UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE ODONTOLOGÍA

TESIS DOCTORAL

Factores de riesgo y parámetros de diagnóstico de la periimplantitis – Un estudio prospectivo de cohorte

Risk factors and diagnostic parameters of peri-implantitis – A prospective cohort study

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Cristina Maria Gonçalves Esteves Rodrigues Lima

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Aos meus pais

Aos meus avós

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PREFACE

This doctoral thesis is based on the following articles:

Study #1:

Romandini, M., Lima, C., Bacaco, D., Azevedo, R., Sanz, M. Incidence and Risk Factors of Peri-implantitis Over Time – A Prospective Cohort Study.

Journal of Periodontology Research. DOI: 10.1111/jre.13367 (accepted for publication)

(Appendix 1)

Study #2:

Romandini, M., Lima, C., Moreno, M., Sanz, M. Accuracy of Clinical Parameters in Predicting/Diagnosing Peri-Implant Bone Loss.

Journal of Clinical Periodontology. DOI: 10.1111/jcpe.14095 (accepted for publication)

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I. ABSTRACT

ABSTRACT

Background: Primary prevention and early diagnosis are essential in managing peri-implantitis, particularly given its high prevalence and rapid progression. Prevention strategies also comprise managing modifiable risk factors. The identification of risk and protective factors requires a longitudinal assessment to validate the temporality criterion. However, most available evidence on peri-implantitis risk factors is based on cross-sectional studies.

The diagnosis of peri-implantitis relies on clinical assessments of probing pocket depth (PPD), bleeding on probing (BoP) and suppuration on probing (SoP), together with a radiographic examination. Identifying clinical parameters relevant for diagnosing a history of bone loss or predicting its future incidence would be clinically relevant. However, studies investigating beyond the dichotomous definition (BoP) (e.g., BoP extent and severity) and changes in PPD / peri-implant soft tissue dehiscence over time are still needed.

Aims: Study #1: To evaluate the incidence and risk factors associated with peri-implantitis in a longitudinal framework; and Study #2: to identify which clinical parameters are relevant for diagnosing a history of bone loss or predicting its future incidence.

Material and Methods: Seventy-three patients with 322 implants were evaluated at baseline and after a mean follow-up of 3.9 (SD=0.3) years.

At baseline, patients underwent thorough data collection in four phases: demographic and medical/dental history, clinical examination, radiographic examination, and analysis of past dental records. At follow-up, clinical and radiographic parameters of the included implants were re-assessed.

The main outcomes were: Study #1: incidence of peri-implantitis, defined as bone loss>1 mm with BoP; Study #2: peri-implant bone loss >1 mm between the two examinations. Multi-level multiple logistic regression analyses were performed to identify (i) baseline putative risk/protective factors associated with incidence of peri-implantitis and (ii) baseline clinical parameters predicting the incidence of bone loss or associated at follow-up with a history of bone loss between the two examinations, reporting sensitivity, specificity, positive/negative predictive values, and area under the curve (AUC) values.

Results: Peri-implantitis was detected in 28 (9.4%) implants. The patient-level risk factors for bone loss were: stage IV periodontitis (OR=41.29), periodontal bone loss/age ratio >1 (OR=8.87), current smoking (OR=7.84), and sleep duration >7 hours (OR=19.97). The implant-level risk factors identified were: incisor position (OR=60.60), full-arch fixed restoration (OR=89.84), juxta-marginal implant-supported rehabilitations (vs. supra-marginal: OR=14.17).

Redness at baseline presented high sensitivity (96.4%) in predicted future bone loss. Conversely, high specificity but low sensitivity was observed for BoP at 6 sites (sensitivity = 25.0%; specificity = 88.1%) and SoP (sensitivity = 14.3%; specificity = 91.5%). At follow-up, high specificity for diagnosing recent bone loss >1 mm was found for: profuse bleeding (91.9%), PPD ≥6mm (81.9%), PPD increase >1 mm (95.9%), and soft-tissue dehiscence increase >1 mm (91.5%). The best diagnostic accuracy was achieved using a combined criterion of site-specific PPD or PISTD increases >1 mm over time (sensitivity = 82.1%; specificity = 70.0%; AUC = 0.76).

Conclusion and Clinical implications: Periodontitis stage and grade, smoking status, sleep duration, implant location, and restorative characteristics are longitudinally

associated with the incidence of bone loss. Peri-implant bone loss appears to be preceded by BoP and visual redness in the peri-implant soft tissues. Implants with BoP at 6 sites or SoP are more likely to exhibit bone loss over time. The presence of profuse bleeding, BoP at six sites, SoP, deep PPD, and increases in PPD or soft-tissue dehiscence are indicative of a history of bone loss, with high levels of specificity.

RESUMEN

Antecedentes: La prevención primaria y el diagnóstico precoz son esenciales para el tratamiento de la periimplantitis, especialmente dada su elevada prevalencia y rápida progresión. Las estrategias de prevención también comprenden la gestión basada en el control de los factores de riesgo modificables. La identificación de los verdaderos factores de riesgo y de protección requiere una evaluación longitudinal para verificar el criterio de temporalidad. Sin embargo, la mayoría de las pruebas disponibles sobre los factores de riesgo de periimplantitis se basan en estudios transversales, lo que dificulta la asociación temporal. El diagnóstico de la periimplantitis se basa en evaluaciones clínicas de la profundidad de sondaje, el sangrado al sondaje y la supuración, junto con un examen radiográfico. La identificación de parámetros clínicos relevantes para diagnosticar un historial de pérdida ósea o predecir su incidencia futura sería clínicamente relevante. Sin embargo, aún son necesarios estudios que investiguen más allá de la definición dicotómica del sangrado a sondaje (por ejemplo, extensión y severidad) y los cambios en la profundidad de sondaje / dehiscencia de tejidos blandos periimplantarios a lo largo del tiempo.

Objetivos: Estudio #1: (i) Evaluar la incidencia y los factores de riesgo/protectores asociados a la incidencia de la periimplantitis; y Estudio #2: (ii) identificar qué parámetros clínicos son relevantes para diagnosticar una historia de pérdida ósea o predecir su incidencia futura.

Material y métodos: Setenta y tres pacientes con 322 implantes fueron evaluados al inicio y tras un seguimiento medio de 3,9 (SD=0,3) años.

En basal, se realizó una exhaustiva recogida de datos en cuatro fases: historia demográfica y médico-dental, examen clínico, examen radiográfico y análisis de los

registros dentales anteriores. En el seguimiento, se volvieron a evaluar los parámetros clínicos y radiográficos de los implantes incluidos.

Los resultados principales fueron: Estudio nº 1: incidencia de periimplantitis, definida como pérdida ósea > 1 mm con sangrado a sondaje en al menos una localización; Estudio nº 2: pérdida ósea periimplantaria > 1 mm entre los dos exámenes.

Se realizaron análisis de regresión logística multinivel para identificar (i) los factores de riesgo/protectores putativos basales asociados a la incidencia de pérdida ósea-periimplantitis y (ii) los parámetros clínicos basales que predecían la incidencia de pérdida ósea; o asociados en la evaluación de seguimiento a histórico de pérdida ósea ocurrida entre los dos exámenes. Los valores de sensibilidad, especificidad, valores predictivos positivos/negativos y área bajo la curva (AUC) fueran determinados.

Resultados: Se detectó periimplantitis en 28 (9,4%) de los implantes. Los factores de riesgo a nivel de paciente para la pérdida ósea fueron: periodontitis estadio IV (OR=41,29), relación pérdida ósea periodontal/edad >1 (OR=8,87), tabaquismo actual (OR=7,84) y duración del sueño >7 horas (OR=19,97). Los factores de riesgo a nivel implante identificados fueron: posición del implante en incisivos (OR=60,60), restauración fija de arcada completa (OR=89,84), rehabilitaciones implanto-soportadas yuxta-marginales (*vs* a supra-marginales: OR=14,17).

El enrojecimiento de los tejidos blandos, valorado en basal, presentó una alta sensibilidad (96,4%) en predecir la pérdida ósea futura. Por el contrario, se observó una alta especificidad, pero una baja sensibilidad, para el sangrado al sondaje en 6 localizaciones (sensibilidad = 25,0%; especificidad = 88,1%) y supuración (sensibilidad = 14,3%; especificidad = 91,5%). En el examen de seguimiento, se observó una alta especificidad para el diagnóstico de la historia reciente de pérdida ósea >1 mm para:

sangrado al sondaje profuso (91,9%), profundidad de sondaje ≥6 mm (81,9%), aumento de la profundidad de sondaje >1 mm (95.9%) y aumento de la dehiscencia de tejido blando >1 mm (91.5%). La mejor exactitud diagnóstica se alcanzó utilizando un criterio combinado de aumentos de profundidad de sondaje y de dehiscencia de tejido blando >1 mm (sensibilidad = 82,1%; especificidad = 70,0%; AUC = 0,76).

Conclusiones e implicaciones clínicas: El estadio y grado de la periodontitis, el hábito tabáquico, la duración del sueño, la localización del implante y las características restauradoras se asocian con la incidencia de pérdida ósea. La presencia de enrojecimiento visual en los tejidos blandos periimplantarios y sangrado a a sondaje parecen predecir la pérdida ósea periimplantaria. Los implantes con sangrado a sondaje en 6 localizaciones o supuración tienen más probabilidades de presentar pérdida ósea en el tiempo. La presencia de sangrado profuso, sangrado en seis localizaciones, supuración, profundidad de sondaje profunda y aumento de la profundidad de sondaje o dehiscencia de los tejidos blandos son indicativos de antecedentes de pérdida ósea, con altos niveles de especificidad.

II.INTRODUCTION

II. INTRODUCTION

Peri-implant diseases are plaque-associated pathologies occurring around dental implants characterized by clinical signs of inflammation (Monje, Insua, et al., 2018; Salvi et al., 2012; Zitzmann et al., 2001) and comprise peri-implant mucositis and peri-implantitis. The primary distinction between the diseases lies in the hallmark feature of bone loss observed in peri-implantitis (Berglundh et al., 2018).

The 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (2017 WWP) proposed case definitions of peri-implant health status, that should be incorporate in future epidemiologic studies (Berglundh et al., 2018). The diagnosis of peri-implantitis is established based on the presence of bleeding on probing (BoP) and/or suppuration on probing (SoP), increased probing depth (PPD) and radiographic evidence of bone loss over time. This case definition implies the longitudinal assessment of clinical and radiographic parameters, underlining the pivotal importance of baseline documentation to identify peri-implantitis in its early phases (Berglundh et al., 2018; Lang et al., 2011). The consensus established a precise clarification and distinction between direct and indirect evidence of peri-implantitis detection, contingent on the availability of previous clinical and radiographic data. In the absence of previous examinations, peri-implantitis diagnosis relies on specific thresholds of PPD (≥6mm) and bone levels (≥3mm), in addition to BoP and/or SoP (Berglundh et al., 2018).

Once peri-implantitis is established progression follows a non-linear accelerating pattern of bone loss, with an initial slower rate phase that increases and accelerates over time (Derks et al., 2016b). Progression usually courses without symptoms

(Romandini, Lima, Pedrinaci, Araoz, Costanza Soldini, et al., 2021) and ultimately culminates in implant loss (Herrera et al., 2023). Early diagnosis is therefore crucial for prompt implementation of therapy that involves a stepwise approach focused in attaining disease resolution, defined as a composite outcome of shallow PPD (≤5 mm), absence of SoP and BoP in ≤1 site (Herrera et al., 2023).

Despite the implementation of recommended therapy high recurrence rates have been reported (Carcuac et al., 2020; Heitz-Mayfield et al., 2018; Karlsson et al., 2023) with probability of treatment success inversely related to the severity of the disease (de Waal et al., 2016; Ichioka et al., 2023; Koldsland et al., 2018; Ravida et al., 2022), further emphasizing the critical importance of early diagnosis.

Considering the aforementioned arguments, it is crucial to enroll patients in supportive peri-implant therapy focusing in the primary prevention of the disease (Carra et al., 2023; Tonetti et al., 2015). Prevention aims to achieve and maintain peri-implant tissues clinically healthy, without signs of inflammation, through effective self-performed and professionally removal of supra- and subgingival biofilm. Additionally, regular assessment of clinical parameters and radiographic examination, when deemed necessary, should be performed to enable early diagnosis of peri-implant diseases (Herrera et al., 2023).

Primary prevention aims on precluding diseases onset and controlling associated risk factor. In the context of peri-implantitis, primary prevention also includes the treatment of peri-implant mucositis to advert disease progression (Jepsen et al., 2015). The preventive strategies implementation must be tailored to the individual risk profile and targeting modifiable risk factors (Carra et al., 2023).

2.1 PREVALENCE OF PERI-IMPLANTITIS

Peri-implant diseases are a frequent clinical finding described across different populations and clinical settings (Dalago et al., 2017; Derks et al., 2016a; Ogata et al., 2017; Rodrigo et al., 2018; Vignoletti et al., 2019).

The heterogeneous sample size, function time and case definitions among cross-sectional studies have a direct impact on the reported prevalence of peri-implantitis. In fact, the bone level thresholds used in case definitions varied from unspecified to 5mm, consequently patient-level prevalence ranged from 8.9 % to 47% (Derks & Tomasi, 2015; Ferreira et al., 2006; Koldsland et al., 2011).

Nevertheless, the weighted mean prevalence of peri-implantitis across meta-analysis reached 21.7% at patient-level (Derks & Tomasi, 2015) and ranged from 9.4% (Lee et al., 2017) to 12.8% (Rakic et al., 2018) at implant-level.

Although the majority of cross-sectional studies that evaluated the prevalence of peri-implantitis have used convenience samples, it is recognized that the extrapolation of the results to the population demands a randomized sample selection (Derks and Tomasi, 2015).

Derks et al., (2016a) cross-sectional study was based on a randomized Swedish population of 588 patients, that received dental implants 9 years before, and reported a prevalence of moderate/severe peri-implantitis (defined as presence of BoP/ /suppuration and bone loss >2 mm) in 14,5% of subjects.

In Spain, among convenience samples of patients undergoing maintenance therapy, the prevalence of peri-implantitis was reported to range from 10.3% to 16.3% at patient level (Aguirre-Zorzano et al., 2015; Canullo, Penarrocha-Oltra, et al., 2016; Mir-Mari et al., 2012).

More recent studies have found an even higher prevalence (Rodrigo et al., 2018; Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021). In a study involving private settings across Spain, 49 sentinel dentists evaluated 275 patients and 474 implants. Peri-implantitis (bone level ≥ 2mm and BoP) was diagnosed in 24% of the patients and 20% of the implants and clinically associated to the presence of plaque, swelling and suppuration (Rodrigo et al., 2018).

2.2 INCIDENCE OF PERI-IMPLANTITIS

The onset of peri-implantitis has been reported to occur early (Derks et al., 2016b). Fransson et al. identified early bone loss ≥ 1 mm in 68% of the implants, at 1 year after loading. Aditionally, bone loss ≥2 mm and ≥3 mm occurred, respectively, in 32% and 10% of the 419 evaluated implants (Fransson et al., 2010). Moreover, baseline bone levels appear to predict subsequent changes in bone levels (Trombelli et al., 2024). In fact, a bone loss ≥ 0.5 mm during the first year of function was related to a higher risk (5.43 higher odds) of peri-implantitis onset (Windael et al., 2021).

A retrospective study evaluated 105 implants (53 patients) diagnosed with moderate/severe peri-implantitis (BoP/suppuration and >2 mm of bone loss) at the 9-year examination. The analysis indicated an estimated bone loss >1 mm in 47% of implants at 3 years and in 73% at 5 years of function. Bone loss >3 mm occurred in 51% of implants. The mean bone loss at the 9-year examination was 3.5 ±1.5 mm, amounting to an annual rate of 0.4mm (Derks et al., 2016b).

The reported incidence of peri-implantitis varies widely, ranging from 0.4% at 3 years to 31.2% at 5 years (Costa et al., 2012; Dreyer et al., 2018; Zetterqvist et al., 2010).

There is a lack of prospective studies evaluating onset and natural progression of peri-

implantitis due to ethical constrains. Nevertheless, a few prospective cohort studies report peri-implantitis incidence, albeit employing heterogeneous definitions of the disease and follow-up periods.

Some longitudinal studies defined peri-implantitis based on the presence of BoP and PPD thresholds, without specifying a bone loss limit.

A prospective cohort study followed 89 patients (179 implants) over a mean of 10-years (8-12 years). Peri-implantitis, defined as PPD ≥ 5 mm, BoP and/or SoP accompanied by bone loss, was observed in 15.4% of implants (Karoussis, Bragger, et al., 2004; Karoussis, Muller, et al., 2004). Using the same case definition and similar sample size (80 patients) a higher incidence (31.2%) was reported at 5-years in implants with peri-implant mucositis at baseline (Costa et al., 2012). Also, a study employing a different PPD threshold (≥4mm) in case definition observed an even lower incidence of peri-implantitis (5.8%) over 5-years. This outcome may be also due to the small sample size (22 patients) and the exclusion of non-compliant patients with supportive therapy (Rodrigo et al., 2012).

Other studies, however, used a bone loss threshold for peri-implantitis case definition. For bone loss > 1 mm, along with BoP/SoP, onset of peri-implantitis was identified in 9.2% of 1.420 implants at 10 years (Mameno et al., 2019).

A similar finding was reported for 116 edentulous patients rehabilitated with maxillary overdentures. For a bone loss threshold ≥ 2 mm, implant-level incidence of peri-implantitis was 3.2% and 8.5%, at 5- and 10-years, respectively (Onclin et al., 2022).

For peri-implantitis definition based on bone loss > 5mm, PPD ≥ 5 mm and BoP/SoP, incidence of peri-implantitis was observed in 0.4% of implants, at 3-years (Zetterqvist et

al., 2010). The residual onset of peri-implantitis in this study may be attributed to the shorter follow-up period and higher bone loss threshold.

Although some studies have reported data on the incidence of peri-implantitis within a longitudinal framework, the majority relied on convenience samples, specific baseline diagnosis (e.g., peri-implant mucositis) (Costa et al., 2012) or targeted particular populations (e.g., periodontal patients) (Roccuzzo et al., 2023; Roccuzzo et al., 2010; Swierkot et al., 2012).

2.3 RISK INDICATORS / RISK FACTORS

Several patient-related risk factors / indicators for peri-implantitis have been advocated as strong evidence, such as periodontitis history (Roccuzzo et al., 2022; Roos-Jansaker, Renvert, et al., 2006), inadequate plaque removal and lack of compliance with supportive peri-implant therapy (Costa et al., 2012; de Araujo Nobre et al., 2015), while smoking (Canullo, Penarrocha-Oltra, et al., 2016; Derks et al., 2016a; Rinke et al., 2011) and diabetes (Dalago et al., 2017; Ferreira et al., 2006; Monje, Catena, et al., 2017; Tawil et al., 2008) still have contradictory findings. Also, peri-implantitis risk has been associated to the implant-supported rehabilitation, such as restoration design (Katafuchi et al., 2018; Serino & Strom, 2009) and full-arch rehabilitations (Rodrigo et al., 2018).

The majority of studies on this topic employ, however, a cross-sectional design. Nevertheless, the identification of true risk factors requires longitudinal evaluations to establish and validate the causal effect (Schwarz et al., 2018).

2.3.1 Plaque

Animal studies confirmed plaque accumulation as the etiologic factor of peri-implant mucositis (Salvi et al., 2012). Similarly, the onset of peri-implantitis was confirmed in animal studies using the "ligature model", validating that its spontaneous progression is associated with clinical and histologic signs of inflammation and tissue destruction (Albouy et al., 2009).

Therefore, peri-implantitis was defined by consensus as a plaque associated disease occurring in peri-implant tissues (Berglundh et al., 2018).

This evidence also emerged in cross-sectional studies confirming the presence of plaque as a risk indicator for peri-implantitis (de Araujo Nobre et al., 2015; Ferreira et al., 2006; Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021). Plaque indexes employed varied among studies and comprised either full-mouth plaque (Aguirre-Zorzano et al., 2015; Canullo, Penarrocha-Oltra, et al., 2016; Ferreira et al., 2006; Schwarz et al., 2017) or implant level assessments (Rokn et al., 2017).

In a study conducted in 212 patients, at a mean period of 3.5 years, the OR for peri-implantitis was 3.8 in patients with poor plaque control (mPI 1.3) and 14.3 in patients with very poor plaque control (mPI 2.5), evaluated by the modified plaque index (Mombelli, 1987) (Ferreira et al., 2006).

A full mouth plaque index ≥25% (versus <25%) was associated with double the prevalence of peri-implantitis (23% versus 12%) (Aguirre-Zorzano et al., 2015). Likewise, for plaque scores exceeding 30%, the OR for peri-implantitis ranged from 7.8 to 9.3, at a mean follow-up of 5.1 and 2.2 years, respectively (Canullo, Penarrocha-Oltra, et al.,

2016; Schwarz et al., 2017).

Nevertheless, the cross-sectional design does not allow to verify the temporality of the association, limiting the confirmation of patient efficacy in maintaining long-term plaque control. This fact may explain why other studies failed to support plaque as risk indicator for peri-implantitis (Marrone et al., 2013).

A longitudinal study also corroborated that plaque scores >20% were found to significantly increase the risk for peri-implantitis (HR=2.61) (Mameno et al., 2019).

2.3.2 PERIODONTITIS

The association between history of periodontitis and peri-implantitis has been described in both cross-sectional and prospective studies of convenience samples (Daubert et al., 2015; Koldsland et al., 2011; Renvert et al., 2014; Roccuzzo et al., 2022; Swierkot et al., 2012), being acknowledge as strong evidence (Carra et al., 2022; Dreyer et al., 2018; Schwarz et al., 2018; Serroni et al., 2024).

Roos-Jansaker et al. evaluated 216 patients at 9 to 14 years follow-up and identified history of periodontitis as a significant predictor for peri-implantitis (OR 4.7) (Roos-Jansaker, Renvert, et al., 2006). Also, a cross-sectional study with similar mean follow-up (10.9 years) examined 96 patients, with 225 implants, confirming severe periodontitis as a risk indicator for peri-implantitis (RR = 7.3) (Daubert et al., 2015).

Moreover, residual PPD ≥ 5mm in periodontal patients are associated with an increased prevalence of peri-implant bone loss and deeper probing depths (Lee et al., 2017; Pjetursson et al., 2012). A prospective study with a follow-up of 1 to 5 years validated this finding. The incidence of peri-implantitis was significantly associated to PPD ≥ 6mm

at time of implant surgery (OR 3.62) in a cohort of 100 patients with severe periodontitis (Zhang et al., 2018).

While most studies underline an increased risk of peri-implantitis in periodontal patients, some cross-sectional studies have not confirmed the association (Canullo, Penarrocha-Oltra, et al., 2016; Dvorak et al., 2011; Rokn et al., 2017).

Marrone et al. evaluated 103 patients at a mean of 8.5 years and found that patients with active periodontitis were at higher risk for peri-implantitis, however without reaching statistical significance (Marrone et al., 2013). Likewise, periodontitis did not emerge as peri-implantitis risk indicator in 1507 implants (534 patients) for a mean of 5.1 years of follow-up (Canullo, Penarrocha-Oltra, et al., 2016).

Discrepancies in the definition of both diseases, periodontitis severity, along with variations in follow-up durations and the possible influence of confounders, such as smoking habits, main explain the conflicting results (Serroni et al., 2024).

Prospective studies (Degidi et al., 2016; Gatti et al., 2008; Karoussis et al., 2003; Roccuzzo et al., 2022; Swierkot et al., 2012) also corroborate that periodontal patients present an overall significantly higher incidence of peri-implantitis (RR=4.09) and greater mean marginal bone loss (weighted mean difference of 0.75mm) (Serroni et al., 2024). Actually, periodontal patients are at higher risk for peri-implant bone loss ≥ 2mm (Trombelli et al., 2024). A 10-year study, enrolling 101 patients, confirmed that bone loss ≥ 3mm was more frequent among patients with a history of severe periodontitis (15.1%) compared to periodontal healthy patients (4.7%) (Roccuzzo et al., 2010).

However, incidence of peri-implantitis in patients with history of periodontitis varied according to follow-up period and case definition.

In studies with follow-up over 10 years and grade C periodontitis the strength of the

association appears notably higher (Annunziata et al., 2024; Serroni et al., 2024).

Karoussis et al. followed for 10 years 112 implants placed in 53 patients. Peri-implantitis definition was based on bone loss >2mm (annual mean of 0.2 mm) and PPD ≥5 mm with BoP. Patients with periodontitis history presented higher incidence of peri-implantitis at implant-level (38.1%) compared to non-periodontitis patients (5.5%) at 10 years (Karoussis et al., 2003). A study using a similar definition (bone loss >2mm, PPD ≥6 mm, BoP), but with a shorter follow-up (5-years), reported a lower incidence (0% for non-periodontal patients and 18.7% for periodontal patients) (Gatti et al., 2008).

Briefly, in studies up to 10-years incidence ranged from 18.7% at 5 years (bone loss >2mm & PPD ≥6 mm) (Gatti et al., 2008) to 26.3% at a mean of 8.3 years (annual bone loss>0.2mm & PPD≥6mm) (Swierkot et al., 2012). Studies with follow-ups over 10 years reported a incidence between 24% (unspecified bone loss threshold) (Degidi et al., 2016) to 38% (bone loss >2mm & PPD ≥5 mm) (Karoussis et al., 2003). At 20 years, using a bone loss threshold >3mm combined with PD>6mm, the incidence rate was 33% (Roccuzzo et al., 2022).

Despite following a regular supportive therapy, patients with history of periodontitis still exhibit higher incidence of peri-implantitis, in comparison to non-periodontal patients.

The supportive therapy intervals in the previous mentioned studies varied, every 3 months (Swierkot et al., 2012), every 3 to 6 months (Gatti et al., 2008; Karoussis et al., 2003), every 6 months (Degidi et al., 2016) to individual tailored intervals (Roccuzzo et al., 2022).

These findings underline the pivotal importance of treating periodontitis prior to implant placement, through a comprehensive stepwise periodontal therapy (Herrera et al., 2022; Sanz, Herrera, et al., 2020). Furthermore, it is essential to integrate periodontal

patients into more stringent supportive peri-implant care with a stricter focus on primary prevention of peri-implantitis (Heitz-Mayfield et al., 2020; Herrera et al., 2023).

2.3.3 SMOKING

Cross-sectional studies report inconsistent findings regarding smoking as a risk indicator for peri-implantitis. While some studies outlined a 2.7 to 31-fold increased likelihood of peri-implantitis in smokers (Rinke et al., 2011; Roos-Jansaker, Lindahl, et al., 2006; Schwarz et al., 2017), others did not corroborate the association (Dvorak et al., 2011; Koldsland et al., 2011).

In longitudinal studies, smokers exhibited greater bone loss (Karoussis, Muller, et al., 2004; Sanchez-Siles et al., 2015). Also, studies with longer follow-ups (> 10 years) consistently identified an increase incidence of peri-implantitis in smokers (Karoussis et al., 2003; Sanchez-Siles et al., 2015; Windael et al., 2021). These findings remain significant even among smokers of less than 10 cigarettes per day (Sanchez-Siles et al., 2015; Velasco-Ortega et al., 2021).

A prospective study observed a 17.9% incidence of peri-implantitis in smokers and 6.0% in non-smokers (Karoussis et al., 2003). A similar trend was confirmed in a retrospective study, including 132 patients with 555 implants, that disclosed a threefold higher incidence in peri-implantitis in smokers (>1 cigarette per day) (72.7% vs 27.3% in non-smokers) (Astolfi et al., 2022).

In summary, a statistically significant association between smoking and peri-implantitis is disclosed in the meta-analysis of both cross sectional (OR 1.7, 95% CI 1.25- 2.3) (Dreyer et al., 2018) and prospective studies, at implant- (RR: 2.04, 95% CI: 1.46–2.85) and patient-level (RR: 2.08, 95% CI: 1.17–3.71) (Reis et al., 2023).

The conflicting results across studies, regarding smoking as risk factor/indicator for peri-implantitis, may stem in the heterogeneous criteria in smokers and non-smokers categorizations, in addition to the variability in the reported smoking dosage (Reis et al., 2023; Schwarz et al., 2018).

The findings may also be partially explained by discrepancies in follow-up periods. In fact, most cross-sectional studies reporting an increased risk of peri-implantitis had longer follow ups (e.g., exceeding 10 years) (Karoussis et al., 2003; Roos-Jansaker, Lindahl, et al., 2006). Conversely, those studies that did not identify an association evaluated patients up to 6 years (Aguirre-Zorzano et al., 2015; Canullo, Penarrocha-Oltra, et al., 2016; Casado et al., 2013; Maximo et al., 2008; Rokn et al., 2017).

Moreover, after adjustment for confounders, smoking was not identified as a risk indicator in the multiple regression analyses of several studies, (de Araujo Nobre et al., 2015; Derks et al., 2016a; Renvert et al., 2014; Swierkot et al., 2012). A masking effect from other patient-level indicators, such as periodontitis, has been suggested (Schwarz et al., 2018).

Interestingly, the combination of risk factors may result in a further elevated risk for peri-implantitis onset (Annunziata et al., 2024). The combination of smoking, periodontal history and early bone loss of >0.5 mm increased 52% the probability for peri-implantitis onset (Windael et al., 2021). This cumulative effect was also addressed in other longitudinal studies, confirming that smokers with history of periodontitis present higher incidence of peri-implantitis than non-smoking periodontitis patients (Karoussis et al., 2003; Swierkot et al., 2012).

2.3.4 LACK OF COMPLIANCE WITH SUPPORTIVE PERI-IMPLANT THERAPY

The protective role of supportive peri-implant therapy is pivotal addressing both primary prevention, focusing on precluding disease onset, and secondary prevention, aiming on reducing the risk of disease recurrence. In either level of prevention, the protective role of supportive peri-implant therapy transcends the mere professional supra- and sub-mucosal instrumentations. Indeed, it serves as a crucial opportunity for the reinforcement and control of systemic and local risk factors (Carra et al., 2023; Stiesch et al., 2023).

Cross-sectional and prospective studies exhibit considerable heterogeneity in the protocols of supportive peri-implant therapy and the intervals between visit. Nevertheless, compliance has been associated to increased survival rates and lower risk of peri-implant diseases (Carra et al., 2023; Lin et al., 2019; Monje et al., 2016).

A cross-sectional study conducted in Spain reported peri-implantitis prevalence of 25% among patients not enrolled in regular supportive therapy, in contrast to a prevalence of 16% among regular compliers (Rodrigo et al., 2018).

This finding was confirmed in Dreyer et al. (2018) systematic review, reporting a double prevalence of peri-implantitis among non–compliers (18.8% vs 9.0%) (Dreyer et al., 2018).

In addition to the higher risk for peri-implantitis, inconsistence adherence with supportive peri-implant therapy conferred a 3.8-fold increase in the likelihood of implant failure (Carra et al., 2023).

The protective effect of compliance with supportive therapy is highlighted in a longitudinal study that followed for 5-years 80 patients with peri-implant mucositis at baseline. The subgroup analysis revealed a significantly higher incidence of peri-

implantitis (43.9%) in patients not enrolled in a maintenance program, compared to those who attended at least five visits during follow-up (18% of peri-implantitis cases) (Costa et al., 2012).

Regarding the annual visit frequency, one visit per year may not be sufficient to effectively prevent peri-implantitis (Marrone et al., 2013). Actually, a supportive peri-implant therapy comprising more than 2 visits per year was found to be a protective indicator (OR=0.13), as patients had 86% fewer cases of disease (Monje, Wang, et al., 2017). The same tendency was confirmed in supportive therapy intervals every three to six months (Aguirre-Zorzano et al., 2015; Rinke et al., 2011).

Although a 5-6 months interval has been previously recommended (Monje et al., 2016), peri-implant supportive therapy visits intervals should be tailor to the individual´s risk profile (Heitz-Mayfield et al., 2020) and to the suitable level of prevention, and therefore may be adjusted to 3-4 months recalls (Herrera et al., 2023).

2.3.5 RESTORATIVE-RELATED FACTORS

An implant-supported restoration convex profile, wide emergence angle (Corbella et al., 2023; Katafuchi et al., 2018; Serino & Hultin, 2019; Yi et al., 2020), and the position of the implant supported rehabilitation to bone crest (Derks et al., 2016a) were found to be associated to peri-implantitis occurrence.

Restorative design related factors that hamper accessibility for self-performed oral hygiene methods are related to an increase risk of peri-implantitis (Pons et al., 2021; Rodrigo et al., 2018; Serino & Strom, 2009). Serino & Strom (2009) identified those circumstances in 48% of implants diagnosed with peri-implantitis, compared to only 4% prevalence in implants with adequate accessibility.

In fact, clinical studies demonstrated a tendency of reduced bone loss in implant supported restorations featuring shallow emergence angles (Inoue et al., 2020; Strauss et al., 2022). Conversely, emergence angle >30º were associated to fourfold greater bone loss (Majzoub et al., 2021).

In addition to a compromised access to self-performed oral hygiene, animal studies disclosed histological differences in the supracrestal tissues according to the abutment angle. Specifically, the use of abutment angles of 60˚ and 80˚ was associated to a closer proximity of the inflammatory infiltrate to the bone and a compromised formation and integrity of the junctional epithelium (Strauss et al., 2024). These findings may provide a biological rationale for the greater bone loss observed in implants with restorations featuring wider angles and a convex profile.

Consequently, peri-implantitis prevalence was found significantly higher, ranging from two to five times higher, under the aforementioned restorative conditions (Katafuchi et al., 2018; Yi et al., 2020).

In the same context, a restorative design that allows access for oral hygiene and, if deemed necessary, the modification of the contour of the prostheses, has a positive impact on treatment outcomes of peri-implant diseases (Carrillo de Albornoz et al., 2024; de Tapia et al., 2022; de Tapia et al., 2019).

2.4 DIAGNOSIS OF PERI-IMPLANTITIS

The diagnosis of peri-implantitis is primarily defined through longitudinal evaluations of clinical parameters and radiographic examinations (“direct evidence”).

Nevertheless, in the absence of previous examinations the diagnosis is based on the one-time assessment (“indirect evidence”). The VIII European Workshop on

Periodontology underlined the importance of prioritizing diagnostic specificity over sensitivity for purposes of timely therapeutic intervention. Therefore, a bone level threshold of 2 mm, beyond the expected initial bone remodeling, was proposed, in addition to BoP /SoP (Sanz et al., 2012). This recommendation of peri-implantitis case definition was recently apprised at the 2017 WWP, establishing the combination of PPD ≥6 mm, bone level threshold ≥ 3mm, together with BoP/SoP (Berglundh et al., 2018).

The 2017 WWP secondary case definition (BoP/SoP at ≥1 site, bone levels ≥3 mm, and PPD ≥6 mm) demonstrated high specificity (99.3%), however was less sensitive in identifying moderate to severe peri-implantitis cases (BoP / SoP and bone loss > 2mm). In these clinical scenarios, the most accurate case definition was the combination of BoP/SoP with bone loss ≥2 mm (Romandini, Berglundh, et al., 2021).

2.4.1 DIAGNOSTIC ACCURACY OF CLINICAL PARAMETERS

PROBING POCKET DEPTH

PPD is recognized as a diagnostic tool for monitoring the health status of implants and is recommended for routine examinations. Moreover, probing does not have a detrimental effect on peri-implant soft tissues, as reestablishment of the junctional epithelium is expected to occur within 5 days (Etter et al., 2002).

Longitudinal changes in PPD or PPD ≥ 6mm at a single assessment, in the absence of previous data, are part of the criterion for peri-implantitis diagnosis (Berglundh et al., 2018).

Experimental studies in animals demonstrated anatomical differences between teeth and implants, revealing that probe penetration is deeper at implant sites compared to teeth. Probing implants with peri-implant health, with a probing force of 0.5N, resulted

in deeper probe penetration (1.3 mm apical to the junctional epithelium) compared to teeth (0.2 mm coronal to junctional epithelium). Consequently, the probe tip was located closer to the bone margin at implant sites (0.2 mm at implants sites *versus* 1.2 mm at teeth) (Ericsson & Lindhe, 1993). The tendency for deeper probing in implants was also found at peri-implant mucositis cases compared to gingivitis (Schou et al., 2002).

Probing diagnostic value in discerning peri-implant health status was implied in histologic studies in animals that found deeper probing depths (3.8mm) in peri-implantitis sites compared to peri-implant health (2.1mm) and peri-implant mucositis (1.8mm). The probe tip was located at the base of the junctional epithelium at peri-implant health and peri-implant mucositis, while at peri-implantitis sites the probe penetrated 0,5mm into the connective tissue (Lang et al., 1994). Accordantly, animal studies indicate PPD as a diagnostic tool, as experimental ligature-induced peri-implant bone loss is accompanied by increased probing depths together with BoP (Monje, Insua, et al., 2018).

Higher PPD in peri-implantitis cases were also confirmed in clinical studies (Monje, Caballe-Serrano, et al., 2018; Ramanauskaite et al., 2018; Rodrigo et al., 2018; Schwarz et al., 2017).

A case-control study compared clinical parameters to determine its diagnostic accuracy in peri-implant health, peri-implant mucositis and peri-implantitis, in 1,572 peri-implant sites (262 implants). Peri-implantitis sites displayed deeper PPD (4.58 ± 1.71 mm) compared to peri-implant health (2.63 ± 1.21 mm). The probability of a peri-implantitis diagnosis increases with each 1mm of increased PPD in respect to peri-implant health (OR=2.43) and to peri-implant mucositis (OR=1.76) (Monje, Caballe-Serrano, et al.,

2018).

Likewise, Ramanauskaite et al, evaluated 269 implants with peri-implant healthy (N=77), peri-implant mucositis (N=77) and peri-implantitis (N=115) and confirmed significantly differences in PPD between peri-implant health diagnosis. At implant-level, the mean PPD in peri-implantitis was 4.91 mm (3.17 - 9.0 mm), while in peri-implant mucositis was found to be 3.10 mm (3.17 - 4.67 mm), and in peri-implant healthy 2.95 mm (1.0 - 4.33 mm) (Ramanauskaite et al., 2018).

The frequency of PPD of 4-6mm was significantly higher in implants with peri-implant diseases (Schwarz et al., 2017), while other study only found PPD ≥6 mm associated to peri-implantitis cases (Ramanauskaite et al., 2018).

Nevertheless, deep probing demonstrated a high specificity (PPD ≥6 mm: 88.0%; PPD ≥7 mm: 96.2%) and a low sensitivity (PPD ≥6 mm: 58.6%; PPD ≥7 mm: 39.1%) to identify peri-implantitis cases with bone loss>2mm (Romandini, Berglundh, et al., 2021).

Although probing depth holds significant clinical value for monitoring implant health, and the relevance in its longitudinally assessment for peri-implantitis diagnosis (Berglundh et al., 2018), the diagnostic accuracy of using PPD as a sole clinical parameter for detecting bone loss has been questioned. In fact, peri-implantitis cases may progress without the presence of deep pockets (Romandini, Berglundh, et al., 2021; Romandini, Lima, Pedrinaci, Araoz, Costanza Soldini, et al., 2021). Indeed, peri-implantitis was found to course either with PPD increase or with peri-implant soft tissue dehiscence (PISTD), underlining that PPD changes used as single parameter may not be sufficient to suspect of bone loss. The combination of PPD with mucosal dehiscence was suggested to improve the diagnostic value than the use of PPD alone (Romandini, Lima, Pedrinaci, Araoz, Costanza Soldini, et al., 2021).

Also, the limited value of PPD as single diagnostic tool may be partial attributed to technical factors, such as probe angulation/ direction, probing force and the prosthetic design, that may compromise accurate PPD assessment. In fact, PPD measurement taken before and after the removal of the implant-supported rehabilitation revealed an under- or over-estimation over 1 mm in the majority of peri-implantitis sites (63%). On the other hand, probing assessment without the prosthesis related to the bone level confirmed during surgery (Serino et al., 2013).

BLEEDING ON PROBING

BoP is interpreted as a clinical sign of inflammation of the soft tissues, and therefore incorporated in the diagnostic criteria of peri-implant diseases (Berglundh et al., 2018; Lang et al., 1994).

BoP is consistently associated to peri-implantitis cases (Derks et al., 2016a; Monje, Caballe-Serrano, et al., 2018; Rodrigo et al., 2018; Vignoletti et al., 2019). Indeed, the presence of BoP at implant-level was found to be significantly higher in patients diagnosed with peri-implantitis (86%) compared to those with peri-implant mucositis (43%) (Ramanauskaite et al., 2018). A meta-analysis evaluating BoP as predictor concluded that implants exhibiting BoP have a 24.1% likelihood of being diagnosed with peri-implantitis (Hashim et al., 2018).

