Multilevel Analysis of Non-surgical Periodontal Treatment of Patients with Generalised Aggressive Periodontitis

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Objective: *To investigate various factors affecting the clinical outcome of nonsurgical periodontal treatment and evaluate the treatment effects of adjunctive amoxicillin and metronidazole (AMX + MET) in patients with generalised aggressive periodontitis (GAgP).*
Methods: *Forty-two patients with GAgP were recruited and randomly assigned to three groups: scaling and root planing (SRP) only, AMX + MET after SRP, and AMX + MET during SRP. The patients were assessed every 2 months post-therapy. Periodontal clinical and subgingival microbiological parameters were analysed at baseline and 6 months post-therapy. The impacts of different covariates on pocket probing depth (PD) reduction were evaluated.*
Results: *A multilevel analysis revealed that 58% of the variability in PD reduction was attributed to site-level parameters, 27.3% to patient-level parameters and 18.7% to tooth-level parameters. Greater PD reduction can be expected at initially deeper PD sites and sites with intrabony defects, and in patients with adjunctive use of AMX + MET. Persistent Tannerella forsythia infection and tooth mobility after treatment were negatively associated with PD reduction.*
Conclusion: *The clinical outcomes of nonsurgical periodontal treatment were mainly influenced by site-level parameters, and adjunctive use of AMX + MET can lead to better clinical results in patients with GAgP in a short time.*
Key words: *aggressive periodontitis, drug therapy, multilevel analysis, periodontal debridement, root planing*
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Periodontitis is an infection that can have many different clinical presentations. Aggressive periodontitis (AgP), as defined in 1999 by the World Workshop in Periodontology, comprises a group of rare and rapidly progressive forms of periodontitis[1]. Generalised aggressive periodontitis (GAgP) causes extensive loss of attachment and bone destruction mainly in young patients, with a prevalence of 0.8% to 4.2% in the general population[2]. Patients with GAgP were reported to have a worse oral health–related quality of life compared to patients with chronic periodontitis or periodontally healthy individuals[3].

A better clinical outcome of nonsurgical periodontal treatment can reduce the need for further surgical therapy in patients with periodontitis; however, the treatment outcome may vary not only from patient to patient, but also between different teeth in the same patient and different sites on the same tooth. Most studies have analysed periodontal treatment outcomes separately at the site, tooth or patient level. Such single-level analyses may be confounded by interrelations between levels. In periodontal research, multilevel factors have been used in the prognosis of periodontal treatment on a large population for a relatively long period of time[4,5], and in the evaluation of bone loss[6]. The lack of periodontal maintenance[5] and the presence

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of furcation involvement, plaque, bleeding on probing and tooth mobility may be associated with a poor periodontal prognosis following periodontal therapy[7]; however, prognostic factors in non-surgical periodontal therapy require further investigation, especially in patients with GAgP. The present study aimed to use a multilevel analysis to better explain the results of non-surgical periodontal treatment in patients with GAgP and to evaluate the adjunctive effects of amoxicillin + metronidazole (AMX + MET).

Materials and methods

The present study was a single-blind randomised clinical trial. The study protocol was approved by the Ethics Committee of Peking University School and Hospital of Stomatology, and the study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008 (trial registry http://www.chictr.org, identifier ChiCTR-IPR-15007666). All patients were individually informed about the nature of the proposed treatment, its risks and benefits and their right to drop out of the study. Written informed consent was obtained from each patient.

Study population: inclusion and exclusion criteria

Patients with GAgP were recruited from the Department of Periodontology, Peking University School and Hospital of Stomatology from April 2013 to August 2014. All patients enrolled belonged to the Han race of the Chinese population and received a physical examination, complete blood cell count and blood biochemical analysis to exclude potential systemic diseases. Each participant completed a questionnaire on their general background, medical and dental care history and oral hygiene habits. The diagnostic criteria for GAgP were based on the classification proposed in 1999[1]. The inclusion criteria were as follows:

- patients aged ≤ 35 years with ≥ 20 teeth in the mouth excluding the third molars and teeth to be extracted;
- at least 8 teeth with pocket probing depth (PD) > 6 mm and clinical attachment loss (CAL) > 3 mm;
- full-mouth periapical radiographic evidence of alveolar bone loss, with at least three involved teeth that were not first molars or incisors.

