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Original article

# The role of *IL-1* gene polymorphisms (*IL1A*,*IL1B*, and *IL1RN*) as a risk factor in unsuccessful implants retaining overdentures

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ABSTRACT

*Purpose:* Implant-supported overdentures are an alternative predictable rehabilitation method that has a high impact on improving the patient's quality of life. However, some biological complications may interfere with the maintenance and survival of these overdenture implants. The goal of this article was to assess the factors that affect peri-implant success, through a hypothetical prediction model for biological complications of implant overdentures.

*Methods:* A retrospective observational, prevalence study was conducted in 58 edentulous Caucasian patients rehabilitated with implant overdentures. A total of 229 implants were included in the study. Anamnestic, clinical, and implant-related parameters were collected and recorded in a single database. "Patient" was chosen as the unit of analysis, and a complete screening protocol was established. The data analytical study included assessing the odds ratio, concerning the presence or absence of a particular risk factor, by using binary logistic regression modeling. Probability values (p values) inferior to 0.05 were considered as representing statistically significant evidence.

*Results:* The performed prediction model included the following variables: mean probing depth, metal exposure, *IL1B*_allele2, maxillary edentulousness, and *Fusobacterium nucleatum*. The *F. nucleatum* showed significant association with the outcome. Introducing a negative coefficient appeared to prevent complications or even boost the biological defense when associated with other factors.

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*Conclusions:* The prediction model developed in this study could serve as a basis for further improved models that would assist clinicians in the daily diagnosis and treatment planning practice of oral rehabilitation with implant overdentures.


## 1. Introduction

The replacement of missing teeth undoubtedly restores function and aesthetics and improves the patient confidence and self-esteem [1–4]. In most cases, dental implants are an alternative rehabilitation method that is predictable and has a high impact on improving the patient's quality of life [1,2,5,6]. The success and implant survival rates of this method are considered high (greater than 90%) even with mini dental implants, in the elderly and in patients suffering from systemic diseases, such as osteoporosis/osteopenia and diabetes mellitus [7–16]. However, some factors may interfere with the maintenance and survival of the implants and respective prosthetic restorations [17–22]. One of these factors is the biofilm formation on the implant surface, which has often been discussed. This factor causes a host response and the establishment of an inflammatory lesion in the peri-implant mucosa, which, when perpetuated, may lead to the development of peri-implant biological complications that might even culminate in implant loss [22–25].

The biological complications of peri-implant tissues include mainly inflammation of the peri-implant mucosa (mucositis), marginal bone loss (periimplantitis) and, less often, other soft-tissue complications (fenestration, bone and gingival tissue dehiscence, hyperplasia, fistulas, among others) [26]. Nevertheless, according to prospective longitudinal studies of at least five years, the most serious biological complication is implant loss [27]. Several factors may contribute to this failure, including infection and/or contamination by pathogenic bacteria, the physical status of the patient, surgical trauma, excessive and/or early occlusal loading, unfavorable axial load, smoking, alcohol consumption, history of periodontitis, and history of radiotherapy [18,27–33].

Therefore, in recent years, we have been witnessing a more detailed description of the success criteria for dental implants [25,32]. Initially, these criteria focused only on implant loss but, more recently, they have started to include other biological and prosthetic aspects, probably to consider the biological and functional issues related to peri-implant tissues and prosthetic rehabilitation [23,24,32]. Although high biological success rates of dental implants and increased predictability of the osseointegration process have been reported, current research is focusing its interest on complications of the restorative phase, which are especially important for implant overdentures, as these are related to both biological and prosthetic factors [34–39].

In the past years, aspects related to individual host susceptibility have been pointed out, including the association of genetic polymorphisms (genome variants) in the genes of interleukin 1 (*IL-1*) (*IL1A*, *IL1B* and *IL1RN*) with the development of peri-implant biological complications and even implant loss in oral rehabilitation with dental implants [22,40–54]. It is also believed that when peri-implant disease onsets after a successful osseointegration process of a dental implant, it results from an imbalance between the peri-implant biofilm and the host response [55]. Moreover, several studies have reported an association between microbiologic aspects and peri-implant disease [23,56–63].

Nowadays, research is faced with the challenge of answering questions concerning the role of biofilm and genetic polymorphisms in the establishment and progression of the peri-implant disease. This paper intends to show how some particular *IL-1* gene polymorphisms (−889 *IL1A*, +3953 *IL1B*, and a variable number tandem repeat (VNTR) *IL1RN*) may contribute to evaluating the risk for biological complications in dental implant overdentures in a Portuguese Caucasian population. Furthermore, the final goal of this study was to provide a hypothetical prediction model for biological complications of dental implant overdentures that could become useful in a near future for the planning of overdentures rehabilitations with dental implants.

