Diagnostic performance of the AAP/EFP classification and the CDC/AAP case definition among pregnant women and a practical screening tool for maternal periodontal diseases

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Abstract
Background and Objective: There is a limited number of studies on the performance assessment of the 2017 AAP/EFP classification and the CDC/AAP case definition among pregnant females. This study evaluated the agreement between these two systems and explored a practical tool for screening maternal periodontal diseases by general dentists.

Materials and Methods: Totally, 204 systemically healthy females at different phases of pregnancy underwent a full-mouth periodontal examination. Demographic characteristics, lifestyles, and systemic conditions were recorded. Referring to the CDC/AAP definition, the diagnostic performance of the AAP/EFP classification was evaluated by the area under the ROC curve (AUC) and statistical tests (e.g., Youden’s index and kappa coefficient). Additionally, a modified scoring system of the FDI Periodontal Diseases Chairside Guide (FDI-CG) was formulated with the addition of pregnancy for testing accordingly.

Results: Overall, there were 22.1% of the participants in early phase of pregnancy (7–13 weeks) and 77.9% in late phase (34–36 weeks). The majority of them were below 35 years and non-smokers without gestational diabetes. Notably, 30.9% of subjects presented with Moderate/Severe periodontitis (CDC/AAP), and 35.8% with Stages II-IV periodontitis (AAP/EFP). Referring to the CDC/AAP definition, the diagnostic performance of the AAP/EFP classification was evaluated by the area under the ROC curve (AUC) and statistical tests (e.g., Youden’s index and kappa coefficient). Additionally, a modified scoring system of the FDI Periodontal Diseases Chairside Guide (FDI-CG) was formulated with the addition of pregnancy for testing accordingly.

Conclusions: This study shows that the AAP/EFP classification is in high agreement with the CDC/AAP definition among the pregnant women. The phases of pregnancy-integrated FDI scoring system may serve as a convenient screening tool for maternal periodontal diseases in general dental practice.
1 | INTRODUCTION

Periodontal diseases are among the major public health burdens worldwide, with considerable effects on oral health and general health like diabetes mellitus (DM), cardiovascular disease (CVD), and adverse pregnancy outcomes (APOs) as well as high socioeconomic impacts.\(^1\)\(^-\)\(^5\) Notably, oral cavity as an important ecological niche plays a critical role in the infection and spread of SARS-CoV-2, the major causative virus of COVID-19 pandemic.\(^6\) Indeed, periodontitis could increase the risk of COVID-19 and its complications.\(^7\)\(^-\)\(^9\) Therefore, increasing public awareness of periodontal health and enhancing prevention and professional care are of great importance for oral health and general well-being.

Pregnant women are prone to notable changes in oral and periodontal tissues, mainly due to increased levels of progesterone and estrogen as well as altered lifestyles. It has been well documented that pregnancy could significantly account for increased gingival inflammation and severity of periodontitis, concurrently with the high burden of dysbiotic bacteria and upregulated immuno-inflammatory responses as well as potential aggravation of periodontal diseases and related inflammatory comorbidities.\(^10\)\(^-\)\(^13\) Conceivably, pregnancy increases to different extents the risk of gingivitis and periodontitis.\(^14\)

Within the framework of periodontal medicine, periodontal diseases have been claimed for the potential link to 57 systemic diseases and disorders.\(^15\) Of them, DM, CVD, and APOs have been highlighted in an updated comprehensive review.\(^4\) APOs are important public health problems with significant socioeconomic implications.\(^16\) In the last two decades, many researchers have explored the association of maternal periodontal diseases with preterm birth (PTB), low birth weight (LBW), and preeclampsia.\(^17\)\(^-\)\(^22\) Overall, periodontal diseases may increase the risk of APOs.\(^5\)\(^,\)\(^24\) While, the strength of such association could be modest and heterogeneous, according to the subject profiles, assessment approaches, and case definitions.\(^25\) Further investigations are needed to clarify whether periodontal intervention may directly contribute to reducing the risk of APOs.\(^16\)\(^,\)\(^26\)\(^,\)\(^27\)

Oral/periodontal healthcare is an important element of comprehensive maternity care. It is noteworthy that the American Academy of Periodontology (AAP) has well established a guideline on the periodontal treatment of pregnant women since 2004, for their well-being and healthy newborn babies,\(^27\) whereas there is a relatively high prevalence of periodontal diseases among pregnant females in both developed and developing countries.\(^28\)\(^,\)\(^29\) However, oral/periodontal health is often neglected, and the pregnant mothers are often unable to receive oral healthcare via regular dental visits.\(^29\) In line with the comprehensive maternity care and support, strengthening periodontal health literacy, screening, and appropriate assessment with a proper case definition is, therefore, essential to early identify gingivitis and periodontitis patients and to deliver individualized healthcare in daily dental practice.