The exclusion criteria were as follows:

- smokers;
- diagnosis of chronic periodontitis;
- pregnancy or lactation;
- drug allergy to penicillin or metronidazole;
- intake of antibiotics or anti-inflammatory drugs in the previous 3 months;
- systemic disease;
- history of periodontal treatment in the preceding 6 months;
- history of orthodontic treatment or noteworthy occlusal disharmony.

Sample size calculation

Power calculations were performed based on an analysis of patient-level PD reduction between the GAgP groups with or without adjunctive AMX + MET after subgingival scaling and root planing (SRP) based on our previous study[8] to detect a difference of 0.5 mm between groups in the PD of pockets > 6.0 mm, and indicated that at least 12 subjects should be included in each group. Assuming a 15% dropout rate, 14 subjects were enrolled in each group, and a minimum of 42 patients were required to complete the study to give a value of 0.05 with 80% power.

Study design and clinical examination

A total of 67 patients with GAgP were assessed for possible inclusion in the study. Eighteen patients were excluded because they did not meet the inclusion criteria, and seven declined to participate. Oral hygiene instruction was given to all participants, hopeless teeth were extracted and supragingival scaling was performed prior to SRP. Two trained and experienced periodontists (LX and XW) carried out the SRP procedures for all patients using an ultrasonic device (Cavitron, Dentsply Sirona, Charlotte, NC, USA) and handpieces (Hu-Friedy, Chicago, IL, USA) under local anaesthesia, and the procedure was completed within 7 days. The endpoint of SRP was determined by the smoothness of the scaled roots. Forty-two patients were randomly assigned into three groups using a computer-generated sequence. The three groups were as follows:

1. SRP only with placebo starting immediately after the last session of SRP;
2. AMX + MET after SRP, treated with amoxicillin (0.5 g, three times a day) and metronidazole (0.2 g, three times a day) for 7 days starting immediately after the last session of SRP;
3. AMX + MET during SRP, treated with amoxicillin (0.5 g, three times a day) and metronidazole (0.2 g, three times a day) for 7 days starting after the first session of SRP.

Medication and placebos were prepared and encased in identical opaque coded bottles according to the com-