## 2. Material and methods

### 2.1. Study subjects

This retrospective observational prevalence study was performed in a population composed of 58 Caucasian patients from the Northern region of Portugal, who had been rehabilitated with oral implant-supported overdentures. A total of 229 implants were included in the study. Patients were recruited in oral rehabilitation appointments conducted within the Master's/Specialization Course on Oral Rehabilitation of the Faculty of Dental Medicine of our University, between September 2012 and September 2014. The sample size was determined based on a statistical estimate, with a confidence interval of 95%, and an estimated error of 6.1%, according to the reported prevalence of the genetic polymorphisms that control the production of interleukin-1 (IL-1) in several European Caucasian populations [22,64,65], and the incidence of biological complications in dental implants [22,27,31,32,64,66–69].

The study was approved by the Ethical Committee of our Faculty, and the study protocol was outlined following the legal norms (Declaration of Helsinki and 2005 Strasbourg Protocol). Informed consent was obtained from all subjects, and patient privacy was ensured.

The patients were classified into two groups:

- Group A (presence of biological complications/unsuccessful) – patients rehabilitated with dental implant

**Table 1 – Amplification products and restriction enzymes used for the detection of polymorphisms in the *IL1A* and *IL1B* genes.**

| Polymorphisms | Primers PCR 5′–3′ | Size of expected product (bp) | Restriction enzyme |
|---|---|---|---|
| −889 *IL1A* | TTACATATGAGCCTTCCATG<br>AAGCTTGTTCTACCACCTGAACTAGGC | 110 | *Ncol*, 65°C |
| +3953 *IL1B* | CTC AGG TGT CCT CGA AGA AAT CAA A<br>GCT TTT TTG CTG TGA GTC CCG | 185 | *Taql*, 37°C |

Bp, base pair.

overdentures that showed a biological complication in at least one dental implant.
- Group B (absence of biological complication/successful) – patients rehabilitated with dental implant overdentures that showed no biological complications.

A compilation of several criteria for unsuccessful implants was used for establishing the biological complications considered in this study [22,31,32,64,66,69,70]. The resulting biological complications of implants included the following situations or entities:

- Peri-implant inflammatory signs (erythema, suppuration or fistula),
- Mobility,
- Pain,
- Peri-implant mucositis,
- Periimplantitis,
- Loss of dental implant.

Only complications related to implants supporting overdentures were recorded in the analysis. The patient that showed none of these situations was classified in the Group B (successful); if he presented some of these entities in one or more implants, it was sufficient to be classified in Group A (unsuccessful). Any other potential implant in the oral cavity was not considered for this study.

The inclusion criteria adopted in this study were the following: adults (at least 18 years) of both sexes that had a maxillary or mandibular implant-supported overdenture for at least six months. Patients who had lost all overdenture supporting implants or who had replaced a lost fixed-restoration supporting implant with a removable prosthesis were not included in this investigation. Other exclusion criteria were: individuals with a history of personal or family genetic disease, and pregnant, postpartum or breastfeeding women.

### 2.2. *Data collection*

All patients who fulfilled the inclusion criteria and agreed to participate voluntarily in the study were included. Each participant answered a structured questionnaire about several personal data (demographic and social data – sex, age, education level, and occupation), their general health status (current diseases, medication, systemic and chronic diseases, menopause, hormone replacement therapy, neoplastic diseases, and chemotherapy and radiotherapy history), and their dental history (motive for tooth loss, type of prosthetic replacement of missing teeth). Behavioral traits (smoking habits, alcohol consumption, oral hygiene habits, and prosthesis hygiene) were also recorded. Participants were questioned about their smoking habits in the moment of the examination, in the previous five years, and in the week after the implant placement surgery. Smoking habits were categorized as “no smoking”, “light smoking” (less than 20 cigarettes per day), “heavy smoking” (more than 20 cigarettes per day) [1–3], and “smoking with abstinence” (smoker who abstained from smoking only in the post-surgery week). Alcohol consumption was recorded in three categories: wine, beer, and spirit drinks. For each category, the amount and frequency of intake were recorded, using glasses or liters as units for measuring the amount and daily, weekly, monthly, and yearly basis for frequency [29]. Participants were asked about their alcohol habits at the time of the observation and in the week after the implant placement surgery [22].

All patients only underwent an intra-oral examination to evaluate their general oral health status and the implant, prosthetic and occlusal conditions. Simultaneously, a radiographic evaluation was conducted, by analyzing the last control panoramic radiography of each participant (present in the clinical file).

