Accepted: 5 January 2018

DOI: 10.1111/clr.13127

REVIEW ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

The diagnosis of peri-implantitis: A systematic review on the predictive value of bleeding on probing

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Abstract

Objectives: Bleeding on gentle probing (BOP) is the key parameter to the diagnosis of mucositis, while changes in crestal bone levels, along with clinical signs of inflammation, are required for the diagnosis of peri-implantitis. This systematic review and meta-analysis focused on the evaluation of BOP as a predictive measure for peri-implantitis.

Materials and methods: An electronic search was performed through Medline and EMBASE databases, followed by a hand search through previous reviews and reference lists. Screening, study selection, data extraction and evaluation of publication bias were conducted by two independent examiners. Clinical studies reporting on the prevalence of peri-implantitis, BOP and/or suppuration (SUP) after more than 1 year of functional loading were selected. Meta-analyses were conducted to combine the proportions of peri-implantitis among BOP- and/or SUP-positive subjects and implants across studies. Subgroups were created and compared to investigate potential sources of heterogeneity.

Results: Thirty-one studies were selected for analysis. Inconsistent definitions of peri-implantitis were reported across the studies. Twenty-nine studies reported data on implant-level and twenty publications reported on subject-level. The combined proportion of peri-implantitis was 24.1% (95% CI 19.3–29.7) in BOP-positive implants and 33.8% (95% CI 26.7–41.6) for BOP-positive cases. However, the degree of variability among studies was high; the prediction intervals were 10.3-69.3 and 6.9-57.8, respectively. Evidence of asymmetry or publication bias could not be statistically detected. Short observation periods were significantly associated with lower proportions of peri-implantitis among BOP-positive implants.

Conclusions: For BOP-positive implants, there was a 24.1% chance to be diagnosed with peri-implantitis; while for BOP-positive patients, there was a 33.8% probability to be diagnosed with peri-implantitis. This probability varied across study populations. Clinicians should be aware of the considerable false-positive rate of BOP to diagnose peri-implantitis.

KEYWORDS

bleeding on probing, implants, peri-implantitis, predictive value, systematic review

1 | INTRODUCTION

Oral implants support and maintain dental prostheses in the jaw bones. The peri-implant bone stability and the presence of an intact seal at the site of passage through the mucosa are key factors for long-term success. The tissues involved in this function can be affected by a destructive process for which more than 30 years ago the term "peri-implantitis" was proposed (Mombelli,

van Oosten, Schürch & Lang, 1987). Since then, the causes of loss of bone, the impact of infection, methods for diagnosis and therapy of peri-implantitis have been intensely debated.

The study of the diseases of the peri-implant tissues started with a theoretical framework that was built in analogy to periodontology. In periodontal diseases, specialized members of the oral microbiota dysregulate the host immune response, which results in destruction of the tissues anchoring the teeth in the jaw bone (Hajishengallis, 2014; Hajishengallis & Korostoff, 2017). Around implants, bone resorption, independent of infection, has been documented when implants are placed too deep (Hämmerle, Brägger, Bürgin & Lang, 1996) or too close to each other (Tarnow, Cho & Wallace, 2000), and after installing abutments on previously submerged implants (Adell, Lekholm, Rockler & Brånemark, 1981). Such bone loss is usually limited in time and extent and should not be misdiagnosed as peri-implantitis. Thus, one of the diagnostic challenges is to discriminate bone loss due to infection from bone "remodelling." Several studies have shown that the thresholds used to account for bone loss unrelated to infection have a substantial impact on peri-implantitis prevalence rates (Derks et al., 2016; Koldsland, Scheie & Aass, 2010; Roos-Jansåker, Lindahl, Renvert & Renvert, 2006). A consensus report published following the 8th European Workshop on Periodontology (Sanz & Chapple, 2012) defined peri-implantitis by "changes in the level of crestal bone accompanied by bleeding on probing, irrespective of peri-implant probing depth. When previous radiographs are unavailable, crestal bone loss of 2 mm after initial remodelling was recommended for diagnosis. However, a more sensitive threshold can be set when radiographs can be utilized for comparison." Unfortunately, few studies adhere to these recommendations and peri-implantitis definitions are widely variable in the literature (Lee, Huang, Zhu & Weltman, 2017).

In analogy to the physiopathology of the periodontium, it is assumed that inflammation increases the risk of bleeding from the peri-implant mucosa due to the rupture of local blood vessels after minimal trauma. Therefore, bleeding upon gentle probing with a blunt instrument (BOP) has been proposed as a sign of mucositis and/or peri-implantitis. However, the extent to which BOP, as a single observation, indicates the presence or the risk of peri-implantitis is unclear. Around natural teeth, bleeding upon probing can occur even in the absence of disease (Lang, Nyman, Senn & Joss, 1991), and its frequency increases with probing force (Karayiannis, Lang, Joss & Nyman, 1992). Around implants, marked disproportions between the incidences of BOP and clinically manifested peri-implantitis, noticeable in many studies (Mombelli, Müller & Cionca, 2012), suggest that BOP may have a high false positive rate when identifying the presence of destructive peri-implant pathology.

The utility of a diagnostic parameter depends on its value to answer a concrete diagnostic question, and on the clinical context in which this question is asked. Diagnostic tasks may include the identification of subjects and implants at risk of developing peri-implantitis, the detection of early stage disease in apparently asymptomatic individuals, the classification of disease categories, the prediction of likely response to a specific therapy, monitoring treatment efficacy and finding recurrent disease. The utility of a diagnostic parameter may not be the same in each of these situations, and therefore needs to be determined separately every time. The evaluation of a diagnostic test has several aspects. In general, primary evaluation of diagnostic tests focuses on accuracy, that is the degree to which the test correctly identifies the presence or absence of disease. In 1947, Yerushalmy proposed the indicators "sensitivity" and "specificity" for dichotomous tests (Yerushalmy, 1947). Ever since, diagnostic tools have often been primarily judged with respect to these two indicators (high sensitivity is desired in order not to miss any positive cases, whereas high specificity is sought to avoid false positives), underestimating the importance of the predictive value (the proportion of positive and negative results that are true positive and true negative results, respectively), which varies depending on the prevalence of the condition within a population, and is key for estimating utility (Mombelli, 2005).

According to the proceedings of the 7th European Workshop on Periodontology (Lang & Berglundh, 2011), the key parameter to the diagnosis of mucositis is BOP with a gentle force (<0.25 N). Changes in crestal bone levels, along with clinical signs of inflammation (BOP and/or suppuration) are required for the diagnosis of peri-implantitis. The question remains: To what extent can clinical signs of infection/inflammation identify peri-implantitis? Therefore, this review aimed to systematically evaluate the predictive value of BOP for the diagnosis of peri-implantitis.

2 | MATERIAL AND METHODS

This systematic review was conducted according to the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher, Liberati, Tetzlaff, Altman & Group, 2009).

2.1 | Focused question

The focused question was formulated according to the PICO principle (Needleman, 2002):

> *For persons with osseointegrated dental implants, is assessing BOP and/or suppuration after probing (SUP) as accurate (i.e., with equal or better sensitivity and specificity) as diagnosis of peri-implantitis based on bone loss after initial remodelling (i.e., identified by comparing new radiographs with radiographs taken upon completion of the prosthetic reconstruction)?*

2.2 | Eligibility criteria

Studies were included according to the following criteria:

- Clinical studies published in the English language.
- Included at least 20 human subjects with implant-supported dental reconstructions.
- Observation period of at least 12 months after functional loading.
- Clear definition of *peri-implantitis*.
- At least one case diagnosed with *peri-implantitis*.