Even in patients receiving supportive therapy, a BoP score greater than 50% across all implant sites was significantly associated to peri-implantitis incidence (OR 37) (Costa et al., 2012).

Conversely, only a minority of implants (<20%) display advanced bone loss in the absence of BoP (Rodrigo et al., 2018; Romandini, Berglundh, et al., 2021) highlighting

that the absence of BoP serves as an indicator of stable peri-implant conditions, due to its high negative predictive value (Jepsen et al., 1996).

The likelihood of a positive-BoP site was found to be related to PPD (de Souza et al., 2012). In fact, for each millimeter of site-specific increment in PPD, there is an increased probability of positive BoP (Farina et al., 2017; Merli et al., 2017).

In a clinical examination of 1.289 implant, at a probing force of 0.20 N, the probability of BoP was 27% for PPD of 4 mm, increasing to 48% for PPD of 6 mm (Farina et al., 2017). Similarly, a study including 52 patients enrolled in supportive therapy observed BoP in 30–40% of sites with PPD of 3 mm and in more than 80% of sites with PPD of 7 mm. A significant higher risk for BoP was found for interproximal sites (OR = 1.55). (Merli et al., 2017).

Nevertheless, the diagnostic value of BoP may be compromised by factors related to the technique and patient habits. BoP can be induced by trauma when excessive probing force is applied, leading to potential false positives. A probing force of 0.15 N has been suggested to minimize this risk (Gerber et al., 2009). Also, smoking was demonstrated to be inversely associated with BoP (OR = 0.3). A lower BoP sensitivity in detecting visible gingival inflammation was found in smoker patients. BoP occurred in 96.3% of nonsmokers (never smokers) and in 77.8% of smokers (≥1 cigarettes per day) (Amerio et al., 2022).

Regarding BoP extent, in the absence of additional clinical signs of inflammation, the presence of BoP at a single site should not be regarded as sufficient for a definitive diagnosis of peri-implantitis (Renvert et al., 2018). Using BoP at ≥3 sites as a single clinical parameter to identify peri-implantitis cases yields greater diagnostic accuracy than BoP at ≥1 site, primarily due to its higher specificity (80.7% for BoP ≥3 sites vs.

43.2% for BoP ≥1 site) (Romandini, Berglundh, et al., 2021). Likewise, Berglundh et al., (2021) reports an OR of 15.3 for peri-implant bone loss >2mm when BoP was present in more than 3 sites/implant.

In accordance, the number of sites exhibiting BoP was associated with greater bone loss. A 15-years retrospective study involving 112 implants found that for each additional BoP-positive site there was a 0.5 mm increase in bone loss (Ramanauskaite et al., 2024). A prospective study monitored for five years 19 patients receiving periodontal and peri-implant supportive therapy every 5 to 8 months. The analysis from the final two years indicated that BoP frequency ≥50% exhibited a sensitivity of 50% and specificity of 100% for detecting either a decrease in bone density or a 2.5mm increase in PPD during the 5-years follow-up (Luterbacher et al., 2000).

The combination of BoP with the radiographic assessment of bone level enhances the diagnostic accuracy of BoP alone. Indeed, BoP/suppuration and bone level ≥2 mm demonstrated a high sensitivity (93.0%) and specificity (93.7%) to identify peri-implantitis cases (with bone loss>2mm) (Romandini, Berglundh, et al., 2021).

Most studies merely rely on the dichotomous definition of BoP (presence / absence). However, the assessment and categorization of BoP severity (e.g., punctiform, profuse) (Mombelli et al., 1987) may provide additional diagnostic and predictive value.

Further research is required to substantiate the diagnostic accuracy of various BoP assessment methods (severity and extent) in the identification of peri-implantitis.

SUPPURATION

The likelihood of suppuration increases with the severity of peri-implantitis. Implants presenting suppuration have deeper PPD (Ramanauskaite et al., 2018), with each

additional 1mm increase in PPD correlating to a 63% higher risk of suppuration (Monje et al., 2021). Moreover, suppuration was associated to defect morphology and more severe bone loss (Monje et al., 2021).

However, suppuration is a relatively uncommon clinical finding in peri-implantitis cases. Studies report its presence in 17.4% to 28.7% of implants with peri-implantitis (Fransson et al., 2008; Monje et al., 2021; Ramanauskaite et al., 2018; Rodrigo et al., 2018), with a higher occurrence at buccal sites (51%) (Monje et al., 2021).

Although Ramanauskaite et al. (2018) identify suppuration exclusively in implants affected by peri-implantitis, has to be acknowledge that suppuration can also be detected in peri-implant mucositis, indicating that is not a distinctively clinical feature of peri-implantitis cases (Monje, Caballe-Serrano, et al., 2018; Rodrigo et al., 2018).

As diagnostic tool for detecting peri-implantitis cases with bone loss >2mm, suppuration demonstrates limited sensitivity and high specificity. Consequently, its presence was suggested as a strong indicator of peri-implantitis (Monje, Insua, et al., 2018; Romandini, Berglundh, et al., 2021).

2.4.2 DIAGNOSTIC ACCURACY OF RADIOGRAPHIC EXAMINATION

Current case definitions of peri-implantitis include the presence of BoP/suppuration, an increase in PPD, combined with progressive bone loss beyond the expected initial remodeling (Berglundh et al., 2021).

Bone loss is defined as the difference in marginal bone levels between two examinations and therefore requires a longitudinal monitoring of bone levels (Berglundh et al., 2021; Renvert et al., 2018).

A baseline standardized radiograph should be obtained 0-1 year after implant-

supported rehabilitation placement to allow precise visualization of implant threads, interproximal bone levels and the identification of distinct reference points. This imaging is essential for establishing direct evidence of progressive peri-implant bone loss by assessment of subsequent radiographs (Renvert et al., 2018).

Nevertheless, if previous documentation is not available, case definition is based on indirect evidence, established by an isolated bone level evaluation. Currently, a bone level threshold ≥3 mm apical to the intraosseous part has been proposed for implant peri-implantitis case definition (Berglundh et al., 2018; Renvert et al., 2018).

Intra-oral radiographs to evaluate peri-implant bone levels are also recommended in case of PPD increase in combination with BoP/suppuration (Lang et al., 2011).

Peri-implantitis bone loss pattern courses with a marked intrabony defect component (Garcia-Garcia et al., 2016; Monje et al., 2019; Schwarz et al., 2007; Shatta et al., 2019), with frequent loss of the buccal bone wall (Garcia-Garcia et al., 2016).

A ligature-induced peri-implantitis model in dogs detected circumferential intrabony defects, without dehiscence of oral or palatal wall, in 86.6% of cases, while the same defect morphology in humans was confirmed intra-surgically in 55.3% of implants (Schwarz et al., 2007). A later study, that evaluated bone morphology through cone beam computed tomography (CBCT), also identified 2/3 walls intrabony defects as the most prevalent in humans (55%) (Monje et al., 2019).

The defect morphology may also combine suprabony with an intrabony component (Monje et al., 2019; Schwarz et al., 2007; Shatta et al., 2019), however the least frequent defect morphology is the horizontal bone loss pattern (1.9% of cases) (Monje et al., 2019).

In addition to interproximal bone levels evaluation, assessing peri-implant defect

morphology is crucial in peri-implantitis treatment, particularly for the decision-making process regarding the surgical approach. Therefore, diagnostic accuracy of radiographic methods is a crucial matter.

Intra-oral periapical radiographs are recommended for routine evaluation of implant bone levels (Kuhl et al., 2016). However, the two-dimensional images may underestimate defect morphology assessment, especially in buccal or palatal defects, including dehiscence and fenestrations (Garcia-Garcia et al., 2016), with discrepancies between intra surgical and radiographic measurements up to 1-2mm (Serino et al., 2017).

Three-dimensional imaging, such as CBCT, have been considered to mitigate periapical radiographs limitations. CBCT demonstrated higher sensitivity for detecting peri-implant bone morphology, including the intrabony component dimensions and identification of dehiscence and fenestrations (Hilgenfeld et al., 2018; Schwindling et al., 2019; Vadiati Saberi et al., 2019). Nevertheless, CBCT may still underestimate bone measurements with an average discrepancy up to 1 mm (Insua et al., 2021; Schriber et al., 2020).

Considering the general recommendation and concern for the rational use of imaging methods, the intra-oral periapical radiograph visualization may be sufficient for monitoring peri-implant bone levels (Vadiati Saberi et al., 2019).

In the absence of previous documentation, diagnosis of a peri-implantitis case relies on the cross-sectional analysis, and therefore the bone level thresholds definition becomes critically important.

A diagnostic accuracy study to identify history of bone loss comprised clinical and radiographic data of 1,577 implants (427 patients) at 9 years. Peri-implantitis cases were more accurately identified through bone levels > 1 mm, with BoP and/or SoP, although

this threshold still presented high false negative (27.6%) and false positive (13.2%). A bone level threshold ≥ 2mm was found to be highly accurate in identifying history of bone loss (Romandini, Berglundh, et al., 2021).

2.5 BASELINE STUDY

A recent cross-sectional study performed by our research group ("baseline study") evaluated a university-representative sample and aimed to report the prevalence of peri-implant diseases and to identify the risk/protective indicators of peri-implantitis (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021).

Ninety-nine patients with 458 dental implants were randomly selected through a stratified multistage sampling process.

A clinical examination was performed on all implants with a manual UNC-15 periodontal probe (PCP15; Hu-Friedy) at 6 sites/implant, comprising presence of visible plaque, PISTD, PPD, BoP/SoP (within 30s). Additionally, keratinized tissue height, mobility of mucosal margin, peri-implant phenotype, tissue thickness, clinical signs of occlusal overloading on implants and of bruxism were also assessed.

Marginal bone levels were measured from the implant shoulder to the first bone-implant contact, using a software program (Autocad 2016 TM, AutoDesk Inc.) by one calibrated investigator (CL) (intra-examiner agreement, ICC = 0.98; 95% CI 0.96–0.99; $p < .001$).

The following case definitions were used: 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 $\leqq$BL < 2

mm; Peri-implantitis: presence of BoP/SoP together with radiographic BL ≧2 mm.

At patient-level, the prevalence of peri-implant health was 1.0% (95% CI: 0.1–7.0), of peri-implant mucositis 11.1% (95% CI: 6.2–19.1), of pre-periimplantitis 31.3% (95% CI: 22.8–41.3), and of peri-implantitis 56.6% (95% CI: 46.5–66.1).

At implant-level, the prevalence of peri-implant health was 8.5% (95% CI: 6.3–11.5), of peri-implant mucositis 31.9% (95% CI: 27.8–36.3), of pre-periimplantitis 31.7% (95% CI: 27.5–36.1), and of peri-implantitis 27.9% (95% CI: 24.0–32.3).

In the multilevel multivariate logistic regression analyses several factors emerged as risk/protective indicators for peri-implantitis (at 0.05 significance level).

The following patient-level factors demonstrated statistical significance: smoking (OR = 3.59; 95% CI: 1.52–8.45), less than 16 remaining teeth (OR = 2.23; 95% CI: 1.05–4.73), moderate/severe periodontitis (vs mild periodontitis, OR = 2.77; 95% CI: 1.20–6.36), use of interproximal flossing/brushing on implants (OR = 0.27; 95% CI: 0.11–0.68).

At implant-level were identified the following factors: 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)

The identified risk indicators were consistent with other studies with similar designs (Canullo, Tallarico, et al., 2016; Derks et al., 2016a; Rodrigo et al., 2018; Roos-Jansaker, Lindahl, et al., 2006).

This study clinical and radiographic examinations (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021) served as the baseline data for the present thesis.

III. JUSTIFICATION

III. JUSTIFICATION

The high prevalence and rapid progression of peri-implantitis underlines the pivotal importance of primary prevention tailored to the patient individual risk profile. The identification of true risk/protective factors requires longitudinal evaluations to establish and validate the causal effect. However, only few cohort studies report peri-implantitis incidence and associated risk factors, mostly based on convenience samples, and at risk of confounding or information bias.

Additionally, the early detection of peri-implantitis onset is dependent on the accuracy of the diagnostic tools. Peri-implantitis is diagnosed once a significant amount of bone loss has already occurred. Therefore, it would be highly valuable if clinical parameters could predict bone loss before is radiographically detected. Additionally, since the current peri-implantitis case definition is based on bone loss assessment, there is also a need for diagnostic tools to identify implants where bone loss has already occurred, thus justifying radiographic exposure.

Clinical parameters are routinely employed to monitor peri-implant health status, yet their effectiveness remains to be clearly validated (e.g., PPD / PISTD changes over time, and BoP extent and severity).

Therefore, there is a need to develop studies grounded in a longitudinal framework to assess the incidence of peri-implantitis, identify associated risk factors, and to evaluate the accuracy of clinical parameters as predictive and diagnostic tools.

IV. AIMS

IV. AIMS

The general objectives of this thesis were to identify the incidence and risk factors of peri-implantitis and to determine the predictive and diagnostic accuracy of clinical parameters for detecting peri-implant bone loss.

The specific objectives were:

Study #1:

- To assess the incidence of peri-implantitis and associated risk factors at 4-years follow-up of a university-representative sample of patients with dental implants (Romandini et al., 2021; Romandini et al., 2020b; Romandini et al., 2020c).

Study #2:

To evaluate the diagnostic accuracy of:

- Clinical parameters recorded at baseline to predict bone loss occurrence over time (direct evidence).
- Clinical parameters recorded at follow-up for the detection of history of bone loss (indirect evidence).

V. MATERIALS AND METHODS

V. MATERIALS AND METHODS

STUDY #1:

Incidence and risk factors of peri-implantitis over time – A prospective cohort study

STUDY #2:

Accuracy of Clinical Parameters in Predicting/Diagnosing Peri-Implant Bone Loss

This present cohort is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007; von Elm et al., 2007).

The study was conducted in accordance with the Declaration of Helsinki for human studies, and its research protocol was ethically approved (19/182-E; 22/385-EC_P) by the CEIm Hospital Clínico San Carlos, Madrid, Spain.

5.1 Population

The Peri-Implant Diseases Follow-Up (PIDFU) study is an ongoing prospective cohort study based on repeated follow-ups over time of a previously reported university-representative population (Romandini, Lima, Pedrinaci, Araoz, Costanza Soldini, et al., 2021; Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021; Romandini, Pedrinaci, et al., 2021) (Figure 1).

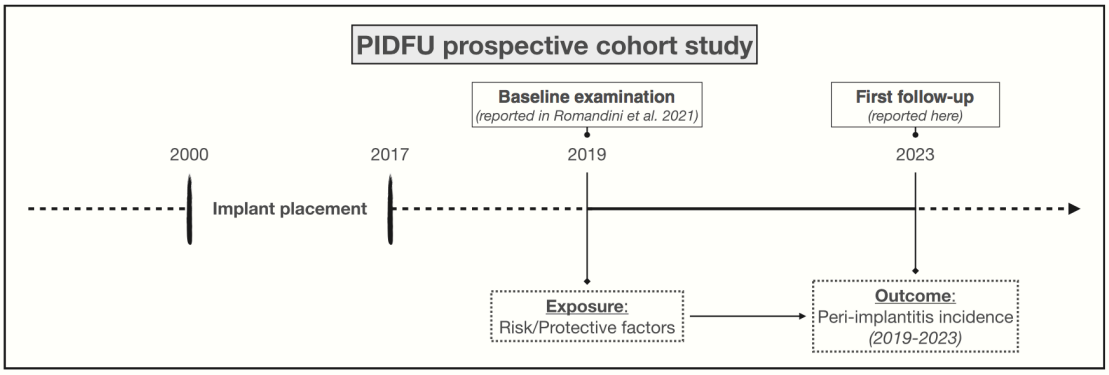

Figure 1. Prospective cohort study design.

During 2019, 99 patients with 458 implants, identified through a stratified multistage sampling process among patients who received dental implants from 2000 to 2017 in the Department of Periodontology at Complutense University of Madrid, were initially examined both clinically and radiographically. This examination served as the baseline for this prospective cohort study. In 2023, the same patients were invited to participate to this follow-up examination through a minimum of five different telephonic attempts made on different days. The patients that accepted the participation constitute the sample of the present study.

5.2 STUDY #1:

Incidence and risk factors of peri-implantitis over time – A prospective cohort study

5.2.1 Risk/Protective Factors Tested (Exposure)

The full list of patient- and implant-level variables tested as putative risk/protective factors were collected during the baseline examination, and their assessment methods are detailed in the baseline study publication (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021) (Appendix Table 1). The present medical/dental history data consisted in the update of the information collected during the baseline study, including: height and weight, medical history (diseases, medication, radiotherapy, chemotherapy, allergies), smoking status, SARS-COV-2 infection, COVID-19 infection (described as mild, moderate or severe), COVID-19 Vaccination. Self-reported information regarding maintenance frequency and implant treatments (non-surgical and/or surgical) since the

baseline study were recorded and crossed with the available information on each patient dental history chart.

Regular maintenance was defined as participating in an average of ≥1 supportive peri-implant therapy recalls per year.

A full-mouth periodontal examination was performed on the residual dentition, for assessing full-mouth plaque and bleeding scores (FMPS/FMBS), the number of probing pocket depth (PD) exceeding different thresholds (≥4, ≥5, ≥6 mm), and the number of furcation involvements (Hamp et al., 1975) (FI) ≥2. Periodontal diagnosis was defined according to the 2017 Classification system (Papapanou et al., 2018)

At implant-level, the location of the restoration margin in relation to the soft-tissue margin (sub-, juxta-, or supra-marginal) was recorded based on its most apical position around the implant. An orthopantomography was also performed, and the periodontal bone loss//age ratio was measured in the most severely affected tooth (Papapanou et al., 2018; Sanz, Papapanou, et al., 2020). Finally, patient files were accessed to extract information about any treatments (non-surgical and/or surgical) performed on study implants during the follow-up period.

5.2.2 Case definitions

The following case definitions were used to describe the peri-implant health status at follow-up:

- peri-implant health: absence of BoP/SoP, bone loss ≤1 mm with respect to the baseline radiographs;
- peri-implant mucositis: presence of BoP/SoP and bone loss ≤1 mm with respect to the baseline radiographs;

- stable peri-implantitis: presence of BoP/SoP and bone loss ≤1 mm with respect to the baseline radiographs, in implants diagnosed with peri-implantitis at baseline;
- progressive peri-implantitis: presence of BoP/SoP and bone bone loss >1 mm with respect to the baseline radiographs, in implants diagnosed with peri-implantitis at baseline.

5.2.3 Peri-implantitis Onset/Progression (Outcome)

The primary outcome of the study was peri-implantitis onset/progression, defined as the incidence of bone loss>1 mm between the baseline and follow-up examinations in implants showing BoP at one or more sites. The 1 mm threshold was chosen to minimize the risk of misclassification bias due to measurement error. Additional bone loss thresholds (>0.5 mm and >2 mm) were also considered for descriptive purposes.

At the follow-up examination, BoP was recorded at six sites per implant by a calibrated examiner (CL). New standardized peri-apical radiographs of the included implants were obtained from the Radiology Department using the parallel technique. The marginal bone level at the follow-up examination was assessed by the same calibrated investigator from the baseline study (CL), applying the same measurement protocol described in the original publication(Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021). Briefly, the radiographic bone level was measured at the mesial and distal aspects of each implant as the distance in millimeters between the intra-osseous portion of the implant (excluding any polished collar) and the first clearly visible contact between the implant surface and the bone. A software program (Autocad 2016 TM, AutoDesk Inc., San Rafael, CA, USA) was used, and the inter-thread pitch distance reported by the manufacturer or the length of the implant was considered for calibration. The largest

value between the mesial and distal measurements was recorded as the bone level for that implant. Bone loss was calculated as the difference in bone levels between the two examinations. The outcome assessor previously demonstrated an excellent intra-rater agreement after re-measuring 50 randomly selected radiographs (ICC=0.98; 95% CI 0.96-0.99; p<0.001).

5.2.4 Data Analysis

Statistical analyses were performed with STATA SE version 18.0 software (StataCorp LP). The characteristics of the study population/implants were summarized. Incidence of peri-implantitis onset/progression was described at both patient- and at implant-level. Risk/protective factors for peri-implantitis onset/progression were studied using multilevel (mixed-effects) logistic regression analyses, accounting for the clustering of multiple implants within the same patients. Each putative factor (Appendix Table 1) was tested individually by adding it to an empty model with the peri-implantitis onset/progression as the dependent variable and testing its significance. All variables with a p value <0.10 were included in an intermediate multiple regression model, and non-significant variables were sequentially removed. The final model integrated all factors that remained with a p value <0.10. However, for results interpretation, statistical significance was *a priori* set at p<0.05. Sensitivity analyses were performed by adjusting the final model *a priori* for the frequency of maintenance per year, treatments performed during follow-up, and peri-implant health status at baseline.

5.3 STUDY #2:

Accuracy of Clinical Parameters in Predicting/Diagnosing Peri-Implant Bone Loss

5.3.1 Predictive Clinical Parameters

In the baseline study, the following clinical diagnostic parameters were recorded using a manual UNC-15 periodontal probe (PCP15; Hu-Friedy) at 6 sites per implant by two previously calibrated examiners: BoP and SoP (both within 30s), PD, and PISTD (Sanz-Martin et al., 2020). For the present analysis, these parameters were synthetized at the implant level as: presence of BoP (i.e., at least one site with BoP), BoP extent (i.e., number of sites with BoP: 0-1, 2-5, 6), presence of SoP (i.e., at least one site with SoP), PD (deepest value), PD≥5 mm and PD≥6 mm (i.e., at least one site with PD≥5 mm or ≥6 mm, respectively), and presence of PISTD (i.e., PISTD>0 mm). Additionally, the same examiners assessed each implant for visual signs of redness and swelling (categorized as: not at all vs. mild/moderate/severe).

5.3.2 Diagnostic Clinical Parameters

At the follow-up examination, the same parameters were recorded by one of the two previously calibrated examiners (CL), and the same implant-level categorizations were applied. Additionally, the modified Bleeding Index (mBI) was assessed by further categorizing the presence of BoP as punctiform, linear, or profuse. Changes in PD and PISTD during follow-up were also computed, both as increases in their deepest implant-level value and as the greatest site-specific increase. PD and PISTD changes were analyzed both as continuous variables and dichotomized with >1 mm as the threshold.

5.3.3 Reference Standard: Peri-implant Bone Loss Occurrence

The diagnostic reference standard of the study was the occurrence of peri-implant bone loss >1 mm between the two examinations. New standardized periapical radiographs of the included implants were obtained from the Radiology Department using the parallel technique. The marginal bone level at the follow-up examination was assessed by same calibrated investigator from the baseline study (CL), applying the same measurement protocol described in the original publication.(Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021) Briefly, the radiographic bone level was measured at the mesial and distal aspects of each implant as the distance in millimeters between the intra-osseous portion of the implant (excluding any polished collar) and the first clearly visible contact between the implant surface and the bone. A software program (Autocad 2016 TM, AutoDesk Inc., San Rafael, CA, USA) was used, and the inter-thread pitch distance reported by the manufacturer or the length of the implant was considered for calibration. The largest value between the mesial and distal measurements was recorded as the bone level for that implant. Bone loss was calculated as the difference in bone levels between the two examinations. The outcome assessor previously demonstrated an excellent intra-rater agreement after re-measuring 50 randomly selected radiographs (ICC=0.98; 95% CI 0.96-0.99; $p<0.001$).

5.3.4 Data analysis

All statistical analyses were performed using STATA SE version 18.0 software (StataCorp LP), with statistical significance *a priori* set at $p<0.05$. The characteristics of the study population and implants were summarized. Incidence/history of peri-implant bone loss was also described according to the different predictive/diagnostic clinical parameters. Baseline clinical (predictive) parameters associated with the incidence of peri-implant bone loss were studied using multilevel (mixed-effects) logistic regression analyses, accounting for the clustering of multiple implants within the same patients. Sensitivity, specificity, area under the curve (AUC), positive and negative predictive values (PPV/NPV), together with their 95% confidence intervals (CI), were calculated for dichotomic parameters.

The same methodology was applied to test the accuracy of clinical (diagnostic) parameters assessed at follow-up to identify recent occurrence of peri-implant bone loss. Finally, a combined multiple regression multilevel model including all significant predictive/diagnostic parameters was presented, after excluding collinear and redundant variables.

VI. RESULTS

VI. RESULTS

6.1 STUDY #1:

Incidence and risk factors of peri-implantitis over time – A prospective cohort study

From the baseline sample of 99 patients, 14 declined to participate in the follow-up visit, three moved to a different city, two missed the scheduled appointment, one passed away, and six could not be reached despite multiple telephone attempts. Consequently, 73 patients with 322 implants were clinically evaluated after a mean follow-up time of 3.9 years (SD=0.3; min: 3.0; max: 4.6). The general characteristics of the population and implants examined at follow-up are detailed in Tables 1 and 2, being consistent with those of the entire baseline population. Most of the included patients were women (61.6%), had a mean age of 62.8 years, had a diagnosis of stage III-IV periodontitis (57.5%), and were currently nonsmoking (80.8%) at baseline (Table 1).

Table 1. General characteristics of the study population.

	Baseline population *(N=99)*	**Follow-up population** *(N=73)*
Age (baseline) (years), mean (SD)	63.7 (9.3)	62.8 (8.0)
Gender, N (%)		
Male	39 (39.4)	28 (38.4)
Female	60 (60.6)	45 (61.6)
BMI (baseline) (kg/m²), mean (SD)	25.6 (3.7)	25.7 (3.8)
Diabetes Status (baseline), N (%)		
No diabetes	83 (83.8)	61 (83.6)
Diabetes	16 (16.2)	12 (16.4)
Smoking (baseline), N (%)		
Non-smokers	41 (41.4)	28 (38.3)
Former smokers	40 (40.4)	31 (42.5)
Current smokers	18 (18.2)	14 (19.2)
Periodontitis Severity (2017 WWP) (baseline), N (%)		
No Periodontitis	7 (7.2)	4 (5.5)
Stage 1	11 (11.3)	7 (9.6)
Stage 2	19 (19.6)	14 (19.2)
Stage 3	30 (30.9)	25 (34.2)
Stage 4	21 (21.7)	17 (23.3)
Edentulous	9 (9.3)	6 (8.2)
Peri-implant Status (baseline), N (%)		
Peri-implant health	1 (1.0)	0 (0.0)
Peri-implant mucositis	11 (11.1)	10 (13.7)
Pre-peri-implantitis	31 (31.3)	25 (34.2)
Peri-implantitis	56 (56.6)	38 (52.1)
Maintenance compliance (during follow-up), N (%)		
Regular maintenance	NA	9 (12.3)
Not regular maintenance	NA	64 (87.7)

Footnote:

Total number varies according to missing data for each variable.

Regular maintenance was defined as participating in an average of ≥1 supportive peri-implant care recalls per year.

SD, standard deviation; N, number; NA, not applicable.

Most of the study implants were located in the maxilla (55.6%), in posterior sites (83.2%), and were part of implant-supported bridge restorations (58.4%). At baseline, 91 implants (28.2%) in 38 patients (52.1%) were diagnosed with peri-implantitis (Table 2).

Table 2. General characteristics of the study implants.

	Whole baseline implants *(N=458)*	**Implants analyzed at follow-up** *(N=322)*
Jaw, N (%)		
Maxilla	253 (55.2)	179 (55.6)
Mandible	205 (44.8)	143 (44.4)
Position, N (%)		
Anterior (canine-canine)	83 (18.1)	54 (16.8)
Posterior	375 (81.9)	268 (83.2)
Implant Brand, N (%)		
S	230 (50.7)	173 (53.9)
N	57 (12.6)	38 (11.8)
A	76 (16.7)	45 (14.0)
Other	91 (20.0)	65 (20.3)
Implant Length (mm), mean (SD)	9.9 (1.7)	9.84 (1.71)
Implant Diameter (mm), mean (SD)	4.1 (0.4)	4.1 (0.4)
Type of Prosthesis (baseline), N (%)		
Single crown	136 (29.7)	103 (32.0)
Bridge	267 (58.3)	188 (58.4)
Overdenture	14 (3.1)	8 (2.5)
Full-arch fixed restoration	41 (8.9)	23 (7.1)
Prosthesis Retention (baseline), N (%)		
Cemented	218 (47.6)	163 (50.6)
Screw-retained	226 (49.3)	151 (46.9)
Locator	8 (1.8)	2 (0.6)
Bar	6 (1.3)	6 (1.9)
Peri-implant Status (baseline), N (%)		
Peri-implant health	39 (8.5)	25 (7.8)
Peri-implant mucositis	146 (31.9)	107 (33.2)
Pre-peri-implantitis	145 (31.7)	99 (30.8)
Peri-implantitis	128 (27.9)	91 (28.2)

Footnote:

Total number varies according to missing data for each variable.

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

SD, standard deviation; N, number.

Most of the included implants (189/58.7%) did not received any treatment during the follow-up period. Non-surgical treatment was performed in 79 (24.6%) implants, while 18 (5.6%) received surgical treatment. Finally, 14 implants (4.3%) underwent removal,

while no reliable information on previous interventions was available for the remaining 22 implants (6.8%).

The mean number of SPIT visits during follow up was 2.0 (SD=1.5; min: 0; max: 7), with an average of 0.5 per year (SD=0.4; min: 0; max: 1.9) and 12.3% of patients were under regular maintenance (i.e., an average of more than one SPIT visit per year).

6.1.1 Incidence of Peri-implantitis Onset/Progression

In addition to the 14 implants lost (9 patients), 10 implants had missing/unreadable follow-up radiographs. Therefore, peri-implantitis onset/progression was assessed on 298 implants.

An incidence of bone loss>1 mm during follow-up was observed in 16 out of 72 patients (22.2%) and 28 out of 298 implants (9.4%) evaluated radiographically (Table 3). Bone loss>1 mm was always associated with the presence of BoP at follow-up. Sixteen events (5.4%) corresponded to new peri-implantitis cases (i.e., peri-implantitis onset), while 12 (4.0%) involved further bone loss of implants already diagnosed with peri-implantitis at baseline (i.e., peri-implantitis progression).

Table 3. Incidence of bone loss during follow-up according to different peri-implant diagnosis at baseline.

		Implant-level (n=298*)		
		Bone loss>0.5 mm	*Bone loss>1 mm*	*Bone loss>2 mm*
Diagnosis at baseline	**Peri-implant health**	1 (4.8%)	1 (4.8%)	1 (4.8%)
	Regular maintenance	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not regular maintenance	1 (6.7%)	1 (6.7%)	1 (6.7%)
	Peri-implant mucositis	15 (14.3%)	9 (8.6%)	1 (1.0%)
	Regular maintenance	3 (20.0%)	2 (13.3%)	0 (0.0%)
	Not regular maintenance	12 (13.3%)	7 (7.8%)	1 (1.1%)
	Pre-Periimplantitis	14 (14.7%)	6 (6.3%)	3 (3.2%)
	Regular maintenance	2 (13.3%)	1 (6.7%)	0 (0.0%)
	Not regular maintenance	12 (15.0%)	5 (6.3%)	3 (3.8%)
	Peri-implantitis	20 (26.0%)	12 (15.6%)	7 (9.1%)
	No treatment after baseline	7 (18.0%)	3 (7.7%)	1 (2.6%)
	Only non-surgical treatment	4 (22.2%)	3 (16.7%)	3 (16.7%)
	Surgical treatment	9 (60.0%)	6 (40.0%)	3 (20.0%)
	Unknown treatment status	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	50 (16.8%)	28 (9.4%)	12 (4.0%)

Footnote:

* Missing data: 24 implants (10 had missing/unreadable radiographs; 14 were lost/removed during follow-up).

Regular maintenance was defined as participating in an average of ≥1 supportive peri-implant care recalls per year.

Peri-implantitis onset was mostly observed among implants diagnosed with peri-implant mucositis (N=9, 8.6%) or pre-periimplantitis (N=6, 6.3%) at baseline, compared with only one implant with peri-implant health (4.8%) at baseline (Table 4). Most of baseline peri-implantitis cases remained stable (84.4%), with no further bone loss. Peri-implantitis progressions was observed around implants that underwent surgical

treatment during follow-up (40.0%), which might have been performed because of the incident bone loss.

		Implant-level						
		Diagnosis at follow-up					Total* *(raw)*	Implant loss**
		Peri-implant health*	Peri-implant mucositis*	Peri-implantitis onset*	Stable peri-implantitis*	Progressive peri-implantitis*		
Diagnosis at baseline	**Peri-implant health**	8 (38.1%)	12 (57.1%)	1 (4.8%)			21 (100.0%)	1 (4.5%)
	Regular maintenance	4 (66.7%)	2 (33.3%)	0 (0.0%)			6 (100.0%)	0 (0.0%)
	Not regular maintenance	4 (26.7%)	10 (66.7%)	1 (6.6%)			15 (100.0%)	1 (6.3%)
	Peri-implant mucositis	10 (9.5%)	86 (81.9%)	9 (8.6%)			105 (100.0%)	2 (1.9%)
	Regular maintenance	2 (13.3%)	11 (73.3%)	2 (13.3%)			15 (100.0%)	0 (0.0%)
	Not regular maintenance	8 (8.9%)	75 (83.3%)	7 (7.8%)			90 (100.0%)	2 (2.2%)
	Pre-Periimplantitis	14 (14.7%)	75 (79.0%)	6 (6.3%)			95 (100.0%)	3 (3.1%)
	Regular maintenance	2 (13.3%)	12 (80.0%)	1 (6.7%)			15 (100.0%)	1 (6.3%)
	Not regular maintenance	12 (15.0%)	63 (78.8%)	5 (6.2%)			80 (100.0%)	2 (2.5%)
	Peri-implantitis				65 (84.4%)	12 (15.6%)	77 (100.0%)	8 (9.4%)
	Implant removal at baseline				NA	NA	0 (100.0%)	5 (100.0%)
	No treatment after baseline				36 (92.3%)	3 (7.7%)	39 (100.0%)	0 (0.0%)
	Only non-surgical treatment				15 (83.3%)	3 (16.7%)	18 (100.0%)	0 (0.0%)
	Surgical treatment				9 (60.0%)	6 (40.0%)	15 (100.0%)	1 (6.3%)
	Unknown treatment status				5 (100.0%)	0 (0.0%)	5 (100.0%)	2 (28.6%)
	Overall	32 (10.7%)	173 (58.1%)	16 (5.4%)	65 (21.8%)	12 (4.0%)	298 (100.0%)	14 (4.5%)

Table 4. Occurrence of peri-implant diseases and implant loss during follow-up according to different peri-implant diagnosis at baseline.

Footnote:

* Percentages refer to implants evaluated radiographically (n=298) (missing data: 10 implants due missing/unreadable radiographs, 14 implants lost during follow-up).

** Percentages refer to implants evaluated clinically (i.e., including implants lost during follow-up) (n=312) (missing data: 10 implants due missing/unreadable radiographs).

NA, not applicable.

Regular maintenance was defined as participating in an average of ≥1 supportive peri-implant care recalls per year.

6.1.2 Risk/Protective Factors Associated with Peri-implantitis Onset/Progression

The distribution of the tested risk/protective factors according to peri-implantitis incidence is detailed in Appendix Tables 2 and 3.

In the multi-level simple regression analyses, the following patient-level exposure variables were associated with peri-implantitis ($p < .10$): marital status, height, osteoporosis/osteopenia, myocardial infarction, hepatitis, smoking, sleep duration, alcohol consumption, intake of bisphosphonates, vitamin D, or immunosuppressants, periodontitis severity (2017 WWP), number of remaining teeth, electric toothbrush use, and periodontal bone loss/age ratio (Appendix Table 4). The following implant-level variables were also associated with peri-implantitis: implant location, presence of at least one adjacent tooth, type of restoration, prosthetic design, restoration margin location, implant malposition and plaque (Appendix Table 5).

In the final multilevel multiple logistic regression model (Table 5), the following factors remained significant at the $p < .05$ level: periodontitis severity (stage IV periodontitis: OR=41.29), periodontal bone loss/age ratio (>1: OR=8.87), smoking (current smokers: OR=7.84), sleep duration (> 7 hours: OR=19.97), implant location (incisor: OR=60.60), restoration type (full-arch fixed restorations: OR=89.84), and restoration margin location (juxta-marginal: OR=14.17). Osteoporosis/osteopenia (yes: OR=5.97) and plaque (6 sites: OR=3.64) also entered the final model ($p<.10$), despite being not statistically significant ($p>.05$). Sensitivity analyses, adjusting the final model *a priori* for frequency of maintenance per year, treatments performed during follow-up, and peri-implant health status at baseline, showed results consistent with the main analyses.

Table 5. Risk/protective indicators associated with incidence of peri-implantitis during follow-up: multilevel multiple logistic regression analysis.

	Empty Model		Final Model		
Variable	**OR**	**95% CI**	**OR**	**95% CI**	***p-value***
Fixed part					
Intercept	0.04	0.01-0.12	0.00	0.00-0.01	
Osteoporosis/osteopenia (yes) (baseline)			5.97	0.98-36.32	0.052
Smoking (baseline)					
Non-Smoker			*Ref*	*Ref*	*Ref*
Current Smoker			7.84	1.83-33.50	**0.005**
Sleep duration (baseline)					
<7 hours			0.80	0.20-3.21	0.751
7-8 hours			*Ref*	*Ref*	*Ref*
>7 hours			19.97	1.69-236.39	**0.018**
Periodontitis Severity (2017 WWP) (baseline)					
No periodontitis or SI-III periodontitis			*Ref*	*Ref*	*Ref*
Stage 4 periodontitis			41.29	4.10-415.54	**0.002**
Edentulous			NE	NE	NE
Periodontal bone loss/age ratio (follow-up)					
≤1			*Ref*	*Ref*	*Ref*
>1			8.87	1.47-53.73	**0.017**
Implant location (baseline)					
Molar			*Ref*	*Ref*	*Ref*
Incisor			60.60	4.04-908.33	**0.003**
Canine			NE	NE	NE
Premolar			0.90	0.28-2.93	0.862
Restoration Type (baseline)					
Single Crown			*Ref*	*Ref*	*Ref*
Bridge			1.19	0.27-5.30	0.817
Overdenture			NE	NE	NE
Full-Arch Fixed Restoration			89.84	3.66-2202.97	**0.006**
Restoration margin location (follow-up)					
Supra-marginal			*Ref*	*Ref*	*Ref*
Sub-marginal			5.97	0.54-66.02	0.145
Juxta-marginal			14.17	1.20-166.76	**0.035**
Plaque (baseline)					
0-5 sites			*Ref*	*Ref*	*Ref*
6 sites			3.64	0.83-15.94	0.086
Random part					
Patient variance	2.60	0.79-8.53	0.00	0.00-0.00	
AIC	177.61		119.64		

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

6.2 STUDY #2:

Accuracy of Clinical Parameters in Predicting/Diagnosing Peri-Implant Bone Loss

6.2.1 Clinical (Predictive) Parameters at Baseline and Incidence of Peri-implant Bone Loss

Except one case, bone loss during follow-up was only observed in implants with BoP at baseline (96.4%) (Table 6). Incident bone loss was more common around implants displaying SoP, redness, and swelling at baseline.

Table 6. Clinical parameters at baseline and incidence of peri-implant bone loss.

Baseline predictive parameters	*Overall (n=298)*	*Incidence of peri-implant bone loss (n=28)*
BoP (baseline), N (%)		
No	21 (7.0%)	1 (3.6%)
Yes	277 (93.0%)	27 (96.4%)
BoP extent (baseline), N (%)		
0-1 site	59 (19.8%)	2 (7.1%)
2-3-4-5 sites	200 (67.1%)	19 (67.9%)
6 sites	39 (13.1%)	7 (25.0%)
SoP (baseline), N (%)		
No	271 (90.9%)	24 (85.7%)
Yes	27 (9.1%)	4 (14.3%)
PPD ≥5 mm (baseline), N (%)		
No	121 (40.6%)	12 (42.9%)
Yes	177 (59.4%)	16 (57.1%)
PPD ≥6 mm (baseline), N (%)		
No	203 (68.1%)	19 (67.9%)
Yes	95 (31.9%)	9 (32.1%)
PISTD (baseline), N (%)		
No	220 (73.8%)	20 (71.4%)
Yes	78 (26.2%)	8 (28.6%)
Redness (baseline), N (%)		
No	71 (23.8%)	1 (3.6%)
Yes	227 (76.2%)	27 (96.4%)
Swelling (baseline), N (%)		
No	130 (43.6%)	8 (28.6%)
Yes	168 (56.4%)	20 (71.4%)

Footnote:

BoP, bleeding on probing; mBI, modified bleeding index; N, number; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; SoP, suppuration on probing.