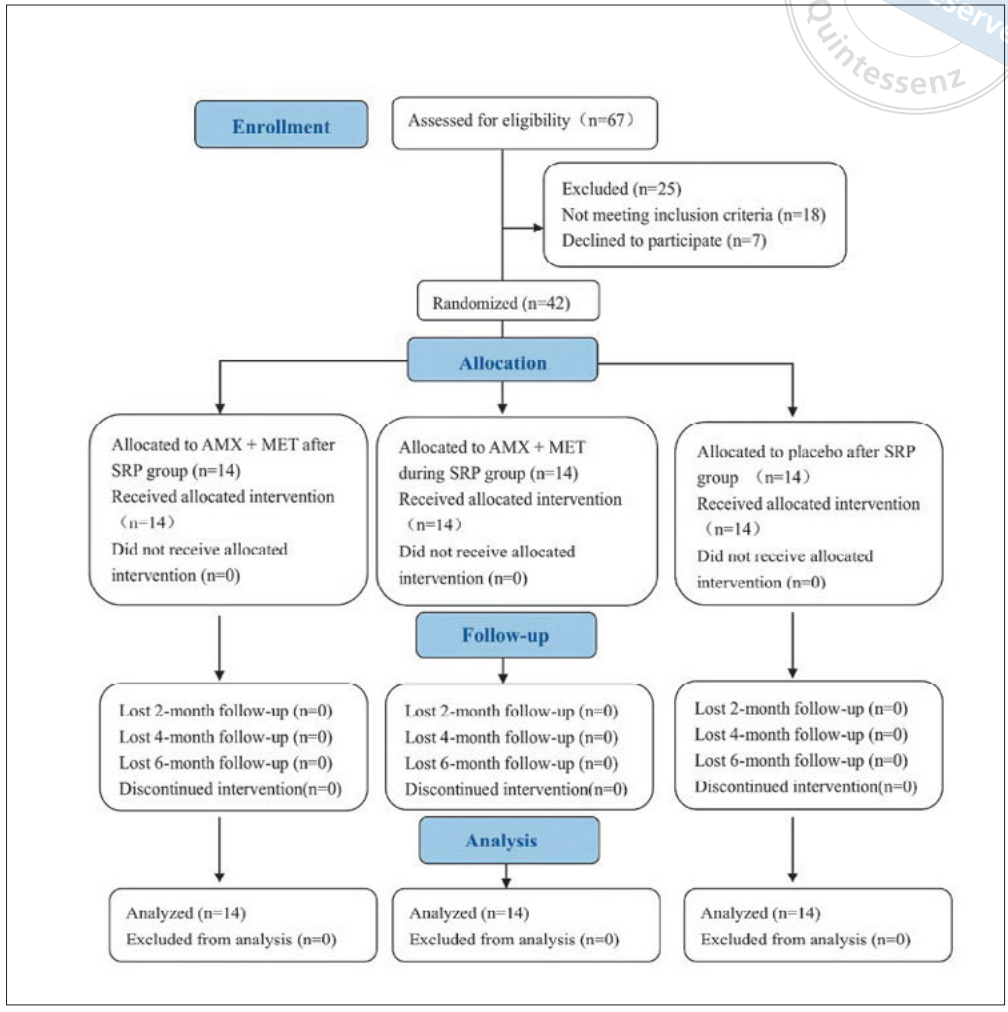

Fig 1 Flow chart illustrating the study design.

puter-generated list. The allocation was managed by an investigator (HM) who did not participate in the examination or periodontal treatment. Identification codes were kept concealed until the final examinations and data collection had been concluded. The patients were asked to bring the packs containing the medication 1 week later to check compliance. They also answered a questionnaire about any self-perceived side-effects of the medication. Patients were reexamined and received supragingival scaling at 2 months, 4 months and 6 months after treatment (Fig 1). All patients received periodontal clinical assessment by a single calibrated examiner (XF) who was blinded to the treatment allocations.

Tooth site parameters (level 3)

A full-mouth assessment of PD and gingival recession was performed at 6 sites per tooth and recorded to the nearest millimetre using a Michigan O periodontal probe with Williams markings (Hu-Friedy). CAL was calculated based on the combined PD and recession measurements. The bleeding index (BI)[9] was recorded 30 seconds after probing. The presence of intrabony defects ≥ 3 mm in depth was identified from a full-mouth set of periapical radiographs.

Tooth parameters (level 2)

The degree of mobility was recorded for all teeth, according to the method introduced by Miller[10]. A tooth-type categorical variable (molar-premolar-anterior teeth) was recorded.

Patient parameters (level 1)

The patient-level parameters collected included the age (years), sex, body mass index (weight in kilograms divided by height in metres squared) and the percentage of sites with PD > 6mm. Subgingival plaque was collected from one site in each quadrant using a fil-

Table 1 Participant characteristics and patient-related factors.

Variable		n (%)	Range (%)
Sex	**Male**	**20 (47.6)**	**NA**
	Female	**22 (52.4)**	**NA**
Treatment	SRP only	14 (33.3)	NA
	AMX + MET during SRP	14 (33.3)	NA
	AMX + MET after SRP	14 (33.3)	NA
Percentage of sites with PD > 6 mm	Baseline	NA (30.1)	25.9–-36.3
	6 months	NA (0.9)	0.0–4.2
A. actinomycetemcomita infection	Baseline	14 (33.3)	NA
	6 months	9 (21.4)	NA
P. gingivalis infection	Baseline	42 (100.0)	NA
	6 months	21 (50.0)	NA
T. forsythia infection	Baseline	38 (90.5)	NA
	6 months	21 (50.0)	NA
T. denticola infection	Baseline	38 (90.5)	NA
	6 months	12 (28.6)	NA

NA, not applicable.

Table 2 Characteristics of tooth- and site-related factors.

Variable		n (%)
Tooth-related (level 2), N = 1163		
Tooth type	Anterior teeth	495 (42.6)
	Premolars	335 (28.8)
	Molars	333 (28.6)
Tooth mobility	No mobility	809 (69.9)
	Degree 1	172 (14.8)
	Degree 2	142 (12.2)
	Degree 3	40 (3.4)
Site-related (level 1)		Mean ± SD
PD, mm	Baseline	5.1 ± 1.0
	6 months	2.8 ± 0.4
BI	Baseline	3.7 ± 0.4
	6 months	1.5 ± 0.3
CAL, mm	Baseline	3.7 ± 1.1
	6 months	2.5 ± 0.9

ter paper strip before periodontal treatment and again 6 months post-treatment, including the deepest site at baseline and excluding hopeless teeth. The prevalence of putative periodontal pathogen bacteria (*Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola*) was assessed in each plaque sample by polymerase chain reaction[11], and the results were calculated in the patient-level analysis.