- Cases are not selected initially based on the presence of peri-implant pathology.
- BOP and/or SUP after peri-implant probing, or the presence of *peri-implant mucositis*, clearly reported.

2.3 | Exclusion criteria

Studies not fulfilling all eligibility criteria were not included in this analysis. Reviews, in vitro and animal experiments were also eliminated. Moreover, studies were full texts could not be obtained, or if the number of peri-implantitis affected subjects or implants could not be calculated, were excluded.

2.4 | Search strategy

An electronic search was performed in the two databases MEDLINE and EMBASE to identify studies published between January 2012 and May 2017. The following MeSH terms were used: "peri-implantitis" OR "biological complication" OR "peri-implant disease."

A previous systematic review (Mombelli et al., 2012), comprising studies reported prior to 2012, was also included. This was complemented by a hand search through selected review articles and reference lists of identified studies for further potentially relevant publications.

2.5 | Quality assessment

Two reviewers (DH and NC) independently performed the methodological quality assessment of the selected studies according to the following criteria: study design, subject and implant characteristics, extent of clinical and radiographic examinations, inter-/intra-examiner calibration, completeness of follow-up and reporting drop-outs, provision of supportive periodontal treatment (SPT), accuracy of peri-implantitis definition, as well as completeness and clarity of data reporting. Local risk factors such as implant malposition, cleansability of reconstructions, excess cement and implant surface characteristics were also considered. In light of the mentioned criteria, studies were evaluated as having low, moderate or high risk of bias.

2.6 | Data extraction

The following data were extracted from each report: publication year, study design, type of patients, maintenance protocol, definitions of mucositis and peri-implantitis, mean follow-up period, number of patients and number of implants. The prevalence of BOP, peri-implant mucositis and peri-implantitis were recorded on the patient and the implant levels. Disagreement regarding data extraction was resolved with discussion. No attempts were made to contact authors in case of ambiguity in data reporting.

2.7 | Statistical analysis

The primary outcome was defined as the proportion of peri-implantitis among BOP- and/or SUP-positive subjects and implants. For the present analysis, it was assumed that BOP occurred whenever a diagnosis of peri-implant mucositis was made. If a study reported the prevalence of peri-implantitis at various time points, results of the latest follow-up were selected for analysis. For each study, the

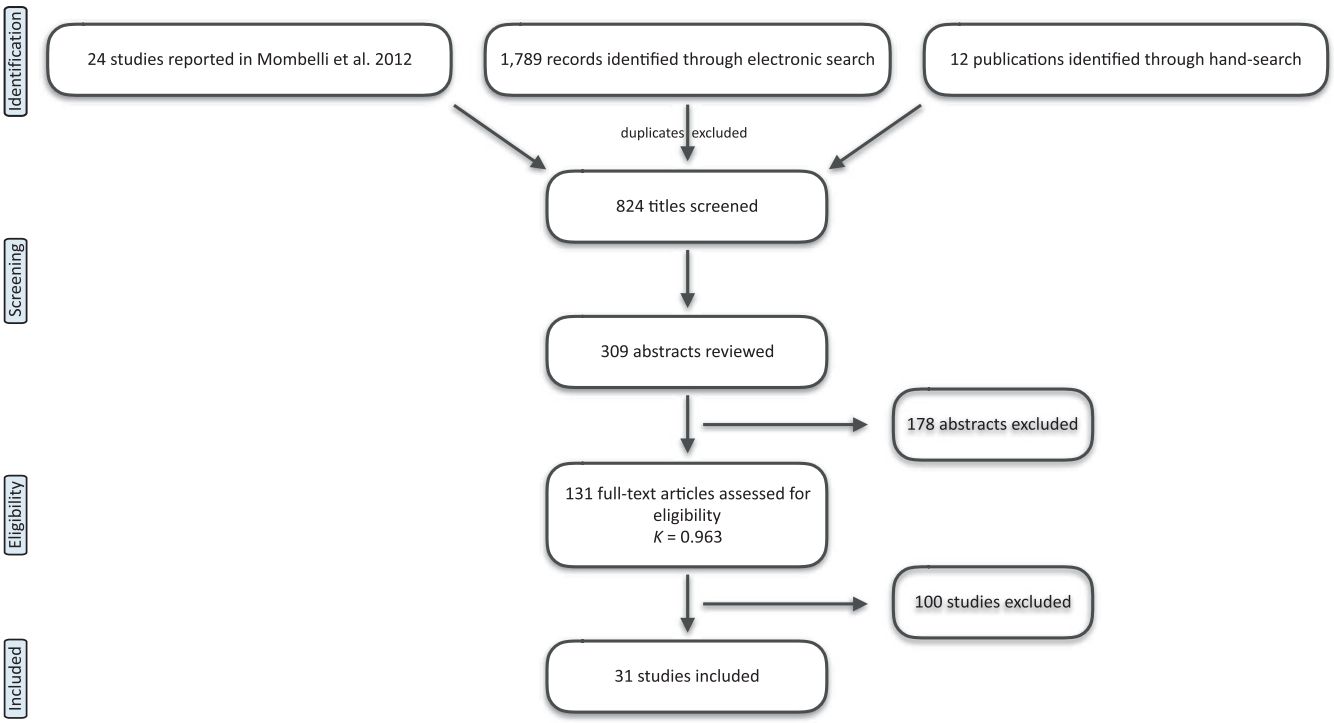

FIGURE 1 Flow chart for the search strategy

proportion of peri-implantitis was reported with Clopper-Pearson's exact 95% confidence interval. Meta-analyses were conducted to combine the proportions of peri-implantitis across studies. Models with random effects were used (Der-Simonian Laird's estimate). Statistical heterogeneity was assessed using Cochran's chi-square test with a significance level set at 0.1, and I^2 statistics. Forest plots were used to show the proportion estimated in each study with its confidence interval and the weight given to each study in the meta-analyses, along with the pooled proportion. Leave-one-out sensitivity analysis was conducted to check the robustness of the findings, and potential publication bias was investigated using funnel plots. Finally, subgroups were created and compared to investigate potential sources of heterogeneity: mean follow-up period (1–3, 3–5 and >5 years), history of periodontal disease and compliance with regular SPT. Analyses were performed using the package meta for R Statistical Software version 3.3.1 (Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study selection (Figure 1)

Initial electronic search yielded 1,789 titles published between 2012 and May 2017. Twenty-four studies were reported in Mombelli et al. (2012), and hand search produced 12 additional articles for review. After removing duplicates, 824 titles were independently screened by two examiners (DH, NC) resulting in 309 abstracts. Finally, 131 articles were reviewed in detail. Reviewers disagreed on the classification of two studies (Cohen's Kappa Index Value 0.963) and this was resolved with discussion. Ultimately, 31 publications were included in this analysis (Table 1).

3.2 | Excluded studies

Out of the 131 full-text articles evaluated, six were excluded due to sample size, two because of short observation periods and 25 because the cases were selected based on the diagnosis of peri-implantitis. Four more studies were omitted because they did not include any cases with peri-implantitis, 22 due to ambiguous data reporting on BOP/SUP or mucositis and three were not clinical studies. Five publications did not correspond to the search criteria, 23 did not provide clear definitions of peri-implantitis and 10 full-text articles were not available or abstracts corresponded to poster/oral presentations (Table 2).