In multi-level regression analyses, only baseline redness was significantly associated with the incidence of bone loss (OR = 13.81), while BoP extent showed a non-significant trend (6 sites: OR = 5.27) (Table 7).

Table 7. Clinical predictive parameters at baseline and incidence of peri-implant bone loss over time: multilevel logistic regression analysis.

Variable	Simple regression		
	OR	**95% CI**	***p-value***
BoP (baseline), yes	1.62	0.15-16.95	0.689
BoP extent (baseline)			
0-1 site	*Ref*	*Ref*	*Ref*
2-3-4-5 sites	3.44	0.65-18.35	0.148
6 sites	5.27	0.75-37.05	0.095
SoP (baseline), yes	1.12	0.23-5.43	0.884
PPD (baseline)	1.00	0.70-1.45	0.981
PPD ≥5 mm (baseline), yes	0.71	0.26-1.92	0.498
PPD ≥6 mm (baseline), yes	0.92	0.31-2.76	0.886
PISTD>0 mm (baseline), yes	1.32	0.42-4.09	0.633
Redness (baseline), yes	13.81	1.39-137-31	**0.025**
Swelling (baseline), yes	2.02	0.68-6.04	0.208

Footnote:

BoP, bleeding on probing; CI, confidence interval; OR, odds ratio; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; Ref, reference category; SoP, suppuration on probing.

BoP at ≥1 site (96.4%) and ≥2 sites (92.9%), as well as redness (96.4%), at baseline exhibited the highest sensitivity for predicting occurrence peri-implant bone loss, but low specificity (7.4-25.9%) (Table 8). Specificity was high for BoP at 6 sites (88.1%) and presence of SoP (91.5%); however, both exhibited low sensitivity (14.3-25.0%). AUC values were generally low, with the highest observed for redness (0.61). PPVs indicated that 17.9% of implants with BoP at 6 sites and 14.8% with SoP at baseline exhibited bone loss during follow-up, whereas NPVs showed that 98.6% of implants without redness did not exhibit future bone loss.

Table 8. Accuracy of different clinical parameters at baseline in predicting peri-implant bone loss occurrence over time.

Peri-implant bone loss occurrence									
Incidence % (95% CI)	9.4 (6.3-13.3)								
	Baseline diagnostic parameters								
	BoP (baseline) ≥1 site	**BoP (baseline)** ≥2 sites	**BoP (baseline)** =6 sites	**SoP+ (baseline)** ≥1 site	**PPD (baseline)** ≥5 mm	**PPD (baseline)** ≥6 mm	**PISTD (baseline)** >0 mm	**Redness (baseline)** yes	**Swelling (baseline)** yes
Sensitivity %(95%CI)	96.4 (81.7-99.9)	92.9 (76.5-99.1)	25.0 (10.7-44.9)	14.3 (4.0-32.7)	57.1 (37.2-75.5)	32.1 (15.9-52.4)	28.6 (13.2-48.7)	96.4 (81.7-99.9)	71.4 (51.3-89.8)
Specificity % (95% CI)	7.4 (4.6-11.2)	21.1 (16.4-26.5)	88.1 (83.7-91.8)	91.5 (87.5-94.5)	40.4 (34.5-46.5)	68.1 (62.2-73.7)	74.1 (68.4-79.2)	25.9 (20.8-31.6)	45.2 (39.1-51.3)
AUC (95% CI)	0.52 (0.48-0.56)	0.57 (0.52-0.62)	0.57 (0.48-0.65)	0.53 (0.46-0.60)	0.49 (0.39-0.59)	0.50 (0.41-0.59)	0.51 (0.42-0.60	0.61 (0.57-0.66)	0.58 (0.49-0.67
PPV % (95% CI)	9.7 (6.5-13.9)	10.9 (7.2-15.5)	17.9 (7.5-33.5)	14.8 (4.2-33.7)	9.0 (5.3-14.3)	9.5 (4.4-17.2)	10.3 (4.5-19.2)	11.9 (8.0-16.8)	11.9 (7.4-17.8)
NPV % (95% CI)	95.2 (76.2-99.9)	96.6 (88.3-99.6)	91.9 (87.9-94.9)	91.1 (87.1-94.2)	90.1 (83.3-94.8)	90.6 (85.8-94.3)	90.9 (86.3-94.4)	98.6 (92.4-100.0)	93.8 (88.2-97.3)

Footnote:
AUC, Area Under the Curve
NPV, Negative Predictive Value
PPV, Positive Predictive Value

6.2.2 Clinical (Diagnostic) Parameters at Follow-Up and History of Peri-implant Bone Loss

At follow-up, peri-implant bone loss was always associated with the concomitant presence of at least one BoP site (Table 9). Most bone loss cases (92.9%) exhibited BoP at ≥2 sites. SoP was only observed in implants with recent peri-implant bone loss. History of bone loss was more frequent in implants showing deep PD (≥5 mm and ≥6 mm) and profuse bleeding at follow-up. Peri-implant bone loss was more commonly detected in implants showing increases in PD or PISTD >1 mm between the examinations.

Table 9. Clinical parameters at follow-up and history of peri-implant bone loss.

Follow-up diagnostic parameters	*Overall (n=298)*	*History of peri-implant bone loss (n=28)*
BoP (follow-up), N (%)		
No	39 (13.1%)	0 (0.0%)
Yes	259 (86.9%)	28 (100.0%)
BoP extent (follow-up), N (%)		
0-1 site	93 (31.2%)	3 (10.7%)
2-3-4-5 sites	158 (53.0%)	13 (46.4%)
6 sites	47 (15.8%)	12 (42.9%)
SoP (follow-up), N (%)		
No	295 (99.0%)	25 (89.3%)
Yes	3 (1.0%)	3 (10.7%)
PPD ≥5 mm (follow-up), N (%)		
No	158 (53.0%)	7 (25.0%)
Yes	140 (47.0%)	21 (75.0%)
PPD ≥6 mm (follow-up), N (%)		
No	232 (77.9%)	11 (39.3%)
Yes	66 (22.1%)	17 (60.7%)
PISTD (follow-up), N (%)		
No	174 (58.4%)	17 (60.7%)
Yes	124 (41.6%)	11 (39.3%)
mBI (follow-up), N (%)		
No BoP	39 (13.1%)	0 (0.0%)
Punctiform	105 (35.4%)	8 (28.6%)
Line	121 (40.7%)	9 (32.1%)
Profuse	32 (10.8%)	11 (39.3%)
Deepest PPD increase >1 mm (follow-up), N (%)		
No	279 (93.69%)	20 (71.4%)
Yes	19 (6.4%%)	8 (28.6%)
Site-specific PPD increase>1 mm (follow-up), N (%)		
No	229 (76.9%)	10 (35.7%)
Yes	69 (23.1%)	18 (64.3%)
Highest PISTD increase >1 (follow-up), N (%)		
No	269 (90.3%)	22 (78.6%)
Yes	29 (9.7%)	6 (21.4%)
Site-specific PISTD increase>1 mm (follow-up), N (%)		
No	255 (85.6%)	19 (67.9%)
Yes	43 (14.4%)	9 (32.1%)

Footnote:

BoP, bleeding on probing; mBI, modified bleeding index; N, number; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; SoP, suppuration on probing.

Multi-level regression analyses identified several follow-up clinical parameters associated with history of recent peri-implant bone loss (Table 10): BoP extent (6 sites: OR = 17.6), deepest PD (per mm increase: OR = 1.23; PD ≥5 mm: OR = 3.77; PD ≥6 mm:

OR = 8.16), mBI (profuse: OR = 10.37), deepest PD change (per mm: OR = 2.21) and increase >1 mm (OR = 10.08), site-specific PD change (per mm: OR = 2.93) and increase >1 mm (OR = 12.05), and site-specific PISTD increase >1 mm (OR = 3.44).

Table 10. Clinical diagnostic parameters at follow-up and recent history of peri-implant bone loss: multilevel logistic regression analyses.

Variable	Simple regressionSo,		
	OR	**95% CI**	***p-value***
BoP (follow-up), yes	NE	NE	NE
BoP extent (follow-up)			
0-1 site	*Ref*	*Ref*	*Ref*
2-3-4-5 sites	3.73	0.78-17.76	0.098
6 sites	17.6	3.25-115.06	**0.001**
SoP (follow-up), yes	NE	NE	NE
Deepest PPD (follow-up), for each mm increase	1.23	1.56-3.19	**0.000**
Deepest PPD ≥5 mm (follow-up), yes	3.77	1.30-10.87	**0.014**
Deepest PPD ≥6 mm (follow-up), yes	8.16	2.96-22.51	**0.000**
PISTD>0 mm (follow-up), yes	0.76	0.27-2.14	0.599
mBI (follow-up)			
No BoP	NE	NE	NE
Punctiform	*Ref*	*Ref*	*Ref*
Line	1.03	0.31-3.35	0.967
Profuse	8.99	2.24-36.04	**0.002**
Profuse mBI mm (follow-up), yes	10.37	3.22-33.43	**0.000**
Deepest PPD change (follow-up), for each mm	2.21	1.52--3.21	**0.000**
Deepest PPD increase >1 mm (follow-up), yes	10.08	2.73-37.29	**0.001**
Site-specific PPD change (follow-up), for each mm increase	2.93	1.79-4.80	**0.000**
Site-specific PPD increase >1 mm (follow-up), yes	12.05	3.69-39.33	**0.000**
Deepest PISTD change (follow-up), for each mm	1.08	0.66-175	0.767
Deepest PISTD increase >1 mm (follow-up), yes	2.61	0.70-9.75	0.154
Site-specific PISTD change (follow-up), for each mm increase	1.24	0.76-2.02	0.391
Site-specific PISTD increase >1 mm (follow-up), yes	3.44	1.02-11.60	**0.047**

Footnote:

BoP, bleeding on probing; CI, confidence interval; mBI, modified bleeding index; NE, not estimable; OR, odds ratio; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; Ref, reference category; SoP, suppuration on probing.

BoP at ≥1 site showed the highest sensitivity for history of peri-implant bone loss (100.0%), followed by BoP at ≥2 sites (89.3%) and PD ≥5 mm (75.0%) (Table 11). Their specificity was however limited (14.4-55.9%) The highest specificity was observed for SoP presence (100.0%), deepest PD increase >1 mm (95.9%), profuse bleeding (91.9%), PISTD increases >1 mm (deepest: 91.5%; site-specific: 87.4%), and BoP at 6 sites (87.0%). The same parameters showed however low sensitivity (10.7-42.9%). The highest AUC values were noted for site-specific PD increase >1 mm (0.73) and PD ≥6 mm at follow-up (0.71). All cases with SoP had a history of bone loss (PPV = 100.0%), as well as 42.1% of cases with an increase in the deepest PD. The absence of BoP corresponded to the absence of bone loss >1 mm during follow-up (NPV = 100.0%).

A combined criterion of site-specific PD or PISTD increase >1 mm yielded the best diagnostic accuracy for detecting recent peri-implant bone loss (sensitivity: 82.1%; specificity: 70.0%; AUC = 0.76). Using this criterion, 97.4% of implants with neither PD nor PISTD increases >1 mm had no recent bone loss (NPV = 97.4%), and 22.1% (PPV) of implants showing at least one of them had bone loss.

Table 11. Diagnostic accuracy of different clinical parameters at follow-up for the detection of recent history of peri-implant bone loss.

	History of peri-implant bone loss													
Prevalence % (95% CI)		9.4 (6.3-13.3)												
		Follow-up diagnostic parameters												
	BoP (follow-up) ≥1 site	**BoP (follow-up)** ≥2 sites	**BoP (follow-up)** =6 sites	**SoP+ (follow-up)** ≥1 site	**PPD (follow-up)** ≥5 mm	**PPD (follow-up)** ≥6 mm	**PISTD (follow-up)** >0 mm	**mBI (follow-up)** Line or Profuse	**mBI (follow-up)** Profuse	**Deepest PPD increase (follow-up)** >1 mm	**Site-specific PPD increase (follow-up)** >1 mm	**Deepest PISTD increase (follow-up)** >1 mm	**Site-specific PISTD increase (follow-up)** >1 mm	**Site-specific PPD or PISTD increase (follow-up)** >1 mm
Sensitivity % (95%CI)	100.0 (87.7-100.0)	89.3 (71.8-97.7)	42.9 (24.5-62.8)	10.7 (2.3-28.2)	75.0 (55.1-89.3)	60.7 (40.6-78.5)	39.3 (21.5-59.4)	71.4 (51.3-86.8)	39.3 (21.5-59.4)	28.6 (13.2-48.7)	64.3 (44.1-81.4)	21.4 (8.3-41.0)	32.1 (15.9-52.4)	82.1 (63.1-93.9)
Specificity % (95% CI)	14.4 (10.5-19.2)	33.3 (27.7-39.3)	87.0 (82.4-90.8)	100.0 (98.6-100.0)	55.9 (49.8-61.9)	81.9 (76.7-86.3)	58.1 (52.0-64.1)	50.4 (44.2-56.5)	91.9 (87.9-94.8)	95.9 (92.8-97.9)	81.1 (75.9-85.6)	91.5 (87.5-94.5)	87.4 (82.8-91.1)	70.0 (64.2-75.4)
AUC (95% CI)	0.57 (0.55-0.59)	0.61 (0.55-0.68)	0.65 (0.55-0.74)	0.55 (0.50-0.61)	0.65 (0.57-0,74)	0.71 (0.62-0.81)	0.49 (0.39-0.58)	0.61 (0.52-0.70)	0.66 (0.56-0.75)	0.62 (0.54-0.71)	0.73 (0.63-0.82)	0.56 (0.49-0.64)	0.60 (0.51-0.69)	0.76 (0.68-0.84)
PPV % (95% CI)	10.8 (7.3-15.2)	12.2 (8.0-17.5)	25.5 (13.9-40.3)	100.0 (29.2-100.0)	15.0 (9.5-22.0)	25.8 (15.8-38.0)	8.9 (4.5-15.3)	13.0 (8.1-19.3)	33.3 (18.0-51.8)	42.1 (20.3-66.5)	26.1 (16.3-38.1)	20.7 (8.0-39.7)	20.9 (10.0-36.0)	22.1 (14.6-31.3)
NPV % (95% CI)	100.0 (91.0-100.0)	96.8 (90.9-99.3)	93.6 (89.9-96.3)	91.5 (87.7-94.4)	95.6 (91.1-98.2)	95.3 (91.7-97.6)	90.2 (84.8-94.2)	94.4 (89.3-97.6)	93.6 (89.9-96.2)	92.8 (89.1-95.6)	95.6 (92.1-97.9)	91.8 (87.9-94.8)	92.5 (88.6-95.5)	97.4 (94.1-99.2)

Footnote:
AUC, Area Under the Curve
NPV, Negative Predictive Value
PPV, Positive Predictive Value

6.2.3 Combined Predictive/Diagnostic Model

A combined predictive/diagnostic model for detecting incidence/history of peri-implant bone loss is presented in Table 12. Statistically significant parameters included BoP extent at baseline (2-5 sites: OR = 9.64), redness at baseline (OR = 53.63), PD ≥6 mm at follow-up (OR = 5.51), and site-specific PD (OR = 13.89) and PISTD (OR = 9.07) increases >1 mm during follow-up. Profuse bleeding at follow-up showed a borderline tendency for association (OR = 4.61), though it did not reach statistical significance.

Table 12. Combined predictive/diagnostic model: clinical parameters at baseline/follow-up and incidence/history of peri-implant bone loss.

Variable	*Multiple regression*		
	OR	**95% CI**	***p-value***
BoP extent (baseline)			
0-1 site	*Ref*	*Ref*	*Ref*
2-3-4-5 sites	9.64	1.13-81.85	**0.038**
6 sites	7.36	0.50-68.61	0.158
Redness (baseline), yes	53.63	2.11-1363.12	**0.016**
PPD ≥6 mm (follow-up), yes	5.51	1.43-21.30	**0.013**
Profuse mBI mm (follow-up), yes	4.61	0.98-21.72	0.053
Site-specific PPD increase >1 mm (follow-up), yes	13.89	2.79-69.10	**0.0001**
Site-specific PISTD increase >1 mm (follow-up), yes	9.07	1.78-45.92	**0.008**

Footnote:

BoP, bleeding on probing; CI, confidence interval; mBI, modified bleeding index; OR, odds ratio; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; Ref, reference category.

VII. DISCUSSION

VII. DISCUSSION

7.1 MAIN FINDINGS

Study #1 This prospective cohort study, based in a previous reported university-representative sample (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021), observed an incidence of peri-implantitis onset/progression of 9.4%, at nearly 4 years. Bone loss was consistently associated with the presence of BoP at follow-up. Several risk factors for peri-implantitis were identified, including: Stage IV periodontitis, a periodontal bone loss/age ratio >1, current smoking, sleep duration >7 hours, implants in incisor position, full-arch fixed restorations, and juxta-marginal margin location. Analyses adjusted for the frequency of maintenance per year, treatments performed during follow-up, and peri-implant health status at baseline showed consistent results.

Study #2: The present findings indicate that the clinical signs of inflammation compatible with peri-implant mucositis diagnosis (presence of BoP, visual redness) often precede peri-implantitis. However, their predictive value is limited due to low specificity. Conversely, BoP at six sites and SoP demonstrated high specificity for predicting peri-implantitis, although its low sensitivity. For diagnosing peri-implantitis, BoP at follow-up was always associated with peri-implant bone loss, while SoP was only observed in implants with peri-implantitis. High specificity was also noted for the severity (profuse) and extent (six sites) of BoP, as well as for changes in PPD and PISTD. The combined criterion of site-specific PPD or PISTD increases achieved the best diagnostic accuracy of peri-implantitis. Overall, these findings suggest that BoP extent and severity, SoP, and changes in PPD/PISTD are relevant and specific parameters for diagnosing peri-implantitis.

7.2 INCIDENCE OF PERI-IMPLANTITIS

Study #1: In this study peri-implantitis was observed in 9.4% of implants, comprising 5.4% new cases and 4.0% progressions, at approximately 4 years of follow-up. Peri-implantitis was defined as presence of BoP / SoP and bone loss > 1mm with respect to baseline radiographs.

There is a limited number of prospective cohort studies available for comparison, with most existing evidence at risk of selection, confounding, or information bias.

Rodrigo et al (2012) identified a similar incidence of peri-implantitis (5.8%) over a five-year period. The employed definition did not include a specific bone loss threshold, and also comprised positive BoP and PPD ≥4 mm. In contrast, our study defined peri-implantitis as bone loss exceeding 1mm with BoP/SoP, without incorporating PPD in the definition.

Costa el al. (2012) followed 80 patients with peri-implant mucositis diagnosis at baseline. A higher incidence of peri-implantitis (31.2%) was reported at 5 years (Costa et al., 2012). In the present study, and for the same baseline diagnosis, onset of peri-implantitis was 3.0%.

Different bone loss cut-offs were used in our analysis and incidence of bone loss>2mm was found in 4.0% of implants. A similar outcome (3.2%) was identified in a prospective study of 528 implants in edentulous patients rehabilitated with maxillary overdentures, at 5 years (Onclin et al., 2022).

Briefly, differences in follow-up length, case definitions, and the use of a convenience sample may explain the discrepancies in the peri-implantitis incidence among studies. Furthermore, our sample included patients with distinct baseline diagnosis (peri-implant health, peri-implant mucositis and peri-implantitis), while other studies followed

implants with specific peri-implant diagnosis (Costa et al., 2012) (e.g., peri-implant mucositis) or included patients directly after implant placement / loading (Mameno et al., 2019; Onclin et al., 2022; Rodrigo et al., 2012).

7.3 RISK FACTORS FOR PERI-IMPLANTITIS

The history of periodontitis has been consistently linked to peri-implantitis with an increased risk ranging 2.2 to 19.0 (Dalago et al., 2017; de Araujo Nobre et al., 2015; Karoussis et al., 2003; Koldsland et al., 2011; Renvert et al., 2014). However, only a few studies have a longitudinal design and a comparison group of patients without history of periodontitis (Degidi et al., 2016; Karoussis et al., 2003; Roccuzzo et al., 2022; Roccuzzo et al., 2023; Roccuzzo et al., 2012; Roccuzzo et al., 2014; Roccuzzo et al., 2017; Swierkot et al., 2012; Zhang et al., 2018), confirming that patients with history of periodontitis are at higher risk for peri-implantitis (Annunziata et al., 2024; Serroni et al., 2024).

In accordance with the baseline study (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021), our findings relate the most severe forms of periodontitis to the risk of peri-implantitis (i.e., Stage IV and bone loss/age ratio >1). According to the 2017 classification, Stage IV complexity features include masticatory dysfunction after tooth loss due to periodontitis, with such cases requiring an increased number of implants to restore function.

Additionally, the periodontal bone loss/age ratio represents the primary criterion for defining the rate of progression of periodontitis (grade). To avoid confounding from smoking and diabetes, this parameter was tested alone. A periodontal bone loss/age ratio >1 (Grade C) emerged as a risk factor for peri-implantitis, highlighting that

periodontitis with rapid progressive rate are at higher risk, as previously described (Monje et al., 2014; Swierkot et al., 2012) .

Current smokers exhibited a higher risk of peri-implantitis in the present study, in accordance to the baseline study findings (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021). This result aligns with longitudinal studies that have reported a threefold increase in the incidence of peri-implantitis among smokers (Astolfi et al., 2022; Karoussis, Muller, et al., 2004). Also, a recent 10-years prospective study including 407 patients, featured a 52% probability for peri-implantitis incidence in smokers (Windael et al., 2021). However, other prospective studies failed to demonstrate this association (Swierkot et al., 2012; Zhang et al., 2018). These studies included patients with a mean age approximately 20 years younger and shorter follow-up periods after implant placement. Considering that the deleterious effect of smoking is related to the habit duration and dose (Martinez-Amargant et al., 2023; Naseri et al., 2020), this may partially account for the observed discrepancy in the literature. Also, the confounder effect of periodontitis and the heterogeneous categorizations of smokers should not be neglected (Derks et al., 2016a; Schwarz et al., 2018).

The observed higher risk of peri-implantitis incidence in long sleepers underlines the relevance of healthy lifestyles beyond non-smoking for promoting peri-implant health. Despite being novel for peri-implant health, this finding is consistent with periodontal literature (Marruganti, Baima, et al., 2023; Marruganti et al., 2024; Marruganti, Romandini, et al., 2023; Romandini et al., 2017).

Several implant-level variables were also associated with the incidence of peri-implantitis. The observed higher risk in anterior zones is consistent with previous studies indicating higher implant loss (Pedrinaci et al., 2023) and peri-implantitis prevalence in

the anterior zones (Aguirre-Zorzano et al., 2015; French et al., 2019; Rodrigo et al., 2018; Song et al., 2020; Sun et al., 2023), specially in the anterior mandible (OR=4.9) (Rodrigo et al., 2018). The unique anatomical and histological features of these zones, along with specific surgical and prosthetic protocols aimed at maximizing aesthetic outcomes that may limit biofilm removal, may contribute to this higher risk.

The higher risk of peri-implantitis observed among full-arch restorations is also in accordance with previous reports (Apaza-Bedoya et al., 2024; Dalago et al., 2017; Rodrigo et al., 2018). In addition to be a proxy of the most severe forms of periodontitis, it may also be related to more challenging access to self-performed oral hygiene procedure (Gong et al., 2023; Menini et al., 2018). Indeed, a high mean plaque index was recorded in implants supporting full-arch rehabilitation (Menini et al., 2018). Furthermore, peri-implantitis occurrence has been consistently associated to prosthesis design related factors that compromise accessibility for oral hygiene (Pons et al., 2021; Rodrigo et al., 2018; Serino & Strom, 2009) and the position of the implant supported rehabilitation to bone crest (Derks et al., 2016a)

The same rational applies to the juxta marginal restorations, identified as a risk factor for bone loss, since the restoration location may limit biofilm removal due to the impaired access, thus favoring microbiological niches. These findings highlight once more the relevance of restoration features on the long-term maintenance of peri-implant health.

A causal association between presence of plaque and peri-implant tissues inflammation has been established (Meyer et al., 2017; Pontoriero et al., 1994; Salvi et al., 2012) and animal studies corroborate that peri-implantitis is related to plaque accumulation (Albouy et al., 2009). Additionally, cross-sectional and case control studies indicate that

plaque accumulation is related to an increased risk of peri-implantitis (Aguirre-Zorzano et al., 2015; Canullo, Penarrocha-Oltra, et al., 2016; de Araujo Nobre et al., 2015; Ferreira et al., 2006; Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021). Also, high full-mouth plaque and bleeding indexes were associated to the increased risk of peri-implantitis in a 20-years longitudinal study (Roccuzzo et al., 2022). Despite we found an association of baseline plaque and the incidence of peri-implantitis, the multilevel model failed to confirm a statistical significant association, probably due to lack of statistical power. Also, the inability to account for variability in self-performed plaque control over time may have further limited our findings.

Implant brand and malposition and keratinized tissue height did not emerge as risk factors, possible due to lack of statistical power, as denoted by their non-significant association in simple regression analyses.

Lack of compliance with supportive therapy also did not reach significance in the statistical analysis. Maintenance frequency could have been subject to a masking effect from periodontitis, as the most severe forms of periodontitis may necessitate more frequent maintenance recalls**.** Nevertheless, bone loss was found to be more frequent in implants without regular maintenance (< 1 visit per year) in accordance to the evidence described in the literature (Costa et al., 2012; Rodrigo et al., 2018).

7.4 DIAGNOSTIC ACCURACY OF CLINICAL PARAMETERS

Study #2: This study employed two strategies to assess the clinical parameters accuracy in diagnosing peri-implant bone loss. Baseline clinical parameters were used to predict incidence of bone loss, whether the parameters evaluated at follow-up were tested to diagnose a history of recent bone loss, confirmed through direct evidence, since previous documentation was available.

7.4.1 Diagnostic accuracy of clinical parameters to predict peri-implant bone loss

In the present study, signs of peri-implant mucosa inflammation preceded 96.4% of bone loss events and were present in 100% of cases with a history of recent bone loss.

Peri-implant mucositis has been assumed as a precursor to peri-implantitis (Costa et al., 2012). However, longitudinal studies including a peri-implant health control group are lacking.

In the present study, signs of peri-implant mucosa inflammation preceded 96.4% of bone loss events and was evident in all cases with a recent history of bone loss. However, BoP high prevalence (>85%) in the population question if it truly reflects an inflammatory disease process in the peri-implant tissues. Although highly sensitive, this parameter has low specificity, potentially leading to the over-diagnosis and consequently over-treatment of peri-implant mucositis. Also, moving the thresholds of BoP from ≥1 to ≥2 sites, as recently proposed, (Tonetti et al., 2023) only provides minimal improvements in its predictive accuracy.

In contrast, BoP extent (6 sites) and SoP demonstrated the highest specificity in predicting peri-implant bone loss (88.1%-91.5%). The predictive value of BoP extent has not been analyzed in previous studies, however the findings related to SoP are consistent with other studies evaluating peri-implantitis cases (Koldsland et al., 2018; Monje et al., 2021; Romandini et al., 2024).

These data emphasize the importance of effectively treating implants exhibiting BoP at 6 sites or SoP, since bone loss is likely to occur during follow-up. However, due to their low sensitivity, most incident peri-implantitis cases occur in implants without SoP and BoP at 6 sites. Consequently, there is a pressing need for research on microbiological and host biomarkers, as well as non-invasive imaging (Galarraga-Vinueza et al., 2024)

and new technologies, to develop more effective tools for predicting bone loss before it becomes radiographically detectable.

7.4.2 Diagnostic accuracy of clinical parameters to detect peri-implant bone loss

Overall, a specificity exceeding 80% was observed for BoP severity (profuse), SoP, PD ≥6 mm and changes in PISTD and PD over time, however these parameters reveled low sensitivity for detecting bone loss >1mm. These findings are in line with preclinical in vivo experimental peri-implantitis studies (Monje, Insua, et al., 2018).

Regarding BoP extent, BoP (≥1 and ≥2 sites) presented with the highest sensitivity (100.0% and 89.3%, respectively), however their diagnostic value may be questioned due to its high frequency in the population. Conversely, BoP extent (6 sites) presented the highest specificity (87.0%) and AUC (0.65), in accordance with clinical studies suggesting an improvement of BoP diagnostic accuracy with an increased number of bleeding sites (Ramanauskaite et al., 2024; Romandini, Berglundh, et al., 2021).

There is a lack of studies evaluating the diagnostic accuracy of BoP severity. Our results demonstrated that BoP severity (i.e., profuse) has a high specificity (91.9%) and overall similar diagnostic accuracy as BoP =6 sites.

Changes in PD over time is part of the diagnostic criteria to define a peri-implantitis case (Berglundh et al., 2018). The results of the present study disclosed that longitudinal PD increase do not enhance the limited diagnostic accuracy of detecting of PD ≥ 6mm at a single assessment. Also, must be considered that the prosthetics design may compromise the accurate assessment of PPD (Serino et al., 2013).

Conversely, the combination of changes in PPD and PISTD exhibited the best overall diagnostic accuracy for detecting history of peri-implantitis, in accordance with previous studies (Romandini, Lima, Pedrinaci, Araoz, Soldini, et al., 2021).

These findings underline that clinicians should not rely solely on any single parameter, as they all demonstrated low sensitivity.

7.5 STRENGHTS AND LIMITATIONS

The population of the present thesis is based on a representative sample and a high participation rate was achieved at the 3.9-years examination. However, it derives from a single center, with specific setting, such as a university clinic. Therefore, the generalizability of these findings to different settings needs to be verified by future studies. The relevance of the present findings lies on the extensive data collection, which enable the analysis of a wide range of risk factors and predictive/diagnostic clinical parameters analyzed within a prospective cohort design.

The use of multi-level regression analyses, adjusted for other risk factors, controls the risk of confounding bias.

Additionally, bone loss assessed through direct evidence within a longitudinal framework and the evaluation performed by the same calibrated operator from the baseline study minimized the risk of information bias.

 # Study 1: Despite a broaden data collection was carried out that allowed the analysis of an extended pool of risk indicators, some limitations should be considered.

The absence of previous studies with a similar design necessitated an exploratory approach for this study design. As such, a specific sample size calculation was not performed for the purposes of these analyses, given that the population is derived from

the cohort established at baseline. Consequently, limited statistical power may have hindered the identification of potential risk factors. A risk of information bias cannot be excluded for some of the tested risk indicators, which were self-reported, while others were assessed through non-gold standard methods (e.g., mucosal thickness evaluated through a probe).

Moreover, two of the emerged risk factors (periodontal bone loss/age ratio and restoration margin location) were only assessed at the follow-up examination, thereby precluding its assessment prior to occurrence of bone loss.

 # Study 2: Clinical examinations performed at only two time points, 3.9 years apart, may limit the accuracy of some baseline clinical parameters to predict peri-implant bone loss (e.g., plaque).

Although an experienced examiner conducted the PPD assessment, the use of a manual probe without controlled and standardized force could influence the BoP evaluation. On the other hand, the accuracy of PPD assessment may have been constrained by factors related to the restoration design that hamper accessibility.

Some of the clinical parameters were only evaluated at one-time point. mBI was only described at the present follow-up examination, since the baseline data only reported BoP in a dichotomous manner, preventing the analysis of its accuracy in predicting bone loss. Conversely, visual redness and swelling were only evaluated at baseline, preventing their diagnostic accuracy evaluation for a history of bone loss.

PISTD evaluation used as reference point the exposure of the metal portion of the rehabilitation or implant and therefore may underestimated soft tissue changes that occurred not involving that landmark. To mitigate that potential information bias improve sensitivity for this parameter could be achieved by utilizing a fixed reference.

VIII. CONCLUSIONS

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The present thesis reported peri-implantitis in 9.4% of implants, including 5.4% new cases and 4.0% progressions, within a university cohort over an approximately four-year follow-up. Several risk factors were identified and should be considered in the implementation of primary prevention measures. Clinical examination of implants is required to monitor peri-implant health, however clinicians should not rely on single clinical parameters for screening of recent bone loss.

Specifically:

- Periodontitis (stage and grade), lifestyles (smoking and sleep duration), implant location, and prosthetic factors (restoration type and margin location) emerged as risk factors for peri-implantitis.
- Incidence of peri-implant bone loss>1 mm was always associated with signs of inflammation at follow-up. Clinical signs of inflammation indicative of peri-implant mucositis (presence of BoP, visual redness) appear to precede peri-implant bone loss.
- The presence of BoP in 1-2 sites has limited value in predicting or diagnosing bone loss, due to low specificity.
- The presence of BoP at 6 sites or SoP warrants treatment and strict monitoring, as affected implants are more likely to present bone loss during follow-up.
- The presence of BoP at 6 sites, profuse bleeding, SoP, PPD ≥6 mm, or increases in PPD/PISTD over time, despite low sensitivity, have demonstrated high

specificity for peri-implantitis diagnosis and therefore their presence justifies additional radiographic examination.

- The best diagnostic accuracy was achieved using a combined criterion of site-specific PPD or PISTD increases >1 mm over time.

IX. REFERENCES

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Aguirre-Zorzano, L. A., Estefania-Fresco, R., Telletxea, O., & Bravo, M. (2015). Prevalence of peri-implant inflammatory disease in patients with a history of periodontal disease who receive supportive periodontal therapy. *Clin Oral Implants Res*, *26*(11), 1338-1344. https://doi.org/10.1111/clr.12462

Albouy, J. P., Abrahamsson, I., Persson, L. G., & Berglundh, T. (2009). Spontaneous progression of ligatured induced peri-implantitis at implants with different surface characteristics. An experimental study in dogs II: histological observations. *Clin Oral Implants Res*, *20*(4), 366-371. https://doi.org/10.1111/j.1600-0501.2008.01645.x

Amerio, E., Blasi, G., Valles, C., Blanc, V., Alvarez, G., Arredondo, A., Nart, J., & Monje, A. (2022). Impact of smoking on peri-implant bleeding on probing. *Clin Implant Dent Relat Res*, *24*(2), 151-165. https://doi.org/10.1111/cid.13062

Annunziata, M., Cecoro, G., Guida, A., Isola, G., Pesce, P., Sorrentino, R., Del Fabbro, M., & Guida, L. (2024). Effectiveness of Implant Therapy in Patients With and Without a History of Periodontitis: A Systematic Review With Meta-Analysis of Prospective Cohort Studies. *J Periodontal Res*. https://doi.org/10.1111/jre.13351

Apaza-Bedoya, K., Galarraga-Vinueza, M. E., Correa, B. B., Schwarz, F., Bianchini, M. A., & Magalhaes Benfatti, C. A. (2024). Prevalence, risk indicators, and clinical characteristics of peri-implant mucositis and peri-implantitis for an internal conical connection implant system: A multicenter cross-sectional study. *J Periodontol*, *95*(6), 582-593. https://doi.org/10.1002/JPER.23-0355

Astolfi, V., Rios-Carrasco, B., Gil-Mur, F. J., Rios-Santos, J. V., Bullon, B., Herrero-Climent, M., & Bullon, P. (2022). Incidence of Peri-Implantitis and Relationship with Different Conditions: A Retrospective Study. *Int J Environ Res Public Health*, *19*(7). https://doi.org/10.3390/ijerph19074147

Berglundh, J., Romandini, M., Derks, J., Sanz, M., & Berglundh, T. (2021). Clinical findings and history of bone loss at implant sites. *Clin Oral Implants Res*, *32*(3), 314-323. https://doi.org/10.1111/clr.13701

Berglundh, T., Armitage, G., Araujo, M. G., Avila-Ortiz, G., Blanco, J., Camargo, P. M., Chen, S., Cochran, D., Derks, J., Figuero, E., Hammerle, C. H. F., Heitz-Mayfield, L. J. A., Huynh-Ba, G., Iacono, V., Koo, K. T., Lambert, F., McCauley, L., Quirynen, M., Renvert, S., Salvi, G. E., Schwarz, F., Tarnow, D., Tomasi, C.,

Wang, H. L., & Zitzmann, N. (2018). Peri-implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*, *45 Suppl 20*, S286-S291. https://doi.org/10.1111/jcpe.12957

Canullo, L., Penarrocha-Oltra, D., Covani, U., Botticelli, D., Serino, G., & Penarrocha, M. (2016). Clinical and microbiological findings in patients with peri-implantitis: a cross-sectional study. *Clin Oral Implants Res*, *27*(3), 376-382. https://doi.org/10.1111/clr.12557

Canullo, L., Tallarico, M., Radovanovic, S., Delibasic, B., Covani, U., & Rakic, M. (2016). Distinguishing predictive profiles for patient-based risk assessment and diagnostics of plaque induced, surgically and prosthetically triggered peri-implantitis. *Clin Oral Implants Res*, *27*(10), 1243-1250. https://doi.org/10.1111/clr.12738

Carcuac, O., Derks, J., Abrahamsson, I., Wennstrom, J. L., & Berglundh, T. (2020). Risk for recurrence of disease following surgical therapy of peri-implantitis-A prospective longitudinal study. *Clin Oral Implants Res*, *31*(11), 1072-1077. https://doi.org/10.1111/clr.13653

Carra, M. C., Blanc-Sylvestre, N., Courtet, A., & Bouchard, P. (2023). Primordial and primary prevention of peri-implant diseases: A systematic review and meta-analysis. *J Clin Periodontol*, *50 Suppl 26*, 77-112. https://doi.org/10.1111/jcpe.13790

Carra, M. C., Range, H., Swerts, P. J., Tuand, K., Vandamme, K., & Bouchard, P. (2022). Effectiveness of implant-supported fixed partial denture in patients with history of periodontitis: A systematic review and meta-analysis. *J Clin Periodontol*, *49 Suppl 24*, 208-223. https://doi.org/10.1111/jcpe.13481

Carrillo de Albornoz, A., Montero, E., Alonso-Espanol, A., Sanz, M., & Sanz-Sanchez, I. (2024). Treatment of peri-implantitis with a flapless surgical access combined with implant surface decontamination and adjunctive systemic antibiotics: A retrospective case series study. *J Clin Periodontol*, *51*(8), 968-980. https://doi.org/10.1111/jcpe.13993

Casado, P. L., Pereira, M. C., Duarte, M. E., & Granjeiro, J. M. (2013). History of chronic periodontitis is a high risk indicator for peri-implant disease. *Braz Dent J*, *24*(2), 136-141. https://doi.org/10.1590/0103-6440201302006

Corbella, S., Morandi, B., Calciolari, E., Alberti, A., Francetti, L., & Donos, N. (2023). The influence of implant position and of prosthetic characteristics on the occurrence of peri-implantitis: a retrospective study on periapical radiographs. *Clin Oral Investig*, *27*(12), 7261-7271. https://doi.org/10.1007/s00784-023-05303-9

Costa, F. O., Takenaka-Martinez, S., Cota, L. O., Ferreira, S. D., Silva, G. L., & Costa, J. E. (2012). Peri-implant disease in subjects with and without preventive maintenance: a 5-year follow-up. *J Clin Periodontol*, *39*(2), 173-181. https://doi.org/10.1111/j.1600-051X.2011.01819.x

Dalago, H. R., Schuldt Filho, G., Rodrigues, M. A., Renvert, S., & Bianchini, M. A. (2017). Risk indicators for Peri-implantitis. A cross-sectional study with 916 implants. *Clin Oral Implants Res*, *28*(2), 144-150. https://doi.org/10.1111/clr.12772

Daubert, D. M., Weinstein, B. F., Bordin, S., Leroux, B. G., & Flemming, T. F. (2015). Prevalence and predictive factors for peri-implant disease and implant failure: a cross-sectional analysis. *J Periodontol*, *86*(3), 337-347. https://doi.org/10.1902/jop.2014.140438

de Araujo Nobre, M., Mano Azul, A., Rocha, E., & Malo, P. (2015). Risk factors of peri-implant pathology. *Eur J Oral Sci*, *123*(3), 131-139. https://doi.org/10.1111/eos.12185

de Souza, J. G., Bianchini, M. A., & Ferreira, C. F. (2012). Relationship between smoking and bleeding on probing. *J Oral Implantol*, *38*(5), 581-586. https://doi.org/10.1563/AAID-JOI-D-10-00061

de Tapia, B., Bonnin, M., Valles, C., Mozas, C., Herrera, D., Sanz, M., & Nart, J. (2022). Clinical outcomes and associated factors in the treatment of peri-implant mucositis, combining mechanical debridement and prosthesis modification: A 30-month follow-up prospective case series. *J Clin Periodontol*, *49*(12), 1357-1365. https://doi.org/10.1111/jcpe.13711

de Tapia, B., Mozas, C., Valles, C., Nart, J., Sanz, M., & Herrera, D. (2019). Adjunctive effect of modifying the implant-supported prosthesis in the treatment of peri-implant mucositis. *J Clin Periodontol*, *46*(10), 1050-1060. https://doi.org/10.1111/jcpe.13169

de Waal, Y. C., Raghoebar, G. M., Meijer, H. J., Winkel, E. G., & van Winkelhoff, A. J. (2016). Prognostic indicators for surgical peri-implantitis treatment. *Clin Oral Implants Res*, *27*(12), 1485-1491. https://doi.org/10.1111/clr.12584

