



# BMJ Open Predictive factors for the treatment success of peri-implantitis: a protocol for a prospective cohort study

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## ABSTRACT

**Introduction** Peri-implantitis, a common biological complication of dental implant, has attracted considerable attention due to its increasing prevalence and limited treatment efficacy. Previous studies have reported several risk factors associated with the onset of peri-implantitis (eg, history of periodontitis, poor plaque control and smoking). However, inadequate data are available on the association between these risk factors and successful outcome after peri-implantitis therapy. This prospective cohort study aims to identify the local and systemic predictive factors for the treatment success of peri-implantitis.

**Methods and analysis** A single-centre cohort study will be conducted by recruiting 275 patients diagnosed with peri-implantitis. Sociodemographic variables, healthy lifestyles and systemic disorders will be obtained using questionnaires. In addition, clinical and radiographic examinations will be conducted at baseline and follow-up visits. Treatment success is defined as no bleeding on probing on more than one point, no suppuration, no further marginal bone loss ( $\geq 0.5$  mm) and probing pocket depth  $\leq 5$  mm at the 12-month follow-up interval. After adjustment for age, sex and socioeconomic status, potential prognostic factors related to treatment success will be identified using multivariable logistic regression models.

**Ethics and dissemination** This cohort study in its current version (2.0, 15 July 2022) is in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Stomatological Hospital, Southern Medical University (EC-CT-(2022)34). The publication will be on behalf of the study site.

**Trial registration number** ChiCTR2200066262.

## INTRODUCTION

With the development of implant dentistry, implant therapy is a widely accepted strategy for restoring missing teeth.<sup>1</sup> As a common biological complication of implant therapy, peri-implantitis has attracted considerable attention because of its increasing prevalence.<sup>2</sup> Peri-implantitis is a plaque-associated pathological condition in tissues around dental implants. The typical clinical characteristics

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This prospective cohort ensures the accuracy and reliability of the findings by recruiting a relatively large sample size and using robust statistical analysis.
- ⇒ This study uses longitudinal and multiple follow-ups for dynamic monitoring of the developmental trajectory of peri-implantitis after treatment.
- ⇒ As patients with peri-implantitis are voluntary to receive treatment, non-responders or recall bias could exist during recruitment.
- ⇒ Recruitment from a single centre may cause selection bias and limited generalisation.
- ⇒ Eighteen months of follow-up duration might be suffice to show the treatment outcome, but a longer follow-up may be of interest to observe the effect of different predictive factors on treatment outcomes.

of sites exhibiting peri-implantitis involve gingival bleeding and/or suppuration, deepening periodontal pockets and supporting bone loss.<sup>3</sup> The pathological bone loss observed in peri-implantitis should not be conflated with the natural process of physiological bone remodelling following implantation. Initial physiological bone remodelling was defined as the bone loss happening from implant placement to the end of the bone remodelling, generally, 1 year after crown placement.<sup>4</sup> Box 1 presents the case definition and diagnosis criteria according to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.<sup>3</sup> Before the consensus was proposed, the prevalence of peri-implantitis varied according to different case definitions. The prevalence of peri-implantitis case definition with a cut-off of 2 mm of bone level is 20% at implant level and 24% at patient level. The prevalences of the peri-implant conditions with a cut-off of 3 mm of bone levels are 11% at implant site and 14% at patient site.<sup>5</sup> A systematic review indicated the prevalence

**BOX 1 DEFINITION AND DIAGNOSIS OF PERI-IMPLANTITIS**

- ⇒ Peri-implantitis is a plaque-associated pathological condition occurring in tissues around dental implants, characterised by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone.
- ⇒ Diagnosis of peri-implantitis requires:
  1. Presence of bleeding and/or suppuration on gentle probing.
  2. Increased probing pocket depth compared with previous examinations.
  3. Presence of bone loss beyond crestal bone level changes resulting from initial bone remodelling.
- ⇒ In the absence of previous examination data, diagnosis of peri-implantitis can be based on the combination of:
  1. Presence of bleeding and/or suppuration on gentle probing.
  2. Probing pocket depths  $\geq 6$  mm.
  3. Bone levels  $\geq 3$  mm apical of the most coronal portion of the intraosseous part of the implant.

of peri-implantitis was estimated at 12.53% and 19.53% at implant and patient levels, respectively.<sup>6</sup> Despite the prevalence threshold and definition varying across studies, the importance of peri-implantitis cannot be underestimated.

