Prognostic factors affecting probing depth reduction following non-surgical periodontal therapy in patients with periodontitis: A linear mixed-effects model analysis

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Abstract. The present study aimed to elucidate the prognostic factors affecting the probing depth (PD) reduction following the non-surgical periodontal treatment of patients with periodontitis using a linear mixed-effects model. A retrospective analysis was performed on 455 patients who met the specific inclusion criteria. Data were gathered from 3-month re-evaluation records in the electronic periodontal charting system at the Department of Periodontology, School and Hospital of Stomatology at Tianjin Medical University between December 2021 and January 2022. Descriptive statistics were used to assess the changes in PD and certain baseline characteristics of the patients. A three-level nested random-effects mixed-effect model (patient/tooth/site) was used to evaluate the prognostic factors for PD reduction. Variance decomposition was conducted to analyze PD reduction across different nested levels. P<0.05 was considered to indicate a statistically significant difference. The overall mean PD reductions at the patient level for all sites were 0.88 mm. Patients diagnosed with Grade C periodontitis exhibited a greater PD reduction compared with those with Grade B periodontitis (0.96 vs. 0.76 mm; P<0.001). The multivariable coefficient for patients with Grade C periodontitis was 0.20 (95% confidence interval, 0.08-0.33; P<0.001). Random-effects analysis demonstrated that the variability in PD reduction was 59.4, 39.1 and 73.8% at the patient, tooth and site levels, respectively. Grade C periodontitis had the most substantial importance on the effect of PD reduction following NSPT. This reduction in PD could primarily be explained at both the site and patient levels.

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Introduction

Periodontal diseases, particularly periodontitis, pose a significant public health concern due to their high prevalence and effect on both oral and systemic health (1,2). The classification of periodontitis into stages I-IV and Grades A-C by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) highlights the critical role of risk factors, including genetic predisposition, systemic diseases, lifestyle choices and environmental influences, in shaping disease progression and treatment outcomes (3). A thorough understanding of these risk factors, integrated with the standardized classification system, is essential for accurately predicting individual disease trajectories and optimizing therapeutic strategies.

Non-surgical periodontal therapy (NSPT), which includes scaling and root planing, remains the foundational treatment for patients with periodontitis. This therapy aims to reduce probing depth (PD) and improve clinical attachment levels (4). However, patient responses to NSPT vary widely, underscoring the need for a deeper understanding of the prognostic factors that influence treatment outcomes (5). Identifying these factors is essential for developing personalized and accurate prognostic and therapeutic strategies.

The reduction in PD achieved through NSPT is influenced by a multitude of factors, including microbial, host immune, genetic and behavioral components (6). Although prior studies have suggested factors such as smoking status, systemic health and periodontal disease severity as potential predictors of treatment response, the true effects of these factors are currently unclear due to variations in study design and analytical methods. Additionally, genetic susceptibility, microbiological characteristics and periodontal conditions differ between Chinese and Caucasian populations (7) and the

existing findings are inconsistent in their conclusions. These inconsistencies highlight the need for rigorous investigation to comprehensively elucidate the determinants of PD reduction.

Traditional statistical analysis methods such as logistic regression and ANOVA can fail to adequately process periodontal data due to their inability to account for the hierarchical structures in these data, involving patients, teeth and sites of disease (8). This limitation can result in underestimated standard errors and potentially misleading conclusions when data at lower levels are aggregated to higher levels. Mixed-effects models, particularly hierarchical linear models (HLM), address these shortcomings by effectively handling multilevel nested data (9). These models decompose variation across different levels and analyze interactions between them, enabling a more precise separation of the effects of predictor variables at each level. Mixed-effects models have been extensively used in periodontal research (10). For instance, Jiao *et al* (11) employed HLM to identify predictors of periodontal disease progression at both the patient and tooth levels. Beyond periodontics, mixed-effects models have also been applied to nested data in endodontics (9) and prosthodontics and orthodontics (12), underscoring their versatility and robustness in dental research.

The null hypothesis of the present study was that any observed changes in PD reduction were due to random variation, rather than the influence of specific prognostic factors. Therefore, the present study aimed to identify prognostic factors associated with PD reduction following NSPT by using a linear mixed effects model which analyzed decomposing variance contributions of these factors across the patient, tooth and site levels. These findings may have the potential to refine clinical decision-making for the treatment of patients with periodontitis and improve prognostic assessments in periodontal therapy.