Data entry and analysis

All the data were entered by two investigators into two separate data files and checked for possible mistakes. Three levels were defined for hierarchical analysis: patient (level 1), tooth (level 2) and tooth site (level 3). A statistical package specifically designed for multilevel modelling (MLwiN 2.02, Centre for Multilevel Modelling, University of Bristol, Bristol, UK) was used to analyse the effects of patient-, tooth- and site-related variables on the outcome[12]. The main outcome of the statistical analysis was PD reduction from baseline to 6 months post-therapy. A secondary outcome of the statistical analysis was PD at 6 months post-treatment. The normality assumption criterion for inclusion of the dependent variables was verified with a Kolmogorov-Smirnov Test. A model residual analysis was done to confirm the validity of the procedure. A null model was constructed without inserting explanatory variables to estimate the PD reduction or PD at 6 months and to attribute differences to the patient, tooth and tooth site levels. A covariate model was then constructed by inserting a series of explanatory variables. Regression estimates were calculated utilising the iterative general-

Table 3 Multilevel linear regression model estimating the relative contribution of PD reduction or PD at 6 months.

Variable	PD reduction*, mm		PD at 6 months, mm	
	β ± standard error	%†	β ± standard error	%†
Intercept	2.25 ± 0.15	NA	2.83 ± 0.06	NA
Patient	0.80 ± 0.19	27.3	0.13 ± 0.03	11.3
Tooth	0.43 ± 0.03	18.7	0.28 ± 0.02	24.3
Site	1.70 ± 0.03	58.0	0.74 ± 0.02	64.4

*PD reduction from baseline to 6 months post-treatment. †Percentage of variances attributed to patient, tooth and site levels. NA, not applicable.

Table 4 Multilevel linear regression model assessing the significance of variables in explaining PD reduction.

Variable		PD reduction*, β ± SE
Patient level	AMX + MET	0.352 ± 0.113†
	T. forsythia at 6 months	–0.457 ± 0.147†
Tooth level	Mobility at 6 months	–0.355 ± 0.080†
Site level	Intrabony defect	0.427 ± 0.190†
	Initial PD	0.575 ± 0.071†

*PD reduction from baseline to 6 months post-treatment. †$P < 0.05$, chi-square test.

ised least square (IGLS) algorithm[12]. SPSS 20.0 (IBM, Armonk, NY, USA) was used for group comparisons. Changes in the clinical parameters and putative periodontal pathogens before and after treatment were analysed using a Kruskal-Wallis test or chi-square test. The level of significance was set at $P < 0.05$.

Results

General status of patients with GAgP

The database consisted of 6978 tooth sites on 1163 teeth in 42 patients with GAgP. The mean age of the patients was 26.1 ± 4.0 years. At baseline, patients enrolled displayed deep pockets, with a mean full-mouth PD of 5.1 ± 2.0 mm and 30.1% (range 25.2%~36.4%) of sites having PD > 6 mm. All patients tested positive for *P. gingivalis* and 90.5% of subjects were infected by *T. forsythia* or *T. denticola*, whereas *A. actinomycetemcomita* was detected in 14 patients at baseline. At 6 months after treatment, the mean PD reduced to 2.8 ± 1.1 mm, 0.9% (range 0.0%~4.2%) of sites had PD > 6 mm, and significant decreases were noted in the detection of *P. gingivalis*, *T. forsythia* and *T. denticola* infection. Intrabony defects were found in 168 sites. All patients reported completion of the antibiotic regimen without any adverse events. Details are provided in Tables 1 and 2.

Continuous model of PD reduction or PD at 6 months as an outcome

The results obtained from the model exploring the covariates influencing PD reduction and PD at 6 months are reported in Table 3. The null model gave a mean value of 2.25 mm for PD reduction. The majority of the variance, 58%, was attributed to the site level. The tooth level accounted for 18.7% of variance and the patient level for 27.3%. The similarity of tooth response within the same patient was 46% (tooth-level variance plus patient-level variance). The null model showed a mean PD of 2.83 mm at 6 months with site-level parameters playing the most important role in explaining the variance, followed by tooth-level and patient-level factors, and the similarity of tooth response within the same patient for PD at 6 months was 35.6%.