3.3 | Quality assessment and risk of bias

Studies were evaluated for bias according to the previously mentioned criteria (Table 3). Three publications were considered to have a high risk of bias mainly due to unclear data reporting and/or ambiguity in their definition of peri-implantitis (Cecchinato, Parpaiola & Lindhe, 2014; Corbella, Del Fabbro, Taschieri, De Siena & Francetti, 2011; Duque, Aristizabal, Londono, Castro & Alvarez, 2016). On the other hand, 13 studies were at low risk of bias while 15 had medium risk.

3.4 | Study characteristics

3.4.1 | Case definitions

Inconsistent definitions of peri-implantitis with variable degrees of bone loss (BL) were reported. Still, each study included BOP and/or probing depth (PD) in the defining criteria. The thresholds of BL ranged between 0.2 and 3.5 mm. Three studies did not identify a cut-off level for BL (Ferreira, Silva, Cortelli, Costa & Costa, 2006; Lee et al., 2016; Rutar, Lang, Buser, Bürgin & Mombelli, 2001) while one did not take it into consideration for the definition of peri-implantitis (Corbella et al., 2011). On the other hand, Rodrigo, Martin and Sanz, (2012) required "significant" BL, defined as 3× standard deviation of repeated measures, for the diagnosis of peri-implantitis. Only eight studies used standardized intra-oral radiographs for measurement of peri-implant bone level (Cecchinato et al., 2014; Duque et al., 2016; Lehmann et al., 2013; Maximo et al., 2008; Meijer, Raghoebar, de Waal & Vissink, 2014; Rodrigo et al., 2012; Schropp, Wenzel & Stavropoulos, 2014; Swierkot, Lottholz, Flores-de-Jacoby & Mengel, 2012), while three studies utilized orthopantomograms (Marrone, Lasserre, Bercy & Brecx, 2013; Rinke, Ohl, Ziebolz, Lange & Eickholz, 2011; van Velzen, Ofec, Schulten & Ten Bruggenkate, 2015). Finally, mucositis was not defined in seven articles which only reported BOP (Table 1).

3.4.2 | Observation period

Two studies (Corbella et al., 2011; Duque et al., 2016) had a short mean follow-up period of less than 3 years, while eight reported results after 3–5 years of observation (Aguirre-Zorzano, Estefania-Fresco, Telletxea & Bravo, 2015; Canullo et al., 2016; Ferreira et al., 2006; Lee et al., 2016; Maximo et al., 2008; Passoni et al., 2014; Rodrigo et al., 2012; Rokn et al., 2017). The rest reported long-term results exceeding 5 years of functional loading (Table 1).

3.4.3 | Subject characteristics

Two studies exclusively included subjects with a history of periodontal disease (Aguirre-Zorzano et al., 2015; Daubert, Weinstein, Bordin, Leroux & Flemming, 2015), while 13 others included both healthy and periodontally treated patients. Marrone et al. even included subjects with active periodontal disease (Marrone et al., 2013). Twenty of the 31 included articles reported regular maintenance care. Various studies included further details on subjects' characteristics, such as age, smoking status and systemic diseases (Table 3). Only two studies were designed as "split-mouth": Duque et al. compared platform switching implants with conventional ones (Duque et al., 2016), while Rodrigo et al. compared immediately placed implants and delayed ones (Rodrigo et al., 2012).

TABLE 1 Characteristics of included studies [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Follow-up period	Type of subjects	Prosthetic reconstruction	SPT	Health (H)	Mucositis (M)	Peri-implantitis 1 (P1)
Aguirre-Zorzano et al. (2015)	Cross-sectional	Mean 5.25 ± 3.41 years	Hx of Perio.	SC or iFDP	Regular SPT	NR	BOP	BOP/SUP, PD, BL ≥ 1.5 mm
Canullo et al. (2016)	Cross-sectional	Mean 5.9 ± 3.3 years	140/534 S with Hx of perio.	iFDP	428/534 S on regular SPT	NR	NR	PD ≥ 4 mm, BOP/SUP, BL > 3 mm
Cecchinato et al. (2014)	Prospective	1–10 years	41/100 S lost teeth due to perio.	NR	66/100 S on regular SPT	NR	BOP	Progressive BL > 0.5 mm, BOP, PD ≥ 4 mm
Cho-Yan Lee, Mattheos, Nixon and Ivanovski (2012)	Retrospective case-control	Mean 8–8.2 years years (Range 5.04–14.40)	30 perio. and 30 healthy S	SC, iFDP, overdentures	Regular SPT	NR	NR	PD ≥ 5 mm, BOP, BL > 2 mm
Corbella et al. (2011)	Prospective	Mean 18.3 months (range 6 months–5 years)	Edentulous S	Full-arch prosthesis supported by straight and tilted implants	Regular SPT	NR	Redness, swelling, BOP or spontaneous bleeding	BOP or spontaneous bleeding, PD ≥ 4 mm
Dalago et al. (2017)	Retrospective	Mean 5.64 years (range 1–14)	33/183 S had Hx of perio.	SC or iFDP	NR	NR	NR	PD > 5 mm, BOP/SUP, BL > 2 mm
Daubert et al. (2015)	Cross-sectional	Mean 10.9 ± 1.5 years (range 8.9–14.8)	Healthy and perio. S	iFDP	NR	NR	BOP/gingival inflammation	BOP/SUP, PD ≥ 4 mm, BL ≥ 2 mm
Derks et al. (2016)	Cross-sectional	Mean 8.9 ± 0.8 years	Edentulous (16%), healthy (60%) and perio. (24%) S	NR	Regular SPT	No BOP/SUP	BOP/SUP	BOP/SUP, BL >0.5 mm i.e., exceeding the measurement error (compared to initial Rx)
Duque et al. (2016)	Cross-sectional	1 year	Healthy S	SC or iFDP	NR	No BOP or BL	BOP, BL < 2 mm	BOP, PD ≥ 5 mm, BL ≥ 2 mm
Ferreira et al. (2006)	Cross-sectional	Mean 3.5 ± 1.4 years (range 6 months–5 years)	30 perio. and 182 healthy S	NR	94/212 S on regular SPT	NR	BOP or PD ≥ 5 mm without vertical BL	BOP/SUP, PD ≥ 5 mm, vertical BL

(Continues)

TABLE 1 (additional columns)

Peri-implantitis 2 (P2)	Peri-implantitis 3 (P3)		Total *n*	H (*n*)	M/BOP (*n*)	P1 (*n*)	P2 (*n*)	P3 (*n*)	M/BOP (%)	P1 (%)	P2 (%)	P3 (%)
		C	239	144	59	36			24.69	15.06		
		I	786	608	101	77			12.85	9.80		
		C	534	NR	NR	53			NR	9.93		
		I	1,507	NR	72	110			59.50	7.30		
Progressive BL > 1 mm, BOP, PD ≥ 4 mm	Progressive BL > 2 mm, BOP, PD ≥ 4 mm	C at ≥ 1 year	100	NR	NR	29	18	5	NR	29	18	5
		I	291	NR	NR	47	28	5	NR	16.15	9.62	1.72
		C After ≥ 3 years	100	NR	NR	34	17	9	NR	34	17	9
		I	291	NR	NR	51	26	10	NR	17.53	8.93	3.44
		C After ≥ 8 years	100	NR	85	40	25	11	85	40	25	11
		I	291	NR	233	75	48	20	80	25.77	16.49	6.87
PD ≥ 5 mm, BOP, BL > 3 mm		C	60	NR	NR	16	9		NR	26.67	15	
		I	117	NR	27	23	12		23.08	19.70	10.26	
		C at 6–12 months	NR	NR	NR	NR			NR	NR		
		I	216	NR	8	3			3.70	1.40		
		C at 12–18 months	NR	NR	NR	NR			NR	NR		
		I	165	NR	13	0			7.70	0		
		C at 24–36 months	NR	NR	NR	NR			NR	NR		
		I	109	NR	7	0			6.30	0		
		C	183	NR	NR	30			NR	16.40		
		I	938	NR	258	69			27.50	7.30		
		C	96	NR	46	25			48	26		
		I	225	NR	74	36			33	16		
BOP/SUP, BL > 1 mm	BOP/SUP, BL > 2 mm	C	427	98	137	192	115	62	32	45	26.93	14.52
		I	1,578	620	554	393	232	126	35.11	24.90	14.70	7.98
		C	24	NR	NR	NR			NR	NR		
		I	62	2	53	7			85.50	11.30		
		I Platform-swith	30	1	27	2			90	6.60		
		I Conventional	32	1	26	5			81.25	15.60		
		C	212	56	137	19			64.60	8.90		
		I	578	NR	362	43			62.60	7.44		

