Factors Associated with Apical Periodontitis: A Multilevel Analysis

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Abstract

Introduction: Ignoring the cluster effect is a common statistical oversight that is also observed in endodontic research. The aim of this study was to explore the use of multilevel modeling in investigating the effect of tooth-level and patient-level factors on apical periodontitis (AP). Methods: A random sample of digital panoramic radiographs from the database of a dental hospital was evaluated. Two calibrated examiners (κ ≥ 0.89) assessed the technical quality of the root fillings and the radiographic periapical health status by using the periapical index. Descriptive statistical analysis was carried out, followed by multilevel modeling by using tooth-level and patient-level predictors. Model fit information was obtained, and the findings of the best-fit model were reported. Results: A total of 6409 teeth were included in the analysis. The predicted probability of a tooth having AP was 0.42%. There was a statistically significant variability between patients (P < .05). Approximately 53.16% of the variability was accounted for by the patients, leaving 46.84% of the variability to teeth or other factors. Posterior tooth, inadequate root filling, and age were found to be significantly associated with AP (P < .05). Conclusions: Multilevel modeling is a valid and efficient statistical method in analyzing AP data. The predicted probability of a tooth having AP was generally small, but there was great variation between individuals. Posterior teeth and those with poor quality root filling were found to be more frequently associated with AP. On the patient level, advancing age was a factor significantly associated with AP. (J Endod 2016;42:1441–1445)

Key Words

Apical periodontitis, endodontic, periapical status, radiographic evaluation, risk factors

Apical periodontitis (AP) is an inflammatory disease of endodontic origin (1); it can develop and persist without obvious clinical signs. Therefore, radiologic examination, confirming the presence of a periapical radiolucency, is essential for the diagnosis of AP (2). In epidemiologic research, the periapical index (PAI) is commonly used to categorize the radiographic presentation of the extent of disease (3). Epidemiologic studies permit a disease of interest such as AP to be put in a wider and multifactorial context, thereby complementing our understanding of experimental and controlled studies (4). Although there are many prevalence reports on AP, the efficient use of cross-sectional design in identifying the predictors of the disease is lacking (5).

In the existing prevalence reports, risk factors analysis of AP was done primarily by using bivariate analysis (6–16). Periapical radiolucencies were found more frequently in molar teeth (6–8). Root-filled teeth were consistently found to be associated with AP, especially if the quality of the root filling was inadequate (6, 7, 9–14). At the other extreme, overfilling the canal may likewise compromise periapical health (15, 16). Radiologic assessment indicated that post placement (16) and defective coronal restoration (13, 14) were associated with the presence of periapical radiolucenties. Although these tooth-level variables are useful indicators, patient-level variables such as age and gender have been identified as confounders and adjusted by using multivariate analysis (17).

However, analyzing AP data at a single level assumes each tooth is an independent entity, ignoring the fact that teeth are clustered and correlated within patients, and the risk factors operate differently at each level (18). This can increase the type I error rates and lead to incorrect conclusions (19). Also, it does not explain the variability at different levels, hence reducing its validity (20). Alternatively, the number of teeth with AP can be aggregated and analyzed for each individual, but this approach undermines the statistical power of the study and overlooks important clinical details at tooth level (21).

To date, multilevel modeling was proven useful in understanding periodontal (22) and caries (23) data, particularly in optimizing the use of tooth and surface...
specific information, as well as addressing issues such as estimating variances and detecting covariate effects. Adoption of such statistical approach in endodontics can potentially give new insights in the epidemiology of AP. Epidemiology and public health are closely intertwined; the data will be relevant to everyday clinical practice. Furthermore, it will facilitate the targeted distribution of valuable resources, alignment, and planning of dental, especially endodontic, manpower and training. Therefore, the aim of this study was to explore the use of multilevel modeling in investigating the effect of tooth-level and patient-level factors on AP. Specifically, the research questions posed were as follows:

1. What is the predicted probability of a tooth having AP?
2. Does the predicted probability of having AP vary between patients?
3. What is the association between each variable and the likelihood of having AP while controlling for other tooth and patient characteristics?

**Materials and Methods**

A retrospective study was conducted by using digital panoramic radiographs taken from patients attending the dental clinics at Faculty of Dentistry, Universiti Kebangsaan Malaysia, Kuala Lumpur. Ethical approval for this study was obtained from the Universiti Kebangsaan Malaysia Research Ethics Committee (UKM 1.5.3.5/244/DD/2014/004(1)). All of the digital panoramic radiographs were taken by 3 trained and qualified radiographers who used Sirona Orthophos (Sirona Dental System GmbH, Bensheim, Germany) and Kodak 9000/9000D (Dental Systems Group, Carestream Health Inc, Kodak Dental Systems, Marne-la-Vallée, France).