All the patient-, tooth- and site-level variables, both at baseline and at 6 months post-treatment, were included in the model, and the statistically significant variables for explaining the PD reduction are shown in Table 4. PD reduction was positively related to adjunctive use of AMX + MET, sites with deeper initial PD sites and sites with intrabony defects. PD reduction was negatively related to persistent *T. forsythia* infection and tooth mobility post-treatment.

At the patient level, greater PD reduction was found in patients with adjunctive use of AMX + MET compared with SRP only, regardless of whether the use of antibiotics was during or after SRP (2.7 ± 0.9 mm and

Table 5 Comparison of PD reduction based on different variables (mean ± SD).

Variable		n	PD at baseline, mm	PD at 6 months, mm	PD reduction*, mm
Treatment group	SRP only	14	5.0 ± 0.9	3.0 ± 0.3	1.8 ± 0.8
	AMX + MET during SRP	14	5.4 ± 1.0	2.8 ± 0.5	2.7 ± 0.9†
	AMX + MET after SRP	14	5.1 ± 0.7	2.7 ± 0.3	2.5 ± 0.7†
Intrabony defects	Without defect	6810	5.0 ± 2.0	2.8 ± 1.0	2.2 ± 1.7
	With defect	168	7.9 ± 1.8†	4.7 ± 1.6†	3.2 ± 1.9†
PD at baseline	PD ≤ 4 mm	1906	2.7 ± 0.5	2.1 ± 0.7	0.6 ± 0.8
	4 mm < PD ≤ 6 mm	2574	4.6 ± 0.5†	2.7 ± 0.8†	1.9 ± 0.9†
	PD > 6 mm	2498	7.3 ± 1.2†‡	3.5 ± 1.2†‡	3.9 ± 1.4†‡

*PD reduction from baseline to 6 months post-treatment. †Significant difference compared with the first line in each subgroup, $P < 0.05$. ‡Significant difference compared with 4 mm < PD ≤ 6 mm group, $P < 0.05$.

2.5 ± 0.7 mm versus 1.8 ± 0.8 mm, $P < 0.05$). At the site level, sites with intrabony defects showed a reduction in PD of 3.2 ± 1.9 mm versus 2.2 ± 1.7 mm in those without ($P < 0.05$). In sites with PD > 6 mm at baseline, PD at 6 months was 3.5 ± 1.2 mm and PD reduction was 3.9 ± 1.4 mm. In sites with PD 4~6 mm at baseline, PD at 6 months was 2.7 ± 0.8 mm and PD reduction was 1.9 ± 0.9 mm. Detailed data are shown in Table 5.

Discussion

The present study analysed factors influencing nonsurgical periodontal treatment in patients with GAgP over a short period of time. PD reduction is predominately attributed to site-level parameters, including initial PD and the presence of an intrabony defect. The similarity in PD reduction responses within the same patient was 46.0% for PD reduction and 35.6% for PD at 6 months post-treatment, which indicates a great difference in the treatment outcome of different teeth in the same patient. Adjunctive AMX and MET can benefit nonsurgical periodontal treatment outcomes, whereas *T. forsythia* infection and tooth mobility after treatment negatively influence outcomes.

When performing periodontal clinical data analyses, several aspects need to be considered. First, if site-level data within patients are aggregated by mean values, there may be a risk of losing information and overestimating the standard error; however, if analyses are performed at the tooth or site level but do not consider the dependence between teeth/sites in a patient, underestimation of the standard error may occur[13]. In previous studies, 17% of the variance in pocket closure was due to variation between patients, and smoking was a significant factor to explain variance[13,14]. The present study did not include smokers, yet a variance of 27.3% in PD reduction and 11.3% in PD at 6 months was found at the patient level. The results indicated that patient-level factors, such as adjunctive use of AMX + MET and putative periodontal pathogen infection, are important factors in explaining variances between patients.

The effectiveness of SRP on sites with 4.0 to 6.0 mm PD has been proven by multiple studies. PD reduction of 1.2 mm can be expected for 4.0- to 5.0-mm pockets, and 2.4 mm for ≥ 6-mm pockets[14]. In a large population investigation on clinical performance of nonsurgical periodontal treatment patients with GAgP, a PD reduction of 1.17 mm was reported[5]. In the present study, in sites with PD > 6.0 mm, PD reduction was 3.9 mm, and a mean PD reduction of 2.25 mm was found from baseline to 6 months post-treatment, showing a better clinical outcome compared to previous studies. This may be because most patients enrolled had never received any periodontal treatment before and gingival inflammation was severe, or because no smokers were enrolled in the study and all patients were regularly maintained every 2 months, so greater PD reduction could be expected.