At the same examination, the genotypic analysis was blindly performed, without clinical information. The genetic test was performed using buccal epithelial cells for the detection of polymorphisms in the *IL1A*, *IL1B*, and *IL1RN* genes and peri-implant crevicular fluid (collected with paper cones in an Eppendorf tube) for the molecular identification of four bacterial specimens (*Actinomyces actinomycetemcomitans*, *Bacteroides forsythus*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*). The single nucleotide gene polymorphisms (SNP) in the *IL1A* (position −889 in the promoter region) and *IL1B* (position +3953 in the fifth exon) genes were detected with the PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method (Table 1). The VNTR polymorphism found in the intron 2 of the *IL1RN* gene was detected by PCR due to the presence of repeats of an 86pb sequence (Table 2). The molecular identification of bacteria was performed with the Platinum PCR Supermix 96 and the composition and length of the primers of each bacterial species are summarized in Table 3. The scanning and quantification of PCR products were automatically performed in agarose gel with the QIAxcel equipment (QIAGEN®, Izasa, Portugal). This identification was carried out after the restriction reaction in the case of the *IL1A* (−889) and *IL1B* (+3953) gene polymorphisms, after the amplification reaction

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**Table 2 – Primers used for detecting the *IL1RN* VNTR polymorphism and its alleles.**

| Polymorphism | Primer PCR 5′–3′ | Alleles (number of repeats/bp) | | | | |
|---|---|---|---|---|---|---|
| *VNTR IL1RN* | TCC TGG TCT GCA GGT AA<br>CTC AGC AAC ACT CCT AT | Allele 1<br>4/410 | Allele 2<br>2/240 | Allele 3<br>3/326 | Allele 4<br>5/498 | Allele 5<br>6/595 |

Bp, base pair. VNTR allele detection according to Avilla-Campos et al. [71].

**Table 3 – Composition and length of the primers of each bacterial species.**

| Primers | Oligonucleotide sequence 5′–3′ | Length (bp) |
|---|---|---|
| *Actinobacillus actinomycetemcomitans* | GCT AAT ACC GCG TAG AGT CGG<br>ATT TCA CAC CTC ACT TAA AGG T | 500 |
| *Bacteroides forsythus* | GCG TAT GTA ACC TGC CCG CA<br>TGC TTC AGT GTC AGT TAT ACC T | 600 |
| *Fusobacterium nucleatum* | ATT GTG GCT AAA AAT TAT GAT T<br>ACC CTC ACT TTG AGG ATT ATA G | 1000 |
| *Porphyromonas gingivalis* | AGG CAG CTT GCC ATA CTG CG<br>ACT GTT AGC AAC TAC CGA TGT | 400 |

Bp, base pair.

of intron 2 in the case of the *IL1RN* gene VNTR polymorphism, and directly by PCR in the case of bacterial identification. After, the DNA of each participant was anonymized from irreversible way.

### 2.3. *Statistical analysis*

The collected data were analyzed with the IBM® SPSS® Statistics 22 (NY Armonk: IBM Corp. 2014) program, using the most appropriate techniques for the variables involved. The data analytical study included assessing the odds ratio, concerning the presence or absence of a particular risk factor, using binary logistic regression modeling. Probability values inferior to 0.05 were considered as representing statistically significant evidence. Clinically, a risk factor was established as a feature that could predispose an individual to the disease or condition. Epidemiologically, it was determined as an independent variable (cause) likely to modify a dependent variable (effect). Considering the factors that may lead to biological complications in oral rehabilitation with overdentures, we have tried to create an empirical model that would determine which of these factors were statistically significant in the process, and, subsequently, assess their odds ratio. For this purpose, we first conducted a univariate selection of candidate variables. Then, a forward stepwise technique was used to optimize variable selection, in order to select a set of variables that could contribute to the result (presence or absence of biological complication in overdentures). Categorical variables were coded in dummy variables, according to the Hosmer–Lemeshow test [72].

The resultant model should contain all the variables that were considered essential according to the pre-established criteria of the pE and pR values (p values of entry and removal of the variable in the model) selected so that the model contains only statistically and clinically significant variables. Thus, even if a variable shows a p value > 0.05, it can be forced to be included in the model, because the individual contribution of this variable may be very different when acting together with other variables. Following the guidelines proposed by Hosmer and Lemeshow [72], it is highly recommended to choose a pE value within the range of 0.15–0.20.

The apparent performance of the created logistic regression model was evaluated with the ROC (Receiver Operating Characteristic) analysis, using the ROC empirical curve and the correspondent measure of area under the curve [73].

## 3. Results

The final sample of 58 individuals was composed of 44 females (75.9%) and 14 males (24.1%) (Table 4). Participants were aged between 50 and 86 years, with an average of 68.8 years and a standard deviation of 8.3 years. The median was slightly higher (70.0 years) in women compared to men (67.0 years).