Sample size estimation was calculated by using the following formula (24):

$$n = \frac{Z^2 \cdot p \cdot (1-p)}{d^2}$$

The prevalence ($p$) of AP found on radiographic assessment was estimated at 13.6% (25). The Z value was 1.96 for 95% confidence interval, and the precision level ($d$) was determined at 0.05. From the above formula, the sample size required was 184 patients. Assuming that 25% of the panoramic radiographs could not be used because of inadequate quality, the sample size was increased by 25%. Therefore, the minimum number of patients required was 230.

The sampling frame consisted of collated prescription forms for digital panoramic radiographs taken during 2011–2012. From the prescription forms, information regarding the patients’ gender and age as well as the reason/s the panoramic radiographs were taken was recorded in chronological order; this then provided guidance as to the suitability of a particular radiograph. The inclusion criterion was a digital panoramic radiograph taken on a patient 18 years or older. If multiple radiographs for a patient were available, only the earliest dated radiograph was used. To avoid overestimation of disease prevalence, radiographs taken for the sole purpose of diagnosing AP were excluded. Radiographs of fully edentulous patients were also excluded. Random sampling was then performed by using the computer-generated random number. Once selected, the corresponding digital panoramic radiograph was retrieved.

**Radiographic Evaluation**

The radiographic periapical health status and technical quality of the root fillings were assessed by 2 examiners who viewed on a 19-inch computer screen calibrated for medical imaging and used Digora for Windows 2.6 (Soredex, Tuusula, Finland). The periapical health status of each tooth was assessed by using the PAI (5). For a multirooted tooth, the worst PAI score was recorded. Teeth were classified as root-treated if they contained a radiopaque material in the pulp chamber and/or in 1 or more root canals (12). The root filling was considered adequate if it terminated within 0–2 mm from the radiographic apex and without any visible void (26). Teeth that were not possible to assess radiographically because of superimposition of anatomic structures were excluded from the study. Additional periapical radiographs, if available, were used to confirm the presence of periapical radiolucencies. The films were examined in a darkened room on an illuminated viewer box by using the PAI.

The 2 examiners were calibrated beforehand by using 10 digital panoramic radiographs that were not part of the randomized sample. Both examiners viewed the panoramic radiographs independently, and intra-examiner and inter-examiner agreement was determined by using Cohen kappa coefficient ($\kappa$). For intra-examiner assessment, a second reading was scored 1 month later. The $\kappa$ for intra-examiner agreement was 0.91 for the evaluation of the periapical health status and 0.95 for technical quality of root canal filling. Similarly, inter-examiner agreement of $\kappa = 0.95$ and $\kappa = 0.89$ was achieved for the detection of AP and the categorization of the quality of the root fillings, respectively. These results indicated a high intra-examiner and inter-examiner agreement.

**Data Analysis**

Multilevel modeling was carried out by using PROC GLIMMIX and the Laplace estimation method in SAS 9.4 (SAS Institute, Cary, NC). Hierarchical generalized linear models were built to investigate the association between AP and risk indicators at both levels. The PAI score was dichotomized and used as the outcome variable. A PAI score of more than 2 was considered a sign of periapical disease. Suppose $y_{ij}$ is the dichotomized PAI outcome for tooth $i$ in patient $j$ and $x_{ij}$ is an explanatory variable at the tooth level. The probability of having AP is represented as $p_{ij} = Pr(y_{ij} = 1)$, where $y_{ij}$ follows a binomial distribution. First, a simple tooth-level model was estimated by using the logit link function.

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \beta_{y} + \beta_{x_1}x_{ij} + \beta_{x_2}x_{ij} + \beta_{x_3}x_{ij} + \beta_{x_4}x_{ij}$$

(Equation 1)

In Equation 1, $\beta_{y}$ represents the intercept, the average log odds of a tooth having AP. The binary predictors are anteroposterior location of the tooth ($x_1$), maxilla-mandibular location of the tooth ($x_2$), root-filling adequacy ($x_3$), and root-filling inadequacy ($x_4$). $\beta_{ij}$ represents the coefficient of tooth-level predictor $x_i$. The error variance is not estimated separately at tooth level because it is determined directly by the population mean (27).

