Received: 25 July 2017 | Revised: 19 September 2017 | Accepted: 20 October 2017

DOI: 10.1002/JPER.17-0454

JOURNAL OF Periodontology

ORIGINAL ARTICLE

Diagnostic accuracy of clinical parameters to monitor peri-implant conditions: A matched case-control study

Alberto Monje[1,2,3] | Jordi Caballé-Serrano[4] | Jose Nart[3] | David Peñarrocha[5] | Hom-Lay Wang[1] | Mia Rakic[6,7]

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

[2]Department of Oral Surgery and Stomatology, ZMK School of Dentistry, Bern, CH

[3]Department of Periodontology, Universitat Internacional de Catalunya, Barcelona, Spain

[4]Department of Oral and Maxillofacial Surgery, Universitat Internacional de Catalunya, Barcelona, Spain

[5]Department of Oral Surgery, Universitat de Valencia, Valencia, Spain

[6]INSERM UMR-1229 RMeS, Faculty of Dental Surgery, University of Nantes, Nantes, France

[7]Institute for Biological Research "Sinisa Stankovic", University of Belgrade, Belgrade, Serbia

Correspondence
Alberto Monje, DDS, MS
Department of Periodontics and Oral Medicine
School of Dentistry, University of Michigan,
Ann Arbor, MI, USA
1011 North University Avenue
Ann Arbor, Michigan, 48109-1078.
Email: amonjec@umich.edu

Abstract

Background: The aim of this case-control study was to estimate the diagnostic accuracy of the standard clinical parameters in diagnosing healthy peri-implant tissues, peri-implant mucositis, and peri-implantitis.

Methods: A case-control study was designed to compare the clinical parameters used in the diagnosis of peri-implant diseases such as: probingdepth (PD), bleeding on probing (BOP), mucosal redness (MR), suppuration (SUP), and plaque index (PI). Furthermore, the influence of patient- (sex, age) and implant-related variables (implant neck configuration, time in function after loading) were evaluated to investigate the association with the clinical findings. The inferential analysis consisted of estimation by generalized estimating equations (GEE) of multilevel logistic regression models.

Results: In total, 1,572 sites were evaluated around 262 implants from 141 patients. Sites with implant mucositis showed significant levels of BOP (OR = 3.56), MR (OR = 7.66) and PD (OR = 1.48) compared to healthy sites. The specificity was 90.3% while the sensitivity was only 43.6%. Likewise, sites exhibiting peri-implantitis showed significant levels of BOP (OR = 2.32), MR (OR = 7.21), PD (OR = 2.43) and SUP (OR = 6.81) compared to healthy sites. Again, the multiple logistic regressions showed high specificity (92.1%) but modest sensitivity (52.5%). PD was the only diagnostic marker displaying significance comparing peri-implant mucositis and peri-implantitis sites (OR = 1.76). Moreover, tissue-level compared to bone-level implants were less associated with SUP+ (OR = 0.20), and PI (OR = 0.36) and demonstrated statistical significance. In addition, age, sex, and function time significantly influenced the tested clinical parameters.

Conclusions: The diagnosis of peri-implant diseases cannot rely solely upon individual clinical parameters but rather require a combination of criteria. The clinical parameters, particularly probing depth, might accurately discern between diagnoses among peri-implant conditions. Nevertheless, the specificity of the clinical parameters surpasses the sensitivity in the detection of peri-implant diseases, validating its potential use as a diagnostic tool.

KEYWORDS

diagnosis, peri-implant diseases, peri-implant mucositis, peri-implantitis, periodontal disease, probing pocket depth, prognosis

1 | INTRODUCTION

Peri-implant diseases is becoming a more common condition, reaching a frequency of 30 to 40% determined at the implant-level.[1] Such a condition was first described in 1965 as soft tissue inflammation and concomitant bone destruction.[2] Later, as the fields of implantology and microbiology advanced, peri-implantitis was described as an imbalance in the bacterial load and host response.[3] Subsequently, mucositis was paralleled with gingivitis and peri-implantitis to chronic periodontitis, and certain putative bacteria were capable of inducing the observed inflammatory response. Hence, mucositis and peri-implantitis were considered pathological counterparts of gingivitis and periodontitis on implants,[4] while the keystone periopathogens were considered responsible for induction of the local immunological dysbiosis.[5] However, recent research revealed that periodontal and peri-implant pathologies express different pathological characteristics since peri-implant lesions demonstrated more aggressive behavior and follow a progressive course[6] In parallel, it was shown that treatment protocols adopted from periodontology provided unpredictable outcomes on implants with high recurrence rates.[7] Hence, peri-implant diseases were defined as important pathological entities due to the increasing prevalence and lack of a standard treatment protocol.[8,9]

Moreover, the high rate of inconsistency among case definitions was identified as an initial problem; thus, the European Federation of Periodontology (EFP) along with the American Academy of Periodontology (AAP) held a series of consensus meetings to define peri-implant diseases based on clinical and radiographic features.[10–13] Hence, it was emphasized that there was a need for standardization of implant clinical parameters in order to provide accurate diagnostic values.[10] As such, it was agreed that the hemostatic biologic bone remodeling triggers up to a maximum acceptable threshold of 2 mm bone loss.[10–13] Pathologic bone loss was defined as progressive bone loss beyond this extent caused by biofilm-induced inflammatory conditions.[10]

It is important to acknowledge that peri-implant tissues histologically depict different anatomical structures when compared to the periodontium due to lack of two periodontal tissues, which compromises homeostatic potential to abrogate infective and biomechanical threats. While evolution has created a tight attachment to dentition surface via the long-junctional epithelium in the periodontium, peri-implant tissues are primarily supported with loose and parallel-oriented fibers, providing a compromised coronal seal.[14] As such, the low diagnostic accuracy and sensitivity of probing depth does not seem to accurately reflect disease/healthy condition per se when compared to natural dentition.[15,16] Moreover, the lack of standardization in dental implant macro- and micro-design leads to difficulty in reaching reproducible diagnostic tools.[10] Nevertheless, probing depth might still be a good diagnostic indicator but it is often suggested to combine the radiographic finding for the final diagnosis.[10,17]