Degidi, M., Nardi, D., & Piattelli, A. (2016). 10-year prospective cohort follow-up of immediately restored XiVE implants. *Clin Oral Implants Res*, *27*(6), 694-700. https://doi.org/10.1111/clr.12642

Derks, J., Schaller, D., Hakansson, J., Wennstrom, J. L., Tomasi, C., & Berglundh, T. (2016a). Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-implantitis. *J Dent Res*, *95*(1), 43-49. https://doi.org/10.1177/0022034515608832

Derks, J., Schaller, D., Hakansson, J., Wennstrom, J. L., Tomasi, C., & Berglundh, T. (2016b). Peri-implantitis - onset and pattern of progression. *J Clin Periodontol*, *43*(4), 383-388. https://doi.org/10.1111/jcpe.12535

Derks, J., & Tomasi, C. (2015). Peri-implant health and disease. A systematic review of current epidemiology. *J Clin Periodontol*, *42 Suppl 16*, S158-171. https://doi.org/10.1111/jcpe.12334

Dreyer, H., Grischke, J., Tiede, C., Eberhard, J., Schweitzer, A., Toikkanen, S. E., Glockner, S., Krause, G., & Stiesch, M. (2018). Epidemiology and risk factors of peri-implantitis: A systematic review. *J Periodontal Res*, *53*(5), 657-681. https://doi.org/10.1111/jre.12562

Dvorak, G., Arnhart, C., Heuberer, S., Huber, C. D., Watzek, G., & Gruber, R. (2011). Peri-implantitis and late implant failures in postmenopausal women: a cross-sectional study. *J Clin Periodontol*, *38*(10), 950-955. https://doi.org/10.1111/j.1600-051X.2011.01772.x

Ericsson, I., & Lindhe, J. (1993). Probing depth at implants and teeth. An experimental study in the dog. *J Clin Periodontol*, *20*(9), 623-627. https://doi.org/10.1111/j.1600-051x.1993.tb00706.x

Etter, T. H., Hakanson, I., Lang, N. P., Trejo, P. M., & Caffesse, R. G. (2002). Healing after standardized clinical probing of the perlimplant soft tissue seal: a histomorphometric study in dogs. *Clin Oral Implants Res*, *13*(6), 571-580. https://doi.org/10.1034/j.1600-0501.2002.130601.x

Farina, R., Filippi, M., Brazzioli, J., Tomasi, C., & Trombelli, L. (2017). Bleeding on probing around dental implants: a retrospective study of associated factors. *J Clin Periodontol*, *44*(1), 115-122. https://doi.org/10.1111/jcpe.12647

Ferreira, S. D., Silva, G. L., Cortelli, J. R., Costa, J. E., & Costa, F. O. (2006). Prevalence and risk variables for peri-implant disease in Brazilian subjects. *J Clin Periodontol*, *33*(12), 929-935. https://doi.org/10.1111/j.1600-051X.2006.01001.x

Fransson, C., Tomasi, C., Pikner, S. S., Grondahl, K., Wennstrom, J. L., Leyland, A. H., & Berglundh, T. (2010). Severity and pattern of peri-implantitis-associated bone loss. *J Clin Periodontol*, *37*(5), 442-448. https://doi.org/10.1111/j.1600-051X.2010.01537.x

Fransson, C., Wennstrom, J., & Berglundh, T. (2008). Clinical characteristics at implants with a history of progressive bone loss. *Clin Oral Implants Res*, *19*(2), 142-147. https://doi.org/10.1111/j.1600-0501.2007.01448.x

French, D., Grandin, H. M., & Ofec, R. (2019). Retrospective cohort study of 4,591 dental implants: Analysis of risk indicators for bone loss and prevalence of peri-implant mucositis and peri-implantitis. *J Periodontol*, *90*(7), 691-700. https://doi.org/10.1002/JPER.18-0236

Galarraga-Vinueza, M. E., Barootchi, S., Mancini, L., Sabri, H., Schwarz, F., Gallucci, G. O., & Tavelli, L. (2024). Echo-intensity characterization at implant sites and novel diagnostic ultrasonographic markers for peri-implantitis. *J Clin Periodontol*. https://doi.org/10.1111/jcpe.13976

Garcia-Garcia, M., Mir-Mari, J., Benic, G. I., Figueiredo, R., & Valmaseda-Castellon, E. (2016). Accuracy of periapical radiography in assessing bone level in implants affected by peri-implantitis: a cross-sectional study. *J Clin Periodontol*, *43*(1), 85-91. https://doi.org/10.1111/jcpe.12491

Gatti, C., Gatti, F., Chiapasco, M., & Esposito, M. (2008). Outcome of dental implants in partially edentulous patients with and without a history of periodontitis: a 5-year interim analysis of a cohort study. *Eur J Oral Implantol*, *1*(1), 45-51. https://www.ncbi.nlm.nih.gov/pubmed/20467643

Gerber, J. A., Tan, W. C., Balmer, T. E., Salvi, G. E., & Lang, N. P. (2009). Bleeding on probing and pocket probing depth in relation to probing pressure and mucosal health around oral implants. *Clin Oral Implants Res*, *20*(1), 75-78. https://doi.org/10.1111/j.1600-0501.2008.01601.x

Gong, Z., Lin, Y., & Di, P. (2023). Plaque accumulation on the fitting surface of full-arch implant-supported fixed prostheses with contact or noncontact pontics: A split mouth randomized controlled trial. *J Esthet Restor Dent*, *35*(7), 1077-1084. https://doi.org/10.1111/jerd.13062

Hamp, S. E., Nyman, S., & Lindhe, J. (1975). Periodontal treatment of multirooted teeth. Results after 5 years. *J Clin Periodontol*, *2*(3), 126-135. https://doi.org/10.1111/j.1600-051x.1975.tb01734.x

Hashim, D., Cionca, N., Combescure, C., & Mombelli, A. (2018). The diagnosis of peri-implantitis: A systematic review on the predictive value of bleeding on probing. *Clin Oral Implants Res*, *29 Suppl 16*, 276-293. https://doi.org/10.1111/clr.13127

Heitz-Mayfield, L. J. A., Heitz, F., & Lang, N. P. (2020). Implant Disease Risk Assessment IDRA-a tool for preventing peri-implant disease. *Clin Oral Implants Res*, *31*(4), 397-403. https://doi.org/10.1111/clr.13585

Heitz-Mayfield, L. J. A., Salvi, G. E., Mombelli, A., Loup, P. J., Heitz, F., Kruger, E., & Lang, N. P. (2018). Supportive peri-implant therapy following anti-infective surgical peri-implantitis treatment: 5-year survival and success. *Clin Oral Implants Res*, *29*(1), 1-6. https://doi.org/10.1111/clr.12910

Herrera, D., Berglundh, T., Schwarz, F., Chapple, I., Jepsen, S., Sculean, A., Kebschull, M., Papapanou, P. N., Tonetti, M. S., Sanz, M., participants, E. F. P. w., & methodological, c. (2023). Prevention and treatment of peri-implant diseases-The EFP S3 level clinical practice guideline. *J Clin Periodontol*, *50 Suppl 26*, 4-76. https://doi.org/10.1111/jcpe.13823

Herrera, D., Sanz, M., Kebschull, M., Jepsen, S., Sculean, A., Berglundh, T., Papapanou, P. N., Chapple, I., Tonetti, M. S., Participants, E. F. P. W., & Methodological, C. (2022). Treatment of stage IV periodontitis: The EFP S3 level clinical practice guideline. *J Clin Periodontol*, *49 Suppl 24*, 4-71. https://doi.org/10.1111/jcpe.13639

Hilgenfeld, T., Juerchott, A., Deisenhofer, U. K., Krisam, J., Rammelsberg, P., Heiland, S., Bendszus, M., & Schwindling, F. S. (2018). Accuracy of cone-beam computed tomography, dental magnetic resonance imaging, and intraoral radiography for detecting peri-implant bone defects at single zirconia implants-An in vitro study. *Clin Oral Implants Res*, *29*(9), 922-930. https://doi.org/10.1111/clr.13348

Ichioka, Y., Trullenque-Eriksson, A., Ortiz-Vigon, A., Guerrero, A., Donati, M., Bressan, E., Ghensi, P., Schaller, D., Tomasi, C., Karlsson, K., Abrahamsson, I., Dionigi, C., Regidor, E., Berglundh, T., & Derks, J. (2023). Factors influencing outcomes of surgical therapy of peri-implantitis: A secondary analysis of 1-year results from a randomized clinical study. *J Clin Periodontol*, *50*(10), 1282-1304. https://doi.org/10.1111/jcpe.13848

Inoue, M., Nakano, T., Shimomoto, T., Kabata, D., Shintani, A., & Yatani, H. (2020). Multivariate analysis of the influence of prosthodontic factors on peri-implant bleeding index and marginal bone level in a molar site: A cross-sectional study. *Clin Implant Dent Relat Res*, *22*(6), 713-722. https://doi.org/10.1111/cid.12953

Insua, A., Ganan, Y., Macias, Y., Garcia, J. A., Rakic, M., & Monje, A. (2021). Diagnostic Accuracy of Cone Beam Computed Tomography in Identifying Peri-implantitis-Like Bone Defects Ex Vivo. *Int J Periodontics Restorative Dent*, *41*(6), e223-e231. https://doi.org/10.11607/prd.5201

Jepsen, S., Berglundh, T., Genco, R., Aass, A. M., Demirel, K., Derks, J., Figuero, E., Giovannoli, J. L., Goldstein, M., Lambert, F., Ortiz-Vigon, A., Polyzois, I., Salvi, G. E., Schwarz, F., Serino, G., Tomasi, C., & Zitzmann, N. U. (2015). Primary prevention of peri-implantitis: managing peri-implant mucositis. *J Clin Periodontol*, *42 Suppl 16*, S152-157. https://doi.org/10.1111/jcpe.12369

Jepsen, S., Ruhling, A., Jepsen, K., Ohlenbusch, B., & Albers, H. K. (1996). Progressive peri-implantitis. Incidence and prediction of peri-implant attachment loss. *Clin Oral Implants Res*, *7*(2), 133-142. https://doi.org/10.1034/j.1600-0501.1996.070207.x

Karlsson, K., Trullenque-Eriksson, A., Tomasi, C., & Derks, J. (2023). Efficacy of access flap and pocket elimination procedures in the management of peri-implantitis: A systematic review and meta-analysis. *J Clin Periodontol*, *50 Suppl 26*, 244-284. https://doi.org/10.1111/jcpe.13732

Karoussis, I. K., Bragger, U., Salvi, G. E., Burgin, W., & Lang, N. P. (2004). Effect of implant design on survival and success rates of titanium oral implants: a 10-year prospective cohort study of the ITI Dental Implant System. *Clin Oral Implants Res*, *15*(1), 8-17. https://doi.org/10.1111/j.1600-0501.2004.00983.x

Karoussis, I. K., Muller, S., Salvi, G. E., Heitz-Mayfield, L. J., Bragger, U., & Lang, N. P. (2004). Association between periodontal and peri-implant conditions: a 10-year prospective study. *Clin Oral Implants Res*, *15*(1), 1-7. https://doi.org/10.1111/j.1600-0501.2004.00982.x

Karoussis, I. K., Salvi, G. E., Heitz-Mayfield, L. J., Bragger, U., Hammerle, C. H., & Lang, N. P. (2003). Long-term implant prognosis in patients with and without a history of chronic periodontitis: a 10-year prospective cohort study of the ITI Dental Implant System. *Clin Oral Implants Res*, *14*(3), 329-339. https://doi.org/10.1034/j.1600-0501.000.00934.x

Katafuchi, M., Weinstein, B. F., Leroux, B. G., Chen, Y. W., & Daubert, D. M. (2018). Restoration contour is a risk indicator for peri-implantitis: A cross-sectional radiographic analysis. *J Clin Periodontol*, *45*(2), 225-232. https://doi.org/10.1111/jcpe.12829

Koldsland, O. C., Scheie, A. A., & Aass, A. M. (2011). The association between selected risk indicators and severity of peri-implantitis using mixed model analyses. *J Clin Periodontol*, *38*(3), 285-292. https://doi.org/10.1111/j.1600-051X.2010.01659.x

Koldsland, O. C., Wohlfahrt, J. C., & Aass, A. M. (2018). Surgical treatment of peri-implantitis: Prognostic indicators of short-term results. *J Clin Periodontol*, *45*(1), 100-113. https://doi.org/10.1111/jcpe.12816

Kuhl, S., Zurcher, S., Zitzmann, N. U., Filippi, A., Payer, M., & Dagassan-Berndt, D. (2016). Detection of peri-implant bone defects with different radiographic techniques - a human cadaver study. *Clin Oral Implants Res*, *27*(5), 529-534. https://doi.org/10.1111/clr.12619

Lang, N. P., Berglundh, T., & Working Group 4 of Seventh European Workshop on, P. (2011). Periimplant diseases: where are we now?--Consensus of the Seventh European Workshop on Periodontology. *J Clin Periodontol*, *38 Suppl 11*, 178-181. https://doi.org/10.1111/j.1600-051X.2010.01674.x

Lang, N. P., Wetzel, A. C., Stich, H., & Caffesse, R. G. (1994). Histologic probe penetration in healthy and inflamed peri-implant tissues. *Clin Oral Implants Res*, *5*(4), 191-201. https://doi.org/10.1034/j.1600-0501.1994.050401.x

Lee, C. T., Huang, Y. W., Zhu, L., & Weltman, R. (2017). Prevalences of peri-implantitis and peri-implant mucositis: systematic review and meta-analysis. *J Dent*, *62*, 1-12. https://doi.org/10.1016/j.jdent.2017.04.011

Lin, C. Y., Chen, Z., Pan, W. L., & Wang, H. L. (2019). The effect of supportive care in preventing peri-implant diseases and implant loss: A systematic review and meta-analysis. *Clin Oral Implants Res*, *30*(8), 714-724. https://doi.org/10.1111/clr.13496

Luterbacher, S., Mayfield, L., Bragger, U., & Lang, N. P. (2000). Diagnostic characteristics of clinical and microbiological tests for monitoring periodontal and peri-implant mucosal tissue conditions during supportive periodontal therapy (SPT). *Clin Oral Implants Res*, *11*(6), 521-529. https://doi.org/10.1034/j.1600-0501.2000.011006521.x

Majzoub, J., Chen, Z., Saleh, I., Askar, H., & Wang, H. L. (2021). Influence of restorative design on the progression of peri-implant bone loss: A retrospective study. *J Periodontol*, *92*(4), 536-546. https://doi.org/10.1002/JPER.20-0327

Mameno, T., Wada, M., Onodera, Y., Fujita, D., Sato, H., & Ikebe, K. (2019). Longitudinal study on risk indicators for peri-implantitis using survival-time analysis. *J Prosthodont Res*, *63*(2), 216-220. https://doi.org/10.1016/j.jpor.2018.12.002

Marrone, A., Lasserre, J., Bercy, P., & Brecx, M. C. (2013). Prevalence and risk factors for peri-implant disease in Belgian adults. *Clin Oral Implants Res*, *24*(8), 934-940. https://doi.org/10.1111/j.1600-0501.2012.02476.x

Marruganti, C., Baima, G., Grandini, S., Graziani, F., Aimetti, M., Sanz, M., & Romandini, M. (2023). Leisure-time and occupational physical activity demonstrate divergent associations with periodontitis: A population-based study. *J Clin Periodontol*, *50*(5), 559-570. https://doi.org/10.1111/jcpe.13766

Marruganti, C., Gaeta, C., Romandini, M., Ferrari Cagidiaco, E., Parrini, S., Discepoli, N., & Grandini, S. (2024). Multiplicative effect of stress and poor sleep quality on periodontitis: A university-based cross-sectional study. *J Periodontol*, *95*(2), 125-134. https://doi.org/10.1002/JPER.23-0209

Marruganti, C., Romandini, M., Gaeta, C., Cagidiaco, E. F., Discepoli, N., Parrini, S., Graziani, F., & Grandini, S. (2023). Healthy lifestyles are associated with a better response to periodontal therapy: A prospective cohort study. *J Clin Periodontol*, *50*(8), 1089-1100. https://doi.org/10.1111/jcpe.13813

Martinez-Amargant, J., de Tapia, B., Pascual, A., Takamoli, J., Esquinas, C., Nart, J., & Valles, C. (2023). Association between smoking and peri-implant diseases: A retrospective study. *Clin Oral Implants Res*, *34*(10), 1127-1140. https://doi.org/10.1111/clr.14147

Maximo, M. B., de Mendonca, A. C., Alves, J. F., Cortelli, S. C., Peruzzo, D. C., & Duarte, P. M. (2008). Peri-implant diseases may be associated with increased time loading and generalized periodontal bone loss: preliminary results. *J Oral Implantol*, *34*(5), 268-273. https://doi.org/10.1563/1548-1336(2008)34[269:PDMBAW]2.0.CO;2

Menini, M., Setti, P., Pera, P., Pera, F., & Pesce, P. (2018). Peri-implant Tissue Health and Bone Resorption in Patients with Immediately Loaded, Implant-Supported,

Full-Arch Prostheses. *Int J Prosthodont*, *31*(4), 327-333. https://doi.org/10.11607/ijp.5567

Merli, M., Bernardelli, F., Giulianelli, E., Toselli, I., Mariotti, G., & Nieri, M. (2017). Peri-implant bleeding on probing: a cross-sectional multilevel analysis of associated factors. *Clin Oral Implants Res*, *28*(11), 1401-1405. https://doi.org/10.1111/clr.13001

Meyer, S., Giannopoulou, C., Courvoisier, D., Schimmel, M., Muller, F., & Mombelli, A. (2017). Experimental mucositis and experimental gingivitis in persons aged 70 or over. Clinical and biological responses. *Clin Oral Implants Res*, *28*(8), 1005-1012. https://doi.org/10.1111/clr.12912

Mir-Mari, J., Mir-Orfila, P., Figueiredo, R., Valmaseda-Castellón, E., & Gay-Escoda, C. (2012). Prevalence of peri-implant diseases. A cross-sectional study based on a private practice environment. *Journal of Clinical Periodontology*, *39*(5), 490-494. https://doi.org/10.1111/j.1600-051X.2012.01872.x

Mombelli, A., van Oosten, M. A., Schurch, E., Jr., & Land, N. P. (1987). The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol Immunol*, *2*(4), 145-151. https://doi.org/10.1111/j.1399-302x.1987.tb00298.x

Monje, A., Alcoforado, G., Padial-Molina, M., Suarez, F., Lin, G. H., & Wang, H. L. (2014). Generalized aggressive periodontitis as a risk factor for dental implant failure: a systematic review and meta-analysis. *J Periodontol*, *85*(10), 1398-1407. https://doi.org/10.1902/jop.2014.140135

Monje, A., Aranda, L., Diaz, K. T., Alarcon, M. A., Bagramian, R. A., Wang, H. L., & Catena, A. (2016). Impact of Maintenance Therapy for the Prevention of Peri-implant Diseases: A Systematic Review and Meta-analysis. *J Dent Res*, *95*(4), 372-379. https://doi.org/10.1177/0022034515622432

Monje, A., Caballe-Serrano, J., Nart, J., Penarrocha, D., Wang, H. L., & Rakic, M. (2018). Diagnostic accuracy of clinical parameters to monitor peri-implant conditions: A matched case-control study. *J Periodontol*, *89*(4), 407-417. https://doi.org/10.1002/JPER.17-0454

Monje, A., Catena, A., & Borgnakke, W. S. (2017). Association between diabetes mellitus/hyperglycaemia and peri-implant diseases: Systematic review and meta-analysis. *J Clin Periodontol*, *44*(6), 636-648. https://doi.org/10.1111/jcpe.12724

Monje, A., Insua, A., Rakic, M., Nart, J., Moyano-Cuevas, J. L., & Wang, H. L. (2018). Estimation of the diagnostic accuracy of clinical parameters for monitoring peri-implantitis progression: An experimental canine study. *J Periodontol*, *89*(12), 1442-1451. https://doi.org/10.1002/JPER.18-0081

Monje, A., Pons, R., Insua, A., Nart, J., Wang, H. L., & Schwarz, F. (2019). Morphology and severity of peri-implantitis bone defects. *Clin Implant Dent Relat Res*, *21*(4), 635-643. https://doi.org/10.1111/cid.12791

Monje, A., Vera, M., Munoz-Sanz, A., Wang, H. L., & Nart, J. (2021). Suppuration as diagnostic criterium of peri-implantitis. *J Periodontol*, *92*(2), 216-224. https://doi.org/10.1002/JPER.20-0159

Monje, A., Wang, H. L., & Nart, J. (2017). Association of Preventive Maintenance Therapy Compliance and Peri-Implant Diseases: A Cross-Sectional Study. *J Periodontol*, *88*(10), 1030-1041. https://doi.org/10.1902/jop.2017.170135

Naseri, R., Yaghini, J., & Feizi, A. (2020). Levels of smoking and dental implants failure: A systematic review and meta-analysis. *J Clin Periodontol*, *47*(4), 518-528. https://doi.org/10.1111/jcpe.13257

Ogata, Y., Nakayama, Y., Tatsumi, J., Kubota, T., Sato, S., Nishida, T., Takeuchi, Y., Onitsuka, T., Sakagami, R., Nozaki, T., Murakami, S., Matsubara, N., Tanaka, M., Yoshino, T., Ota, J., Nakagawa, T., Ishihara, Y., Ito, T., Saito, A., Yamaki, K., Matsuzaki, E., Hidaka, T., Sasaki, D., Yaegashi, T., Yasuda, T., Shibutani, T., Noguchi, K., Araki, H., Ikumi, N., Aoyama, Y., Kogai, H., Nemoto, K., Deguchi, S., Takiguchi, T., Yamamoto, M., Inokuchi, K., Ito, T., Kado, T., Furuichi, Y., Kanazashi, M., Gomi, K., Takagi, Y., Kubokawa, K., Yoshinari, N., Hasegawa, Y., Hirose, T., Sase, T., Arita, H., Kodama, T., Shin, K., Izumi, Y., & Yoshie, H. (2017). Prevalence and risk factors for peri-implant diseases in Japanese adult dental patients. *J Oral Sci*, *59*(1), 1-11. https://doi.org/10.2334/josnusd.16-0027

Onclin, P., Slot, W., Vissink, A., Raghoebar, G. M., & Meijer, H. J. A. (2022). Incidence of peri-implant mucositis and peri-implantitis in patients with a maxillary overdenture: A sub-analysis of two prospective studies with a 10-year follow-up period. *Clin Implant Dent Relat Res*, *24*(2), 188-195. https://doi.org/10.1111/cid.13071

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., Flemmig, T. F., Garcia, R., Giannobile, W. V., Graziani, F., Greenwell, H., Herrera, D., Kao, R. T., Kebschull, M., Kinane, D. F., Kirkwood, K. L., Kocher, T., Kornman,

K. S., Kumar, P. S., Loos, B. G., Machtei, E., Meng, H., Mombelli, A., Needleman, I., Offenbacher, S., Seymour, G. J., Teles, R., & Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*, *45 Suppl 20*, S162-S170. https://doi.org/10.1111/jcpe.12946

Pedrinaci, I., Sun, T. C., Sanz-Alonso, M., Sanz-Esporrin, J., Hamilton, A., & Gallucci, G. O. (2023). Implant survival in the anterior mandible: A retrospective cohort study. *Clin Oral Implants Res*, *34*(5), 463-474. https://doi.org/10.1111/clr.14052

Pjetursson, B. E., Helbling, C., Weber, H. P., Matuliene, G., Salvi, G. E., Bragger, U., Schmidlin, K., Zwahlen, M., & Lang, N. P. (2012). Peri-implantitis susceptibility as it relates to periodontal therapy and supportive care. *Clin Oral Implants Res*, *23*(7), 888-894. https://doi.org/10.1111/j.1600-0501.2012.02474.x

Pons, R., Nart, J., Valles, C., Salvi, G. E., & Monje, A. (2021). Self-administered proximal implant-supported hygiene measures and the association to peri-implant conditions. *J Periodontol*, *92*(3), 389-399. https://doi.org/10.1002/JPER.20-0193

Pontoriero, R., Tonelli, M. P., Carnevale, G., Mombelli, A., Nyman, S. R., & Lang, N. P. (1994). Experimentally induced peri-implant mucositis. A clinical study in humans. *Clin Oral Implants Res*, *5*(4), 254-259. https://doi.org/10.1034/j.1600-0501.1994.050409.x

Rakic, M., Galindo-Moreno, P., Monje, A., Radovanovic, S., Wang, H. L., Cochran, D., Sculean, A., & Canullo, L. (2018). How frequent does peri-implantitis occur? A systematic review and meta-analysis. *Clin Oral Investig*, *22*(4), 1805-1816. https://doi.org/10.1007/s00784-017-2276-y

Ramanauskaite, A., Becker, K., & Schwarz, F. (2018). Clinical characteristics of peri-implant mucositis and peri-implantitis. *Clin Oral Implants Res*, *29*(6), 551-556. https://doi.org/10.1111/clr.13152

Ramanauskaite, A., Padhye, N., Kallab, S., Dahmer, I., Begic, A., Tiede, S., & Schwarz, F. (2024). Progressive bone loss and bleeding on probing: A cohort study. *Clin Implant Dent Relat Res*, *26*(4), 809-818. https://doi.org/10.1111/cid.13356

Ravida, A., Siqueira, R., Di Gianfilippo, R., Kaur, G., Giannobile, A., Galindo-Moreno, P., Wang, C. W., & Wang, H. L. (2022). Prognostic factors associated with implant loss, disease progression or favorable outcomes after peri-implantitis

surgical therapy. *Clin Implant Dent Relat Res*, *24*(2), 222-232. https://doi.org/10.1111/cid.13074

Reis, I., do Amaral, G., Hassan, M. A., Villar, C. C., Romito, G. A., Spin-Neto, R., & Pannuti, C. M. (2023). The influence of smoking on the incidence of peri-implantitis: A systematic review and meta-analysis. *Clin Oral Implants Res*, *34*(6), 543-554. https://doi.org/10.1111/clr.14066

Renvert, S., Aghazadeh, A., Hallstrom, H., & Persson, G. R. (2014). Factors related to peri-implantitis - a retrospective study. *Clin Oral Implants Res*, *25*(4), 522-529. https://doi.org/10.1111/clr.12208

Renvert, S., Persson, G. R., Pirih, F. Q., & Camargo, P. M. (2018). Peri-implant health, peri-implant mucositis, and peri-implantitis: Case definitions and diagnostic considerations. *J Periodontol*, *89 Suppl 1*, S304-S312. https://doi.org/10.1002/JPER.17-0588

Rinke, S., Ohl, S., Ziebolz, D., Lange, K., & Eickholz, P. (2011). Prevalence of periimplant disease in partially edentulous patients: a practice-based cross-sectional study. *Clin Oral Implants Res*, *22*(8), 826-833. https://doi.org/10.1111/j.1600-0501.2010.02061.x

Roccuzzo, A., Imber, J. C., Marruganti, C., Salvi, G. E., Ramieri, G., & Roccuzzo, M. (2022). Clinical outcomes of dental implants in patients with and without history of periodontitis: A 20-year prospective study. *J Clin Periodontol*, *49*(12), 1346-1356. https://doi.org/10.1111/jcpe.13716

Roccuzzo, A., Weigel, L., Marruganti, C., Imber, J. C., Ramieri, G., Sculean, A., Salvi, G. E., & Roccuzzo, M. (2023). Longitudinal assessment of peri-implant diseases in patients with and without history of periodontitis: A 20-year follow-up study. *Int J Oral Implantol (Berl)*, *16*(3), 211-222. https://www.ncbi.nlm.nih.gov/pubmed/37767616

Roccuzzo, M., Bonino, F., Aglietta, M., & Dalmasso, P. (2012). Ten-year results of a three arms prospective cohort study on implants in periodontally compromised patients. Part 2: clinical results. *Clin Oral Implants Res*, *23*(4), 389-395. https://doi.org/10.1111/j.1600-0501.2011.02309.x

Roccuzzo, M., Bonino, L., Dalmasso, P., & Aglietta, M. (2014). Long-term results of a three arms prospective cohort study on implants in periodontally compromised patients: 10-year data around sandblasted and acid-etched (SLA) surface. *Clin Oral Implants Res*, *25*(10), 1105-1112. https://doi.org/10.1111/clr.12227

Roccuzzo, M., De Angelis, N., Bonino, L., & Aglietta, M. (2010). Ten-year results of a three-arm prospective cohort study on implants in periodontally compromised patients. Part 1: implant loss and radiographic bone loss. *Clin Oral Implants Res*, *21*(5), 490-496. https://doi.org/10.1111/j.1600-0501.2009.01886.x

Roccuzzo, M., Savoini, M., Dalmasso, P., & Ramieri, G. (2017). Long-term outcomes of implants placed after vertical alveolar ridge augmentation in partially edentulous patients: a 10-year prospective clinical study. *Clin Oral Implants Res*, *28*(10), 1204-1210. https://doi.org/10.1111/clr.12941

Rodrigo, D., Martin, C., & Sanz, M. (2012). Biological complications and peri-implant clinical and radiographic changes at immediately placed dental implants. A prospective 5-year cohort study. *Clin Oral Implants Res*, *23*(10), 1224-1231. https://doi.org/10.1111/j.1600-0501.2011.02294.x

Rodrigo, D., Sanz-Sanchez, I., Figuero, E., Llodra, J. C., Bravo, M., Caffesse, R. G., Vallcorba, N., Guerrero, A., & Herrera, D. (2018). Prevalence and risk indicators of peri-implant diseases in Spain. *J Clin Periodontol*, *45*(12), 1510-1520. https://doi.org/10.1111/jcpe.13017

Rokn, A., Aslroosta, H., Akbari, S., Najafi, H., Zayeri, F., & Hashemi, K. (2017). Prevalence of peri-implantitis in patients not participating in well-designed supportive periodontal treatments: a cross-sectional study. *Clin Oral Implants Res*, *28*(3), 314-319. https://doi.org/10.1111/clr.12800

Romandini, M., Berglundh, J., Derks, J., Sanz, M., & Berglundh, T. (2021). Diagnosis of peri-implantitis in the absence of baseline data: A diagnostic accuracy study. *Clin Oral Implants Res*, *32*(3), 297-313. https://doi.org/10.1111/clr.13700

Romandini, M., Bougas, K., Alibegovic, L., Hosseini, S., Carcuac, O., Berglundh, T., & Derks, J. (2024). Long-term outcomes and prognostic factors of surgical treatment of peri-implantitis - A retrospective study. *Clin Oral Implants Res*, *35*(3), 321-329. https://doi.org/10.1111/clr.14228

Romandini, M., Gioco, G., Perfetti, G., Deli, G., Staderini, E., & Lafori, A. (2017). The association between periodontitis and sleep duration. *J Clin Periodontol*, *44*(5), 490-501. https://doi.org/10.1111/jcpe.12713

Romandini, M., Lima, C., Pedrinaci, I., Araoz, A., Costanza Soldini, M., & Sanz, M. (2021). Clinical signs, symptoms, perceptions, and impact on quality of life in patients suffering from peri-implant diseases: a university-representative cross-

sectional study. *Clin Oral Implants Res*, *32*(1), 100-111. https://doi.org/10.1111/clr.13683

Romandini, M., Lima, C., Pedrinaci, I., Araoz, A., Soldini, M. C., & Sanz, M. (2021). Prevalence and risk/protective indicators of peri-implant diseases: A university-representative cross-sectional study. *Clin Oral Implants Res*, *32*(1), 112-122. https://doi.org/10.1111/clr.13684

Romandini, M., Pedrinaci, I., Lima, C., Soldini, M. C., Araoz, A., & Sanz, M. (2021). Prevalence and risk/protective indicators of buccal soft tissue dehiscence around dental implants. *J Clin Periodontol*, *48*(3), 455-463. https://doi.org/10.1111/jcpe.13417

Roos-Jansaker, A. M., Lindahl, C., Renvert, H., & Renvert, S. (2006). Nine- to fourteen-year follow-up of implant treatment. Part II: presence of peri-implant lesions. *J Clin Periodontol*, *33*(4), 290-295. https://doi.org/10.1111/j.1600-051X.2006.00906.x

Roos-Jansaker, A. M., Renvert, H., Lindahl, C., & Renvert, S. (2006). Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. *J Clin Periodontol*, *33*(4), 296-301. https://doi.org/10.1111/j.1600-051X.2006.00908.x

Salvi, G. E., Aglietta, M., Eick, S., Sculean, A., Lang, N. P., & Ramseier, C. A. (2012). Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. *Clin Oral Implants Res*, *23*(2), 182-190. https://doi.org/10.1111/j.1600-0501.2011.02220.x

Sanchez-Siles, M., Munoz-Camara, D., Salazar-Sanchez, N., Ballester-Ferrandis, J. F., & Camacho-Alonso, F. (2015). Incidence of peri-implantitis and oral quality of life in patients rehabilitated with implants with different neck designs: A 10-year retrospective study. *J Craniomaxillofac Surg*, *43*(10), 2168-2174. https://doi.org/10.1016/j.jcms.2015.10.010

Sanz, M., Chapple, I. L., & Working Group 4 of the, V. E. W. o. P. (2012). Clinical research on peri-implant diseases: consensus report of Working Group 4. *J Clin Periodontol*, *39 Suppl 12*, 202-206. https://doi.org/10.1111/j.1600-051X.2011.01837.x

Sanz, M., Herrera, D., Kebschull, M., Chapple, I., Jepsen, S., Beglundh, T., Sculean, A., Tonetti, M. S., Participants, E. F. P. W., & Methodological, C. (2020). Treatment

of stage I-III periodontitis-The EFP S3 level clinical practice guideline. *J Clin Periodontol*, *47 Suppl 22*(Suppl 22), 4-60. https://doi.org/10.1111/jcpe.13290

Sanz, M., Papapanou, P. N., Tonetti, M. S., Greenwell, H., & Kornman, K. (2020). Guest Editorial: Clarifications on the use of the new classification of periodontitis. *J Clin Periodontol*, *47*(6), 658-659. https://doi.org/10.1111/jcpe.13286

Sanz-Martin, I., Regidor, E., Navarro, J., Sanz-Sanchez, I., Sanz, M., & Ortiz-Vigon, A. (2020). Factors associated with the presence of peri-implant buccal soft tissue dehiscences: A case-control study. *J Periodontol*, *91*(8), 1003-1010. https://doi.org/10.1002/JPER.19-0490

Schou, S., Holmstrup, P., Stoltze, K., Hjorting-Hansen, E., Fiehn, N. E., & Skovgaard, L. T. (2002). Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. A histologic comparison in cynomolgus monkeys (Macaca fascicularis). *Clin Oral Implants Res*, *13*(2), 113-126. https://doi.org/10.1034/j.1600-0501.2002.130201.x

Schriber, M., Yeung, A. W. K., Suter, V. G. A., Buser, D., Leung, Y. Y., & Bornstein, M. M. (2020). Cone beam computed tomography artefacts around dental implants with different materials influencing the detection of peri-implant bone defects. *Clin Oral Implants Res*, *31*(7), 595-606. https://doi.org/10.1111/clr.13596

Schwarz, F., Becker, K., Sahm, N., Horstkemper, T., Rousi, K., & Becker, J. (2017). The prevalence of peri-implant diseases for two-piece implants with an internal tube-in-tube connection: a cross-sectional analysis of 512 implants. *Clin Oral Implants Res*, *28*(1), 24-28. https://doi.org/10.1111/clr.12609

Schwarz, F., Derks, J., Monje, A., & Wang, H. L. (2018). Peri-implantitis. *J Clin Periodontol*, *45 Suppl 20*, S246-S266. https://doi.org/10.1111/jcpe.12954

Schwarz, F., Herten, M., Sager, M., Bieling, K., Sculean, A., & Becker, J. (2007). Comparison of naturally occurring and ligature-induced peri-implantitis bone defects in humans and dogs. *Clin Oral Implants Res*, *18*(2), 161-170. https://doi.org/10.1111/j.1600-0501.2006.01320.x

Schwindling, F. S., Hilgenfeld, T., Weber, D., Kosinski, M. A., Rammelsberg, P., & Tasaka, A. (2019). In vitro diagnostic accuracy of low-dose CBCT for evaluation of peri-implant bone lesions. *Clin Oral Implants Res*, *30*(12), 1200-1208. https://doi.org/10.1111/clr.13533

Serino, G., & Hultin, K. (2019). Periimplant Disease and Prosthetic Risk Indicators: A Literature Review. *Implant Dent*, *28*(2), 125-137. https://doi.org/10.1097/ID.0000000000000841

Serino, G., Sato, H., Holmes, P., & Turri, A. (2017). Intra-surgical vs. radiographic bone level assessments in measuring peri-implant bone loss. *Clin Oral Implants Res*, *28*(11), 1396-1400. https://doi.org/10.1111/clr.12999

Serino, G., & Strom, C. (2009). Peri-implantitis in partially edentulous patients: association with inadequate plaque control. *Clin Oral Implants Res*, *20*(2), 169-174. https://doi.org/10.1111/j.1600-0501.2008.01627.x

Serino, G., Turri, A., & Lang, N. P. (2013). Probing at implants with peri-implantitis and its relation to clinical peri-implant bone loss. *Clin Oral Implants Res*, *24*(1), 91-95. https://doi.org/10.1111/j.1600-0501.2012.02470.x

Serroni, M., Borgnakke, W. S., Romano, L., Balice, G., Paolantonio, M., Saleh, M. H. A., & Ravida, A. (2024). History of periodontitis as a risk factor for implant failure and incidence of peri-implantitis: A systematic review, meta-analysis, and trial sequential analysis of prospective cohort studies. *Clin Implant Dent Relat Res*, *26*(3), 482-508. https://doi.org/10.1111/cid.13330

Shatta, A., Bissada, N. F., Ricchetti, P., Paes, A., & Demko, C. (2019). Impact of Implant and Site Characteristics on the Pattern of Bone Loss in Peri-implantitis. *Int J Oral Maxillofac Implants*, *34*(6), 1475-1481. https://doi.org/10.11607/jomi.7434

Song, X., Li, L., Gou, H., & Xu, Y. (2020). Impact of implant location on the prevalence of peri-implantitis: A systematic review and meta- analysis. *J Dent*, *103*, 103490. https://doi.org/10.1016/j.jdent.2020.103490

Stiesch, M., Grischke, J., Schaefer, P., & Heitz-Mayfield, L. J. A. (2023). Supportive care for the prevention of disease recurrence/progression following peri-implantitis treatment: A systematic review. *J Clin Periodontol*, *50 Suppl 26*, 113-134. https://doi.org/10.1111/jcpe.13822

Strauss, F. J., Park, J. Y., Lee, J. S., Schiavon, L., Smirani, R., Hitz, S., Chantler, J. G. M., Mattheos, N., Jung, R., Bosshardt, D., Cha, J. K., & Thoma, D. (2024). Wide Restorative Emergence Angle Increases Marginal Bone Loss and Impairs Integrity of the Junctional Epithelium of the Implant Supracrestal Complex: A Preclinical Study. *J Clin Periodontol*. https://doi.org/10.1111/jcpe.14070

Strauss, F. J., Siegenthaler, M., Hammerle, C. H. F., Sailer, I., Jung, R. E., & Thoma, D. S. (2022). Restorative angle of zirconia restorations cemented on non-original

titanium bases influences the initial marginal bone loss: 5-year results of a prospective cohort study. *Clin Oral Implants Res*, *33*(7), 745-756. https://doi.org/10.1111/clr.13954

Sun, J. S., Liu, K. C., Hung, M. C., Lin, H. Y., Chuang, S. L., Lin, P. J., & Chang, J. Z. (2023). A cross-sectional study for prevalence and risk factors of peri-implant marginal bone loss. *J Prosthet Dent*. https://doi.org/10.1016/j.prosdent.2023.11.002

Swierkot, K., Lottholz, P., Flores-de-Jacoby, L., & Mengel, R. (2012). Mucositis, peri-implantitis, implant success, and survival of implants in patients with treated generalized aggressive periodontitis: 3- to 16-year results of a prospective long-term cohort study. *J Periodontol*, *83*(10), 1213-1225. https://doi.org/10.1902/jop.2012.110603

Tawil, G., Younan, R., Azar, P., & Sleilati, G. (2008). Conventional and advanced implant treatment in the type II diabetic patient: surgical protocol and long-term clinical results. *Int J Oral Maxillofac Implants*, *23*(4), 744-752. https://www.ncbi.nlm.nih.gov/pubmed/18807573

Tonetti, M. S., Chapple, I. L., Jepsen, S., & Sanz, M. (2015). Primary and secondary prevention of periodontal and peri-implant diseases: Introduction to, and objectives of the 11th European Workshop on Periodontology consensus conference. *J Clin Periodontol*, *42 Suppl 16*, S1-4. https://doi.org/10.1111/jcpe.12382

Tonetti, M. S., Sanz, M., Avila-Ortiz, G., Berglundh, T., Cairo, F., Derks, J., Figuero, E., Graziani, F., Guerra, F., Heitz-Mayfield, L., Jung, R. E., Lai, H., Needleman, I., Papapanou, P. N., Sailer, I., Sanz-Sanchez, I., Schwarz, F., Shi, J., & Thoma, D. (2023). Relevant domains, core outcome sets and measurements for implant dentistry clinical trials: The Implant Dentistry Core Outcome Set and Measurement (ID-COSM) international consensus report. *Clin Oral Implants Res*, *34 Suppl 25*, 4-21. https://doi.org/10.1111/clr.14074

Trombelli, L., Farina, R., Tomasi, C., Vignoletti, F., Paolantoni, G., Giordano, F., Ortensi, L., & Simonelli, A. (2024). Factors affecting radiographic marginal bone resorption at dental implants in function for at least 5 years: A multicenter retrospective study. *Clin Oral Implants Res*. https://doi.org/10.1111/clr.14327

Vadiati Saberi, B., Khosravifard, N., Ghandari, F., & Hadinezhad, A. (2019). Detection of peri-implant bone defects using cone-beam computed tomography and digital

periapical radiography with parallel and oblique projection. *Imaging Sci Dent*, *49*(4), 265-272. https://doi.org/10.5624/isd.2019.49.4.265

Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gotzsche, P. C., Mulrow, C. D., Pocock, S. J., Poole, C., Schlesselman, J. J., Egger, M., & Initiative, S. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*, *18*(6), 805-835. https://doi.org/10.1097/EDE.0b013e3181577511

Velasco-Ortega, E., Jimenez-Guerra, A., Ortiz-Garcia, I., Moreno-Munoz, J., Nunez-Marquez, E., Cabanillas-Balsera, D., Lopez-Lopez, J., & Monsalve-Guil, L. (2021). Immediate Loading of Implants Placed by Guided Surgery in Geriatric Edentulous Mandible Patients. *Int J Environ Res Public Health*, *18*(8). https://doi.org/10.3390/ijerph18084125

Vignoletti, F., Di Domenico, G. L., Di Martino, M., Montero, E., & de Sanctis, M. (2019). Prevalence and risk indicators of peri-implantitis in a sample of university-based dental patients in Italy: A cross-sectional study. *J Clin Periodontol*, *46*(5), 597-605. https://doi.org/10.1111/jcpe.13111

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotzsche, P. C., Vandenbroucke, J. P., & Initiative, S. (2007). Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*, *335*(7624), 806-808. https://doi.org/10.1136/bmj.39335.541782.AD

Windael, S., Collaert, B., De Buyser, S., De Bruyn, H., & Vervaeke, S. (2021). Early peri-implant bone loss as a predictor for peri-implantitis: A 10-year prospective cohort study. *Clin Implant Dent Relat Res*, *23*(3), 298-308. https://doi.org/10.1111/cid.13000

Yi, Y., Koo, K. T., Schwarz, F., Ben Amara, H., & Heo, S. J. (2020). Association of prosthetic features and peri-implantitis: A cross-sectional study. *J Clin Periodontol*, *47*(3), 392-403. https://doi.org/10.1111/jcpe.13251

Zetterqvist, L., Feldman, S., Rotter, B., Vincenzi, G., Wennstrom, J. L., Chierico, A., Stach, R. M., & Kenealy, J. N. (2010). A prospective, multicenter, randomized-controlled 5-year study of hybrid and fully etched implants for the incidence of peri-implantitis. *J Periodontol*, *81*(4), 493-501. https://doi.org/10.1902/jop.2009.090492

Zhang, H., Li, W., Zhang, L., Yan, X., Shi, D., & Meng, H. (2018). A nomogram prediction of peri-implantitis in treated severe periodontitis patients: A 1-5-year prospective cohort study. *Clin Implant Dent Relat Res*, *20*(6), 962-968. https://doi.org/10.1111/cid.12686

Zitzmann, N. U., Berglundh, T., Marinello, C. P., & Lindhe, J. (2001). Experimental peri-implant mucositis in man. *J Clin Periodontol*, *28*(6), 517-523. https://doi.org/10.1034/j.1600-051x.2001.028006517.x

X. APPENDIX

Appendix 1: STUDY #1

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Incidence and Risk Factors of Peri-Implantitis Over Time—A Prospective Cohort Study

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Keywords: dental implants | dental prosthesis | epidemiologic factors | epidemiology | maintenance | peri-implant diseases | periodontal diseases

ABSTRACT

Aim: This prospective cohort study aimed to evaluate the incidence and risk/protective factors of peri-implantitis over time.