The criterion of the Centers for Disease Control and Prevention and American Academy of Periodontology (CDC/AAP) has been widely used.\(^30\) While the current classification scheme of periodontal and peri-implant diseases and conditions, jointly presented by the AAP and the European Federation of Periodontology (AAP/EFP), has been launched since 2018.\(^31\)\(^-\)\(^33\) Recently, several population-based studies have reported the diagnostic performance and agreement between the CDC/AAP system and AAP/EFP classification.\(^34\)\(^-\)\(^36\) Currently, there is a lack of such comparative studies on these diagnostic systems in pregnant females. It has been shown that different diagnostic approaches considerably account for the variation in the prevalence of periodontitis among pregnant women.\(^37\) Additionally, appropriate screening tools for maternal periodontal diseases are needed in general dental practice. Thus, the present study was to compare the profile of periodontal diseases among pregnant women using the CDC/AAP and AAP/EFP systems and attempted to develop a clinically applicable and easy-to-use tool for screening maternal periodontal diseases by general dentists.

2 | MATERIALS AND METHODS

2.1 | Subjects

This cross-sectional study was conducted in a sample of Chinese pregnant women recruited from the clinic of the Department of Obstetrics & Gynecology at the Shenzhen Maternity and Child Healthcare Hospital (SZMCH) from August 2020 to July 2021. The exclusion criteria included (i) ≥ 36 years old; (ii) edentulism; (iii) use of antibiotics within 3 months; (iv) periodontal treatment received within 12 months; (v) self-reported systemically unhealthy prior to pregnancy; and (vi) history of pathological abortion confirmed by medical records. This study was approved by the Medical Ethics Committee of SZMCH (No. SFYLS [2020]013), and oral and written consents were obtained from all subjects prior to the study. This study was conducted in line with the Declaration of Helsinki 2013.

2.2 | Periodontal examination and data collection

All subjects underwent a full-mouth periodontal examination (6 sites/tooth) by a single calibrated examiner (HJL), using a periodontal probe (UNC-15; Hu Friedy). The intra-examiner reliability was assessed by repeated measurements at site level in four subjects. Intraclass correlation coefficient (ICC) was calculated, with
0.887 (95% CI: 0.860–0.909) for the absolute agreement on probing depth (PD) and 0.873 (95% CI: 0.829–0.905) on clinical attachment loss (CAL), respectively. The periodontal parameters were then recorded, including full-mouth plaque score (FMPS), bleeding on probing (BOP), PD, furcation involvement, tooth mobility, number of tooth loss due to periodontitis (excluding the third molar), and number of remaining teeth. CAL was calculated on the basis of PD and the gingival margin level relative to the cementoenamel junction.

2.3 | Case definitions

All subjects were classified following the CDC/AAP30 and the AAP/EFP systems.31,33,38,39 In the present study, according to the CDC/AAP definition, Severe periodontitis was defined as the presence of ≥2 interproximal sites on different teeth with CAL ≥6 mm and ≥one interproximal site with PD ≥5 mm. Moderate periodontitis was defined as having ≥2 interproximal sites on different teeth with CAL ≥4 mm or ≥2 interproximal sites with PD ≥5 mm. All subjects without Severe or Moderate periodontitis were defined as Mild periodontitis or No periodontitis, respectively. With reference to the AAP/EFP classification,31,33 periodontitis was defined as exhibiting interdental CAL at ≥2 non-adjacent teeth, or buccal/oral CAL ≥3 mm with PD >3 mm at ≥2 teeth. Gingivitis was defined as the presence of gingival inflammation (BOP ≥10% of sites) and the absence of detectable CAL due to periodontitis.38 Periodontal health was defined as the absence of gingival inflammation (BOP <10% of sites) and the absence of CAL resulting from periodontitis.38,39 As the radiographic examination was not performed in this study, grading was not given in the final classification of periodontitis. For staging, Mild periodontitis (Stage I), Moderate periodontitis (Stage II), and Severe periodontitis (Stages III and IV) were defined, respectively, on the basis of interdental CAL at the most affected sites (1–2, 3–4 and ≥5 mm).31