Bleeding on probing is reported to have a high specificity and reasonable sensitivity to detect periodontitis.[18–20] Again, understanding the weak hemidesmosome attachment to the implant surface is imperative to discern appropriate probe penetration and bleeding. In the presence of inflammation, bleeding should be present indicating high sensitivity when probing deeper sites;[21] however, the lack thereof in healthy condition does not seem to translate with high specificity.[22] In this regard, it is noteworthy to mention that the mucogingival shift after implant placement often decreases the presence of keratinized mucosa, triggering a greater inflammatory status on peri-implant tissues.[23] Thereupon, bleeding on probing, although it might reliably indicate presence of disease, does not seem to be a suitable single diagnostic parameter for peri-implantitis. On the other side, suppuration is caused by necrosis of peri-implant tissues, rich in polymorphonuclear cells. Thus, suppuration is logically and statistically a sensitive indicator of bone turnover.[24] In this scenario, it must be noted that, if detected in early stages where bone resorption has not occurred yet, it might be a consequence of a foreign body reaction (i.e., residual cement or dental floss remnants) or biofilm.[25,26]

Therefore, although the use of clinical parameters with radiological proof of bone changes represents a "gold standard", the diagnostic value of clinical parameters of

implants is still controversially reported and not well defined.[10] Standardization of the diagnostic parameter implies well defined methodological approach intended to estimate the accuracy, precision, sensitivity and specificity of the parameter to distinguish different states of the target tissue or organ. The main pre-condition for reliable estimates is the use of a strict case definition and related criteria as well as use of appropriate analytical methods for data analysis. To the best of our knowledge, this is the first study to estimate diagnostic accuracy of the clinical parameters on implants using multiple analytical methods indicated for validation of diagnostic parameters. It is of the authors' hypothesis that assessment of multiple clinical parameters will provide more accurate diagnostic information than independent parameters in evaluation of peri-implant tissues. Hence, the aim of this case-control study was to estimate the diagnostic accuracy of the standard clinical parameters to diagnose healthy peri-implant tissues, peri-implant mucositis, and peri-implantitis.

2 | MATERIALS AND METHODS

The present case-control study was conducted in accordance with the Helsinki declaration of human studies and received approval from the ethics committee from the University of Extremadura (Badajoz, Spain; approval # 18002909) as monitoring center. Moreover, this study was registered and approved by Clinicaltrials.gov (NCT 03031392). The current study was reported according to the EQUATOR guidelines and followed the STARD statement on diagnostic accuracy.[27] All participants provided written informed consent.

2.1 | Study population

All participants enrolled had to be consecutively evaluated in the routine peri-implant maintenance therapy with dental implants in function with fixed prosthesis for a minimum of 12 months after final prosthesis delivery from July 2016 up to April 2017. Patients were contacted and informed to participate in a cross-sectional assessment to identify the presence of peri-implant diseases or the evaluation was carried out during supportive periodontal/peri-implant therapy. Baseline periapical x-ray at the time of prosthesis delivery was retrospectively assessed to exclude implants with excessive early peri-implant bone loss before function that might lead to misdiagnosis (i.e., ≥2 mm from implant-abutment connection). If no baseline x-ray was available, the implant was automatically excluded from the analysis. Two independent examiners conducted the clinical assessment. To compensate the possible variability of the data prior to the analysis, the Chi^2 test was applied to check for homogeneity. Additionally, to check the homogeneity of the variables provided by the examiners, the Kruskal-Wallis statistical method was applied.

A matched case-control study was conducted on 141 implant patients (62.4% males and 37.6% females with a mean age of 57.6 ± 10.2 | range = 23 to 79 years). Of these patients, 47 had implants with mucositis, 47 patients with peri-implantitis and the remaining 47 patients with healthy implants. There were a total of 262 implants where 90 were healthy, 76 with mucositis and 96 with peri-implantitis. In total, 1,572 sites were evaluated. Table 1 presents the demographic data at patient-, implant- and site-specific levels.

2.2 | Eligibility criteria

The following inclusion criteria were applied: patients within the age range of 18 to 80 years, non- or light-smokers (<10 cigarettes/day), no presence of infectious diseases at the time of implant placement or during the maintenance program, implants placed in pristine bone, no presence of systemic disease or condition or medication known to alter bone metabolism (i.e. bisphosphonates), partial edentulous patients without sign of active periodontal disease with or without history of chronic periodontitis. On the contrary, individuals were excluded for the following reasons: pregnancy, lactation, history of or current heavy smoking (≥10 cigarettes/day), uncontrolled medical conditions such as diabetes mellitus, not adequate 3-dimensional implant position, implants placed in sites known to have received grafting procedures to augment the edentulous ridges, cement-retained restorations, not properly restored (i.e., overcontoured) impeding accurate probing depth recording or lack/minimal of keratinized mucosa.

2.3 | Case definition of peri-implant mucositis

As suggested by the AAP academy statement[11] and the VIII EFP Workshop[10] peri-implant mucositis was defined as an inflammatory condition that courses with swelling (tumor) and bleeding in the lack of radiographic peri-implant marginal bone loss beyond initial physiological bone remodeling. As such, implants with no bleeding, or only bleeding on probing at one surface assuming a point of bleeding as a consequence of trauma from probing, no suppuration, and bone loss < 2.0 mm were considered healthy. On the other side, overt bleeding (≥2 sites), tissue edema with minimal isolated or no suppuration and radiographic marginal bone loss < 2 mm was defined as mucositis.[28]

2.4 | Case definition of peri-implantitis

Definition peri-implantitis based was based upon clinical inflammation combined with radiographic bone loss. Accordingly, the presence of clinical inflammation in combination with radiographic bone loss > 2 mm as earlier proposed in the VIII EFP Workshop[10] The landmark used to evaluate the peri-implant bone level was the neck in the case of rough full-bodied implants, or the rough-to-smooth interface in case of

