INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

VALIDATION OF A PREDICTIVE MODEL OF EARLY TOOTH LOSS IN PERIODONTITIS PATIENTS

Trabalho submetido por
Frederico Marcelo Rodrigues Beato
para a obtenção do grau de Mestre em Medicina Dentária

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Trabalho orientado por
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RESUMO

Introdução: A periodontite é uma doença oral altamente prevalente, caracterizada por perda dos tecidos de suporte da dentição e que culmina em perda de dentes, se não for tratada. Pacientes com periodontite e com perda de dentes vêem a sua qualidade de vida grandemente impactada. O contínuo crescimento da medicina dentária de precisão e de modelos preditivos em Periodontologia tem com objetivo melhorar os tratamentos e reduzir custos desnecessários, naquilo que acaba por ser uma abordagem mais informada e personalizada, melhorando a qualidade de vida dos pacientes ao permitir tratamentos mais efetivos e previsíveis. Tais modelos não existem para a população portuguesa e este estudo explora a validação de um modelo de previsão previamente desenvolvido para perda precoce de dentes em pacientes periodontais, definida como extrações após o diagnóstico e antes do tratamento periodontal.

Materiais e métodos: O modelo desenvolvido apresenta a seguinte equação: $\text{Log}[\text{Prob. (Ext.)}/(1\text{-Prob. (Ext.)})] = -7.850 + 0.589 \times \text{TD(Incisivo)} + 0.661 \times \text{PIC}$. A amostra de validação contém pacientes do Departamento de Periodontologia da Clínica Dentária Egas Moniz, avaliados retrospetivamente e recrutados consecutivamente de Junho de 2018 a Março de 2020. O modelo foi aplicado e a sua performance foi avaliada. Este estudo segue as orientações da *Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement*.

Resultados: De uma amostra inicial de 111 pacientes, 99 foram considerados para este estudo. Foram avaliados 2177 dentes, tendo sido realizadas 12 extrações. A discriminação do modelo foi considerada boa, com um valor de AUC de 0.809 (IC 95%: 0.629 - 0.989).

Conclusão: Dentro das limitações deste estudo, o modelo previamente desenvolvido foi validado com uma boa performance. Futuras investigações devem ser desenvolvidas, com amostras de maior dimensão e representativas da população portuguesa. Testar a aplicabilidade e o impacto do uso deste modelo poderá fornecer informações relevantes.

Palavras-chave: periodontite, doença periodontal, perda de dentes, modelos de previsão, medicina de precisão, saúde oral

ABSTRACT

Introduction: Periodontitis is a highly prevalent oral disease characterized by tissue destruction with loss of the dentition's attachment apparatus and ultimately results in tooth loss, if not treated. Patients with periodontitis and tooth loss see their quality of life greatly impacted. The continuing growth of precision dentistry and prediction modeling approaches to Periodontology aims to excel treatments while minimizing unnecessary costs in what ends up being a more informed and tailored approach, improving the patient's quality of life by providing more effective and predicted treatments. Importantly, such models do not exist for the Portuguese population and this study aims to validate a previously developed prediction model for early tooth loss in periodontitis patients, defined as extractions after diagnosis and before periodontal treatment.

Materials and methods: A previously developed model with the following equation: Log[Prob. (Ext.)/(1-Prob. (Ext.))] = -7.850 + 0.589 × TD(Incisive) + 0.661 × CAL (clinical attachment loss) was used. The validation sample involved a retrospective cohort of patients from the Periodontology Department of the Egas Moniz Dental Clinic, and recruited consecutively from June 2018 to March 2020. The validation process was carried out following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement for validation.

Results: From an initial sample of 111 patients, 99 were considered for this study. A total of 2177 teeth were examined, with 12 performed extractions. The discrimination of the model was considered good, with an area under the curve value of 0.809 (95% CI: 0.629 - 0.989).

Conclusion: Within the limitations of this study, the previously developed predictive model for early tooth loss had a good performance and, therefore, shows validity to be used in this population. Further studies with larger samples and of national representativeness shall be developed to validate this predictive model. Testing the applicability and impact of this model may provide relevant information.

Keywords: periodontitis, periodontal disease, tooth loss, predictive models, precision medicine, oral health

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INDEX OF ABBREVIATIONS

AUC – Area Under the Curve

BMI – Body Mass Index

BoP – Bleeding on Probing

CAL – Clinical Attachment Loss

CI – Confidence Interval

DALY – Disability-adjusted life year

EMDC – Egas Moniz Dental Clinic

GBD – Global Burden of Disease

GI – Gingival Index

HALE – Health Adjusted Life Expectancy

NCD – Non-communicable diseases

NHANES - National Health and Nutrition Examination Surveys

NUTS – Nomenclatura de unidades territoriais para fins estatísticos

OR – Odds Ratio

PPD – Pocket Probing Depth

REC – Gingival Recession

ROC – Receiver-Operating Characteristic

SD – Standard Deviation

SPT – Supportive periodontal therapy

TRIPOD – Transparent Reporting of multivariable prediction model for Individual Prognosis Or Diagnosis

YLD – Years Lived with Disability

YLL – Years of Life Lost

I. INTRODUCTION

1. Periodontitis

1.1 Definition, etiology and pathogenesis

Periodontal diseases account for two distinct entities: gingivitis and periodontitis (Hajishengallis & Korostoff, 2017). Gingivitis is characterized by an inflammatory process on the superior compartment of the periodontium, being limited to the gingival component as well as the connective tissue (Hajishengallis & Korostoff, 2017). On the other hand, periodontitis is described as an inflammation affecting both compartments that produces connective tissue breakdown, bone and cementum destruction and loss of the periodontal ligament (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015). Destroying what is the attachment apparatus of the dentition, this progressive disease results in tooth mobility and ultimately in tooth loss (Hajishengallis & Korostoff, 2017).

The mechanisms responsible for the initiation and progression of periodontal diseases are complex and multifactorial, among which we have environmental, behavioural or genetic factors (Meyle & Chapple, 2015). Thus, pathogenic oral biofilm is considered to be necessary but not enough to cause periodontal diseases *per se* (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015; Page & Schroeder, 1976), where these other factors modulate the response of an individual towards that threat. Some of these factors are modifiable, particularly those related to environment and patient behaviour (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015; Page & Schroeder, 1976). Furthermore, there are also site-specific factors (Haffajee & Socransky, 1986).

For periodontitis to develop, a state of clinical health must evolve to gingivitis and further progress to periodontitis (Meyle & Chapple, 2015). In other words, gingivitis always precedes periodontitis. Furthermore, the host-microbe interaction must evolve from a symbiotic relationship to one characterized by dysbiosis (Roberts & Darveau, 2015). Initially, a clinically healthy individual presents a proportionate host response to a health-related biofilm (symbiosis) (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015). In gingivitis, there is an incipient dysbiosis that elicits a proportionate host response leading to a chronic resolution of inflammation (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015). When the biofilm changes to one with significant pathogenicity, the host response is disproportionate and fails to resolve the inflammation (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015). By means of several mechanisms and interactions only briefly discussed here, this hyper-inflammatory state leads to connective tissue destruction and bone resorption in the periodontium (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015).

The journey from health to periodontitis can be described as a process with several phases, with distinct molecular interactions and participants (Hajishengallis & Korostoff, 2017; Meyle & Chapple, 2015; Page & Schroeder, 1976). One of the most popular models to explain this is that of Page & Schroeder described in 1976 comprising 4 stages of disease, where the first three describe the clinical entity that is called gingivitis, with the last stage relating to periodontitis (Page & Schroeder, 1976). With additional information, the 4 scenes of the host-microbe interactions in periodontal diseases was presented in 1997 (Kornman et al., 1997). Today, new research has provided additional information about periodontal disease and its pathogenesis but most of the information of those studies still remain acceptable today (Hajishengallis & Korostoff, 2017). Nevertheless, significant gaps remain about all the mechanisms underlying periodontal disease pathogenesis and the interactions between all of its elements (Hajishengallis & Korostoff, 2017).

Regarding distribution, patterns of progression and changes in clinical attachment, periodontitis shows great variability (Haffajee & Socransky, 1986). Some individuals display extended periodontitis with deep pockets and poor response to treatment, while others have localized areas with greater severity, or even sites with mild lesions (Haffajee & Socransky, 1986). Moreover, periodontally affected sites show active bursts of disease followed by periods of inactivity (Goodson et al., 1982; Haffajee & Socransky, 1986). Remarkably, this pattern of exacerbation/remission periods is characteristic of some viral diseases, and for this reason the involvement of viruses in the pathogenesis of periodontal diseases has been proposed (Slots, 2010, 2015).

Thus, as stated, patients are very different regarding disease susceptibility, distribution and severity. Understanding the reasons behind those differences is mandatory to provide the information that will ultimately guide clinicians to effective preventive and treatment measures. For these reasons, predictability in periodontal diseases has been challenging, which justifies the current efforts in developing prognostic tools to assess risk for tooth loss, periodontitis initiation or progression.

1.2 Risk factors

Several factors have been associated with periodontal diseases, as discussed below. Importantly, a careful analysis of the studies reporting risk factors is very important, as well as a special attention to the methods used and what they mean (Bouchard et al., 2017; Genco & Borgnakke, 2013). A distinction should be made between predisposing factors, risk indicators and true risk factors (Bouchard et al., 2017). This particular terminology should be employed according to the proximity of the factor in the causal chain that leads to disease (Bouchard et al., 2017). This means that a particular factor might not be the true cause of the disease but may contribute decisively (Bouchard et al., 2017).

Oral biofilm

As stated, the presence of an oral biofilm is mandatory for periodontitis to develop and progress (Ebersole et al., 2017). While it is not the sole responsible, the disease will not begin without it. The three-dimensional architecture of oral biofilm houses hundreds of bacteria that interact with each other within an extracellular matrix (Ebersole et al., 2017). This organization, in combination with host factors like saliva, results in a protective commensal microbial community that protects the host from the colonization of pathogenic organisms (Ebersole et al., 2017). Commensalism is characterized by a symbiosis in which an organism benefits from another, while the other is not helped or harmed (Ebersole et al., 2017). However, the host-microbe interactions in the relationship between our bodies and our microbiome has several positive effects, such as the maintenance of a healthy digestive tract and the protection against pathogen colonization, among others (Kilian et al., 2016). Be that as it may, at a given point specific ecological changes are responsible for the emergence of pathogens that finally result in disease (Ebersole et al., 2017).

Several bacteria have been shown to be present in periodontitis patients, namely the members of the "red complex": *treponema denticola, tannerella forsythia* and *porphyromonas gingivalis* (Holt & Ebersole, 2005). In addition, *aggregatibacter actinomycetemcomitans, fusobacterium nucleatum* and *filifactor alocis*, among others, also play a major role in the development of periodontitis (Ebersole et al., 2017). In addition to bacteria, several viruses as well as parasites have been suggested to have a role in the pathogenesis of periodontal diseases (Bao et al., 2020; Contreras et al., 2014; Slots, 2015). It must be noted, however, that infection regarding periodontitis is poly-microbial and current evidence has not been able to show a specific pathogen to be responsible for the entirety of events that result in periodontal inflammation and destruction (Ebersole et al., 2017).