In comparison, periodontitis is a chronic inflammatory disease affecting the supporting structures of natural teeth. Although peri-implantitis and periodontitis share similar clinical phenotypes and risk factors, they have distinct clinical progression, histological characteristics and microbial composition.<sup>7,8</sup> A recent *in vivo* study suggested that dental implants had an excessive inflammatory response to bacterial infection compared with natural teeth.<sup>9</sup> Next, the surface of dental implants differs from dental roots as implants are rough, coated and have screw windings. The difference in pathogenesis and surface structures might explain why the routine therapy for periodontitis (eg, scaling, root planing and polishing) is effective in periodontitis but does not equally fare well against peri-implantitis. Briefly, the successful treatment of peri-implantitis has become one of the most critical challenges in implant dentistry.

Numerous clinical studies have focused on risk factors for the onset of peri-implantitis, with mainly two identified categories: history of periodontitis and poor plaque control (including lack of regular maintenance therapy).<sup>10–12</sup> Recently, a long-term retrospective study indicated that the stages and grades of periodontitis are risk indicators for peri-implant diseases.<sup>13</sup> Peri-implant disease was more common in patients with stage IV periodontitis, and implant loss due to peri-implantitis was higher in patients who had bone augmentation. In addition, there are other risk factors for the incidence of peri-implantitis: patient-related factors (eg, smoking behaviour, diabetes and susceptibility genes), implant-related factors (eg, implant surface characteristics, implant designs, titanium particles and the width of keratinised mucosa), prosthesis-related factors (eg, occlusal forces, overcontoured restorations and excess cement) and iatrogenic factors.<sup>14</sup> In contrast, rare cohort studies

focused on the associations between potential predictive indicators and treatment outcomes.<sup>15–17</sup> Several factors were reported to possibly influence the outcome of peri-implantitis surgical therapy, such as the history of periodontitis, serve peri-implant bone loss, deep probing pocket, suppuration, smoking and poor postoperative control of plaque. Further longitudinal studies are warranted to screen the predictors of peri-implantitis progression after non-surgical or surgical treatment.

Therefore, we proposed a prospective cohort study aiming to identify the local and systemic predictive factors to predict the treatment success of peri-implantitis.

**METHODS****Study design**

This single-centre prospective cohort study will be conducted by the Center of Oral Implantology of the Stomatological Hospital, Southern Medical University. Patients treated with implants at the Center of Oral Implantology from January 2010 to December 2019 will be recalled by phone calls. We will ask eligible volunteers to participate in the cohort study based on the inclusion and exclusion criteria. Informed consent will then be obtained from all the patients. Recruitment will last for 6 months. We intend to recruit 275 patients with peri-implantitis. Peri-implantitis rarely occurs in isolation but frequently coexisting with periodontitis. A 3-year longitudinal study suggested that adjacent teeth may become the microbial reservoir for peri-implant bacteria.<sup>18</sup> Thus, the patients with peri-implantitis will receive supragingival and subgingival scaling for natural teeth concomitant with treatment for implant. Treating peri-implantitis involves a non-surgical, surgical therapy (if necessary) and supportive treatment. The recruitment will last from 1st December 2022 to 1st July 2023 and patients will be followed at 6-month, 12-month and 18-month intervals after non-surgical peri-implantitis treatment. In order to ensure the minimum loss of follow-up, patients with good compliance will be preferentially included in this experiment. This cohort study in its current version (2.0, 15 July 2022) is in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Stomatological Hospital, Southern Medical University (EC-CT-(2022)34), see online supplemental file 1). In addition, this protocol has already been registered on the Chinese Clinical Trials Registry (ChiCTR2200066262). The reporting of this study protocol will conform to the STrengthening the Reporting of OBServational studies in Epidemiology guideline (online supplemental file 2).

**Sample size calculation**

The sample size was calculated based on the results of our pilot study. In the routine treatment, the proportion of successful treatment for peri-implantitis was approximately 20% at the 18-month follow-up interval. Therefore, the sample size was calculated with a precision of

5% and a type 1 error of 5%. The formula for the sample size is as follows.

$$\text{Sample size} = \frac{Z_{1-\frac{\alpha}{2}}^2 p(1-p)}{d^2} = \frac{1.96^2 \times 0.20(1-0.20)}{0.05^2} = 246$$

where  $Z_{1-\frac{\alpha}{2}}$  is the standard normal variate,  $\alpha$  is the type I error,  $p$  is the expected proportion of successful treatment, and  $d$  is the absolute error or precision.<sup>19</sup> Therefore, we need to recruit 246 patients with peri-implantitis. Predicting >10% loss to follow-up, 275 patients with peri-implantitis will be enrolled.