$$\beta_{y} = \gamma_{00} + \gamma_{01}W_{x} + \gamma_{02}W_{y} + u_{y}$$

(Equation 2)

$$\beta_{y} = \gamma_{00}$$

Equation 2 represents a simple patient-level model, in which $\gamma_{00}$ is the log odds of a patient having AP, $W_{x}$ is the age (continuous variable), and $W_{y}$ is the gender of the patient. $\gamma_{ij}$ represents the coefficient of patient-level predictor $W_{x}$, and $u_{ij}$ is the patient-level error term. Each of the coefficients of tooth-level predictor ($\beta_{ij}$) is equal to the
average effect of the tooth-level predictor ($\gamma_{00}$). Substituting these into Equation 1 will give us the combined tooth-level and patient-level model, represented by Equation 3.

\[
\log\left(\frac{p_j}{1-p_j}\right) = \gamma_{00} + \gamma_{01}w_j + \gamma_{02}x_{ij} + \gamma_{10}x_{ij} + \gamma_{20}x_{2j} \\
+ \gamma_{30}x_{3j} + \gamma_{40}x_{4j} + u_{ij}
\]

(Equation 3)

**Results**

The digital panoramic radiographs of 233 patients, who consisted of 147 women (63.1%) and 86 men (36.9%), were assessed. The age range was 16–70 years (median, 26 years). A total 93.1% of patients had 20 teeth or more. AP was detected in 59 patients (25.2%), with 1–6 teeth involved.

A total of 6478 teeth were assessed (Fig. 1). However, 69 teeth (none root-treated) were excluded from the study because of image distortion or superimposition. Of the 6409 teeth included in the analysis, 43 (0.7%) were root-treated. The frequency distribution of AP, according to tooth type as denoted by the International Dental Federation nomenclature, is shown in Figure 2. AP was found in 1.5% of teeth without root filling ($n = 96$) and 37.2% of root-filled teeth ($n = 16$), whereas the overall prevalence was 1.7%. Of the 112 teeth shown with PAI in panoramic radiographs, 44 were complemented with periapical radiographs. Periapical radiolucencies were confirmed in all these cases (weighted $k = 0.72$). On the other hand, 32 teeth were deemed unrestorable clinically and radiographically, so no additional radiographs were prescribed. The remaining 36 teeth did not have additional radiographs taken without any specific reason.

Table 1 shows the comparison between the null model (Model 1), model with tooth-level predictors (Model 2), and model with tooth-level and patient-level predictors (Model 3). In the null model where each tooth was regarded as independent, the predicted probability of a tooth having AP was 0.42%. Model 2 takes into consideration individual variation. There was a statistically significant amount of variability between the patients ($t_{00} = 3.73; Z(232) = 3.40; P < .05$). The intra-class correlation coefficient indicated that approximately 53.16% of the variability was accounted for by the patients, leaving 46.84% of the variability to teeth or other unknown factors.

On the basis of the parsimonious model (Model 3), it was found that a posterior tooth had increased odds of AP (adjusted odds ratio [OR], 5.10; 95% confidence interval [CI], 2.91–8.94; $P < .05$) when compared with an anterior tooth. On the other hand, the location of the tooth, whether mandibular or maxillary, did not seem to matter ($P = .30$). When other tooth and patient characteristics were controlled, inadequate root filling greatly increased the odds of having AP (adjusted OR, 132.45; 95% CI, 38.90–451.05; $P < .05$). In contrast, the effect of having a root filling with adequate overall technical quality was not statistically significant ($P = .81$). There was a significant positive association between age and AP (adjusted OR, 1.08; 95% CI, 1.05–1.11; $P < .05$). On the other hand, the association between gender and AP was not apparent ($P = .08$).

**Discussion**

The choice of measurement for AP prevalence is debatable. Although histologic analysis remains the gold standard for diagnosing AP accurately, noninvasive imaging methods are more feasible in clinics. However, not all lesions are evident radiographically (28). Cone-beam computed tomography (CBCT) supersedes periapical and
panoramic radiographs, because 3-dimensional view allows more precise estimation of the location and size of the lesion as well as the detection of missed canals and lateral voids in the assessment of technical quality (29). Periapical and panoramic radiographs were reported with high specificity (0.98 and 1.00, respectively) but low sensitivity (0.55 and 0.28, respectively) when compared against CBCT (28). Hence, the use of these conventional imaging methods tends to detect only advanced lesions and therefore underestimate disease prevalence.

Despite these drawbacks, several prevalence studies have used panoramic radiographs (6, 9, 11, 12) with good reasons. In reality, not all dental practices are equipped with CBCT (28). More importantly, because of increased radiation risk, the indications for CBCT are highly controlled, mostly restricted to the area of interest instead of the entire dentition (30). Assessing existing CBCT images could therefore bias the estimation of association. On the other hand, prescriptions of full-mouth periapical radiographs are often limited to periodontal patients. Hence, the findings should not be extrapolated to the general population (31). Panoramic radiographs could overcome these issues by giving the full view of the dentition with less radiation exposure (6).