Materials and methods

Study design and patients. The present retrospective observational study evaluated prognostic factors influencing probing depth reduction following NSPT in patients with periodontitis. A three-level nested random-effects mixed-effects model was employed to assess the effect of clinical characteristics and periodontal disease classification on treatment outcomes.

Patients who received NSPT treatment at the Department of Periodontology, School and Hospital of Stomatology at Tianjin Medical University (Tianjin, China), were considered for inclusion in the present study. Patients with ≥1 documented periodontal re-evaluation record between January 2021 and January 2022 were included. The research protocol was approved by the Ethics Committee of the Tianjin Medical University School and Hospital of Stomatology (approval no. TMUhME20200307; Tianjin, China). All subjects provided written informed consent for participation in the present study.

The criteria for inclusion were as follows: i) Patients aged ≥18 years; ii) patients diagnosed with periodontitis according to the classification of periodontitis into stages (I-IV) and Grades (A-C) by the AAP and the EFP (13); iii) patients completed NSPT and attended a follow-up evaluation at 3 months; and iv) full availability of complete baseline and follow-up records in the electronic periodontal charting system. The following exclusion criteria were used: i) Patients with acquired immune deficiency syndrome, nephrosis, hepatitis or pregnancy which affected periodontal treatment outcomes; ii) recent use of antibiotics or undergoing periodontal surgeries prior to the evaluation period; and iii) incomplete records or loss to follow-up. Fig. 1 illustrates the process of selecting and screening patients.

Data extraction and variables collected. Data were extracted from the electronic periodontal charting record system at Tianjin Medical University. A detailed assessment of patient-related parameters was conducted during the first visit (T0) and final follow-up visit (T1).

The variables collected at the patient level were demographic data (patient age and sex), frequency of daily tooth brushing, diabetes mellitus status, smoking status and the stage and Grade of periodontal disease classification. The variables collected at the tooth level were the tooth type (central incisors, lateral incisors, cuspid teeth, premolars or molars 1-28) and the tooth mobility (0-III). The variables collected at the site level were the results of the follow-up assessment, which was the PD at the 3-month time point. PD was measured at six different sites: Mesial, distal and middle sites of both the buccal and lingual surfaces. The data from the third molars and teeth lost during NSPT were excluded.

Primary outcome measure. The primary outcome measure of the present study was the reduction in PD observed at the 3-month follow-up point after the completion of NSPT. To assess PD reduction, baseline measurements were recorded prior to the NSPT, followed by subsequent evaluations conducted at a standardized 3-month post-treatment timeframe. The difference between the mean baseline PD and the mean PD recorded at the 3-month re-evaluation constituted the PD reduction.

Periodontal examinations and treatments. Standardized protocols for periodontal examinations and treatments were adhered to, ensuring that all procedures were uniformly applied by qualified clinical periodontists. This process involved oral hygiene instruction (OHI) and scaling and root planing (SRP) utilizing both ultrasonic scalers (Cavitron® Ultrasonic Scaler; Dentsply Sirona) and hand instruments (Gracey Curettes; Hu-Friedy) for sites demonstrating PD ≥4 mm following the initial evaluation. All patients were scheduled for a re-evaluation at the 3-month time point post-treatment. During the maintenance phase, comprehensive periodontal charting, reinforcement of OHI, prophylactic scaling and SRP were also performed. The probing depths at baseline (T0) and at the follow-up assessment (T1), along with the reductions observed at various sites, were analyzed.

Sample size estimation. The sample size calculation was primarily guided by the complexity of the model and the need to ensure robust parameter estimation. A key factor in determining the required sample size was the ratio of the number of observations (N) to the number of parameters to be estimated (K). Following best practices outlined in previously published literature (14), a conservative N/K ratio of 10 was used to ensure robust parameter estimation and avoid overparameterization. This approach accounted for the complexity of the model,