Age

Age as risk factor or risk indicator has been the topic of a certain amount of discussion (Billings et al., 2018). Periodontal diseases are chronic, and its repercussions are in a certain way cumulative (Johnson et al., 1989). Therefore, with increasing age, one would expect to find increased levels of attachment loss, tooth loss and periodontal breakdown, which is true (Billings et al., 2018; Botelho et al., 2019; Machado et al., 2018). However, this destruction should not be regarded as normal and must be assumed as an outcome of a disease but not forgetting the alterations in the innate and immune systems that occur with aging (Ebersole et al., 2016; Johnson et al., 1989). With that said, it is also important to distinguish what is a relatively common pattern of destruction from another that is more severe, particularly in older groups (Billings et al., 2018). With this in mind, one should recognize that simply looking at probing depth and attachment loss does not produce a complete picture of the true impact of periodontitis. There is an overestimation of the prevalence of disease, particularly in older patients, and at the same time an underestimation by not incorporating other significant factors such as systemic and psychosocial ones (Papapanou & Susin, 2017), as discussed in the section "Epidemiology and Impact".

Nevertheless, common patterns of disease are important to understand, and the same level of attachment loss has different meanings regarding risk for progression and tooth loss at different ages (Papapanou & Susin, 2017). In the early stages, clinical attachment loss levels are caused mainly by pocket probing depth. As time progresses, gingival recession becomes the main trend, and the pocket probing depth remains somewhat similar across all age groups which allows for the conclusion that pocket probing depths are not age-related (Billings et al., 2018; Botelho et al., 2019).

Importantly, one should keep in mind that good oral health is part of a healthy aging process and that preventive measures are essential to reduce the cumulative effects of periodontal diseases which have a more significant presence in the older population (Lamster et al., 2016).

Gender

Considering gender, being of male sex is associated with a higher risk for periodontal diseases, assessed by prevalence, extent and severity (Eke et al., 2015; Genco & Borgnakke, 2013; Shiau & Reynolds, 2010). However, this relationship was not found in two Portuguese studies (Botelho et al., 2019; Machado et al., 2018). The prevalence of clinical attachment loss > 3mm was higher for males, but this difference was not found to be statistically significant (Machado et al., 2018). Genetically, there are no known differences between the sexes that might explain this discrepancy and, rather, social and lifestyle differences might be behind the reported dissimilarities in previous studies (Genco & Borgnakke, 2013).

Socio-economic status and education

Current scientific evidence is suggestive of a relationship where lower income levels and lower education are both related to increased prevalence and severity of periodontitis as well as tooth loss (Boillot et al., 2011; Borrell et al., 2006; Borrell & Crawford, 2012; Eke et al., 2015; Nakahori et al., 2019). These are both risk indicators, since there is not a direct interference of income or education in the pathogenesis of periodontal diseases. Rather, increased risk of periodontitis due to lower education is probably related to less access to oral health care, less awareness of it and worse personal and oral hygiene measures that result in increased amounts of plaque (Boillot et al., 2011; Bouchard et al., 2017). Furthermore, in a study on a Portuguese population, education level (middle and elementary compared to higher) were found to be associated with periodontitis (Botelho et al., 2019).

Smoking

Cigarette smoke reportedly contains more than 4000 toxic substances and smoking has long been associated with periodontal diseases (Genco & Borgnakke, 2013). The scientific evidence that supports the adverse effects of cigarette smoking, as well as cigar and pipe, is vast (Albandar et al., 2000; Bergström et al., 2000; Chapple et al., 2017; Genco & Borgnakke, 2013; Nociti et al., 2015). Epidemiologic and clinical studies show a worse periodontal scenario in smokers than in non-smokers, with increased susceptibility for the disease, long-term vertical bone loss, frequency of diseased sites, increased progression rate and higher risk for tooth loss (Baljoon et al., 2005; Bergström et al., 2000; Leite et al., 2019; Nociti et al., 2015). Evidence suggests that this behaviour is also dose-dependent, where heavy smokers exhibit higher levels of periodontal disease and bone loss, compared to light smokers (Baljoon et al., 2005). Moreover, treatment responses are also different, with smokers demonstrating an impaired healing, evidenced in the responses of non-surgical and surgical periodontal therapy, and also regenerative and plastic periodontal surgeries (Nociti et al., 2015). The vasculature effects of nicotine may be behind the paradoxically lower inflammation levels of smokers compared with non-smokers (Genco & Borgnakke, 2013; Nociti et al., 2015).

Two Portuguese studies concluded that both former and current smokers were considered to be risk indicators towards periodontitis and clinical attachment loss (Botelho et al., 2019; Machado et al., 2018). Furthermore, smoking cessation approaches have been shown to benefit periodontitis patients (Leite et al., 2019; Silveira Souto et al., 2019). Importantly, smoking is also associated with several other systemic conditions such as heart disease and cancer, which makes smoking cessation practices even more powerful and significant (Bergström et al., 2000; Chapple et al., 2017). This is both a preventive measure and a treatment complement (Chapple et al., 2017; Leite et al., 2019; Nociti et al., 2015; Silveira Souto et al., 2019).

The importance of smoking as a risk factor for periodontal disease and its dose-dependent response is further recognized by the addition of this parameter to the 2017 classification of periodontal diseases (Tonetti et al., 2018), as discussed in the section “Staging and Grading”.

Diabetes

Diabetes is a chronic disease characterized by a state of hyperglycemia caused by a lack of insulin or an impaired action of that hormone, or both. The global age-standardized prevalence of diabetes was about 9.0% in men and 7.9% in women in 2014 (NCD Risk Factor Collaboration [NCD-RisC], 2016). The number of people with diabetes increased from 108 million in 1980 to 422 million in 2014 (NCD Risk Factor Collaboration [NCD-RisC], 2016).

Diabetes has long been associated with periodontal diseases in a two-way relationship, which means that diabetes may affect periodontal diseases but the inverse is also true, where periodontitis has been shown to interfere with diabetic patients (Genco & Borgnakke, 2013; Graziani et al., 2018; Knight et al., 2016; Kocher et al., 2018).

Prediabetes, the precursor of diabetes, is also associated with periodontal disease, with a higher percentage of deep pockets and a higher number of missing teeth (Genco & Borgnakke, 2013; Lalla et al., 2011). The association between tooth loss and prediabetes was not found in the review by Kocher et al. (2018), but prediabetes was associated with increased prevalence and incidence of periodontal disease. Importantly, hyperglycemia, even among undiagnosed patients regarding diabetes, has been shown to be associated with more severe periodontal conditions (Katz, 2001).

Considering diabetes-diagnosed patients, not only are type 2 diabetics associated with increased bone loss and higher progression of periodontal disease compared to non-diabetic patients, the glycemic control also plays an important role: patients with type 2 diabetes with poor metabolic control, defined as glycated hemoglobin ≥ 7, are at higher risk for periodontal disease progression and tooth loss than diabetics with good metabolic control (Bandyopadhyay et al., 2010; Demmer et al., 2012; Genco & Borgnakke, 2013;

Kocher et al., 2018). In a Portuguese study, Diabetes Mellitus was found to be a risk factor for periodontitis with an OR=1.52 (95% CI: 1.06 – 2.21) (Botelho et al., 2019).

The effect of periodontal diseases on diabetes is also important. Even in non-diabetic patients, periodontitis has been shown to be associated with increased levels of glycated hemoglobin, impaired fasting glucose and a higher prevalence of pre-diabetes, compared to healthy individuals (Graziani et al., 2018). Moreover, severe periodontitis is associated with a higher risk of developing diabetes (Graziani et al., 2018). As for diagnosed type 2 diabetics, periodontitis is significantly related to the prevalence and severity of diabetes-related complications (Graziani et al., 2018).

In spite of the 2015 Cochrane systematic review, and the 2016 overview of systematic reviews on the subject, which concluded that the evidence of the beneficial effects of periodontal treatment on glycemic control of patients with diabetes was of low quality, more recent clinical trials have suggested otherwise (Faggion et al., 2016; Simpson et al., 2015). In regard to periodontal disease treatment and its effects on diabetes, intensive treatment of periodontitis and regular oral health care have been suggested to be important in controlling glycemia levels of type 2 diabetics as well as reducing diabetes-related complications (D'Aiuto et al., 2018; Mauri-Obradors et al., 2018). Notably, several studies have stated that even minor reductions on glycated hemoglobin (HbA1c) levels represent significant decreases in diabetes-related deaths and complications (Genco & Borgnakke, 2013).

Therefore, practicing Periodontology should involve preventive measures for non-diabetic patients in an attempt to halt the initiation of disease and also efforts to keep diabetic patients with their glycemic levels controlled (Genco & Borgnakke, 2013; Kocher et al., 2018). On the other hand, treatment of diabetic patients should involve oral health care (D'Aiuto et al., 2018). In other words, the dental clinician should strive for control of periodontal disease as well as diabetes (Lalla et al., 2015). As seen for other risk factors, this benefits the patient at both the oral and systemic levels (Genco & Borgnakke, 2013; Kocher et al., 2018).

Diabetes thresholds measured by Hb1Ac have also been incorporated into the new classification of periodontal diseases (Tonetti et al., 2018), as discussed in the section "Staging and Grading".

Obesity and Metabolic Syndrome

Data from the World Health Organization states that in 2016 39% of adults were classified as overweight (BMI 25 - 29.9), while 13% were obese (BMI ≥ 30) (World Health Organization, 2020). Similarly, a Portuguese study with a sample from the same Clinic as this study found a prevalence of 39.3% of overweight people, while 19.5% of the sample was obese (Machado et al., 2018).

Obesity is associated with periodontal diseases as well as with several other chronic diseases and infections mainly because of its effect on chronic systemic inflammation (Falagas & Kompoti, 2006; Genco & Borgnakke, 2013).

Being obese is associated with greater prevalence and severity of periodontal diseases (Genco & Borgnakke, 2013; Keller et al., 2015; Suvan et al., 2011). Both obesity and overweight were considered to be risk factors for periodontitis with a combined OR=2.13 (95% CI: 1.40 - 3.26) (Suvan et al., 2011). Furthermore, attachment loss progression seems to be associated with obesity as well, although this connection was interestingly evident only for obese females and the same was not true for males or overweight females (Gaio et al., 2016). In addition to prevalence, severity and progression, a systematic review also found weight gain to be associated with incidence of periodontitis, albeit with limited evidence (Nascimento et al., 2015). In a Portuguese study, however, BMI was not concluded to be significantly associated with clinical attachment loss ≥ 3mm and therefore was not considered as a risk factor (Machado et al., 2018). With this in mind, some limitations of using BMI as a body fat measure should be taken into account (Meeuwsen et al., 2010).

Metabolic syndrome is characterized by abnormal body fat distribution, insulin resistance, atherogenic dyslipidemia, elevated blood pressure, a proinflammatory state and a prothrombotic state (Alberti et al., 2006). The ultimate implications of this syndrome are its effects on cardiovascular diseases and diabetes (Alberti et al., 2006). As is the case for diabetes, patients with metabolic syndrome are associated with periodontal diseases, as concluded by a meta-analysis revealing an OR=2.09 (95% CI: 1.28 - 3.44) (Nibali et al., 2013). The management of patients with this syndrome should involve proper oral healthcare and efforts in order to modify risk factors, promoting a healthy diet and physical activity (Gomes-Filho et al., 2016; Knight et al., 2016; Nibali et al., 2013).

Stress

Stress and psychosocial disorders have been associated with periodontal diseases (Botelho et al., 2018; Genco et al., 1999; Knight et al., 2016; Peruzzo et al., 2007; Warren et al., 2014). This link may also be attributable, to a certain extent but not entirely, to the behavioral changes that occur with stress, such as smoking, alcohol consumption, altered diet, poor oral hygiene measures and lack of commitment to support appointments (Aleksejuniené et al., 2002; Knight et al., 2016; Warren et al., 2014).

