noted that conflicting findings exist regarding the association of PR and subsequent development of PI, where an association with moderate and severe, but not mild, periodontitis was found.[18-20] Different findings can possibly be attributed to the use of different case definitions in previous studies.[9] Adoption of the 2017 World Workshop case definitions of PR and PI to investigate potential associations can lead to more accurate interstudy analyses and comparisons. Hence, the primary aim of this study was to determine if a previous history of periodontitis associated with higher-level stage (severity) and grade (rate of progression) increases the risk of implant failure or PI according to the 2017 World Workshop case definitions. Secondary aims were to investigate whether PR stage and grade have an influence on the severity of subsequent PI.

2 | MATERIALS AND METHODS

The present study was conducted in compliance with the Helsinki Declaration of 1975, as revised in 2013. The protocol of this study was approved by the University of Michigan, School of Dentistry, Institutional Review Board for Human Studies (HUM00157260).

Data were acquired from the physical and electronic charts of patients who received nonsurgical and, if indicated, surgical corrective therapy between January 1996 and January 2018 at the University of Michigan, School of Dentistry, Ann Arbor, MI, USA. Patients treated for periodontal disease (scaling and root planing [SRP] and/or surgical therapy) with a complete medical history, baseline periodontal charting, and full-mouth radiographs were included in the present study. All included patients were maintained after active periodontal therapy with at least one session of supportive periodontal therapy (SPT) per year at the University of Michigan, School of Dentistry. Furthermore, the following exclusion criteria were implemented: non-periodontal patients, patients receiving implant-related or periodontal care outside the School of Dentistry, periodontal patients that did not receive a dental implant or received an implant with a follow-up period of <1 year, and patients with incomplete or unclear data.

Staging and grading algorithms published by Tonetti and Sanz[21] were used to classify patient periodontal status. Determination of baseline periodontal staging and grading was conducted by a single investigator (MS) using clinical and radiographic data collected at the time of initial active periodontal therapy (T0).[22] 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. Radiographic bone loss (RBL, % of root length) at baseline was measured from periapical radiographs to assess PR stage and grade.[23] 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 (BOP), and furcation involvement were also recorded. Information about masticatory dysfunction, drifting, flaring, bite collapse, and plaque accumulation were retrieved from patient records where available. As part of the data collection process, additional information was gathered at the time of implant placement including: age, tobacco usage and diabetic history, the number of implants placed and their locations, implant characteristics (brand, length, diameter, soft tissue/bone level), mechanism of crown retention (screw or cement-retained), number of follow-up visits and maintenance appointments, type of implant-abutment connection, as well timing of bone grafting (prior/during implant placement).

2.1 | Survival rate and PI definition

Based on the goal of conducting data analyses for both implant survival rates as well as PI prevalence/severity, two distinct follow-up periods were defined prior to data acquisition. These were a) follow-up based on implant survival, and b) follow-up based on the occurrence of PI. Follow-up based on implant survival was defined as the time period between implant placement and the last follow-up of the implant. At this date, each individual implant was classified as present or explanted.[24] Follow-up based on the occurrence of PI was defined as the duration of time between implant-supported prosthetic placement and the last radiograph in which peri-implant bone could clearly be visualized. The definition for PI proposed by the American Academy of Periodontology/European Federation of Periodontology 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions guidelines[25] was used to classify cases in a binary fashion as either positive or negative for PI (0 for peri-implant health, 1 for PI). Because baseline data were available, PI diagnosis was based on: 1) progressive bone loss beyond initial bone remodeling, 2) increased probing depth, and 3) presence of bleeding and/or suppuration on gentle probing.[25] The marginal bone level changes were radiographically examined by two authors (AR, MV) at the mesial and distal aspects of the affected implants using commercially available software (ImageJ, U. S. National Institutes of Health, Bethesda, MD, USA). If significant differences arose, a third reviewer (HLW) was included for reassessing the radiographs in a joint session and to give a final judgment. Interproximal marginal bone levels were radiographically calculated as a percentage of implant length, utilizing the most coronal bone-implant contact point to represent the marginal bone level to classify implants based on the severity of bone loss (<25%; 25% to 50%; or >50% of the implant

length). For implants with a polished collar, the length was measured from the smooth-rough interface to the apex. For bone level implants, the platform level was used as the coronal demarcation point when evaluating implant length for calculation of radiographic peri-implant bone levels.