Of the 58 subjects, 32 (55.2%) were classified as Group A (presence of biological complications) and the remaining 26 (44.8%) as Group B (successful) (Fig. 1). The sample distribution according to the presence or absence of biological complication in implant-supported overdentures occurred in the same way in both sexes. In men, 9 had biological complications (28.1%), and 5 had successful overdentures (19.2%), while in women, 23 had biological complications (71.9%) and 21 had successful overdentures (80.8%) (Table 4). The average age was 68.4 years for Group A and 69.3 years for Group B. The result of the t-student test ($t=0.425$, $df=56$, $p=0.672$) confirmed that there were no significant differences in mean age between subjects with and without biological complications.

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**Table 4 – Sample distribution according to sex and age, in the Group A (presence of biological complication) and in the Group B (absence of biological complications/successful) (N=58).**

| | Group A (Presence of biological complications) | | Group B (Absence of biological complications/successful) | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Male | 9 | 28.1 | 5 | 19.2 | 14 | 24.1 |
| Female | 23 | 71.9 | 21 | 80.8 | 44 | 75.9 |
| Average age (years) | 68.4 | | 69.3 | | 68.8 | |

N, number of individuals in the sample.

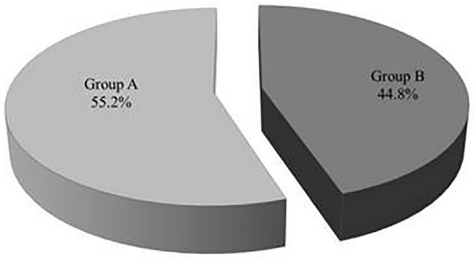


**Fig. 1 – Sample distribution according to the presence (Group A) or absence (Group B) of biological complications related to overdenture.**

All implants supporting the overdenture at the moment of the observation were evaluated and the clinical variables are summarized in Table 5. The total maxillary edentulousness was 63.8% (N=37) and the partial maxillary edentulousness was 36.2% (N=21).

The frequency of the biological complications considered is summarized in Fig. 2. Clinical manifestations of fistula and mobility/pain were reported in only 1.7% (N=1) of our study's sample, which corresponds to one individual positive for each of these parameters. Suppuration occurred in 8.6% (N=5) of the sample, erythema in 34.5% (N=20), peri-implant mucositis in 43.1% (N=25) and periimplantitis in 31.0% (N=18). Early implant loss (15.5%, N=9) occurred more often than late implant loss (3.4%, N=2).

The univariate logistic regression analysis included the following slope coefficients: logistic regression containing only the variable, estimated standard error for the estimated coefficient, Wald statistics, p value associated with the statistical coefficient test, estimated odds ratio, and the limits of the 95% confidence interval for odds ratio (Table 6).

After the statistical stabilization of the model, and considering the evidence found in the literature that bacteria are associated with the occurrence of biological complications, bacteria were included in the multivariate analysis to assess their joint influence, even though their p values were greater than 0.20. The *F. nucleatum* showed significant association with the outcome in all of the variables found. Introducing a negative coefficient appeared to prevent complications or even potentiate the biological defense when associated with other factors.

After the application of the stepwise forward technique with pE=0.15 and pR=0.20, the final model was completed with "biological complication" as the dependent variable (y=0, absence of biological complication and y=1, presence of biological complication) and the following selected variables: mean probing depth, metal exposure, *IL1B_allele2*, maxillary edentulousness, and *F. nucleatum* (Table 7). Apparent internal validation of the model was performed with the generated ROC curve analysis (Fig. 3), considering the probability estimated by the model as a variable test. The result is shown in Table 8.

The final model is the one that has the greatest number of explanatory variables and obeys the principle of parsimony [73]. If the area under the ROC curve is 0.950, the model correctly predicts the outcome in 95% of cases. Thus, the estimated logit model translates into:

$$g(x_i) = B_0 + B_1x_1 + \ldots + B_px_p$$

$$g(x_i) = -16.299 + 3.005 * \textbf{\textit{MeanPD}} + 6.247 * \textbf{\textit{Metalexposure}} + 3.224 * \textbf{\textit{IL1B\_alelle2}} + 1.953 * \textbf{\textit{Maxillary edentulousness}} - 3.76 * \textbf{\textit{F. nucleatum}}$$

In terms of estimated probability, the model would be:

$$\hat{\pi}(x_i) = \frac{\exp(g(x_i))}{1 + \exp(g(x_i))}$$

## 4. Discussion

The size of our sample, although restricted to a specific group of oral rehabilitation implants (dental implant overdentures), is similar, and even bigger, to that of other studies that investigated genetic polymorphisms of interleukin-1 in subjects rehabilitated with dental implants [40,41,43,45,46,48,49]. Nonetheless, it is also smaller than the sample sizes of other studies on the same area [22,42,44,47,51,52]. In this regard, we emphasize that the election of a particular type of oral rehabilitation (overdenture with dental implants) may have probably contributed to the sample size achieved. However, we have noted that most of the conducted studies similar to ours included all types of oral rehabilitation on dental implants and some of them did not reveal the type of oral rehabilitation studied [40,42,43,45–47,49,51,52].