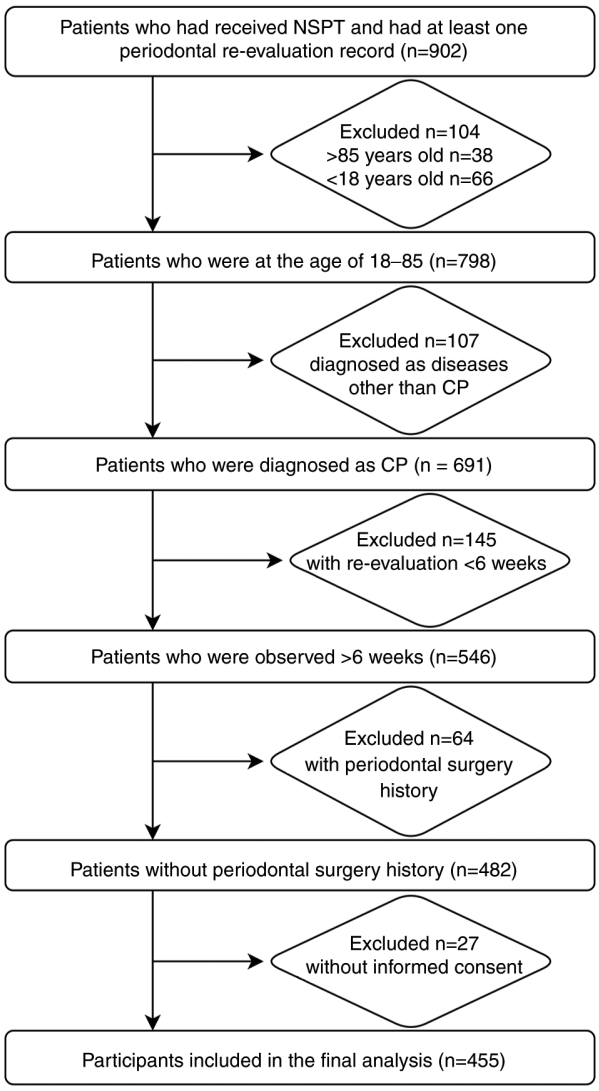

Figure 1. Flow diagram showing the selection of the study participants. NSPT, non-surgical periodontal therapy; CP, chronic periodontitis.

including fixed effects, random effects and interaction terms. The parameters of the present study included the intercept, fixed effects, random effects, nested effects and the residual term, totaling ~15 items. A model with 15 estimated parameters would require a ≥150 observations to meet this threshold. The final dataset comprised 455 patients, which ensured that the sample size was sufficiently large to provide reliable estimates for all parameter estimates included in the model.

Statistical analysis. R (version 4.2.2; R Foundation for Statistical Computing; https://cran.r-project.org/) for Windows was used for all statistical analyses (15,16). Categorical variables were expressed as absolute frequencies [n (%)], whereas continuous variables were expressed as the mean (SD). The linear mixed effects model (LMM) was adopted to explain the hierarchical and clustered structure of the patient, tooth and side periodontal data. The site, tooth and patient level were included as nested random effects to help to account for non-independence using the R package 'lme4' (15).

A multi-model inference procedure was applied using the R package 'MuMIn' (version 1.47.5) (17). This method was used to select the model by creating a set of models with all possible combinations of the initial variables and sorting them according to the Akaike Information Criterion (AIC) fitted with the Maximum Likelihood (18). All models with ΔAIC <2 were selected and the model averaging approach with lmer was used to estimate parameters and associated P-values, using the function model.avg (19). Variance decomposition was performed to determine the variation of PD reduction within the patient, tooth and site levels using the R package 'ape' (version 5.8) (20). P<0.05 was considered to indicate a statistically significant difference.

Table I. Baseline clinical and periodontal parameters by variables for all patients (n=455).

Characteristic	Value
Mean age ± SD, years	49.36±12.34
Male sex, n (%)	197 (43.3)
Non-smoking, n (%)	397 (87.3)
Diabetes mellitus, n (%)	427 (93.8)
Daily brushing frequency, n (%)	
1	18 (4.0)
2	356 (78.2)
3	71 (15.6)
4	6 (1.3)
5	4 (0.9)
Stage of periodontitis, n (%)	
I	1 (0.2)
II	57 (12.5)
III	331 (72.7)
IV	66 (14.5)
Grade of periodontitis, n (%)	
A	0 (0.0)
B	185 (40.7)
C	270 (59.3)
Patient-level, n	455
Tooth-level, n	12,119
Site-level, n	72,688

Results

Baseline characteristic of participants. A total of 72,688 sites distributed on 12,119 teeth in the 455 patients were included in the final analysis (Fig. 1). Characteristics and patient-related factors analyzed were described in Table I.

