**Abstract**

**Introduction:** Ignoring the cluster effect is a common statistical oversight, observed also in endodontic research. The aim of this study was to explore the use of multilevel modeling in investigating the effect of tooth- 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 using the Periapical Index (PAI). Descriptive statistical analysis was carried out, followed by multilevel modeling using tooth- and patient-level predictors. Model fit information was obtained, and the findings of the best-fit model 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.

**Key Words**

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

**Introduction**

Apical periodontitis (AP) is an inflammatory disease of endodontic origin (1); it can develop and persist without obvious clinical signs. Therefore, radiological examination, confirming the presence of a periapical radiolucency, is essential for the diagnosis of AP (2). In epidemiological research, the Periapical Index (PAI) is commonly used to categorize the radiographic presentation of the extent of disease (3). Epidemiological studies permits 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 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). Radiological assessment indicated that post-placement (16) and defective coronal restoration (13, 14) were associated with the presence of periapical radiolucencies. While these tooth-level variables are useful indicators, patient-level variables, such as age and gender, have been identified as confounders and adjusted using multivariate analysis (17).

However, analyzing AP data at a single level assume 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 like 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- and patient-level factors on AP. Specifically, the research questions posed were as follows:

1. What is the predicted probability of a tooth in 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, using digital panoramic radiographs taken from patients attending the dental clinics at Faculty of Dentistry, Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur. Ethical approval for this study was obtained from the UKM Research Ethics Committee [UKM (1.5.3.5/244/DD/2014/004(1)]. All of the digital panoramic radiographs were taken by three trained and qualified radiographers using 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 using the following formula (24):

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 due to inadequate quality, the sample size was increased by 25%. Therefore, the minimum number of patients required was 230.

The sampling frame consists of collated prescription forms for digital panoramic radiographs taken during 2011–12. 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 criteria was a digital panoramic radiograph taken on a patient aged 18 years or above. 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 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 two examiners, viewed on a 19-inch computer screen calibrated for medical imaging and using Digora for Windows 2.6 (Soredex, Tuusula, Finland). The periapical health status of each tooth was assessed using the Periapical Index (PAI) (3). For a multi-rooted 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 one or more root canals (12). The root-filling was considered adequate if it terminates within 0–2 mm from the radiographic apex and without any visible void (26). Teeth that were not possible to assess radiographically due to superimposition of anatomical 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 using the PAI.

The two examiners were calibrated beforehand using 10 digital panoramic radiographs that were not part of the randomized sample. Both examiners viewed the panoramic radiographs independently and intra- and inter-examiner agreement were determined using Cohen’s kappa coefficient (κ). For intra-examiner assessment, a second reading was scored one month later. The κ 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 κ = 0.95 and κ = 0.89 were achieved for the detection of AP and the categorization of the quality of the root fillings, respectively. These results indicated a high intra- and inter-examiner agreement.

*Data Analysis*

Multilevel modeling was carried out using PROC GLIMMIX and the Laplace estimation method in SAS 9.4 (SAS Institute, Cary, NC, USA). Hierarchical Generalized Linear Models (HGLMs) 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 is the dichotomized PAI outcome for tooth in patient and is an explanatory variable at the tooth level. The probability of having AP is represented as , where follows a binomial distribution. First, a simple tooth-level model was estimated using the logit link function.

 (Equation 1)

In equation 1, represents the intercept, the average log odds of a tooth in having AP. The binary predictors are anteroposterior location of the tooth (, maxilla-mandibular location of the tooth (), root filling adequacy () and root filling inadequacy (). represents the coefficient of tooth-level predictor . The error variance is not estimated separately at tooth level because it is determined directly by the population mean (27).

 (Equation 2)

Equation 2 represents a simple patient-level model, in which is the log odds of a patient in having AP, is the age (continuous variable) and is the gender of the patient. represents the coefficient of patient-level predictor , while is the patient-level error term. Each of the coefficient of tooth-level predictor () is equal to the average effect of the tooth-level predictor (). Substituting these into Equation 1 will give us the combined tooth- and patient-levels model, represented by Equation 3.

 (Equation 3)

**Results**

The digital panoramic radiographs of 233 patients were assessed, consisting of 147 (63.1%) females and 86 (36.9%) males. The age range was 16–70 years (median = 26 years). A total of 93.1% of patients have 20 teeth or more. AP was detected in 59 (25.2%) patients, with one to six teeth involved.

A total of 6478 teeth were assessed (Figure 1). However, 69 teeth (none root-treated) were excluded from the study due to 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 FDI nomenclature, is shown in Figure 2. AP was found in 1.5% (n = 96) of teeth without root filling and 37.2% (n = 16) of root-filled teeth, while the overall prevalence was 1.7%. Of the 112 teeth shown with PAI ≥ 3 in panoramic radiographs, 44 were complemented with periapical radiographs. Periapical radiolucencies were confirmed in all these cases (weighted κ = 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- and patient-level predictors (Model 3). In the null model where each tooth was regarded as independent, the predicted probability of a tooth in having AP was 0.42%. Model 2 takes into consideration of individual variation. There was a statistically significant amount of variability between the patients [= 3.73; *Z*(232) = 3.40, *P* < .05]. The intraclass correlation coefficient (ICC) 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.