Furthermore, the ability of a particular individual to cope with those situations also influences the severity of periodontitis as well as its treatment outcomes. Proper coping mechanisms can even nullify the effects of stressful events and improve periodontitis severity and periodontal therapy, suggesting a possible positive impact of social and personal support (Genco et al., 1999; Kiecolt-Glaser et al., 1995; Knight et al., 2016; Wimmer et al., 2005). On the other hand, it is of general consensus that further good-quality longitudinal studies must be made with standardized measurements in order to provide for a more complete understanding of this relationship (Genco & Borgnakke, 2013; Knight et al., 2016; Warren et al., 2014).

Diet

Current evidence suggests that periodontal diseases are associated with diet (Chapple et al., 2017; Dommisch et al., 2018; Hujoel & Lingström, 2017). Lack of macronutrients, mainly responsible for energy supply, and micronutrients, that function as cofactors necessary for enzymes to function, as well as transport, are harmful for periodontal health (Dommisch et al., 2018). This depletion can have several causes, such as systemic diseases, drugs, lifestyle, malabsorption and diarrhea, loss or an increased requirement (Dommisch et al., 2018).

Specifically, micronutrient deficiencies have been shown to be associated with periodontitis (Chapple et al., 2017). Lower levels of vitamin C intake, vitamin C serum concentrations, serum magnesium levels, serum calcium levels, anti-oxidants, docohexanoic acids and serum vitamin B12 levels have been shown to be associated with increased severity of periodontitis (Chapple et al., 2017; Ebersole et al., 2018; Zong et al., 2016). Supplementation of vitamin D and calcium has been shown to improve periodontal health and reduce tooth loss (Krall et al., 2001) as Vitamin D deficiency has been associated with periodontitis (Botelho, Machado, Proença, Delgado, et al., 2020; Machado, Lobo, Proença, Mendes, et al., 2020). However, the micronutrients levels that exist on a certain individual differ according to several factors, and specific guidelines for treatment and preventive measures are yet to be defined (Dommisch et al., 2018). As for macronutrient intake, carbohydrates are associated with increased risk of inflammation (Chapple et al., 2017; Hujoel & Lingström, 2017; Woelber et al., 2017).

Adding to this, periodontitis and tooth loss are correlated with nutrient poor diets that in turn will affect several other diseases, such as cardiovascular ones (Mendonça et al., 2019). This suggests that the relationship between periodontal diseases and diet is also bi-directional. With the lack of guidelines regarding diet and periodontal diseases, one should follow the generally healthiest and most sustainable diet possible, while focusing on the health of an individual as well as the planet's (Springmann et al., 2018; Willett et al., 2019).

Hormonal changes

Changes in hormone levels regarding the effects on periodontal diseases arise mainly in puberty, pregnancy and menopause (Knight et al., 2016). Increased concentrations of sex hormones during puberty, estrogen, progesterone and glucocorticoids during pregnancy, and the loss of ovarian activity at menopause all induce several changes on the periodontium (Knight et al., 2016).

The possible increased probing depths are due to coronal enlargement and do not necessarily indicate loss of attachment, which is usually not present in these circumstances (Cohen et al., 1971; Knight et al., 2016). Furthermore, maternal periodontitis has been found to double the risk of pre-term birth (Manrique-Corredor et al., 2019). Given the keratinization effects of estrogen, the decrease in secretion of this hormone in the menopausal period can be represented clinically by desquamation of the marginal gingival epithelium (Knight et al., 2016). Although there are reductions in bone density caused by declines in estrogen during menopause, inducing osteoporosis, its repercussions on clinical attachment loss are still not clear (Genco & Borgnakke, 2013; Knight et al., 2016).

Genetics and epigenetics

Currently available information is conclusive of a genetic role on periodontal disease susceptibility (Morelli et al., 2020; Nibali et al., 2017; Zhang et al., 2020). Importantly, subsequent environmental, behavioral and lifestyle factors further act upon this susceptibility to determine the initiation and progression of periodontal disease (Chapple et al., 2017). Furthermore, there are some studies trying to associate common genetic risk factors of periodontal diseases and other chronic illnesses (Genco & Borgnakke, 2013). Nonetheless, current knowledge does not allow specific approaches for specific gene variants, and genes in themselves do not explain the existing variability in periodontal diseases (Morelli et al., 2020; Schaefer, 2018). Rather, complex interactions between genes and the environment account for the distinct susceptibility of different individuals and there is not sufficient information to provide for specialized treatments (Morelli et al., 2020; Schaefer, 2018).

Additionally, epigenetic mechanisms responsible for phenotypic plasticity allow biologic systems to interfere with transcription and hence to adapt to environmental stimuli, by silencing or activating certain genes (Barros et al., 2018; Feinberg, 2007). Once there is a more complete understanding of the effects of these environmental factors on the epigenetics of periodontal diseases, such as infection and inflammation products, the formulation of additional treatment and preventive measures will become easier (Barros et al., 2018, 2020).

In conclusion, increasing knowledge regarding the role of the genome and epigenome on periodontal disease pathogenesis, along with proportionate diagnostic tools, will presumably generate more personalized approaches to prevention and treatment (Barros et al., 2020; Bartold, 2018; Morelli et al., 2020; Zhang et al., 2020).

For detailed descriptions on the role of risk factors on periodontal diseases the reader is referred to key reviews (Chapple et al., 2017; Genco & Borgnakke, 2013; Knight et al., 2016; Reynolds, 2014).

1.3 Diagnosis and classification

Assessment of periodontal status can be made according to clinical and radiographic observations, with additional genetic and microbiologic evaluation of the patient profile as well as their microbiome (Lang & Bartold, 2018). Clinical measures involve pocket probing depth, gingival recession, clinical attachment loss, tooth mobility, furcation involvement, bleeding on probing, and assessment of periodontal index and gingival index. With the additional information taken from the radiographic assessment as well as from the patient anamnesis, with inquiries related to patient lifestyle and environment risk factors, a proper diagnosis is made (Tonetti et al., 2018). Today, this diagnosis is preformed according to the current classification system (Tonetti et al., 2018).

Staging and Grading

Periodontitis classification has recently been updated in the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions, incorporating a Staging and Grading system, similar to what is seen in the oncology field (Caton et al., 2018; Tonetti et al., 2018).

First, a patient must be defined as a periodontitis case, then the specific form of periodontitis should be identified (periodontitis, necrotizing periodontitis or periodontitis as a direct manifestation of systemic diseases), and finally the disease should be staged and graded in accordance to the classification system (Tonetti et al., 2018).

The staging classification is divided into four categories (I, II, III and IV) and enables the clinicians to describe the severity, extent and complexity of treatment. Therefore, it is possible to assess the extent of periodontitis-caused destruction as well as the complexity in achieving long-term function and esthetics. The severity is assessed by the interdental clinical attachment loss, which is the initial stage determinant. The classification system acknowledges that there are cases where quality radiographs are all that is needed to establish the stage, and therefore radiographic bone loss may be the stage determinant. In addition, several modifying factors that increase the complexity of the case may shift the initial stage to a higher one (e.g. furcation involvement, bite collapse, etc). However, if a particular stage shifting complexity factor is eliminated through proper treatment, the specific stage should not change because of the importance of the initial stage for maintenance phase management. In addition, the extent of the disease should be specified: localized if it affects less than 30% of the dentition, generalized if it affects 30% or more of the dentition, or presented in a molar/incisor pattern (Tonetti et al., 2018).

On the other hand, the grading degree allows for the estimation of risk of future progression but also the responsiveness of a particular case to the standard treatment. It is divided into three grades (A, B and C). The primary criteria to define the degree can be measured directly or indirectly. Direct evidence of progression is based on longitudinal observations such as previous radiographic images. Indirect evidence of progression is based on the relation between the current bone loss at the worst affected tooth and the patients age. The resulting grade can be modified by risk factors. By adding systemic indicators to the process, the potential health impact of periodontitis is also taken into consideration as well as the impact of life habits in the prognosis of this multidimensional disease (Tonetti et al., 2018). Currently, the only systemic indicators are the smoking status and the levels of glycated hemoglobin (HbA1c), reflecting glycemic control of the patient. Importantly, the classification system is designed to have the ability to be updated so that new discoveries can be imbedded in the system in order to constantly improve it (Tonetti et al., 2018).

The value of this classification system as a prognostic tool is discussed in the section "Personalized periodontal medicine".

1.4 Epidemiology and impact

Assessing the prevalence and characteristics of periodontal diseases globally shows a very high variability which makes it difficult to draw any precise conclusions. This may be due to the fact that different studies often employ different methodologies, different case definitions and may not report several characteristics that could provide additional information about periodontal diseases (Demmer & Papapanou, 2010; Holtfreter et al., 2015). Some epidemiologic studies have to be interpreted carefully due to bias related to partial reporting protocols, different probes, case definitions, sample selection, and examiner variability (Kingman et al., 2008; Kingman & Albandar, 2002).

Moreover, some studies mention that the prevalence of periodontitis is underestimated (Albandar, 2011; Eke et al., 2010), particularly regarding the National Health and Nutrition Examination Surveys (NHANES) in the United States. However, other authors say that periodontitis is overestimated and that epidemiologic studies must take into account other dimensions of the disease, such as psychosocial and systemic ones and that the impact of the disease on esthetics and function should be addressed (Papapanou & Susin, 2017).

For these reasons, there have been efforts aimed at designing guidelines and reporting standards in order to improve the reporting quality so that it can be easier to compare the numbers between different studies of different population groups (Holtfreter et al., 2015; Vandenbroucke et al., 2007). The ultimate goal is to provide a better understanding of periodontal diseases to reduce its global burden.

The prevalence reported by NHANES was 45.9% in the period of 2009-2012 in a sample comprising 141 million adults 30 years or older (Eke et al., 2015). Based on CDC/AAP case definitions, 8.9% had severe periodontitis while the remaining 37.1% had other forms of less severe periodontitis. A clinical attachment loss ≥ 3 mm was found in about 88% of the population and 42% showed pocket probing depth ≥ 4 mm at one or more sites. Regarding ethnic and racial groups, Hispanics and non-Hispanic blacks showed the highest prevalence, while Non-Hispanic whites had the lowest. Smoking, lower socioeconomic status and lower education was associated with a higher prevalence of periodontitis (Eke et al., 2015).

In a German survey, and also according to CDC/AAP case definitions, 17.4% of adults were found to have severe periodontitis, and 53.5% had moderate forms of periodontitis (Holtfreter et al., 2010). Regarding seniors (65 – 74 ears), the prevalence of severe and moderate forms of periodontitis was 41.9% and 45.5%, respectively. Clinical attachment loss ≥ 3 mm was found in 95.0% of adults with 68.7% of affected teeth. 40.3% of the subjects showed a clinical attachment loss ≥ to 6 mm with 11.7% of affected teeth. Pocket probing depth ≥ 4 mm was measured in 76.9% of the population, affecting 34.0% of all teeth. This study also noted differences in the distribution among different regions of the country (Holtfreter et al., 2010).