TABLE 1 Table of demographics at patient- implant- and site-levels

	Category	n	%	Mean ± SD	Total
Patient Level (n = 141)					
Group	Healthy	47	33.3		
	Mucositis	47	33.3		
	Peri-implantitis	47	33.3		
Age (years)				57.6 ± 10.2	
Sex	Men	88	62.4		
	Women	53	37.6		
Implants (n)				1.9 ± 1.3	262
Healthy implants (n)				0.9 ± 1.2	127
Mucositis implants (n)				0.5 ± 1.9	74
Peri-implantitis implants (n)				0.4 ± 0.7	61
Implant Level (n = 262)					
Group	Healthy	127	48.5		
	Mucositis	74	28.2		
	Peri-implantitis	61	23.3		
Time in function (years)				3.17 ± 2.04	
Position	MD ant.	26	9.9		
	MD post.	97	37.0		
	MX ant.	39	14.9		
	MX post.	100	38.2		
System	NB	84	32.1		
	STR	67	25.6		
	MG	52	19.8		
	BH	27	10.3		
	MIS	16	6.1		
	Other	16	6.1		
Neck design	BL	205	78.2		
	TL	57	21.8		
Rx MBL (mm)				1.06 ± 1.42	
Sites with plaque (n)				2.14 ± 2.46	
Sites with BOP (n)				2.14 ± 2.28	
PD average on implants (mm)				3.26 ± 1.40	
Sites with MR (n)				1.40 ± 2.16	
Sites with SUP (n)				0.61 ± 1.71	
Site Level (n = 1,572)					
Plaque	Yes	560	35.6		
BOP	Yes	1011	64.3		
PD (mm)				3.26 ± 1.57	
MR	Yes	347	22.7		
Suppuration	Yes	159	10.1		

MD = mandibular; MX = maxillary; ant = anterior; post = posterior; BL = bone level; TL = tissue level; Rx MBL = radiographic marginal bone loss; BH = Biohorizon (Birmingham, AL); MG = MozoGrau (Valladolid, Spain); NB = Nobel Biocare (Gothenburg, Sweden); STR = Straumann (Basel, Switzerland); MIS (Savion, Israel).

tissue level implants. As such, signs as presence of suppuration, bleeding on probing, mucosal redness, and probing depth were recorded at six sites per implant applying 0.15N/cm force as suggested by the AAP academy statement.[11]

2.5 | Alternative case definitions of peri-implantitis

Besides of the case definition proposed in the VIII EFP Workshop,[10] alternative case definitions as proposed

elsewhere[29] were further applied to assess the diagnostic accuracy. As such, peri-implant marginal bone loss of ≥0.5 mm, ≥1 mm, ≥3 mm and ≥4 mm in the presence of clinical inflammation were thresholds to study on the different case definitions for peri-implantitis.

2.6 | Radiographic assessment

One calibrated (AM) examiner conducted the radiographic assessment. The peri-implant radiographic bone loss (RBL) was determined by taking linear measurements from the most mesial and distal point of the implant platform to the crestal bone on each peri-apical radiograph, corrected according to the known height and width of each implant using ImageJ (National Institute of Health). Moreover, a baseline x-ray (after prosthesis delivery) was obtained from the records to measure the initial physiological marginal bone loss to determine the progressed bone loss as consequence of an inflammatory condition (i.e. peri-implantitis).

2.7 | Clinical assessment

The following clinical parameters were recorded: probing pocket depth (PD), plaque index (PI), bleeding on probing (BOP), mucosal redness (MR) and suppuration (SUP). All these aforementioned parameters were recorded at six sites per implant. In addition, the implant's neck design was subdivided in tissue-level or bone-level according to implant's manufacturer description to further investigate the impact of these on the peri-implant disease-related parameters.

2.8 | Statistical analysis

The statistical package IBM SPSS 15.0 was used to analyze the data. The three diagnosed groups were compared in pairs, aiming to identify the factors related to patient, implant and clinical parameters in the site able to distinguish between groups. The inferential analysis consisted of estimation by generalized estimating equations (GEE) of multilevel logistic regression models. Three levels of analyses were taken into consideration: patient, implant and site. The impact or degree of association between a predictive factor and the implant diagnose were estimated as odds ratio (OR) and confidence interval of 95% using a Chi^2 of Wald statistical test. The exactitude of the outcomes studied was evaluated by means of tables of classification of forecasts against real diagnoses. The statistical significance used in the analysis was set to 5% ($\alpha = 0.05$).

A logistic model was described for the association between the outcome and an independent factor of two levels to reach a power of 80% to detect a significant OR of 2.0 within the sample, assuming a 95% confidence level. The power was calculated assuming an intra-class correlation (ICC) of 0.25 based on previous studies.[20,30,31]

3 | RESULTS

3.1 | Diagnostic accuracy of peri-implant mucositis-related parameters vs. health

The following parameters demonstrated significance: 1) BOP: A site presenting as BOP+ significantly increased its diagnosis as mucositis (OR = 3.56; $P < 0.001$). The multiple logistic regression further demonstrated significance (OR = 2.13; $P = 0.013$); 2) MR: A site presenting as MR+ significantly increased its diagnosis of mucositis (OR = 7.66; $P < 0.001$). The multiple logistic regression further demonstrated significance (OR = 4.61; $P = 0.001$); and 3) PD: The mean PD for healthy implants was 2.63±1.21 mm and for mucositis was 3.26±1.57 mm. For each 1 mm of increased PD, it significantly increased its diagnosis of mucositis by 48% (OR = 1.48; $P < 0.001$). The multiple logistic regression further demonstrated every 1 mm increase of PD (OR = 1.39; $P = 0.001$) was associated with a 39% greater likelihood of mucositis.

Accordingly, the following equation summarizes the findings to accurately diagnose peri-implant mucositis when compared to healthy sites based on the clinical parameters (Figure 1):

$$\frac{p}{1-p} = 0.12\ 2.13^{BOP}\ 4.61^{MR} 1.39^{PD}$$

Therefore, 90.3% of the sites could be accurately diagnosed as healthy, showing high specificity, while only 43.6% could accurately diagnose mucositis, demonstrating low sensitivity. The positive and negative predictive values were 71.2% and 74.4%, respectively. As such, in total, 73.7% implants were accurately diagnosed using this diagnostic formula. The area under curve (AUC) of the ROC curve (Figure 2) associated to logistic model was 0.77 (95%CI: 0.74 to 0.89).