Based on the parsimonious model (Model 3), it was found that a posterior tooth had an increased odds of AP (adjusted OR = 5.10, 95% CI = 2.91–8.94, *P* < .05) when compared to 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. While histologic analysis remains the gold standard for diagnosing AP accurately, non-invasive imaging methods are more feasible in clinics. However, not all lesions are evident radiographically (28). Cone beam computed tomography supersedes periapical and panoramic radiographs, as 3-D 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 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, due to 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 biased the estimation of association. On the other hand, prescription 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). This, coupled with the retrospective nature of this study 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. Additionally, the cross-sectional study design does not reflect the dynamic nature of the disease (17).

Since 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, given that 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 of the radiographs 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 (3).

In the present study, only the risk factors with readily available information were examined. We caution against the generalization of the research finding, since 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, 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 a quarter of the patients, with a varying number of teeth showing signs of a periapical radiolucency. This pointed towards variability that exists not just between individuals, but also between teeth. Hence, the need for further analysis is warranted. 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, 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 due to 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 employing 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– 4mm short of the radiographic apex), overextended root-fillings (> 2mm 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 histological findings (33).

Age was found to be a significant factor in this study, in agreement with earlier findings (6, 8), probably due to the cumulative experience of caries and dental interventions over time (6). However, unlike a cavitated carious lesion, AP is a dynamic disease, which 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 as this ratio may also be driven by the negating 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*. (2012) (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 limit 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. 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.