In a Swedish survey done in 2003 the clinical attachment loss was not recorded, and the alveolar bone level was used to measure periodontal destruction (Hugoson et al., 2008). The level was 65.6% in the 20-years age group and decreased successively to 52.0% in the 80-years age group. The percentage of sites with pocket probing depth of 4-5 mm ranged from 0.9% in the 20-years age group to a maximum of 14.2% in 60-years age group. This study used a different classification system and divided patients into 5 groups, where 44% were reported healthy with normal bone height and minimal bleeding, 18% showed gingivitis with no bone loss, 28% had alveolar bone loss not exceeding 1/3 of the root representing a mild form of periodontitis, the loss was between 1/3 and 2/3 of the root in around 7% of the population and appeared as a more advanced disease exceeding 2/3 of the root in 4% of all participants (Hugoson et al., 2008).

In Portugal, the study by Botelho & Machado et al. (2019) estimated a prevalence of 59.9% of mild periodontitis, 22.2% of moderate periodontitis and 24.0% of the most severe disease presentation. The mean pocket probing depth was 1.9 mm while the mean clinical attachment loss was 2.7 mm. 24.1% of the population exhibited a clinical attachment loss ≥ 4 mm and 8.0% a pocket probing depth ≥ 4 mm. Importantly, 81.9% of the sample reported not knowing what periodontal disease was (Botelho et al., 2019).

The Global Burden of Disease 2017 study has identified oral disorders as the most prevalent conditions, globally, with a total of 3.47 billion cases (95% UI: 3.27 - 3.68) (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; GBD 2017 Oral Disorders Collaborators, 2020). Particularly, severe periodontitis accounted for 796 million cases (95% UI: 671 - 930) with a total prevalence of 9.8% (95% UI: 8.2% - 11.4%), whereas edentulism and severe tooth loss amounted to a total of 267 million cases (95% UI: 235 - 300) with a prevalence of 3.3% (95% UI: 2.9% - 3.7%) (GBD 2017 Oral Disorders Collaborators, 2020).

Even though, between 1990 and 2017, the age-standardized prevalence of oral conditions and severe tooth loss decreased by 5.5% (95% UI: 4.9% - 6.0%) and 10.4% (95% UI: 9.6% - 11.2%), respectively, this trend was not observed regarding periodontal diseases: the age-standardized prevalence increased by 5.8% in the same period (95% UI: 4.9% - 6.6%) (GBD 2017 Oral Disorders Collaborators, 2020).

In terms of incidence, oral disorders were the third main conditions with a total of 3.60 billion new cases in 2017 (95% UI: 3.23 - 3.99) (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; GBD 2017 Oral Disorders Collaborators, 2020). Particularly, severe periodontitis accounted for 71 million new cases (95% UI: 62 - 81), whereas edentulism and severe tooth loss amounted to a total of 18 million new cases (95% UI: 16 - 21) (GBD 2017 Oral Disorders Collaborators, 2020).

Similarly, between 1990 and 2017, the trend in prevalence of oral conditions and severe tooth loss was also observed in incidence values, with a decrease of 0.3% (95% UI, -0.6% - 1.1%) and 8.0% (95% UI, 7.3% - 8.6%), respectively (GBD 2017 Oral Disorders Collaborators, 2020). Again, the incidence rate for periodontal diseases provides a contrast, with an increase of 4.3% in the same period (95% UI, 3.3% - 5.3%) (GBD 2017 Oral Disorders Collaborators, 2020).

Impact

One must recognize the importance of complementing prevalence and incidence data of a particular disease with its global burden, patient perception of illness, and quality of life to get a clearer picture of the true impact of a disease on people's lives. Attention should be given not only to the global burden of periodontal diseases but also to the global burden of tooth loss (Petersen & Ogawa, 2012).

Periodontitis has a major impact not only on the oral health of the population but also on their systemic health and quality of life, accompanied by a significant psychologic, social, and economic impact (Buset et al., 2016; Listl et al., 2015). Tooth mobility, tooth loss, gingival recession and the possible consequent hypersensitivity, ultimately leads to a decrease in the masticatory function, and affects the esthetic perception of the patients (Buset et al., 2016). The economic impact amounted to a global cost of 54 billion US dollars in 2010 simply due to productivity losses (Listl et al., 2015). Its impact on oral health-related quality of life has also been established, with a higher impact with greater periodontitis severity or extent (Buset et al., 2016; Machado, Botelho, Proença, Alves, et al., 2020).

Important concepts regarding the global burden of a disease and its impact are Year of Life Lost (YLL), Year Lived with Disability (YLD), and Disability-Adjusted Life Year (DALY), which is the sum of YLL and YLD (GBD 2017 DALYs and HALE Collaborators, 2018).

Year of Life Lost takes into account the years that are lost due to premature death caused by a certain condition, whereas Year Lived with Disability is related to the number of years where people have to live with a particular condition or its consequences (GBD 2017 DALYs and HALE Collaborators, 2018). The Disability-Adjusted Life Year, then, accounts for the number of "healthy" years that are lost (GBD 2017 DALYs and HALE Collaborators, 2018).

Premature death would be an extreme event regarding periodontal diseases, and therefore Disability-Adjusted Life Year (DALY) takes into account YLD only (GBD 2017 Oral Disorders Collaborators, 2020).

Oral conditions were responsible for 18.3 million Years Lived with Disability, with 5.2 million (95% UI: 2.0 - 10.7) and 7.3 million (95% UI: 4.9 - 10.4) Years Lived with Disability being caused by severe periodontitis and total tooth loss, respectively (GBD 2017 Oral Disorders Collaborators, 2020). Severe periodontitis was accountable for 63.5 Years Lived with Disability per 100.000 population (95% UI: 25.0 - 130.3), while total tooth loss was responsible for 91.7 Years Lived with Disability per 100.000 population (95% UI: 61.3 - 129.9) (GBD 2017 Oral Disorders Collaborators, 2020).

Between the period of 1990 to 2017, the Years Lived with Disability per 100.000 population decreased by 4.0% (95% UI, 2.4% - 5.7%) and 10.1% (95% UI, 9.3% - 10.9%), respectively, for oral conditions and total tooth loss (GBD 2017 Oral Disorders Collaborators, 2020). However, the rate increased by 6.0% (95% UI, 5.2% - 6.8%) for severe periodontitis (GBD 2017 Oral Disorders Collaborators, 2020).

Furthermore, periodontitis has been shown to influence and impact several other systemic diseases and conditions, such as Diabetes Mellitus (Graziani et al., 2018; Sanz et al., 2018), cardiovascular diseases and hypertension (Czesnikiewicz-Guzik et al., 2019; Machado, Aguilera, et al., 2020; Muñoz Aguilera et al., 2020; Tonetti & Van Dyke, 2013), rheumatoid arthritis (Hussain et al., 2020) immunity (Machado, Botelho, Lopes, et al., 2020) and stress (Botelho et al., 2018).

Importantly, periodontitis treatment has been shown to increase the oral health-related quality of life, with significant results remaining stable after 3 months of treatment (Botelho, Machado, Proença, Bellini, et al., 2020). Particularly, non-surgical periodontal treatment appears to have a greater beneficial impact than surgical approaches (Shanbhag et al., 2012).

Thus, as seen, contrary to oral conditions in general, periodontitis prevalence, incidence and its global burden have been increasing (GBD 2017 Oral Disorders Collaborators, 2020). Additionally, periodontal health and disease is distributed in a variable way and impact people around the world in different manners (Jin et al., 2011). The reasons behind those inequalities are several, such as presence or absence of risk factors, social and economic determinants, as well as perception and awareness of disease (Jin et al., 2011), again justifying the attention attributed to prognostic and risk assessment tools in order to increase disease predictability.

1.5 Prevention

Given the high prevalence and high burden of periodontal diseases, prevention efforts are of extreme importance (Tonetti, Chapple, et al., 2015). The importance of oral biofilm for the pathogenesis of gingivitis and periodontitis, as well as the role of several risk factors, undoubtably means that the patients must become increasingly responsible for their oral health care with proper clinician's advice focusing on education and motivation towards behaviour change (Tonetti, Chapple, et al., 2015). Therefore, depending on the lifestyle factors and the clinical findings, the dental clinician should tailor the preventive and treatment approaches to that specific patient (Tonetti, Chapple, et al., 2015).

Since gingivitis always precedes periodontitis, treatment of gingival inflammation becomes a key prevention target (Chapple et al., 2015). This means that public health actions and oral health care products should underscore the importance of treating gingival bleeding by appropriate professionals (Tonetti, Chapple, et al., 2015). The need for biofilm to accumulate and progress to a dysbiosis state was already discussed as the key to periodontitis initiation and progression. Therefore, mechanical control of the oral plaque, by professionals and by patients in their daily hygiene routine is of paramount importance (Chapple et al., 2015; Jepsen et al., 2017; Tonetti, Chapple, et al., 2015). Removing plaque as a preventive measure made by the professional should always be accompanied by the specific education of the patient in order to produce long-lasting health results (Jepsen et al., 2017; Tonetti, Chapple, et al., 2015). Specific recommendations for primary prevention of periodontitis by effective plaque control and management of gingivitis were made following the 2014 workshop of the European Federation of Periodontology and can be summarized as follows (Chapple et al., 2015; Tonetti, Chapple, et al., 2015; Tonetti, Eickholz, et al., 2015):

- Professional oral health instructions should be provided, and posterior reinforcement may be beneficial;
- Manual and power tooth brushing is recommended, and re-chargeable power toothbrushes may be considered when increased plaque control is required;
- Interdental cleaning should be made, preferably using interdental brushes and its usage should be taught to the patients. When the use of these devices is not appropriate and would traumatize gingival tissues, other devices may be discussed. However, regardless of the device chosen, clinicians should make sure that patients are well educated about the best way to use them;
- Where improvements in plaque control are required and in patients with gingivitis, additional chemical plaque control offers advantages, particularly using mouth-rinses.

Managing the modifiable risk factors is also very important. This should produce efforts aimed at achieving: smoking cessation, better glycemic control in diabetics, healthy diet and regular physical activity targeting weight loss in obese patients and stress-reduction measures (Genco & Borgnakke, 2013; Knight et al., 2016). However, patients need to modify their behaviour in order to modify the present risk factors, which gives rise to the need of addressing techniques and solutions to encourage patients towards behaviour change (Jepsen et al., 2017; Tonetti, Eickholz, et al., 2015). This was also addressed in the already mentioned workshop and provided the following recommendations (Tonetti, Eickholz, et al., 2015):

- Clinicians should incorporate behaviour change techniques in their individual oral hygiene program and this can be based on the GPS approach which means Goal setting, Planning and Self-monitoring;
- This change in behaviour is related to the patient's perceptions of the harmful consequences, his own susceptibility and benefits of change;
- Additionally, brief interventions of up to 5 minutes of conversation with the patient should be applied regarding tobacco use and are efficient at increasing the smoking cessation rate;
- Regarding smoking habits, it is recommended to adopt the AAR (Ask, Advise, Refer) approach: Ask if the patient smokes and Advise him to quit, while presenting the effects of smoking on oral health as well as the benefits of stopping the tobacco use and the methods available to do that. Finally, the patient can be Referred to any service that specializes in smoking cessation.

With the goal of improving resource distribution, minimize unnecessary side-effects and limit under-treatment as well as over-treatment, there is a need to implement tools that are designed to assess the risk for periodontitis progression and tooth loss to prevent any of those outcomes (Tonetti, Eickholz, et al., 2015).

Secondary prevention of periodontitis, that is, after the implementation of a diagnosis and the proper treatment, will be discussed in the section "Prognosis" as it refers to supportive periodontal treatment.