### Study procedures

Two research assistants (RAs) will call the participants to ask for their willingness to participate in the examination. The RAs will explain the purposes of the research and answer all the questions about potential risks, benefits and confidentiality. Peri-implantitis will be diagnosed by clinical examinations, during which the inclusion and exclusion criteria will be applied. Patients with peri-implantitis willing to participate will sign an informed consent form. A copy of the consent form will be included in patients' medical records, and another copy will be given to them. Two dentists (YL and PZ) who have already passed the standardised training and now worked as periodontist and implantologist desperately will conduct clinical examinations and treatment for patients with peri-implantitis. Kappa values ranged from 0.50 (for keratinised tissue) to 0.81 (probing depth). To calibrate the cone-beam CT (CBCT) images reproducibly measuring the peri-implant marginal bone loss, two individuals (YZ and AL) will independently measure the implant marginal bone loss. If there is conflict, a referee will be called to conduct reassessment and make final decision. Patients will attend four follow-up visits in this cohort study which are scheduled at the baseline (T0) and 6 (T1), 12 (T2) and 18 months (T3) (figure 1). At T0, the subjects will provide basic information, including age, gender, healthy lifestyles, oral hygiene behaviours and systemic diseases. Clinical and radiographic pretreatment information will be collected at T0. Reassessment will be performed after non-surgical treatment for 6–8 weeks. Patients with persistent inflammatory lesion (ie, suppuration and/or gingival bleeding as well as deep pockets (probing pocket depth (PPD)  $\geq 6$  mm))<sup>3</sup> and adequate oral hygiene will be receiving surgical treatment based on bone defect morphology. Clinical (T1, T2 and T3) and radiographic examinations (T2 and T3) will also be conducted. At each follow-up visit, those who voluntarily leave the cohort or are lost to follow-up will be recorded as drop-outs. The examination on each follow-up visit is shown in figure 1.

### Patient inclusion and exclusion criteria

The inclusion and exclusion criteria are consistent with the previous study<sup>20</sup> and are described as follows:

1. Inclusion criteria: (a) adults aged 18–80 years with autonomous ability; (b) at least one implant with PPD  $\geq 6$  mm, bleeding on probing/suppuration and

bone levels  $\geq 3$  mm apical of the most coronal portion of the intraosseous part of the implant; (c) ability to provide an informed consent form and complete the questionnaires.