In the sample evaluated in this study, 75.9% of the participants were female and 24.1% male. Some of the studies mentioned above did not reveal the sex of their participants [41,42]. However, in most of the studies similar to ours, the distribution of the sample by sex with female predominance is the most reported [22,43,44,46–48,51,52]. The average age of our

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**Table 5 – Clinical variables related to peri-implant evaluation in both groups.**

| | | Group A (complication) | Group B (successful) | Total |
|---|---|---|---|---|
| Average plaque modified index | Mean | 1.178 | 0.550 | 0.897 |
| | Standard deviation | 0.808 | – | 0.815 |
| | Median | 1.375 | 0.000 | 0.889 |
| | Minimum | 0.000 | 0.000 | 0.000 |
| | Maximum | 3.000 | 2.000 | 3.000 |
| Average bleeding modified index | Mean | 1.187 | 0.000 | 0.655 |
| | Standard deviation | 0.557 | – | 0.723 |
| | Median | 1.000 | 0.000 | 0.500 |
| | Minimum | 0.250 | 0.000 | 0.000 |
| | Maximum | 2.667 | 0.000 | 2.667 |
| Mean probing depth (mm) | Mean | 3.782 | 2.698 | 3.296 |
| | Standard deviation | 0.797 | 0.890 | 0.994 |
| | Median | 3.704 | 2.584 | 3.282 |
| | Minimum | 2.375 | 1.000 | 1.000 |
| | Maximum | 5.429 | 4.750 | 5.429 |
| Mean attached gingiva (mm) | Mean | 1.091 | 1.350 | 1.207 |
| | Standard deviation | 1.001 | 0.781 | 0.911 |
| | Median | 1.000 | 1.646 | 1.125 |
| | Minimum | 0.000 | 0.000 | 0.000 |
| | Maximum | 4.125 | 2.500 | 4.125 |

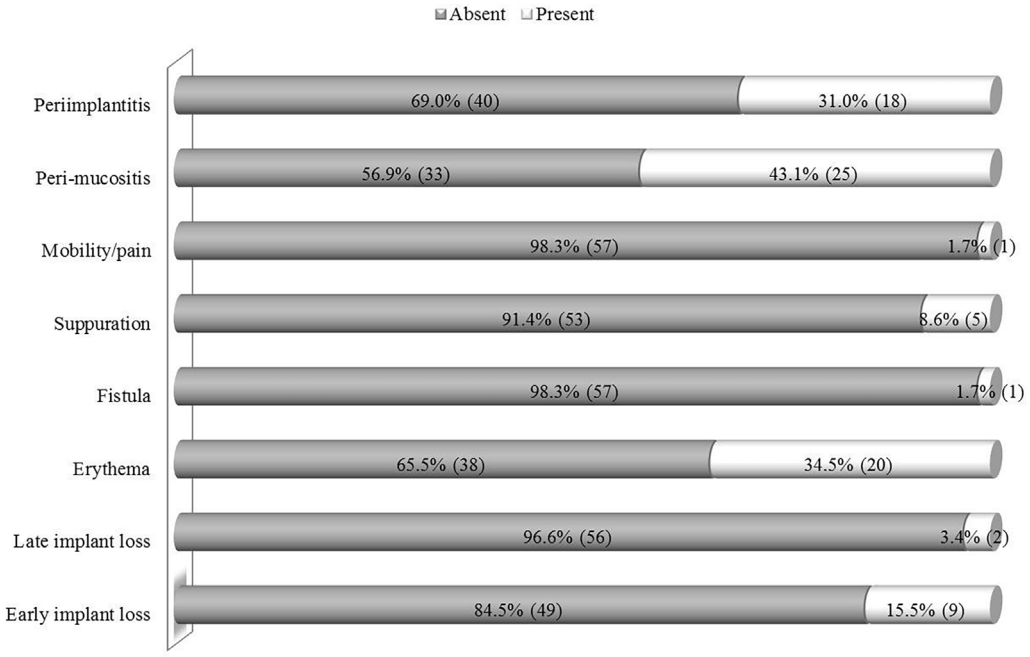


**Fig. 2 – Sample distribution according to the peri-implant biological complications (N=58).**

sample was higher than that of other research studies on interleukin-1 genetic polymorphisms in populations rehabilitated with dental implants, which reported values ranging between 44 and 57 years [43,45,49,51,52]. However, it was similar to that found in the studies of Rogers and Laine [41,47]. This fact is probably related to the type of oral rehabilitation selected in our investigation – overdenture – as it is most common in the elderly.