Model selection and PD reduction. The overall mean PD reduction at the patient level across all sites was 0.88 mm. The model selection process for the linear mixed-effects models, which estimated the influence of PD reduction, is detailed in Table II. A total of seven models were chosen based on an ΔAIC of <2 from all possible combinations of the initial variables (Table II). Grade C periodontitis was included, with a model-averaged coefficient of 0.20 [95% confidence interval (CI), 0.08-0.33; P<0.001). The model-averaged coefficients for fixed effects

Table II. Model selection process for the linear mixed-effect models estimates the influence of PD reduction with ΔAIC <2.

Model	Model type	df	logLik	AIC	ΔAIC	AIC weight
Model 1	DL + (1|Patient/Tooth/Site)	6	-100402.8	200817.6	0.00	0.24
Model 2	DL + Age + (1|Patient/Tooth/Site)	7	-100402.1	200818.1	0.59	0.18
Model 3	DL + DB + (1|Patient/Tooth/Site)	7	-100402.1	200818.2	0.64	0.17
Model 4	DL + DS + (1|Patient/Tooth/Site)	9	-100400.3	200818.7	1.09	0.14
Model 5	DL + Age + DB + (1|Patient/Tooth/Site)	8	-100401.6	200819.2	1.67	0.10
Model 6	DL + Sex + (1|Patient/Tooth/Site)	7	-100402.8	200819 5	1.95	0.09
Model 7	DL + Smoking + (1|Patient/Tooth/Site)	7	-100402.8	200819.5	1.96	0.09

Linear mixed-effects models were employed to estimate the influence of age, sex, smoking status, brushing habits, DB, the DS and DL on PD reduction, incorporating nested random effects at the patient, tooth, and site levels (with sites nested within teeth, and teeth nested within patients). Model selection was performed by creating a set of models and calculating the AIC for each, along with ΔAIC values relative to the model with the lowest AIC and AIC weights. Seven models with ΔAIC <2 were selected from all possible combinations of the initial variables and were ranked according to AIC, fitted using Maximum Likelihood estimation via the R MuMIn package. Lower AIC values indicate a better-fitting model. The number of levels for patient, tooth, and site were 455, 12,119, and 72,688, respectively. Degrees of freedom (Df) and log-likelihood (logLik) values were also reported for each model. PD, probing depth; AIC, Akaike Information Criterion; DB, diabetes mellitus; DS, stage of periodontitis; DL, grade of periodontitis.

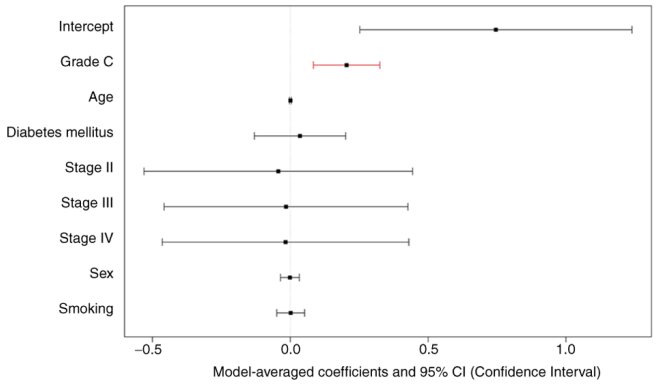

Figure 2. A forest plot was generated to illustrate the relationship between various variables and PD reduction, based on model-averaged coefficient estimates. This analysis was conducted by fitting all subsets of the full model, which included all covariates, and averaging the best-supported models (those with a difference in AIC from the best-supported model of <2). The dredge and model.avg functions from the MuMIn R package were used. PD, probing depth; AIC, Akaike Information Criterion.

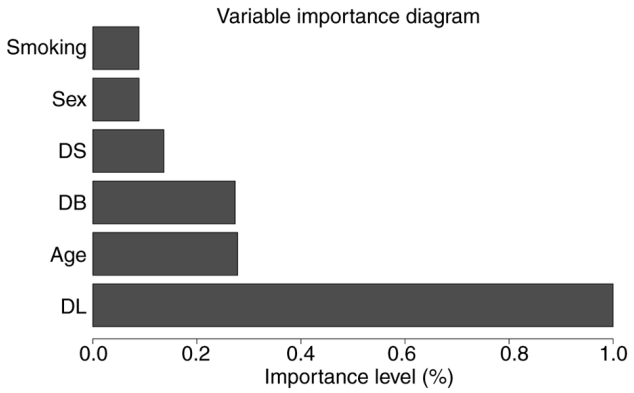

Figure 3. A histogram plot was generated to rank the importance of each independent fixed variable in the averaged model. This plot illustrates the significance of each variable in predicting PD reduction. The variables included the DL, DB and DS. PD, probing depth; DL, grade of periodontitis; DB, diabetes mellitus; DS, stage of periodontitis.