1.6 Treatment

The ultimate goal of periodontal treatment is the conservation of self-esteem and improvement of an individual's quality of life, that are achieved by avoiding disease progression that ends up causing tooth loss (Tonetti et al., 2017). By controlling gingivitis and periodontitis, the retention of a functional detention for a lifetime becomes feasible (Tonetti et al., 2017).

Traditional periodontal treatment begins with a hygienic phase that comprises risk factor assessment and management, with promotion of healthy lifestyles and oral hygiene instructions, followed by non-surgical periodontal therapy aimed at plaque removal which, if necessary, evolves to a second phase of surgical periodontal treatment of diseased pockets (Tonetti et al., 2017). A combination of resective, conservative or regenerative surgical interventions may be accomplished, depending on the individual, tooth and site-specific factors (Tonetti et al., 2017). In more severe cases, functional and esthetic problems may provide the need for further rehabilitation of the masticatory organ that has suffered from tooth loss and/or tooth migration with a functional and esthetic compromise (Tonetti et al., 2017). Appropriate follow-up programs personalized to the specific needs of an individual are elaborated and should be maintained for the rest of the patient's life (Tonetti et al., 2017). This is mandatory for the long-term maintenance of the dentition to prevent recurrence of disease and tooth loss (Tonetti et al., 2017).

The definition of periodontal health in an anatomically reduced periodontium is crucial in order to establish end-points of periodontal therapy that are compatible with long-term maintenance of clinical attachment and existing teeth (Lang & Bartold, 2018). Periodontal disease stability should be attained after successful periodontal treatment with proper risk factor management, including smoking cessation and well-controlled glycemic levels in diabetic patients (Lang & Bartold, 2018). This means minimal signs of inflammation or even absence of sites with bleeding on probing with significant reductions in probing depths and improvements in attachment levels (Lang & Bartold, 2018). In patients with long-standing disease or with uncontrollable or unpreventable risk factors, a state of minimal inflammation with low disease activity may be an acceptable target as long as it meets a proper state of remission with improvements in periodontal conditions compared to the baseline situation (Lang & Bartold, 2018). Importantly, probing depth, attachment levels and bone height should not be used alone to classify health or disease since these measures are not related to future sites with recurrence (Lang & Bartold, 2018). They must be accompanied by clear signs of inflammation (bleeding on probing) and risk factors (Lang & Bartold, 2018). Specifically, bleeding on probing has a high negative predictive value and a low positive predictive value, which means that the absence of bleeding on probing is the most clear sign of absence of inflammation and thus should be considered a good treatment target (Lang & Bartold, 2018). Additionally, patient-related outcomes that address their perceptions and the impact of oral health on the quality of life of periodontitis patients should also be taken into consideration when talking about end-points of periodontal treatment (Loos &

Needleman, 2020). As already mentioned, non-surgical periodontal therapy has been shown to have a positive impact on the oral health-related quality of life of periodontitis patients (Botelho, Machado, Proença, Bellini, et al., 2020; Shanbhag et al., 2012). In summary, absence of clinical inflammation (bleeding on probing ≤ 15%), shallow pockets (pocket probing depth ≤ 4mm) and absence of suppuration should ideally be accomplished at the end of treatment for all periodontitis patients (Sanz et al., 2015).

1.7 Prognosis

Secondary prevention of periodontitis in the form of supportive periodontal therapy (SPT) after the treatment phase is a key for long-term retention of the dentition and therefore is crucial to achieve a good prognosis (Tonetti et al., 2017). Professional mechanical plaque removal, assessment of oral hygiene habits and reinforcement of instructions coupled with, when necessary, appropriate advice towards the management of existing risk factors (smoking, diabetes, diet) should be routinely performed in every appointment of SPT (Sanz et al., 2015). A full periodontal screening process to identify pockets with recurring disease is also mandatory (Sanz et al., 2015). Current scientific evidence shows tooth loss rates that range from 0.15 to 0.08 per year, which means that a tooth will be lost in a time period of 7-14 years (Sanz et al., 2015). Furthermore, the majority of patients preserve the entire dentition while a particular minority experience most of the tooth loss (Sanz et al., 2015). This long-term retention of teeth is expected to be optimized with the personalization of the SPT appointments frequency to the specific risk profile of a particular patient. Typically, appointments are made in a 3, 4 or 6-month interval (Sanz et al., 2015).

Ideally, other conditions associated with periodontal diseases and the adverse effects of therapy and mechanical plaque control should also be taken into consideration. These include gingival recession, dentinal hypersensitivity and halitosis (Sanz et al., 2015).

2. Personalized periodontal medicine

2.1 Precision dentistry

Precision dentistry refers to an approach that stratifies similar patients into phenotypic groups based on individual characteristics with the goal of giving clinicians the tools to improve treatment planning as well as the patient's response to therapy (Beck et al., 2020).

This is an approach that has been used in medicine, in areas such as oncology (Shariat et al., 2008) and cardiology (Damen et al., 2016), but is somewhat new in the oral health care field (Beck et al., 2020).

Instead of trying to provide a treatment that fits every patient, which is impractical given the different characteristics, risk classes and responses to treatment of different patients, precision dentistry aims to categorize patients into distinct and homogenous groups regarding the disease at hand, and then structure a treatment regime that better suits each subgroup (Bartold, 2017; Beck et al., 2020). It should also be noted that this does not mean a personalized approach in which each patient receives a unique and individualized treatment but rather a treatment that better suits a particular group of patients that are similar considering the factors studied.

This approach to care has not only a clinical advantage but also an economic one, with an increase in efficiency in the treatments by preventing the wrong or unnecessary options to be applied into a specific patient (Bartold, 2017). Therefore, the allocation of resources can be optimized while everyone benefits.

To spread the patients into distinct categories or subgroups there must be a method or a model that takes into consideration all the known risk factors of a disease and distributes them in such way that the patients in each subgroup are as similar as possible (Beck et al., 2020). These subgroups can be created by a team of experts in a given field, as is the case of the new classification system for periodontal diseases with its four stages and three grades (Tonetti et al., 2018). This is an example of a supervised learning system, where the model is created in light of the current knowledge about the characteristics, risk factors, treatment options and responses to those treatments (Beck et al., 2020). The framework of the new classification system should behave as a predictive model in itself, where a patient in a higher stage should be expected to lose more teeth (Beck et al., 2020).

On the other hand, there is the unsupervised learning system, which makes use of a database that characterizes a certain sample with human chosen metrics, taking into consideration the current knowledge of the disease (Beck et al., 2020). However, the classes/stages/categories are produced exclusively by computers and so it is different from a supervised learning system because it allows the data to speak for itself when producing risk categories (Beck et al., 2020). In a review of these two systems, the model produced in the World Workshop - a supervised learning system with manmade categories - was compared to an unsupervised learning system, the Periodontal Profile Class (Beck et al., 2020). The latter produced 3 new categories that were not included in the World Workshop Model. Even though both models showed an increase in tooth loss when the stage was higher, the Periodontal Profile Class categories were more strongly correlated with 10-year tooth loss and attachment loss progression (Beck et al., 2020).

2.2 Predictive models in Periodontology

Besides the two models discussed above, several others have been developed to assess the risk of periodontal disease incidence and progression, as well as tooth loss, both in the short-term and in the long-term, as discussed below (Avila et al., 2009; Du et al., 2018; Faggion et al., 2007; Martinez-Canut et al., 2018; Schwendicke et al., 2018). In addition, approaches aimed at predicting adherence to initial periodontal treatment have also been developed (Machado, Botelho, Proença, & Mendes, 2020). Given the fact that, as stated, periodontal diseases show great variability regarding disease prevalence, extent and severity, these models provide enhanced information about disease history patterns and therefore allows better allocation of resources and a more favorable prognosis (Beck et al., 2020; Du et al., 2018). Furthermore, prediction model accuracy has been shown to be superior to the subjective predictions of clinicians (Kattan et al., 2013).

Du et al. (2018) produced a recent systematic review on existing models regarding incidence and progression of periodontitis, with seven included studies. Three risk assessment tools and twelve prediction models were included, with four models predicting periodontitis incidence and the remaining eight predicting disease progression. Common predictors included in the models were age, smoking and diabetes, as well as bleeding on probing, clinical attachment loss and tooth loss (considered as periodontitis progression). Importantly, the majority of the studies selected predictors based on literature and clinical knowledge, with only two models producing a multivariable analysis to such end. The included studies were characterized by high heterogeneity, with different methods used and a poor reporting approach. Differences in outcome definitions and classifications, as well as in setting, sample size, predictor selection, model development and performance metrics precluded any precise comparison between the studies.

From the included models in the aforementioned systematic review (Du et al., 2018), the one with the highest performance was developed by Martinez-Canut et al. (2018) and predicted the risk for tooth loss (considered in the systematic review as periodontitis progression) associated with survival rates for molars and non-molars, during supportive periodontal therapy. This model was developed in a sample of 500 patients followed for a mean 20 years and included eleven predictors commonly associated with tooth loss, five patient-related factors and six tooth-related factors. The area under the receiver-operating characteristic curve (AUC) was 0.93 and 0.97, for molars and non-molars, respectively. Furthermore, the model had high specificity and low sensibility (98%/99% vs 39%/43%) which is regarded as preferable in predicting long-term tooth loss, given the fact that predicting the loss of a tooth that could be retained (false-positive) is worse than predicting the maintenance of a tooth that ends up being lost (false-negative) (Martinez-Canut et al., 2018; Pretzl et al., 2009; Schwendicke et al., 2017).

The first article with a quantitative prognostic assessment of tooth loss dates back to 2007 and produced a color-coding system based on five predictors and assigned a prognosis of tooth survival, evaluating tooth loss during active periodontal treatment and supportive periodontal treatment (Faggion et al., 2007). That is, early tooth loss and long-term tooth loss. The latter is the study object of the majority of the articles. Several factors have been associated with long-term tooth loss: these may be clinical, social and economic (Faggion et al., 2007; Lee et al., 2015). Additionally, patient-related factors and tooth-related factors can be distinguished. Common patient-related factors are age, smoking habits and diabetes, as well as patient compliance (Faggion et al., 2007; Graetz et al., 2015, 2017; Helal et al., 2019; Lee et al., 2015; Rahim-Wöstefeld et al., 2020). Tooth-related factors frequently associated with an increased risk of tooth loss are furcation involvement, tooth mobility, bone loss, clinical attachment loss, mean pocket depth, and, sometimes, type of tooth (multi-rooted or molars) (Faggion et al., 2007; Graetz et al., 2015; Helal et al., 2019; Nibali et al., 2016; Rahim-Wöstefeld et al., 2020).

Schwendicke et al. (2018) evaluated six models aimed at predicting tooth loss by analyzing their prediction and comparing it to what actually happened in a cohort of 301 periodontitis patients on supportive periodontal therapy for a mean time of 21.7±5.6 years. Three models evaluated risk on a continuous scale, while the other three used classification systems (the previously described model from Martinez-Canut et al. (2018) was not included). They concluded that such predictions were only limitedly possible. In a specific risk factor analysis, patient-related factors showed very limited accuracy with AUC values close to 0.5, and only tooth-related factors had a limited accuracy close to 0.6 – tooth type, pocket probing depth and furcation involvement. Furthermore, most models showed low accuracy represented by the area under the curve (AUC), with values ranging between 0.52 and 0.67. Importantly, with higher sensibility thresholds, the majority of the models overestimated the risk, predicting tooth loss in teeth that were maintained. Again, given how rare an event tooth loss is in Periodontology specialty settings, high specificity thresholds are generally preferable when predicting long-term tooth loss (Schwendicke et al., 2018).