2.2 | Statistical analysis

Descriptive statistics were employed for analysis of categorical (absolute and relative frequencies) and continuous (mean, standard deviation, range, and median) variables taking into account both implant failure events and PI diagnosis. At the implant-level, time-to-event "implant failure" and time-to-event "PI diagnosis" were analyzed using Kaplan-Meier survival methodology. Cumulative survival functions were plotted and compared between different patient profiles and clinical factors using a Log-rank test. In order to consider dependence between observations (implant-level data clustered by patients), univariate Cox regression frailty models were performed analyzing the influence of individual factors and covariates on failures and PI diagnosis. Hazard ratio estimations and corresponding 95% confidence intervals (CIs) were obtained. Wald test was used to consider within-patient correlations. Then, multiple Cox regression frailty models were used to adjust for potential confounders. Schoenfeld's tests for proportional hazard and residual analysis were carried out to validate theoretical hypotheses.

For non-failed PI-afflicted implants, severity of bone loss (<25% or ≥25%) was related to stage and grade, adjusting by radiographic follow-up duration using logistic regression with generalized estimation equations (GEE). Odds ratios and 95% CIs were obtained using the Wald's Chi2 statistic. The significance level for statistical analyses was set at 5% ($\alpha = 0.05$). Regarding the power analysis, a post-hoc estimation was obtained.

A sample size of 221 independent implants provided 96.5% power at 95% confidence to detect a relative risk (RR) of 3.0 as significant using a Cox multiple regression model to assess the influence of a two-level factor (e.g., maxillary or mandibular implant location), assuming that 80% of observations were censored (the proportion of no PI diagnosis was roughly 80%). In the power calculation, correction was performed to account for the two-level structure of the data. Each patient provided 2.23 implants on average and within-subject correlation CCI = 0.5 (moderate) was assumed, leading to a correcting coefficient D = 1.62. Therefore, 221 dependent implants provided the same power as 137 independent implants, calculated at 84% under the described conditions (RR = 3.0; 95% confidence).

TABLE 1 Demographic characteristics of the sample and periodontitis status at baseline, as well as results of Kruskal-Wallis test (KW) for comparison between different levels of stage and grade

		N of maintenances per year	P (KW)	Follow-up since IP (years)	Follow-up since CP (years)
Number of patients	99	2.2 ± 1.0		10.6 ± 4.5	10.0 ± 4.5
Mean age (years)	60.6 ± 10.2				
Gender					
Male	49 (49.5)				
Female	50 (50.5)				
Smoking					
No	63 (63.6)				
Former smoker	20 (20.2)				
Yes (<10 c/d)	8 (8.1)				
Yes (>10 c/d)	8 (8.1)				
Diabetes					
No	90 (90.9)				
Yes	9 (9.1)				
Stage					
1	7 (7.1)	2.7 ± 2.0	0.515	6.8 ± 3.4	6.1 ± 3.5
2	27 (27.3)	1.9 ± 0.8		9.8 ± 4.8	9.2 ± 4.8
3	56 (56.6)	2.2 ± 0.9		11.3 ± 4.0	10.7 ± 4.0
4	9 (9.1)	2.2 ± 1.3		12.1 ± 5.5	11.1 ± 5.7
Grade					
A	5 (5.1)	2.2 ± 1.0	0.526	10.0 ± 2.9	9.4 ± 3.0
B	68 (66.7)	2.2 ± 1.0		10.1 ± 4.6	9.5 ± 4.6
C	26 (26.3)	2.2 ± 1.0		12.2 ± 4.1	11.5 ± 4.2
Extension					
Localized	78 (78.8)				
Generalized	21 (21.2)				

$^{*}P < 0.05; ^{\dagger}P < 0.01; ^{\ddagger}P < 0.001.$

3 | RESULTS

3.1 | Characteristics of the patient cohort

In total, 99 patients composed of 49 males (49.5%) and 50 females (50.5%), with a mean age of 60.6 ± 10.2 years at the time of implant placement (range 38 to 86 years) were included in the present study. Overall, 221 implants were followed for a mean duration of 10.6 ± 4.5 years from implant placement, and 10.0 ± 4.5 years from prosthetic insertion. The loading protocol for all included implants followed a delayed approach (≥4 months after placement). Demographic characteristics of the included cohort are reported in Table 1.