3.2 | Diagnostic accuracy of peri-implantitis-related parameters vs. health

The following parameters demonstrated significance: 1) BOP: A site presenting BOP+ significantly increased its diagnosis of peri-implantitis (OR = 2.32; $P = 0.003$). However, with adjustment via the multiple logistic regression model, no significance was observed; 2) MR: A site presenting MR+ significantly increased its diagnosis of peri-implantitis (OR = 7.21; $P < 0.001$). The multiple logistic regression model further demonstrated significance (OR = 3.28; $P = 0.003$); 3) PD: The mean PD for healthy implants was 2.63 ± 1.21 mm and for peri-implantitis was 4.58 ± 1.71 mm. For each 1 mm of increased PD, it significantly increased its diagnosis of peri-implantitis (OR = 2.43; $P < 0.001$). The multiple logistic regression model further demonstrated significance for every 1 mm increase of PD (OR = 2.03; $P < 0.001$) a 200% greater

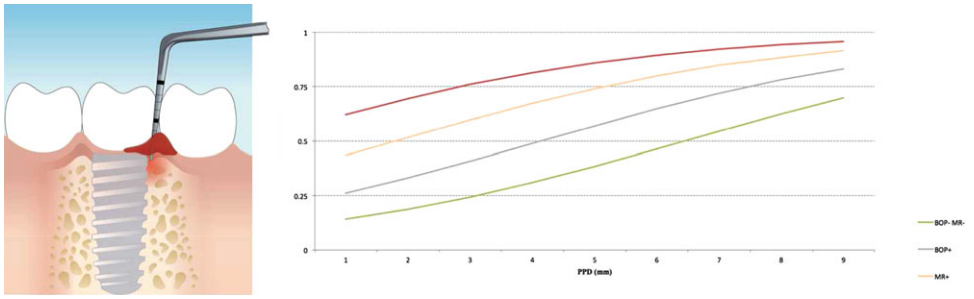

FIGURE 1 Graph of the predicted probability of peri-implant mucositis compared to healthy condition by different levels of significant predictors from generalized estimating equation (GEE) of multilevel logistic regression model

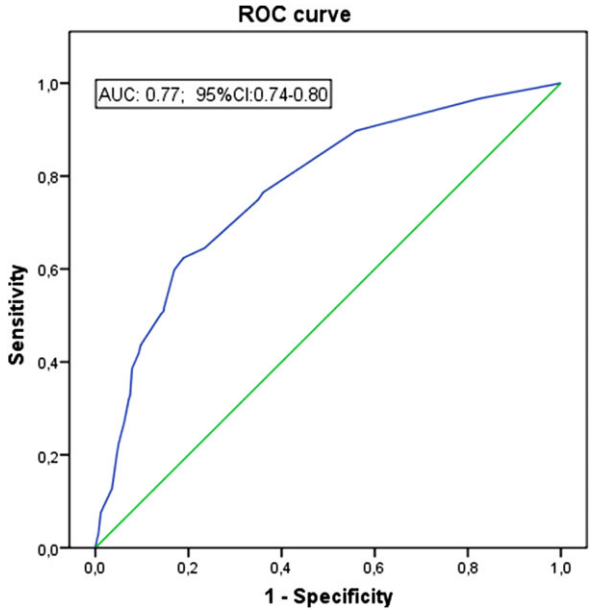

FIGURE 2 Receiving operating characteristics (ROC) curve graph on the sensitivity and specificity to detect peri-implant mucositis compared to health according to the generalized estimating equation (GEE)

the odds of peri-implantitis; and 4) SUP: A site presenting SUP+ significantly increased its diagnosis of peri-implantitis (OR = 6.81; $P < 0.001$).

Moreover, PI was observed to play a dominant role in the peri-implantitis status, as PI was significantly higher at sites diagnosed with peri-implantitis (OR = 2.32; $P = 0.003$). Although not reaching statistical significance, the logistic regression model did verified its importance (OR = 1.7; $P = 0.096$)

Accordingly, the following equation summarizes the findings to accurately diagnose peri-implantitis when compared to healthy sites based on the described clinical parameters (Figure 3):

$$\frac{p}{1-p} = 0.023\ 1.70^{PI} 3.28^{MR} 2.03^{PD}$$

Applying the equation in Figure 3, the sensitivity to diagnose peri-implantitis was 52.5% with a specificity of 92.1%. The positive and negative predictive values were 72.7% and 82.8% respectively. As such, in total, 82.8% implants were accurately diagnosed using this model system. The AUC of the ROC curve (Figure 4) was 0.81 (95%CI: 0.78 to 0.84).

3.3 | Diagnostic accuracy of peri-implantitis-related parameters vs. mucositis

The following parameters demonstrated significance: 1) PD: For each 1 mm of increased PD, each site significantly increased its diagnosis of peri-implantitis (OR = 1.76; $P < 0.001$). The multiple logistic regression model demonstrated with statistical significance that every 1 mm increase of

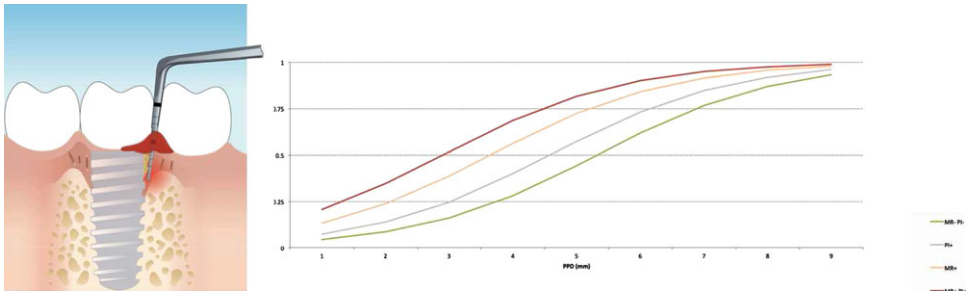

FIGURE 3 Graph of the predicted probability of peri-implantitis compared to healthy condition by different levels of significant predictors from generalized estimating equation (GEE) of multilevel logistic regression model

JOURNAL OF Periodontology

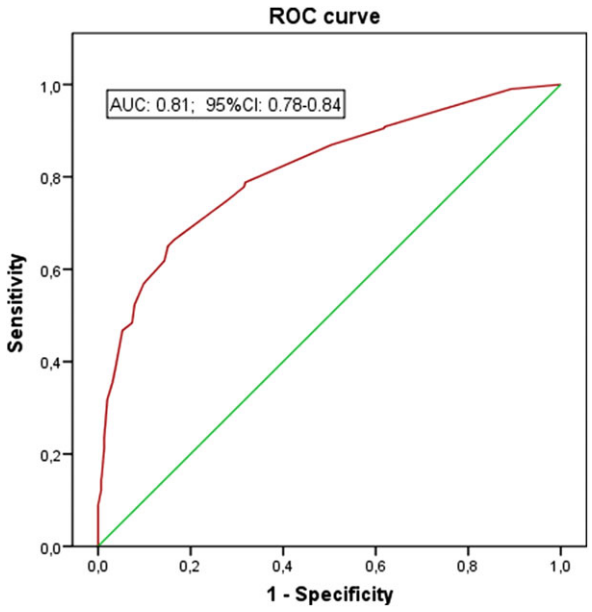

FIGURE 4 Receiving operating characteristics (ROC) on the sensitivity and specificity to detect peri-implantitis compared to health according to the generalized estimating equation (GEE)

PD (OR = 1.75; $P < 0.001$) was associated with a 75% greater likelihood of peri-implantitis; and 2) SUP: Although statistical significance was not achieved, a site presenting SUP+ showed a positive trend associated with peri-implantitis compared to mucositis sites (OR = 2.5; $P = 0.088$).