Methods: A university-representative cohort was evaluated at baseline and after a mean follow-up time of 3.9 years. The main outcome was the incidence of peri-implantitis, defined as bone loss > 1 mm between the two examinations in implants showing bleeding on probing. Putative risk/protective factors assessed at baseline were tested through multilevel (mixed-effects) logistic regression analyses.

Results: A total of 73 patients with 322 implants were included. During the follow-up period, 14 implants (4.3%) were lost in 9 patients (12.3%). Incidence of peri-implantitis was observed in 22.2% of patients and 9.4% of implants. In the final multilevel multiple logistic regression model, the following factors were associated with occurrence of peri-implantitis: periodontitis severity (stage IV periodontitis: OR = 41.29; 95% CI: 4.10–415.54), periodontal bone loss/age ratio (> 1: OR = 8.87; 95% CI: 1.47–53.73), smoking (current smokers: OR = 7.84; 95% CI: 1.83–33.50), sleep duration (> 7 h: OR = 19.97; 95% CI: 1.69–236.39), implant location (incisor: OR = 60.60; 95% CI: 4.04–908.33), restoration type (full-arch fixed restorations: OR = 89.84; 95% CI: 3.66–2202.97), and restoration margin location (juxta-marginal: OR = 14.17; 95% CI: 1.20–166.76). Keratinized tissue width assessed at baseline was not associated with incidence of peri-implantitis.

Conclusion: Approximately one in five patients and one in 10 implants experienced incident peri-implantitis over a nearly four-year period. Periodontitis (Stage IV and Grade C), lifestyles (smoking and sleep duration), implant location, and prosthetic factors (restoration type and margin location) emerged as risk factors for peri-implantitis.

1 | Introduction

Given its high prevalence [1–5], rapid progression [6], and the limited efficacy of current treatment procedures [7–11], primary prevention and early diagnosis [12, 13] are essential in managing peri-implantitis. The main strategies of peri-implantitis prevention, rely on (i) treating peri-implant mucositis, since it is considered its precursor [14, 15] and (ii) implementing interventions aimed at controlling the modifiable risk factors [1, 16–20]. A recent cross-sectional study performed by our research group identified several risk indicators for peri-implantitis, including moderate/severe periodontitis, smoking, implant brand and malposition, restorative factors, and plaque [2]. These identified risk indicators were consistent with other studies with similar designs [1, 5, 21, 22]. However, the identification of true risk/protective factors requires a longitudinal evaluation to verify the

Mario Romandini and Cristina Lima equally contributed to this work.

Summary

- Background
  - Identifying true risk and protective factors requires a longitudinal evaluation to verify the temporality criterion.
  - Since many identified putative risk factors for peri-implantitis are either not modifiable or not amenable to randomized clinical trials due to ethical reasons, cohort studies are the most appropriate design.
  - However, only a few cohort studies exist in the field, mostly at risk of selection, confounding, or information bias.
- Added value of this study
  - Approximately one in five patients and one in 10 implants experienced incident peri-implantitis over a nearly four-year period.
  - This study identified periodontitis (stage and grade), lifestyle behaviours (smoking and sleep duration), implant location, and prosthetic factors (restoration type and margin location) as risk factors for peri-implantitis within a longitudinal framework of a representative sample.
- Clinical implications
  - Clinicians should address these factors when they are modifiable and consider them for implementing more stringent preventive measures when they are not modifiable.

temporality criterion, ideally through randomized clinical trials to minimize the risk of confounding bias [23]. Since many of the identified putative risk factors for peri-implantitis are either not modifiable or not amenable to randomized clinical trials due to ethical reasons, cohort studies are the most appropriate design. However, only a few cohort studies exist in the field [24–26], mostly at risk of selection, confounding, or information bias. Therefore, this prospective cohort study aimed to evaluate the incidence of peri-implantitis over time and associated risk/protective factors.

2 | Methods

This manuscript adheres to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [27, 28]. The study was conducted in accordance with the Declaration of Helsinki for human studies, and its research protocol was ethically approved (19/182-E; 22/385-EC_P) by the CEIm Hospital Clínico San Carlos, Madrid, Spain.

2.1 | Population

The Peri-Implant Diseases Follow-Up (PIDFU) study is an ongoing prospective cohort study based on the repeated follow-ups over time of a previously reported university-representative population [2, 29, 30]. During 2019, 99 patients with 458 implants, identified through a stratified multistage sampling process among patients who received dental implants from 2000 to 2017 in the Department of Periodontology at Complutense University of Madrid, were initially examined both clinically and radiographically. This examination served as the baseline for this prospective cohort study (Figure 1). In 2023, the same patients were invited to participate to the first follow-up examination through a minimum of five different telephonic attempts made on different days.

2.2 | Risk/Protective Factors Tested (Exposure)

The full list of patient- and implant-level variables tested as putative risk/protective factors is reported in Table 1. They were collected during the baseline examination, and their assessment methods are detailed in the baseline study publication [2].

During the presently reported follow-up examination, patients additionally self-reported (no, yes) about their SARS-CoV-2 and COVID-19 history and vaccination status. Additionally, patients indicated the number of supportive peri-implant care (SPIC) recalls and any treatments (non-surgical and/or surgical) performed on the study implants since the baseline examination. For interventions conducted in-house, information regarding the number of SPIC recalls and treatments was cross-verified by accessing patient files. Regular maintenance was defined as participating in an average of ≥ 1 SPIC recalls per year.

A full-mouth periodontal examination was also performed on the residual dentition, and full-mouth plaque and bleeding scores (FMPS/FMBS), the number of probing pocket depth (PPD) exceeding different thresholds (≥ 4, ≥ 5, ≥ 6 mm), and the number of furcation involvements [31] (FI) ≥ 2 were recorded. At implant-level, the location of the restoration margin in relation to the soft-tissue margin (sub-, juxta-, or supra-marginal) was recorded based on its most apical position around the implant. An orthopantomography was also performed, and the periodontal bone loss/age ratio was measured in the most severely affected tooth [32, 33].

2.3 | Peri-Implantitis Onset/Progression (Outcome)

The primary outcome of the study was peri-implantitis onset/progression, defined as the incidence of bone loss >1 mm between the baseline and follow-up examinations in implants showing bleeding on probing (BoP) at one or more sites during follow-up. The 1 mm threshold was chosen to minimize the risk of misclassification bias due to measurement error. Additional bone loss thresholds (>0.5 mm and >2 mm) were also considered for descriptive purposes.

At the follow-up examination, BoP was recorded at six sites per implant by a calibrated clinical examiner (CL). New standardized peri-apical radiographs of the included implants were obtained from the Radiology Department using the parallel technique. The marginal bone level at the follow-up examination was assessed by the same calibrated radiographic examiner from the baseline study (CL), applying the same measurement protocol described in the original publication [2]. Briefly, the radiographic bone level was measured at the mesial and distal aspects of each implant as the distance in millimeters between

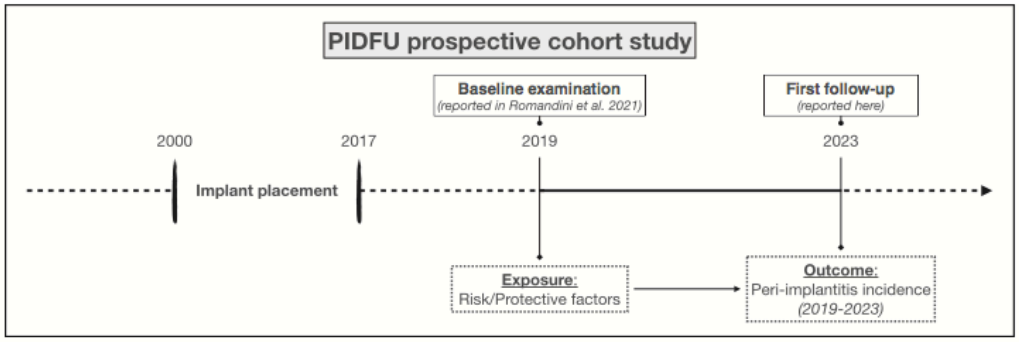

FIGURE 1 | PIDFU prospective cohort study design.

the intra-osseous portion of the implant (excluding any polished collar) and the first clearly visible contact between the implant surface and the bone. A software program (Autocad 2016 TM, AutoDesk Inc. San Rafael, CA, USA) was used, and the inter-thread pitch distance reported by the manufacturer or the length of the implant was considered for calibration. The largest value between the mesial and distal measurements was recorded as the bone level for that implant. Bone loss was calculated as the difference in bone levels between the two examinations. The radiographic examiner previously demonstrated an excellent intra-rater agreement after re-measuring 50 randomly selected radiographs (ICC = 0.98; 95% CI: 0.96–0.99; $p < 0.001$).

2.4 | Data Analysis

Statistical analyses were performed with STATA SE version 18.0 software (StataCorp LP). The characteristics of the study population/implants were summarized. Incidence of peri-implantitis onset/progression was described at both patient- and at implant-level.

Risk/protective factors for peri-implantitis onset/progression were studied using multilevel (mixed-effects) logistic regression analyses, accounting for the clustering of multiple implants within the same patients. Each putative factor was tested individually by adding it to an empty model with the peri-implantitis onset/progression as the dependent variable and testing its significance. All variables with a $p < 0.10$ were included in an intermediate multiple regression model, and non-significant variables were sequentially removed. The final model integrated all factors that remained with a $p < 0.10$. However, for results interpretation, statistical significance was a priori set at $p < 0.05$. Sensitivity analyses were performed by adjusting the final model a priori for the frequency of maintenance per year, treatments performed during follow-up, and peri-implant health status at baseline.

3 | Results

From the baseline sample of 99 patients, 14 declined to participate in the follow-up visit, three moved to a different city, two missed the scheduled appointment, one passed away, and six could not be reached despite multiple telephone attempts. Consequently, 73 patients with 322 implants were clinically evaluated after a mean follow-up time of 3.9 years (SD = 0.3; min: 3.0; max: 4.6). The general characteristics of the population and implants examined at follow-up are detailed in Tables 2 and 3, being consistent with those of the entire baseline population. Most of the included patients were women (61.6%), had a mean age of 62.8 years, had a diagnosis of stage III-IV periodontitis (57.5%), and were currently nonsmoking (80.8%) at baseline. Most of the study implants were located in the maxilla (55.6%), and were part of implant-supported bridge restorations (58.4%). At baseline, 91 implants (28.2%) in 38 patients (52.1%) were diagnosed with peri-implantitis.

3.1 | Interventions During Follow-Up

Most of the included implants (189/58.7%) did not receive any treatment during the follow-up period. Non-surgical treatment only was performed in 79 (24.6%) implants, whereas 18 (5.6%) underwent surgical treatment. Finally, 14 implants (4.3%) underwent removal, whereas no reliable information on previous interventions was available for the remaining 22 implants (6.8%).

The mean number of SPIC visits during follow up was 2.0 (SD = 1.5; min: 0; max: 7), with an average of 0.5 per year (SD = 0.4; min: 0; max: 1.9); 12.3% of patients were under regular maintenance, since they had an average of more than one SPIC visit per year.

3.2 | Incidence of Peri-Implantitis Onset/Progression

In addition to the 14 implants lost (9 patients), 10 implants had missing/unreadable follow-up radiographs. Therefore, peri-implantitis onset/progression was assessed on 298 implants.

An incidence of bone loss > 1 mm during follow-up was observed in 16 out of 72 patients (22.2%) and 28 out of 298 implants (9.4%) evaluated radiographically (Table 4). Bone loss > 1 mm was always associated with the presence of BoP at

TABLE 1 | Putative risk/protective factors tested.

Patient-level				Implant-level	
Demographic	Age (baseline)	Medications	Bisphosphonates (baseline)	General	Implant location (baseline)
	Gender (baseline)		Corticosteroids (baseline)		Jaw (baseline)
	Educational level (baseline)		NSAIDs (baseline)		Implant brand (baseline)
	Marital status (baseline)		Antiplatelet (baseline)		Implant type (tissue- vs. bone-level) (baseline)
	Height (baseline)		Anticoagulant (baseline)		Implant length (baseline)
	Weight (baseline)		Hypolipidemic agent (baseline)		Implant diameter (baseline)
	BMI (kg/m^2) (baseline)		Antidepressant (baseline)		At Least one adjacent tooth (baseline)
Systemic diseases	Diabetes (baseline)		Proton pump inhibitor (baseline)		Reason of tooth loss (baseline)
	Osteoporosis/ Osteopenia (baseline)		Vitamin D (baseline)	Soft-tissue	Keratinized tissue height (baseline)
	Myocardial infarction (baseline)		Calcium (baseline)		Adherent mucosa (baseline)
	Hypertension (baseline)		Thyroid drug (baseline)		Tissue thickness (baseline)
	Stroke (baseline)		Immunosuppressant (baseline)		
	Anemia (baseline)		Insulin (baseline)		Mucosal margin mobility (baseline)
	Cancer (baseline)		Oral hypoglycemic agent (baseline)	Restorative factors	Type of restoration (baseline)
	Depression (baseline)		Other anti-diabetic (baseline)		Restoration retention (baseline)
	Asthma (baseline)		Beta-blockers (baseline)		Prosthesis gap (baseline)
	Cognitive or memory disorders (baseline)		Diuretics (baseline)		Prosthesis step (baseline)
	Neurological disorders (baseline)		ACE inhibitors (baseline)		Emergence angle (highest) (baseline)
	Immunological disorders (baseline)		Other antihypertensive Drugs (baseline)		Emergence profile (baseline)
	Hypercholesterolemia (baseline)		Other medications (baseline)		Mesial cantilever (baseline)
	Hepatitis (baseline)		Supplements (baseline)		Distal cantilever (baseline)
	HIV/AIDS (baseline)	Oral/periodontal variables	Periodontal status (CDC/AAP) (baseline)		Prosthesis mobility (baseline)
	Rheumatoid arthritis (baseline)		Periodontal status (2017 WWP) (baseline)		Abutment presence (baseline)

(Continues)

TABLE 1 | (Continued)

Patient-level				Implant-level	
	Respiratory diseases (baseline)		Number of remaining teeth (baseline)		Platform switching (baseline)
	Liver diseases (baseline)		Number of dental implants (baseline)		Crown dimension (baseline)
	Cardiovascular diseases (baseline)		History of orthodontic treatment (baseline)		Crown to implant ratio (baseline)
	Gastrointestinal disorders (baseline)		Toothbrushing frequency (baseline)		Residual cement visible on radiograph (baseline)
	Kidney diseases (baseline)		Electric toothbrush (baseline)		Clinical signs of occlusal overloading (baseline)
	Thyroid disorders (baseline)		Interproximal flossing/brushing on implants (baseline)		Prosthetic design allowing access to hygiene (baseline)
	Cataract (baseline)		Bruxism signs (baseline)		Restoration margin location (follow-up)
	Other systemic diseases (baseline)		Bruxism symptoms (baseline)	Other	Vestibular-lingual malposition (baseline)
	Sars-CoV 2 history (follow-up)		Dry mouth (baseline)		Plaque (baseline)
	Covid-19 history (follow-up)		Number of maintenances between baseline and follow-up (follow up)		Peri-implant health status (baseline)
	Sars-CoV 2 vaccine (follow-up)		FMPS, excluding implants (follow-up)		
Lyfestiles	Smoking (baseline)		FMBS, excluding implants (follow-up)		
	Sleep duration (baseline)		Number PPD ≥ 4 or ≥ 5 or ≥ 6 mm, excluding implants (follow-up)		
	Physical activity (baseline)		Number FI ≥ 2 (follow-up)		
	Stress (baseline)		Periodontal bone loss/age ratio (follow-up)		
	Coffee consumption (baseline)	Other	Allergies (baseline)		
	Alcohol consumption (baseline)		Chemotherapy history (baseline)		
			Radiotherapy history (baseline)		

follow-up. Sixteen events (5.4%) corresponded to new peri-implantitis cases (i.e., peri-implantitis onset), whereas 12 (4.0%) involved further bone loss of implants already diagnosed with peri-implantitis at baseline (i.e., peri-implantitis progression). Peri-implantitis onset was mostly observed among implants diagnosed with peri-implant mucositis (9%–8.6%) or pre-periimplantitis (6%–6.3%) at baseline, compared with only one implant with peri-implant health (4.8%) at baseline (Table 5). Most peri-implantitis progressions were observed around implants that underwent surgical treatment during follow-up (40.0%), which might have been performed because of the incident bone loss. Sixty-five (84.4%) implants diagnosed with peri-implantitis at baseline did not show further bone loss.

3.3 | Risk/Protective Factors Associated With Peri-Implantitis Onset/Progression

The distribution of the tested risk/protective factors according to peri-implantitis incidence is detailed in Tables S1 and S2.

TABLE 2 | General characteristics of the study population.

	Baseline population (*N* = 99)	Follow-up population (*N* = 73)
Age (baseline) (years), mean (SD)	63.7 (9.3)	62.8 (8.0)
Gender, *N* (%)		
Male	39 (39.4)	28 (38.4)
Female	60 (60.6)	45 (61.6)
BMI (baseline) (kg/m^2), mean (SD)	25.6 (3.7)	25.7 (3.8)
Diabetes status (baseline), *N* (%)		
No diabetes	83 (83.8)	61 (83.6)
Diabetes	16 (16.2)	12 (16.4)
Smoking (baseline), *N* (%)		
Non-smokers	41 (41.4)	28 (38.3)
Former smokers	40 (40.4)	31 (42.5)
Current smokers	18 (18.2)	14 (19.2)
Periodontitis severity (2017 WWP) (baseline), *N* (%)		
No Periodontitis	7 (7.2)	4 (5.5)
Stage 1	11 (11.3)	7 (9.6)
Stage 2	19 (19.6)	14 (19.2)
Stage 3	30 (30.9)	25 (34.2)
Stage 4	21 (21.7)	17 (23.3)
Edentulous	9 (9.3)	6 (8.2)
Peri-implant status (baseline), *N* (%)		
Peri-implant health	1 (1.0)	0 (0.0)
Peri-implant mucositis	11 (11.1)	10 (13.7)
Pre-peri-implantitis	31 (31.3)	25 (34.2)
Peri-implantitis	56 (56.6)	38 (52.1)
Maintenance compliance (during follow-up), *N* (%)		
Regular maintenance	NA	9 (12.3)
Not regular maintenance	NA	64 (87.7)

Note: Total number varies according to missing data for each variable. Regular maintenance was defined as participating in an average of ≥ 1 supportive peri-implant care recalls per year.
Abbreviations: *N*, number; NA, not applicable; SD, standard deviation.

TABLE 3 | General characteristics of the study implants.

	Whole baseline implants (*N* = 458)	Implants analyzed at follow-up (*N* = 322)
Jaw, *N* (%)		
Maxilla	253 (55.2)	179 (55.6)
Mandible	205 (44.8)	143 (44.4)
Position, *N* (%)		
Anterior (canine-canine)	83 (18.1)	54 (16.8)
Posterior	375 (81.9)	268 (83.2)
Implant brand, *N* (%)		
S	230 (50.7)	173 (53.9)
N	57 (12.6)	38 (11.8)
A	76 (16.7)	45 (14.0)
Other	91 (20.0)	65 (20.3)
Implant Length (mm), mean (SD)	9.9 (1.7)	9.84 (1.71)
Implant Diameter (mm), mean (SD)	4.1 (0.4)	4.1 (0.4)
Type of prosthesis (baseline), *N* (%)		
Single crown	136 (29.7)	103 (32.0)
Bridge	267 (58.3)	188 (58.4)
Overdenture	14 (3.1)	8 (2.5)
Full-arch fixed restoration	41 (8.9)	23 (7.1)
Prosthesis retention (baseline), *N* (%)		
Cemented	218 (47.6)	163 (50.6)
Screw-retained	226 (49.3)	151 (46.9)
Locator	8 (1.8)	2 (0.6)
Bar	6 (1.3)	6 (1.9)
Peri-implant status (baseline), *N* (%)		
Peri-implant health	39 (8.5)	25 (7.8)
Peri-implant mucositis	146 (31.9)	107 (33.2)
Pre-peri-implantitis	145 (31.7)	99 (30.8)
Peri-implantitis	128 (27.9)	91 (28.2)

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.

In the multi-level simple regression analyses, the following patient-level exposure variables were associated with peri-implantitis ($p < 0.10$): marital status, height, osteoporosis/osteopenia, myocardial infarction, hepatitis, smoking, sleep duration, alcohol consumption, intake of bisphosphonates, vitamin D, or immunosuppressants, periodontitis severity (2017 WWP), number of remaining teeth, electric toothbrush use, and periodontal bone loss/age ratio (Table A1). The following implant-level variables were also associated with peri-implantitis: implant location, presence of at least one adjacent tooth, type of restoration, prosthetic design, restoration margin location, implant malposition, and plaque (Table A2).

In the final multilevel multiple logistic regression model, the following factors remained significant at the $p < 0.05$ level:

TABLE 4 | Incidence of bone loss during follow-up according to different peri-implant diagnosis at baseline.

		Implant-level ($n = 298$*)		
		Bone loss > 0.5 mm	**Bone loss > 1 mm**	**Bone loss > 2 mm**
Diagnosis at baseline	Peri-implant health	1 (4.8%)	1 (4.8%)	1 (4.8%)
	Regular maintenance	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Not regular maintenance	1 (6.7%)	1 (6.7%)	1 (6.7%)
	Peri-implant mucositis	15 (14.3%)	9 (8.6%)	1 (1.0%)
	Regular maintenance	3 (20.0%)	2 (13.3%)	0 (0.0%)
	Not regular maintenance	12 (13.3%)	7 (7.8%)	1 (1.1%)
	Pre-Periimplantitis	14 (14.7%)	6 (6.3%)	3 (3.2%)
	Regular maintenance	2 (13.3%)	1 (6.7%)	0 (0.0%)
	Not regular maintenance	12 (15.0%)	5 (6.3%)	3 (3.8%)
	Peri-implantitis	20 (26.0%)	12 (15.6%)	7 (9.1%)
	No treatment after baseline	7 (18.0%)	3 (7.7%)	1 (2.6%)
	Only non-surgical treatment	4 (22.2%)	3 (16.7%)	3 (16.7%)
	Surgical treatment	9 (60.0%)	6 (40.0%)	3 (20.0%)
	Unknown treatment status	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Overall	50 (16.8%)	28 (9.4%)	12 (4.0%)

Note: Regular maintenance was defined as participating in an average of ≥ 1 supportive peri-implant care recalls per year.
*Missing data: 24 implants (10 had missing/unreadable radiographs; 14 were lost/removed during follow-up).

periodontitis severity (stage IV periodontitis: OR = 41.29), periodontal bone loss/age ratio (> 1: OR = 8.87), smoking (current smokers: OR = 7.84), sleep duration (> 7 h: OR = 19.97), implant location (incisor: OR = 60.60), restoration type (full-arch fixed restorations: OR = 89.84), and restoration margin location (juxta-marginal: OR = 14.17) (Table 6). Osteoporosis/osteopenia (yes: OR = 5.97) and plaque (6 sites: OR = 3.64) also entered the final model ($p < 0.10$), despite being not statistically significant ($p > 0.05$). Sensitivity analyses, adjusting the final model a priori for frequency of maintenance per year, treatments performed during follow-up, and peri-implant health status at baseline, showed results consistent with the main analyses.

4 | Discussion

In this prospective cohort study, the incidence of peri-implantitis was ~10% over a period of ~4 years, comprising 5.4% new cases and 4.0% progressions. Identified risk factors for peri-implantitis included Stage IV periodontitis, a periodontal bone loss/age ratio > 1, current smoking, sleep duration > 7 h, incisor position, full-arch fixed restorations, and juxta-marginal margin location. Additionally, there was a non-statistically significant trend for plaque and osteoporosis. Analyses adjusted for the frequency of maintenance per year, treatments performed during follow-up, and peri-implant health status at baseline showed results consistent with the main analyses.

Few prospective cohort studies are available for comparison, with most existing evidence at risk of selection, confounding, or information bias. Costa el al. [14] followed 80 patients for 5 years, reporting a higher incidence of peri-implantitis (31.2%). Differences in follow-up length and case definitions may explain the discrepancies in peri-implantitis incidence over time.

The history of periodontitis has been consistently linked to peri-implantitis [34]; however, only a few studies have a longitudinal design [25, 35], and none used the current classification system [32]. Consistent with the baseline study [2], our findings indicate that the most severe forms of periodontitis are the ones at higher risk of peri-implantitis. According to the 2017 classification, Stage IV cases are indeed the ones where dental implants are used to restore masticatory function after periodontitis-related tooth loss. Furthermore, the periodontal bone loss/age ratio represents the indirect criterion for defining the rate of progression of periodontitis (grade) in cases lacking previous records. A periodontal bone loss/age ratio > 1 (Grade C) emerged as a risk factor for peri-implantitis, highlighting how the most aggressive forms of periodontitis are also at higher risk, as previously reported for the 1999 classification system [36].

Although some cohort studies have indicated smoking as a risk factor for peri-implantitis [24], the majority have not [37–39]. This controversial relationship may be due to a masking effect by periodontitis [1]. Consistent with the baseline study [2], current smokers exhibited a higher risk of peri-implantitis in the present study, possibly caused by its microvascular effects and the associated changes in peri-implant microbiota [40].

The observed higher risk of peri-implantitis incidence in long sleepers underlines the relevance of healthy lifestyles beyond

TABLE 5 | Occurrence of peri-implant diseases and implant loss during follow-up according to different peri-implant diagnosis at baseline.

		Implant-level						
		Diagnosis at follow-up						
		Peri-implant health*	Peri-implant mucositis*	New peri-implantitis*	Stable peri-implantitis*	Progressive peri-implantitis*	Total* (raw)	Implant loss**
Diagnosis at baseline	Peri-implant health	8 (38.1%)	12 (57.1%)	1 (4.8%)			21 (100.0%)	1 (4.5%)
	Regular maintenance	4 (66.7%)	2 (33.3%)	0 (0.0%)			6 (100.0%)	0 (0.0%)
	Not regular maintenance	4 (26.7%)	10 (66.7%)	1 (6.6%)			15 (100.0%)	1 (6.3%)
	Peri-implant mucositis	10 (9.5%)	86 (81.9%)	9 (8.6%)			105 (100.0%)	2 (1.9%)
	Regular maintenance	2 (13.3%)	11 (73.3%)	2 (13.3%)			15 (100.0%)	0 (0.0%)
	Not regular maintenance	8 (8.9%)	75 (83.3%)	7 (7.8%)			90 (100.0%)	2 (2.2%)
	Pre-Periimplantitis	14 (14.7%)	75 (79.0%)	6 (6.3%)			95 (100.0%)	3 (3.1%)
	Regular maintenance	2 (13.3%)	12 (80.0%)	1 (6.7%)			15 (100.0%)	1 (6.3%)
	Not regular maintenance	12 (15.0%)	63 (78.8%)	5 (6.2%)			80 (100.0%)	2 (2.5%)
	Peri-implantitis				65 (84.4%)	12 (15.6%)	77 (100.0%)	8 (9.4%)
	Implant removal at baseline				NA	NA	0 (100.0%)	5 (100.0%)
	No treatment after baseline				36 (92.3%)	3 (7.7%)	39 (100.0%)	0 (0.0%)
	Only non-surgical treatment				15 (83.3%)	3 (16.7%)	18 (100.0%)	0 (0.0%)
	Surgical treatment				9 (60.0%)	6 (40.0%)	15 (100.0%)	1 (6.3%)
	Unknown treatment status				5 (100.0%)	0 (0.0%)	5 (100.0%)	2 (28.6%)
	Overall	32 (10.7%)	173 (58.1%)	16 (5.4%)	65 (21.8%)	12 (4.0%)	298 (100.0%)	14 (4.5%)

Note: Regular maintenance was defined as participating in an average of ≥1 supportive peri-implant care recalls per year.
Abbreviation: NA, not applicable.
*Percentages refer to implants evaluated radiographically ($n = 298$) (missing data: 10 implants due missing/unreadable radiographs, 14 implants lost during follow-up).
**Percentages refer to implants evaluated clinically (i.e., including implants lost during follow-up) ($n = 312$) (missing data: 10 implants due missing/unreadable radiographs).

TABLE 6 | Risk/protective indicators associated with incidence of peri-implantitis during follow-up: Multilevel multiple logistic regression analysis.

	Empty model		Final model		
Variable	**OR**	**95% CI**	**OR**	**95% CI**	***p***
Fixed part					
Intercept	0.04	0.01–0.12	0.00	0.00–0.01	
Osteoporosis/osteopenia (yes) (baseline)			5.97	0.98–36.32	0.052
Smoking (baseline)					
Non-smoker			Ref	Ref	Ref
Current smoker			7.84	1.83–33.50	0.005
Sleep duration (baseline)					
<7 h			0.80	0.20–3.21	0.751
7–8 h			Ref	Ref	Ref
>7 h			19.97	1.69–236.39	0.018
Periodontitis severity (2017 WWP) (baseline)					
No periodontitis or SI-III periodontitis			Ref	Ref	Ref
Stage 4 periodontitis			41.29	4.10–415.54	0.002
Edentulous			NE	NE	NE
Periodontal bone loss/age ratio (follow-up)					
≤1			Ref	Ref	Ref
>1			8.87	1.47–53.73	0.017
Implant location (baseline)					
Molar			Ref	Ref	Ref
Incisor			60.60	4.04–908.33	0.003
Canine			NE	NE	NE
Premolar			0.90	0.28–2.93	0.862
Restoration type (baseline)					
Single crown			Ref	Ref	Ref
Bridge			1.19	0.27–5.30	0.817
Overdenture			NE	NE	NE
Full-arch fixed restoration			89.84	3.66–2202.97	0.006
Restoration margin location (follow-up)					
Supra-marginal			Ref	Ref	Ref
Sub-marginal			5.97	0.54–66.02	0.145
Juxta-marginal			14.17	1.20–166.76	0.035
Plaque (baseline)					
0–5 sites			Ref	Ref	Ref
6 sites			3.64	0.83–15.94	0.086
Random part					
Patient variance	2.60	0.79–8.53	0.00	0.00–0.00	
AIC	177.61		119.64		

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

non-smoking for promoting peri-implant health. Despite being novel for peri-implant health, this finding is consistent with periodontal literature [41–44]. Longer sleep durations may additionally indicate poor general or mental health status, specifically depression and related medication intakes, which have been previously strongly related to peri-implantitis and implant loss [45, 46].

Several implant-level variables were also associated with the incidence of peri-implantitis. The higher risk observed in anterior zones aligns with previous cross-sectional studies [5] and recent reports indicating elevated rates of implant loss in the anterior mandible [47]. The unique anatomical and histological characteristics of these zones, combined with the specific surgical and prosthetic protocols aimed at maximizing esthetic outcomes - yet potentially limiting access for biofilm removal - may contribute to this increased risk. Similarly, the higher risk of peri-implantitis observed for full-arch restorations, apart from being interpretable as a proxy of the most severe forms of periodontitis, may also be related to the increased difficulty in accessing and performing self-administred oral hygiene procedures [5, 48]. The formation of sub-marginal- microbiological niches may also explain the association between restoration margin location and peri-implantitis, highlighting the relevance of restoration designs in mantaining peri-implant health [1, 49].

Although there is substantial evidence supporting the role of biofilm accumulation hosting a dysbiotic microbiota as a risk factor for peri-implantitis [2, 17, 50–52], the presence of plaque was not longitudinally associated with incident peri-implantitis in this cohort, despite entering in the final model. This finding may be explained by potential variation in plaque control over time. In addition to plaque, also implant brand and malposition, keratinized tissue width, and maintenance frequency were not associated with peri-implantitis. The first three factors may have lacked statistical power, as suggested by their non-significant tendencies for association in simple regression analyses. In contrast, maintenance frequency could have been subject to a masking effect from periodontitis, because the most severe forms of periodontitis may necessitate more frequent maintenance recalls.

The relevance of the present findings lies in the prospective cohort study design. The risk of selection bias is mitigated by the representative methods used to select the study population at baseline and the similar characteristics of patients examined at follow-up. The use of multi-level regression analyses, adjusted for other risk factors, controls the risk of confounding bias. Additionally, the use of direct evidence to assess bone loss within a longitudinal framework and the consistent assessment performed by the same calibrated examiner from the baseline study help minimize the risk of information bias. However, some limitations need consideration. The absence of previous studies with a similar design and scope necessitated an exploratory approach for this study design. Consequently, while limited statistical power may have prevented the identification of relevant additional risk factors, the risk of a type I error cannot be ruled out. Moreover, some risk indicators were self-reported, whereas others were assessed using methods that do not meet gold-standard criteria (e.g., mucosal thickness measured with a probe), introducing a potential risk of information bias. Additionally, two of the emerged risk factors (periodontal bone loss/age ratio and restoration margin location) were only assessed at the follow-up examination, preventing verification of their presence before peri-implantitis occurred. Finally, despite selected through a stratified multistage sampling process, the analyzed population is derived from a single center primarily including periodontitis patients in a specific country. Therefore, the generalizability of these findings to different settings needs to be verified by future studies.

5 | Conclusions

In this prospective cohort study, approximately one in five patients and one in ten implants experienced incident peri-implantitis over a nearly four-year period. Periodontitis (stage and grade), lifestyle behaviours (smoking and sleep duration), implant location, and prosthetic factors (restoration type and margin location) were identified as risk factors for peri-implantitis. Clinicians should address these factors when modifiable or consider them for implementing more stringent preventive measures when not modifiable.

Author Contributions

M.R. contributed to study conception and design, to data acquisition, analysis and interpretation, and manuscript drafting. C.L. contributed to data acquisition, analysis and interpretation, and manuscript drafting. D.B. and R.A. contributed to data acquisition, and critically revised the manuscript. M.S. contributed to study design, data analysis and interpretation, and critically revised the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest related to this study.

Data Availability Statement

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

References

1. J. Derks, D. Schaller, J. Hakansson, J. L. Wennstrom, C. Tomasi, and T. Berglundh, "Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-Implantitis," *Journal of Dental Research* 95, no. 1 (2016): 43–49.

2. M. Romandini, C. Lima, I. Pedrinaci, A. Araoz, M. C. Soldini, and M. Sanz, "Prevalence and Risk/Protective Indicators of Peri-Implant Diseases: A University-Representative Cross-Sectional Study," *Clinical Oral Implants Research* 32, no. 1 (2021): 112–122.

3. M. Romandini, M. Cordaro, S. Donno, and L. Cordaro, "Discrepancy Between Patient Satisfaction and Biologic Complication Rate in Patients Rehabilitated With Overdentures and Not Participating in a

Structured Maintenance Program After 7 to 12 Years of Loading," *International Journal of Oral & Maxillofacial Implants* 34, no. 5 (2019): 1143–1151.

4. F. Vignoletti, G. L. Di Domenico, M. Di Martino, E. Montero, and M. de Sanctis, "Prevalence and Risk Indicators of Peri-Implantitis in a Sample of University-Based Dental Patients in Italy: A Cross-Sectional Study," *Journal of Clinical Periodontology* 46, no. 5 (2019): 597–605.

5. D. Rodrigo, I. Sanz-Sanchez, E. Figuero, et al., "Prevalence and Risk Indicators of Peri-Implant Diseases in Spain," *Journal of Clinical Periodontology* 45, no. 12 (2018): 1510–1520.