Coupled with the retrospective nature of this study, this rendered panoramic radiographs the most realistic choice of outcome measurement tool. Furthermore, the findings were comparable with existing periapical radiographs in this study.

In cross-sectional studies, a significant association does not in any way imply causality. For instance, a periapical radiolucency detected close to an inadequately root-filled tooth might be an indication of persistent infection, or it could be incomplete healing. In addition, the cross-sectional study design does not reflect the dynamic nature of the disease (17).

Because disease proportion was analyzed inherently in the model, the selection criteria must take the disease prevalence into account. Panoramic radiographs taken solely for diagnosing AP were generally uncommon, because periapical radiographs would yield better accuracy. In this study, we were only interested in undiagnosed cases in new patients. Patients who were diagnosed with AP and/or receiving endodontic treatment at the time the radiographs were taken were excluded. These cases were identified as panoramic radiographs taken solely for AP in the prescription forms. Inclusion of these known cases amidst the new cases would result in an overestimation of the occurrence of AP. On the other hand, because panoramic radiographs were not commonly available for edentulous patients and non-attenders, this would also overestimate the occurrence of the disease (5).

In the present study, only the risk factors with readily available information were examined. We caution against the generalization of the research findings, because the university hospital setting in an urban area would give access to higher proportions of educated city dwellers. Nevertheless, universities remain the predominant location for scholarly research around the world. Therefore, it makes sense that many prevalence studies were carried out in dental school clinics (6, 7, 12, 13, 15, 29).

Disregarding the cluster effect is a common statistical oversight that is observed also in endodontic research (32). The strength of this present study lies in the ability to look at cross-sectional prevalence data of AP in the light of multilevel modeling. Initial descriptive analysis revealed that the burden of the disease was concentrated in one fourth of the patients, with a varying number of teeth showing signs of periapical radiolucency. This pointed toward variability that exists not just between individuals but also between teeth. Hence, the need for further analysis is warranted. By using multilevel analysis, the predicted probability of having AP was shown to be due to greater variability between individuals than between teeth. Thus, this translates to a more informed conclusion for clinicians in risk assessment rather than a one-size-fits-all number.

Posterior teeth were significantly associated with AP, which is consistent with earlier findings (6–8). A possible explanation for this is the intricate anatomy of these teeth (6, 8). The use of panoramic radiographs, which have lower sensitivity than periapical radiographs in detecting periapical lesions especially in the anterior region (28, 30), may also be partly contributory. As observed in Figure 1, no periapical radiolucency was found in the lower anterior region, perhaps because of blurring of the image (6) because the region falls in front of or behind the focal trough.

The maxillary-mandibular location of the tooth was not a significant factor in this study, but previous studies that used bivariate analysis reported a higher prevalence of AP in maxillary teeth (6, 8). We postulate that the contradicting findings between studies were partly due to the increased type I error rates with single-level studies. Also, there might be an interaction effect of tooth location and tooth type on AP (17). In this study, similar to most prevalence studies, AP was more commonly found in root-filled teeth than non–root-filled teeth (6, 7, 9–11). Generally, underextended root fillings (2–4 mm short of the radiographic apex), overextended root fillings (>2 mm from the radiographic apex), and fillings containing voids were more frequently found with periapical lesions than teeth with a satisfactory root filling (6). Extension of the root filling to apical constriction favors healing, as confirmed by histologic findings (33).

Age was found to be a significant factor in this study in agreement with earlier findings (6, 8), probably because of the cumulative experience of caries and dental interventions over time (6). However,
unlike a cavitated carious lesion, AP is a dynamic disease that can be healed with appropriate treatment (5). Furthermore, an increased ratio of AP with age does not necessarily indicate that older individuals are more affected by periapical disease because this ratio may also be driven by the negative effect of tooth loss (34). On the other hand, the lack of evidence in the association between gender and AP is contradictory to the findings of López-López et al (35). Nevertheless, earlier positive findings were probably driven by discrepancies in health behaviors (35) rather than biological functions. Similarly, the effect of unadjusted correlation between teeth could not be ruled out.

Conclusions

Multilevel modeling is a valid and efficient statistical method in analyzing AP data. Within the limits of this study, it can be concluded that the predicted probability of a tooth having AP in this defined population was small, but there is great variation between individuals. By using multilevel modeling, it was found that posterior teeth and teeth with poor quality root fillings tend to have increased odds of having AP. On the patient level, advancing age poses as a significant factor of having AP.

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The authors deny any conflicts of interest related to this study.

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