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Prevalence and risk/protective indicators of peri-implant diseases: A university-representative cross-sectional study

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Abstract

Aim: To evaluate the prevalence of peri-implant diseases and to identify risk/protective indicators of peri-implantitis.

Materials and Methods: Two hundred and forty randomly selected patients from a university clinic database were invited to participate. Those who accepted, once data from their medical and dental history were collected, were examined clinically and radiographically to assess the prevalence of peri-implant health and diseases. Peri-implantitis was defined as the presence of BoP/SoP together with radiographic bone levels (BL) ≧2 mm. An intermediate peri-implant health category between peri-implant mucositis and peri-implantitis was also identified, defined by the presence of BoP/SoP together with 1 mm ≦BL < 2 mm. A multilevel multivariate logistic regression analysis was carried out to identify those factors associated either positively (risk) or negatively (protective) with peri-implantitis.

Results: Ninety-nine patients with a total of 458 dental implants were analyzed. The prevalences of pre-periimplantitis and of peri-implantitis were, respectively, 31.3% and 56.6% at patient-level, while 31.7% and 27.9% at implant level. The following factors were identified as risk indicators for peri-implantitis: smoking (OR = 3.59; 95% CI: 1.52–8.45), moderate/severe periodontitis (OR = 2.77; 95% CI: 1.20–6.36), <16 remaining teeth (OR = 2.23; 95% CI: 1.05–4.73), plaque (OR = 3.49; 95% CI: 1.13–10.75), implant malposition (too vestibular: OR = 2.85; 95% CI: 1.17–6.93), implant brand (Nobel vs. Straumann: OR = 4.41;95% CI: 1.76–11.09), restoration type (bridge vs. single crown: OR = 2.47; 95% CI: 1.19–5.12), and trauma as reason of tooth loss (vs. caries: OR = 6.51; 95% CI: 1.45–29.26). Conversely, the following factors were identified as protective indicators: interproximal flossing/brushing (OR = 0.27; 95% CI: 0.11–0.68), proton pump inhibitors (OR = 0.08; 95% CI: 0.01–0.90), and anticoagulants (OR = 0.08; 95% CI: 0.01–0.56).

Conclusions: Peri-implant diseases are highly prevalent among patients with dental implants in this university-based population. Several factors were identified as risk- and protective- indicators of peri-implantitis.

KEYWORDS
biological complications, biotype, cardiovascular diseases, cemented, cross-sectional studies, dental implants, dental prosthesis, diabetes mellitus, epidemiology, implant failure, implant loss, keratinized tissue, medications, oral hygiene, osteoporosis, overloading, peri-implantitis, periodontal diseases, platform switching, prevalence, risk factors, tooth-brushing, university-based

1 | INTRODUCTION

Peri-implantitis has been defined in the 2017 World Workshop as a plaque-associated pathological condition affecting tissues around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone (Berglundh, Armitage, et al., 2018; Schwarz et al., 2018). Peri-implantitis has shown a high prevalence among patients with dental implants for extended periods of time (Derks et al., 2016a; Derks & Tomasi, 2015; Rakic et al., 2018; Rodrigo et al., 2018; Romandini et al., 2019; Vignoletti et al., 2019; Wada et al., 2019) and, when proper therapy is not provided, its progression follows a non-linear and accelerating pattern, which can ultimately result in implant loss (Derks et al., 2016c).

Despite different non-surgical and surgical treatment strategies proposed for treating peri-implantitis, disease resolution is seldom the long-term outcome and even when achieved, recurrence may occur (Berglundh et al., 2018; Carcuac et al., 2017; Cha et al., 2019; Fig uero et al., 2014; Heitz-Mayfield et al., 2018; Nart et al., 2020; Ravidà, Saleh, et al., 2020; Roccuzzo et al., 2020; Roccuzzo et al., 2018; de Tapia et al., 2019). In light of this limited predictability, its prevention becomes of uttermost importance. The main strategy for preventing peri-implantitis is the management of peri-implant mucositis (Barootchi et al., 2020; Jepsen et al., 2015), since this condition is its reversible precursor (Berglundh, Armitage, et al., 2018; Costa et al., 2012). This approach should be combined with the control of modifiable risk factors, although presently there are a limited number of true risk factors of peri-implantitis demonstrated in prospective cohort investigations (Heitz-Mayfield et al., 2020; Heitz-Mayfield & Salvi, 2018; Schwarz et al., 2018). Consequently, a fundamental thrive in current implant research is the identification of further risk factors and indicators of peri-implant diseases.