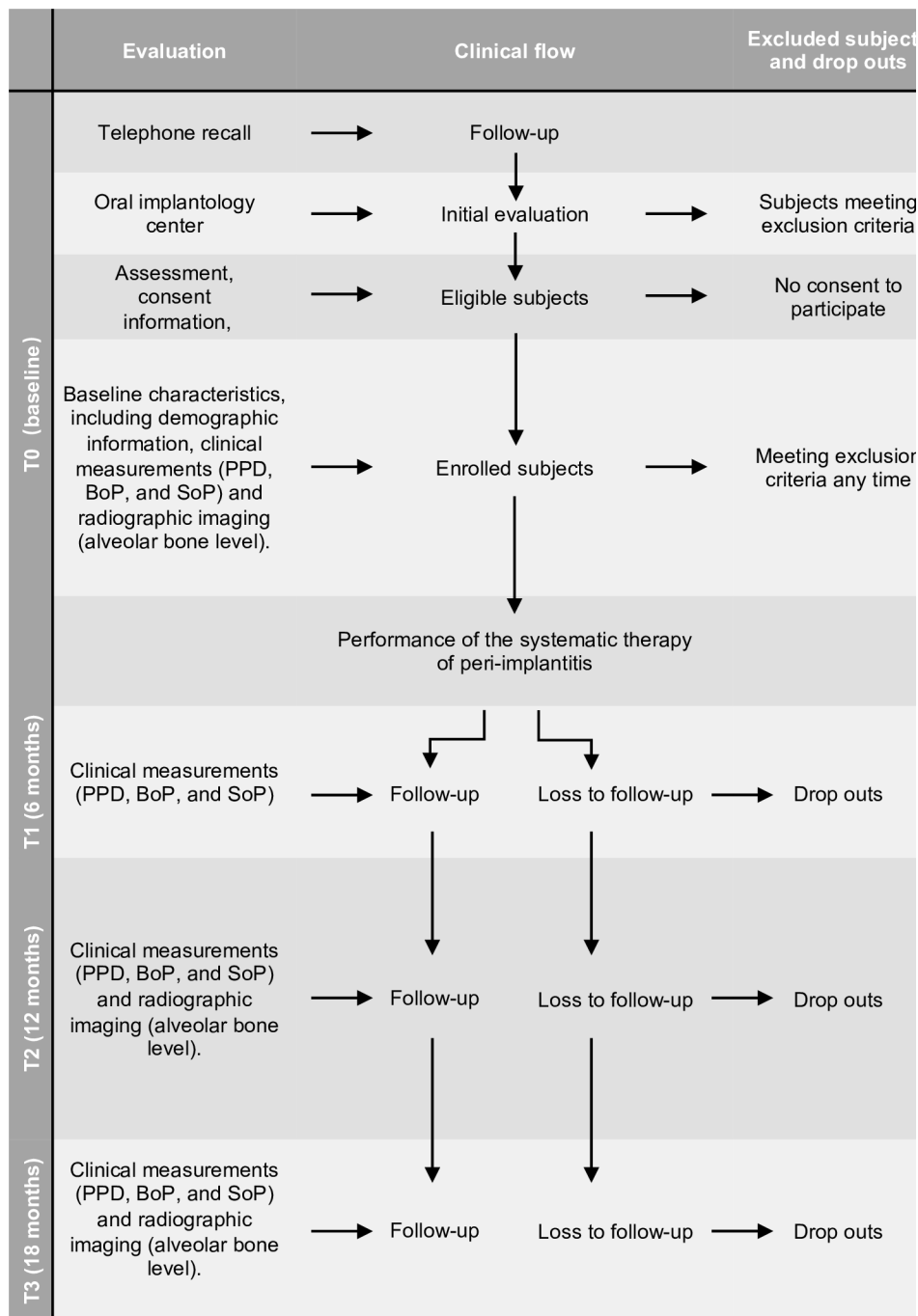
2. Exclusion criteria: (a) systemic diseases that are known to affect soft tissue or bone (eg, side-effect of hypertension medication and osteoporosis) or increase the risk of dental procedures, such as uncontrolled diabetes (blood sugar  $\geq 200$  mg/dL) and uncontrolled hypertension (systolic or diastolic blood pressure  $\geq 180$  or 110); (b) history of radiotherapy for head and neck tumours; (c) pregnancy; (d) antibiotic use in the past 6 months; (e) implants received treatment in the past 6 months; (f) inability to be contacted over the phone during follow-ups.

### Data collection

Basic information of the patients with peri-implantitis will be collected by questionnaire at T0. Online supplemental file 3 presents the details of the questionnaire. Basic information, systematic diseases, implant-related factors, prosthesis-related factors, periodontal probing measurement, oral hygiene, peri-implant probing measurement and radiographic examinations to be collected are listed in table 1. Basic information will include sex, age, education level (a proxy for socioeconomic status (SES)),<sup>21</sup> smoking, drinking, physical activity and oral health behaviours.

Implant-related information will be collected at baseline, such as the brand of implant, location in the arch (ie, implant malposition), the profile of implant (eg, length and diameter), surface modification, PPD/bone loss and the distance of the restorative margin to the bone crest.<sup>22 23</sup> Prosthesis-related factors will also be recorded, including type of connection, implant-abutment emergence angle and profile,<sup>24</sup> residual excess cement, poor marginal fit of the suprastructure, interproximal contact loss between implant-supported restorations and adjacent natural teeth, and occlusal overload (eg, porcelain wear and chipping).