The FDI Periodontal Diseases Chairside Guide (FDI-CG) was developed in 2018 as an easy-to-use screening tool for general dentists in clinical practice, and it has recently been validated in three selected samples from Europe and Asia.40,41 The 7-item scoring system of FDI-CG for periodontal disease profiling consists of age, tobacco smoking, diabetes mellitus, tooth loss due to periodontitis, plaque deposits, BOP, and PD.40 Each item is ranged from 0 to 2 or 3, and the total score is then calculated accordingly. Individual profile of periodontal diseases is then categorized into three levels accordingly, namely Mild (0–5), Moderate (6–10), and Severe (≥11).40

2.4 | Sample size estimation and statistical analysis

Estimation of sample size was performed using a software (Power Analysis & Sample Size Software: PASS 2021, NCSS). According to our recent data from 141 adult subjects in Hong Kong, the sensitivity and specificity of identifying Moderate periodontitis with the AAP/EFP classification and CDC/AAP definition as the reference modality were 100.0% and 47.4%, respectively. For these childbearing-age women, the present study set the expected sensitivity of 100.0% and specificity of 60%. Therefore, at least 42 Moderate periodontitis patients and 127 No or Mild periodontitis subjects were needed by a 5% significance level tested with 80% power. The total sample size was then set as minimally 200, considering the possible no-show participants and potentially higher prevalence of periodontitis in China.28

The data analysis was conducted with a software (Version 9.4 SAS Institute Inc.). All results were presented as mean ± standard deviations (SD), median (interquartile range) or number/percentage (%) as appropriate. With the CDC/AAP definition as the reference modality, the area under the ROC (receiver operating characteristic) curve (AUC) for AAP/EFP classification and FDI-CG scoring system were calculated, respectively. For the AUC analysis, the subjects with Moderate or Severe periodontitis and the others were categorized, respectively, into Moderate/Severe group (moderate to severe periodontitis) and No/Mild group (periodontal health, gingivitis and mild periodontitis). To correlate with CDC/AAP definition, the cut-off level should be Stage II periodontitis for the AAP/EFP classification and a score of 6 for the FDI-CG system. Regarding the original version of FDI-CG scoring system, a new item was added for pregnant women, and two versions of the system were established for testing. One version was that pregnancy would be scored with 2 additional points (FDI-CG all +2). Another one was that early phase of pregnancy was scored with 1 additional point, and late phase of pregnancy was given 2 additional points (FDI-CG early phase +1 and late phase +2). Diagnostic tests were undertaken to measure the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden’s index. Furthermore, the agreement of the three approaches was analyzed by the kappa coefficient (κ), and α was adjusted to 0.0167 (two-sided) by Bonferroni test for multiple tests. The statistical significance level was set at 0.05 (two-sided).

3 | RESULTS

3.1 | Demographic characteristics of the subjects

A total of 381 Chinese women in the early and late phases of pregnancy were recruited. Of them, two subjects taking antibiotics in the preceding 3 months and six subjects with age ≥36 years were excluded. Moreover, 62 participants self-reported systemically unhealthy prior to pregnancy and 42 not having medical records in the database of SZMCH were not recruited. Of the remaining 269 subjects, 60 with a history of pathological abortion and 5 with a record of assisted reproduction were further excluded. Finally, 204 pregnant females (29.8 ± 2.5 years, ranged 24–35 years) were included in the study for subsequent assessments (Figure 1). There were 45 (22.1%) subjects in the early phase of pregnancy (7–13 weeks) and 159 (77.9%) in the late phase of pregnancy (34–36 weeks) (Table 1). Most of them (70.1%) had 28 teeth excluding the third molars, and the main cause of tooth loss for the rest was caries and tooth extraction for orthodontic treatment. There were five subjects aged 35 yrs and two former smokers. The item of diabetes in the FDI-CG was
modified with gestational diabetes, and there was only one subject with controlled gestational diabetes (HbA1c < 7.0%).