Although many epidemiological studies have reported data on the prevalence and risk indicators of peri-implant diseases, there are only two epidemiological studies that have used representative samples (Derks et al., 2016a; Rodrigo et al., 2018), both of them referring to private settings and not to university clinics. Therefore, there is still a need of further studies in different settings and with representative samples, since the use of convenience samples (e.g., maintenance patients) may hamper the true analysis of the disease prevalence and risk indicators (Sanz & Chapple, 2012). It was, therefore, the aim of this cross-sectional study to analyze in a university-representative sample, the prevalence of peri-implant diseases as well as to study the risk/protective indicators of peri-implantitis.

2 | MATERIAL AND METHODS

The present cross-sectional study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007; Elm et al., 2007). It was conducted in accordance with the Helsinki Declaration of human studies, and the research protocol was ethically approved by the CEIC Hospital Clínico San Carlos, Madrid, Spain (19/182-E). All participants have provided their informed consent prior to the inclusion in the study.

2.1 | Sampling procedures

The sample size calculation was based on the null hypothesis that the prevalence of peri-implantitis in the present sample was the same as 45.0% in Derks et al., (2016a). For a 10% threshold in prevalence difference and with an alpha level set at 0.05, a sample of 96 participants would result in 80% power to reject the null hypothesis. Considering that this study was carried out on a representative sample, it was reasonable to select at least 200 participants, as it was expected a high declination rate (about 50%) of those invited to participate (e.g., due to change of city or telephone number, or death).

To generalize the results to all the patients who received implants in the Master of Periodontology of the Complutense University of Madrid, we used a complex protocol through a stratified multistage sampling (Sanz & Chapple, 2012; Tomasi & Derks, 2012). Three patients were randomly selected, by computer-generated randomization lists, from each periodontist (or postgraduate student in periodontology) that placed implants in at least 10 patients, from September 2000 to July 2017, in the referred clinic. During each academic year, periodontists who placed implants in less than 10 patients were grouped in a single category and 3 patients were also selected for this group.

The selected patients were invited to participate in the study by telephone calls on the numbers reported in their clinical charts, and if no response, the patient was not discarded until at least five attempts on different days have been made. All the implants osteointegrated in the patients' mouth at the time of the examination (including those placed in external clinics) and having at least 1 year of loading, either proven by dental charts or confirmed by the patients, were evaluated.

2.2 | Data collection

The participants who accepted to participate underwent a through data collection process, consisting of four phases: collection of demographic and medical/dental history data, a clinical examination, a radiographic examination, and an analysis of their past dental records. Its detailed description is reported in the Appendix S1.

Briefly, the history collection was structured in two steps. The first one (self-reported questionnaire) was based on the completion of written questionnaires by the study participants, after a brief explanation by one interviewer. The second step (structured interview) was based on a series of standardized questions asked by a trained interviewer.

The clinical oral examination was carried out by 2 calibrated examiners (CL & IP) and included the assessment of patient-, restoration-, and implant-related variables. Regarding patient-related variables, they included the assessment of periodontal status according to the AAP/CDC case definitions (Eke et al., 2012) and the number of remaining teeth. The implant supported restoration data included the type of restoration and its retention. The implant-related examination included the assessment of the location of each implant, its correct placement (adequate or mispositioned), the presence of adjacent teeth, keratinized tissue height (KTH), mobility of mucosal margin, peri-implant phenotype, tissue thickness, clinical signs of occlusal overloading on implants and of bruxism (Carra et al., 2012), and presence of a prosthetic design not allowing access to hygiene. Each implant was examined using a manual UNC-15 periodontal probe (PCP15; Hu-Friedy) at 6 sites/implant for the following measurements: presence of visible plaque, recession depth (Sanz-Martín et al., 2020), probing pocket depth (PPD), bleeding and suppuration on probing (BoP/SoP, within 30s). The two examiners were calibrated at the start of the study to apply the same examination criteria for each item, and the inter-rater agreement on 10 patients was also calculated (Appendix S1).

Peri-apical digital radiographs of the included implants were obtained from the Radiology Department. One calibrated investigator (CL) measured the marginal bone level (BL) from the implant shoulder to the first bone-implant contact, using a software program (Autocad 2016 TM, AutoDesk Inc.) (Flores-Guillen et al., 2018). One month after the initial evaluation, 50 randomly selected radiographs were re-measured by the same investigator to calculate the intra-examiner agreement (ICC = 0.98; 95% CI 0.96–0.99; $p < .001$).