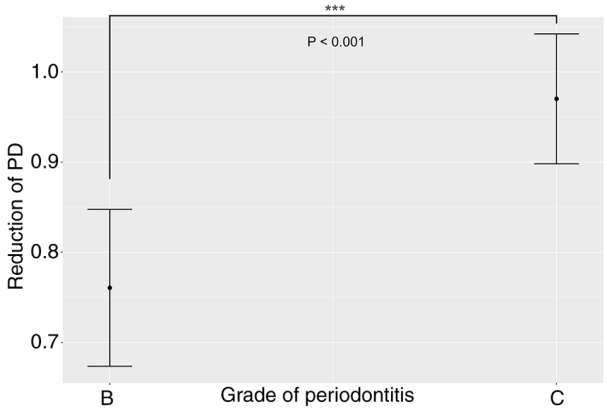

Figure 4. A comparison was made between the reduction in PD for patients with Grade C periodontitis and those with Grade B periodontitis. ***The representative differences are statistically significant. PD, probing depth.

were measured (Fig. 2) and the significance of each independent fixed effect in the averaged model was analyzed (Fig. 3). After adjusting for other pertinent variables, the mixed-effects model demonstrated a statistically significant effect of periodontitis Grade on PD reduction following NSPT (Fig. 4).

Prognostic factors for the reduction of PD. The Grade of periodontitis demonstrated a significant association with PD reduction following model selection. A greater mean decrease in PD was observed in patients with Grade C periodontitis compared with patients with Grade B periodontitis (0.96 vs. 0.76 mm, respectively; z=3.32; P<0.001) (Fig. 4). No significant differences were observed concerning age, sex, diabetes mellitus or daily brushing frequency.

Random effects and variance components of PD reduction at the patient, tooth and site levels. Random effects analysis in the model-averaged analysis indicated standard deviations of 59.4% for patient, 39.1% for tooth and 73.8% for site levels.

Table III. Statistics of random effects (standard device) for seven models with ΔAIC <2 and model-averaged value.

Model	SD (patient)	SD (tooth)	SD (site)	SD (residual)	Marginal R2	Conditional R2	ICC
Model 1	0.595	0.391	0.685	0.574	0.013	0.611	0.61
Model 2	0.594	0.391	0.685	0.574	0.014	0.611	0.61
Model 3	0.594	0.391	0.757	0.476	0.016	0.696	0.69
Model 4	0.593	0.391	0.769	0.456	0.020	0.714	0.71
Model 5	0.594	0.391	0.756	0.478	0.017	0.694	0.69
Model 6	0.595	0.391	0.756	0.478	0.014	0.694	0.69
Model 7	0.595	0.391	0.755	0.478	0.014	0.694	0.69
Model-average	0.594	0.391	0.738	0.502	0.015	0.673	0.67

Model 1, DL + (1|Patient/Tooth/Site); Model 2, DL + Age+(1|Patient/Tooth/Site); Model 3, DL + DB + (1|Patient/Tooth/Site); Model 4, DL + DS + (1|Patient/Tooth/Site); Model 5, DL + Age + DB + (1|Patient/Tooth/Site); Model 6, DL + Sex + (1|Patient/Tooth/Site); Model 7, DL + Smoking + (1|Patient/Tooth/Site). SD, standard deviation; Marginal R2, R2 for fixed effects only; Conditional R2, R2 for both fixed and random effects. ICC, intraclass correlation coefficient, refers to the proportion of the variance of random effects in the random variation part of the model. DL, Grade of periodontitis; DB, diabetes mellitus; DS, Stage of periodontitis.