Periodontal status will be determined using full-mouth periodontal examination protocol at baseline. In specific, two qualified examiners (YL and PZ) who have already experienced 3-year standardised training will perform dental examinations. Standardised training refers to the training programme in which doctors rotate in each subspecialty department of stomatology within 3 years and pass the corresponding technical and theoretical examination. Implant probing will be performed with a manual probe (PCP 12, Jakobi Dental) with a probing force of about 0.25 N.<sup>25</sup> Periodontal examination will be conducted at six probing sites (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual and distolingual) per natural tooth. Periodontal parameters include PPD, bleeding on probe (BoP), attachment loss<sup>26</sup> and suppuration on probing (SoP). In this study, we also included initial PPD/bone loss as a



**Figure 1** Study procedure of the prospective cohort study for peri-implantitis. BoP, bleeding on probing; PPD, probing pocket depth; SoP, suppuration on probing.

potential prognostic factor.<sup>27</sup> In addition, the Simplified Oral Hygiene Index will be scored based on six index teeth, as our previous work.<sup>21</sup> Full Mouth Plaque Score was also used to assess the oral hygiene.<sup>28</sup> In terms of implant-related examination, peri-implant probing at baseline will be performed after removing the implant-supported restorations using a plastic probe. Clinical examination parameters for dental implant include PPD, BoP, SoP and keratinised mucosa width.<sup>29–31</sup> Probing measurements of natural teeth and dental implants will be made at follow-up visits (T0–T3), similar to the baseline examinations.

In addition, radiographic examinations will be performed in the Department of Radiology, Stomatological Hospital, Southern Medical University. CBCT scans will be obtained at T0, T2 and T3. Peri-implant marginal bone loss (MBL) will be measured before and after treatment to identify if further bone loss exists. Implant platform or the most coronal portion of the implant will serve as a fixed point to accurately measure MBL. The volumetric change of the alveolar bone around an implant fixture will be calculated according to CBCT images. The volumetric changes

**Table 1** Data collection for patients with peri-implantitis

Domain	Subdomain	Definition	T0	T1	T2	T3
Basic data	Sex	Male or female	x			
	Age	Years	x			
	Education level	Primary school; junior middle school; senior middle school; bachelor's degree; master's degree or above	x			
	Smoking history	Never; ever; still have	x			
	Drinking history	Never; ever; still have	x			
	Physical activity	Never; sometimes; usually	x			
	Details of oral health	Information including overall self-impression, symptoms, daily care, reasons for dental extraction, dental treatment experiences	x			
	Systematic diseases	HBP	Yes or no	x		
Diabetes		Yes or no	x			
CVD		Yes or no	x			
Stroke		Yes or no	x			
Cancer		Yes or no	x			
Hyperlipidaemia		Yes or no	x			
Rheumatism		Yes or no	x			
Liver disease		Yes or no	x			
CKD		Yes or no	x			
Gallstones		Yes or no	x			
Other systemic diseases		Yes or no	x			
Implant-related factors	Implant site	FDI World Dental Federation notation	x			
	Brand of implant	Brand name	x			
	Location in the arch	Implant malposition	x			
	Profile of implant	Length and diameter	x			
	Implant surface	Rough; moderately rough; smooth	x			
	Surface modification	Acid etching; grit blasting; laser treatment; UV light, chemical vapour deposition and physical vapour deposition; coating	x			
	The distance of the restorative margin to the bone crest	<1.5 mm or ≥1.5 mm	x			
	Bone augmentation at implant installation	Yes or no	x			
Implant function (years)	Years of implant function	x				
Prosthesis-related factors	Type of connection	Screw or cemented	x			

Continued

**Table 1** Continued

Domain	Subdomain	Definition	T0	T1	T2	T3
	Implant-abutment emergence angle and profile <sup>24</sup>	Emergence angle is defined as the angle of an implant restoration's transitional contour as determined by the relation of the surface of the abutment to the long axis of the implant body. Emergence profile is defined as the contour of a tooth or restoration, such as a crown on a natural tooth or dental implant abutment, as it relates to the adjacent tissues.	x			
	Residual excess cement	Yes or no	x			
	Poor marginal fit of the suprastructure	Yes or no	x			
	Interproximal contact loss	Yes or no	x			
	Occlusal overload	Porcelain wear and chipping	x			
	Type of prosthesis	Single-unit; multi-unit fix; overdenture	x			
Periodontal probing measurement	PPD	PPD was calculated as the distance from the gingival margin to the bottom of the periodontal pocket or gingival sulcus	x	x	x	x
	AL	AL was measured with the graduated probe and represented the distance between the cemento-enamel junction and the base of the probable pocket <sup>26</sup>	x	x	x	x
	BoP	BoP evaluates bleeding after insertion of a probe to the base of the sulcus or pocket, recorded as positive or negative	x	x	x	x
	SoP	SoP evaluates suppuration after insertion of a probe to the base of the sulcus or pocket, recorded as positive or negative	x	x	x	x
	Gingival biotype	Thin biotype or thick biotype	x			
	Periodontitis severity	≥50% of the teeth with ≥50% of bone loss; <50% of the teeth with ≥50% of bone loss; no teeth with ≥50% of bone loss; total edentulism/stage (I, II, III, IV) and grade (A, B, C)	x			
Oral hygiene	S-OHI	DI-S=0–3, CI-S=0–3	x	x	x	x
	FMPS	Full Mouth Plaque Score				