3.2 | Periodontal status

91.7% of the subjects presented with over 50% of sites with plaque, and 70.6% showed 10%–50% of sites with BOP. The majority of them (84.8%) exhibited PD < 4 mm or 4–5 mm. None had tooth loss due to periodontitis. As the total score of disease profile based on the FDI-CG was not normally distributed, the median (interquartile range) of the score was presented (4, 3–4).

The overall periodontal condition varied with the three case definitions used (Table 2). According to the CDC/AAP definition, 69.1% of subjects presented with Mild or No periodontitis and 30.4% with Moderate periodontitis. Based on the AAP/EFP classification, 22.5% exhibited periodontally healthy status, 19.6% with gingivitis, and various stages of periodontitis (I: 22.1%, II: 23.5%, and III: 25, 12.3%). None of the subjects had Stage IV periodontitis. While scoring by FDI-CG, the majority (93.1%) got scores 0–5 (Mild) and 6.9% had scores 6–10 (Moderate), and no one had total score over 10 (Severe).

3.3 | Performance assessment of the AAP/EFP classification and FDI-CG scoring system with reference to the CDC/AAP definition

AUC was calculated for the assessment results of AAP/EFP classification and FDI-CG scoring system, respectively, with reference to the CDC/AAP definition (Figure 2). To distinguish subjects from No/Mild periodontitis group or Moderate/Severe periodontitis group, the AUC based on AAP/EFP classification (Model 1) was 0.979 (95% CI: 0.963–0.995) with the optimal cut-off for Stage II. For the FDI-CG scoring system, three testing models were built to find out the most appropriate one among these pregnant women. According to the original version with a cut-off score of 6 (FDI-CG original model, Model 2), the AUC was 0.600 (95% CI: 0.510, 0.689). Notably, the AUC for those two adjusted versions improved markedly from 0.600 (Model 2) to 0.809 (FDI-CG all +2, Model 3) and 0.815 (FDI-CG early phase +1 and late phase +2, Model 4), respectively ($p < .001$). Accordingly, the proportion of subjects scoring 6–10 (Moderate) increased to 57.3% (FDI-CG all +2) and 48.5% (FDI-CG early phase +1 and late phase +2), respectively (Table 2). None of them got scores over 10 in these two additional models.

The sensitivity, specificity, PPV, NPV, and Youden’s index were further calculated to clarify the diagnostic performance of both AAP/EFP and FDI-CG systems with the CDC/AAP as the reference (Table 3). In general, the AAP/EFP system exhibited excellent dichotomous diagnostic performance (Youden’s index: 92.9%) with a high sensitivity (100.0%), specificity (92.9%), PPV (86.3%), and NPV (100%), while the original FDI-CG system exhibited the highest specificity and PPV, and the two modified FDI-CG scoring systems demonstrated similar sensitivity and NPV which were higher than those of the original one. Moreover, the adjusted FDI-CG models showed greater performance as indicated by the Youden’s index (>60.0%) with reference to the original one (19.9%). Herein, the modified FDI-CG (early phase +1 and late phase +2) model performed slightly better than another modified one (all +2) model.
3.4 Overall assessment agreements of the three case definitions

The diagnoses of Moderate and Severe periodontitis with different case definitions showed varying agreements (Table 4). There was almost a perfect agreement between the AAP/EFP and CDC/AAP (κ = 0.890, p < .001), while the consistencies of the FDI-CG original model with CDC/AAP and AAP/EFP were fair (κ = 0.254 and 0.234, respectively, p < .001). Notably, the FDI-CG (all +2) model revealed moderate agreement with both CDC/AAP and AAP/EFP classifications having a kappa value of 0.499 and 0.586, respectively (p < .001). Moreover, the modified FDI-CG (early phase +1 and late phase +2) model further improved the agreement with CDC/AAP case definition from 0.499 to 0.544, while both adjusted FDI-CG models exhibited similar agreements with the AAP/EFP classification (0.585 vs. 0.586).