The positive genotype of interleukin-1 (allele 2 in both −889*IL1A* and +3953*IL1B* genes) was found to be associated with the evaluated outcome (presence or absence of biological complication in overdentures). In the univariate analysis (Table 6), this variable revealed a statistically significant p value (p=0.025) and so it was selected as one of the candidate variables to integrate the final logistic regression model. However, after model stabilization in the set of all the

**Table 6 – Univariate logistic regression analysis.**

| Variable | B | S.E. | Wald | df | p value | exp(B) | CI at 95% for exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | LL | UL |
| Medical treatment | −1.099 | 0.729 | 2.271 | 1 | 0.132 | 0.333 | 0.080 | 1.391 |
| Surgery | 1.248 | 0.723 | 2.984 | 1 | 0.084 | 3.485 | 0.845 | 14.366 |
| Implant technique | 0.766 | 0.671 | 1.305 | 1 | 0.253 | 2.152 | 0.578 | 8.015 |
| Postsurgical | 0.766 | 0.671 | 1.305 | 1 | 0.253 | 2.152 | 0.578 | 8.015 |
| Average plaque modified index | 1.084 | 0.386 | 7.886 | 1 | 0.005 | 2.956 | 1.387 | 6.298 |
| Mean probing depth (PD) | 1.633 | 0.464 | 12.407 | 1 | 0.000 | 5.121 | 2.064 | 12.709 |
| Mean attached gingiva | −0.322 | 0.300 | 1.157 | 1 | 0.282 | 0.724 | 0.403 | 1.303 |
| Metal exposure | 3.344 | 1.080 | 9.595 | 1 | 0.002 | 28.333 | 3.415 | 235.091 |
| IL1A_allele2 | 0.686 | 0.553 | 1.537 | 1 | 0.215 | 1.985 | 0.671 | 5.871 |
| IL1B_allele2 | 1.329 | 0.585 | 5.163 | 1 | 0.023 | 3.778 | 1.200 | 11.889 |
| IL-1 Genotype | 1.453 | 0.650 | 5.001 | 1 | 0.025 | 4.278 | 1.197 | 15.292 |
| *A. actinomycetemcomitans* | 0.557 | 0.596 | 0.875 | 1 | 0.350 | 1.746 | 0.543 | 5.615 |
| *B. forsythus* | 0.405 | 0.531 | 0.584 | 1 | 0.445 | 1.500 | 0.530 | 4.245 |
| *F. nucleatum* | −0.468 | 0.633 | 0.546 | 1 | 0.460 | 0.626 | 0.181 | 2.166 |
| *P. gingivalis* | 0.385 | 0.545 | 0.498 | 1 | 0.480 | 1.469 | 0.505 | 4.274 |
| Maxillary edentulousness | 1.110 | 0.543 | 4.186 | 1 | 0.041 | 3.035 | 1.048 | 8.789 |
| Gingiva hypertrophy | 1.056 | 0.614 | 2.954 | 1 | 0.086 | 2.874 | 0.862 | 9.576 |

B, logistic regression containing only the variable; S.E., estimated standard error for the estimated coefficient; Wald, Wald statistics; df, degrees of freedom; p value, value associated with the statistical coefficient test; exp(B), estimated odds ratio; CI, confidence interval of 95% for odds ratio; LL, lower limit; UL, upper limit.

**Table 7 – Final model.**

| | B | S.E. | Wald | df | p value | exp(B) | CI at 95% for exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | LL | UL |
| Mean probing depth (PD) | 3.005 | 1.052 | 8.159 | 1 | 0.004 | 20.192 | 2.568 | 158.773 |
| Metal exposure | 6.247 | 2.385 | 6.859 | 1 | 0.009 | 516.567 | 4.817 | 55400.21 |
| IL1B_allele2 | 3.224 | 1.331 | 5.864 | 1 | 0.015 | 25.118 | 1.849 | 341.264 |
| Maxillary edentulousness | 1.953 | 1.433 | 1.857 | 1 | 0.173 | 7.047 | 0.425 | 116.866 |
| *F. nucleatum* | −3.76 | 1.848 | 4.14 | 1 | 0.042 | 0.023 | 0.001 | 0.871 |
| Constant | −16.299 | 6.542 | 6.208 | 1 | 0.013 | | | |

B, estimates for the slope coefficients of the univariate logistic regression model containing only this variable; S.E., estimated standard error for the estimated coefficient; Wald, Wald statistics; df, degrees of freedom; p value, value associated with the statistical coefficient test; exp(B), estimated odds ratio; CI, confidence interval of 95% for odds ratio; LL, lower limit; UL, upper limit.

variables, due to the unstableness related to its inclusion, the interleukin-1 genotype was ultimately not included in the final model.

