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Cotinine: Exploring the Impact of Smoking Habits on Periodontal Disease

João Onofre[1,a)], Luzia Mendes[1], Pereira J.A.[1,2]

[1] Faculty of Dental Medicine of University of Porto, Portugal,
[a)] up201907471@edu.fmd.up.pt
[3] Centro de Estatística Aplicações da Universidade de Lisboa, Portugal

Abstract

1 Introduction

Smoking is a recognized risk factor for the onset and exacerbation of periodontal disease. Researches into the relationship between tobacco use and periodontal health began in the 20th century, highlighting tobacco's significant impact on the initiation, progression, and severity of periodontal disorders. Smoking is the principal behavioral risk factor for periodontitis, impacting its prevalence, extent, and severity.

Cotinine, an alkaloid found in tobacco and the primary active metabolite of nicotine, serves as a biomarker to measure tobacco smoke exposure, with a minimal amount being excreted through the kidneys. Cotinine provides a more precise measure of nicotine intake than self-reported smoking habits due to its detectability in blood, saliva, or urine. The extended half-life of cotinine, ranging from 15 to 20 hours—contrasted with nicotine's shorter half-life of approximately 2 hours—establishes it as a reliable biochemical marker for assessing nicotine consumption.

Periodontitis is defined as a chronic multifactorial inflammatory disease associated with a dysbiotic biofilm and characterized by the progressive destruction of the tooth-supporting apparatus. The periodontal apparatus, comprising the gingiva, cementum, periodontal ligament, and alveolar bone, plays a critical role in maintaining dental stability within the oral cavity. The pathogenesis of periodontitis is initiated by gingivitis, a condition characterized by localized gingival inflammation due to dental biofilms. Without clinical intervention, this preliminary inflammatory phase can evolve into chronic periodontitis. This advancement is marked by the emergence of profound periodontal pockets, a critical indicator of progressed periodontal disease, potentially leading to tooth loss. The pathophysiological framework of this progression is characterized by the intricate interaction between the pathogenic biofilm and the host's immune response, perpetuating a chronic inflammatory state that amplifies the systemic inflammatory burden.

The GAMLSS framework is a flexible approach for modeling a wide variety of distributions for the response variable. Unlike traditional linear models, GAMLSS allows for the simultaneous modeling of location, scale, and shape parameters, providing a comprehensive understanding of the data's distribution. This flexibility is particularly useful for handling non-normal data and accommodating heteroscedasticity and skewness in the response variable. GAMLSS supports a wide range of distributions, enabling the selection of the most appropriate distribution for the data. The model allows for the separate modeling of location (mean), scale (variance), and shape (skewness and kurtosis) parameters, offering a detailed characterization of the data. GAMLSS incorporates smooth functions of explanatory variables, which can capture non-linear relationships effectively and provides robust diagnostic tools for model checking and validation, ensuring the reliability of the model's inferences. In this study, the GAMLSS model was used to analyze the behavior of the dependent variable PPDmax in relation to serum cotinine levels, gender, and smoking habits. The flexibility of GAMLSS allowed for the accommodation of the skewed distribution of PPDmax and the inclusion of covariates affecting different aspects of the distribution.

CART is a non-parametric decision tree learning technique that can be used for both classification and regression tasks. The method builds a tree by recursively splitting the data into subsets based on the values of the predictor variables, aiming to create homogenous groups with respect to the response variable. It handles non-linear relationships between predictors and the response variable without requiring transformations or pre-specification of the functional form. The model naturally identifies interactions between variables, as splits are based on the combined effect of predictors. CART provides measures of variable importance, indicating the relative contribution of each predictor to the model. The resulting tree structure is easy to interpret and visualize, showing the decision rules used to split the data. In this study, the CART model was used to analyze the impact of smoking habits on periodontal health, particularly on PPDmean and CALmean. The ability of CART to capture non-linear interactions and provide clear variable importance measures was crucial for understanding the complex relationships in the data.

2 AIM

The study aimed to determine if the maximum probing pocket depth (PPDmax) and the Clinical Attachment Loss (CAL) are associated with serum cotinine levels, age, gender, and smoking habits.