Moreover, PI demonstrated to have a dominant role in peri-implantitis, as it was significantly more present in sites diagnosed with peri-implantitis (OR = 3.46; $P = 0.001$). Although not reaching statistical significance, the logistic regression model could verify its importance (OR = 3.40; $P = 0.002$)

Consequently, the following equation summarizes the findings to accurately diagnose peri-implantitis when compared to mucositis sites based on the clinical parameters:

$$\frac{p}{1-p} = 0.060\ 3.40^{PI}\ 1.75^{PD}$$

Therefore, applying that equation, the sensitivity to diagnose peri-implantitis when compared to mucositis was 58.2% with a specificity of 81.3%. The positive and negative predictive values were 71.9% and 70.2%, respectively. The AUC of the ROC curve (see supplementary Figure 1 in online *Journal of Periodontology*) is 0.76 (95%CI: 0.72 to 0.79).

3.4 | Association of implant's neck design and peri-implant disease-related parameters

Tissue-level compared to bone-level implants were less associated with SUP+ (OR = 0.20; $P = 0.041$), and PI (OR = 0.36; $P = 0.002$), representing a lower risk of 80% and 64% of being present in tissue-level Implants, respectively. A linear regression was calculated for PD and it was shown that tissue-level implants have an average reduction of 0.38 mm compared to bone-level implants, showing a considerable trend towards significance ($P = 0.082$). Conversely, neither BOP nor MR displayed significance ($P = 0.803$ and $P = 0.554$, respectively).

3.5 | Association of patient-specific factors and function time

While neither sex nor age significantly influenced the odds of a health, mucositis, or peri-implantitis diagnosis, the function time was associated on the diagnostic accuracy when health was compared to peri-implantitis (OR = 2.44; $P < 0.001$) and when mucositis was compared to peri-implantitis (OR = 1.87; $P < 0.001$).

In addition, the following parameters were statistically significantly associated to patient-specific factors: 1) PI was associated solely with function time (OR = 1.27; $P < 0.001$); 2) BOP+ was associated with sex (females OR = 2.27; $P < 0.001$) and age (each increased year of age OR = 1.03; $P = 0.010$); 3) MR+ was associated with sex (females OR = 2.17; $P = 0.023$) and function time (OR = 1.22; $P = 0.002$); 4) increase in PD was associated with sex and function time. As such, PD in females was on average 0.69 mm greater than in males ($P = 0.001$) and each year in function was 0.22 mm greater ($P < 0.001$); and 5) SUP+ was associated only with sex (females OR = 3.05; $P = 0.006$).

3.6 | Diagnostic accuracy for alternative peri-implantitis case definitions (Table 2)

3.6.1 | RBL ≥0.5 mm

To define peri-implantitis compared to health, BOP+ (OR = 1.87; $P = 0.040$), PD (OR = 1.99; $P < 0.001$), MR+ (OR = 4.67; $P = 0.004$) and SUP+ (OR = 4.68; $P = 0.045$) demonstrated significance; and to define peri-implantitis compared to mucositis only PI (OR = 1.94; $P = 0.091$), and BOP+ (OR = 1.04; $P = 0.025$) reached significance.

3.6.2 | RBL ≥1 mm

To define peri-implantitis to health, BOP+ (OR = 2.52; $P < 0.001$), PD (OR = 2.04; $P < 0.001$), MR+ (OR = 45.28; $P < 0.001$) and SUP+ (OR = 3.89; $P = 0.018$) demonstrated significance; and to define peri-implantitis compared to mucositis only PI (OR = 2.62; $P = 0.010$) reached significance.

3.6.3 | RBL ≥3 mm

To define peri-implantitis compared to health, PI (OR = 2.27; $P = 0.009$), BOP+ (OR = 3.77; $P < 0.001$), PD (OR = 2.92; $P < 0.001$), MR+ (OR = 6.01; $P < 0.001$) and SUP+

TABLE 2 Diagnostic accuracy (%) of the decisive parameters according to the generalized estimating equations (GEE) of multilevel logistic regression on the alternative definitions of peri-implantitis based upon the different marginal bone loss (MBL) thresholds with signs of inflammation

Radiographic bone loss (RBL)		Decisive parameters (GEE)	Diagnostic accuracy (%)		
		Site Level	S	SP	Total
RBL ≥0.5 mm	Healthy vs. Mucositis	PD	46.1	84.1	71.0
	Healthy vs. Peri-implantitis	PD, MR	92.1	23.6	71.1
	Mucositis vs. Peri-implantitis	BOP, PI	100	0	81.2
RBL ≥1 mm	Healthy vs. Mucositis	PD, MR, BOP	41.9	87.7	73.0
	Healthy vs. Peri-implantitis	PD, MR	80.8	57.9	70.5
	Mucositis vs. Peri-implantitis	PI	100	0	72.2
RBL ≥2 mm	Healthy vs. Mucositis	PD, MR, BOP	43.6	90.3	73.7
	Healthy vs. Peri-implantitis	PD, MR, PI	52.3	92.1	80.7
	Mucositis vs. Peri-implantitis	PD, PI	58.2	81.3	70.9
RBL ≥3 mm	Healthy vs. Mucositis	MR, BOP	41.4	91.5	72.2
	Healthy vs. Peri-implantitis	PD, PI	43.8	96.4	87.3
	Mucositis vs. Peri-implantitis	PD, PI	17.3	96.3	78.1
RBL ≥4 mm	Healthy vs. Mucositis	PD, MR, BOP	58.5	83.5	72.3
	Healthy vs. Peri-implantitis	PD	14.1	98.3	90.6
	Mucositis vs. Peri-implantitis	PD	0	100	88.9

S = sensitivity; SP = specificity.