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Follow-up period	Type of subjects	Prosthetic reconstruction	SPT	Health (H)	Mucositis (M)	Peri-implantitis 1 (P1)
Frisch et al. (2015)	Retrospective	Mean 12.1 ± 4.93 years (range 2.37–20.35)	S with Implants exhibiting <1 mm keratinized mucosa	NR	Regular SPT	NR	BOP	BOP, PD ≥ 5 mm, BL > 3.5 mm
Frisch et al. (2013)	Retrospective	Mean 14.1 ± 2.8 years (range 10.2–18.9)	Edentulous S	Implant-supported removable double-crown dentures	Regular SPT	NR	BOP	BOP, PD ≥ 5 mm, BL > 3.5 mm after 10 years of functional loading
Koldsland et al. (2010)	Cross-sectional	Mean 8.4 ± 4.6 years	NR	NR	No	NR	BOP/SUP but no BL	BOP/SUP, PD ≥ 4 mm, BL ≥ 2 mm
Lee et al. (2016)	Retrospective	Mean 3.6 years (range 2.6–4.7)	NR	Lateral screw-retained SC	Regular SPT	NR	BOP, swelling, or redness	BOP, swelling, or redness, PD > 5 mm, BL and/or mobility
Lehmann et al. (2013)	Prospective	Mean 9.1 years (range 5.3–11.2)	Edentulous S	Implant-supported bar-retained overdentures	No	PD < 5 mm, no BOP	BOP, PD ≥ 5 mm, no pathological BL	BOP, PD ≥ 5 mm, pathological BL > 0.5 mm 1st year and > 0.2 mm each subsequent year
Marrone et al. (2013)	Cross-sectional	Mean 8.5 ± 3.2 years (range 5–18)	34 healthy S, 39 with stabilized periodontitis, and 15 with active periodontitis. 7 Edentulous	SC, iFDP, overdentures	58 S with regular SPT, 45 S with irregular SPT,	NR	BOP, PD ≤ 5 mm, BL ≤ 2 mm	BOP, PD > 5 mm, BL > 2 mm
Maximo et al. (2008)	Prospective case series	Mean 3.4 ± 2 years	Partially or fully edentulous (29%), healthy and perio. S	NR	No	PD ≤ 5 mm, no gingival inflammation, no BOP/SUP, no BL	Gingival inflammation, BOP, BL < 3 threads	PD ≥ 5 mm, BOP/SUP, BL ≥ 3 threads
Meijer et al. (2014)	Retrospective	10 years	Edentulous S	Bar-retained overdentures	Regular SPT	NR	BOP/SUP	BOP/SUP, BL ≥ 2 mm
Mir-Mari, Mir-Orfila, Figueiredo, Valmaseda-Castellon and Gay-Escoda (2012)	Cross-sectional	Mean 6.3 ± 4.3 years (range 1–18)	NR	NR	Regular SPT	No BOP, BL < 2 threads or clinical stability (BL ≥ 2 threads without BOP)	BOP, BL < 2 threads	BOP/SUP, BL ≥ 2 threads
Passoni et al. (2014)	Cross-sectional	Mean 4.7 ± 2 years (range 1–5.4)	NR	iFDP	No	NR	NR	BOP/SUP, PD ≥ 5 mm, BL > 2 mm

(Continues)

TABLE 1 (additional columns - continued)

Peri-implantitis 2 (P2)	Peri-implantitis 3 (P3)		Total *n*	H (*n*)	M/BOP (*n*)	P1 (*n*)	P2 (*n*)	P3 (*n*)	M/BOP (%)	P1 (%)	P2 (%)	P3 (%)
		C	60	NR	NR	2			NR	3.33		
		I	105	NR	38	2			36.19	1.87		
		C	22	NR	8	2			36.40	9.10		
		I	88	NR	19	7			21.40	8		
BOP/SUP, PD ≥ 4 mm, BL ≥ 3 mm		C	104	NR	41	49	12		39.40	47.10	11.70	
		I	300	NR	82	108	20		27.30	36.60	6	
		C	70	NR	NR	NR			NR	NR		
		I	73	NR	11	1			15.10	1.40		
		C	31	NR	NR	NR			NR	NR		
		I	131	121	9	1			92.37	0.76		
		C	103	33	32	38			31	37		
		I	266	103	101	61			38	23		
		C	113	58	41	14			36.30	12.40		
		I	347	210	111	26			32	7.50		
		C at 5 years	150	NR	78	25			51.90	16.90		
		I	300	NR	123	34			41.20	11.50		
		C at 10 years	150	NR	85	45			57	29.70		
		I	300	NR	141	61			47	20.30		
		C	245	102	96	40			38.80	16.30		
		I	964	494	208	88			21.60	9.10		
		C	32	3	9	20			28.13	62.50		
		I	161	16	100	45			62.11	27.95		
		S with I ≤ 5 (*n* implants)	NR	11	63	19			67.74	20.43		
		S with I > 5 (*n* implants)	NR	5	37	26			54.41	38.24		

(Continues)

TABLE 1 (Continued) [In PDF format, this table is best viewed in two-page mode]