Continued

**Table 1** Continued

Domain	Subdomain	Definition	T0	T1	T2	T3
Peri-implant probing measurement	PPD	PPD was calculated as the distance from the gingival peri-implant margin to the bottom of the peri-implant pocket	x	x	x	x
	BoP	BoP was assessed dichotomously in six sites per implant, recorded as positive or negative	x	x	x	x
	SoP	An objective indicator of gingival inflammation according to the presence or absence of suppuration after probing, recorded as positive or negative	x	x	x	x
	Keratinised mucosa width	Distance measured between the free mucosal margin to the mucogingival junction	x	x	x	x
	Peri-implantitis severity	Class (I, II, III) and grade (S, M, A) <sup>31</sup>	x	x	x	x
Radiological examination	Alveolar bone level based on CBCT	1. MBL changes around dental implant 2. Bone volumetric changes around dental implants	x		x	x

AL, attachment loss; BoP, bleeding on probing; CBCT, cone-beam CT; CI-S, calculus index; CKD, chronic kidney disease; CVD, cardiovascular disease; DI-S, debris index; HBP, high blood pressure; MBL, marginal bone loss; PPD, probing pocket depth; S-OHI, Simplified Oral Hygiene Index; SoP, suppuration on probing; T0, baseline; T1, 6 months; T2, 12 months; T3, 18 months; UV, ultraviolet.