**References**

1. Nair PNR. Pathobiological of apical periodontitis. In: Ørstavik D, Pitt Ford TR, editors. Essential Endodontology: prevention and treatment of apical periodontitis. 2nd ed. Oxford: Blackwell Munksgaard Ltd.; 2008. p. 81-123.
2. Huumonen S, Ørstavik D. Radiological aspects of apical periodontitis. Endod Topics 2002;1:3–25.
3. Ørstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol 1986;2:20–34.
4. Eriksen HM, Kirkevang LL, Petersson K. Endodontic epidemiology and treatment outcome: general considerations. Endod Topics 2002;2:1–9.
5. Pak JG, Fayazi S, White SN. Prevalence of periapical radiolucency and root canal treatment: a systematic review of cross-sectional studies. J Endod 2012;38:1170–6.
6. Lupi-Pegurier L, Bertrand MF, Muller-Bolla M, Rocca JP, Bolla M. Periapical status, prevalence and quality of endodontic treatment in an adult French population. Int Endod J 2002;35:690–7.
7. Kabak Y, Abbott PV. Prevalence of apical periodontitis and the quality of endodontic treatment in an adult Belarusian population. Int Endod J 2005;38:238–45.
8. Peters LB, Lindeboom JA, Elst ME, Wesselink PR. Prevalence of apical periodontitis relative to endodontic treatment in an adult Dutch population: a repeated cross-sectional study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:523–8.
9. Sunay H, Tanalp J, Dikbas I, Bayirli G. Cross-sectional evaluation of the periapical status and quality of root canal treatment in a selected population of urban Turkish adults. Int Endod J 2007;40:139–45.
10. Estrela C, Leles CR, Hollanda ACB, Moura MS, Pécora JD. Prevalence and risk factors of apical periodontitis in endodontically treated teeth in a selected population of Brazilian adults. Braz Dent J 2008;19:34–9.
11. Di Filippo G, Sidhu SK, & Chong BS. Apical periodontitis and the technical quality of root canal treatment in an adult sub-population in London. Br Dent J 2014;216: E22.
12. De Moor RJ, Hommez GM, De Boever JG, Delmé KI, Martens GE. Periapical health related to the quality of root canal treatment in a Belgian population. Int Endod J 2000;33:113–20.
13. Dugas NN, Lawrence HP, Teplitsky PE, Pharoah MJ, Friedman S. Periapical health and treatment quality assessment of root-filled teeth in two Canadian populations. Int Endod J 2003;36:181–92.
14. Kirkevang LL, Ørstavik D, Horsted-Bindslev P, Wenzel A. Periapical status and quality of root canal fillings and coronal restorations in a Danish population. Int Endod J 2000;33:509–15.
15. Tsuneishi M, Yamamoto T, Yamanaka R, Tamaki N, Sakamoto T, Tsuji K, Watanabe T. Radiographic evaluation of periapical status and prevalence of endodontic treatment in an adult Japanese population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:631–5.
16. Eckerbom M, Magnusson T, Martinsson T. Prevalence of apical periodontitis, crowned teeth and teeth with posts in a Swedish population. Endod Dent Traumatol 1991;7:214–20.
17. Kirkevang LL, Væth M, Hörsted-Bindslev P, Bahrami G, Wenzel A. Risk factors for developing apical periodontitis in a general population. Int Endod J 2007;40:290–9.
18. Gilthorpe MS, Griffiths GS, Maddick IH, Zamzuri AT. The application of multilevel modelling to periodontal research data. Community Dent Health 2000;17:227–35.
19. Aarts E, Verhage M, Veenvliet JV, Dolan CV, Van der Sluis S. A solution to dependency: using multilevel analysis to accommodate nested data. Nat Neurosci 2014;17:491–6.
20. Albandar JM, Goldstein H. Multi-level statistical models in studies of periodontal diseases*.* J Periodontol 1992;63:690–5.
21. Caplan DJ. Epidemiologic issues in studies of association between apical periodontitis and systemic health. Endod Topics 2004;8:15–35.
22. Tu Y-K, Gilthorpe MS, Griffiths GS, Maddick IH, Eaton KA, Johnson NW. The application of multilevel modeling in the analysis of longitudinal periodontal data – part I: absolute levels of disease. J Periodontol 2004;75:127–36.
23. Burnside G, Pine CM, Williamson PR. The application of multilevel modelling to dental caries data. Stat Med 2007;26:4139–49.
24. Daniel WW. Biostatistics: a foundation for analysis in the health sciences. 7th ed. New York: John Wiley & Sons; 1999.
25. Georgopoulou MK, Spanaki-Voreadi AP, Pantazis N, Kontakiotis EG. Frequency and distribution of root filled teeth and apical periodontitis in a Greek population. Int Endod J 2005;38:105–11.
26. European Society of Endodontology. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. Int Endod J 2006;39:921–30.
27. Ene M, Leighton EA., Genine BL, Bell BA. Multilevel models for categorical data using SAS ® PROC GLIMMIX : The Basics. Southeast SAS Users Gr Conf 2014;134:1–12.
28. Estrela C, Bueno MR, Leles CR, Azavedo B, Azevedo JR. Accuracy of cone beam computed tomography and panoramic radiography for detection of apical periodontitis. J Endod 2008;34:273–9.
29. Karabucak B, Bunes A, Chehoud C, Kohli MR, Setzer F. Prevalence of apical periodontitis in endodontically treated premolars and molars with untreated canal: a cone-beam computed tomography study. J Endod 2016;42:538–41.
30. The American Dental Association Council on Scientific Affairs. The use of cone-beam computed tomography in dentistry. J Am Dent Asso 2012;143:899–902.
31. Ridao-Sacie C, Segura-Egea JJ, Fernández-Palacín A, Bullón-Fernández P, Ríos-Santos JV. Radiological assessment of periapical status using the periapical index: comparison of periapical radiography and digital panoramic radiography. Int Endod J 2007;40:433–40.
32. Fleming PS, Koletsi D, Polychronopoulou A, Eliades T, Pandis N. Are clustering effects accounted for in statistical analysis in leading dental specialty journals? J Dent 2013;41:265–70.
33. Ricucci D, Langeland K. Apical limit of root canal instrumentation and obturation, part 2. A histological study. Int Endod J 1998;31:394–409.
34. Frisk F, Hugoson A, Hakeberg M. Technical quality of root fillings and periapical status in root filled teeth in Jönköping, Sweden. Int Endod J 2008;41:958–68.
35. López-López J, Jané-Salas E, Estrugo-Devesa A, Castellanos-Cosano L., Martín-González J, Velasco-Ortega E, Segura-Egea JJ. Frequency and distribution of root-filled teeth and apical periodontitis in an adult population of Barcelona, Spain. Int Endod J 2012;62:40–6.

**Figure Legends**

**Figure 1** Flow diagram of sample selection.

**Figure 2** Frequency distribution of AP according to tooth type (FDI nomenclature).

**Table 1** Coefficients from models with different level structures and model fit information

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Model 1 | Model 2 | Model 3ⱡ |
| *Fixed effects* |  |  |  |
| Intercept | -5.469\* (0.338) | -8.601\* (0.777) | -9.523\* (1.099) |
| Anterior tooth versus posterior tooth |  | 1.655\* (0.293) | 1.629\* (0.287) |
| Maxillary versus mandibular tooth |  | -0.205 (0.219) | -0.225 (0.218) |
| Adequate root filling versus no root filling |  | -10.091 (462.77) | -2.172 (8.826) |
| Inadequate root filling versus no root filling |  | 5.985\* (0.729) | 4.886\* (0.625) |
| Age |  |  | 0.074\* (0.014) |
| Female versus male |  |  | -0.674\* (0.390) |
|  |  |  |  |
| *Error Variance* |  |  |  |
| Level-2 Intercept | 3.733\*(1.099) | 5.159\*(1.601) | 3.031\*(0.87) |
|  |  |  |  |
| *Model Fit* |  |  |  |
| -2LL | 1010.30 | 872.24\* | 834.19\* |

Entries show coefficients with standard errors in parentheses.

\*Statistically significant difference (*P* < .05).

ⱡBest fitting model.