Apart from multivariable prediction models, long-term tooth loss information can be obtained by utilizing other types of associations and predictors. Interestingly, long-term tooth loss may even be predicted without any clinical measures, and this has been showed in a model capable of predict tooth loss at 5 and 10 years using just self-reported oral health status, albeit with low specificity (Meisel et al., 2018). Additionally, two periodontal profile classes are also associated with increased risk for tooth loss (Morelli et al., 2018).

Additionally, there are also decision trees that provide an attempt to help the clinician choosing a particular outcome, for example, when it is time to decide if whether a tooth should be maintained or extracted in the present or in the very near future (Avila et al., 2009; Nunn et al., 2012). In other words, it helps to predict the early tooth loss. A study made by Avila et al. (2009) produced a decision-making chart that aimed to assist clinicians when they had to choose the fate of a particular tooth. Interestingly, they used a color-coded system with green, yellow and red to indicate whether a particular outcome was favorable or not in relation to the long-term retention of a particular tooth. This model included, apart from periodontal parameters, restorative characteristics, socioeconomic circumstances and other determinants, with twenty-seven parameters in total. Then, the presence or absence of those characteristics would place the tooth into one of five categories, ranging from the recommendation of extraction to the recommendation of tooth conservation. For further understanding of the study, the reader is referred to the original article (Avila et al., 2009). All of the parameters chosen and the categories that they produced were based on clinical expertise and literature. That is, the specific number of unfavorable outcomes that would make a tooth recommended to be extracted was entirely chosen by the authors and therefore it excludes the patterns that the experts did not see and perhaps a statistic model would (Beck et al., 2020). Additionally, some of the parameters used were subjective, as the authors discussed (Avila et al., 2009). Nonetheless, this model was the most accurate between the six models evaluated in the study by Schwendicke et al. (2018).

With another method, Nunn et al. (2012) produced survival trees for molars and non-molars, attributing prognosis categories: Good, Fair, Poor, Questionable and Hopeless. Prediction was based on patient-related factors as well as tooth-related factors. With increasing prognostic category, teeth were lost in a higher percentage. For example, from the 1402 non-molar teeth classified with a Good prognosis, only 4 were lost (0.3%). On the other hand, the percentage of lost Hopeless non-molars was 45.2% (14 out of 31). Even though the study had some limitations, the usefulness of survival trees as a prognostic tool was established.

Importantly, a model capable of predicting the early tooth loss in a Portuguese population is yet to be validated.

When in doubt, it seems ethical to maintain a tooth. Even when analyzing economic implications of maintaining or extracting molars, it seems to be less costly to maintain molars or eventually extract molars with furcation involvement class III (Schwendicke et al., 2017). Extracting all other molars results in an added cost, both economically and physically (Schwendicke et al., 2017). Therefore, specificity in prediction models should be high in order to prevent unnecessary costs associated with tooth extraction and replacement (Schwendicke et al., 2017).

Even though there will always be a difference between the predicted and the observed outcome, efforts should be made to try to reduce the risk of bias in such prediction models as well as improving their reproducibility (Du et al., 2020; Kundu et al., 2017; Schwendicke et al., 2018). Furthermore, study heterogeneity has significantly affected study comparison and conclusion making, therefore limiting the applicability of prediction models (Du et al., 2018; Schwendicke et al., 2018).

In order to enhance the quality of prediction models, the PROBAST (Prediction Model Risk of Bias Assessment Tool) and the TRIPOD statement (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) have been developed (Collins et al., 2015; Wolff et al., 2019). Du et al. (2020) reviewed a total of 34 prediction model studies using these two tools, and the authors concluded that none of the included studies rigorously followed the TRIPOD recommendations, particularly in reporting model performance metrics and missing data handling. Some parameters of the PROBAST yielded a high risk of bias in a great number of studies, such as missing data, overfitting/underfitting, categorizing continuous variables, univariate variable selection and measurement error (Du et al., 2020). Furthermore, small samples and internal validation strategies can affect the model's performance, whereas more complex models do not necessarily perform better than simpler ones regarding tooth loss prediction (Krois et al., 2019). New models should be developed and validated according to these guidelines in order to improve transparency and minimize the risk of bias, while allowing the reproducibility of the methods used (Du et al., 2020).

In the interpretation of validation studies, it is important to assess the value of the presented results. A framework has been proposed to such end, which divides the process into three steps (Debray et al., 2015). First, the differences between the development and validation samples should be considered, then the model performance in the validation sample is analyzed. Based on these two steps, an interpretation is made regarding reproducibility (good performance in similar populations) or transportability (good performance in different but related populations) (Debray et al., 2015). In addition to reproducibility and transportability, generalizability is of great value to allow a particular model to perform adequately in different populations with different characteristics, which is essential to make a model widely applicable in clinical practice (Kundu et al., 2017).

Importantly, besides raw accuracy and performance, a model must be easy to use in order to make it applicable (Du et al., 2018). An extremely accurate model but highly complex is of little value, as is a simple model with poor performance, and, therefore, a balance should be obtained regarding accuracy and practicality (Du et al., 2018).

3. Objectives

The objectives of this study are to validate a previously developed predictive model to assess the risk of early tooth loss in periodontitis patients, defined as teeth extracted after periodontal diagnosis and before treatment.

This model aims to provide a pattern that explains the specific factors that would make dentists extract a particular tooth based on the periodontal examination. The goal is to provide the clinician with an additional tool that may improve or complement the clinical decision regarding extraction or maintenance of a tooth, ultimately improving the patient's treatment.

II. MATERIALS AND METHODS

This study was approved by the Egas Moniz Ethics Committee (process number 818) and was carried out in accordance with Helsinki Declaration of 1975, and its revision of 2013. Written informed consent was voluntarily signed from each participant.

This investigation followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement, for validation purposes (Collins et al., 2015).

1. Source of data, participants, sample size and missing data

1.1 Setting

This retrospective study included a consecutive cohort of patients from the Periodontology Department of Egas Moniz Dental Clinic (EMDC), between June 2018 and March 2020.

1.2 Participants

The EMDC is located in the municipality of Almada, in Setúbal Peninsula (a NUTS III subregion, part of NUTS II Lisbon Region) and provides dental health services to the general public. Participants diagnosed with periodontitis in the Department of Periodontology received proper care.

1.3 Inclusion and Exclusion criteria

The inclusion criteria were: patients aged 18 years old or older and with a signed written informed consent.

The exclusion criteria were as follows: patients who missed follow-up appointments; records with missing data; and, patients considered healthy according to the new periodontitis classification system (Tonetti et al., 2018).

1.4 Sample size and missing data

The sample size was arrived at by using a 75/25 split sample approach combined with a temporal validation strategy (Krois et al., 2019; Moons et al., 2015). In the temporal validation strategy, the data originates from the same setting as the development phase but from a different time period (Krois et al., 2019; Moons et al., 2015). Particularly, the development sample was constituted by the cohort from May 2015 to May 2018, while the validation sample was constituted from June 2018 to March 2020 until 25% of the combined sample was achieved.

Incomplete periodontal diagnosis data led to the exclusion of the respective patient from the sample and no imputation methods were used.

2. Outcome

The outcome of the prediction model is early tooth loss as defined by tooth loss or extraction for periodontal reasons after the periodontal diagnosis and prior to periodontal treatment. That is, a tooth was considered clinically hopeless and was, therefore, surgically extracted. The outcome was retrospectively confirmed via records.

This study was conducted in a triple-blinded basis regarding diagnosis and clinical outcome, data collection and statistical analysis.

3. Predictors

For the validation of this previously developed prediction model, only the predictors used in the final equation will be discussed here. For a detailed description of the predictors used in the development phase, the reader is referred to the original publication (Santos, 2019).

The model equation is as follows:

$$Log\left[Prob.\frac{Ext.}{1-Prob.(Ext.)}\right]=-7.850+0.589\times TD(Incisive)+0.661\times CAL$$

“Ext.” is the outcome and refers to the probability of early tooth loss. “TD” means Type of Tooth and assumes a value of TD (Incisive) = 1 if the tooth is an incisive, and TD (Incisive) = 0 if it is any other tooth. CAL refers to clinical attachment loss. In the periodontal diagnosis, pocket probing depths were assessed in mm in six locations per tooth as the distance from the gingival margin to the bottom of the periodontal sulcus or pocket. Gingival recession was recorded as the distance from the gingival margin to the cementoenamel junction. The value for the clinical attachment loss was arrived at by adding the pocket probing depth to the gingival recession value. The periodontal probe used was a CP-12 SE (Hu-Friedy, Chicago, IL, USA).

4. Statistical analysis methods

Predictions are to be calculated by using the full regression model, applying it to the sample available and comparing the predicted outcome with the actual outcome.

Discrimination is the ability of a particular model to differentiate between those who do or do not experience the outcome event. This is to be quantified by analyzing the area under the receiver-operating characteristic curve (AUC). An AUC of 0.5 is indicative of no discrimination, whereas an AUC of 1.0 means perfect discrimination (Moons et al., 2015).

5. Risk groups

The establishment of risk groups is often conducted in an arbitrarily manner, and there is no significant information regarding the assignment of cut-points or thresholds to accurately categorize the risk of early tooth loss (Altman, 2009; Moons et al., 2015). Therefore, the attribution of risk groups was not included in this study.

6. Development vs validation

The setting, eligibility criteria, outcome and predictors in the validation sample are similar to the development sample.

III. RESULTS

From an initial sample of 111 patients referred to the Department of Periodontology, all met the inclusion criteria. From these 111 subjects, 9 (7.2%) were excluded due to incomplete periodontal data, 2 patients dropped out (1.6%) and one was diagnosed as periodontally healthy (0.8%) (Figure 1).

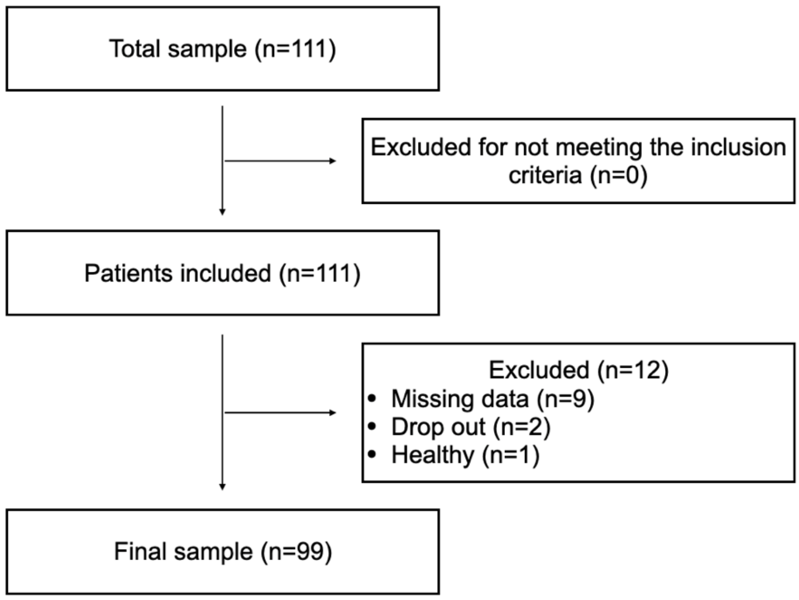

Figure 1 - Participants flowchart

Regarding sociodemographic characteristics of the validation sample, 56.6% of the participants were female while 43.4% were male, whereas in the development sample 54.7% were female and 45.3% were male (Table 1). Overall, patients were younger in the validation sample with a mean age of 45.8 years (±0.26), compared with a mean age of 54.7 years (±0.12) in the development sample (Table 1). In terms of smoking habits, the presence of active smokers was lower in the validation sample, 44.1% vs 53.0% in the development sample (Table 1).