(OR = 5.45; $P = 0.010$) demonstrated significance; and to define peri-implantitis compared to mucositis only PI (OR = 2.44; $P = 0.017$), and BOP+ (OR = 1.71; $P = 0.001$) reached significance.

3.6.4 | RBL ≥4 mm

To define peri-implantitis compared to health, BOP+ (OR = 2.33; $P = 0.044$), PD (OR = 3.03; $P < 0.001$), and MR+ (OR = 5.51; $P < 0.001$) demonstrated significance; and to define peri-implantitis compared to mucositis only PD (OR = 1.33; $P < 0.024$) reached significance.

4 | DISCUSSION

Peri-implant diseases are defined by inflammatory, clinical, and radiographic findings.[13] While peri-implantitis was characterized as progressive bone pathology, according to the case definition, the clinical parameters have been a matter of discussion due to implication of a variety of biological and implant-related factors affecting their respective accuracy.[1,12,32,33] The present investigation estimated the diagnostic accuracy of the clinical parameters for diagnosis of peri-implant diseases using advanced analytical algorithms intended for validation and standardization of diagnostic parameters. Additionally, the study was carefully designed to constitute a representative study sample regarding qualitative and quantitative characteristics to ensure highly reliable outcomes. Our study agreed on the fact that the diagnosis of peri-implant conditions could be led by monitoring the clinical parameters, being PD the most reliable prognostic indicator of disease progression followed by MR and BOP, particularly on the diagnosis of peri-implant mucositis compared to health. However, it is noteworthy that none of these parameters can be used alone for the diagnosis; rather a combination of them is required. While high specificity was presented in all the scenarios, sensitivity remained modest. Therefore, these findings are consistent with previous studies[24,34–37] suggesting that these clinical parameters must be cautiously interpreted for adequate diagnosis.

4.1 | Probing pocket depth

The establishment of biological width around implants mandates the consistent PD monitoring, which indicates a shift from a non-pathologic to pathologic status.[24,36,38,39] Indeed, the present study has shown that PD significantly differs according to the peri-implant condition. Interestingly, it was demonstrated that these could vary based on the implant-neck design. An animal study found that healthy implants with a supra-crestal polished collar (i.e., tissue-level) tends to have a roughly similar biological width to natural teeth in contrast with bone-level implants.[40] These findings can be explained, as there is an increase of laxity of the collagen fibers around the collar of the implant restoration,[22,41] especially in the presence of inflammation.[15] Other factors significantly influencing the PD included patient sex and implant time in function. For example, PD increased 0.22 mm every year the implant

remained in function. This finding could be explained as 'progressive bone loss' increases over time in function and is supported by the previous study.[1] Also, greater the peri-implant bone loss was observed with more apical migration of the long junctional epithelium and connective tissue.[17] Moreover, the increase of PD, together with BOP+, was associated with the female sex, due to hormone fluctuation (i.e., estrogen).[42]

4.2 | Bleeding on probing

In the field of periodontology, the lack of BOP+ was proven to be a predictor for the periodontal tissue stability.[19,43] In contrast, Ericsson and Lindhe using beagle dogs reported that a deeper probe penetration with BOP+ does not necessarily reflect disease, as it was displayed around healthy implants as well.[22] Interestingly, Lang et al. did not notice BOP+ around healthy implants, while it was significantly present in mucositis (67%) and peri-implantitis (91%) sites.[17] Recent clinical studies seem to agree on the site-specific phenomenon positively correlated with PD[30,44] and marginal bone loss.[45]For instance Merli et al. found the odds ratio of a site to be BOP+ by 1.81 for each 1 mm increment in PD.[44] Conversely, Fransson et al. showed that BOP+ occurred in more than 90% of implants with no progressive bone loss, indicating that such measurement cannot be used alone for the detection of peri-implantitis.[24] The multiple logistic regression conducted in the present study identified BOP+ to be sensitive in the diagnosis of peri-implant mucositis compared to healthy conditions (OR = 2.13). Nevertheless, the generalized estimating equations indicated that BOP+ is significantly associated with peri-implantitis compared to health (OR = 2.32).

Moreover, the present study is consistent with previous findings in regard to the manifestation of BOP+ in females.[30] Thus, there is speculation that the transient increase of gingival inflammation owing to hormonal variations might mislead the periodontal and peri-implant conditions. Additionally, age also reached significance, agreeing then previous findings when probing natural teeth.[31] This fact is reasonable as with age increases the intake of anticoagulant medications. In contrast, none of the other factors analyzed in the present study yielded significance.

4.3 | Mucosal redness

The phenomenon of inflammation presents as a biological response to extrinsic or intrinsic insult. The Roman physician Cornelius Celsus (ca. 30 BC to 38 AD) described four cardinal signs including *rubor*, *calor*, *tumor* and *dolor*.[46] *Rubor* (redness) is increased in the tissues as a result of the vasodilation during the onset and process of inflammation. The cause-effect relationship of plaque accumulation on soft tissue condition was demonstrated around natural dentition[47] and dental implants.[48] The present study found that MR is an accurate diagnostic tool to monitor the presence of pathology. Accordingly, when applied the multiple logistic regression, statistical significance was reached for the diagnosis of mucositis and peri-implantitis compared to health. Interestingly, a correlation between MR+ and female sex was observed. Unsurprisingly, this finding was concomitant with BOP+. Again, the hypothesis of the hormonal variations could explain this observation. These findings should be interpreted with caution as the patients evaluated presented with an adequate band of keratinized mucosa (≥2 mm), which could positively impact on the gingival index.[23]

4.4 | Suppuration

Suppuration is defined as a pus formation followed by discharge within a natural aperture or fistula. Pus qualitatively represent the turbid viscous inflammatory exudate consisting of dead leukocytes, living or dead microorganisms, necrotic tissues, and protein-rich fluid called *liquor puris* rich in pro-inflammatory mediators and bacterial toxins. These components represent byproducts of the host reaction directed towards to persistent pathological irritants (e.g., infection or foreign body). Therefore, SUP is accepted as a highly specific clinical parameter of peri-implant inflammation since it reflects ongoing inflammatory processes in the tissues.[3] For that reason, SUP was initially associated with the progressive forms of periodontal disease and recently has been proposed as an indicator for progressive bone loss on implants.[24,34] In this regard, low predictability rate of SUP+ in peri-implant mucositis together with inversely high predictability in peri-implantitis confirms the SUP as an accurate clinical end point to disclose peri-implant bone loss.[34] In agreement with those findings, the estimated predictability of SUP+ was compatible at both implant (OR = 1.47) and site level (OR = 6.81), thus supporting the accuracy of this parameter for dental implant diseases monitoring. Nevertheless, it is worth mentioning, that SUP did not reach significance for the logistic regression model, as it might have been masked by other more discriminative parameters (i.e. BOP or MR). Moreover, in line with findings related to other parameters investigated, SUP was more frequently associated with the female sex and bone level implants, as these had significantly higher proportions of PI together with other signs of inflammation such as MR+ and BOP+. It is, therefore the authors' opinion that future research studies should aim to identify peri-implantitis patient clusters that discern SUP and related underlying factors.