Study	Study design	Follow-up period	Type of subjects	Prosthetic reconstruction	SPT	Health (H)	Mucositis (M)	Peri-implantitis 1 (P1)
Poli et al. (2016)	Retrospective cross-sectional	2–15 years	NR	NR	Regular SPT	No BOP/SUP or BOP at one surface only	BOP from more than one surface	BOP/SUP, PD ≥ 4 mm, BL ≥ 2 mm
Rinke et al. (2011)	Retrospective cross-sectional	Mean 68.2 months (range 2–11.2 years)	Healthy and perio. S	iFDP	58 S with regular SPT, 31 S with irregular SPT	NR	BOP, PD ≥ 4 mm	BOP/SUP, PD ≥ 5 mm, progressive BL (BL > 3.5 mm apical to implant shoulder on last Rx)
Rodrigo et al. (2012)	Prospective	5 years	7 healthy and 15 perio. S	NR	Regular SPT	NR	BOP, PD ≥ 4 mm, no significant BL	BOP, PD ≥ 4 mm, significant BL (3xSD of repeated measures)
Rokn et al. (2017)	Retrospective cross-sectional	Mean 4.43 ± 2.25 years (range 1–11)	17/134 S with Hx of perio.	iFDP	No	NR	BOP/SUP, BL ≤ 2 mm	BOP/SUP, BL > 2 mm
Roos-Jansåker et al. (2006)	Retrospective case series	9–14 years	Healthy and perio., 29.4% edentulous S	iFDP or removable prosthesis	SPT performed by reffering dentist	NR	BOP, PD ≥ 4 mm, no BL	BOP/SUP, PD ≥ 4 mm, BL ≥ 3 threads (1.8 mm)
Rutar et al. (2001)	Retrospective	5–10 years	NR	NR	Regular SPT	NR	NR	BOP/SUP, PD > 4 mm, BL
Schropp et al. (2014)	RCT	10 years	Healthy and perio. Subjects	SC (all cemented except 2 which were screw retained)	NR	NR	NR	BOP/SUP, PD ≥ 5 mm, BL > 1 mm
Swierkot et al. (2012)	Retrospective	5–16 years	35 Hx of aggressive Perio. and 18 healthy S	SC, iFDP, removable prosthesis	Regular SPT	NR	BOP, PD ≥ 5 mm, no BL	BOP, PD > 5 mm, annual BL > 0.2 mm after 1 year of loading
Trullenque-Eriksson and Guisado Moya (2015)	Retrospective	Mean 13.19 ± 3.7 years	Healthy and perio. S	NR	NR	NR	BOP/SUP, PD ≥ 5 mm, BL < 3 mm	BOP/SUP, PD ≥ 5 mm, BL ≥ 3 mm
van Velzen et al. (2015)	Prospective	10 years	Healthy and perio. S	SC, iFDP, removable prosthesis	Regular SPT	NR	NR	BOP, BL ≥ 1.5 mm
Wahlstrom, Sagulin and Jansson (2010)	Retrospective	Mean 5.1 years (range 3.3–7)	Healthy and perio. (29%) S	iFDP	Regular SPT	NR	Color and shape of mucosa, BOP, PD < 4 mm, no BL	BOP/SUP, PD ≥ 4 mm, BL > 2 mm after minimum loading of 1 year

BL, bone loss; BOP, bleeding on probing; C, control; Hx, history; I, implant; iFDP, implant supported fixed dental prosthesis; NR, not reported; PD, probing depth; RCT, randomized controlled trial; S, subject; SC, single crown; SPT, supportive periodontal therapy; SUP, suppuration.

TABLE 1 (additional columns - continued)

Peri-implantitis 2 (P2)	Peri-implantitis 3 (P3)		Total *n*	H (*n*)	M/BOP (*n*)	P1 (*n*)	P2 (*n*)	P3 (*n*)	M/BOP (%)	P1 (%)	P2 (%)	P3 (%)
		C	103	NR	NR	NR			NR	NR		
		I	421	248	173	19			41.10	4.50		
		C	89	NR	40	10			44.90	11.20		
		I	NR	NR	NR	NR			NR	NR		
		C	22	NR	NR	NR			NR	NR		
		I	68	NR	13	4			19.10	5.80		
		C	134	NR	65	27			48.50	20.10		
		I	478	NR	191	42			40	8.80		
BOP/SUP, PD ≥ 4 mm, BL ≥ 5 threads (4.3 mm)		C	218	NR	105	35			48	16	24	
		I	999	NR	160	66			16	6.60	5.60	
		C	45	NR	NR	NR			NR	NR		
		I	64	NR	51	15			80	23.43		
		C	46	NR	NR	2			NR	NR		
		I	46	NR	32	2			70	4.30		
		C	53	NR	34	17			64.15	32.10		
		I	179	NR	96	42			53	23		
		C	100	NR	14	3			14	3		
		I	242	NR	27	4			11.20	1.70		
BOP, BL ≥ 2 mm		C	169	NR	101	25	NR		59.80	14.80	NR	
		I	356	NR	162	25	15		45.50	7	4.20	
		C	46	21	10	2			21.74	4.34		
		I	116	NR	NR	NR			NR	NR		

TABLE 2 Excluded studies and reasons for exclusion

Reason for exclusion	Study (Author, year)
Study included less than 20 human subjects	Poli et al. (2017), Chang et al. (2016), Zuo et al. (2015), Quaranta et al. (2015), Li et al. (2015), Li et al. (2014)
Less than 12 months of mean functional loading	Al Jaboobi et al. (2017), Goncalves Junior et al. (2016)
Cases selected based on diagnosis of PI	Zani et al. (2016), Wang et al. (2016), Teixeira et al. (2016), Severino et al. (2016), Mardegan et al. (2016), Heitz-Mayfield et al. (2016), Renvert et al. (2015), Rakic et al. (2015), Neilands et al. (2015), Lopez-Martinez et al. (2015), Jemt et al. (2015), Guo et al. (2015), Garcia-Delaney et al. (2015), Canullo et al. (2015), Ata-Ali et al. (2015), Albertini et al. (2015), de Araujo Nobre et al. (2014a, b), Cecchinato et al. (2014), Wu et al. (2013), Raki et al. (2013), Ebadian et al. (2013), Darabi et al. (2013), Cortelli et al. (2013), Charalampakis et al. (2012)
PI not diagnosed in any of the cases	Bechara et al. (2017), Glibert et al. (2016), Frisch et al. (2015b), Guljé et al. (2014)
BOP, SUP or mucositis not clearly reported	Troeltzsh et al. (2016), Canullo et al. (2016b), Sanchez-Siles et al. (2015), Rinke et al. (2015), Papantonopoulos et al. (2015), Renvert et al. (2014), Malo et al. (2014), Fardal et al. (2013), Pjetursson et al. (2012), Roccuzzo et al. (2012), Dierens et al. (2012), Dvorak et al. (2011), Schmidlin et al. (2010), Simonis et al. (2010), Zetterqvist et al. (2010), Gatti et al. (2008), Bragger et al. (2005), Fransson et al. (2005), Baelum et al. (2004), Gruica et al. (2004), Karoussis et al. (2003), Bragger et al. (2001)
Not a clinical study	Maret et al. (2017), Schwendicke et al. (2015), Cañaveral Cavero et al. (2015)
Study not corresponding to search criteria	Sampaio-Fernandes et al. (2015), Korsch et al. (2015), Silva et al. (2014), Becker et al. (2014), Olmedo et al. (2013)
No clear definition of PI	Mencio et al. (2017), Jemt et al. (2017), Badea et al. (2017), Lopez et al. (2016), Esposito et al. (2016), Ernst et al. (2016), Cotic et al. (2016), Jervoe-Storm et al. (2015), Galindo-Moreno et al. (2015), Moreno Vazquez et al. (2014), Galindo-Moreno et al. (2014), Qu et al. (2013), Manev et al. (2013), Malo et al. (2013), Lam et al. (2013), Lachmann et al. (2013), Casado et al. (2013), Bignozzi et al. (2013), Atalay et al. (2013), Aguirre-Zorzano et al. (2013), Becker et al. (2016), Lopez-Piriz et al. (2012), Astrand et al. (2004)
Full text not available or abstracts for oral/poster presentations	de Arriba et al. (2016), Kang et al. (2015), Dastaran et al. (2015), Pigatto et al. (2014), Nobre de et al. (2014), Lombardo et al. (2014), Kim et al. (2014), Bazikyan et al. (2014), Parmar et al. (2013), Ihan Hrenet al. (2013)

3.5 | Meta-analyses of the proportion of peri-implantitis

3.5.1 | Implant-level analysis

Twenty-nine studies reported data on an implant-level. The proportion of peri-implantitis among implants presenting with BOP varied between 0% (Corbella et al., 2011) and 62.1% (Canullo et al., 2016). However, significant heterogeneity was noted (I^2 = 93.3%) and a model with random effects was used to combine the studies. Over all studies, 24.1% (95% CI 19.3–29.7) of implants presenting with BOP were diagnosed with peri-implantitis. The 95% prediction interval for the proportion of peri-implantitis among implants with BOP in a new study was 6.9% to 57.8%. The wide prediction interval is attributed to the heterogeneity of the studies (Figure 2). Leave-one-out sensitivity analysis did not reveal a specific study explaining the heterogeneity, and the pooled proportion was similar when any of the studies was removed. The funnel plot did not show evidence of asymmetry (p value = .35). No publication bias was detected (Figure 3).