Table 1 - Sociodemographic characteristics of the development and validation samples, including gender, mean age (SD) and smoking habits

Variable		Sample	
		Development	Validation
Gender	Female	54.7%	56.6%
	Male	45.3%	43.4%
Age		54.7 (0.12)	45.8 (0.26)
Smoking	Yes	53.0%	44.1%
	No	47.0%	55.9%

Canines were the least prevalent teeth, comprising 14.3% of the final sample, while incisors, premolars and molars accounted for 28.6% of the sample. These proportions were exactly the same as in the development sample.

From a total of 2,177 teeth examined, 12 were extracted due to periodontal reasons, representing 0.6% of all teeth. The extractions were performed in 8 patients, whereas 91 did not experience the outcome.

By adding the 9,377 teeth analyzed in the development sample with this validation sample, a total of 11,544 teeth were analyzed.

Extractions were performed in 1.1% of the teeth in the development sample, contrasting with the 0.6% in the validation sample, resulting in a total of 0.9% extracted teeth. 89.7% of the extracted teeth originated from the development sample.

As shown in Table 2, the development sample was characterized by retained teeth with a mean pocket probing depth (PPD) of 2.97 (±1.08) mm, a mean gingival recession (REC) of 0.71 (±1.20) mm, and a mean clinical attachment loss (CAL) of 3.67 (±1.59) mm, while the extracted teeth presented a mean pocket probing depth of 4.99 (±1.43) mm, a mean gingival recession of 2.02 (±1.02) mm and a mean clinical attachment loss of 7.01 (±2.26) mm. Similarly, the retained teeth in the validation sample presented a mean pocket probing depth of 2.23 (±0.01) mm, a mean gingival recession of 0.52 (±0.00) mm and a mean clinical attachment loss of 2.65 (±0.01) mm. As for the extracted teeth in the validation sample, the values increased to a mean pocket probing depth of 4.86 (±0.16) mm, a mean gingival recession of 1.87 (±0.16) mm and a mean clinical attachment loss of 6.65 (±0.23) mm.

The differences between the extracted teeth and the retained teeth were statistically significant for these 3 variables in both samples ($p < 0.001$).

Table 2 - Comparison of clinical variables, expressed as mean (SD), in mm, between the development and validation samples and Mann-Whitney's *p values*

Variable	Sample					
	Development			Validation		
	Surgery		*p* value	Surgery		*p* value
	No	Yes		No	Yes	
PPD	2.97 (1.08)	4.99 (1.43)	<0.001	2.23 (0.01)	4.86 (0.16)	<0.001
REC	0.71 (1.20)	2.02 (1.02)	<0.001	0.52 (0.00)	1.87 (0.16)	<0.001
CAL	3.67 (1.59)	7.01 (2.26)	<0.001	2.65 (0.01)	6.65 (0.23)	<0.001

The area under the curve (AUC) was 0.809 (95% CI: 0.629 - 0.989) for the validation sample and 0.920 (95% CI: 0.891 - 0.950) for the development sample, as illustrated in Table 3. The receiver-operating characteristic (ROC) curves of both groups are shown in Figure 2.

Table 3 - Receiver-operating characteristic curve analysis

	Group	AUC	95% CI	
			Inferior limit	Superior limit
Predictive probability	Development	0.920	0.891	0.950
	Validation	0.809	0.629	0.989

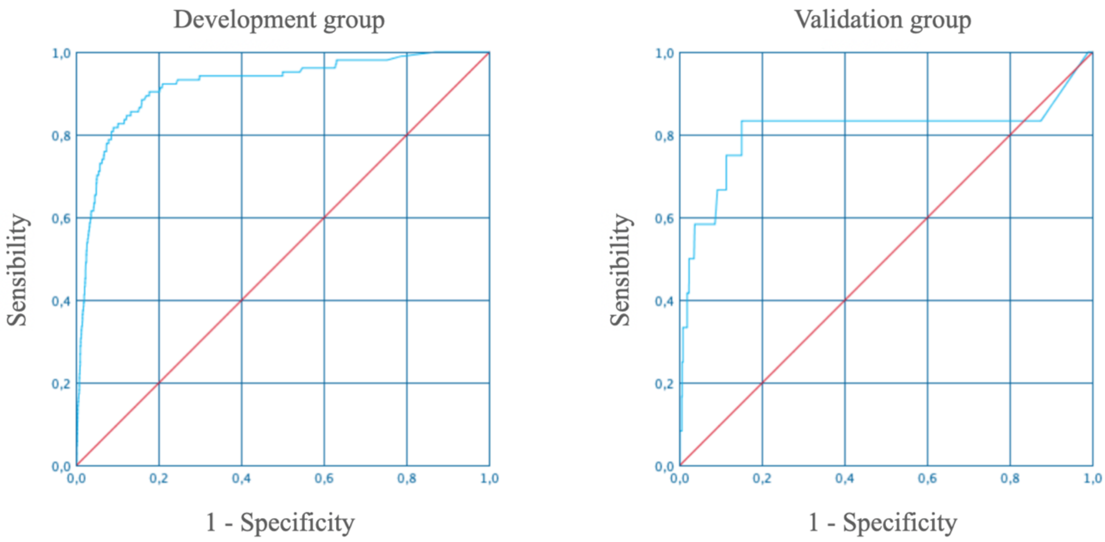

Figure 2 - Receiver-operating characteristic curves of the development and validation groups

IV. DISCUSSION

Clinical relevance

Periodontal diseases are highly prevalent and cause a significant impact on the quality of life of the population (GBD 2017 Oral Disorders Collaborators, 2020). Furthermore, the number of missing teeth has been shown to be related with increased treatment needs (Botelho, Machado, Proença, Bellini, et al., 2020; Buset et al., 2016). The great variability regarding disease presentation, initiation and progression makes periodontitis predictability challenging (Haffajee & Socransky, 1986). Ultimately, this destructive disease ends up causing tooth loss and sometimes the clinician is faced with the decision to extract or retain a particular tooth for periodontal reasons. Removing a tooth that could be successfully maintained incurs the patient with added costs regarding its replacement, with its associated complications (Schwendicke et al., 2016, 2017). On the other hand, retaining a tooth that ends up being lost has its costs as well (Schwendicke et al., 2017). In fact, regular supportive periodontal therapy may be more expensive, even though it extends tooth retention (Schwendicke et al., 2016). However, immediate removal and replacement of teeth (early-tooth loss) is usually more expensive (Schwendicke et al., 2016). Therefore, it becomes crucial to conserve as many teeth as possible and extract only the ones considered clinically hopeless. Additionally, predicting extractions or tooth retentions may help in the resource allocation, as well as in predicting social, psychological and economic impacts of treatment decisions.

In light of these issues, the application of a prediction model for early tooth loss is highly valuable. Predictive models are a helpful tool to assist clinicians in their daily activity by allowing them to perform more informed choices (Beck et al., 2020). The previously developed model has been validated in this study with good performance and has potential to be used clinically as well as epidemiologically.

In the daily practice routine, the clinician has the possibility to make a more informed decision regarding retention vs extraction. By incorporating it into practice, an improvement in the clinical decision is to be expected, ultimately resulting in a better treatment for the patient. It should be noted that this model aims to predict what is a somewhat subjective choice, since different clinicians would base their decision according to the evidence that they are aware of, as well as to their own experience. This model aims to provide a more objective and precise approach. The clinician should assess the clinical, social and economic characteristics of the patient, consider the overall treatment, the current external evidence and his own clinical experience. Then, the model serves as an additional tool to further inform the clinician and assist in the decision-making process.

Importantly, on the other hand, epidemiology may benefit from the use of prediction models as well, such as this one. It is possible to apply the model to a group of patients in a particular setting and assess what are the early tooth loss risks of that particular sample, that is, what teeth are at risk of being extracted. This approach may improve the allocation of resources by analyzing the population's treatment needs, and will ultimately provide a better treatment for the community, with practical implications for screening and prevention measures.

Teeth are considered hopeless or unworthy of treatment when the attachment loss reaches, approximately, the root apex of a tooth and it is associated with a degree III mobility (Sanz et al., 2020). However, most teeth that were extracted for periodontal reasons in the development and validation samples did not meet these criteria. Therefore, it is of value to understand what other characteristics would predispose a clinician to find a particular tooth not worthy of a conservation attempt.

Methodology and model performance

In regard to the methods used, the first question is related to the sample size that was used for the validation phase. Although there is a lack of a clear manner in which the sample size should be calculated, some studies suggest that there should be at least 100 outcome events and preferably 200 (Collins et al., 2016; Moons et al., 2015). A small sample may have a strong impact on a model's performance (Krois et al., 2019). The methods chosen in this study are therefore considered valid and involved a 75/25 split sample approach associated with a temporal validation strategy (Krois et al., 2019; Moons et al., 2015). In this sample, only 12 teeth were extracted for periodontal reasons after the diagnosis and before the beginning of the treatment, even though the final sample incorporated 99 patients and a total of 2,177 teeth. To achieve the ideal amount of outcome events, a more extensive sample is needed. For this to be possible, the cohort period should be significantly elongated. Additionally, as periodontitis treatments develop, increasing tooth retention is to be expected, and therefore the larger the sample will have to be to contain the ideal number of outcome events. This difference was even noted when comparing the two samples regarding the proportion of extractions. In the development sample, 1.1% of all teeth were extracted where in the validation sample only 0.6% of the teeth had such a fate. Furthermore, 89.7% of the extractions in the combined sample originated from the development phase. Contrasting with this extraction rate, the study from Faggion et al. (2007) examined 198 patients with 4,559 teeth present at baseline, from which 166 teeth were removed, representing 3.64% of the sample. Another example of a higher extraction rate originates from a study by König et al. (2002) where 4.98% of the teeth were extracted - 167 out of 3353 teeth. Early-tooth loss is, therefore, regarded as an extremely rare event in the EMDC. As such, a wider study with a higher number of outcome events should be developed to consolidate the performance of the model and further assess its characteristics. Nonetheless, it must be noted that this sample originates from a Periodontology Department and the extraction rate may arguably be lower than in the general practice.

Secondly, any missing data on the predictors and/or outcome variables precluded the exclusion of the patient from the sample, thereby implying a complete-case analysis. Even though this approach can lead to bias, we estimated the excluded sample to be representative of the original sample and that the missing data was missing completely at random, which means that it was not related to other observed variables (Moons et al., 2015). A total of 9 (7.2%) patients were excluded because of missing data.

Third, even though there are different approaches to model development, with some more complex than others, logistic regression methods are equivalent to more complex methods and this was the method chosen (Krois et al., 2019).

Finally, with this model, the clinician is able to address what is the likelihood of a particular tooth to be extracted since the model output is a risk probability in a scale of 0 to 100. It is possible to attribute risk groups based on the risk probability of extraction and define a certain number of categories to assist the clinician in decision making (Altman, 2009; Moons et al., 2015). Primarily, a dichotomous model output, i.e. conserve vs extract, was ruled out. For example, if the cut-off value was 50%, a risk probability of

49% would indicate conservation whereas a value of 51% would indicate extraction even though in reality both situations would be very similar. Another approach could be the risk categorization, assigning a certain number of classes based on risk intervals. However, categorizing risk is often done arbitrarily and without any specific rationale, as there is no consensus about the methods to attribute such categories or even how many should be used (Altman, 2009; Moons et al., 2015). Therefore, it was decided not to categorize risk and use the model output as a raw value of risk probability.