3.2 | Correlation between stage and grade and implant failure

Analysis at the patient-level revealed that five patients (5.1%) experienced implant failure at least at one site (one patient experienced two failures). At the implant-level, a mean survival rate of 97.3% was found at the end of the follow-up period, and six implants (2.7%) failed. The cumulative survival rate (Kaplan Mayer analysis) was 99% at 5-years, 98% at 10-years, 94% at 15-years, and 92% at 20-years follow-up (Figure S1A). In the present study, the only cause of implant failure found was PI (Figure S1B). Table 2A shows Kaplan Meier univariate implant survival analysis according to clinical variables related to the patient,

TABLE 2 Results of Kaplan Meier survival analysis of time-to-event data implant survival and peri-implantitis diagnosis

A: Kaplan Meier survival analysis of time-to-event data based on clinical variables related to the patient, implant position, characteristics, and surgery			
	Total (%)	Failure rate (%)	*P*
Number of implants	221	6 (2.7)	
Mean age (years)	60.3 ± 9.3		
Gender			0.516
Male	110 (49.8)	2 (1.8)	
Female	111 (50.2)	4 (3.6)	
Smoking			0.141
No	121 (54.8)	2 (1.7)	
Former smoker	48 (21.7)	0 (0.0)	
Yes (<10 c/d)	18 (8.1)	1 (5.6)	
Yes (>10 c/d)	34 (15.4)	3 (8.8)	
Diabetes			0.104
No	204 (92.3)	5 (2.5)	
Yes	17 (7.7)	1 (5.9)	
Stage			p=0.411 (STAGE 1+2 versus 3 versus 4)
1	8 (3.6)	0 (0.0)	p=0.226 (STAGE 1+2 versus 3+4)
2	48 (21.7)	0 (0.0)	p=0.267 (STAGE 1+2 versus 3)
3	134 (60.6)	4 (3.0)	p=0.131 (STAGE 1+2 versus 4)
4	31 (14.0)	2 (6.5)	
Grade			0.048* (GRADE A+B versus C)
A	5 (2.3)	0 (0.0)	
B	131 (59.3)	1 (0.8)	
C	85 (38.5)	5 (5.9)	
Extension			0.465
Localized	171 (77.4)	4 (2.3)	
Generalized	50 (22.6)	2 (4.0)	
Arch			0.172
Maxilla	122 (55.2)	5 (4.1)	
Mandible	99 (44.8)	1 (1.0)	
Position			0.223
Anterior	37 (16.7)	0 (0.0)	
Posterior	184 (83.3)	6 (3.3)	
Prosthesis type			0.956 (Single versus Splinted)
Single	153 (69.2)	3 (2.0)	
Splinted	59 (26.7)	2 (3.4)	
Overdenture	9 (4.1)	1 (11.1)	–
Level			0.806
Soft	48 (21.7)	1 (2.1)	
Bone	173 (78.3)	5 (2.9)	
Connection			0.769 (Internal versus External)
Internal	200 (90.5)	5 (2.5)	
External	18 (8.1)	1 (5.6)	
Locator	3 (1.4)	0 (0.0)	–
Retention			<0.001[‡] (Cemented versus Screw)
Cemented	204 (92.3)	4 (2.0)	
Screwed	14 (6.3)	1 (7.1)	

(Continues)

TABLE 2 (Continued)

A: Kaplan Meier survival analysis of time-to-event data based on clinical variables related to the patient, implant position, characteristics, and surgery			
	Total (%)	Failure rate (%)	*P*
Ball atachment	3 (1.4)	1 (33.3)	–
Implant length			0.110
<=11 mm	66 (29.9)	1 (1.5)	
11.5 mm	45 (20.4)	3 (6.7)	
12 mm	34 (15.4)	1 (2.9)	
>=13 mm	76 (34.4)	1 (1.3)	
Implant diameter			0.183
<4 mm	52 (23.5)	0 (0.0)	
4-4.5 mm	90 (40.7)	3 (3.3)	
>4.5 mm	79 (35.7)	3 (3.8)	
Bone graft			0.755
No	149 (68.3)	4 (2.7)	
Yes	69 (31.7)	2 (2.9)	
FAILURE			
No	215 (97.3)		
Yes	6 (2.7)		
Peri-implantitis			<0.001[‡]
No	176 (79.6)	0 (0.0)	
Yes	45 (20.4)	6 (13.3)	