In two of the retrieved studies, each participant received two different implant treatments (Duque et al., 2016; Rodrigo et al., 2012). As the types of implants are potentially associated with the risk of peri-implantitis, a sensitivity analysis was conducted by removing these two comparative studies from the meta-analyses. The exclusion of these two studies did not significantly modify the results of the meta-analysis on the implant level.

3.5.2 | Subject-level analysis

Twenty studies reported data on a subject level. The proportion of peri-implantitis among subjects presenting with BOP varied from 9.1% (Frisch, Ziebolz & Rinke, 2013) to 69% (Passoni et al., 2014). Again, significant heterogeneity was noted (I^2 = 88.9%) and a random effects model was utilized. The combined proportion of peri-implantitis in BOP-positive cases was 33.8% (95% CI 26.7–41.6). The 95% prediction interval for the proportion of peri-implantitis among subjects with BOP in a new study was 10.3% to 69.3%. Once more, the considerable heterogeneity contributed to the width of the prediction interval (Figure 4). No specific study explained the heterogeneity, and the pooled proportion was similar when any of the studies was removed. Finally, the funnel plot did not show asymmetry (p value = .57) and publication bias was not detected (Figure 5).

3.6 | Subgroup analysis

An association was found between the mean follow-up period and the proportion of implants affected by peri-implantitis (Table 4). Short observation periods (1–3 years) were significantly associated with

lower proportions of peri-implantitis among BOP-positive implants (p value < .05).

4 | DISCUSSION

This systematic review and meta-analysis focused on the evaluation of BOP as a predictive measure for peri-implantitis. In the studies included in this review, whenever bleeding occurred after probing, there was a 24% chance that the corresponding implant was diagnosed with peri-implantitis. In addition, there was a 33.8% probability that patients with BOP-positive implants were diagnosed with peri-implantitis. In other words, in the majority of instances, bleeding after probing of implants was observed in the absence of peri-implantitis. The generally high rate of BOP around implants noted in our analysis, may be attributed in part to the mechanical fragility of healthy peri-implant mucosae. Indeed, comparative assessments of teeth and implants in the same patients have indicated that, even in the absence of disease, the bleeding tendency and gingival index scores were higher at implants than at teeth (Cionca, Hashim, Cancela, Giannopoulou & Mombelli, 2016). BOP positive and negative gingival tissues have been compared histologically (Greenstein, Caton & Polson, 1981). Specimens from sites bleeding after light probing showed a significantly increased percentage of cell-rich and collagen-poor connective tissue, but no increase of blood vessel lumens. Similar information is presently unavailable for human peri-implant tissues. The documented relationship between probing force and frequency of BOP at healthy teeth (Karayiannis et al., 1992) suggests that tissue trauma due to probing with a high force may occasionally be the reason for bleeding at implants. None of the studies included in the present review used force-controlled probes. Thus, excessive probing forces, causing rupture of small blood vessels, cannot be excluded. To avoid false-positive readings, probing with controlled forces not exceeding 0.25 N have been recommended for teeth (Karayiannis et al., 1992). However, recommendations for ideal probing forces at implants can not presently be made based on currently available evidence.

Continual absence of BOP at teeth during maintenance care has been suggested as an indicator of periodontal stability. In patients incorporated in a maintenance programme for more than 2.5 years following periodontal therapy, only 1.3% dental sites that rarely bled on probing (never or only at one of six assessments) lost ≥2 mm clinical attachment. In contrast, 28% of the sites that bled frequently (5 or 6 times of six assessments) lost ≥2 mm clinical attachment (Lang, Adler, Joss & Nyman, 1990). In another study (Luterbacher, Mayfield, Brägger & Lang, 2000), 19 patients were monitored, both at teeth- and implant-levels, during 2 years of rigid maintenance care. At implants, a BOP frequency of ≥50% showed a sensitivity of 50% and specificity of 100% to indicate change in bone density or probing attachment loss. The authors reported better positive predictive values for frequent BOP at implant sites than at tooth sites. Negative predictive values indicating periodontal or peri-implant stability did not differ substantially.

This review was limited in its analysis of risk factors that could contribute to the development of peri-implantitis. Such analysis was hindered by the heterogeneity of the studies and the small number of articles evaluating a single factor in association with peri-implantitis. Six of the 31 included studies evaluated both patient and implant factors in relation to peri-implantitis (Canullo et al., 2016; Dalago, Schuldt Filho, Rodrigues, Renvert & Bianchini, 2017; Daubert et al., 2015; Derks et al., 2016; Marrone et al., 2013; Rokn et al., 2017), yet data were only presented in terms of relative risk in Daubert et al. (2015). van Velzen et al. (2015) reported on both implant and subject characteristics but did not attempt to analyse their effects on the prevalence of peri-implantitis. Only three studies (Frisch, Ziebolz, Vach & Ratka-Kruger, 2015; Passoni et al., 2014; Poli, Beretta, Grossi & Maiorana, 2016) examined the effect of keratinized mucosa on peri-implant disease. Ferreira et al. (2006), on the other hand, evaluated the effect of patient-related risk factors and plaque index on the prevalence of peri-implantitis without examining local implant factors. The diversity in diagnostic criteria and disease definition, the differences regarding length of the observation period, prosthetic reconstructions, treatment of peri-implantitis, statistical methodology and data presentation, in addition to the differences in sample selection and the variability in subjects' susceptibility to peri-implant disease, present major limitations of this meta-analysis. Despite a consensus report from the proceedings of the 8th European Workshop on Periodontology (Sanz & Chapple, 2012) recommending the use of unequivocal case definitions and the expression of outcomes at subject level, a large number of studies still fail to adhere to such directions.

The results of this analysis showed a significant association between the observation period and the proportion of implants with a mucosa bleeding after probing being affected by peri-implantitis. Yet, the reliability of such association could be questioned due to the scarcity of studies with short follow-up periods (n = 2). Nonetheless, a recent systematic review also established that a longer observation period is associated with a higher prevalence of peri-implantitis (Lee et al., 2017). It is also worth considering that one study (Corbella et al., 2011), which reported 0% prevalence of peri-implantitis after 3 years, could have affected the analysis. This was a prospective study which evaluated immediately loaded implants placed in edentulous subjects over an observation period of 4 years. The authors reported peri-implantitis affecting 1.4% of implants (three implants in two subjects) after 6–12 months of function. Surgical debridement was performed, and no further complications were reported. Hence, the lack of peri-implantitis at the 3-year follow-up. For the rest of the studies reporting data at different time points, the results of the latest follow-up were included in this report. However, this could not be applied to Corbella et al. which, at 4 years, only analysed 29 of the initial 244 implants. As 109 implants were examined at 3 years, those were the data analysed in this review. A leave-one-out statistical analysis was performed to reduce the risk of bias generated by this study, and the results did not show a statistically significant difference when Corbella et al. were omitted.