6. J. Derks, D. Schaller, J. Hakansson, J. L. Wennstrom, C. Tomasi, and T. Berglundh, "Peri-Implantitis—Onset and Pattern of Progression," *Journal of Clinical Periodontology* 43, no. 4 (2016): 383–388.

7. M. Romandini, K. Bougas, L. Alibegovic, et al., "Long-Term Outcomes and Prognostic Factors of Surgical Treatment of Peri-Implantitis—A Retrospective Study," *Clinical Oral Implants Research* 35, no. 3 (2024): 321–329.

8. J. Derks, A. Ortiz-Vigon, A. Guerrero, et al., "Reconstructive Surgical Therapy of Peri-Implantitis: A Multicenter Randomized Controlled Clinical Trial," *Clinical Oral Implants Research* 33, no. 9 (2022): 921–944.

9. G. Baima, F. Citterio, M. Romandini, et al., "Surface Decontamination Protocols for Surgical Treatment of Peri-Implantitis: A Systematic Review With Meta-Analysis," *Clinical Oral Implants Research* 33, no. 11 (2022): 1069–1086.

10. M. Romandini, A. Lafori, I. Pedrinaci, et al., "Effect of Sub-Marginal Instrumentation Before Surgical Treatment of Peri-Implantitis: A Multi-Centre Randomized Clinical Trial," *Journal of Clinical Periodontology* 49, no. 12 (2022): 1334–1345.

11. E. Regidor, A. Ortiz-Vigon, M. Romandini, C. Dionigi, J. Derks, and M. Sanz, "The Adjunctive Effect of a Resorbable Membrane to a Xenogeneic Bone Replacement Graft in the Reconstructive Surgical Therapy of Peri-Implantitis: A Randomized Clinical Trial," *Journal of Clinical Periodontology* 50, no. 6 (2023): 765–783.

12. J. Berglundh, M. Romandini, J. Derks, M. Sanz, and T. Berglundh, "Clinical Findings and History of Bone Loss at Implant Sites," *Clinical Oral Implants Research* 32, no. 3 (2021): 314–323.

13. M. Romandini, J. Berglundh, J. Derks, M. Sanz, and T. Berglundh, "Diagnosis of Peri-Implantitis in the Absence of Baseline Data: A Diagnostic Accuracy Study," *Clinical Oral Implants Research* 32, no. 3 (2021): 297–313.

14. F. O. Costa, S. Takenaka-Martinez, L. O. Cota, S. D. Ferreira, G. L. Silva, and J. E. Costa, "Peri-Implant Disease in Subjects With and Without Preventive Maintenance: A 5-Year Follow-Up," *Journal of Clinical Periodontology* 39, no. 2 (2012): 173–181.

15. A. Verket, O. C. Koldsland, D. Bunaes, S. A. Lie, and M. Romandini, "Non-surgical Therapy of Peri-Implant Mucositis-Mechanical/Physical Approaches: A Systematic Review," *Journal of Clinical Periodontology* 50, no. Suppl 26 (2023): 135–145.

16. M. C. Carra, N. Blanc-Sylvestre, A. Courtet, and P. Bouchard, "Primordial and Primary Prevention of Peri-Implant Diseases: A Systematic Review and Meta-Analysis," *Journal of Clinical Periodontology* 50, no. Suppl 26 (2023): 77–112.

17. E. B. S. Carvalho, M. Romandini, S. Sadilina, A. C. P. Sant'Ana, and M. Sanz, "Microbiota Associated With Peri-Implantitis-A Systematic Review With Meta-Analyses," *Clinical Oral Implants Research* 34, no. 11 (2023): 1176–1187.

18. B. Bencze, B. G. N. Cavalcante, M. Romandini, et al., "Prediabetes and Poorly Controlled Type-2 Diabetes as Risk Indicators for Peri-Implant Diseases: A Systematic Review and Meta-Analysis," *Journal of Dentistry* 146 (2024).

19. M. Annunziata, G. Cecoro, A. Guida, et al., "Effectiveness of Implant Therapy in Patients With and Without a History of Periodontitis: A Systematic Review With Meta-Analysis of Prospective Cohort Studies," *Journal of Periodontal Research* (2024).

20. S. C. Isler, M. Romandini, G. Akca, et al., "Soft-Tissue Phenotype as a Risk Indicator of Peri-Implantitis and Peri-Implant Soft-Tissue Dehiscence-A Cross-Sectional Study," *Journal of Clinical Periodontology* 51 (2024): 1443–1457.

21. L. Canullo, M. Tallarico, S. Radovanovic, B. Delibasic, U. Covani, and M. Rakic, "Distinguishing Predictive Profiles for Patient-Based Risk Assessment and Diagnostics of Plaque Induced, Surgically and Prosthetically Triggered Peri-Implantitis," *Clinical Oral Implants Research* 27, no. 10 (2016): 1243–1250.

22. A. M. Roos-Jansaker, C. Lindahl, H. Renvert, and S. Renvert, "Nine- to Fourteen-Year Follow-Up of Implant Treatment. Part II: Presence of Peri-Implant Lesions," *Journal of Clinical Periodontology* 33, no. 4 (2006): 290–295.

23. D. A. Grimes and K. F. Schulz, "An Overview of Clinical Research: The Lay of the Land," *Lancet* 359, no. 9300 (2002): 57–61.

24. I. K. Karoussis, S. Muller, G. E. Salvi, L. J. Heitz-Mayfield, U. Brager, and N. P. Lang, "Association Between Periodontal and Peri-Implant Conditions: A 10-Year Prospective Study," *Clinical Oral Implants Research* 15, no. 1 (2004): 1–7.

25. A. Roccuzzo, L. Weigel, C. Marruganti, et al., "Longitudinal Assessment of Peri-Implant Diseases in Patients With and Without History of Periodontitis: A 20-Year Follow-Up Study," *International Journal of Oral Implantology* 16, no. 3 (2023): 211–222.

26. M. Roccuzzo, G. Grasso, and P. Dalmasso, "Keratinized Mucosa Around Implants in Partially Edentulous Posterior Mandible: 10-Year Results of a Prospective Comparative Study," *Clinical Oral Implants Research* 27, no. 4 (2016): 491–496.

27. E. von Elm, D. G. Altman, M. Egger, et al., "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies," *BMJ* 335, no. 7624 (2007): 806–808.

28. J. P. Vandenbroucke, E. von Elm, D. G. Altman, et al., "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration," *Epidemiology* 18, no. 6 (2007): 805–835.

29. M. Romandini, I. Pedrinaci, C. Lima, M. C. Soldini, A. Araoz, and M. Sanz, "Prevalence and Risk/Protective Indicators of Buccal Soft Tissue Dehiscence Around Dental Implants," *Journal of Clinical Periodontology* 48, no. 3 (2021): 455–463.

30. M. Romandini, C. Lima, I. Pedrinaci, A. Araoz, M. Costanza Soldini, and M. Sanz, "Clinical Signs, Symptoms, Perceptions, and Impact on Quality of Life in Patients Suffering From Peri-Implant Diseases: A University-Representative Cross-Sectional Study," *Clinical Oral Implants Research* 32, no. 1 (2021): 100–111.

31. S. E. Hamp, S. Nyman, and J. Lindhe, "Periodontal Treatment of Multirooted Teeth. Results After 5 Years," *Journal of Clinical Periodontology* 2, no. 3 (1975): 126–135.

32. P. N. Papapanou, M. Sanz, N. Buduneli, et al., "Periodontitis: Consensus Report of Workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions," *Journal of Clinical Periodontology* 45, no. Suppl 20 (2018): S162–S170.

33. M. Sanz, P. N. Papapanou, M. S. Tonetti, H. Greenwell, and K. Kornman, "Guest Editorial: Clarifications on the Use of the New Classification of Periodontitis," *Journal of Clinical Periodontology* 47, no. 6 (2020): 658–659.

34. H. Dreyer, J. Grischke, C. Tiede, et al., "Epidemiology and Risk Factors of Peri-Implantitis: A Systematic Review," *Journal of Periodontal Research* 53, no. 5 (2018): 657–681.

35. I. K. Karoussis, G. E. Salvi, L. J. Heitz-Mayfield, U. Bragger, C. H. Hammerle, and N. P. Lang, "Long-Term Implant Prognosis in Patients

With and Without a History of Chronic Periodontitis: A 10-Year Prospective Cohort Study of the ITI Dental Implant System," *Clinical Oral Implants Research* 14, no. 3 (2003): 329–339.

36. A. Monje, G. Alcoforado, M. Padial-Molina, F. Suarez, G. H. Lin, and H. L. Wang, "Generalized Aggressive Periodontitis as a Risk Factor for Dental Implant Failure: A Systematic Review and Meta-Analysis," *Journal of Periodontology* 85, no. 10 (2014): 1398–1407.

37. G. Dvorak, C. Arnhart, S. Heuberer, C. D. Huber, G. Watzek, and R. Gruber, "Peri-Implantitis and Late Implant Failures in Postmenopausal Women: A Cross-Sectional Study," *Journal of Clinical Periodontology* 38, no. 10 (2011): 950–955.

38. A. M. Roos-Jansaker, H. Renvert, C. Lindahl, and S. Renvert, "Nine- to Fourteen-Year Follow-Up of Implant Treatment. Part III: Factors Associated With Peri-Implant Lesions," *Journal of Clinical Periodontology* 33, no. 4 (2006): 296–301.

39. K. Swierkot, P. Lottholz, L. Flores-de-Jacoby, and R. Mengel, "Mucositis, Peri-Implantitis, Implant Success, and Survival of Implants in Patients With Treated Generalized Aggressive Periodontitis: 3- to 16-Year Results of a Prospective Long-Term Cohort Study," *Journal of Periodontology* 83, no. 10 (2012): 1213–1225.

40. E. Amerio, G. Blasi, C. Valles, et al., "Impact of Smoking on Peri-Implant Bleeding on Probing," *Clinical Implant Dentistry and Related Research* 24, no. 2 (2022): 151–165.

41. C. Marruganti, G. Baima, S. Grandini, et al., "Leisure-Time and Occupational Physical Activity Demonstrate Divergent Associations With Periodontitis: A Population-Based Study," *Journal of Clinical Periodontology* 50, no. 5 (2023): 559–570.

42. C. Marruganti, C. Gaeta, M. Romandini, et al., "Multiplicative Effect of Stress and Poor Sleep Quality on Periodontitis: A University-Based Cross-Sectional Study," *Journal of Periodontology* 95, no. 2 (2024): 125–134.

43. C. Marruganti, M. Romandini, C. Gaeta, et al., "Healthy Lifestyles Are Associated With a Better Response to Periodontal Therapy: A Prospective Cohort Study," *Journal of Clinical Periodontology* 50, no. 8 (2023): 1089–1100.

44. M. Romandini, G. Gioco, G. Perfetti, G. Deli, E. Staderini, and A. Lafori, "The Association Between Periodontitis and Sleep Duration," *Journal of Clinical Periodontology* 44, no. 5 (2017): 490–501.

45. H. Strooker, Y. C. M. de Waal, and M. M. Bildt, "Psychological Risk Indicators for Peri-Implantitis: A Cross-Sectional Study," *Journal of Clinical Periodontology* 49, no. 10 (2022): 980–987.

46. B. R. Chrcanovic, J. Kisch, T. Albrektsson, and A. Wennerberg, "Factors Influencing Early Dental Implant Failures," *Journal of Dental Research* 95, no. 9 (2016): 995–1002.

47. I. Pedrinaci, T. C. Sun, M. Sanz-Alonso, J. Sanz-Esporrin, A. Hamilton, and G. O. Gallucci, "Implant Survival in the Anterior Mandible: A Retrospective Cohort Study," *Clinical Oral Implants Research* 34, no. 5 (2023): 463–474.

48. R. Pons, J. Nart, C. Valles, G. E. Salvi, and A. Monje, "Self-Administered Proximal Implant-Supported Hygiene Measures and the Association to Peri-Implant Conditions," *Journal of Periodontology* 92, no. 3 (2021): 389–399.

49. M. Katafuchi, B. F. Weinstein, B. G. Leroux, Y. W. Chen, and D. M. Daubert, "Restoration Contour Is a Risk Indicator for Peri-Implantitis: A Cross-Sectional Radiographic Analysis," *Journal of Clinical Periodontology* 45, no. 2 (2018): 225–232.

50. J. P. Albouy, I. Abrahamsson, L. G. Persson, and T. Berglundh, "Spontaneous Progression of Ligatured Induced Peri-Implantitis at Implants With Different Surface Characteristics. An Experimental Study in Dogs II: Histological Observations," *Clinical Oral Implants Research* 20, no. 4 (2009): 366–371.

51. R. Pontoriero, M. P. Tonelli, G. Carnevale, A. Mombelli, S. R. Nyman, and N. P. Lang, "Experimentally Induced Peri-Implant Mucositis. A Clinical Study in Humans," *Clinical Oral Implants Research* 5, no. 4 (1994): 254–259.

52. G. E. Salvi, M. Aglietta, S. Eick, A. Sculean, N. P. Lang, and C. A. Ramseier, "Reversibility of Experimental Peri-Implant Mucositis Compared With Experimental Gingivitis in Humans," *Clinical Oral Implants Research* 23, no. 2 (2012): 182–190.

Supporting Information

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

Appendix A

TABLE A1 | Patient-level risk/protective indicators associated with incidence of peri-implantitis during follow-up: Multilevel simple logistic regression analysis.

Variable	OR	95% CI	*p*
Age (years) (each unit increase) (baseline)	1.06	0.97–1.17	0.183
Age ≧ 65 years (yes) (baseline)	1.75	0.48–6.47	0.399
Gender (female) (baseline)	2.37	0.56–10.00	0.239
Educational level (baseline)			
Primary school	Ref	Ref	Ref
High school	1.17	0.25–5.51	0.840
Middle grade	0.31	0.04–2.47	0.269
University/College	0.19	0.02–1.56	0.121
Marital status (baseline)			
Married	Ref	Ref	Ref
Widow	7.27	1.05–50.48	**0.045**
Divorced	0.28	0.022–3.59	0.330
Never married	1.51	0.16–14.36	0.719
Living with unmarried partner	1.64	0.75–35.99	0.753
Height (cm) (each unit increase) (baseline)	0.92	0.85–0.98	**0.017**
Weight (kg) (each unit increase) (baseline)	0.96	0.92–1.01	0.120
BMI (kg/m^2) (each unit increase) (baseline)	0.95	0.79–1.14	0.578
Diabetes* (yes) (baseline)	1.65	0.32–8.63	0.552
Osteoporosis/Osteopenia (yes) (baseline)	3.49	0.82–14.81	**0.090**
Myocardial Infarction (yes) (baseline)	11.08	0.156–787.56	0.269
Hypertension* (yes) (baseline)	1.30	0.317–5.29	0.718
Stroke (yes) (baseline)	5.58	0.14–229-47	0.365
Anemia (yes) (baseline)	0.51	0.08–3.17	0.467
Cancer (yes) (baseline)	0.99	0.11–8.60	0.996
Depression* (yes) (baseline)	2.05	0.45–9.21	0.351
Asthma (yes) (baseline)	0.90	0.04–21.16	0.950
Cognitive or memory disorders (yes) (baseline)	1.10	0.07–17.77	0.945
Neurological disorders (yes) (baseline)	NE	NE	NE
Immunological disorders (yes) (baseline)	NE	NE	NE
Hypercholesterolemia (yes) (baseline)	0.80	0.21–3.09	0.745
Hepatitis (yes) (baseline)	0.43	0.02–0.12	**0.000**
HIV/AIDS (yes) (baseline)	NE	NE	NE
Rheumatoid arthritis (yes) (baseline)	2.59	0.49–13.79	0.264
Respiratory diseases (yes) (baseline)	0.64	0.071–5.77	0.692
Liver diseases (yes) (baseline)	NE	NE	NE
Cardiovascular diseases (yes) (baseline)	0.46	0.04–5.34	0.538
Gastrointestinal disorders (yes) (baseline)	1.38	0.27–7.15	0.699
Kidney diseases (yes) (baseline)	1.19	0.86–16.35	0.899
Thyroid disorders (yes) (baseline)	2.26	0.51–10.08	0.285
Cataract (yes) (baseline)	1.67	0.37–7.55	0.507
Other medical diseases (yes) (baseline)	0.58	0.7–5.01	0.618
Sars-CoV 2 history (yes) (follow-up)	0.78	0.20–3.03	0.725
Covid-19 history (yes) (follow-up)	0.53	0.13–2.20	0.383
Sars-CoV 2 vaccine (yes) (follow-up)	NE	NE	NE
At least one systemic disease (yes) (baseline)	0.39	0.73–2.07	0.269
Number of systemic diseases (each unit increase) (baseline)	1.12	0.86–1.45	0.394
Smoking (baseline)			
Non-smokers	Ref	Ref	Ref
Current smokers	4.48	1.05–19.10	**0.043**
Sleep duration (baseline)			
< 7 h	1.97	0.56–6.95	0.290
7–8 h	Ref	Ref	Ref
> 7 h	50.91	1.46–1770.05	**0.030**
Regular moderate (≥ 3 times/week ≥ 20 min) physical activity (baseline)	1.35	0.23–7.94	0.741
Stress (baseline)			
Absolutely nothing	Ref	Ref	Ref
Mild/Moderate	0.64	0.13–3.14	0.581
High	0.97	0.11–8.77	0.979
Coffee consumption (yes) (baseline)	1.73	0.31–9.57	0.529
Alcohol consumption (baseline)			
Never	Ref	Ref	Ref
Less than 2 times/week	0.24	0.60–0.94	**0.040**
Almost everyday	0.46	0.07–3.17	0.432
1/day	0.24	0.25–2.32	0.217

(Continues)

TABLE A1 | (Continued)

Variable	OR	95% CI	p
2 or more times/day	NE	NE	NE
Alcohol consumption (yes) (baseline)			
Never	Ref	Ref	Ref
At least sometimes	0.26	0.78–0.88	**0.030**
Bisphosphonates (yes) (baseline)	0.04	0.01–0.12	**0.000**
Corticosteroids (yes) (baseline)	0.84	0.04–19.18	0.911
NSAIDs (yes) (baseline)	0.50	0.03–9.98	0.652
Antiplatelet (yes) (baseline)	2.14	0.20–22.60	0.528
Anticoagulant (yes) (baseline)	2.13	0.20–22.60	0.528
Hypolipidemic agent (yes) (baseline)	2.33	0.56–9.70	0.244
Antidepressant (yes) (baseline)	2.21	0.43–11.38	0.341
Proton pump inhibitor (yes) (baseline)	1.91	0.13–27.02	0.633
Vitamin D (yes) (baseline)	0.04	0.02–0.12	**0.000**
Calcium (yes) (baseline)	2.82	0.45–17.82	0.446
Thyroid drug (yes) (baseline)	2.49	0.55–11.28	0.236
Immunosuppressant (yes) (baseline)	0.41	0.01–0.12	**0.000**
Insulin (yes) (baseline)	3.02	0.22–40.70	0.406
Oral hypoglycemic agent (yes) (baseline)	1.31	0.18–9.57	0.790
Other anti-diabetic drug (yes) (baseline)	NE	NE	NE
Beta-blockers (yes) (baseline)	1.48	0.13–16.75	0.750
Diuretics (yes) (baseline)	0.92	0.09–9.36	0.944
ACE inhibitors (yes) (baseline)	1.56	0.21–11.65	0.666
Other antihypertensive drugs (yes) (baseline)	NE	NE	NE
Other drugs (yes) (baseline)	1.00	0.24–4.11	0.996
Number of medications (each unit increase) (baseline)	1.18	0.86–1.61	0.312
Supplements (yes) (baseline)	1.58	0.34–7.33	0.561
Periodontal status (AAP) (baseline)			
No/Mild periodontitis	Ref	Ref	Ref
Moderate/severe periodontitis	0.80	1.78–3.60	0.771
Edentulous	0.58	0.04–8.33	0.686
Periodontal status (2017 WWP) (baseline)			
No periodontitis or SI-III periodontitis	Ref	Ref	Ref
Stage 4 periodontitis	9.08	2.58–31.92	**0.001**
Edentulous	1.42	0.19–10.69	0.736
Number of remaining teeth (each unit increase) (baseline)	0.91	0.83–0.99	**0.044**
Number of remaining teeth (≥16) (baseline)	9.68	2.56–36.57	**0.001**
Number of dental implants (each unit increase) (baseline)	1.24	0.95–1.63	0.120
Number of dental implants (≥4) (baseline)	4.14	0.63–27.06	0.139
History of orthodontic treatment (yes) (baseline)	1.20	0.30–4.75	0.795
Toothbrushing frequency (baseline)			
Not everyday	NE	NE	NE
1 time/day	1.68	0.22–12.89	0.615
2 times/day	1.24	0.30–5.09	0.766
3 or more times/day	Ref	Ref	Ref
Electric toothbrush (yes) (baseline)	4.68	1.00–21.96	**0.050**
Interproximal flossing/Brushing on implants (at least on some implants) (baseline)	4.59	0.31–67.48	0.267
Bruxism signs (yes) (baseline)	1.19	0.29–4.80	0.809
Bruxism symptoms (yes) (baseline)	2.03	0.46–8.92	0.346
Dry mouth (yes) (baseline)	2.50	0.66–9.51	0.177
Number of maintenances between baseline and follow-up (each unit increase) (follow up)	1.15	0.70–1.87	0.584
Regular maintenance between baseline and follow-up (≥1 per year) (follow up)	0.75	0.11–5.12	0.768
FMPS, excluding implants (each unit increase) (follow-up)	1.01	0.95–1.06	0.810
FMBS, excluding implants (each unit increase) (follow-up)	1.00	0.94–1.06	0.997
Number PPD ≥4 mm, excluding implants (each unit increase) (follow-up)	1.00	0.95–1.06	0.885
Number PPD ≥5 mm, excluding implants (each unit increase) (follow-up)	1.04	0.95–1.13	0.403
Number PPD ≥6 mm, excluding implants (each unit increase) (follow-up)	1.10	0.96–1.26	0.181
Number FI ≥2 (each unit increase) (follow-up)	1.16	0.75–1.77	0.509
Periodontal bone loss/age ratio (each unit increase) (follow-up)	12.58	0.94–167.61	**0.055**
Allergies (yes) (baseline)	2.32	0.52–10.26	0.268
Chemotherapy (yes) (baseline)	5.58	0.14–229.47	0.365
Radiotherapy (yes) (baseline)	NE	NE	NE

Note: $p < 0.10$ are reported in bold.
Abbreviations: CI, confidence interval; FI, furcation involvement; FMBS, full mouth bleeding score; FMPS, full mouth plaque score; NE, not estimable; OR, odds ratio; PPD, probing pocket depth; Ref, reference category.
*Self-reported history or medication.

(Continues)

TABLE A2 | Implant-level risk/protective indicators associated with incidence of peri-implantitis during follow-up: Multilevel simple logistic regression analysis.

Variable	OR	95% CI	*p*
Jaw (maxilla) (baseline)	1.47	0.53–4.06	0.454
Position (baseline)			
Anterior (canine-canine)	Ref	Ref	Ref
Posterior	0.61	0.17–2.23	0.434
Side (left) (baseline)	1.70	0.68–4.26	0.261
Replaced tooth (baseline)			
Molar	Ref	Ref	Ref
Premolar	1.06	0.37–3.00	0.914
Canine	NE	NE	NE
Incisor	5.48	1.07–28.04	**0.041**
Mouth zone (baseline)			
Posterior maxilla	Ref	Ref	Ref
Anterior maxilla	1.04	0.18–6.13	0.963
Posterior mandible	1.27	0.41–3.87	0.679
Anterior mandible	4.25	0.66–27.54	0.129
Implant brand (baseline)			
Straumann	Ref	Ref	Ref
Nobel biocare	2.56	0.43–15.27	0.304
Astratech	2.11	0.47–9,53	0.332
Other	1.10	0.26–4.73	0.894
Implant collar (baseline)			
0 mm	Ref	Ref	Ref
≤ 1.5 mm	0.61	0.50–7.36	0.693
> 1.5 mm	0.68	0.19–2.45	0.560
Implant length (each mm increase) (baseline)	0.94	0.68–1.30	0.690
Implant diameter (each mm increase) (baseline)	0.35	0.08–1.43	0.143
At least one adjacent tooth (yes) (baseline)	0.30	0.11–0.82	**0.019**
Reason of tooth loss (baseline)			
Caries	Ref	Ref	Ref
Periodontitis	1.19	0.31–4.57	0.803
Trauma	NE	NE	NE
Agenesia	NE	NE	NE
Other reason/Unknown	NE	NE	NE
Keratinized tissue width (KTW) (baseline)			
KTW = 0 mm	Ref	Ref	Ref
KTW > 0 mm & < =2 mm	0.38	0.10–1.43	0.153
KTW > 2 mm	1.02	0.25–4.12	0.983
Adherent mucosa (yes) (baseline)	1.22	0.42–3.58	0.715
Tissue thickness (mm) (baseline)	0.79	0.38–1.67	0.536
Peri-implant phenotype (thick) (baseline)	0.83	0.30–2.28	0.711
Mucosal margin mobility (yes) (baseline)	0.60	0.20–1.83	0.370
Type of restoration (baseline)			
Single crown	Ref	Ref	Ref
Bridge	3.06	0.83–11.27	**0.093**
Overdenture	NE	NE	NE
Full-arch fixed restoration	12.48	1.13–137.67	**0.039**
Restoration retention (baseline)			
Screw-retained	Ref	Ref	Ref
Cemented	0.68	0.21–2.19	0.520
Locator	NE	NE	NE
Bar	NE	NE	NE
Prosthesis gap (yes) (baseline)	1.31	0.46–3.71	0.607
Prosthesis step (yes) (baseline)	2.25	0.80–6.35	0.126
Emergence angle (Highest) (each degree increase) (baseline)	1.01	0.98–1.03	0.707
Emergence angle (Highest) (> 30°) (baseline)	1.74	0.58–5.24	0.322
Emergence Profile (Worst) (baseline)			
Concave	NE	NE	NE
Straight	Ref	Ref	Ref
Convex	0.67	0.23–1.92	0.458
Mesial cantilever (yes) (baseline)	1.23	0.38–3.94	0.726
Distal cantilever (yes) (baseline)	0.52	0.12–2.24	0.377
Prosthesis mobility (yes) (baseline)	0.52	0.05–5.93	0.601
Abutment (yes) (baseline)	2.51	0.86–7.32	**0.093**
Platform switching (yes) (baseline)	1.13	0.31–4.09	0.854
Crown dimension (each mm increase) (baseline)	0.97	0.77–1.23	0.805
Crown to implant ratio (each mm increase) (baseline)	0.65	0.09–4.72	0.675
Residual cement visible on radiograph (yes) (baseline)	NE	NE	NE
Clinical signs of occlusal overloading (yes) (baseline)	1.16	0.37–3.59	0.799
Prosthetic design allowing access to hygiene (yes) (baseline)	0.21	0.059–0.73	**0.014**

(Continues)

TABLE A2 | (Continued)

Variable	OR	95% CI	*p*
Restoration margin location (follow-up)			
Sub-marginal	Ref	Ref	Ref
Supra-marginal	0.61	0.063–5.81	0.664
Juxta-marginal	2.87	0.87–9.48	**0.085**
Vestibular-lingual position (baseline)			
Correct	Ref	Ref	Ref
Too vestibular	4.12	0.87–19.49	**0.074**
Too lingual	NE	NE	NE
Plaque (baseline)			
0–5 sites/implant	Ref	Ref	Ref
6 sites/implant	6.04	1.64–22.18	**0.007**
Peri-implant health status (baseline)			
Peri-implant health	Ref	Ref	Ref
Peri-implant mucositis	1.76	0.16–19.82	0.646
Pre-peri-implantitis	1.08	0.94–12.58	0.946
Peri-implantitis	2.34	0.20–27.13	0.498

Note: $p < 0.10$ are reported in bold.
Abbreviations: CI, confidence interval; OR, odds ratio; Ref, reference category.

Appendix 2: STUDY #2

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ORIGINAL ARTICLE OPEN ACCESS

Accuracy of Clinical Parameters in Predicting/Diagnosing Peri-Implant Bone Loss

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Keywords: clinical attachment levels | cohort studies | dental implants | diagnosis | gingival recession | peri-implant diseases | sensitivity and specificity

ABSTRACT

Aim: To determine whether clinical parameters can serve as (i) predictive tools (before occurrence) and (ii) diagnostic tools (after occurrence) of peri-implant bone loss.

Materials and Methods: A representative cohort of 72 patients with 298 implants was evaluated at baseline and after a mean follow-up period of 3.9 years. Peri-implant bone loss > 1 mm between the two examinations represented the reference standard. The accuracy of the following clinical parameters in predicting (at baseline) or diagnosing (at follow-up) peri-implant bone loss was assessed: presence of bleeding (BoP) or suppuration (SoP) on probing, visual signs of redness or swelling, BoP extent (number of sites with BoP) and severity (modified Bleeding Index—mBI), probing pocket depth (PPD) at various cut-offs, peri-implant soft-tissue dehiscence (PISTD) and changes in PPD/PISTD over time. Predictive/diagnostic performance was evaluated using mixed model logistic regression analyses and reporting sensitivity, specificity, positive/negative predictive values and area under the curve (AUC) values.

Results: Bone loss > 1 mm was observed in 9.4% of implants and was frequently preceded by BoP (sensitivity = 96.4%; specificity = 7.4%). At follow-up, bone loss was always associated with the concomitant presence of BoP (sensitivity = 100.0%; specificity = 14.4%).

In predicting the future occurrence of peri-implant bone loss, high sensitivity (94.4%) was also noted for visual redness at baseline, although its specificity was low (25.9%). Conversely, high specificity but low sensitivity was observed for BoP at 6 sites (sensitivity = 25.0%; specificity = 88.1%) and SoP (sensitivity = 14.3%; specificity = 91.5%).

For diagnosing recent peri-implant bone loss, high specificity was noted for SoP (100.0%), profuse bleeding (91.9%), BoP at 6 sites (87.0%), PPD ≥ 6 mm (81.9%), changes in PPD (95.9%) and changes in PISTD (91.5%). However, all these parameters showed limited sensitivity. The best diagnostic accuracy was achieved using a combined criterion of site-specific PPD or PISTD increases > 1 mm over time (sensitivity = 82.1%; specificity = 70.0%; AUC = 0.76).

Conclusions: Clinical signs considered indicative of peri-implant mucositis (presence of BoP, visual redness) usually precede peri-implant bone loss. Implants with a recent history of bone loss always present with concomitant BoP. However, the predictive/diagnostic value of detecting one or two spots of BoP is limited by its low specificity. Implants with BoP at six sites or SoP are more likely to exhibit bone loss over time. During follow-up, BoP at six sites, profuse bleeding, SoP, PPD ≥ 6 mm, or increases in PPD/PISTD over time have high specificity for diagnosis of recent peri-implant bone loss.

Mario Romandini and Cristina Lima contributed equally to this study.

1 | Introduction

Peri-implantitis is highly prevalent (Derks et al. 2016a; Romandini et al. 2019; Romandini, Lima, et al. 2021b), rapidly progressing (Derks et al. 2016b) and challenging to treat (Baima et al. 2022; Derks et al. 2022; Regidor et al. 2023; Romandini et al. 2022, 2024; Monje and Nart 2024). Given these premises, primary prevention and early diagnosis are crucial aspects of its management. Primary prevention focuses on treating peri-implant mucositis as its precursor and addressing modifiable risk factors (Verket et al. 2023; Carra et al. 2023; Carvalho et al. 2023; Bencze et al. 2024; Isler et al. 2024; Annunziata et al. 2024). Early diagnosis of peri-implantitis relies on identifying radiographically assessed bone loss in implants exhibiting inflammation of the peri-implant mucosa (Berglundh et al. 2018).

Based on this currently accepted case definition (Berglundh et al. 2018), peri-implantitis can only be diagnosed once a significant amount of bone loss has already occurred. However, identifying clinical parameters that could anticipate bone loss before it is radiographically detectable (i.e., predictive tools) would be highly valuable. It remains especially unclear whether peri-implant mucositis is a necessary precursor to peri-implant bone loss. Although there is evidence indicating the conversion of peri-implant mucositis to peri-implantitis among patients without maintenance (Costa et al. 2012), the lack of a control group with peri-implant health at baseline in this study precludes definite conclusions.

Since the current peri-implantitis case definition is based on bone loss assessment, there is also a need for diagnostic tools to identify implants where bone loss has already occurred, thus justifying radiographic exposure (Berglundh et al. 2021; Romandini, Berglundh, et al. 2021). Clinical parameters, due to their non-invasive nature, ease of use and cost-effectiveness, may be ideal. However, studies investigating whether more complex assessments of peri-implant inflammation beyond the mere presence of BoP (e.g., BoP extent and severity, mucosal redness and swelling) and changes in PPD/peri-implant soft tissue dehiscence (PISTD—i.e., recession) over time may serve as effective diagnostic tools are currently lacking. Notably, longitudinal changes in PPD are already included in the current peri-implantitis case definition (Berglundh et al. 2018), despite uncertainty regarding their diagnostic accuracy, given that bone loss may also manifest through the occurrence of a PISTD (Romandini, Pedrinaci, et al. 2021; Romandini, Lima, et al. 2021a; Monje et al. 2018).

Therefore, the aim of this prospective cohort study was to determine whether clinical parameters could serve as (i) predictive tools (before occurrence) and (ii) diagnostic tools (after occurrence) of peri-implant bone loss.

2 | Materials and Methods

This manuscript adheres to the STAndards for Reporting of Diagnostic accuracy studies (STARD) guidelines (Cohen et al. 2016). The study was conducted in accordance with the Declaration of Helsinki for human studies, and its research protocol was ethically approved (19/182-E; 22/385-EC_P) by the CEIm Hospital Clínico San Carlos, Madrid, Spain.

2.1 | Population (PIDFU Study)

The Peri-Implant Diseases Follow-Up (PIDFU) study is an ongoing prospective cohort study based on repeated follow-ups over time of a previously reported university-representative population (Romandini, Lima, et al. 2021a, 2021b; Romandini, Pedrinaci, et al. 2021). During 2019, 99 patients with 458 implants, identified through a stratified multistage sampling process among patients who received dental implants from 2000 to 2017 in the Department of Periodontology at Complutense University of Madrid, were initially examined both clinically and radiographically. This examination served as the baseline for this prospective cohort study (Figure 1). In 2023, the same patients were invited to participate in this first follow-up examination through a minimum of five different telephonic attempts made on different days.

2.2 | Predictive Clinical Parameters

In the baseline study, the following clinical parameters were recorded using a manual UNC-15 periodontal probe (PCP15; Hu-Friedy) at 6 sites per implant by two previously calibrated examiners: BoP and SoP (both within 30s), PPD and PISTD (Sanz-Martin et al. 2020). For the present analysis, these parameters were synthesized at the implant level as: presence of BoP (i.e., at least one site with BoP), BoP extent (i.e., number

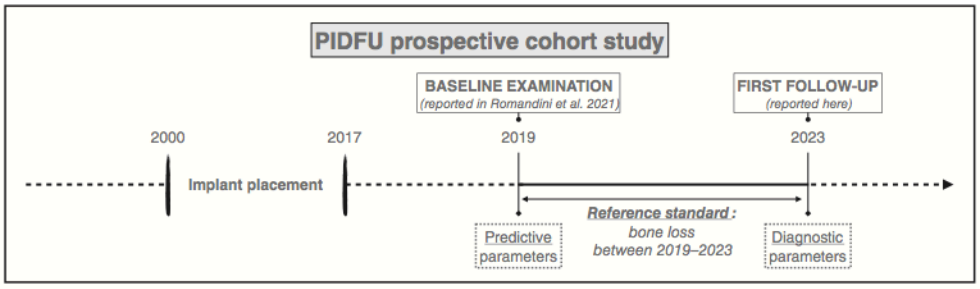

FIGURE 1 | PIDFU prospective cohort study design.

TABLE 1 | General characteristics of the study population and implants.

Patients ($N=72$)	
Age (baseline) (years), mean (SD)	62.6 (7.8)
Gender, *N* (%)	
Male	27 (37.5)
Female	45 (62.5)
Smoking status (baseline), *N* (%)	
Non-smokers	28 (38.9)
Former smokers	30 (41.7)
Current smokers	14 (19.4)
BMI (baseline) (kg/m^2), mean (SD)	25.8 (3.8)
Diabetes status (baseline), *N* (%)	
No diabetes	61 (84.7)
Diabetes	11 (15.3)
Periodontal status (EFP/AAP) (baseline), *N* (%)	
No periodontitis	4 (5.6)
Stage 1	7 (9.7)
Stage 2	14 (19.5)
Stage 3	24 (33.3)
Stage 4	17 (23.6)
Edentulous	6 (8.3)
Implants ($N=298$)	
Jaw, *N* (%)	
Maxilla	161 (54.0)
Mandible	137 (46.0)
Position, *N* (%)	
Anterior (canine-canine)	49 (16.4)
Posterior	249 (83.6)
Type of prosthesis (baseline), *N* (%)	
Single crown	98 (32.9)
Bridge	174 (58.4)
Overdenture	7 (2.3)
Full-arch fixed restoration	19 (6.4)
Prosthesis retention (baseline), *N* (%)	
Cemented	154 (51.7)
Screw-retained	137 (45.9)
Locator	2 (0.7)
Bar	5 (1.7)
Implant brand, *N* (%)	
Straumann	164 (55.2)
Nobel biocare	36 (12.1)
AstraTech	40 (13.5)
Other	57 (19.2)
Implant length (mm), mean (SD)	9.9 (1.7)
Implant diameter (mm), mean (SD)	4.1 (0.4)
Peri-implant status (baseline), *N* (%)	
Peri-implant health	21 (7.1)
Peri-implant mucositis	105 (35.2)
Pre-peri-implantitis	95 (31.9)
Peri-implantitis	77 (25.8)

Abbreviations: *N*, number; SD, standard deviation.

of sites with BoP: 0–1, 2–5, 6), presence of SoP (i.e., at least one site with SoP), PPD (deepest value), PPD ≥ 5 mm and PPD ≥ 6 mm (i.e., at least one site with PPD ≥ 5 mm or ≥ 6 mm, respectively) and presence of PISTD (i.e., PISTD > 0 mm). Additionally, the same examiners assessed each implant for visual signs of redness and swelling (categorised as: not at all vs. mild/moderate/severe).

2.3 | Diagnostic Clinical Parameters

At the follow-up examination, the same clinical parameters were recorded by one of the two previously calibrated clinical examiners (CL), and the same implant-level categorisations were applied. Additionally, the modified Bleeding Index (mBI) was assessed by further categorising the presence of BoP as punctiform, linear, or profuse. Changes in PPD and PISTD during follow-up were also computed, both as increases in their deepest implant-level value and as the greatest site-specific increase per implant. PPD and PISTD changes were analysed both as continuous variables and dichotomised with > 1 mm as the threshold.

2.4 | Reference Standard: Peri-Implant Bone Loss Occurrence

The diagnostic reference standard of the study was the occurrence of peri-implant bone loss > 1 mm between the two examinations. New standardised periapical radiographs of the included implants were obtained from the Radiology Department using the parallel technique. The marginal bone level at the follow-up examination was assessed by the same calibrated radiographic assessor from the baseline study (CL), applying the same measurement protocol described in the original publication (Romandini, Lima, et al. 2021b). Briefly, the radiographic bone level was measured at the mesial and distal aspects of each implant as the distance in millimetres between the intra-osseous portion border of the implant (excluding any polished collar) and the first clearly visible contact between the implant surface and the bone. A software program (Autocad 2016 TM, AutoDesk Inc., San Rafael, CA, USA) was used, and the inter-thread pitch distance reported by the manufacturer or the length of the implant was considered for

TABLE 2 | Clinical parameters and incidence/history of peri-implant bone loss.