4.5 | Recommendations for future research

Peri-implant diseases represents a growing problem in the current field of dentistry due to increasing prevalence and lack of standard treatment protocols.[9] Additionally,

peri-implant diseases have a progressive and asymptomatic course. In that context, the reliable diagnostic protocol for the adequate monitoring of peri-implant tissues remains of essential importance. The results of the present study clearly demonstrate that the assessment of multiple clinical parameters provide more accurate diagnostic information simultaneously, suggesting the limitation of using isolated clinical parameters for the diagnosis of peri-implant diseases. When considering the results as a whole, investigation of the biological features of peri-implant tissues and better understanding of the underlying pathogenetic mechanisms will certainly contribute to improvement of the peri-implant diagnostics. This will continue to be a charge for future research. Furthermore, it seems that the personalized medicine approach proposed for multifactorial diseases and combines multiple clinical and biological markers might be a promising tool in monitoring peri-implant tissues.

5 | CONCLUSIONS

The diagnosis of peri-implant diseases cannot rely on a single clinical parameter but rather requires a combination. This study showed that the clinical parameters, in particular, probing depth, might accurately discern between diagnoses among peri-implant conditions. Nevertheless, the specificity of the clinical parameters surpasses the sensitivity in the detection of peri-implant diseases. Therefore, progressive radiographic bone loss must be cautiously examined to reach the definitive diagnosis and avoid overtreatment.

ACKNOWLEDGMENTS

This study was partially supported by FEDICOM foundation (Foundation for the Study and Development of Implantology and Oral Surgery, Badajoz, Spain). The authors want to express their gratitude for the comprehensive statistical analysis to Mr. Juan Luis Gomez-Martinez (Valencia, Spain). Moreover, the authors acknowledge the clinical assistance of Alberto Novillo-Davalos (CICOM, Badajoz, Spain), Purificación Barragán-Bernal (Center of Implantology, Oral and Maxillofacial Surgery, Badajoz, Spain), and Begoña Ortigosa (CICOM, Badajoz, Spain). Moreover, the authors are thankful to Dr. Ann Decker (Ann Arbor, Michigan, USA) for the kind assistance with the English language. Dr. A. Monje thanks the International Team of Implantology (ITI, Basel, Switzerland) for the academic support. The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

REFERENCES

1. Derks J, Tomasi C. Peri-implant health and disease. A systematic review of current epidemiology. *Journal of Clinical Periodontology*. 2015;42(Suppl 16):S158–S171.
2. Levignac J. [Periimplantation osteolysis- periimplantosis – periimplantitis]. *Revue Francaise d'odonto-stomatologie*. 1965;12:1251–1260.
3. Mombelli A, Lang NP. The diagnosis and treatment of peri-implantitis. *Periodontology 2000*. 1998;17:63–76.
4. Heitz-Mayfield LJ, Lang NP. Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis. *Periodontology 2000*. 2010;53:167–181.
5. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nature Reviews Microbiology*. 2012;10:717–725.
6. Carcuac O, Berglundh T. Composition of human peri-implantitis and periodontitis lesions. *Journal of Dental Research*. 2014;93:1083–1088.
7. Esposito M, Ardebili Y, Worthington HV. Interventions for replacing missing teeth: different types of dental implants. *The Cochrane Database of Systematic Reviews*. 2014:CD003815.
8. Salvi GE, Cosgarea R, Sculean A. Prevalence and Mechanisms of Peri-implant Diseases. *Journal of Dental Research*. 2017;96:31–37.
9. Figuero E, Graziani F, Sanz I, Herrera D, Sanz M. Management of peri-implant mucositis and peri-implantitis. *Periodontology 2000*. 2014;66:255–273.
10. Sanz M, Chapple IL, Working Group 4 of the VEWoP. Clinical research on peri-implant diseases: consensus report of Working Group 4. *Journal of Clinical Periodontology*. 2012;39(Suppl 12):202–206.
11. Peri-implant mucositis and peri-implantitis: a current understanding of their diagnoses and clinical implications. *Journal of Periodontology* 2013;84:436–443.
12. Lang NP, Berglundh T, Working Group 4 of Seventh European Workshop on P. Periimplant diseases: where are we now?–Consensus of the Seventh European Workshop on Periodontology. *Journal of Clinical Periodontology*. 2011;38(Suppl 11):178–181.
13. Lindhe J, Meyle J, Group DoEWoP. Peri-implant diseases: consensus Report of the Sixth European Workshop on Periodontology. *Journal of Clinical Periodontology*. 2008;35:282–285.
14. Berglundh T, Lindhe J. Dimension of the periimplant mucosa. Biological width revisited. *Journal of Clinical Periodontology*. 1996;23:971–973.
15. Schou S, Holmstrup P, Stoltze K, Hjorting-Hansen E, Fiehn NE, Skovgaard LT. Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. A histologic comparison in cynomolgus monkeys (Macaca fascicularis). *Clinical Oral Implants Research*. 2002;13:113–126.
16. Abrahamsson I, Soldini C. Probe penetration in periodontal and peri-implant tissues. An experimental study in the beagle dog. *Clinical Oral Implants Research*. 2006;17:601–605.
17. Lang NP, Wetzel AC, Stich H, Caffesse RG. Histologic probe penetration in healthy and inflamed peri-implant tissues. *Clinical Oral Implants Research*. 1994;5:191–201.
18. Joss A, Adler R, Lang NP. Bleeding on probing. A parameter for monitoring periodontal conditions in clinical practice. *Journal of Clinical Periodontology*. 1994;21:402–408.
19. Lang NP, Joss A, Orsanic T, Gusberti FA, Siegrist BE. Bleeding on probing. A predictor for the progression of periodontal disease?. *Journal of Clinical Periodontology*. 1986;13:590–596.