Original dental charts for each of the included implants were also analyzed to extract data on the implant brand and the implant dimensions (length, width, eventual collar length, and follow-up). If the original information was not available (i.e., lost dental chart or implant placed outside the clinic), we attempted to deduce the obtainable information from the radiographs (Appendix S1). A validation of this method was performed on thirty randomly selected implants of known dimensions, which resulted in an ICC for implant length of 0.95 (95% CI 0.89–0.97; $p < .001$).

2.3 | Peri-implant health and diseases case definitions

Given the cross-sectional design of this investigation and the inclusion also of implants placed in external clinics where there was often no reliable information in regard to loading times, in most cases the baseline documentation to evaluate changes in PPD and in bone levels (i.e., bone loss) from 0 to 1 years after loading was unavailable. As a consequence, the following case definitions were used (Sanz & Chapple, 2012):

- Peri-implant health: absence of BoP/SoP;
- Peri-implant mucositis: presence of BoP/SoP together with radiographic BL <1 mm;
- Pre-periimplantitis: presence of BoP/SoP together with 1 mm ≦BL < 2 mm;
- Peri-implantitis: presence of BoP/SoP together with radiographic BL ≧2 mm.

Also in order to facilitate the comparison of the present findings with other studies, peri-implantitis was further reported with a BL ≧3 mm as severity cut-off (severe peri-implantitis), which corresponds to the 2017 World Workshop classification case definition for epidemiological studies (Berglundh, Armitage, et al., 2018).

2.4 | Data analysis

All statistical analyses were performed with STATA version 13.1 software (StataCorp LP). Descriptive characteristics regarding all the covariates were summarized. Peri-implant health and diseases prevalence (95% Confidence Interval—95% CI) were calculated both at implant- and at patient-level.

Peri-implantitis severity was expressed, in addition to reporting the prevalence of severe peri-implantitis (BL ≥3 mm threshold), as the mean bone levels among all the study implants with peri-implantitis and as the percentage of bone levels in relation to the implant length among all the implants with peri-implantitis.

The extent of peri-implantitis was assessed in patients with >1 implant, as the mean number and the percentage of affected implants in subjects with peri-implantitis.

Risk/protective indicators for peri-implantitis were studied using multilevel (mixed-effects) multivariate logistic regression analyses (patient- and implant-level). Due to the paucity of information on true risk factors available in literature, an exploratory approach was used. Each potential indicator was tested individually by adding it to an empty model having as dependent variable the peri-implantitis status and testing the significance. All variables that were significant at the 0.10 level were included in an intermediate multivariate model, and non-significant variables were sequentially removed. The final model included all factors that remained significant ($p < .05$).

3 | RESULTS

The sampling strategy resulted in the selection of 240 subjects and 109 of them accepted to participate receiving the examination. From this initial sample, one patient was excluded as only presenting one implant loaded from <1 year, while another patient was excluded due to the loss of all the implants. Due to the absence of readable radiographs of all the implants (i.e., the patient did not attend the radiographic examination or the image quality was low), 8 further patients were excluded from the present analysis, resulting in a total analyzed sample of 99 patients. Those 99 patients had a total of 475 implants; however, 2 implants were excluded since were loaded from <1 year and 15 of them due to the absence of readable radiographs. Consequently, the present analysis included a total of 99 patients with 458 dental implants with at least 1 year of loading time.

TABLE 1 General characteristics of the study population

	N = 99
Age (years), mean (*SD*)	63.7 (9.3)
Gender, *N* (%)	
Male	39 (39.4)
Female	60 (60.6)
Educational level, *N* (%)	
Primary school	32 (32.3)
High school	26 (26.3)
Middle grade	20 (20.2)
University/College	21 (21.2)
Smoking status, *N* (%)	
Non-smokers	41 (41.4)
Former smokers	40 (40.4)
Current smokers	18 (18.2)
Marital status, *N* (%)	
Married	73 (73.7)
Widow	6 (6.1)
Divorced	9 (9.1)
Never married	8 (8.1)
Living with unmarried partner	3 (3.0)
BMI (kg/m^2), mean (*SD*)	25.6 (3.7)
Diabetes status, *N* (%)	
No diabetes	83 (83.8)
Diabetes	16 (16.2)
Periodontal status (AAP), *n* (%)	
No/Mild periodontitis	27 (27.8)
Moderate/Severe periodontitis	61 (62.9)
Edentulous	9 (9.3)
Regular maintenance, *N* (%)	
No	46 (46.9)
Less than one/year	8 (8.2)
One/year	21 (21.4)
Two/year	19 (19.4)
Three or more/year	4 (4.1)

Note: Total number varies according to missing data for each variable.
Abbreviations: *N*, number; *SD*, standard deviation.