B: Kaplan Meier survival analysis of time-to-event peri-implantitis diagnosis according to clinical variables related to the patient, implant position, characteristics, and surgery.			
	Total (%)	PI rate (%)	*P*
Number of implants	221	45 (20.4)	
Age (years)	60.3 ± 9.3		
Gender			0.825
Male	110 (49.8)	21 (19.1)	
Female	111 (50.2)	24 (21.6)	
Smoking			0.723
No	121 (54.8)	23 (19.0)	
Former smoker	48 (21.7)	11 (22.9)	
Yes (<10 c/d)	18 (8.1)	6 (33.3)	
Yes (>10 c/d)	34 (15.4)	5 (14.7)	
Diabetes			0.094
No	204 (92.3)	40 (19.6)	
Yes	17 (7.7)	5 (29.4)	
Stage			0.411 (STAGE 1+2 versus 3 versus 4)
1	8 (3.6)	1 (12.5)	
2	48 (21.7)	10 (20.8)	
3	134 (60.6)	23 (17.2)	
4	31 (14.0)	11 (35.5)	
Grade			0.990 (GRADE A+B versus C)
A	5 (2.3)	2 (40.0)	
B	131 (59.3)	25 (19.1)	
C	85 (38.5)	18 (21.2)	
Extension			0.650
Localized	171 (77.4)	33 (19.3)	

(Continues)

TABLE 2 (Continued)

B: Kaplan Meier survival analysis of time-to-event peri-implantitis diagnosis according to clinical variables related to the patient, implant position, characteristics, and surgery.			
	Total (%)	PI rate (%)	*P*
Generalized	50 (22.6)	12 (24.0)	
Time since 1st SRP to IP (years)	12.9 ± 8.1		
Total follow up (years)	10.7 ± 5.1		
RX follow up (years)	9.6 ± 5.1		
Number of maintenances per year	2.3 ± 1.0		
Arch			0.546
Maxilla	122 (55.2)	22 (18.0)	
Mandible	99 (44.8)	23 (23.2)	
Position			0.110
Anterior	37 (16.7)	8 (21.6)	
Posterior	184 (83.3)	37 (20.1)	
Prosthesis type			0.409 (Single versus splinted)
Single	153 (69.2)	20 (13.1)	
Splinted	59 (26.7)	18 (30.5)	
Overdenture	9 (4.1)	7 (77.8)	–
Level			0.120
Soft	48 (21.7)	5 (10.4)	
Bone	173 (78.3)	40 (23.1)	
Connection			0.008[†] (Internal versus External)
Internal	200 (90.5)	41 (20.5)	
External	18 (8.1)	3 (16.7)	
Locator	3 (1.4)	1 (33.3)	–
Retention			0.002[‡] (Cemented versus Screw)
Cemented	204 (92.3)	39 (19.1)	
Screwed	14 (6.3)	3 (21.4)	
Ball atachment	3 (1.4)	3 (100)	–
Implant length			0.009[†]
<=11 mm	66 (29.9)	10 (15.2)	
11.5 mm	45 (20.4)	12 (26.7)	
12 mm	34 (15.4)	2 (5.9)	
>=13 mm	76 (34.4)	21 (27.6)	
Implant diameter			0.009[†]
<4 mm	52 (23.5)	7 (13.5)	
4-4.5 mm	90 (40.7)	22 (24.4)	
>4.5 mm	79 (35.7)	16 (20.3)	
Bone graft			0.551
No	149 (68.3)	29 (19.5)	
Yes	69 (31.7)	14 (20.3)	
Failure			
No	215 (97.3)	39 (18.1)	
Yes	6 (2.7)	6 (100.0)	
Peri-implantitis			
No	176 (79.6)		
Yes	45 (20.4)		