The proportion of implants with BOP being affected by peri-implantitis was not significantly associated with either periodontal history or regular maintenance care. This could be attributed to the differences in the degree of periodontal involvement, the variability in

TABLE 3 Quality assessment of the included studies [In PDF format, this table is best viewed in two-page mode]

Study ID		Design	Evidence level[a]	Details on clinical examination	Inter/Intra-examiner calibration	Details on implant characteristics	Local factors[b]
1	Aguirre-Zorzano et al. (2015)	Cross-sectional	III	No	No	Yes	No
2	Canullo et al. (2016)	Cross-sectional	III	Yes	No	Yes	Yes
3	Cecchinato et al. (2014)	Prospective	III	Yes	NC	No	NC
4	Cho-Yan Lee et al. (2012) (46)	Retrospective case-control	IIa	Yes	No	Yes	No
5	Corbella et al. (2011)	Prospective	III	Yes	No	No	No
6	Dalago et al. (2017)	Retrospective	III	Yes	No	Yes	Yes
7	Daubert et al. (2015)	Cross-sectional	III	No	Yes	Yes	Yes
8	Derks et al. (2016)	Cross-sectional	III	Yes	No	Yes	Yes
9	Duque et al. (2016)	Cross-sectional	III	Yes	Yes	Yes	No
10	Ferreira et al. (2006)	Cross-sectional	III	Yes	Yes	Yes	Yes
11	Frisch et al. (2015)	Retrospective	III	Yes	No	Yes	Yes
12	Frisch et al. (2013)	Retrospective	III	Yes	No	Yes	No
13	Koldsland et al. (2010)	Cross-sectional	III	Yes	Yes	NC	No
14	Lee et al. (2016)	Retrospective	III	No	No	Yes	No
15	Lehmann et al. (2013)	Prospective	III	Yes	No	Yes	No
16	Marrone et al. (2013)	Cross-sectional	III	Yes	No	Yes	Yes
17	Maximo et al. (2008)	Prospective case series	III	No	Yes	Yes	No
18	Meijer et al. (2014)	Retrospective	III	Yes	No	Yes	No
19	Mir-Mari et al. (2012)	Cross-sectional	III	Yes	Yes	Yes	No
20	Passoni et al. (2014)	Cross-sectional	III	Yes	Yes	NC	Yes
21	Poli et al. (2016)	Retrospective cross-sectional	III	Yes	No	NC	Yes
22	Rinke et al. (2011)	Retrospective cross-sectional	III	No	No	NC	No
23	Rodrigo et al. (2012)	Prospective	III	Yes	No	Yes	No
24	Rokn et al. (2017)	Retrospective cross-sectional	III	No	No	Yes	Yes
25	Roos-Jansåker et al. (2006)	Retrospective case series	III	Yes	No	No	No
26	Rutar et al. (2001)	Retrospective	III	Yes	No	No	No
27	Schropp et al. (2014)	RCT	Ib	Yes	Yes	No	No
28	Swierkot et al. (2012)	Retrospective	III	No	Yes	Yes	No
29	Trullenque-Eriksson and Guisado Moya (2015)	Retrospective	III	Yes	No	No	No
30	van Velzen et al. (2015)	Prospective	III	Yes	No	Yes	Yes
31	Wahlstrom et al. (2010)	Retrospective	III	Yes	No	Yes	NC

Ib, evidence from at least one randomized controlled trial; III, evidence from well-designed non-experimental studies, such as comparative, correlational or case studies; IIa, evidence from at least one well-designed controlled study without randomization. PI = Peri-implantitis. BL = Bone loss. SPT = Supportive periodontal treatment. RCT = Randomized controlled trial. NC = Not clear.

[a]According to the definitions of types of evidence originating from the US Agency for Health Care Policy and Research (1993).

[b]Risk factors for peri-implantitis such as implant malpositioning, cleansability of reconstruction, excess cement, absence of keratinized gingiva etc.

[c]Such as history of periodontal disease, oral hygiene and smoking status.

TABLE 3 (additional columns)

Standardized radiographic examination	Completeness of follow-up/report of drop outs	Details on subjects characteristics[c]	SPT reported	Definition PI with BL	Treatment of PI	Completeness/ clarity of data reporting on PI	Risk of bias
No	Yes	Yes	Yes	Yes	No	Yes	Low
No	Yes	Yes	Yes	Yes	No	No	Medium
Yes	Yes	NC	Yes	Yes	Yes	No	High
No	Yes	Yes	Yes	No	No	No	Medium
No	Yes	NC	Yes	No	Yes	No	High
No	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	Yes	No	Yes	No	Yes	Low
Yes	Yes	Yes	No	Yes	Yes	No	High
No	Yes	Yes	Yes	Yes	No	Yes	Low
No	Yes	No	Yes	Yes	No	No	Medium
No	Yes	NC	Yes	Yes	No	Yes	Low
No	Yes	No	No	Yes	No	Yes	Medium
No	Yes	No	Yes	Yes	No	No	Medium
Yes	Yes	NC	Yes	Yes	No	No	Medium
Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Yes	Yes	Yes	No	Yes	No	Yes	Low
Yes	Yes	No	Yes	Yes	Yes	No	Medium
No	Yes	No	Yes	Yes	No	Yes	Low
No	Yes	No	No	Yes	No	Yes	Medium
No	Yes	NC	Yes	Yes	No	No	Medium
Yes	Yes	Yes	Yes	Yes	No	No	Medium
Yes	Yes	Yes	Yes	Yes	Yes	No	Medium
No	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	No	Yes	Yes	No	Yes	Medium
No	Yes	NC	Yes	Yes	Yes	No	Medium
Yes	Yes	NC	Yes	Yes	No	Yes	Low
Yes	Yes	Yes	No	Yes	No	Yes	Low
No	Yes	NC	No	Yes	No	Yes	Medium
Yes	Yes	Yes	Yes	Yes	No	Yes	Low
No	Yes	Yes	Yes	Yes	No	No	Medium

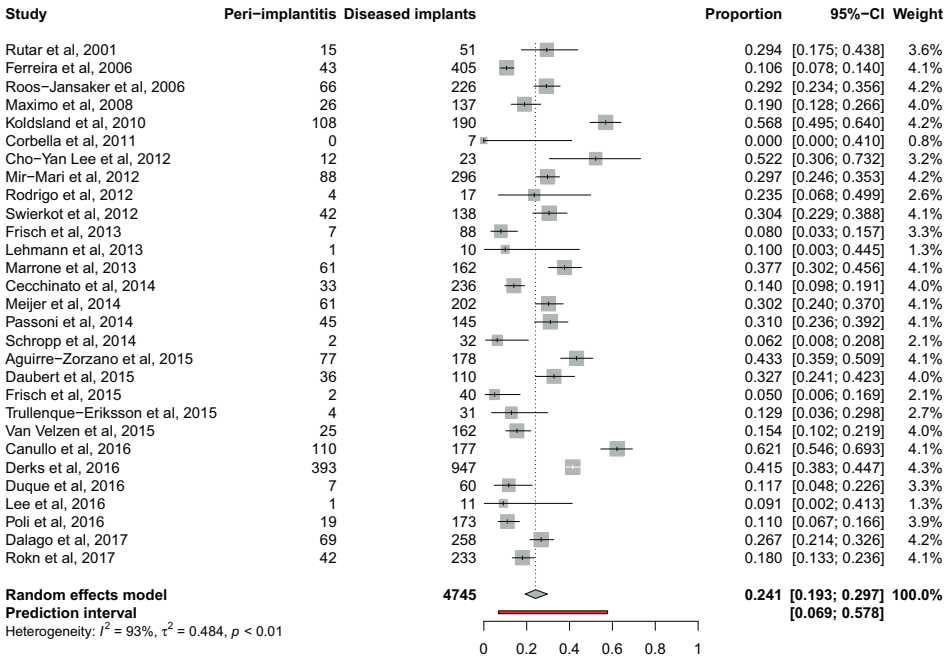

FIGURE 2 Forest plot for the proportion of peri-implantitis among implants presenting with BOP/SUP