In terms of model performance, the key aspect to evaluate here is the discrimination. As already mentioned, discrimination is the ability of the model to differentiate between those who do or do not experience the outcome. In this case, we evaluated this by analyzing the receiver-operating characteristic (ROC) curve. The obtained area under the curve was good, with a value of 0.809 (95% CI: 0.629 - 0.989). It was inferior to the model performance on the development sample: 0.920 (95% CI: 0.891 - 0.950), which is to be expected given that the model's performance tends to decrease in validation samples when compared to the development phase (Krois et al., 2019; Siontis et al., 2015).

Importantly, the validation sample showed a lower representation of active smokers (44.1% vs 53.0% in the development sample) (Table 1). Additionally, participants in the validation sample were younger than in the development sample, with a mean age of 45.8 years vs 54.7 years in the development sample (Table 1). These differences may, in part, explain the variation in model performance as well as in the extraction rate, where, arguably, a younger sample with fewer smokers would experience less extractions. Interestingly, 14.3% of the validation sample was comprised of canines, whereas incisors, premolars and molars each made up 28.6% of the sample. These proportions were exactly the same as in the development sample. Furthermore, as seen in Table 3, the development and validation samples were similar in terms of mean pocket probing depth, gingival recession and clinical attachment loss, except for the mean clinical attachment loss of the retained teeth between the two samples (3.67 mm in development vs 2.65 mm in validation) (Table 3). Although this study does not confer generalizability - provided by external validation in a different setting or geographical area - it validated the model and showed a good degree of reproducibility and even transportability, considering the differences between the development and validation samples (Debray et al., 2015; Kundu et al., 2017).

As stated, there are no similar models aiming at predicting early tooth loss, but other models focused on predicting long-term tooth loss exist. For reference, a recent review analyzed the performance of different models on a sample with 301 patients and most models showed low accuracy with AUC values ranging between 0.52 to 0.67 (Schwendicke et al., 2018). Any value close to 0.5 demonstrates irrelevance (Moons et al., 2015). The most accurate model showed an AUC of 0.67 (95% CI: 0.65 - 0.69) (Avila et al., 2009; Schwendicke et al., 2018). As already mentioned, this model provides a decision chart to help distinguish teeth that are to be extracted or conserved, it incorporates several characteristics and categorizes the recommendation in five stages (Avila et al., 2009). Comparisons between these values and the ones of this model should be made carefully as they derive from different samples.

Finally, an analysis of the included variables in the final model should be done. When looking at predictive models for long-term tooth loss, it is understandable that it includes a significant number of risk factors, both clinical and social (Graetz et al., 2015, 2017; Helal et al., 2019; Rahim-Wöstefeld et al., 2020). This is not the case when looking at early tooth loss with this model, even though several factors influence the outcome (Avila et al., 2009). In the development study, early tooth loss was associated with several risk factors as well, when an univariate analysis was done (Santos, 2019). However, when producing the multivariate analysis, the model incorporated just two variables: the clinical attachment loss and the type of tooth (if it is an incisor or not), both of them being clinical parameters or tooth-related factors, which denotes ease-of-use and practicality. Therefore, the final model did not incorporate any patient-related factors, whose value has been questioned in tooth loss predictions (Schwendicke et al., 2018).

Regarding clinical attachment loss, the inclusion of this parameter is understandable, given the fact that when a clinician is faced with the decision of maintaining or extracting a tooth for periodontal reasons, will be motivated to look at how periodontally affected the tooth is. The ultimate indicator of periodontal destruction is the clinical attachment loss, which takes into account both the pocket probing depth and the gingival recession. This clinical parameter is also the primary criteria for addressing periodontitis severity in the current classification system (Tonetti et al., 2018). It is somewhat understandable that the clinician would not take into account if the patient smokes or if he has diabetes (patient-related outcomes) when assigning a subjective prognosis for a particular tooth.

But why not periodontal probing depth, bleeding on probing, furcation involvement or even tooth mobility? As mentioned in the development study, even though some of these variables, such as pocket probing depth and smoking habits, were associated with the extractions on an univariable analysis, the same was not true when the logistic regression model was elaborated. Further studies may focus on the added benefit of including a particular predictor on the model's performance.

And regarding tooth type, why are incisors more prone to be extracted? Other studies have found the opposite, with multi-rooted teeth being a negative prognostic factor for long-term tooth loss (Faggion et al., 2007; Saminsky et al., 2015). However, this study did not separate multi-rooted from single-rooted teeth, but it made a distinction between incisors and the other types of teeth, including canines and premolars. Even though a single-rooted tooth can be retained for several years, it can be speculated that a multi-rooted tooth with the same attachment loss may be perceived as being more stable and therefore more durable, in part explaining why such teeth are maintained more often. Regardless of this, molars tend to be the most extracted teeth in other samples (Martinez-Canut et al., 2018).

Strengths and limitations

This study presents some limitations. As also stated in the original study for the model development, several known risk factors could not be incorporated into the model because the data was not available, even though the majority of them are not usually regarded as risk factors for tooth loss. Concerning smoking status, only a dichotomous approach was possible as patients were classified as smokers or non-smokers. Past smoking behaviour was not documented and hence the smoking cessation effect was missing (Leite et al., 2019; Silveira Souto et al., 2019). Moreover, smoking is known to express a dose-response behaviour with periodontitis, as is conveyed in the periodontitis classification system (Tonetti et al., 2018), and the number of cigarettes smoked was not recorded. Additionally, smoking habits also involve other types apart from cigarettes and this information was also absent (Albandar et al., 2000). Therefore, the possible relationship with number of cigarettes, past experience and type of smoking was not assessed in this model.

As for diabetes, the new classification system asks for the metabolic control of a diabetic patient when assigning a grade (Tonetti et al., 2018). This is carried out by analyzing the levels of hemoglobin A1c and using a 7.0% threshold to designate the grade: grade B if HbA1c < 7.0% and grade C if HbA1c ≥ 7.0%. However, only a dichotomous analysis was performed here as well (diabetes present or not), due to the absence of HbA1c levels. Hence, the connection between the risk for tooth loss and the levels of HbA1c was not addressed.

Associations between the periodontal diagnosis and tooth loss, namely the stage and grade, were not performed as the classification had not been incorporated at the time of the model development (Tonetti et al., 2018). Lastly, information regarding other risk factors, conditions and disorders that may be related with periodontal diseases was absent and therefore was not included in the present model. Future studies may address this issue, even though, as stated, most unavailable factors are not commonly considered relevant regarding tooth loss.

Importantly, as evidenced by the model developed by Avila et al., several factors influence the decision to extract or retain a tooth and hence it must be noted that the overall treatment plan may supersede the individual prognosis of a particular tooth (Avila et al., 2009). The distinction between extractions for periodontal reasons and prosthetic reasons may not always be possible to do because these may overlap. Even if a tooth's destiny is being analyzed because of periodontal reasons, its rehabilitation potential may sometimes be decisive. Even though this study aims to analyze extractions strictly for periodontal reasons, excluding the ones performed for prosthetic or restorative reasons, there are other important factors not strictly related to periodontology or other clinical areas that can predispose the clinician towards a particular approach. Sometimes, a patient's level of hygiene, self-perception and expectations should be weighted along with the other determinants. It is possible that a tooth with no hard tissue loss (i.e., no carious or non-carious lesions) and with moderate periodontal destruction may be extracted if the patient is particularly willing to extract the tooth or has long-term expectations regarding the survival of a tooth. Esthetic involvement, financial constraints and poor compliance may also affect a tooth's fate. These factors are taken into consideration in the model developed by Avila et al., but the data was not available to be incorporated in this model and therefore its implications could not be analyzed (Avila et al., 2009).

Finally, the number of outcome events in the sample was small (12), despite the number of participants (99) and teeth evaluated (2,177). Tooth extraction in the Periodontology Department of the EMDC is, therefore, regarded as a rare event. It is suggested that a further study should involve a larger and nationally representative sample.

This study has several strengths, and a major one of both the development and the validation phase, is the implementation of the TRIPOD guidelines (Moons et al., 2015). This will not only help the readers to assess the evidence but also to give significant insights to the investigators related to the strengths and limitations of the study. Reproducibility is also made possible through a transparent reporting of the methodology used. The majority of studies describing the external validation of a previously developed model showed some level of poor reporting with key aspects not being included, such as poor design and lack of acknowledgment of missing data (Collins et al., 2014). Particularly, predictor assessment and selection, outcome assessment, data collection, sample size definition, validation strategy and statistical analysis have been reported transparently and based on existing guidelines and are regarded as important strengths of this study.

Additionally, there are no predictive models of tooth loss for the Portuguese population, neither long-term nor short-term and this is the first one developed and validated to this end. It may be feasible and logical to use this model in the population attending the EMDC, and it must be noted that the outcome was assessed in a Periodontology Department environment. Further applications in epidemiological studies may provide significant benefits to the population by predicting economic, social and psychological costs of tooth loss.

Implications for future research

- Validation studies targeted to specific populations should be developed in order to confer generalizability to this model and to further assess its strengths and limitations;

- The incorporation of new predictors in the model, including the ones that were not available in the original sample, may improve the model's performance;
- The potential added value of a predictor that is already available may provide interesting insights. However, a balance between predictability and ease-of-use should be obtained;
- Designing a proper interface for the model application is crucial, and this might be accomplished using an App, a Website or medical software;
- Applying existing prediction models for tooth loss in the same sample as this model may provide further insights;
- Similar to machine learning concepts, it might be interesting to enable the model to learn from the newly produced data from the patients being diagnosed and update itself continuously in relation to the teeth that are actually extracted or maintained;
- The possible value of long-term tooth loss predictions and its association with early tooth loss may improve the model's applicability.

V. CONCLUSION

A previously developed predictive model for early-tooth loss in periodontitis patients was validated in the EMDC with a good performance [AUC = 0.809 (95% CI: 0.629-0.989)]. The model incorporated two clinical parameters, with prospective practical usefulness.

This model is the first to be developed and validated in a Portuguese subpopulation and may have clinical relevance when the time comes to choose between extracting or maintaining a tooth for periodontal reasons. It must be noted that clinical criteria, external evidence and personal experience should be the key components to decision-making, and this model represents an additional tool to assist and complement the clinician's choice. Furthermore, such predictions may enhance resource allocation and help predict the economic, social and phycological impact of tooth loss.

In the future, and in light of this study shortcomings, this model shall be validated to expanded large-scale representative populations in order to enhance the benefits of precision dentistry and predictive models. Furthermore, models incorporating new predictors into the model may provide improved perceptions.

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VII. APPENDIX

Comissão de Ética EGAS MONIZ

Proc. Interno nº 818

Ex.mo Senhor
Frederico Marcelo Rodrigues Beato

Monte de Caparica, 19 de dezembro de 2019.

Ex.mo Senhor,

Em resposta ao Pedido de Parecer que submeteu à apreciação da Comissão de Ética da Egas Moniz, com o tema denominado **"Validation of a predictive modelo f early tooth loss in periodontitis patients"**, foi aprovado.

Com os melhores cumprimentos,

A Presidente da Comissão de Ética da Egas Moniz

Profª. Doutora Maria Fernanda de Mesquita

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