20. Farina R, Tomasi C, Trombelli L. The bleeding site: a multi-level analysis of associated factors. *Journal of Clinical Periodontology*. 2013;40:735–742.
21. Trombelli L, Farina R. A review of factors influencing the incidence and severity of plaque-induced gingivitis. *Minerva Stomatologica*. 2013;62:207–234.
22. Ericsson I, Lindhe J. Probing depth at implants and teeth. An experimental study in the dog. *Journal of Clinical Periodontology*. 1993;20:623–627.
23. Lin GH, Chan HL, Wang HL. The significance of keratinized mucosa on implant health: a systematic review. *Journal of Periodontology*. 2013;84:1755–1767.
24. Fransson C, Wennstrom J, Berglundh T. Clinical characteristics at implants with a history of progressive bone loss. *Clinical oral Implants Research*. 2008;19:142–147.
25. Wilson TG, Jr, Valderrama P, Burbano M, et al. Foreign bodies associated with peri-implantitis human biopsies. *Journal of Periodontology*. 2015;86:9–15.
26. van Velzen FJ, Lang NP, Schulten EA, Ten Bruggenkate CM. Dental floss as a possible risk for the development of peri-implant disease: an observational study of 10 cases. *Clinical Oral Implants Research*. 2016;27:618–621.
27. Altman DG, Simera I, Hoey J, Moher D, Schulz K. EQUATOR: reporting guidelines for health research. *Lancet*. 2008;371:1149–1150.
28. Monje A, Wang HL, Nart J. Association of Preventive Maintenance Therapy Compliance and Peri-implant Diseases: a Cross-Sectional Study. *Journal of Periodontology*. 2017 Oct;88(10):1030–1041. https://doi.org/10.1902/jop.2017.170135.
29. Derks J, Schaller D, Hakansson J, Wennstrom JL, Tomasi C, Berglundh T. Effectiveness of Implant Therapy Analyzed in a Swedish Population: prevalence of Peri-implantitis. *Journal of Dental Research*. 2016;95:43–49.
30. Farina R, Filippi M, Brazzioli J, Tomasi C, Trombelli L. Bleeding on probing around dental implants: a retrospective study of associated factors. *Journal of Clinical Periodontology*. 2017;44:115–122.
31. Farina R, Scapoli C, Carrieri A, Guarnelli ME, Trombelli L. Prevalence of bleeding on probing: a cohort study in a specialist periodontal clinic. *Quintessence International*. 2011;42:57–68.
32. Salvi GE, Lang NP. Diagnostic parameters for monitoring peri-implant conditions. *The International Journal of Oral & Maxillofacial Implants*. 2004;19:116–127. Suppl.
33. Coli P, Christiaens V, Sennerby L, Bruyn H. Reliability of periodontal diagnostic tools for monitoring peri-implant health and disease. *Periodontology 2000*. 2017;73:203–217.
34. Roos-Jansaker AM, Renvert H, Lindahl C, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. *Journal of Clinical Periodontology*. 2006;33:296–301.
35. Roos-Jansaker AM, Lindahl C, Renvert H, Renvert S. Nine-to fourteen-year follow-up of implant treatment. Part II: presence of peri-implant lesions. *Journal of Clinical Periodontology*. 2006;33:290–295.
36. Fransson C, Tomasi C, Pikner SS, et al. Severity and pattern of peri-implantitis-associated bone loss. *Journal of Clinical Periodontology*. 2010;37:442–448.
37. Fransson C, Lekholm U, Jemt T, Berglundh T. Prevalence of subjects with progressive bone loss at implants. *Clinical Oral Implants Research*. 2005;16:440–446.
38. Cochran DL, Hermann JS, Schenk RK, Higginbottom FL, Buser D. Biologic width around titanium implants. A histometric analysis of the implanto-gingival junction around unloaded and loaded nonsubmerged implants in the canine mandible. *Journal of Periodontology*. 1997;68:186–198.
39. Hermann JS, Buser D, Schenk RK, Higginbottom FL, Cochran DL. Biologic width around titanium implants. A physiologically formed and stable dimension over time. *Clinical Oral Implants Research*. 2000;11:1–11.
40. Hermann JS, Buser D, Schenk RK, Schoolfield JD, Cochran DL. Biologic Width around one- and two-piece titanium implants. *Clinical Oral Implants Research*. 2001;12:559–571.
41. Sculean A, Gruber R, Bosshardt DD. Soft tissue wound healing around teeth and dental implants. *Journal of Clinical Periodontology*. 2014;41(Suppl 15):S6–S22.
42. Mascarenhas P, Gapski R, Al-Shammari K, Wang HL. Influence of sex hormones on the periodontium. *Journal of Clinical Periodontology*. 2003;30:671–681.
43. Lang NP, Adler R, Joss A, Nyman S. Absence of bleeding on probing. An indicator of periodontal stability. *Journal of Clinical Periodontology*. 1990;17:714–721.
44. Merli M, Bernardelli F, Giulianelli E, Toselli I, Mariotti G, Nieri M. Peri-implant bleeding on probing: a cross-sectional multilevel analysis of associated factors. *Clinical Oral Implants Research*. 2017.
45. French D, Cochran DL, Ofec R. Retrospective Cohort Study of 4,591 Straumann Implants Placed in 2,060 Patients in Private Practice with up to 10-Year Follow-up: the Relationship Between Crestal Bone Level and Soft Tissue Condition. *The International Journal of Oral & Maxillofacial Implants*. 2016;31:e168–e178.
46. Rather LJ. Disturbance of function (functio laesa): the legendary fifth cardinal sign of inflammation, added by Galen to the four cardinal signs of Celsus. *Bulletin of the New York Academy of Medicine*. 1971;47:303–322.
47. Loe H, Theilade E, Jensen SB. Experimental Gingivitis in Man. *Journal of Periodontology*. 1965;36:177–187.
48. Salvi GE, Aglietta M, Eick S, Sculean A, Lang NP, Ramseier CA. Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. *Clinical Oral Implants Research*. 2012;23:182–190.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Monje A, Caballé-Serrano J, Nart J, Peñarrocha D, Wang H-L, Rakic M. Diagnostic accuracy of clinical parameters to monitor peri-implant conditions: A matched case-control study. *J Periodontol*. 2018;89:407–417. https://doi.org/10.1002/JPER.17-0454