In fact, our results of an association between a positive *IL-1* genotype and the presence of biological complications are discordant with some similar studies [22,40,41,44,46,47], probably due to the sample size or due to differences in the division of the population sample into groups. However, it should be noted that currently there is still no evidence to support or refute an association between the positive interleukin-1 genotype and the development of peri-implant biological complications. The outcome (presence or absence of complication in overdentures with dental implants) distribution revealed that biological complications were more associated with the presence of allele 2 of the *IL1B* gene (+3953). In fact, it was the only statistically significant p value (p=0.023) in the univariate analysis (Table 6). For this reason, this variable integrated our final logistic regression model. In this investigation, no significant association between the allelic or genotypic composition of *IL1RN* and the outcome (presence or absence of biological complications) was found.

Implant loss may be preceded by clinical signs related to the mean probing depth and the implant metal exposure. However, these signs correspond to variables very difficult to apply to the final model because their assessment is very subjective, as the mean probing depth is based on an average and the metal exposure is not even commonly measurable. In fact, in our final model, these variables showed an underestimated value, which may be caused by its subjective assessment or by the limited number of cases in our study (Table 7). Nevertheless, it should be noted that late implant loss has been associated with genetic polymorphisms of interleukin-1 (−889*IL1A*, +3954*IL1B*, and VNTR *IL1RN*), either alone or in combination. Although the −511*IL1B* gene polymorphism was not investigated in our research, it was reported to be associated with marginal bone loss around dental implants [43,49]. It should be noted that this peri-implant bone loss (corresponding to an early type) occurs

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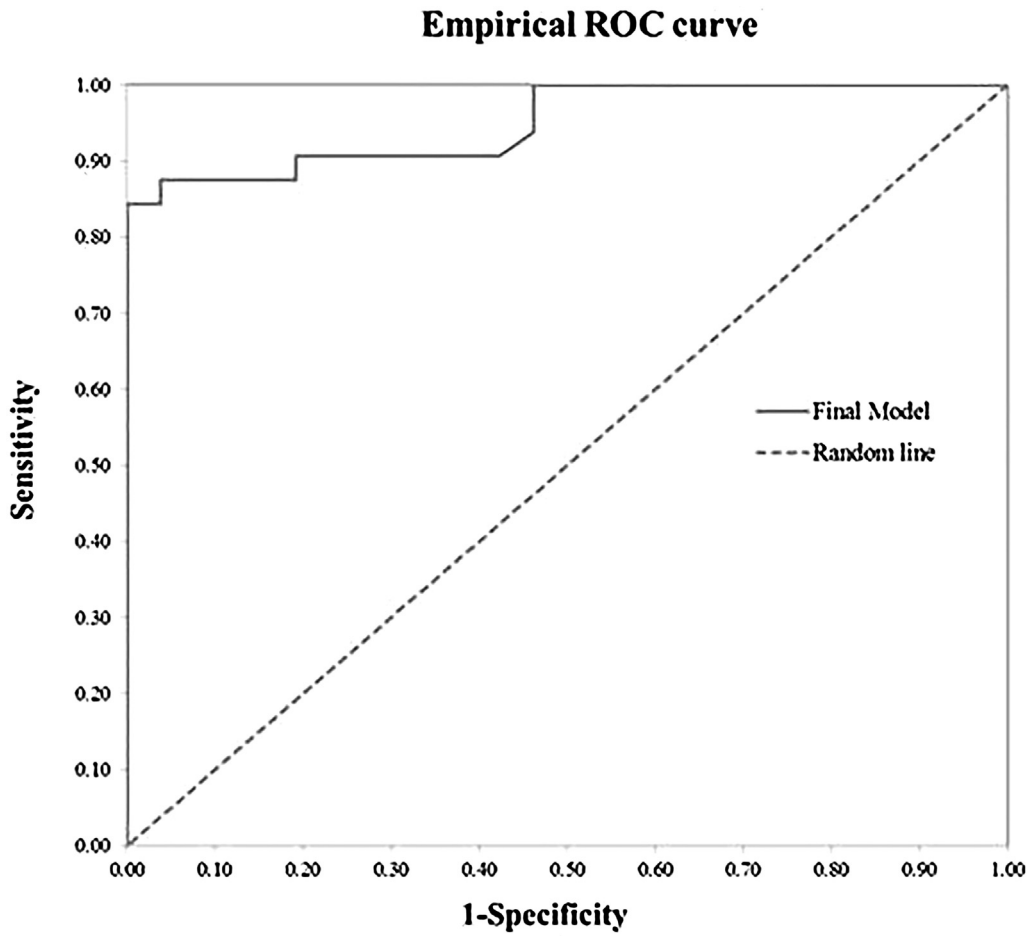