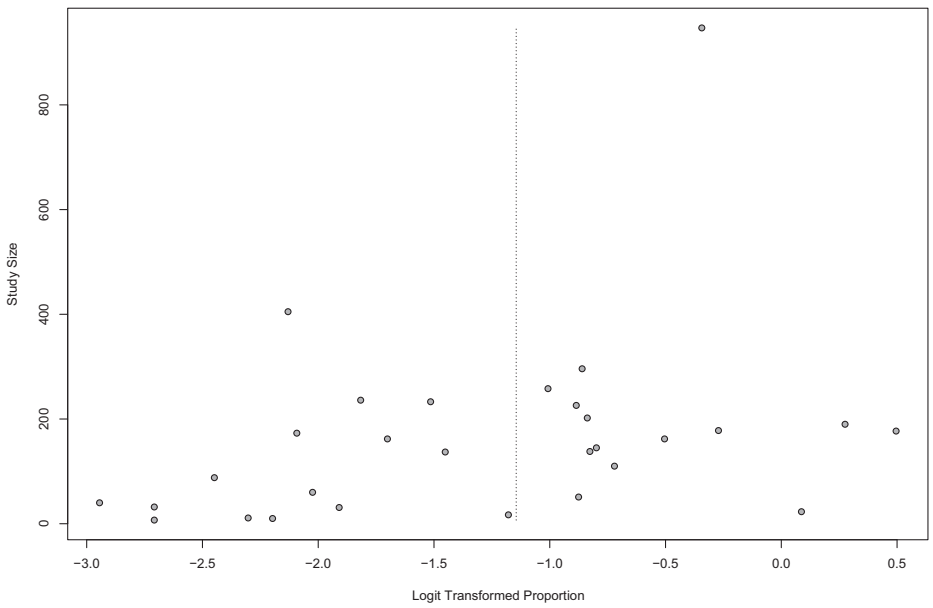

FIGURE 3 Funnel plot for publication bias in studies presenting data on implant level (n = 29 studies)

maintenance intervals and patient compliance, as well as the length of the observation period.

Attempts to classify the data according to implant risk factors or prosthetic connection's design had failed due to the extreme variability in between, and within, studies. Most studies evaluated different implant brands with extremely variable characteristics. Rough and machined surfaces were analysed, as well as tissue-level and bone-level implants, platform switching, removable and fixed reconstructions, in healthy and periodontally compromised patients, with or without regular maintenance care.

In conclusion, the present systematic review and meta-analysis demonstrated that for BOP-positive implants, there was a 24.1% chance to be diagnosed with peri-implantitis; while for BOP-positive patients, there was a 33.8% probability of being diagnosed with peri-implantitis. Clinicians should be aware of the considerable false-positive rate of BOP to diagnose peri-implantitis.

TABLE 4 Subgroup analysis on implant level

Subgroups of studies	Category	*n* studies	Pooled proportion	I^2 (%)	*p* value
Type of subjects	Healthy	2	19.5% (7.3 to 42.6)	80.6	.2409
	Healthy + Perio.	12	26.6% (18.4 to 36.7)	95.2	
	Perio.	3	35% (26.9 to 44.1)	78.0	
Regular SPT	No	4	27.3% (12.4 to 49.7)	96.2	.7125
	Yes	17	23.5% (16.9 to 31.8)	94.8	
Mean follow-up period	1–3 years	2	11.2% (5.6 to 21.2)	0	**.0439***
	3–5 years	8	25.8% (14.4 to 41.7)	96.1	
	>5 years	18	26.1% (20.8 to 32.3)	91	

*P value in bold characters indicates a statistically significant association between the pooled proportion and the length of the mean follow-up period (p value < .05)

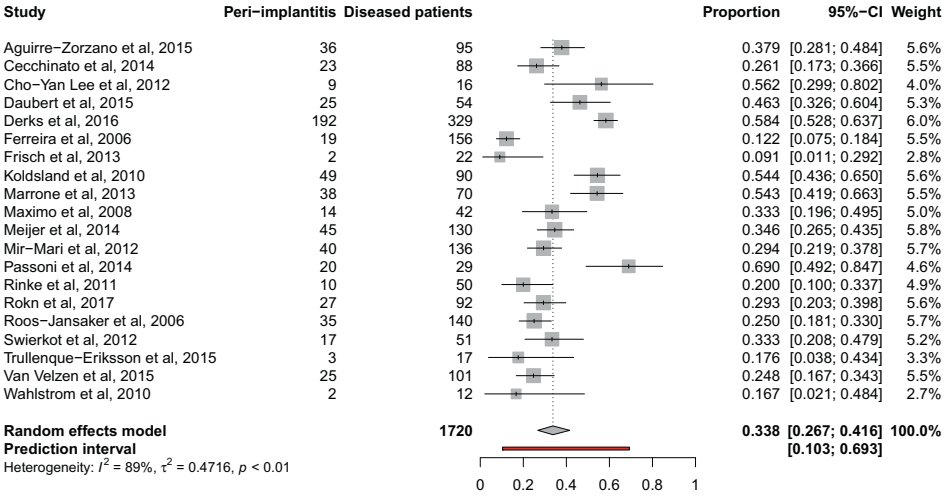

FIGURE 4 Forest plot for the proportion of peri-implantitis among subjects presenting with BOP/SUP

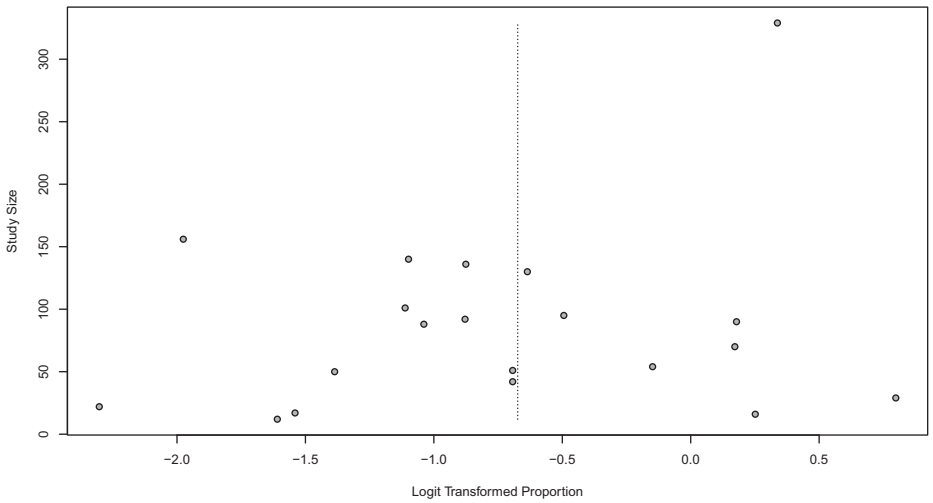

FIGURE 5 Funnel plot for publication bias in studies presenting data on subject level (*n* = 20 studies)

ACKNOWLEDGEMENTS

The study was entirely financed by research funds of the Division of Periodontology, University Clinics of Dental Medicine, University of Geneva, Geneva, Switzerland.

CONFLICT OF INTEREST

The authors have been involved in clinical trials evaluating titanium implants (Institut Straumann AG, Basel, Switzerland) and zirconia implants (Dentalpoint AG, Zürich Switzerland). These studies were supported by funds from the respective manufacturers. NC and AM have also received lecturing honoraria from these companies.

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