of the alveolar bone around an implant fixture will be measured.<sup>32</sup>

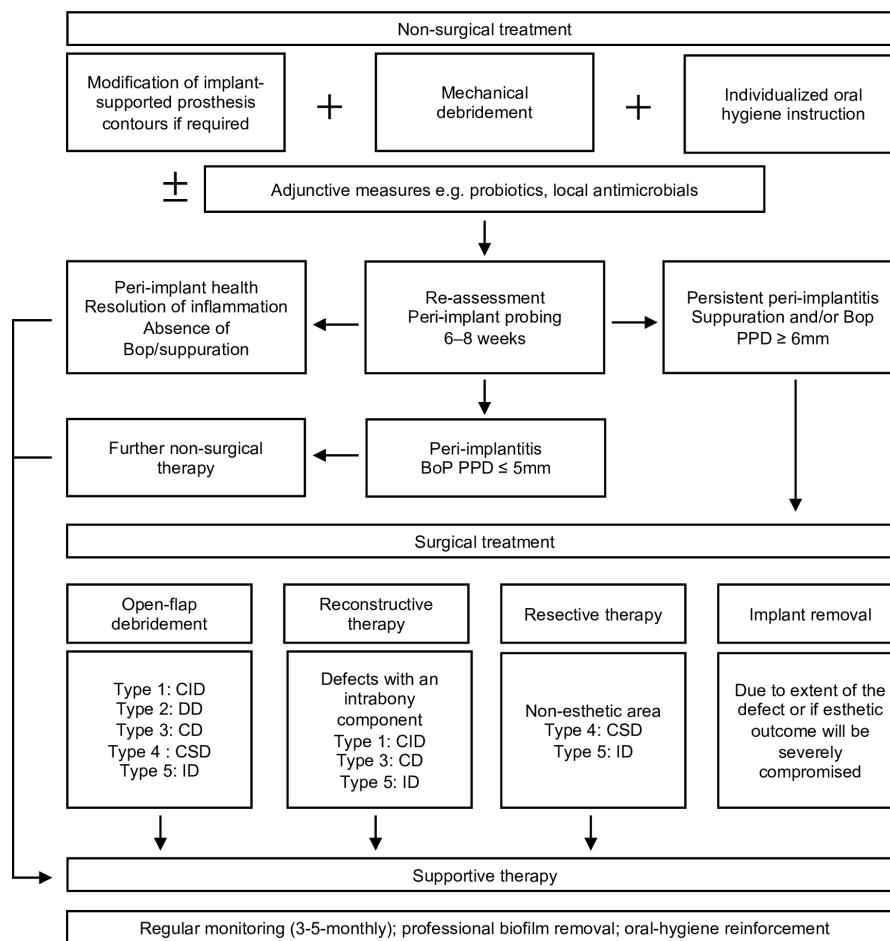
### Peri-implantitis treatment

Peri-implantitis treatment consists of non-surgical treatment, surgical treatment and supportive therapy, according to the International Team for Implantology (ITI) treatment guide (figure 2).<sup>33</sup> All patients with peri-implantitis will receive the periodontal treatment and oral hygiene instruction first. After 1 or 2 weeks, dentists will evaluate the inflammatory status of soft tissue around teeth and implants. Non-surgical treatment will then be conducted. Peri-implant condition will be evaluated 6–8 weeks after non-surgical treatment. Surgical treatment is generally required if PPD is still  $\geq 6$  mm and accompanied by BoP and SoP. At the same time, the patients present adequate oral hygiene. Inflamed granulation tissue will be removed during surgery.

1. Periodontal treatment: At the first visit, the patient will receive oral health education and instruction on the use of Bass brushing method, floss and interdental brush. Then, a whole-mouth ultrasonic supragingival scaling will be conducted. Patients will be asked to gargle with 0.12% chlorhexidine volume solution before scaling. The ultrasonic therapy instrument will be

used for ultrasonic supragingival scaling. The operator gently removes the calculus with the ultrasonic scaler in a certain order. Finally, the surfaces of all teeth will be polished, second supragingival scaling will be performed to remove supragingival and limited subgingival calculus. For deep subgingival calculus, subgingival scaling will be performed after inflammation and bleeding are reduced. Probing should be conducted before treatment since the tissue is prone to be damaged due to improper operation because the operator cannot see directly. During the operation, the operator should scale the teeth surface with light lateral pressure. The flow of water should be misty. The root surface and periodontal pockets will be rinsed with 3% hydrogen peroxide solution.

2. Non-surgical peri-implantitis treatment: Local anaesthesia will be applied if indicated. The implant-supported restorations will be removed. Routine mechanical debridement will include supragingival scaling, subgingival scaling, and air polishing for natural teeth and dental implant. Supragingival and subgingival scaling will be conducted with an ultrasonic scaler to remove the plaque and calculus using the EMS Instrument PI, which features a tip-coating made of high-



**Figure 2** Treatment pathway of peri-implantitis. BoP, bleeding on probing; CD, combined defect; CID, circumferential intrabony defect; CSD, circumferential suprabony defect; DD, dehiscence defect; ID, interproximal defect; PPD, probing pocket depth.

- tech polyether ether ketone. Air-polishing treatment will be conducted with erythritol powder (Air-Flows Plus Powder, EMS) to polish minor scratches on the implant surface. The instrumentation time at each aspect (ie, mesio, distal, vestibular and oral) will be limited to 5 s.<sup>34</sup> Then, the tooth will be polished with rubber cups and polishing paste. All the subjects will be provided with oral hygiene instructions individually and at all study intervals. Implant-supported prosthesis contours will be modified if needed. All the procedures will be performed by the same experienced operator.
3. Surgical peri-implantitis treatment: The implant surface will be decontaminated mechanically using ultrasonic decontamination (EMS Instrument PI). Adequate postoperative care will be provided. Different surgical modalities will be conducted according to bone defect morphology. In principle, suprabony defects are treated with resective therapy and implantoplasty. Infrabony defects can be managed with regenerative therapy (eg, guided bone regeneration). Details are shown in [figure 2](#).
  4. Supportive therapy: All the patients will be regularly monitored through follow-up visits 3 months in which professional biofilm removal and oral hygiene reinforcement will be adopted according to the specific

situation. Supportive therapy will be conducted if the inflammation is resolved and SoP disappears in the peri-implant tissues. If not, surgical (re)treatment will be adopted to treat the persistent inflammation.

### Outcome measures

1. Primary outcome: peri-implant PPD.
2. Secondary outcome: peri-implant alveolar bone resorption.
3. Additional outcome: oral hygiene.