**Fig. 3 – Empirical ROC curve to the final model.**

**Table 8 – Statistics for ROC analysis.**

| Test variable | Area | S.E. | p value | CI at 95% | |
|---|---|---|---|---|---|
| | | | | LL | UL |
| Final model | 0.950 | 0.027 | ≈0.000 | 0.898 | 1.000 |

The null hypothesis considers that the true value of the area is 0.5.
Test variable, estimated probability for the final model; Area, area under the ROC curve; S.E., estimate of the standard error for the area; p value, value associated with the statistical coefficient test; CI, confidence interval of 95% for odds ratio; LL, lower limit; UL, upper limit.

before the placement of the implant in function, and thus should not be confused with the one that was evaluated in our study. The peri-implant bone loss that occurs after implant connection (late), often called periimplantitis, has been studied by several authors and has been related to the −889*IL1A* and +3953*IL1B* gene polymorphisms [40-42,44,47,74].

Currently, there is a consensus in the literature regarding the association of peri-implant health and periodontal tissues with biofilm with few gram-positive cocci and rods, and the fact that extensive areas of inflammation harbor large numbers of Gram-negative anaerobic bacteria [75]. Nevertheless, some authors also reported that when integrated into a biofilm, bacteria act in a complex way and may even act contrary to how they act when alone, i.e., instead of acting more aggressively, they act in cooperation [76–78]. In our study, the *F. nucleatum* was the bacterium less often detected in cases of periimplantitis and peri-implant mucositis. The absence of this bacterium appears to be associated with cases of no biological complications. When included in the logistic regression analysis, together with other variables, the *F. nucleatum* had a slightly protective influence on the possibility of biological complications. This finding may result from the individual characteristics of the studied sample, the type of rehabilitation (overdenture) and the qualitative method used in bacterial detection (present/absent). The detected protective mechanism of the *F. nucleatum* together with other variables should be investigated in a more comprehensive clinical context, with larger samples in both situations – disease and peri-implant health.

The value found for maxillary edentulousness was significantly associated with biological complications in the univariate logistic regression (p=0.041) and, therefore, this variable was a candidate to be included in the construction of the final model (Table 6). Thus, in the final model, a positive value for maxillary edentulousness means that the presence of biological complications is associated with the highest classification level of this variable – total maxillary edentulousness. The risk of a biological complication is seven times greater for a situation of total maxillary edentulousness when compared with a situation of partial maxillary edentulousness (Table 7).

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The international literature on dental implants rehabilitations and interleukin-1 genotype polymorphisms [40–49,51,52] does not address aspects related to occlusion and level of edentulousness of the subjects. In the study by Laine et al., 58 of the included subjects were reported to be edentulous and 62 were dentate [47], but no association with *IL1RN* polymorphisms was reported. In the study by Gruica, individuals were rehabilitated with single crowns or extensive fixed bridges, suggesting that subjects were partially edentulous, but no information is given regarding this parameter and the genotypic profile of the sample [44]. Therefore, we think that more evaluation studies of these genetic polymorphisms are required, involving larger samples and a detailed evaluation of the type of prosthesis and level of edentulousness.

Each regression coefficient of the logit model describes the level of contribution of that risk factor. Thus, a positive regression coefficient means that the presence of the factor increases the likelihood of the outcome. On the other hand, when the regression coefficient is negative, the presence of the factor decreases the likelihood of the outcome. Accordingly, when the coefficient is high, the factor strongly influences the probability of the outcome, while if it is close to zero, the factor has little influence on the probability of the result. The area under the ROC curve is one of the most widely used indexes for evaluating the model quality and, therefore, its discriminative power. Also, this method was already used in the study of models with implant fixed prostheses, with prediction value of 0.789 [73]. Thus, for example, an area under the ROC curve of 0.950 means that the model corresponds to the prediction in 95% of the cases, and so it can be considered a good fit [22,72,73,79]. Finally, to assess the significance of the model regarding the area under the ROC curve (AUC), its estimate is compared with that occurring by chance, which corresponds to an AUC=0.5.

More studies with bigger samples are required to construct and validate this decision model so that it can become a valid tool to assist clinicians in daily diagnosis and treatment planning of oral rehabilitation with implant overdentures.

## 5. Conclusions

Biological complications in implant-supported overdentures were found to be mostly associated with the presence of allele 2 of the *IL1B* gene (+3953). *F. nucleatum* had a slightly protective influence on the possibility of biological complications in implant-supported overdentures.

The model developed in this study could serve as a basis for further improved models in a near future, aimed to assist clinicians in the daily diagnosis and treatment planning practice of oral rehabilitation with implant overdentures.

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