4 DISCUSSION

The present study firstly shows that the overall profile of periodontal conditions in the pregnant women investigated was consistent, using the CDC/AAP and AAP/EFP systems. Then, a practical screening tool was explored for maternal periodontal diseases by general dentists. According to the CDC/AAP system, the AUC for AAP/EFP classification to distinguish Moderate/Severe periodontitis (Stages II-IV) from No/Mild periodontitis (periodontal health, gingivitis, and Stage I periodontitis) was 0.979. As anticipated, the
diagnostic performance of AAP/EFP (92.9%) was excellent.35 The agreement of CDC/AAP with AAP/EFP was high (89.0%) as well. Moreover, the modified FDI-CG scoring systems with the addition of maternal phases as a new item markedly improved the AUC up to 0.815 and thereby enhanced the diagnostic performance to 63.0%. The agreement of the modified FDI-CG (early +1 and late +2) model with CDC/AAP definition was the highest among the three FDI-CG models, while the two modified FDI-CG models had similar agreements with AAP/EFP classification. It should be noted that the pregnant women with generally young age and low prevalence of severe periodontitis to some extent may have affected the results and the external validity.

Periodontal diagnosis is traditionally made on the basis of assessing the presence and extent of PD, CAL, and the profile of alveolar bone loss on radiographs, and subsequently the patients are generally categorized as mild, moderate, or severe cases,30 whereas these periodontal parameters reflect different aspects of periodontitis. High PD values denote currently existing lesions, while CAL and bone loss are the measurements of accumulated periodontal destruction.42 Indeed, the lack of generally accepted case definitions of periodontitis is a long-standing challenge for effective surveillance of periodontitis, and it has therefore been considered as a major issue in determining and comparing the prevalence of a disease across various surveys worldwide.43 The current AAP/EFP classification consists of the newly added periodontal/gingival health, classical form of plaque biofilm-induced gingivitis and periodontitis that is multidimensionally subcategorized by Stages I-IV/Grades A-C with the extent of disease and potential complexity of treatments.31,32 Certainly, it is the great breakthrough for appropriate assessment and diagnosis of periodontal patients. The accuracy and comprehensiveness of the AAP/EFP classification are the great advantages for patient assessment, diagnosis, formulation of treatment plan, and subsequent therapies in clinical practice, whereas for the purposes of clinical screening, estimation of treatment needs and population-based epidemiological studies, the critical elements such as easiness, convenience, operation time, and participants’ acceptance need to be considered in developing the relevant systems.

The FDI-CG scoring system as an easy-to-use screening tool has recently been validated in a multicenter study with reference to the CDC/AAP system.41 This 7-item scoring tool primarily includes age, measurement of disease experience (tooth loss due to periodontitis), existing plaque control and periodontal condition (plaque score, BoP, and PD) and the important risk factors (tobacco use and diabetes) that are integrated in the current AAP/EFP classification.40 This tool allows general dental practitioners to quickly and conveniently perform periodontal screening in daily practice and give relevant professional advice to their patients. Here, some items like age and tobacco smoking may be not highly applicable to many pregnant women. Meanwhile,
considering the anticipated risk of periodontal diseases, it is proposed to add pregnancy as an essential item in the FDI-CG scoring system for appropriately screening periodontal conditions among the mothers-to-be. Furthermore, it remains to be a debatable clinical issue whether radiographic examination should be included in a routine periodontal examination during the period of pregnancy, although it is needed for determining the grade of periodontitis with the AAP/EFP classification. It is worth noting that radiographic examination is not purposely included in the FDI-CG scoring system as a practical and convenient screening tool. Taken together, the proposed phases of pregnancy-integrated FDI scoring system could be used for periodontal screening, disease prevention, and periodontal healthcare in line with the clinical guideline among the mothers-to-be.

AUC was used to demonstrate the ability of disease prediction and the appropriate cut-off value for an ordinary or continuous variable accordingly. Diagnostic performance presents how accurate the subjects are distinguished by a new definition as compared to the previous one. However, only when every single subject has the same diagnosis, accuracy can be achieved. Recently, several studies have focused on the comparison of CDC/AAP and AAP/EFP case definitions; and AUC, diagnostic performance, and agreement have been used appropriately. Overall, these studies show the high agreement of AAP/EFP classification with CDC/AAP system.

It is apparent that maternal oral/periodontal healthcare is crucial for the general health and well-being of the mothers and their babies. There are anticipated dynamic changes in oral cavity during the period of pregnancy and postpartum, due to various alterations in lifestyle factors, personal behaviors, stress, and the well-noted fluctuations of sex hormones (estrogen and progesterone). These factors and conditions to varying extents may collectively account for dysregulated inflammatory responses and decreased immunocompetence, thereby increasing the host susceptibility to the onset and progression of oral diseases. Meanwhile, these changes in periodontium could complicate periodontal assessment and diagnosis to be appropriately performed by general dentists. It is, therefore, desirable to set up an easy and convenient tool for screening periodontal conditions of pregnant women, in order to enhance maternal oral healthcare in general dental practice.