TABLE 2 General characteristics of the study implants

	N = 458
Jaw, *N* (%)	
Maxilla	253 (55.2)
Mandible	205 (44.8)
Position, *N* (%)	
Anterior (canine-canine)	83 (18.1)
Posterior	375 (81.9)
Side, *N* (%)	
Right	234 (51.1)
Left	224 (48.9)
Type of prosthesis, *N* (%)	
Single crown	136 (29.7)
Bridge	267 (58.3)
Overdenture	14 (3.1)
Full-arch fixed restoration	41 (8.9)
Prosthesis retention, *N* (%)	
Cemented	218 (47.6)
Screw-retained	226 (49.3)
Locator	8 (1.8)
Bar	6 (1.3)
Reason of tooth loss, *N* (%)	
Caries	185 (40.4)
Periodontitis	151 (32.9)
Trauma	15 (3.3)
Agenesia	8 (1.8)
Other reason/Unknown	99 (21.6)
Implant brand, *N* (%)	
S	230 (50.7)
N	57 (12.6)
A	76 (16.7)
Other	91 (20.0)
Implant length (mm), mean (*SD*)	9.9 (1.7)
Implant diameter (mm), mean (*SD*)	4.1 (0.4)

Note: Total number varies according to missing data for each variable.
Implant brands: S, Straumann; N, Nobel Biocare; A, AstraTech.
Abbreviations: *N*, number; *SD*, standard deviation.

3.1 | Descriptive statistics of the study population and implants

Table 1 and Table 2 provide descriptive statistics of the study population and implants. Most of the included patients were women

(60.61%), currently non-smokers (81.81%), with moderate/severe periodontitis (62.89%), and with a mean age at examination of 63.71 years. Most of the implants were placed in the maxilla (55.24%) and rehabilitated through bridges (58.30%) and screw-retained prostheses (49.34%). The follow-up time (or an estimation of it) was only available for 379 implants, resulting in a mean of 7.8 (*SD* = 4.4) years of loading; however, this value should be considered cautiously as—especially for the oldest cases—the information was often not available. The distribution of the potential risk/protective indicators in the study population and implants according to their peri-implant status is reported in Tables S1 and S2.

3.2 | Prevalence and severity of peri-implant health and diseases

The prevalence of peri-implant health and diseases is reported in Table 3.

At patient-level, the prevalence of peri-implant health was 1.0% (95% CI: 0.1–7.0), of peri-implant mucositis of 11.1% (95% CI: 6.2–19.1), of pre-periimplantitis of 31.3% (95% CI: 22.8–41.3), and of peri-implantitis of 56.6% (95% CI: 46.5–66.1). Severe peri-implantitis, corresponding to the case definition of the 2017 World Workshop classification, was present in 23.2% (95% CI: 15.8–32.7) of the participants.

At implant-level, the prevalence of peri-implant health was 8.5% (95% CI: 6.3–11.5), of peri-implant mucositis of 31.9% (95% CI: 27.8–36.3), of pre-periimplantitis of 31.7% (95% CI: 27.5–36.1), and of peri-implantitis of 27.9% (95% CI: 24.0–32.3). Severe peri-implantitis with BL ≧3 mm was present in 12.4% of the study implants (95% CI: 9.7–15.8).

The mean bone levels in the 128 implants presenting with peri-implantitis were 3.15 (*SD* = 1.30), while for the 57 implants with severe peri-implantitis were 4.10 (*SD* = 1.45). The bone levels at implants with peri-implantitis corresponded to 32.21% (*SD* = 13.14) of the intraosseous portion of the implant, while for severe peri-implantitis to 41.97% (*SD* = 13.74).

When considering a threshold of at least 4/6 sites with BoP/SoP, the prevalence of peri-implantitis decreased, with a corresponding increase of peri-implant health cases (27.27%–95% CI: 19.3–37.0 at patient-level and 55.24%–95% CI: 50.6–59.8 at implant-level).

3.3 | Extent of peri-implantitis

Peri-implantitis was detected in 55 of 89 patients with >1 implant. The mean number of implants in this category of participants was 5.20 ± 2.91, and the mean number of implants with peri-implantitis was 2.31 (DS = 1.71), which represented 43.57% (*SD* = 25.44) of their implants.