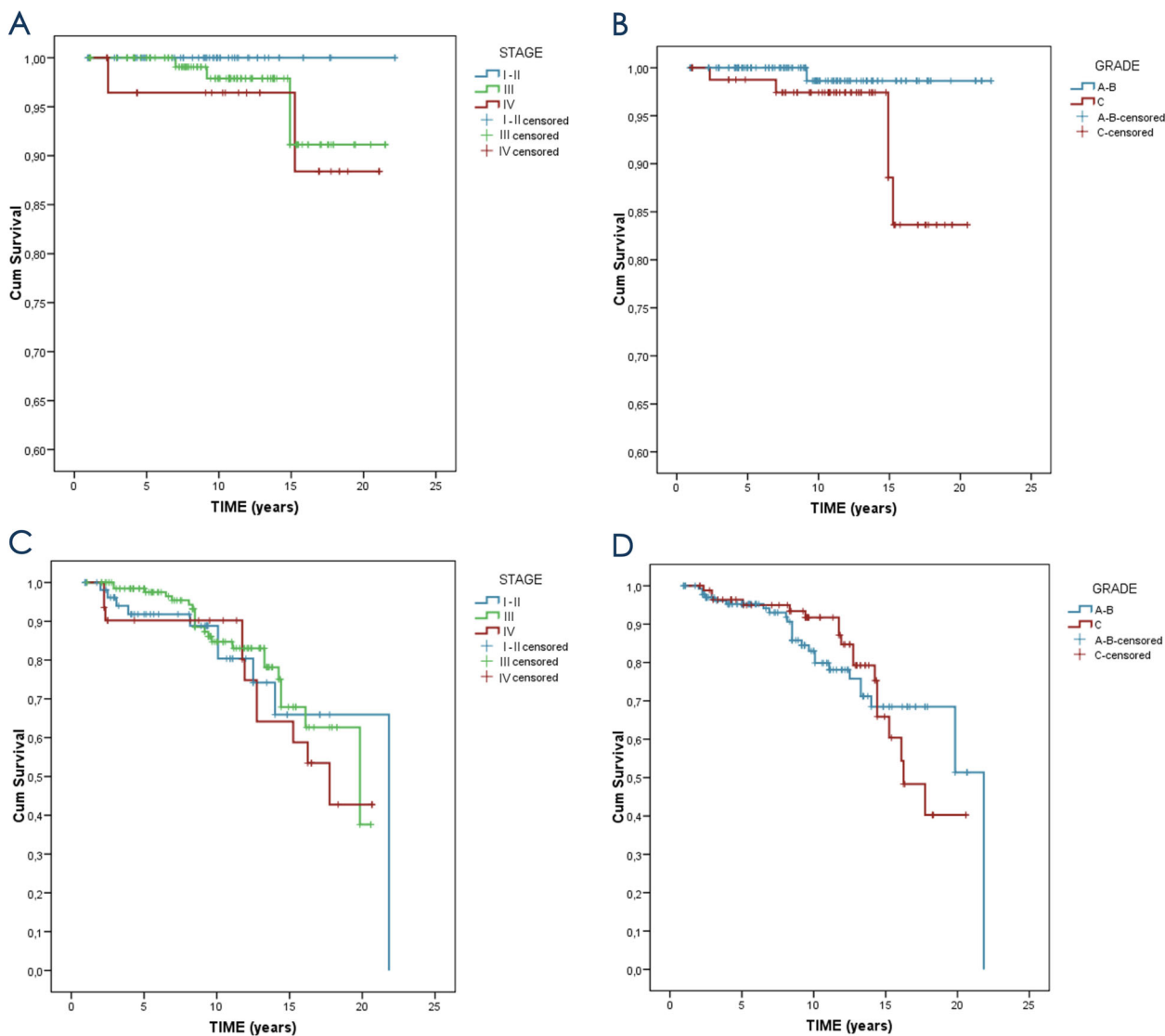[*]$P < 0.05$; [†]$P < 0.01$; [‡]$P < 0.001$.

FIGURE 1 (**A**) Implant failure survival analysis by stage; (**B**) implant failure survival analysis by grade; (**C**) peri-implantitis (PI) prevalence survival analysis by stage; the drop of the blue curve (represents stages I/II) at 23 years follow-up is because of the reduced sample size at that time (**D**) PI prevalence survival analysis by grade. The drop of the blue curve (represents grades A/B) at 23 years follow-up is because of the small sample size at that time

implant position, characteristics, and surgery. Similarly, Table 2B illustrates Kaplan Meier survival analysis of time-to-event PI diagnosis based upon above scenarios.

Regarding PR staging, four implant failures were recorded in patients with stage III PR at baseline, whereas the remaining two failures occurred in patients with a previous history of stage IV disease ($P > 0.05$). Mean implant failure rates were 0% for stages I-II, 3% for stage III, and 6.5% for stage IV. Cumulative implant survival rates are shown in Figure 1A and Table S1.

In terms of grading, one failure was recorded in a patient with a previous history of grade B PR, whereas the remaining five failures occurred in patients with a history of grade C disease. The mean failure rate was 0% for grade A, 0.8% for grade B, and 5.9% for grade C ($P < 0.05$) (Figure 1B and Table S2). Cox proportional hazard regression analysis showed that implants placed in grade C patients were associated with a trend towards a higher failure rate than those placed in grade A/B patients (HR = 6.57; $P = 0.075$) (Table 3). The same model demonstrated that implants placed in current heavy smokers were associated with a significantly higher failure rate compared to never-smokers (HR = 4.71; $P = 0.04$). Six implants were lost in patients with a history of stage III/IV PR, whereas no implants were lost in those with a history of stage I and II PR. Stage was not a significant predictor of implant failure ($P = 0.635$)