Baseline predictive parameters	Overall ($n=298$)	Incidence of peri-implant bone loss ($n=28$)
BoP (baseline), *N* (%)		
No	21 (7.0%)	1 (3.6%)
Yes	277 (93.0%)	27 (96.4%)
BoP extent (baseline), *N* (%)		
0–1 site	59 (19.8%)	2 (7.1%)
2–3–4–5 sites	200 (67.1%)	19 (67.9%)
6 sites	39 (13.1%)	7 (25.0%)
SoP (baseline), *N* (%)		
No	271 (90.9%)	24 (85.7%)
Yes	27 (9.1%)	4 (14.3%)
PPD ≥ 5 mm (baseline), *N* (%)		
No	121 (40.6%)	12 (42.9%)
Yes	177 (59.4%)	16 (57.1%)
PPD ≥ 6 mm (baseline), *N* (%)		
No	203 (68.1%)	19 (67.9%)
Yes	95 (31.9%)	9 (32.1%)
PISTD (baseline), *N* (%)		
No	220 (73.8%)	20 (71.4%)
Yes	78 (26.2%)	8 (28.6%)
Redness (baseline), *N* (%)		
No	71 (23.8%)	1 (3.6%)
Yes	227 (76.2%)	27 (96.4%)
Swelling (baseline), *N* (%)		
No	130 (43.6%)	8 (28.6%)
Yes	168 (56.4%)	20 (71.4%)
Follow-up diagnostic parameters	**Overall ($n=298$)**	**History of peri-implant bone loss ($n=28$)**
BoP (follow-up), *N* (%)		
No	39 (13.1%)	0 (0.0%)
Yes	259 (86.9%)	28 (100.0%)
BoP extent (follow-up), *N* (%)		
0–1 site	93 (31.2%)	3 (10.7%)
2–3–4–5 sites	158 (53.0%)	13 (46.4%)
6 sites	47 (15.8%)	12 (42.9%)
SoP (follow-up), *N* (%)		
No	295 (99.0%)	25 (89.3%)
Yes	3 (1.0%)	3 (10.7%)
PPD ≥ 5 mm (follow-up), *N* (%)		
No	158 (53.0%)	7 (25.0%)

(Continues)

TABLE 2 | (Continued)

Follow-up diagnostic parameters	Overall ($n = 298$)	History of peri-implant bone loss ($n = 28$)
Yes	140 (47.0%)	21 (75.0%)
PPD ≥ 6 mm (follow-up), *N* (%)		
No	232 (77.9%)	11 (39.3%)
Yes	66 (22.1%)	17 (60.7%)
PISTD (follow-up), *N* (%)		
No	174 (58.4%)	17 (60.7%)
Yes	124 (41.6%)	11 (39.3%)
mBI (follow-up), *N* (%)		
No BoP	39 (13.1%)	0 (0.0%)
Punctiform	105 (35.4%)	8 (28.6%)
Line	121 (40.7%)	9 (32.1%)
Profuse	32 (10.8%)	11 (39.3%)
Deepest PPD increase > 1 mm (follow-up), *N* (%)		
No	279 (93.69%)	20 (71.4%)
Yes	19 (6.4%)	8 (28.6%)
Site-specific PPD increase > 1 mm (follow-up), *N* (%)		
No	229 (76.9%)	10 (35.7%)
Yes	69 (23.1%)	18 (64.3%)
Highest PISTD increase > 1 (follow-up), *N* (%)		
No	269 (90.3%)	22 (78.6%)
Yes	29 (9.7%)	6 (21.4%)
Site-specific PISTD increase > 1 mm (follow-up), *N* (%)		
No	255 (85.6%)	19 (67.9%)
Yes	43 (14.4%)	9 (32.1%)

Abbreviations: BoP, bleeding on probing; mBI, modified bleeding index; *N*, number; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; SoP, suppuration on probing.

calibration. The largest value between the mesial and distal measurements was recorded as the bone level for that implant. Bone loss was calculated as the difference in bone levels between the two examinations. The radiographic assessor previously demonstrated an excellent intra-rater agreement after re-measuring 50 randomly selected radiographs (ICC = 0.98; 95% confidence interval [CI] 0.96–0.99; $p < 0.001$).

2.5 | Data Analysis

All statistical analyses were performed using STATA SE version 18.0 software (StataCorp LP), with statistical significance a priori set at $p < 0.05$. The characteristics of the study population and implants were summarised. Incidence/history of peri-implant bone loss was also described according to the different predictive/diagnostic clinical parameters.

Baseline clinical (predictive) parameters associated with the incidence of peri-implant bone loss were studied using multilevel (mixed-effects) logistic regression analyses, accounting for the clustering of multiple implants within the same patients. Sensitivity, specificity, area under the curve (AUC), positive and negative predictive values (PPV/NPV), together with their 95% CIs, were calculated for dichotomic parameters.

The same methodology was applied to test the accuracy of clinical (diagnostic) parameters assessed at follow-up to identify recent occurrence of peri-implant bone loss. Finally, a combined multiple regression multilevel model including all significant predictive/diagnostic parameters was presented, after excluding collinear and redundant variables.

3 | Results

From an initial cohort of 99 patients, 14 declined follow-up participation, three relocated, two missed their scheduled appointments, one passed away and six were unreachable

despite multiple contact attempts. Consequently, 73 patients with 322 implants were clinically evaluated after a mean follow-up of 3.9 years (SD = 0.3; range: 3.0–4.6 years). During this period, 14 implants were lost in nine patients, and 10 implants had missing or unreadable follow-up radiographs. Thus, the final analysis included 72 patients and 298 implants. The general characteristics of these patients, detailed in Table 1, were consistent with the baseline population (Romandini, Lima, et al. 2021b). Most participants were women (62.5%), had stage III and IV periodontitis (56.9%), were nonsmokers (80.6%) and had a mean age of 62.6 years at baseline. A majority of the implants were located in the maxilla (54.0%) and were part of implant-supported bridge restorations (58.8%). During follow-up, peri-implant bone loss > 1 mm occurred in 28 implants (9.4%) (Table 2).

3.1 | Interventions During Follow-Up

Most of the included implants (179/60.1%) did not receive any treatment during the follow-up period. Non-surgical treatment only was performed in 79 (26.5%) implants, while 18 (6.0%) underwent surgical treatment. No reliable information on previous interventions was available for the remaining 22 implants (7.4%). 12.5% of patients were under regular maintenance since they had an average of more than one SPIC visit per year.

3.2 | Clinical (Predictive) Parameters at Baseline and Incidence of Peri-Implant Bone Loss

Except in one case, bone loss during follow-up was only observed in implants with BoP at baseline (96.4%) (Table 2). Incident bone loss was more common around implants displaying SoP, redness and swelling at baseline.

In multi-level regression analyses, only baseline redness was significantly associated with the incidence of bone loss (OR = 13.81), while BoP extent showed a non-significant trend (6 sites: OR = 5.27) (Table 3).

BoP at ≥1 site (96.4%) and ≥2 sites (92.9%), as well as redness (96.4%) at baseline, exhibited the highest sensitivity for predicting peri-implant bone loss occurrence but low specificity (7.4%–25.9%) (Table 4). Specificity was high for BoP at 6 sites (88.1%) and the presence of SoP (91.5%); however, both exhibited low sensitivity (14.3%–25.0%). AUC values were generally low, with the highest observed for redness (0.61). PPVs indicated that 17.9% of implants with BoP at 6 sites and 14.8% with SoP at baseline exhibited bone loss during follow-up, whereas NPVs showed that 98.6% of implants without redness did not exhibit future bone loss.

3.3 | Clinical (Diagnostic) Parameters at Follow-Up and History of Peri-Implant Bone Loss

At follow-up, peri-implant bone loss was always associated with the concomitant presence of at least one BoP site (Table 2). Most bone loss cases (92.9%) exhibited BoP at ≥2 sites. SoP was only observed in implants with recent peri-implant bone loss. History of bone loss was more frequent in implants showing deep PPD (≥5 mm and ≥6 mm) and profuse bleeding at follow-up. Peri-implant bone loss was more commonly detected in implants showing increases in PPD or PISTD > 1 mm between the examinations.

TABLE 3 | Clinical predictive parameters at baseline and incidence of peri-implant bone loss over time: Multilevel logistic regression analysis.

	Simple regression		
Variable	**OR**	**95% CI**	***p*-value**
BoP (baseline), yes	1.62	0.15–16.95	0.689
BoP extent (baseline)			
0–1 site	Ref	Ref	Ref
2–3–4–5 sites	3.44	0.65–18.35	0.148
6 sites	5.27	0.75–37.05	0.095
SoP (baseline), yes	1.12	0.23–5.43	0.884
PPD (baseline)	1.00	0.70–1.45	0.981
PPD ≥ 5 mm (baseline), yes	0.71	0.26–1.92	0.498
PPD ≥ 6 mm (baseline), yes	0.92	0.31–2.76	0.886
PISTD > 0 mm (baseline), yes	1.32	0.42–4.09	0.633
Redness (baseline), yes	13.81	1.39–137-31	**0.025**
Swelling (baseline), yes	2.02	0.68–6.04	0.208

Note: Bold indicates statistical significance ($p < 0.05$).
Abbreviations: BoP, bleeding on probing; CI, confidence interval; OR, odds ratio; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; Ref, reference category; SoP, suppuration on probing.

Multi-level regression analyses identified several follow-up clinical parameters associated with history of recent peri-implant bone loss (Table 5): BoP extent (6 sites: OR = 17.6), deepest PPD (per mm increase: OR = 1.23; PPD ≥ 5 mm: OR = 3.77; PPD ≥ 6 mm: OR = 8.16), mBI (profuse: OR = 10.37), deepest PPD change (per mm: OR = 2.21) and increase > 1 mm (OR = 10.08), site-specific PPD change (per mm: OR = 2.93) and increase > 1 mm (OR = 12.05) and site-specific PISTD increase > 1 mm (OR = 3.44).

BoP at ≥1 site showed the highest sensitivity for history of recent peri-implant bone loss (100.0%), followed by BoP at ≥2 sites (89.3%) and PPD ≥ 5 mm (75.0%) (Table 6). Their specificity was however limited (14.4%–55.9%). The highest specificity was observed for SoP presence (100.0%), deepest PPD increase > 1 mm (95.9%), profuse bleeding (91.9%), PISTD increases > 1 mm (deepest: 91.5%; site-specific: 87.4%) and BoP at 6 sites (87.0%). The same parameters showed however low sensitivity (10.7%–42.9%). The highest AUC values were noted for site-specific PPD increase > 1 mm (0.73) and PPD ≥ 6 mm at follow-up (0.71). All cases with SoP had a history of recent bone loss (PPV = 100.0%), as well as 42.1% of cases with an increase in the deepest PPD. The absence of BoP corresponded to the absence of bone loss > 1 mm during follow-up (NPV = 100.0%).

TABLE 4 | Accuracy of different clinical parameters at baseline in predicting peri-implant bone loss occurrence over time.

	Peri-implant bone loss occurrence								
Incidence% (95% CI)									9.4 (6.3–13.3)
	Baseline diagnostic parameters								
	BoP (baseline) ≥1 site	**BoP (baseline) ≥2 sites**	**BoP (baseline) = 6 sites**	**SoP+ (baseline) ≥1 site**	**PPD (baseline) ≥5 mm**	**PPD (baseline) ≥6 mm**	**PISTD (baseline) >0 mm**	**Redness (baseline), yes**	**Swelling (baseline), yes**
Sensitivity% (95% CI)	96.4 (81.7–99.9)	92.9 (76.5–99.1)	25.0 (10.7–44.9)	14.3 (4.0–32.7)	57.1 (37.2–75.5)	32.1 (15.9–52.4)	28.6 (13.2–48.7)	96.4 (81.7–99.9)	71.4 (51.3–89.8)
Specificity% (95% CI)	7.4 (4.6–11.2)	21.1 (16.4–26.5)	88.1 (83.7–91.8)	91.5 (87.5–94.5)	40.4 (34.5–46.5)	68.1 (62.2–73.7)	74.1 (68.4–79.2)	25.9 (20.8–31.6)	45.2 (39.1–51.3)
AUC (95% CI)	0.52 (0.48–0.56)	0.57 (0.52–0.62)	0.57 (0.48–0.65)	0.53 (0.46–0.60)	0.49 (0.39–0.59)	0.50 (0.41–0.59)	0.51 (0.42–0.60)	0.61 (0.57–0.66)	0.58 (0.49–0.67)
PPV% (95% CI)	9.7 (6.5–13.9)	10.9 (7.2–15.5)	17.9 (7.5–33.5)	14.8 (4.2–33.7)	9.0 (5.3–14.3)	9.5 (4.4–17.2)	10.3 (4.5–19.2)	11.9 (8.0–16.8)	11.9 (7.4–17.8)
NPV% (95% CI)	95.2 (76.2–99.9)	96.6 (88.3–99.6)	91.9 (87.9–94.9)	91.1 (87.1–94.2)	90.1 (83.3–94.8)	90.6 (85.8–94.3)	90.9 (86.3–94.4)	98.6 (92.4–100.0)	93.8 (88.2–97.3)

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

TABLE 5 | Clinical diagnostic parameters at follow-up and recent history of peri-implant bone loss: Multilevel logistic regression analyses.

	Simple regression		
Variable	**OR**	**95% CI**	***p*-value**
BoP (follow-up), yes	NE	NE	NE
BoP extent (follow-up)			
0–1 site	Ref	Ref	Ref
2–3–4–5 sites	3.73	0.78–17.76	0.098
6 sites	17.6	3.25–115.06	**0.001**
SoP (follow-up), yes	NE	NE	NE
Deepest PPD (follow-up), for each mm increase	1.23	1.56–3.19	**0.000**
Deepest PPD ≥ 5 mm (follow-up), yes	3.77	1.30–10.87	**0.014**
Deepest PPD ≥ 6 mm (follow-up), yes	8.16	2.96–22.51	**0.000**
PISTD > 0 mm (follow-up), yes	0.76	0.27–2.14	0.599
mBI (follow-up)			
No BoP	NE	NE	NE
Punctiform	Ref	Ref	Ref
Line	1.03	0.31–3.35	0.967
Profuse	8.99	2.24–36.04	**0.002**
Profuse mBI mm (follow-up), yes	10.37	3.22–33.43	**0.000**
Deepest PPD change (follow-up), for each mm	2.21	1.52–3.21	**0.000**
Deepest PPD increase > 1 mm (follow-up), yes	10.08	2.73–37.29	**0.001**
Site-specific PPD change (follow-up), for each mm increase	2.93	1.79–4.80	**0.000**
Site-specific PPD increase > 1 mm (follow-up), yes	12.05	3.69–39.33	**0.000**
Deepest PISTD change (follow-up), for each mm	1.08	0.66–175	0.767
Deepest PISTD increase > 1 mm (follow-up), yes	2.61	0.70–9.75	0.154
Site-specific PISTD change (follow-up), for each mm increase	1.24	0.76–2.02	0.391
Site-specific PISTD increase > 1 mm (follow-up), yes	3.44	1.02–11.60	**0.047**

Note: Bold indicates statistical significance ($p < 0.05$).

Abbreviations: BoP, bleeding on probing; CI, confidence interval; mBI, modified bleeding index; NE, not estimable; OR, odds ratio; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; Ref, reference category; SoP, suppuration on probing.

A combined criterion of site-specific PPD or PISTD increase > 1 mm yielded the best diagnostic accuracy for detecting recent peri-implant bone loss (sensitivity: 82.1%; specificity: 70.0%; AUC = 0.76). Using this criterion, 97.4% of implants with no increase in either PPD or PISTD > 1 mm did not experience recent bone loss (NPV = 97.4%). Conversely, 22.1% (PPV) of implants showing at least one of these increases had recent bone loss.

3.4 | Combined Predictive/Diagnostic Model

A combined predictive/diagnostic model for detecting incidence/history of peri-implant bone loss is presented in Table 7. Statistically significant parameters included BoP extent at baseline (2–5 sites: OR = 9.64), redness at baseline (OR = 53.63), PPD ≥ 6 mm at follow-up (OR = 5.51) and site-specific PPD (OR = 13.89) and PISTD (OR = 9.07) increases > 1 mm during follow-up. Profuse bleeding at follow-up showed a tendency for association (OR = 4.61) though it did not reach statistical significance.

4 | Discussion

The present findings indicate that the clinical signs considered indicative of peri-implant mucositis (presence of BoP, visual redness) usually precede peri-implant bone loss. However, their value to accurately anticipate bone loss is limited due to low specificity. Conversely, BoP at six sites and SoP demonstrated high specificity for anticipating future bone loss, although these parameters exhibited low sensitivity. In terms of diagnosis, implants with a history of recent bone loss always presented with concomitant BoP, whereas SoP was only observed in implants with bone loss. High specificity was also noted for the severity (profuse) and extent (six sites) of BoP, as well as for changes in

TABLE 6 | Diagnostic accuracy of different clinical parameters at follow-up for the detection of a recent history of peri-implant bone loss.

History of peri-implant bone loss							
Prevalence% (95% CI)							9.4 (6.3–13.3)
	Follow-up diagnostic parameters						
	BoP (follow-up) ≥ 1 site	**BoP (follow-up) ≥ 2 sites**	**BoP (follow-up) = 6 sites**	**SoP+ (follow-up) ≥ 1 site**	**PPD (follow-up) ≥ 5 mm**	**PPD (follow-up) ≥ 6 mm**	**PISTD (follow-up) > 0 mm**
Sensitivity% (95% CI)	100.0 (87.7–100.0)	89.3 (71.8–97.7)	42.9 (24.5–62.8)	10.7 (2.3–28.2)	75.0 (55.1–89.3)	60.7 (40.6–78.5)	39.3 (21.5–59.4)
Specificity% (95% CI)	14.4 (10.5–19.2)	33.3 (27.7–39.3)	87.0 (82.4–90.8)	100.0 (98.6–100.0)	55.9 (49.8–61.9)	81.9 (76.7–86.3)	58.1 (52.0–64.1)
AUC (95% CI)	0.57 (0.55–0.59)	0.61 (0.55–0.68)	0.65 (0.55–0.74)	0.55 (0.50–0.61)	0.65 (0.57–0.74)	0.71 (0.62–0.81)	0.49 (0.39–0.58)
PPV % (95% CI)	10.8 (7.3–15.2)	12.2 (8.0–17.5)	25.5 (13.9–40.3)	100.0 (29.2–100.0)	15.0 (9.5–22.0)	25.8 (15.8–38.0)	8.9 (4.5–15.3)
NPV % (95% CI)	100.0 (91.0–100.0)	96.8 (90.9–99.3)	93.6 (89.9–96.3)	91.5 (87.7–94.4)	95.6 (91.1–98.2)	95.3 (91.7–97.6)	90.2 (84.8–94.2)
	Follow-up diagnostic parameters						
	mBI (follow-up), line or profuse	**mBI (follow-up), profuse**	**Deepest PPD increase (follow-up) > 1 mm**	**Site-specific PPD increase (follow-up) > 1 mm**	**Deepest PISTD increase (follow-up) > 1 mm**	**Site-specific PISTD increase (follow-up) > 1 mm**	**Site-specific PPD or PISTD increase (follow-up) > 1 mm**
Sensitivity% (95% CI)	71.4 (51.3–86.8)	39.3 (21.5–59.4)	28.6 (13.2–48.7)	64.3 (44.1–81.4)	21.4 (8.3–41.0)	32.1 (15.9–52.4)	82.1 (63.1–93.9)
Specificity% (95% CI)	50.4 (44.2–56.5)	91.9 (87.9–94.8)	95.9 (92.8–97.9)	81.1 (75.9–85.6)	91.5 (87.5–94.5)	87.4 (82.8–91.1)	70.0 (64.2–75.4)
AUC (95% CI)	0.61 (0.52–0.70)	0.66 (0.56–0.75)	0.62 (0.54–0.71)	0.73 (0.63–0.82)	0.56 (0.49–0.64)	0.60 (0.51–0.69)	0.76 (0.68–0.84)
PPV % (95% CI)	13.0 (8.1–19.3)	33.3 (18.0–51.8)	42.1 (20.3–66.5)	26.1 (16.3–38.1)	20.7 (8.0–39.7)	20.9 (10.0–36.0)	22.1 (14.6–31.3)
NPV % (95% CI)	94.4 (89.3–97.6)	93.6 (89.9–96.2)	92.8 (89.1–95.6)	95.6 (92.1–97.9)	91.8 (87.9–94.8)	92.5 (88.6–95.5)	97.4 (94.1–99.2)

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

TABLE 7 | Combined predictive/diagnostic model: Clinical parameters at baseline/follow-up and incidence/history of peri-implant bone loss.

	Multiple regression		
Variable	**OR**	**95% CI**	***p*-value**
BoP extent (baseline)			
0–1 site	Ref	Ref	Ref
2–3–4–5 sites	9.64	1.13–81.85	**0.038**
6 sites	7.36	0.50–68.61	0.158
Redness (baseline), yes	53.63	2.11–1363.12	**0.016**
PPD ≥ 6 mm (follow-up), yes	5.51	1.43–21.30	**0.013**
Profuse mBI mm (follow-up), yes	4.61	0.98–21.72	0.053
Site-specific PPD increase > 1 mm (follow-up), yes	13.89	2.79–69.10	**0.0001**
Site-specific PISTD increase > 1 mm (follow-up), yes	9.07	1.78–45.92	**0.008**

Note: Bold indicates statistical significance ($p < 0.05$).

Abbreviations: BoP, bleeding on probing; CI, confidence interval; mBI, modified bleeding index; OR, odds ratio; PISTD, peri-implant soft-tissue dehiscence; PPD, probing pocket depth; Ref, reference category.

PPD and PISTD. Despite being suboptimal, the best diagnostic accuracy for the history of recent peri-implant bone loss was achieved using a combined criterion of site-specific PPD or PISTD increases greater than 1 mm. Overall, these findings suggest that BoP extent and severity, SoP and changes in PPD/PISTD are relevant and specific parameters for diagnosing recent peri-implant bone loss. However, clinicians should not rely solely on any single parameter, as they all suffer from low sensitivity.

Peri-implant mucositis has long been considered a necessary precursor to peri-implantitis (Costa et al. 2012). However, longitudinal studies including a peri-implant health control group are lacking. In this study, signs of peri-implant mucosa inflammation preceded 96.4% of bone loss events and were present in 100% of cases with a history of recent bone loss. Despite this, the high prevalence of BoP in at least one site (> 85%), both at baseline and follow-up, prevents drawing definitive conclusions. Furthermore, the almost ubiquitous presence of BoP in this sample raises the question of whether a single drop of BoP truly reflects an inflammatory disease process in the peri-implant tissues. Although highly sensitive, this parameter has indeed extremely low specificity, potentially leading to the over-diagnosis and over-treatment of peri-implant mucositis. It should also be emphasised that moving the thresholds of BoP from ≥1 to ≥2 sites, as recently proposed (Tonetti et al. 2023), only provides minimal improvements in its predictive accuracy.

In contrast, BoP extent (6 sites) and SoP demonstrated high specificity in anticipating future peri-implant bone loss (88.1%–91.5%). While the predictive value of BoP extent had not been analysed in previous studies, the findings related to SoP are consistent with other studies only evaluating peri-implantitis cases (Romandini et al. 2024; Koldsland, Wohlfahrt, and Aass 2018; Monje et al. 2021). These data highlight the importance of effectively treating implants exhibiting BoP at 6 sites or SoP since affected implants are more likely to show bone loss during follow-up. However, due to their low sensitivity, most incident bone loss cases occur in implants without BoP at 6 sites or SoP. Consequently, there is a pressing need for research on microbiological and host biomarkers, as well as non-invasive imaging (Galarraga-Vinueza et al. 2024) and new technologies, to develop more effective tools for predicting bone loss before it becomes radiographically detectable.

For the diagnosis of recent peri-implant bone loss, a similar scenario was observed. BoP (≥1 and ≥2 sites) was the only sensitive parameter (100.0% and 89.3%, respectively), but its almost ubiquitous presence in the population limits its value as a screening tool to avoid unnecessary radiographic exposure. In contrast, BoP extent (6 sites) and severity (profuse), SoP, PPD ≥6 mm and changes in PPD/PISTD over time, showed high specificity but low sensitivity, in line with findings from preclinical experimental peri-implantitis studies (Monje et al. 2018) and observational studies around teeth (Lang et al. 1986). It is worth noting that changes in PPD over time, a diagnostic criterion included in the current case definition of peri-implantitis (Berglundh et al. 2018), do not improve the limited diagnostic accuracy of one-time assessment of PPD at follow-up considering a 6-mm cut-off. Apart from the well-documented difficulties in assessing PPD around implants (Serino, Turri, and Lang 2013), bone loss may indeed manifest as a combination of increased PPD and/or PISTD. Therefore, it is not surprising that the best overall diagnostic accuracy for detecting a recent peri-implant bone loss in this study was observed for a combination of changes in both parameters, similar to clinical attachment levels around teeth.

Overall, the present diagnostic findings suggest that radiographic assessment of dental implants is justified and recommended in the presence of BoP at 6 sites, profuse bleeding, SoP, PPD ≥6 mm or increases in PPD/PISTD, given their high specificity for bone loss. However, due to the low sensitivity of these parameters, occasional radiographic assessment may also be considered even in their absence.

The relevance of the present study lies in the wide range of predictive/diagnostic clinical parameters analysed within a prospective cohort design, minimising the risk of selection (due to the use of a representative sample) and information bias (with bone loss assessed through direct evidence and the involvement of calibrated clinical/radiographic assessors). However, some limitations need to be considered, paving the way for future research. Clinical examinations performed at only two time points 3.9 years apart may lead to speculation on changes in their values over time. The mBI was evaluated after deep probing and only at follow-up, preventing the analysis of its accuracy in predicting future bone loss. Conversely, visual redness and swelling were only evaluated at baseline, preventing their diagnostic accuracy evaluation for a history of recent bone loss. The absence of previous studies with a similar design and scope necessitated an exploratory approach, which may have resulted

in reduced statistical power in some analyses. Additionally, the assessment methods of PISTD (i.e., exposure of abutment or implant neck/surface) may introduce some form of information bias for this parameter. A better sensitivity for this parameter may be observed if measuring the soft-tissue level from a fixed reference point. Finally, the population is derived from a single center primarily composed of periodontitis patients. Therefore, the generalisability of these findings to different settings needs to be verified.

5 | Conclusions

Clinical signs considered indicative of peri-implant mucositis (presence of BoP, visual redness) usually precede peri-implant bone loss. Implants with a recent history of bone loss always present with concomitant BoP. However, given the ubiquitous presence of BoP, the presence of BoP in 1–2 sites has limited value in predicting or diagnosing bone loss. The presence of BoP at 6 sites or SoP warrants treatment and strict monitoring, as affected implants are more likely to suffer bone loss during follow-up. During follow-up examinations, clinicians should not rely on single clinical parameters for screening of recent bone loss. The presence of BoP at 6 sites, profuse bleeding, SoP, PPD ≥ 6 mm, or increases in PPD/PISTD over time, justifies radiographic exposure due to their high specificity. However, given their low sensitivity, occasional radiographic assessments may also be considered in their absence. Future research should focus on the predictive/diagnostic value of microbiological and host biomarkers, as well as non-invasive imaging and new technologies.

Author Contributions

M.R. contributed to study conception and design, data acquisition, analysis and interpretation and manuscript drafting. C.L. contributed to data acquisition, analysis and interpretation and manuscript drafting. M.M. contributed to data acquisition and critically revised the manuscript. M.S. contributed to the study design, data analysis and interpretation and critically revised the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest related to this study.

Data Availability Statement

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

References

Annunziata, M., G. Cecoro, A. Guida, et al. 2024. "Effectiveness of Implant Therapy in Patients With and Without a History of Periodontitis: A Systematic Review With Meta – Analysis of Prospective Cohort Studies." *Journal of Periodontal Research*.

Baima, G., F. Citterio, M. Romandini, et al. 2022. "Surface Decontamination Protocols for Surgical Treatment of Peri-Implantitis: A Systematic Review With Meta-Analysis." *Clinical Oral Implants Research* 33, no. 11: 1069–1086.

Bencze, B., B. G. N. Cavalcante, M. Romandini, et al. 2024. "Prediabetes and Poorly Controlled Type-2 Diabetes as Risk Indicators for Peri-Implant Diseases: A Systematic Review and Meta-Analysis." *Journal of Dentistry* 146: 105094.

Berglundh, J., M. Romandini, J. Derks, M. Sanz, and T. Berglundh. 2021. "Clinical Findings and History of Bone Loss at Implant Sites." *Clinical Oral Implants Research* 32, no. 3: 314–323.

Berglundh, T., G. Armitage, M. G. Araujo, et al. 2018. "Peri-Implant Diseases and Conditions: Consensus Report of Workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions." *Journal of Clinical Periodontology* 45, no. Suppl 20: S286–S291.

Carra, M. C., N. Blanc-Sylvestre, A. Courtet, and P. Bouchard. 2023. "Primordial and Primary Prevention of Peri-Implant Diseases: A Systematic Review and Meta-Analysis." *Journal of Clinical Periodontology* 50, no. Suppl 26: 77–112.

Carvalho, E. B. S., M. Romandini, S. Sadilina, A. C. P. Sant'Ana, and M. Sanz. 2023. "Microbiota Associated With Peri-Implantitis – A Systematic Review With Meta-Analyses." *Clinical Oral Implants Research* 34, no. 11: 1176–1187.

Cohen, J. F., D. A. Korevaar, D. G. Altman, et al. 2016. "STARD 2015 Guidelines for Reporting Diagnostic Accuracy Studies: Explanation and Elaboration." *BMJ Open* 6, no. 11: e012799.

Costa, F. O., S. Takenaka-Martinez, L. O. Cota, S. D. Ferreira, G. L. Silva, and J. E. Costa. 2012. "Peri-Implant Disease in Subjects With and Without Preventive Maintenance: A 5-Year Follow-Up." *Journal of Clinical Periodontology* 39, no. 2: 173–181.

Derks, J., A. Ortiz-Vigon, A. Guerrero, et al. 2022. "Reconstructive Surgical Therapy of Peri-Implantitis: A Multicenter Randomized Controlled Clinical Trial." *Clinical Oral Implants Research* 33, no. 9: 921–944.

Derks, J., D. Schaller, J. Hakansson, J. L. Wennstrom, C. Tomasi, and T. Berglundh. 2016a. "Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-Implantitis." *Journal of Dental Research* 95, no. 1: 43–49.

Derks, J., D. Schaller, J. Hakansson, J. L. Wennstrom, C. Tomasi, and T. Berglundh. 2016b. "Peri-Implantitis – Onset and Pattern of Progression." *Journal of Clinical Periodontology* 43, no. 4: 383–388.

Galarraga-Vinueza, M. E., S. Barootchi, L. Mancini, et al. 2024. "Echo-Intensity Characterization at Implant Sites and Novel Diagnostic Ultrasonographic Markers for Peri-Implantitis." *Journal of Clinical Periodontology*.

Isler, S. C., M. Romandini, G. Akca, et al. 2024. "Soft-Tissue Phenotype as a Risk Indicator of Peri-Implantitis and Peri-Implant Soft-Tissue Dehiscence – A Cross-Sectional Study." *Journal of Clinical Periodontology* 51: 1443–1457.

Koldsland, O. C., J. C. Wohlfahrt, and A. M. Aass. 2018. "Surgical Treatment of Peri-Implantitis: Prognostic Indicators of Short-Term Results." *Journal of Clinical Periodontology* 45, no. 1: 100–113.

Lang, N. P., A. Joss, T. Orsanic, F. A. Gusberti, and B. E. Siegrist. 1986. "Bleeding on Probing. A Predictor for the Progression of Periodontal Disease?" *Journal of Clinical Periodontology* 13, no. 6: 590–596.

Monje, A., A. Insua, M. Rakic, J. Nart, J. L. Moyano-Cuevas, and H. L. Wang. 2018. "Estimation of the Diagnostic Accuracy of Clinical Parameters for Monitoring Peri-Implantitis Progression: An

Experimental Canine Study." *Journal of Periodontology* 89, no. 12: 1442–1451.

Monje, A., and J. Nart. 2024. "Disease Recurrence During Supportive Therapy Following Peri-Implantitis Treatment: A Retrospective Study." *Journal of Periodontal Research* 59: 918–928.

Monje, A., M. Vera, A. Munoz-Sanz, H. L. Wang, and J. Nart. 2021. "Suppuration as Diagnostic Criterium of Peri-Implantitis." *Journal of Periodontology* 92, no. 2: 216–224.

Regidor, E., A. Ortiz-Vigon, M. Romandini, C. Dionigi, J. Derks, and M. Sanz. 2023. "The Adjunctive Effect of a Resorbable Membrane to a Xenogeneic Bone Replacement Graft in the Reconstructive Surgical Therapy of Peri-Implantitis: A Randomized Clinical Trial." *Journal of Clinical Periodontology* 50, no. 6: 765–783.

Romandini, M., J. Berglundh, J. Derks, M. Sanz, and T. Berglundh. 2021. "Diagnosis of Peri-Implantitis in the Absence of Baseline Data: A Diagnostic Accuracy Study." *Clinical Oral Implants Research* 32, no. 3: 297–313.

Romandini, M., K. Bougas, L. Alibegovic, et al. 2024. "Long-Term Outcomes and Prognostic Factors of Surgical Treatment of Peri-Implantitis – A Retrospective Study." *Clinical Oral Implants Research* 35, no. 3: 321–329.

Romandini, M., M. Cordaro, S. Donno, and L. Cordaro. 2019. "Discrepancy Between Patient Satisfaction and Biologic Complication Rate in Patients Rehabilitated With Overdentures and Not Participating in a Structured Maintenance Program After 7 to 12 Years of Loading." *International Journal of Oral and Maxillofacial Implants* 34, no. 5: 1143–1151.

Romandini, M., A. Lafori, I. Pedrinaci, et al. 2022. "Effect of Sub-Marginal Instrumentation Before Surgical Treatment of Peri-Implantitis: A Multi-Centre Randomized Clinical Trial." *Journal of Clinical Periodontology* 49, no. 12: 1334–1345.

Romandini, M., C. Lima, I. Pedrinaci, A. Araoz, M. C. Soldini, and M. Sanz. 2021a. "Clinical Signs, Symptoms, Perceptions, and Impact on Quality of Life in Patients Suffering From Peri-Implant Diseases: A University-Representative Cross-Sectional Study." *Clinical Oral Implants Research* 32, no. 1: 100–111.

Romandini, M., C. Lima, I. Pedrinaci, A. Araoz, M. C. Soldini, and M. Sanz. 2021b. "Prevalence and Risk/Protective Indicators of Peri-Implant Diseases: A University-Representative Cross-Sectional Study." *Clinical Oral Implants Research* 32, no. 1: 112–122.

Romandini, M., I. Pedrinaci, C. Lima, M. C. Soldini, A. Araoz, and M. Sanz. 2021. "Prevalence and Risk/Protective Indicators of Buccal Soft Tissue Dehiscence Around Dental Implants." *Journal of Clinical Periodontology* 48, no. 3: 455–463.

Sanz-Martin, I., E. Regidor, J. Navarro, I. Sanz-Sanchez, M. Sanz, and A. Ortiz-Vigon. 2020. "Factors Associated With the Presence of Peri-Implant Buccal Soft Tissue Dehiscences: A Case-Control Study." *Journal of Periodontology* 91, no. 8: 1003–1010.

Serino, G., A. Turri, and N. P. Lang. 2013. "Probing at Implants With Peri-Implantitis and Its Relation to Clinical Peri-Implant Bone Loss." *Clinical Oral Implants Research* 24, no. 1: 91–95.

Tonetti, M. S., M. Sanz, G. Avila-Ortiz, et al. 2023. "Relevant Domains, Core Outcome Sets and Measurements for Implant Dentistry Clinical Trials: The Implant Dentistry Core Outcome Set and Measurement (ID-COSM) International Consensus Report." *Clinical Oral Implants Research* 34, no. Suppl 25: 4–21.

Verket, A., O. C. Koldsland, D. Bunaes, S. A. Lie, and M. Romandini. 2023. "Non-Surgical Therapy of Peri-Implant Mucositis-Mechanical/Physical Approaches: A Systematic Review." *Journal of Clinical Periodontology* 50, no. Suppl 26: 135–145.

Appendix Table 1. Putative risk/protective factors tested.

PATIENT-LEVEL				IMPLANT-LEVEL	
DEMOGRAPHIC	**Age** (baseline)	MEDICATIONS	**Bisphosphonates** (baseline)	GENERAL	**Implant location** (baseline)
	Gender (baseline)		**Corticosteroids** (baseline)		**Jaw** (baseline)
	Educational Level (baseline)		**NSAIDs** (baseline)		**Implant Brand** (baseline)
	Marital Status (baseline)		**Antiplatelet** (baseline)		**Implant Type (tissue- vs. bone-level)** (baseline)
	Height (baseline)		**Anticoagulant** (baseline)		**Implant length** (baseline)
	Weight (baseline)		**Hypolipidemic agent** (baseline)		**Implant diameter** (baseline)
	BMI (kg/m²) (baseline)		**Antidepressant** (baseline)		**At Least One adjacent Tooth** (baseline)
SYSTEMIC DISEASES	**Diabetes** (baseline)		**Proton Pump Inhibitor** (baseline)		**Reason of Tooth Loss** (baseline)
	Osteoporosis/Osteopenia (baseline)		**Vitamin D** (baseline)	SOFT-TISSUE	**Keratinized Tissue Height** (baseline)
	Myocardial Infarction (baseline)		**Calcium** (baseline)		**Adherent mucosa** (baseline)
	Hypertension (baseline)		**Thyroid Drug** (baseline)		**Tissue Thickness** (baseline)
	Stroke (baseline)		**Immunosuppressant** (baseline)		**Mucosal Margin Mobility** (baseline)
	Anemia (baseline)		**Insulin** (baseline)	RESTORATIVE FACTORS	**Type of Restoration** (baseline)
	Cancer (baseline)		**Oral Hypoglycemic Agent** (baseline)		**Restoration Retention** (baseline)
	Depression (baseline)		**Other Anti-diabetic** (baseline)		**Prosthesis Gap** (baseline)
	Asthma (baseline)		**Beta-blockers** (baseline)		**Prosthesis Step** (baseline)
	Cognitive or Memory Disorders (baseline)		**Diuretics** (baseline)		**Emergence Angle (Highest)** (baseline)
	Neurological Disorders (baseline)		**ACE Inhibitors** (baseline)		**Emergence Profile** (baseline)
	Immunological Disorders (baseline)		**Other Antihypertensive Drugs** (baseline)		**Mesial Cantilever** (baseline)
	Hypercholesterolemia (baseline)		**Other Medications** (baseline)		**Distal Cantilever** (baseline)
	Hepatitis (baseline)		**Supplements** (baseline)		**Prosthesis Mobility** (baseline)
	HIV/AIDS (baseline)	ORAL/PERIODONTAL VARIABLES	**Periodontal Status (CDC/AAP)** (baseline)		**Abutment Presence** (baseline)
	Rheumatoid Arthritis (baseline)		**Periodontal status (2017 WWP)** (baseline)		**Platform Switching** (baseline)
	Respiratory Diseases (baseline)		**Number of Remaining Teeth** (baseline)		**Crown Dimension** (baseline)
	Liver Diseases (baseline)		**Number of Dental Implants** (baseline)		**Crown to Implant Ratio** (baseline)
	Cardiovascular Diseases (baseline)		**History of Orthodontic Treatment** (baseline)		**Residual Cement Visible on Radiograph** (baseline)
	Gastrointestinal Disorders (baseline)		**Toothbrushing Frequency** (baseline)		**Clinical Signs of Occlusal Overloading** (baseline)
	Kidney Diseases (baseline)		**Electric Toothbrush** (baseline)		**Prosthetic design allowing access to hygiene** (baseline)
	Thyroid Disorders (baseline)		**Interproximal Flossing/Brushing on Implants** (baseline)		**Restoration margin location** (follow-up)
	Cataract (baseline)		**Bruxism Signs** (baseline)	OTHER	**Vestibular-Lingual Malposition** (baseline)
	Other Systemic Diseases (baseline)		**Bruxism Symptoms** (baseline)		**Plaque** (baseline)
	Sars-CoV 2 History (follow-up)		**Dry Mouth** (baseline)		**Peri-implant health status** (baseline)
	Covid-19 History (follow-up)		**Number of maintenances between baseline and follow-up** (follow up)		
	Sars-CoV 2 vaccine (follow-up)		**FMPS, excluding implants** (follow-up)		
LYFESTILES	**Smoking** (baseline)		**FMBS, excluding implants** (follow-up)		
	Sleep Duration (baseline)		**Number PPD≥4 or ≥5 or ≥6 mm, excluding implants** (follow-up)		
	Physical Activity (baseline)		**Number FI ≥ 2** (follow-up)		
	Stress (baseline)		**Periodontal bone loss/age ratio** (follow-up)		
	Coffee Consumption (baseline)	OTHER	**Allergies** (baseline)		
	Alcohol Consumption (baseline)		**Chemotherapy history** (baseline)		
			Radiotherapy history (baseline)		

Appendix Table 2. Descriptive statistics of the putative patient-level risk/protective factors, overall and according to incidence of peri-implantitis (N=72 patients).