### Statistical analysis

Descriptive statistics will be performed using means ( $\pm$ SDs) for continuous variables and frequencies (percentages) for categorical variables. We will use a univariable logistic regression model to identify the significant predictive factors for the treatment success. Successful treatment was defined as (1) implant sites presenting with a PPD  $\leq 5$  mm; (2) absence of BoP/SoP at the 12-month examination; (3) bone loss  $\leq 0.5$  mm between 2 weeks and 12 months after surgical therapy if it was conducted.<sup>35</sup> Then, a multivariable logistic regression model will be applied using age, sex and SES as covariates. The OR and 95% CI will be estimated. A complete case analysis will be performed, excluding participants with missing values for



the covariates. All the analyses will be conducted using the R Project for Statistical Computing (V.4.2.1, Vienna, Austria), with statistical significance defined as two-sided  $p < 0.05$ .

### Patient and public involvement

None.

### DISCUSSION

Our proposed prognostic cohort study may have significant clinical implications in managing peri-implantitis. Besides the unpredictable treatment outcome, another dilemma in treating peri-implantitis is a lack of clinical trial-based evidence. It can be stated that current treatment approaches are rather empirical.<sup>36 37</sup> Conventional treatment of peri-implantitis mainly includes plaque control, mechanical debridement, local/systemic antibiotics, surgical treatment, and smoking cessation.<sup>38 39</sup> Mechanical non-surgical treatment has been suggested to effectively resolve inflammatory lesions in peri-implant mucositis. In contrast, the treatment outcome of peri-implantitis was favorable in the short term but with a strong tendency to recur.<sup>40 41</sup> Moreover, whether to use adjunctive antimicrobials in non-surgical treatment is also controversial. A study suggest that the use of systemic metronidazole as an adjunct to non-surgical treatment of peri-implantitis resulted in significant additional improvements in clinical, radiographic, and microbiological parameters while another study suggest that the addition of metronidazole and amoxicillin to the treatment protocol of patients undergoing non-surgical subgingival debridement for with severe peri-implantitis does not.<sup>42 43</sup>

A clinical research demonstrated the pathological characteristics of peri-implantitis are non-linear, with different peri-implant bone levels between two main clusters of implant-treated patients.<sup>23</sup> Five predictive factors for peri-implant bone levels were identified, including the number of teeth, age, gender, periodontitis severity and years of implant service. Although the complexity of peri-implantitis has been noted, there continues to be a 'one-size-fits-all' paradigm about prognosis and treatment until now. There is a pressing need for precision medicine in improving clinical diagnosis and prognosis of peri-implantitis.<sup>44</sup> Based on different causes, several subtypes of peri-implantitis include purely plaque-induced or prosthetically or surgically triggered peri-implantitis; these subtypes are different with predictive profiles and risk factors.<sup>45</sup> Therefore, the cause-given treatment approach is necessary. Identifying the predictive factors of successful treatment outcome is a prerequisite for promoting 'one-size-fits-all' treatment shifting to individualised or precision medicine.

The present study will provide a unique opportunity to investigate the local and systemic factors predictive of successful outcomes after peri-implantitis treatment. First, this study will include a relatively larger sample size compared with the previous prospective cohort studies

for peri-implantitis treatment.<sup>15 16</sup> The adequate sample size of this study ( $n=275$ ) could contribute to detecting the differences between different subjects, avoiding false negative results. Second, the therapeutic outcomes will continuously be monitored at multiple follow-up intervals. The disease progression can be followed to further understand the developmental trajectory of peri-implantitis after treatment. Third, the separate and combined risk factors of peri-implantitis treatment will be systematically quantified to identify underlying factors for the treatment so that appropriate interventions can be implemented to increase the success rate of peri-implant therapy.

However, this study has limitations since the follow-up duration lasts  $< 5$  years. It makes it easier for subjects to maintain compliance, avoiding loss to follow-up bias. Another limitation of this study is that minor periodontal tissue regeneration may be missed due to the accuracy errors of the manual probe (division value=1 mm). Additionally, non-responders or recall bias could exist as patients with peri-implantitis were voluntary to receive treatment. A single centre may also cause selection bias and limited generalisation; future studies should include multiple centres.

In conclusion, the proposed longitudinal cohort study aims to identify prognostic factors for therapeutic outcomes of peri-implantitis since understanding peri-implantitis treatment is limited.

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