TABLE 3 Cox proportional hazard regression model illustrating time-to-event failure by clinical variables related to the patient, implant position, characteristics, and surgery

	HR	95% CI	*P*
Age (years)	1.02	0.95–1.10	0.538
Gender			
Male	1		
Female	1.75	0.36–8.60	0.491
Smoking			0.102
No	1		
Former smoker	–	–	–
Yes (<10 c/d)	1.82	0.21–15.6	0.578
Yes (>10 c/d)	4.71	1.08–20.6	0.040*
Diabetes			
No	1		
Yes	5.79	0.63–53.5	0.122
Stage			
1-2	–	–	–
3	1		
4	1.54	0.26–9.17	0.635
Grade			
A-B	1		
C	6.57	0.82–52.4	0.075
Extension			
Localized	1		
Generalized	1.86	0.40–8.58	0.429
Arch			
Maxilla	1		
Mandible	0.25	0.03–2.18	0.209
Prosthesis type			
Single	1		
Splinted	1.04	0.10–10.5	0.971
Overdenture	–	–	–
Level			
Soft	1		
Bone	1.31	0.16–10.9	0.801
Connection			
Internal	1		
External	0.72	0.07–7.29	0.777
Locator	–	–	–
Retention			
Cemented	1		
Screwed	51.9	4.89–550.4	0.001†
Ball atachment	–	–	–
Implant length	1.05	0.79–1.39	0.743
Implant diameter	2.23	0.79–6.26	0.128
Bone graft			
No	1		
Yes	1.30	0.25–6.94	0.756

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

when stage IV was compared to stage III (Table 3). It should be noted that stages I-II were excluded from the model because of a lack of convergence because these categories were both associated with 0% implant failure rates.

3.3 | Analysis of the association between stage and grade with the onset and severity of PI

A total of 45 implants (20.4%) were diagnosed with PI during the follow-up period. At the implant-level, the cumulative probability of PI occurrence (based on Kaplan Mayer analysis) was 5% at 5-years, 15% at 10-years, 35% at 15-years, and 54% at 20-years follow-up (Figure S2A). At the patient-level, the cumulative probability of PI occurrence is shown in Figure S2B. Univariate survival analysis of PI diagnosis according to clinical variables (implant position, implant characteristics, as well as patient-specific and surgical-related parameters) is shown in Table 2B. Overall, no correlation was found between increased staging and grading and increased prevalence of PI at both the implant- (Table 2B, Figures 1C and 1D) and patient-levels (Figures S3A and S3B). Cox proportional hazard regression analysis (Table S3) demonstrated a HR of 1.90 ($P = 0.027$) based on implant diameter, such that each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis. Furthermore, external connections were associated with a lower risk of PI compared to internal connections (HR = 0.11; $P = 0.018$). Distribution of implants diagnosed with PI ($n = 45$) according to the severity of bone loss is shown in Figure 2A. Severity of MBL was associated with increased grading (A-B versus C), but not with increased staging (Figure 2B). Results from the binary logistic regression model using GEE with fixed follow-up, showed that grading significantly influenced the risk of high MBL (>25%) ($P = 0.022$). Risk of severe MBL increased roughly 7.6 times for patients with a previous history of grade C PR compared to the reference grades A/B. Furthermore, there was no significant difference in risk of severe MBL according to stage ($P = 0.399$) (Table 4).

4 | DISCUSSION

4.1 | Main findings

This study investigated the potential association between baseline PR stage and grade and future implant failure as well as PI prevalence and severity. Ninety-nine treated PR patients were subsequently rehabilitated with dental implants (n = 221) and followed over a mean period of
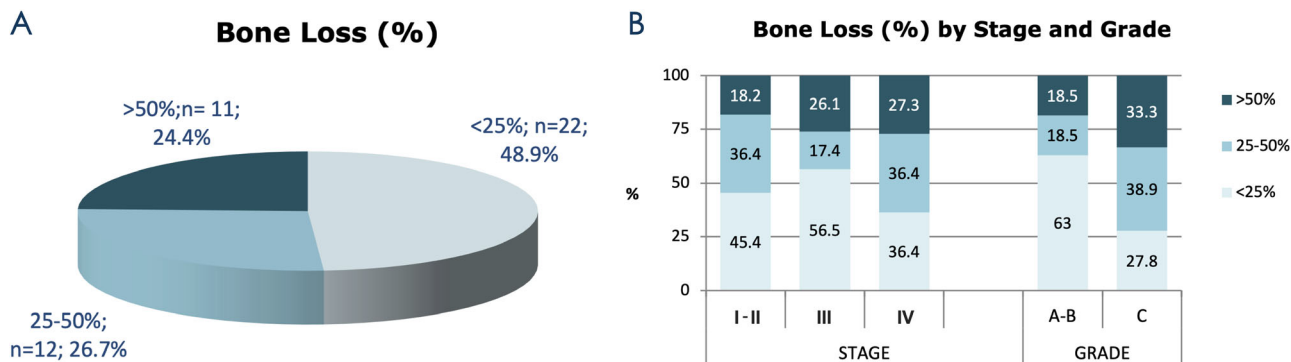
FIGURE 2 (**A**) Distribution of implants diagnosed with peri-implantitis (PI) (*n* = 45) according to marginal bone loss severity (<25%/25% to 50%/>50% of implant length); (**B**) categorization of implants diagnosed with PI according to baseline staging/grading and severity of MBL