Currently, early diagnosis of periodontal diseases remains a considerable challenge, partly due to relatively low awareness of oral/periodontal health in the public community. Indeed, the quality of life in periodontal patients can be significantly affected when advanced stages of periodontitis occur. Obviously, awareness of periodontal healthcare and health literacy should be re-enforced for improving early diagnosis, disease prevention, and timely intervention. General dentists need to promote effective oral hygiene practice and routinely deliver preventive care. As such, effective screening and assessment tools are critical to identify susceptible individuals and thereby undertake proactive professional healthcare as early as possible. For the childbearing women with potentially increased risk of gingivitis and progression of periodontitis, it is imperative to enhance periodontal health literacy and help them adopt good oral hygiene regimen through regular dental visits prior to getting pregnant. In addition, essential oral/periodontal care could be delivered appropriately through a mid-pregnancy dental appointment, and yet preventive healthcare and necessary treatments need to be undertaken for mothers during the postpartum dental visits.

TABLE 4  Comparison of periodontal conditions assessed with the three different case definitions

| Periodontitis case definitions | CDC/AAP case definition | AAP/EFP case definition |
|-------------------------------|------------------------|------------------------|
|                               | No & mild (N = 141)   | Healthy or gingivitis orStage I (N = 131) |
|                               | Moderate & Severe (N = 63) | Stage II & III (N = 73) |
| Kappa (κ)                     |                        |                        |
| AAP/EFP                      |                        |                        |
| Healthy or gingivitis orStage I | 131 (92.9) 0 (0.0) | 131 (100.0) 59 (80.8) |
| Stage II & III               | 10 (7.1) 63 (100.0)   | 0 (0.0) 14 (19.2)     |
| FDI-CG                       |                        |                        |
| Mild (0–5)                   | 140 (99.3) 50 (79.4)   | 131 (100.0) 59 (80.8) |
| Moderate & Severe (6–10)     | 1 (0.7) 13 (20.6)     | 0 (0.0) 14 (19.2)     |
| FDI-CG (all +2)              |                        |                        |
| Mild (0–5)                   | 87 (61.7) 0 (0.0)     | 87 (66.4) 0 (0.0)     |
| Moderate & Severe (6–10)     | 54 (38.3) 63 (100.0)  | 44 (33.6) 73 (100.0) |
| FDI-CG (early+1 and late+2)  |                        |                        |
| Mild (0–5)                   | 100 (70.9) 5 (7.9)    | 97 (74.0) 8 (11.0)    |
| Moderate & Severe (6–10)     | 41 (29.1) 58 (92.1)   | 34 (26.0) 65 (89.0)   |

Abbreviation: FDI-CG, FDI periodontal diseases chairside guide.

* p < .001.
Therefore, an easy and effective screening tool like the modified FDI-CG scoring system with a reasonable diagnostic performance could facilitate oral/periodontal health promotion, early identification of diseases, and effective healthcare during the periods of pre-pregnancy, pregnancy, postpartum, and lactating. Further studies on different ethnic groups are needed to refine the modified FDI-CG screening system, through appropriate integration with the current AAP/EFP classification and potential diagnostic biomarkers.

5 | CONCLUSIONS

Within the limitations of the study, the present work demonstrates that the AAP/EFP classification has a high agreement with the CDC/AAP definition among pregnant females. The modified FDI-CG scoring system with the addition of pregnant phases may serve as a relatively easy-to-use and convenient tool for screening maternal periodontal diseases in general dental practice.

AUTHOR CONTRIBUTIONS

L.J.J. contributed to conceptualization and critical revision of the manuscript; D.Z., T.C., P.W., and L.J.J. contributed to study design; H.L., P.W., X.X., R.Y., and F.Z. involved in data acquisition; D.Z. and X.X. involved in data analysis; H.L., D.Z., Z.Z., H.Y., C.Y., J.Y., P.W., and L.J.J. contributed to data interpretation; H.L., D.Z., F.Z., T.C., and P.W. involved in writing draft; All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST

All authors declare they have no conflicts of interest related to this study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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