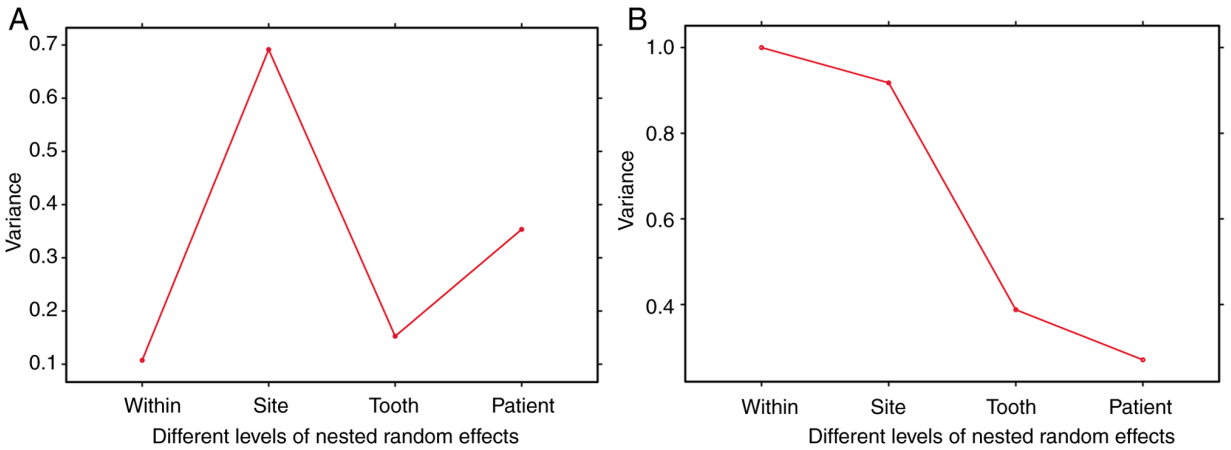

Figure 5. Different levels of nested random effects account for the variance components in periodontal data. Variance decomposition was conducted to ascertain the variation in PD reduction using linear mixed-effects models with nested random effects at the patient, tooth, and site levels. The analysis involved two key aspects: (A) the estimation of random effects variance parameters within residuals, sites, teeth, and patients, and (B) the cumulative magnitudes of these random effects variance parameters within residuals, sites, teeth, and patients. PD, probing depth.

The marginal and conditional R^2 values in the model-average were 0.015 and 0.673, respectively. The intraclass correlation coefficient was 0.67 (Table III). The R^2 of the LMM was also calculated (Table III). Variance components for PD reductions across all random effects were measured (Fig. 5).

Discussion

The present retrospective analysis of 455 patients provided findings which could potentially determine the effect of periodontitis grade on treatment outcomes. The mean reduction in PD observed in the present study was 0.88 mm at the patient level across all sites measured. Notably, patients with Grade C periodontitis demonstrated a markedly greater reduction in PD compared with patients with Grade B periodontitis. The multivariable coefficient for Grade C periodontitis was 0.20, indicating an independent association with enhanced treatment efficacy. These findings were consistent with the hypothesis that Grade C periodontitis, characterized by rapid progression and a higher inflammatory burden, may respond more robustly to intensive NSPT measures.

The findings of the present study were consistent with a study that investigated the factors predicting responses to NSPT in 40 Chinese patients over a 1-year observation period (21). The mean PD reductions in the aforementioned study were 0.62, 0.66 and 0.60 mm at 3, 6 and 12 months, respectively. Additionally, a systematic review assessing the clinical efficacy of NSPT reported a weighted mean PD reduction of 0.64 mm in pockets initially >5 mm in size (22). These results are generally aligned with the present study, with minor variations probably due to ethnographic differences. For instance, studies have demonstrated differences between Caucasian and Asian populations (23). Previous research has used 16S pyrosequencing to analyze bacterial profiles in patients with chronic periodontitis demonstrated a relatively higher abundance of *Porphyromonas gingivalis* in the Chinese population (17.85%) and compared with other groups (11.26%) (24,25). This may be one of the reasons for the difference in the results of the present study.

The present study further corroborated previous findings. Nascimento *et al* (26) suggested that individuals with severe periodontitis at the baseline experienced more significant treatment effects, whereas those with moderate periodontitis had a limited benefit. Jiao *et al* (10,11) reported that PD reduction was primarily influenced by baseline PD and baseline attachment loss, which are both pivotal factors in determining the stage of chronic periodontitis. In addition, Chen *et al* (27) proposed that a wider radiographic angle in teeth might predict improved outcomes from NSPT.