3.4 | Risk/protective indicators for peri-implantitis

In univariate analyses, peri-implantitis was associated ($p < .1$), either in a direct or inverse manner, with the following patient-level characteristics (Table S3): smoking status, history of cardiovascular diseases, history of osteopenia/osteoporosis, periodontal status, history of periodontal treatment, interproximal flossing and/or brushing on implants, tooth-brushing frequency, number of remaining teeth, use of proton pump inhibitors (PPIs), use of anticoagulants, and use of insulin. Moreover, it was associated ($p < .1$) with the following implant-level variables (Table S4): presence of plaque, keratinized tissue height, tissue thickness, peri-implant phenotype, vestibular-lingual position of the implant, implant brand, restoration type, restoration retention, reason of tooth loss, position of the replaced tooth, presence of an adjacent tooth, clinical signs of occlusal overloading, and presence of platform switching.

However, in the final multilevel multivariate logistic regression model (Table 4), only the following patient-level factors remained significant at the 0.05 level: smoking status (smokers versus non-smokers: OR = 3.59; 95% CI: 1.52–8.45), periodontal status (moderate/severe periodontitis versus no/mild periodontitis: OR = 2.77; 95% CI: 1.20–6.36), interproximal flossing/brushing

TABLE 3 Prevalence of peri-implant health and diseases

	Patient-level		Implant-level	
	Inflammation cut-off: BoP/SoP at least 1/6 site	*Inflammation cut-off: BoP/SoP at least 4/6 sites*	*Inflammation cut-off: BoP/SoP at least 1/6 site*	*Inflammation cut-off: BoP/SoP at least 4/6 sites*
Peri-implant health, *N* (%) (95% CI)	1 (1.0) (0.1–7.0)	27 (27.3) (19.3–37.0)	39 (8.5) (6.3–11.5)	253 (55.2) (50.6–59.8)
Peri-implant mucositis, *N* (%) (95% CI)	11 (11.1) (6.2–19.1)	18 (18.2) (11.7–27.2)	146 (31.9) (27.8–36.3)	82 (17.9) (14.6–21.7)
Pre-Periimplantitis, *N* (%) (95% CI)	31 (31.3) (22.8–41.3)	23 (23.2) (15.8–32.7)	145 (31.7) (27.5–36.1)	65 (14.2) (11.3–17.7)
Peri-implantitis[a], *N* (%) (95% CI)	56 (56.6) (46.5–66.1)	31 (31.3) (22.8–41.3)	128 (27.9) (24.0–32.3)	58 (12.7) (9.9–16.0)

Note: N, number; BoP, bleeding on probing; SoP, suppuration on probing; BL, bone levels at the examination.

[a]Corresponding to the Sanz and Chapple (2012) peri-implantitis case definition. The prevalence of severe cases (corresponding to the 2017 World Workshop peri-implantitis case definition for epidemiological studies) is reported in the text.

TABLE 4 Risk/protective indicators associated with peri-implantitis: multilevel multivariate logistic regression analysis

	Empty model		Final model		
Variable	**OR**	**95% CI**	**OR**	**95% CI**	***p-value***
Fixed part					
Intercept	0.27	0.18–0.41	0.06	0.01–0.27	
Smoking status					
Non-smoker			*Ref*	*Ref*	*Ref*
Former smoker			1.89	0.90–3.98	.094
Current smoker			3.59	1.52–8.45	.003
Periodontal status (AAP)					
No/Mild periodontitis			*Ref*	*Ref*	*Ref*
Moderate/Severe periodontitis			2.77	1.20–6.36	.017
Edentulous			1.30	0.31–5.52	.719
Interproximal flossing/Brushing on implants					
No			*Ref*	*Ref*	*Ref*
At least on some implants			0.27	0.11–0.68	.006
Number of remaining teeth					
≥16 Teeth			*Ref*	*Ref*	*Ref*
<16 Teeth			2.23	1.05–4.73	.036
Proton pump inhibitors					
No			*Ref*	*Ref*	*Ref*
Yes			0.08	0.01–0.90	.040
Anticoagulants					
No			*Ref*	*Ref*	*Ref*
Yes			0.08	0.01–0.56	.010
Plaque					
0 sites/implant			*Ref*	*Ref*	*Ref*
1–5 sites/implant			1.35	0.66–2.77	.407
6 sites/implant			3.49	1.13–10.75	.030
Implant brand					
S			*Ref*	*Ref*	*Ref*
N			4.41	1.76–11.09	.002
A			0.49	0.20–1.16	.104
Other			1.51	0.73–3.12	.269
Restoration type					
Single crown			*Ref*	*Ref*	*Ref*
Bridge			2.47	1.19–5.12	.015
Overdenture			4.58	0.46–45.35	.193
Full-arch fixed restoration			3.99	0.82–19.54	.087
Reason of tooth loss					
Caries			*Ref*	*Ref*	*Ref*
Periodontitis			1.36	0.65–2.85	.419
Trauma			6.51	1.45–29.26	.015
Agenesia			1.48	0.21–10.43	.696
Other reason/Unknown			0.59	0.24–1.42	.239
Vestibular-lingual position					
Correct			*Ref*	*Ref*	*Ref*