There is a visible trend suggesting that AMT + MET is the most potent antibiotic combination as an adjunct to AgP treatment[15-17], and showed better clinical results when used in the initial phase[18]. There are usually two ways to perform SRP, SRP per quadrant and SRP by one-stage full-mouth disinfection (FMD), both of which show improvements in periodontal parameters[19]. Recently, studies have reported the effectiveness of AMX + MET as an adjunct to SRP by FMD[20,21]. Considering that the mean PD was more than 5.0 mm in this group of patients with GAgP, with the presence of multiple subgingival calculus and severe gingival inflammation, it would have been impossible to finish FMD with both ultrasonic instruments and handpieces within 24 hours. A modified SRP protocol was applied,

i.e., full-mouth SRP was completed within 7 days. The adjunctive use of AMX + MET from the first session of SRP covered the whole period of SRP therapy. The preliminary results showed similar clinical outcomes compared to AMX + MET starting from the last session of the SRP group in the present study; however, the long-term effectiveness of AMX + MET during SRP and its effects on the subgingival microbiome still need further investigation. The potential adverse effects and cost-effectiveness of antibiotics should also be considered.

The multilevel analysis showed that persistent *T. forsythia* infection post-treatment indicated a poor treatment outcome, which is consistent with previous studies of AgP[22,23]. There may be racial differences in the prevalence of putative periodontal pathogens in GAgP[24]; *A. actinomycetemcomitans* has been strongly correlated with AgP in certain populations[25], but was found in only a small fraction of our group of GAgP patients. Meanwhile, *P. gingivalis*, *T. forsythia* and *T. denticola* were detected in over 90% of the GAgP patients. The divergent findings for subgingival putative periodontal pathogens may also be due to differences in sampling sites and sampling methods[26]. Neither *A. actinomycetemcomitans* nor other species studied to date have been found to be unique to or able to differentiate between chronic periodontitis and AgP[27]. Following the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions[28], periodontal diseases previously diagnosed as "chronic" or "aggressive" according to the classification in 1999 are now grouped under a single category, "periodontitis", which is further characterised based on a staging and grading system[29]. The present group of GAgP patients all belonged to Stage III or Stage IV and Grade C.

The role of tooth-level parameters was relatively less important in explaining treatment outcomes in the present study. Molars showed the highest risk of tooth loss[30,31], and teeth with mobility due to periodontal destruction have an uncertain prognosis.

There are several limitations to the present study. First, this is a single-centre study, which limits the generalisation of the results. Second, the sample size was relatively small; as some of the patients needed further periodontal surgery or orthodontic treatment, the observation period was only 6 months, and a larger number of patients may be needed to better explain the results. Third, further study on the quantity of subgingival bacteria or a microbiome study might better assess the adjunctive roles of antibiotics. The present study also has several strengths: it is an initial study analysing the multilevel factors in explaining nonsurgical periodontal treatment outcomes in patients with GAgP in a short time and, to the best of the present authors' knowledge, it is the first study to demonstrate that adjunctive AMX + MET during SRP is effective in treating patients with GAgP.

Conclusion

In conclusion, the present clinical study demonstrated the roles of patient-, tooth- and site-level parameters in explaining the short-term nonsurgical periodontal treatment outcomes of patients with GAgP. Site-level parameters were found to be the most important factors in explaining treatment outcomes. Deeper initial PD and sites with intrabony defects presented PD reduction and persistent *T. forsythensis* infection, and tooth mobility indicated a poor prognosis. Adjunctive use of AMX + MET is recommended in patients with GAgP receiving nonsurgical periodontal treatment; however, further clinical investigation is required.

Conflicts of interest

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

Author contribution

Dr Rui Fang LU analyzed the data and drafted the manuscript; Drs Li XU, Xian E WANG and Xiang Hui FENG were involved in enrolling patients, periodontal treatment and data collection; Dr Huan Xin MENG supervised the study and revised the manuscript critically. All authors approved the final manuscript.

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