The present study identified that neither sex nor age were confounding factors, aligning with prior research. In the multivariable analysis, the brushing frequency used did not markedly influence PD reduction, which contradicts the results of a previous study (28). This discrepancy may be attributed to differences in sample size, ethnicity and certain population characteristics. It is also important to consider that definitions of adherence varied across studies, potentially contributing to the observed differences. Therefore, the results of the present study may require further validation.

The variance decomposition analysis underscored the substantial influence of patient-level and site-level factors on PD reduction. The standard deviations attributable to random effects at the patient, tooth and site levels were 59.4, 39.1 and 73.8%, respectively. These results highlighted the complexity and multi-faceted nature of periodontal disease and its response to therapy. The significant variance at the site level suggested that local factors, potentially including site-specific bacterial load, local immune response and anatomical considerations, serve a crucial role in therapeutic outcomes (29). The findings of the present study aligned with existing literature, which emphasized that localized bacterial load and the immune response were critical determinants of periodontal healing as sites with higher bacterial loads often demonstrated poorer patient outcomes despite effective treatment (30). Additionally, anatomical factors such as root morphology and pocket depth markedly influence the accessibility and efficacy of non-surgical therapy, underscoring the challenges posed by site-specific characteristics (31). Future studies should investigate recently introduced preventive treatments such as ozone (32), photobiomodulation (33) and paraprobiotics (34) to understand their potential effects on periodontal tissues.

The nested random-effects model provides a robust framework for evaluating hierarchical data (35). By accounting for the nested structure of periodontal data, such as sites within teeth and teeth within patients, the model allowed for a more nuanced understanding of how different levels of variation contributed to treatment efficacy. This methodology aligned with contemporary analytic approaches aimed at disentangling the complex interrelationships inherent in clinical periodontal data.

The present study adopted an observational design, wherein all participants underwent a uniform NSPT. Instead of using a randomized methodology, the study's primary aim was to document the clinical characteristics and prognostic outcomes of patients in real-world settings who are subjected to a standardized treatment protocol. Although baseline differences among participants may be present, these were systematically addressed through a linear mixed-effects model that incorporated relevant covariates and adjusted for both measured and unmeasured confounding variables. This methodological approach facilitated an integrated analysis of the interactions among various prognostic factors and their influence on therapeutic outcomes, thereby offering a comprehensive understanding of the determinants of NSPT efficacy. Nonetheless, future prospective studies employing randomized designs could further validate and refine these findings.

Despite the strengths of the present study, including a large sample size and rigorous statistical analysis, certain limitations warrant consideration. The retrospective design inherently introduced potential biases related to medical record accuracy and completeness. Additionally, the follow-up period was limited to 3 months, precluding long-term assessment of PD reduction sustainability. The research sample was obtained from the Tianjin area of China and did not adequately represent populations from different regions, ethnicities or socioeconomic backgrounds. Moreover, the lack of consistent data on eating habits and details of oral hygiene maintenance habits, which are known to influence periodontal disease progression and treatment response. The absence of these variables may have introduced residual confounding, potentially affecting the observed associations and outcomes. Future studies incorporating comprehensive data on these parameters are essential to improved understand how external factors interact with clinical characteristics.

In conclusion, the present study demonstrated that Grade C periodontitis was independently associated with a greater PD reduction following NSPT, emphasizing the importance of individualized treatment approaches. Moreover, the prominent role of site-specific factors underscores the necessity for targeted therapeutic strategies that address local periodontal conditions. These insights may contribute to the growing body of evidence supporting tailored periodontal care aimed at optimizing clinical outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PK and CW designed the clinical study and coordinated the research activities. CW and XB conducted patient recruitment and managed clinical data collection. YY and FQ performed the statistical analysis and contributed to data interpretation. FQ, XL and MZ were responsible for the histological examination and provided critical insights into the findings. PK drafted the manuscript and incorporated comments from all authors. CL made substantial contributions to the conception and design of the study, critically revised the manuscript for important intellectual content, approved the final version for publication and agreed to be accountable for all aspects of the work. XB and MZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The research protocol was approved by the Ethics Committee of the Tianjin Medical University School and Hospital of Stomatology (approval no. TMUhME20200307).

Patient consent for publication

Written informed consent for publication was obtained from all patients involved in the study.

Competing interests

The authors declare that they have no competing interests.

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