(Continues)

TABLE 4 (Continued)

Variable	Empty model OR	Empty model 95% CI	Final model OR	Final model 95% CI	*p-value*
Too vestibular			2.85	1.17–6.93	.021
Too lingual			1.57	0.62–4.00	.345
Random part					
Patient variance	1.65	0.81–3.35	0.39	0.96–1.59	
AIC	510.411		462.979		

Note: Implant brands: S, Straumann; N, Nobel Biocare; A, AstraTech.

Abbreviations: AIC, Akaike´s information criterion; CI, confidence interval; OR, odds ratio; Ref, reference category.

The estimate of $\sigma 2$ was 0.39 with standard error (*SE*) 0.28 A likelihood-ratio test comparing the model to ordinary logistic regression was performed and identified as highly significant for these data ($p < .001$). The intra-class correlation (ICC) at the patient level showed that 33.4% (ICC 0.33; 95% CI 0.19–0.50) of the correlation was due to variation among patients and 66.6% due to variations among implants.

on implants (OR = 0.27; 95% CI: 0.11–0.68), number of remaining teeth (<16 versus ≧16: OR = 2.23; 95% CI: 1.05–4.73), use of PPIs (OR = 0.08; 95% CI: 0.01–0.90), and use of anticoagulants (OR = 0.08; 95% CI: 0.01–0.56). Moreover, also the following implant-level factors were significant ($p < .05$): presence of plaque (6 sites/implant versus 0 sites/implant: OR = 3.49; 95% CI: 1.13–10.75), implant brand (N versus S: OR = 4.41; 95% CI: 1.76–11.09), restoration type (bridge versus single crown: OR = 2.47; 95% CI: 1.19–5.12), reason of tooth loss (trauma versus caries: OR = 6.51; 95% CI: 1.45–29.26), and vestibular-lingual position (too vestibular versus correct: OR = 2.85; 95% CI: 1.17–6.93). A sensitivity analysis adding to the final model the presence or not of an implant collar (inferior to 1.8 mm or ≧1.8 mm) did not lead either to a significance of that variable or to the loss of significance of the implant brand. Similarly, no differences were observed when separating in the reference group brand the tissue-level implants from the bone-level ones 4.

4 | DISCUSSION

This cross-sectional investigation on a representative sample from patients treated in a university postgraduate clinic has shown that peri-implant diseases are highly prevalent among subjects with dental implants. More than 50% of the participants had peri-implantitis, which affected a mean of more than 2 implants in each of those patients. Smoking, moderate/severe periodontitis, having less than 16 remaining teeth, plaque, too vestibular position, implant brand, bridge as restoration type, and trauma as reason of tooth loss were identified as risk indicators of peri-implantitis, while interproximal flossing/brushing, PPIs, and anticoagulants as protective ones.

A peculiarity of the data reported in the present study was the use of an intermediate peri-implant health category between peri-implant mucositis and peri-implantitis, denominated pre-periimplantitis. The need to establish this category resulted from the difficulty in identifying initial bone loss in the absence of baseline radiographs. Indeed, it is likely that in such category, cases of both peri-implant mucositis and incipient peri-implantitis have been included. This condition was present in 31.7% of the included implants, what highlights the need of having reliable documentation to detect early bone changes and hence, diagnose incipient peri-implantitis, which should be amenable for predictable treatment outcomes. Similarly, if the cases of peri-implant mucositis present bone levels between 1 and 2 mm, these are probably more amenable for evolving to peri-implantitis and therefore their appropriate management should be a priority.