TABLE 4 Risk of ≥25% bone loss according to periodontal diagnosis (stage and grade) adjusted by time since crown placement to radiographic analysis (RX)

	OR	95% CI	*P*
Stage			0.399
1-2	1		
3	0.26	0.04–1.93	0.186
4	0.25	0.03–2.16	0.209
Grade			
A-B	1		
C	7.61	1.35–43.1	0.022*
RX follow up (years)	1.11	0.97–1.28	0.127

The results of the binary logistic regression model were evaluated using GEE, adjusted odds ratio (OR), and 95% CI.

*$P < 0.05$;

†$P < 0.01$;

‡P < 0.001.

10.6 years. Patients were classified according to periodontal stage and grade at the time of active periodontal therapy. Over the follow-up period, only six implants (2.7%) failed. Although the implant failure rate increased from stage I/II (0%) to stage IV (6.5%), this trend was not statistically significant. A statistically significant increase was seen from grade A (0%) to grade C (5.9%). Interestingly, our results showed no correlation between PR staging or grading and increased prevalence/incidence of PI at either implant- or patient-levels. Although the 2017 World Workshop proposed case definitions for PI, these definitions do not facilitate differentiation between severity levels of PI based on the magnitude of MBL.[25,26] For the current analysis, a MBL severity threshold of 25% of the implant length was chosen to be correlated with PR stage and grade. The present study found that the severity of peri-implant MBL was directly associated with higher-level of grading. The periodontitis grade (C versus A-B) significantly influenced

risk of high MBL (>25%) (*P* = 0.022). Risk of severe MBL increased 7.6 times for patients with a previous history of periodontal grade C compared to grades A/B.

Overall, these results suggest that staging and grading may not play a role in modulating probability of PI onset, but once PI pathogenesis is initiated, higher-level grading is associated with increased severity of MBL and higher probability of implant failure, whereas staging is not.

4.2 | Agreement and disagreement with previous studies

There are conflicting results in the literature regarding the association between history of periodontitis and implant failure. Some of the previous studies utilizing the 1999 periodontal classification[27] reported higher long-term implant failure rates in patients who exhibited more severe forms of PR (survival rate range: 88% to 98.4%) compared to those who had moderate/mild PR (survival rate range: 92.8% to 100%).[28–32] However, others did not confirm this correlation.[33,34] In the present study, although a higher trend for implant failure was found in patients with a previous history of severe PR (stages III-IV), no statistically significant differences were found because of the small number of implants lost (only six).

Grade is a risk assessment tool composed of a composite of systemic (smoking and diabetes mellites) and local parameters (radiographic bone loss/age). To allow for a more precise analysis of the effects of grading on implant failure, systemic risk factors were evaluated separately. Implants placed in current heavy smokers were associated with a significantly higher failure rate compared to never-smokers (HR = 4.71; *P* = 0.04). A recent systematic review showed that heavy smokers (>20 cigarettes/d) were

at a higher risk for implant failure (HR = 4; $P < 0.001$) compared with non-smokers.[35] In addition, De Boever et al.[36] reported a 17% increased implant failure rate in current smokers with a history of aggressive periodontitis, and a 2% increase in former smokers. In spite of these findings, the 2017 World Workshop recently referred to smoking and diabetes as "inconclusive" risk indicators[1] for PI development because of a lack of conclusive evidence.[9]