3 Materials and Methods

Data from the National Health and Nutrition Examination Survey was analyzed using GAMLSS and CART models within the R software. The variables considered in this study were maximum probing pocket depth (PPDmax); mean

probing pocket (PPDmean); maximum clinical attachment level (CALmax); mean clinical attachment level (CALmean), serum cotinine levels, age, gender, and smoking habits.

4 Results

The sample consisted of 835 males (62.4%) and 504 females (37.6%), indicating a significant gender imbalance. The mean age was 52.68 years, with a standard deviation of 14.15 years. Periodontal variables included PPDmean, PPDmax, CALmean, and CALmax. Descriptive statistics provided insights into the central tendencies and distributions within the sample.

The clinical attachment loss variables, CALmean and CALmax, exhibited means of 1.99 mm and 4.91 mm, respectively, with significant skewness and kurtosis, indicating a wide range of attachment loss severity within the sample. Cotinine levels, a biomarker for tobacco exposure, showed substantial variation, with a mean of 108.14 ng/mL. The duration of smoking had a mean of 34.90 years, further emphasizing the long-term tobacco exposure in this population.

Comparing the two models GAMLSS models for PPDmax (Table 3 and Table 5), the model with age as a factor presented a lower AIC (3715.331) compared to the model with smoking habits as a variable (AIC = 3744.620), suggesting that age is a more significant predictor for PPDmax than smoking habits when considering model complexity. The model with age also showed lower RMSE (1.543) and MAE (1.190) values compared to the model with smoking habits (RMSE = 1.574, MAE = 1.218), further demonstrating that the model with age provides more accurate predictions. Additionally, the model with age as a predictor had a higher $\mathbf{R^2}$ (0.084) compared to the other model ($\mathbf{R^2}$ = 0.046). The higher $\mathbf{R^2}$ value for the age model indicates that it explains a greater proportion of the variance in PPDmax, highlighting age as a more substantial factor in predicting periodontal probing depth.

In the GAMLSS model for CALmax (Table 13), cotinine levels ($\beta = 3.2 \times 10^{-3}$; p-value $= 1.72 \times 10^{-13}$) suggested a positive relationship between cotinine levels and CALmax, indicating that higher cotinine levels are associated with increased clinical attachment loss. Female gender ($\beta = -0.967$; p-value = ¡ 2×10^{-16}) was associated with lower CALmax compared to males, suggesting gender differences in periodontal health. Age ($\beta = 0.0541$; p-value = ¡ 2×10^{-6}) indicated that CALmax increases with age, implying that older individuals tend to have higher clinical attachment loss.

The analysis of smoking habits ($\beta = 2.6 \times 10^{-3}$; p-value $= 1.48 \times 10^{-7}$) indicated a significant positive relationship between smoking and CALmax. This suggests that smoking contributes to increased clinical attachment loss. However, this was not observed in the PPDmax model, highlighting the need for further investigation into the differential impact of smoking on various periodontal health measures.

The CART model analysis demonstrated that the primary split is based on cotinine levels, underscoring its significance in predicting PPDmean. Gender

and smoking duration were also significant predictors.

The choice of the CART model over the GAMLSS model for analyzing the impact of smoking habits on periodontal health is justified by CART's capacity to handle non-linear relationships and interactions more effectively.

The CART model provides a clearer interpretation of variable importance and reveals critical insights into the influence of cotinine, gender, and smoking duration on PPDmean.

5 Conclusions

The results suggest that cotinine is associated with the severity of periodontal disease, being linked to increased values of PPDmax and CALmax. The GAMLSS models demonstrated a significant relationship between cotinine and both PPDmax and CALmax, which remained robust even after the inclusion of additional predictors such as age, gender, and smoking habits. Furthermore, the CART models indicated that cotinine is the most important factor influencing the severity of periodontal disease compared to age, gender, and smoking habits. These findings can help patients understand the detrimental effects of tobacco use on periodontal health.

Keywords: Serum cotinine levels, Probing pocket depth, Clinical Attachment Level, GAMLSS model, CART model