When comparing the present results with the available literature, these participants demonstrate a slightly higher prevalence and severity of peri-implantitis, counterbalanced by a low prevalence of peri-implant health (Derks et al., 2016a; Derks & Tomasi, 2015; Kordbacheh Changi et al., 2019; Rakic et al., 2018; Rodrigo et al., 2018; Romandini et al., 2019; Wada et al., 2019). This finding may be partially related to the characteristics of the present population, which was extrapolated from a university periodontal clinic, resulting in an inferior proportion (27.8%) of participants with no/mild periodontitis when compared to the other studies. Despite this higher prevalence of periodontitis, the present sample was characterized by a scarce control of the disease, being <50% the patients with at least one maintenance session/year (Amerio et al., 2020) and 17.9% the plaque-free implants, thus predisposing even more to high peri-implantitis prevalence.

Another aspect that is likely to have influenced the reported prevalence was related to the clinical assessment methods employed. In the present study, BoP was considered positive even in case of one single site out of six presenting with a punctiform drop of blood after deep probing to assess PPD. This strict evaluation method resulted in 91.5% of BoP + implants, potentially contributing to the high prevalence of peri-implant diseases. We may speculate that, around implants, there are different methods to assess BoP, including profuse versus punctiform bleeding (Renvert et al., 2018), or evaluating bleeding after deep probing to assess PPD versus its evaluation *per sé* by walking marginally with the probe through the peri-implant sulcus. Since these methods have not been standardized among the published studies, this may have contributed to the different reported prevalence in comparison to the present study. The use of a more conservative threshold for peri-implant inflammation (BoP/

SoP in at least 4 sites/implant) resulted in 55.2% of the implants presenting with peri-implant health.

Finally, another possible explanation is that the present study included all the implants loaded from at least 1 year which were in the mouth of the selected participants at the time of the examination, resulting in a mean of 4.6 implants/patient. Conversely, most of the studies in the literature only analyzed a subset of implants of the included patients (e.g., the ones placed in the same clinic), leading to a lower number of implants/patient (e.g., 1.7 for Rodrigo et al., 2018; 2.5 for Kordbacheh Changi et al., 2019; 3.0 for Wada et al., 2019; 3.5 for Vignoletti et al., 2019). This approach prevented in the present study the risk to underestimate the patient-level prevalence of diseases (as, on the contrary, affected implants may be excluded from the analysis in otherwise healthy patients).

The extent of peri-implantitis in patients with >1 implant was 43.6%. This percentage is similar to the few reports of this epidemiological descriptor which are present in the literature, which ranges from 37.2% of Mir-Mari et al. (Mir-Mari et al., 2012) to 38.2% of Vignoletti et al., (2019), 40.1% of Derks et al. (Derks et al., 2016a), and 41.8% of Fransson et al. (Fransson et al., 2009).

When it comes to risk/protective indicators, the present study was able to identify several factors associated with peri-implantitis. Presence of plaque and the non-use of interproximal hygiene devices were indicators of poor oral hygiene, what has previously reported as a risk indicator with strong evidence for peri-implantitis (Ferreira et al., 2006; Schwarz et al., 2018). Similarly, the association of the restoration type (bridges versus single crowns) has also been reported in previous studies (e.g., Rodrigo et al., 2018) and may be explained by the more difficult access to oral hygiene procedures.

An association with moderate/severe, but not mild, periodontitis was also found, which is in agreement with most of the epidemiological evidence (Derks et al., 2016a; Roos-Jansaker et al., 2006) (Kordbacheh Changi et al., 2019). The association with the number of remaining teeth could also be interpreted as due to periodontitis, where stage IV cases with extensive tooth loss are characterized by worst peri-implant conditions, and this agrees with studies reporting a different measure of tooth loss (the number of implants) as risk indicator (Derks et al., 2016a; Vignoletti et al., 2019).

Regarding the association with smoking, the literature is controversial, with some studies reporting a significant association (Pimentel et al., 2018; Roos-Jansaker et al., 2006), while others not (Dalago et al., 2017; Derks et al., 2016a). This might be interpreted as a "masking effect" due to periodontitis. However, in the present study, this was not the case and smoking had even a stronger association with peri-implantitis than periodontitis.

Implant brand has been previously reported as a risk indicator for peri-implantitis (Derks et al., 2016a), which is in agreement with the present findings. While in the study of Derks et al., (2016a) this finding was potentially explainable by the simple presence or not of a collar in the implant design (the reference group was represented by a brand composed at that time only of tissue-level implants), in the present study the sensitivity analyses adding to the final model the presence or not of an implant collar, or separating in the reference group the tissue-level implants from the bone-level ones, allowed to discard this hypothesis.