Our findings also did not show a significant correlation between PR severity and PI prevalence. It is important to note that the present study population was entirely composed of PR patients with varying levels of severity. Most existing studies investigating the association between PR and PI compared PR patients to those with no previous history of PR.[10,36–38] However, very few correlated different levels of PR severity with prevalence and severity of PI.[28,31,39] Utilizing stage to categorize patients based on PR severity, results of the present investigation were similar to those from previously published studies which used other systems for diagnosing PR severity. Roccuzzo and co-workers reported a PI prevalence of 27% in patients with moderate PR, and 47.2% in patients with severe PR.[39] In a subsequent study, they reported a PI prevalence of 52.2% in patients with moderate PR, and 66.7% in patients with severe PR. In the current study, patients with mild and moderate severity PR (stage I and II) had a PI prevalence of 33.3%, whereas patients with severe PR (stage III and IV) had a PI prevalence of 52.7%. Despite this, the present study did not find any statistically significant association between PI prevalence and PR severity (stage).

The prevalence of PI at both the implant- and patient-levels in the present study can be compared to the results of Romandini et al., because this study also used the 2017 World Workshop definition of PI in a PR population.[3] Over a mean follow-up of 7.8 years at the patient-level, the authors reported a PI prevalence of 23.2% in healthy versus 56.6% in PR patients. At the implant-level, they found PI prevalence in healthy and PR patients was 12.4% and 27.9%, respectively. In comparison, the prevalence of PI in the present study was lower at a rate of 20.4% at the patient-level, and 15% at the implant-level after 10-years follow-up.

4.3 | Additional factors which influenced incidence of PI

Implant diameter and type of abutment-fixture connection were significantly associated with risk of PI development. Each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis (HR = 1.90; $P = 0.027$) (Table S3). Previous studies reported contradictory findings regarding implant diameter and PI

risk. The majority of studies reported a higher rate of PI for narrow diameter implants.[40–42] Others agreed with our study and showed that wider implants were associated with a higher MBL and risk of PI.[43,44] Overall, the evidence regarding implant diameter as a contributing factor towards PI pathogenesis is limited.

Additionally, implants with external connections were associated with significantly lower prevalence of PI when compared to internal connections (HR = 0.11; $P = 0.018$). Further investigation revealed that 100% of the implants with external connection in the current study had a machined surface, which have been associated with lower PI rates.[45,46] Previous meta-analyses have reported reduced MBL in conical internal connection implants, suggesting that the stability of the abutment-fixture connection is an important determinant of peri-implant bone levels.[47,48] Prior clinical studies have also demonstrated better bone preservation associated with internal connection implants relative to external connection implants.[49,50] The low number of external connection implants in our sample (18 fixtures), in conjunction with a machined surface for all of them, can potentially explain this controversial result.

4.4 | Limitations

The present study is not exempt from limitations. First of all, severe forms of PR may have reduced available bone quality and quantity, which in turn may potentially influence PI prevalence and severity.[15] Although this statement cannot be validated from our findings, our results did not show any significant difference in PI rates between different levels of PR staging or grading. Secondly, the small sample size in lower severity classes (stage I and grade A), which was dictated by their lower prevalence in the population[26] and by the exclusion of non-compliant patients (<1 maintenance/y) could have influenced the strength of the relationships evaluated during statistical analysis. For instance, grade C PR patients were associated with a much higher implant failure rate (HR = 6.57; $P = 0.075$), but the difference did not reach a level of statistical significance. The same can be seen for the stage; although all failed implants were found in patients with a history of stage III and IV PR, the comparison with stages I and II did not reach significance. Finally, factors contributing to PI were not totally accounted for, including but not limited to: implant (mal)positioning, residual cement, and prosthetic considerations (emergence profile and abutment height). Future studies should consider these factors to have a better understanding of how they may interact with a previous history of periodontitis in order to influence PI prevalence and severity.

5 | CONCLUSIONS

In a well-maintained compliant population with a history of periodontitis, no statistically significant association between staging or grading and prevalence of PI was found. However, when PI was diagnosed, increased severity of MBL and probability of implant failure were associated with a previous history of grade C periodontitis. Further studies are needed to confirm these preliminary findings.

CONFLICTS OF INTEREST

The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

AUTHOR CONTRIBUTIONS

Andrea Ravidà: Contributed to the conception and design of the study, acquisition of the data and drafting of the article. Musa Qazi: contributed to the acquisition of data. Maria Vera: contributed to the acquisition of data. Matthew Galli: contributed to the conception and design of the study and drafting of the article. Muhammad H. A. Saleh: contributed to the 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. Pablo Galindo Moreno: contributed to the conception, critical revision of the article and final approval of the version to be published.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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