Variable	Overall	Incidence of peri-implantitis	
		No	Yes
Age (years), (baseline), mean (SD)	62.58 (7.84)	61.54 (7.66)	66.25 (7.59)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Age ≧ 65 years (yes) (baseline), N (%)			
No	42 (58.3)	35 (62.5)	7 (43.8)
Yes	30 (41.7)	21 (37.5)	9 (56.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Gender (female) (baseline), N (%)			
Male	27 (37.5)	23 (41.1)	4 (25.0)
Female	45 (62.5)	33 (58.9)	12 (75.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Educational Level (baseline), N (%)			
Primary school	22 (30.6)	15 (26.8)	7 (43.8)
High school	17 (23.6)	11 (19.6)	6 (37.5)
Middle grade	15 (20.8)	14 (25.0)	1 (6.2)
University/College	18 (25.0)	16 (28.6)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Marital Status (baseline), N (%)			
Married	53 (73.6)	42 (75.0)	11 (68.8)
Widow	4 (5.6)	2 (3.6)	2 (12.5)
Divorced	8 (11.1)	7 (12.5)	1 (6.2)
Never married	5 (6.9)	4 (7.1)	1 (6.2)
Living with unmarried partner	2 (2.8)	1 (1.8)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Height (cm) (baseline), mean (SD)	164.42 (8.50)	165.29 (7.88)	161.38 (10.10)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg) (baseline), mean (SD)	70.26 (14.81)	70.94 (14.95)	67.88 (14.51)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m²) (baseline), mean (SD)	25.80 (3.75)	25.77 (3.78)	25.88 (3.77)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes* (baseline), N (%)			
No	63 (87.5)	51 (91.1)	12 (75.0)
Yes	9 (12.5)	5 (8.9)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Osteoporosis/Osteopenia (baseline), N (%)			
No	58 (80.6)	49 (87.5)	9 (56.3)
Yes	14 (19.4)	7 (12.5)	7 (43.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial Infarction (baseline), N (%)			
No	71 (98.6)	56 (100.0)	15 (93.6)
Yes	1 (1.4)	0 (0.0)	1 (6.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension* (baseline), N (%)			

No	55 (76.4)	46 (82.1)	9 (56.2)
Yes	17 (23.6)	10 (17.9)	7 (43.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Stroke (baseline), N (%)			
No	71 (98.6)	56 (100.0)	15 (93.6)
Yes	1 (1.4)	0 (0.0)	1 (6.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Anemia (baseline), N (%)			
No	57 (79.2)	43 (76.8)	14 (87.5)
Yes	15 (20.8)	13 (23.2)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Cancer (baseline), N (%)			
No	66 (91.7)	52 (92.9)	14 (87.5)
Yes	6 (8.3)	4 (7.1)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Depression* (baseline), N (%)			
No	61 (84.7)	48 (85.7)	13 (81.3)
Yes	11 (15.3)	8 (14.3)	3 (18.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Asthma (baseline), N (%)			
No	68 (94.4)	53 (94.6)	15 (93.8)
Yes	4 (5.6)	3 (5.4)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Cognitive or Memory Disorders (baseline), N (%)			
No	69 (95.8)	54 (96.4)	15 (93.8)
Yes	3 (4.2)	2 (3.6)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Neurological Disorders (baseline), N (%)			
No	69 (95.8)	53 (94.6)	16 (100.0)
Yes	3 (4.2)	3 (5.4)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Immunological Disorders (baseline), N (%)			
No	71 (98.6)	55 (98.2)	16 (100.0)
Yes	1 (1.4)	1 (1.8)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypercholesterolemia (baseline), N (%)			
No	44 (61.1)	34 (60.7)	10 (62.5)
Yes	28 (38.9)	22 (39.3)	6 (37.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hepatitis (baseline), N (%)			
No	70 (97.2)	54 (96.4)	16 (100.0)
Yes	2 (2.8)	2 (3.6)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
HIV/AIDS (baseline), N (%)			
No	72 (100.0)	56 (100.0)	16 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis (baseline), N (%)			

No	60 (83.3)	49 (87.5)	11 (68.8)
Yes	12 (16.7)	7 (12.5)	5 (31.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory Diseases (baseline), N (%)			
No	64 (88.9)	50 (89.3)	14 (87.5)
Yes	8 (11.1)	6 (10.7)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Liver Diseases (baseline), N (%)			
No	69 (95.8)	53 (94.6)	16 (100.0)
Yes	3 (4.2)	3 (5.4)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular Diseases (baseline), N (%)			
No	65 (90.3)	50 (89.3)	15 (93.8)
Yes	7 (9.7)	6 (10.7)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders (baseline), N (%)			
No	58 (80.6)	46 (82.1)	12 (75.0)
Yes	14 (19.4)	10 (17.9)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Kidney Diseases (baseline), N (%)			
No	68 (94.4)	53 (94.6)	15 (93.8)
Yes	4 (5.6)	3 (5.4)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid Disorders (baseline), N (%)			
No	59 (81.9)	47 (83.9)	12 (75.0)
Yes	13 (18.1)	9 (16.1)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Cataract (baseline), N (%)			
No	58 (80.6)	48 (85.7)	10 (62.5)
Yes	14 (19.4)	8 (14.3)	6 (37.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Other Medical Diseases (baseline), N (%)			
No	62 (86.1)	48 (85.7)	14 (87.5)
Yes	10 (13.9)	8 (14.3)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sars-CoV 2 History (follow-up), N (%)			
No	30 (41.7)	21 (37.5)	9 (56.3)
Yes	42 (58.3)	35 (62.5)	7 (43.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Covid-19 History (follow-up), N (%)			
No	36 (50.0)	25 (44.6)	11 (68.8)
Yes	36 (50.0)	31 (53.4)	5 (31.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sars-CoV 2 vaccine (follow-up), N (%)			
No	1 (1.4)	1 (1.8)	0 (0.0)
Yes	71 (98.6)	55 (98.2)	16 (100.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
At least one systemic disease (baseline), N (%)			
No	11 (15.3)	8 (14.3)	3 (18.7)

Yes	61 (84.7)	48 (85.7)	13 (81.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Number of systemic diseases (baseline), mean (SD)	2.78 (2.50)	2.5 (2.45)	3.75 (2.49)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking (baseline), N (%)			
Non-smokers	58 (80.6)	46 (82.1)	12 (75.0)
Current smokers	14 (19.4)	10 (17.9)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sleep Duration (baseline), N (%)			
<7 hours	29 (40.3)	20 (35.7)	9 (56.3)
7-8 hours	*42 (58.3)*	36 (64.3)	6 (37.5)
>7 hours	1 (1.4)	0 (0.0)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Regular Moderate (≥3 times/week ≥20 minutes) Physical Activity (baseline), N (%)			
No	14 (19.4)	11 (19.6)	3 (18.7)
Yes	58 (80.6)	45 (80.4)	13 (81.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Stress (baseline), N (%)			
Absolutely nothing	16 (22.2)	13 (23.2)	3 (18.8)
Mild / Moderate	47 (65.3)	37 (66.1)	10 (62.4)
High	9 (12.5)	6 (10.7)	3 (18.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Coffee Consumption (baseline), N (%)			
No	15 (20.8)	12 (21.4)	3 (18.8)
Yes	57 (79.2)	44 (78.6)	13 (81.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol Consumption (baseline), N (%)			
Never	23 (32.0)	15 (26.8)	8 (50.0)
Less than 2 times/week	33 (45.8)	28 (50.0)	5 (31.3)
Almost everyday	8 (11.1)	6 (10.7)	2 (12.5)
1/day	6 (8.3)	5 (8.9)	1 (6.2)
2 or more times/day	2 (2.8)	2 (3.6)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Alcohol Consumption) (baseline), N (%)			
Never	23 (31.9)	15 (26.8)	8 (50.0)
At least sometimes	49 (68.1)	41 (73.2)	8 (50.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Bisphosphonates (baseline), N (%)			
No	72 (100.0)	56 (100.0)	16 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Corticosteroids) (baseline), N (%)			
No	68 (94.4)	53 (94.6)	15 (93.8)
Yes	4 (5.6)	3 (5.4)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
NSAIDs (baseline), N (%)			
No	68 (94.4)	53 (94.6)	15 (93.8)
Yes	4 (5.6)	3 (5.4)	1 (6.2)

Missing	0 (0.0)	0 (0.0)	0 (0.0)
Antiplatelet (baseline), N (%)			
No	68 (94.4)	54 (96.4)	14 (87.5)
Yes	4 (5.6)	2 (3.6)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Anticoagulant (baseline), N (%)			
No	68 (94.4)	54 (96.4)	14 (87.5)
Yes	4 (5.6)	2 (3.6)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Hypolipidemic agent (baseline), N (%)			
No	56 (77.8)	46 (82.1)	10 (62.5)
Yes	16 (22.2)	10 (17.9)	6 (37.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Antidepressant (baseline), N (%)			
No	61 (84.7)	49 (87.5)	12 (75.0)
Yes	11 (15.3)	7 (12.5)	4 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Proton Pump Inhibitor (baseline), N (%)			
No	69 (95.8)	55 (98.2)	14 (87.5)
Yes	3 (4.2)	1 (1.8)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Vitamin D (baseline), N (%)			
No	69 (95.8)	43 (94.6)	16 (100.0)
Yes	3 (4.2)	3 (5.4)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Calcium(baseline), N (%)			
No	65 (90.3)	53 (94.6)	12 (75.0)
Yes	7 (9.7)	3 (5.4)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Thyroid Drug (baseline), N (%)			
No	60 (93.3)	48 (85.7)	12 (75.0)
Yes	12 (16.7)	8 (14.3)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppressant (baseline), N (%)			
No	71 (98.6)	55 (98.2)	16 (100.0)
Yes	1 (1.4)	1 (1.8)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Insulin (baseline), N (%)			
No	69 (95.8)	54 (96.4)	15 (93.8)
Yes	3 (4.2)	2 (3.6)	1 (6.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Oral Hypoglycemic Agent (baseline), N (%)			
No	65 (90.3)	55 (91.1)	14 (87.5)
Yes	7 (9.7)	5 (8.9)	2 (12.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Other Anti-diabetic Drug (baseline), N (%)			
No	70 (97.2)	54 (96.4)	16 (100.0)
Yes	2 (2.8)	2 (3.6)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

Beta-blockers (baseline), N (%)			
No	68 (94.4)	53 (94.6)	15 (93.8)
Yes	4 (5.6)	3 (5.4)	1 (6.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Diuretics (baseline), N (%)			
No	67 (93.1)	52 (98.9)	15 (93.8)
Yes	5 (6.9)	4 (7.1)	1 (6.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
ACE Inhibitors (baseline), N (%)			
No	66 (91.7)	53 (94.6)	13 (81.3)
Yes	6 (8.3)	3 (5.4)	3 (18.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Other Antihypertensive Drugs (baseline), N (%)			
No	70 (97.2)	54 (96.4)	16 (100.0)
Yes	2 (2.8)	2 (3.6)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Other Drugs (baseline), N (%)			
No	51 (70.8)	40 (71.4)	11 (68.8)
Yes	21 (29.2)	16 (28.6)	5 (31.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Number of medications (baseline), mean (SD)	1.65 (1.92)	1.43 (1.82)	2.44 (2.13)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Supplements (baseline), N (%)			
No	58 (80.6)	46 (82.1)	12 (75.0)
Yes	14 (19.4)	10 (17.9)	4 (25.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Periodontal status (2017 WWP) (baseline), N (%)			
No periodontitis or SI-III periodontitis	49 (68.1)	43 (76.8)	6 (37.5)
Stage 4 periodontitis	17 (23.6)	8 (14.3)	9 (56.3)
Edentulous	6 (8.3)	5 (8.9)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Number of Remaining Teeth (baseline), mean (SD)	18.89 (7.50)	20.30 (7.28)	13.94 (6.22)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Remaining Teeth (≥16) (baseline), N (%)			
No	20 (27.8)	9 (16.1)	11 (68.8)
Yes	52 (72.2)	47 (83.9)	5 (31.2)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Dental Implants (baseline), mean (SD)	4.51 (2.71)	3.89 (2.44)	6.69 (2.52)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Number of Dental Implants (≥4) (baseline), N (%)			
No	30 (41.7)	28 (50.0)	2 (12.5)
Yes	42 (58.3)	28 (50.0)	14 (87.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
History of Orthodontic Treatment (baseline), N (%)			
No	50 (64.4)	40 (71.4)	10 (62.5)
Yes	22 (33.6)	16 (28.6)	6 (37.5)

Missing	0 (0.0)	0 (0.0)	0 (0.0)
Toothbrushing Frequency (baseline), N (%)			
Not everyday	1 (1.4)	1 (1.8)	0 (0.0)
1 time/day	7 (9.7)	4 (7.1)	3 (18.7)
2 times/day	31 (43.1)	25 (44.7)	6 (37.5)
3 or more times/day	33 (45.8)	26 (46.4)	7 (43.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Electric Toothbrush (baseline), N (%)			
No	27 (37.5)	24 (42.9)	3 (18.7)
Yes	45 (62.5)	32 (57.1)	13 (81.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Interproximal Flossing/Brushing on Implants (at least on some implants) (baseline), N (%)			
No	8 (11.1)	7 (12.5)	1 (6.2)
Yes	64 (88.9)	49 (87.5)	15 (93.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Bruxism Signs (baseline), N (%)			
No	47 (65.3)	36 (64.3)	11 (68.8)
Yes	25 (34.7)	20 (35.7)	5 (31.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Bruxism Symptoms (baseline), N (%)			
No	56 (77.8)	45 (80.4)	11 (68.8)
Yes	16 (22.2)	11 (19.6)	5 (31.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Dry Mouth (baseline), N (%)			
No	51 (79.8)	42 (75.0)	9 (56.3)
Yes	21 (29.2)	14 (25.0)	7 (43.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Number of maintenances between baseline and follow-up (follow up), mean (SD)	2.06 (1.47)	1.95 (1.53)	2.44 (1.21)
Missing, N (%)	0 (0.0)	0 (0.0)	0 (0.0)
Regular maintenance between baseline and follow-up (≥1 per year) (follow up), N (%)			
No	33 (45.8)	26 (46.4)	7 (43.7)
Yes	39 (54.2)	30 (53.6)	9 (56.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
FMPS, excluding implants (follow-up), mean (SD)	33.47 (16.13)	33.51 (16.47)	33.32 (15.29)
Missing, N (%)	9 (3.0)	5 (1.8)	4 (14.3)
FMBS, excluding implants (follow-up), mean (SD)	19.86 (12.50)	19.69 (12.44)	20.54 (13.19)
Missing, N (%)	8 (2.7)	5 (1.9)	3 (10.7)
Number PD≥4mm, excluding implants (follow-up), mean (SD)	16.54 (14.27)	16.77 (14.01)	15.62 (15.87)
Missing, N (%)	7 (2.3)	4 (1.5)	3 (10.7)
Number PD≥5mm, excluding implants (follow-up), mean (SD)	5.83 (7.42)	5.56 (6.89)	6.92 (9.51)
Missing, N (%)	7 (2.3)	4 (1.5)	3 (10.7)
Number PD≥6mm, excluding implants (follow-up), mean (SD)	2.38 (4.12)	2.08 (3.20)	3.62 (6.70)
Missing, N (%)	7 (2.3)	4 (1.5)	3 (10.7)
Number FI ≥ 2 (follow-up), mean (SD)	0.83 (1.68)	0.84 (1.63)	0.77 (1.92)
Missing, N (%)	9 (3.0)	6 (2.2)	3 (10.7)

Periodontal bone loss/age ratio (follow-up), mean (SD)	0.65 (0.29)	0.61 (0.27)	0.78 (0.31)
Missing, N (%)	10 (3.4)	8 (3.0)	2 (7.1)
Allergies (baseline), N (%)			
No	55 (76.4)	45 (80.4)	10 (62.5)
Yes	17 (23.6)	11 (19.6)	6 (37.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Chemotherapy (baseline), N (%)			
No	71 (93.6)	56 (100.0)	15 (93.8)
Yes	1 (1.4)	0 (0.0)	1 (6.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Radiotherapy (baseline), N (%)			
No	70 (97.2)	54 (96.4)	16 (100.0)
Yes	2 (2.8)	2 (3.6)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

Footnote:
FI, furcation involvement; FMBS, full mouth bleeding score; FMPS, full mouth plaque score; N, number; PD, probing pocket depth; SD, standard deviation.
* self-reported history or medication

Appendix Table 3. Descriptive statistics of the putative implant-level risk/protective factors, overall and according to incidence of peri-implantitis (N=298 implants).

Variable	Overall	Incidence of peri-implantitis	
		No	Yes
Jaw (baseline), N (%)			
Maxilla	160 (53.7)	150 (55.6)	10 (35.7)
Mandible	138 (46.3)	120 (44.4)	18 (64.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Position (baseline), N (%)			
Anterior (canine-canine)	49 (16.4)	44 (16.3)	5 (17.9)
Posterior	249 (85.6)	226 (83.7)	23 (82.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Side (baseline), N (%)			
Right	152 (51.0)	140 (51.9)	12 (42.9)
Left	146 (49.0)	130 (48.1)	16 (57.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Replaced tooth (baseline), N (%)			
Molar	145 (48.7)	132 (48.9)	13 (46.4)
Premolar	104 (34.9)	94 (34.8)	10 (35.7)
Canine	20 (6.7)	20 (7.4)	0 (0.0)
Incisor	29 (9.7)	24 (8.9)	5 (17.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Mouth zone (baseline), N (%)			
Posterior Maxilla	127 (42.6)	119 (44.1)	8 (28.6)
Anterior Maxilla	33 (11.1)	31 (11.5)	2 (7.1)
Posterior Mandible	122 (40.9)	107 (39.6)	15 (53.6)
Anterior Mandible	16 (5.4)	13 (4.8)	3 (10.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Implant Brand (baseline), N (%)			
Straumann,	164 (55.0)	150 (55.6)	14 (50.0)
Nobel Biocare	36 (12.1)	31 (11.5)	5 (17.9)
AstraTech	40 (13.4)	35 (13.0)	5 (17.9)
Other	57 (19.1)	53 (19.6)	4 (14.3)
Missing	1 (0.4)	1 (0.4)	0 (0.0)
Implant Collar (baseline), N (%)			
0 mm	88 (29.5)	81 (30.0)	7 (25.0)
≤ 1.5 mm	28 (9.4)	27 (10.0)	1 (3.6)
> 1.5 mm	148 (49.7)	139 (51.5)	9 (32.1)
Missing	34 (11.4)	23 (8.5)	11 (39.3)
Implant length (baseline), mean (SD)	9.88 (1.68)	9.92 (1.68)	9.46 (1.61)
Missing, N (%)	5 (1.7)	4 (1.5)	1 (3.6)
Implant diameter (baseline), mean (SD)	4.14 (0.40)	4.15 (0.40)	4.04 (0.35)
Missing, N (%)	3 (1.0)	2 (0.7)	1 (3.6)
At Least One adjacent Tooth (baseline), N (%)			

No	122 (40.9)	104 (38.5)	18 (64.3)
Yes	176 (59.1)	166 (61.5)	10 (35.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Reason of Tooth Loss (baseline), N (%)			
Caries	118 (39.6)	107 (39.6)	11 (39.3)
Periodontitis	119 (39.9)	107 (39.6)	12 (42.8)
Trauma	9 (3.0)	9 (3.3)	0 (0.0)
Agenesia	4 (1.4)	4 (1.5)	0 (0.0)
Other reason/Unknown	48 (16.1)	43 (16.0)	5 (17.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Keratinized Tissue Height (baseline), N (%)			
KTH=0 mm	49 (16.4)	42 (15.6)	7 (25.0)
>0 mm & <=2mm	125 (42.0)	116 (42.9)	9 (32.1)
KTH>2mm	124 (41.6)	112 (41.5)	12 (42.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Adherent mucosa (baseline), N (%)			
No	203 (68.1)	183 (67.8)	20 (71.4)
Yes	95 (31.9)	87 (32.2)	8 (28.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Tissue Thickness (baseline,) mean (SD)	1.46 (0.74)	1.47 (0.75)	1.33 (0.67)
Missing, N (%)	17 (5.7)	17 (6.3)	0 (0.0)
Peri-implant phenotype (baseline), N (%)			
Thin	111 (37.3)	99 (36.7)	12 (42.9)
Thick	183 (61.4)	167 (61.8)	16 (57.1)
Missing	4 (1.3)	4 (1.5)	0 (0.0)
Mucosal Margin Mobility (baseline), N (%)			
No	152 (51.0)	137 (50.7)	15 (53.6)
Yes	114 (38.3)	105 (38.9)	9 (32.1)
Missing	32 (10.7)	28 (10.4)	4 (14.3)
Type of Restoration (baseline), N (%)			
Single crown	98 (32.9)	94 (34.8)	4 (14.3)
Bridge	174 (58.4)	154 (57.0)	20 (71.4)
Overdenture	7 (2.4)	7 (2.6)	0 (0.0)
Full-arch fixed restoration	19 (6.4)	15 (5.6)	4 (14.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Restoration Retention (baseline), N (%)			
Screw-Retained	137 (45.9)	125 (46.3)	12 (42.9)
Cemented	154 (51.7)	138 (51.1)	16 (57.1)
Locator	2 (0.7)	2 (0.7)	0 (0.0)
Bar	5 (1.7)	5 (1.9)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Prosthesis Gap (baseline), N (%)			
No	219 (73.5)	201 (74.4)	18 (64.3)
Yes	79 (26.5)	69 (25.6)	10 (35.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Prosthesis Step (baseline), N (%)			
No	129 (43.3)	120 (44.4)	9 (32.1)
Yes	169 (56.7)	150 (55.6)	19 (67.9)

Missing	0 (0.0)	0 (0.0)	0 (0.0)
Emergence Angle (Worst) (baseline), mean (SD)	41.54 (19.78)	41.46 (20.05)	42.26 (17.24)
Missing, N (%)	4 (1.3)	3 (1.1)	1 (3.6)
Emergence Angle (>30°) (baseline), N (%)			
No	99 (32.2)	92 (34.1)	7 (25.0)
Yes	195 (65.4)	175 (64.8)	20 (71.4)
Missing	4 (1.3)	3 (1.1)	1 (3.6)
Emergence Profile (Worst) (baseline), N (%)			
Concave	13 (4.4)	13 (4.8)	0 (0.0)
Straight	81 (27.2)	72 (26.7)	9 (32.2)
Convex	199 (66.8)	182 (67.4)	17 (60.7)
Missing	5 (1.7)	3 (1.1)	2 (7.1)
Mesial Cantilever (baseline), N (%)			
No	244 (81.9)	222 (82.2)	22 (78.6)
Yes	49 (16.4)	43 (15.9)	6 (21.4)
Missing	5 (1.7)	5 (1.9)	0 (0.0)
Distal Cantilever (baseline), N (%)			
No	243 (81.5)	218 (80.7)	25 (89.3)
Yes	50 (16.8)	47 (14.4)	3 (10.7)
Missing	5 (1.7)	5 (1.9)	0 (0.0)
Prosthesis Mobility (baseline), N (%)			
No	273 (91.6)	246 (91.1)	27 (96.4)
Yes	25 (8.4)	24 (8.9)	1 (3.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Abutment (baseline), N (%)			
No	212 (71.1)	198 (73.3)	14 (50.0)
Yes	86 (28.9)	72 (26.7)	14 (50.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Platform Switching (baseline), N (%)			
No	234 (78.5)	212 (78.5)	22 (78.6)
Yes	64 (21.5)	58 (21.5)	6 (21.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Crown Dimension (baseline), mean (SD)	11.36 (2.34)	11.42 (2.34)	10.80 (2.30)
Missing, N (%)	17 (5.7)	15 (5.6)	2 (7.1)
Crown to Implant Ratio (baseline), mean (SD)	1.19 (0.33)	1.19 (0.34)	1.15 (0.22)
Missing, N (%)	22 (7.4)	19 (7.0)	3 (10.7)
Residual Cement Visible on Radiograph (baseline), N (%)			
No	294 (98.7)	266 (98.5)	28 (100.0)
Yes	4 (1.3)	4 (1.5)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Clinical Signs of Occlusal Overloading (baseline), N (%)			
No	184 (61.7)	167 (61.9)	17 (60.7)
Yes	114 (38.3)	103 (38.1)	11 (39.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Prosthetic design allowing access to hygiene (baseline), N (%)			
No	52 (17.5)	43 (15.9)	9 (32.1)

Yes	246 (82.6)	227 (84.1)	19 (67.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Restoration margin location (follow-up), N (%)			
Sub-marginal	231 (77.5)	213 (78.9)	18 (64.3)
Supra-marginal	22 (7.4)	20 (7.4)	2 (7.1)
Juxta-marginal	40 (13.4)	32 (11.9)	8 (28.6)
Missing	5 (1.7)	5 (1.8)	0 (0.0)
Vestibular-Lingual Position (baseline), N (%)			
Correct	249 (83.6)	225 (83.3)	24 (85.7)
Too vestibular	22 (7.4)	18 (6.7)	4 (14.3)
Too lingual	27 (9.1)	27 (10.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Plaque (baseline), N (%)			
0-5 sites/implant	276 (92.6)	256 (94.8)	20 (71.4)
6 sites/implant	22 (7.4)	14 (5.2)	8 (28.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Peri-implant health status (baseline), N (%)			
Peri-implant health	21 (7.1)	20 (7.4)	1 (3.6)
Peri-implant mucositis	105 (35.2)	96 (35.6)	9 (32.1)
Pre-peri-implantitis	95 (31.9)	89 (32.9)	6 (21.4)
Peri-implantitis	77 (25.8)	65 (24.1)	12 (42.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

Footnote:
N, number; SD, standard deviation.

Appendix Table 4. Patient-level risk/protective indicators associated with incidence of peri-implantitis during follow-up: multilevel simple logistic regression analysis.

Variable	OR	95% CI	*p-value*
Age (years) (each unit increase) (baseline)	1.06	0.97-1.17	0.183
Age ≧ 65 years (yes) (baseline)	1.75	0.48-6.47	0.399
Gender (female) (baseline)	2.37	0.56-10.00	0.239
Educational Level (baseline)			
Primary school	*Ref*	*Ref*	*Ref*
High school	1.17	0.25-5.51	0.840
Middle grade	0.31	0.04-2.47	0.269
University/College	0.19	0.02-1.56	0.121
Marital Status (baseline)			
Married	*Ref*	*Ref*	*Ref*
Widow	7.27	1.05-50.48	**0.045**
Divorced	0.28	0.022-3.59	0.330
Never married	1.51	0.16-14.36	0.719
Living with unmarried partner	1.64	0.75-35.99	0.753
Height (cm) (each unit increase) (baseline)	0.92	0.85-0.98	**0.017**
Weight (kg) (each unit increase) (baseline)	0.96	0.92-1.01	0.120
BMI (kg/m²) (each unit increase) (baseline)	0.95	0.79-1.14	0.578
Diabetes* (yes) (baseline)	1.65	0.32-8.63	0.552
Osteoporosis/Osteopenia (yes) (baseline)	3.49	0.82-14.81	**0.090**
Myocardial Infarction (yes) (baseline)	11.08	0.156-787.56	0.269
Hypertension* (yes) (baseline)	1.30	0.317-5.29	0.718
Stroke (yes) (baseline)	5.58	0.14-229-47	0.365
Anemia (yes) (baseline)	0.51	0.08-3.17	0.467
Cancer (yes) (baseline)	0.99	0.11-8.60	0.996
Depression* (yes) (baseline)	2.05	0.45-9.21	0.351
Asthma (yes) (baseline)	0.90	0.04-21.16	0.950
Cognitive or Memory Disorders (yes) (baseline)	1.10	0.07-17.77	0.945
Neurological Disorders (yes) (baseline)	NE	NE	NE
Immunological Disorders (yes) (baseline)	NE	NE	NE
Hypercholesterolemia (yes) (baseline)	0.80	0.21-3.09	0.745
Hepatitis (yes) (baseline)	0.43	0.02-0.12	**0.000**
HIV/AIDS (yes) (baseline)	NE	NE	NE
Rheumatoid Arthritis (yes) (baseline)	2.59	0.49-13.79	0.264
Respiratory Diseases (yes) (baseline)	0.64	0.071-5.77	0.692
Liver Diseases (yes) (baseline)	NE	NE	NE
Cardiovascular Diseases (yes) (baseline)	0.46	0.04-5.34	0.538
Gastrointestinal Disorders (yes) (baseline)	1.38	0.27-7.15	0.699
Kidney Diseases (yes) (baseline)	1.19	0.86-16.35	0.899
Thyroid Disorders (yes) (baseline)	2.26	0.51-10.08	0.285
Cataract (yes) (baseline)	1.67	0.37-7.55	0.507
Other Medical Diseases (yes) (baseline)	0.58	0.7-5.01	0.618
Sars-CoV 2 History (yes) (follow-up)	0.78	0.20-3.03	0.725
Covid-19 History (yes) (follow-up)	0.53	0.13-2.20	0.383
Sars-CoV 2 vaccine (yes) (follow-up)	NE	NE	NE
At least one systemic disease (yes) (baseline)	0.39	0.73-2.07	0.269

Number of systemic diseases (each unit increase) (baseline)	1.12	0.86-1.45	0.394
Smoking (baseline)			
Non-smokers	*Ref*	*Ref*	*Ref*
Current smokers	4.48	1.05-19.10	**0.043**
Sleep Duration (baseline)			
<7 hours	1.97	0.56-6.95	0.290
7-8 hours	*Ref*	*Ref*	*Ref*
>7 hours	50.91	1.46-1770.05	**0.030**
Regular Moderate (≥3 times/week ≥20 minutes) Physical Activity (baseline)	1.35	0.23-7.94	0.741
Stress (baseline)			
Absolutely nothing	*Ref*	*Ref*	*Ref*
Mild / Moderate	0.64	0.13-3.14	0.581
High	0.97	0.11-8.77	0.979
Coffee Consumption (yes) (baseline)	1.73	0.31-9.57	0.529
Alcohol Consumption (baseline)			
Never	*Ref*	*Ref*	*Ref*
Less than 2 times/week	0.24	0.60-0.94	**0.040**
Almost everyday	0.46	0.07-3.17	0.432
1/day	0.24	0.25-2.32	0.217
2 or more times/day	NE	NE	NE
Alcohol Consumption (yes) (baseline)			
Never	*Ref*	*Ref*	*Ref*
At least sometimes	0.26	0.78-0.88	**0.030**
Bisphosphonates (yes) (baseline)	0.04	0.01-0.12	**0.000**
Corticosteroids (yes) (baseline)	0.84	0.04-19.18	0.911
NSAIDs (yes) (baseline)	0.50	0.03-9.98	0.652
Antiplatelet (yes) (baseline)	2.14	0.20-22.60	0.528
Anticoagulant (yes) (baseline)	2.13	0.20-22.60	0.528
Hypolipidemic agent (yes) (baseline)	2.33	0.56-9.70	0.244
Antidepressant (yes) (baseline)	2.21	0.43-11.38	0.341
Proton Pump Inhibitor (yes) (baseline)	1.91	0.13-27.02	0.633
Vitamin D (yes) (baseline)	0.04	0.02-0.12	**0.000**
Calcium (yes) (baseline)	2.82	0.45-17.82	0.446
Thyroid Drug (yes) (baseline)	2.49	0.55-11.28	0.236
Immunosuppressant (yes) (baseline)	0.41	0.01-0.12	**0.000**
Insulin (yes) (baseline)	3.02	0.22-40.70	0.406
Oral Hypoglycemic Agent (yes) (baseline)	1.31	0.18-9.57	0.790
Other Anti-diabetic Drug (yes) (baseline)	NE	NE	NE
Beta-blockers (yes) (baseline)	1.48	0.13-16.75	0.750
Diuretics (yes) (baseline)	0.92	0.09-9.36	0.944
ACE Inhibitors (yes) (baseline)	1.56	0.21-11.65	0.666
Other Antihypertensive Drugs (yes) (baseline)	NE	NE	NE
Other Drugs (yes) (baseline)	1.00	0.24-4.11	0.996
Number of medications (each unit increase) (baseline)	1.18	0.86-1.61	0.312
Supplements (yes) (baseline)	1.58	0.34-7.33	0.561
Periodontal Status (AAP) (baseline)			
No/Mild Periodontitis	*Ref*	*Ref*	*Ref*
Moderate/Severe Periodontitis	0.80	1.78-3.60	0.771

Edentulous	0.58	0.04-8.33	0.686
Periodontal status (2017 WWP) (baseline)			
No periodontitis or SI-III periodontitis	*Ref*	*Ref*	*Ref*
Stage 4 periodontitis	9.08	2.58-31.92	**0.001**
Edentulous	1.42	0.19-10.69	0.736
Number of Remaining Teeth (each unit increase) (baseline)	0.91	0.83-0.99	**0.044**
Number of Remaining Teeth (≥16) (baseline)	9.68	2.56-36.57	**0.001**
Number of Dental Implants (each unit increase) (baseline)	1.24	0.95-1.63	0.120
Number of Dental Implants (≥4) (baseline)	4.14	0.63-27.06	0.139
History of Orthodontic Treatment (yes) (baseline)	1.20	0.30-4.75	0.795
Toothbrushing Frequency (baseline)			
Not everyday	NE	NE	NE
1 time/day	1.68	0.22-12.89	0.615
2 times/day	1.24	0.30-5.09	0.766
3 or more times/day	*Ref*	*Ref*	*Ref*
Electric Toothbrush (yes) (baseline)	4.68	1.00-21.96	**0.050**
Interproximal Flossing/Brushing on Implants (at least on some implants) (baseline)	4.59	0.31-67.48	0.267
Bruxism Signs (yes) (baseline)	1.19	0.29-4.80	0.809
Bruxism Symptoms (yes) (baseline)	2.03	0.46-8.92	0.346
Dry Mouth (yes) (baseline)	2.50	0.66-9.51	0.177
Number of maintenances between baseline and follow-up (each unit increase) (follow up)	1.15	0.70-1.87	0.584
Regular maintenance between baseline and follow-up (≥1 per year) (follow up)	0.75	0.11-5.12	0.768
FMPS, excluding implants (each unit increase) (follow-up)	1.01	0.95-1.06	0.810
FMBS, excluding implants (each unit increase) (follow-up)	1.00	0.94-1.06	0.997
Number PD≥4mm, excluding implants (each unit increase) (follow-up)	1.00	0.95-1.06	0.885
Number PD≥5mm, excluding implants (each unit increase) (follow-up)	1.04	0.95-1.13	0.403
Number PD≥6mm, excluding implants (each unit increase) (follow-up)	1.10	0.96-1.26	0.181
Number FI ≥ 2 (each unit increase) (follow-up)	1.16	0.75-1.77	0.509
Periodontal bone loss/age ratio (each unit increase) (follow-up)	12.58	0.94-167.61	**0.055**
Allergies (yes) (baseline)	2.32	0.52-10.26	0.268
Chemotherapy (yes) (baseline)	5.58	0.14-229.47	0.365
Radiotherapy (yes) (baseline)	NE	NE	NE

Footnote:
CI, confidence interval; FI, furcation involvement; NE, not estimable; FMBS, full mouth bleeding score; FMPS, full mouth plaque score; OR, odds ratio; PD, probing pocket depth; Ref, reference category.
* self-reported history or medication
P<0.10 are reported in bold

Appendix Table 5. Implant-level risk/protective indicators associated with incidence of peri-implantitis during follow-up: multilevel simple logistic regression analysis.

Variable	OR	95% CI	*p-value*
Jaw (maxilla) (baseline)	1.47	0.53-4.06	0.454
Position (baseline)			
Anterior (canine-canine)	*Ref*	*Ref*	*Ref*
Posterior	0.61	0.17-2.23	0.434
Side (left) (baseline)	1.70	0.68-4.26	0.261
Replaced tooth (baseline)			
Molar	*Ref*	*Ref*	*Ref*
Premolar	1.06	0.37-3.00	0.914
Canine	NE	NE	NE
Incisor	5.48	1.07-28.04	**0.041**
Mouth zone (baseline)			
Posterior Maxilla	*Ref*	*Ref*	*Ref*
Anterior Maxilla	1.04	0.18-6.13	0.963
Posterior Mandible	1.27	0.41-3.87	0.679
Anterior Mandible	4.25	0.66-27.54	0.129
Implant Brand (baseline)			
Straumann	*Ref*	*Ref*	*Ref*
Nobel Biocare	2.56	0.43-15.27	0.304
AstraTech	2.11	0.47-9,53	0.332
Other	1.10	0.26-4.73	0.894
Implant Collar (baseline)			
0 mm	*Ref*	*Ref*	*Ref*
≤ 1.5 mm	0.61	0.50-7.36	0.693
> 1.5 mm	0.68	0.19-2.45	0.560
Implant length (each mm increase) (baseline)	0.94	0.68-1.30	0.690
Implant diameter (each mm increase) (baseline)	0.35	0.08-1.43	0.143
At Least One adjacent Tooth (yes) (baseline)	0.30	0.11-0.82	**0.019**
Reason of Tooth Loss (baseline)			
Caries	*Ref*	*Ref*	*Ref*
Periodontitis	1.19	0.31-4.57	0.803
Trauma	NE	NE	NE
Agenesia	NE	NE	NE
Other reason/Unknown	NE	NE	NE
Keratinized Tissue Height (baseline)			
KTH=0 mm	*Ref*	*Ref*	*Ref*
>0 mm & <=2mm	0.38	0.10-1.43	0.153
KTH>2mm	1.02	0.25-4.12	0.983
Adherent mucosa (yes) (baseline)	1.22	0.42-3.58	0.715
Tissue Thickness (mm) (baseline)	0.79	0.38-1.67	0.536
Peri-implant phenotype (thick) (baseline)	0.83	0.30-2.28	0.711
Mucosal Margin Mobility (yes) (baseline)	0.60	0.20-1.83	0.370
Type of Restoration (baseline)			
Single crown	*Ref*	*Ref*	*Ref*

Bridge	3.06	0.83-11.27	**0.093**
Overdenture	NE	NE	NE
Full-arch fixed restoration	12.48	1.13-137.67	**0.039**
Restoration Retention (baseline)			
Screw-Retained	*Ref*	*Ref*	*Ref*
Cemented	0.68	0.21-2.19	0.520
Locator	NE	NE	NE
Bar	NE	NE	NE
Prosthesis Gap (yes) (baseline)	1.31	0.46-3.71	0.607
Prosthesis Step (yes) (baseline)	2.25	0.80-6.35	0.126
Emergence Angle (Highest) (each degree increase) (baseline)	1.01	0.98-1.03	0.707
Emergence Angle (Highest) (>30°) (baseline)	1.74	0.58-5.24	0.322
Emergence Profile (Worst) (baseline)			
Concave	NE	NE	NE
Straight	*Ref*	*Ref*	*Ref*
Convex	0.67	0.23-1.92	0.458
Mesial Cantilever (yes) (baseline)	1.23	0.38-3.94	0.726
Distal Cantilever (yes) (baseline)	0.52	0.12-2.24	0.377
Prosthesis Mobility (yes) (baseline)	0.52	0.05-5.93	0.601
Abutment (yes) (baseline)	2.51	0.86-7.32	**0.093**
Platform Switching (yes) (baseline)	1.13	0.31-4.09	0.854
Crown Dimension (each mm increase) (baseline)	0.97	0.77-1.23	0.805
Crown to Implant Ratio (each mm increase) (baseline)	0.65	0.09-4.72	0.675
Residual Cement Visible on Radiograph (yes) (baseline)	NE	NE	NE
Clinical Signs of Occlusal Overloading (yes) (baseline)	1.16	0.37-3.59	0.799
Prosthetic design allowing access to hygiene (yes) (baseline)	0.21	0.059-0.73	**0.014**
Restoration margin location (follow-up)			
Sub-marginal	*Ref*	*Ref*	*Ref*
Supra-marginal	0.61	0.063-5.81	0.664
Juxta-marginal	2.87	0.87-9.48	**0.085**
Vestibular-Lingual Position (baseline)			
Correct	*Ref*	*Ref*	*Ref*
Too vestibular	4.12	0.87-19.49	**0.074**
Too lingual	NE	NE	NE
Plaque (baseline)			
0-5 sites/implant	*Ref*	*Ref*	*Ref*
6 sites/implant	6.04	1.64-22.18	**0.007**
Peri-implant health status (baseline)			
Peri-implant health	*Ref*	*Ref*	*Ref*
Peri-implant mucositis	1.76	0.16-19.82	0.646
Pre-peri-implantitis	1.08	0.94-12.58	0.946
Peri-implantitis	2.34	0.20-27.13	0.498

Footnote:
OR, odds ratio; CI, confidence interval; Ref, reference category; KTH, Keratinized Tissue Height.
P<0.10 are reported in bold