New associations were also found for previously neglected factors. Malposition implants have been considered associated to peri-implant diseases (Canullo et al., 2016), but most of the previous studies have not systematically studied this factor. In the present study, implants placed too facially accounted for an OR superior than periodontitis, thus supporting this hypothesis. Medications have previously shown to influence implant failures (Chappuis et al., 2018); however, there is a paucity of studies analyzing their relation with peri-implant diseases. The use of anticoagulants and of PPIs have resulted as significant protective indicators, what may be explained by their secondary anti-inflammatory effects (Kedika et al., 2009; Müller et al., 2015). Finally, trauma as reason for tooth extraction has shown in the present study the highest OR for an association with peri-implantitis. It may be speculated that implants placed after trauma are more frequently placed with type 1 protocols and/or in conjunction with bone augmentation procedures, thus indirectly suggesting a potential role of those factors as risk indicators for peri-implantitis.

Contrarily to other studies, other putative risk indicators were not associated with peri-implantitis in this investigation. Among them, the KTH (Monje & Blasi, 2019; Vignoletti et al., 2019), the retention type (cemented-retained restorations—Kordbacheh Changi et al., 2019; Staubli et al., 2017), the emergence angle and profile (Katafuchi et al., 2018), the fitness of the prosthesis (Kordbacheh Changi et al., 2019), and a prosthetic design not allowing access to hygiene (Rodrigo et al., 2018). The final multilevel multivariate model of the present study included plaque and interproximal brushing/flossing around implants, and this may be the reason why those factors were not associated with peri-implantitis, even if KTH and cemented restorations were significantly associated in the univariate analyses. Similarly, clinical signs of occlusal overloading were associated to peri-implantitis in univariate but not in multivariate models, which is supported by previous studies (Schwarz et al., 2018). Conversely, even if a strong evidence exists for the absence of regular maintenance (Monje et al., 2016, 2017; Schwarz et al., 2018), the present study was not able to highlight this factor as risk indicator for peri-implantitis. This might be due to the self-reported assessment of maintenance frequency, as well as to a higher frequency of maintenance recalls of the most severe periodontitis patients, which are also at increased risk for peri-implantitis.

The present study has reported the prevalence and the risk/protective indicators of peri-implant diseases from a representative sample in a university postgraduate dental clinic, thus minimizing the risk of selection bias. Contrarily to most published data, all implants present in the selected participants (not only the ones placed in the clinic) were analyzed, thus preventing the risk to underestimate the patient-level prevalence of peri-implant diseases. The analysis of many risk/protective indicators of peri-implantitis has allowed to construct a model explaining a great proportion of patient variance. However, this study also has some limitations worth mentioning. Its cross-sectional design does not allow to prove any

causality of the identified risk/protective indicators on peri-implantitis. Moreover, as with most of similar studies reported in the literature, the absence of baseline documentation did not allow to identify peri-implantitis through direct evidence, what may lead to misclassification bias. Moreover, some of the tested potential risk/protective indicators were not collected with gold standard methods (e.g., self-reported history) or suffered from subjective evaluation methods (e.g., malposition, overloading). Since the sample size calculation was performed based on prevalence data, some of the tested risk/protective indicators may lack the appropriate statistical power to enter in the final model; on the contrary, some of the associations found (e.g., PPIs and anticoagulants) are based on only few cases. Another limitation was the impossibility to obtain reliable information regarding previous peri-implantitis treatment (Ravidà, Galli, et al., 2020), loading times, and the implant placement surgical protocols employed, which prevented us to include such information in the analyses. Finally, even if representative from a university clinic, the present results suffer from limited generalizability since different prevalence and risk/protective indicators may be found in other populations.

The symptoms and perception reported in the present cohort by patients with peri-implant diseases, as well as their signs and their potential impact on the oral health quality of life, are reported elsewhere (Romandini et al., 2020).

5 | CONCLUSIONS

According to the present study, peri-implant diseases are highly prevalent among patients with dental implants. Several patient-level and implant-level factors were identified as risk and protective indicators of peri-implantitis, which in case of future proof of causality should be included in preventive and therapeutic strategies. Consequently, randomized clinical trials or, when not possible for ethical reasons or as not modifiable, prospective cohort studies are needed to demonstrate true causality of the identified risk/protective indicators and to study the preventive efficacy of their modification.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study. This study was partially funded by the Osteology Foundation through a Young Research Grant to Dr. Mario Romandini (project n. 15–251).

AUTHOR CONTRIBUTION

M.R. conceived the ideas; C.L., I.P., A.A., M.C.S. and M.R. collected the data; M.R., M.C.S. and M.S. analysed the data; and M.R. and M.S. led the writing.

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SUPPORTING INFORMATION

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

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