Association between Interleukin-1 Polymorphisms and Susceptibility to Dental Peri-Implant Disease: A Meta-Analysis

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Abstract: Background and objective: Interleukins (ILs), as important biochemical mediators, control the host response to inflammation and are associated with bone resorption. In the present meta-analysis, we investigated the association between IL−1 polymorphisms and susceptibility to dental peri-implant disease (PID). Materials and methods: We searched Web of Science, Cochrane Library, Scopus, and PubMed/Medline databases for studies published until 9 September 2021, without any restrictions. We calculated the crude OR and 95% confidence intervals (CI) to estimate the associations between IL−1 polymorphisms and PID risk in the five genetic models. We further performed the subgroup analysis, sensitivity analysis, meta-regression, trial sequential analysis, and calculated the publication bias. Results: Out of 212 retrieved records, sixteen articles were used in the meta-analysis. There was no association between IL−1A (−889), IL−1B (−511), IL−1B (+3953), and IL−1RN (VNTR) polymorphisms and the risk of dental PIDs, but there was an increased risk of IL−1B (−3954) in the patients with PIDs. In addition, an association of the composite genotype of IL−1A (−889)/IL−1B (−3953) was observed with the risk of PIDs, but not for the composite genotype of IL−1A (−889)/IL−1B (−3954). The publication year, the ethnicity, sample size, and the outcome were significantly influenced pooled estimates of some genetic models. Trial sequential analysis showed the lack of sufficient sample sizes in the studies. Conclusions: Among IL−1 polymorphisms evaluated in the meta-analysis, the composite genotype of IL−1A (−889)/IL−1B (−3953) and IL−1B...
were the only polymorphisms associated with the risk of PID. The T allele and CT genotype of IL−1B (+3954) polymorphism were also associated with an elevated risk of PID.

**Keywords:** peri-implant disease; peri-implantitis; bone loss; polymorphism; interleukin−1

1. Introduction

Dental implants are currently considered an effective treatment for functional and cosmetic rehabilitation of patients with partial or complete edentulousness [1,2]. The clinical success of dental implants is based on the principle of osseointegration, which involves bone growth in metal implants. Multiple factors, including biological [3], may affect the success of the osseointegration. Peri-implantitis can lead to bone loss and finally implant failure [4,5]. Peri-implantitis, marginal bone loss, and implant failure are three outcomes associated with peri-implant diseases (PIDs) [6,7]. PID is a collective term for reversible peri-implant mucositis and irreversible peri-implantitis [8]. Peri-implantitis could negatively affect the quality of life [9].

In this view, meta-analyses [6–10], reviews [11], and original articles [12,13] demonstrated the role of several polymorphisms in PIDs. Proinflammatory cytokines, such as interleukins (ILs), are important biochemical mediators to control the host response to inflammation and to also stimulate the production and secretion of prostaglandins. Prostaglandins are associated with bone resorption and the metalloproteinases, which are involved in collagen degradation [14]. As such, IL−1 may be a useful indicator and biomarker in diagnosing peri-implantitis, especially because it has an important role in the periodontitis pathogenesis, and because it interferes with immune and inflammation processes, tissue damage, and homeostasis [15]. IL−1 is composed of 11 genes in the 430-kb fragment in the long arm DNA of chromosome 2, in the 2q12-q21 region. These genes produce the IL−1 alpha (IL−1A) and IL−1 beta (IL−1B) with genetic and biochemical differences but with the same biological functions [10–16]. IL−1 receptor antagonist (IL−1RN) gene regulates the synthesis of the IL−1ra antagonist protein, which can disrupt IL−1A and IL−1B function in competition for receptor binding [17].

A thorough literature search identified five systematic reviews [3–20] and three meta-analyses [10–22] focusing on the associations between IL−1 polymorphisms and PIDs. Among these meta-analyses, one meta-analysis [10] included the highest number of articles (13 articles) and reported an association between the occurrence of IL−1A (−889), IL−1B (−511), and IL−1B (+3954) polymorphisms in patients with PIDs. In contrast, the meta-analysis [10] reported no subgroup analysis, meta-regression, or trial sequential analysis (TSA); further, IL−1B (+3954) and IL−1B (+3954) polymorphisms were entered in the analyses without further distinctions, and last, the meta-analysis [10] included studies with a deviation from the Hardy–Weinberg equilibrium (HWE) in their control groups, along with studies with sample sizes with less than 10 cases. To counter this, the present meta-analysis expanded upon previous meta-analyses in three ways. First, the number of included studies was higher. Second, the number of statistical procedures was higher, and the statistical procedures were more complex and sophisticated. More specifically, to counterbalance possible biases and heterogeneity in the results, we employed procedures such as meta-regression and trial sequential analysis (TSA). Third and relatedly, we deleted those studies, in the event that in their control conditions a deviation from the Hardy–Weinberg equilibrium (HWE) could be observed. Given this background, the aims of the present comprehensive meta-analyses were as follows: to evaluate the association of 1A (−889), IL−1B (−511), and IL−1B (+3954), IL−1B (+3954), and IL−1RN (VNTR) polymorphisms with PIDs; and to conduct subgroup analysis, meta-regression, and TSA. To this end, we removed those studies with a deviation from HWE, separately analyzed IL−1B (+3954) and IL−1B (+3954) polymorphisms, and we considered only studies with a minimum of 10 cases.
2. Materials and Methods

2.1. Study Design

The guidelines of PRISMA were followed while reporting this meta-analysis [23]. The PECO (population, exposure, comparison, and outcomes) question [24] was: are IL−1 polymorphisms associated with PID risk among people with dental implants?

2.2. Search Strategy

One author (M.S.) extracted the specific studies from the databases, and the same author removed duplicates and irrelevant studies.

The Web of Science, Cochrane Library, Scopus, and PubMed/Medline databases were searched for studies published until 9 September 2021, without any restrictions. The searched terms were:

("oral implant*" or "dental implant*" or "peri-implant disease*" or "implant failure" or "implant loss" or "peri-implant" or "peri-implantitis" or "failing implant" or "implant bone loss") and ("interleukin*" or "interleukin-1*" or "IL−1*" or "IL1*") and ("variant*" or "polymorphism*" or "allele" or "genotype*"). In addition, we searched several sources (Google Scholar, Free Medical Journals, Library Genesis, and Science Direct) to retrieve relevant missed articles.

2.3. Inclusion and Exclusion Criteria

Inclusion criteria were (1) case-control studies; (2) dental PID was the outcome of interest; (3) studies reporting IL−1A (−889), IL−1B (−511); IL−1B (+3953); IL−1RN (VNTR), and composite genotype of IL−1A (−889)/IL−1B (+3953) and IL−1A (−889)/IL−1B (+3954) polymorphisms; (4) studies with the required data to calculate the odds ratios (ORs) with 95% confidence intervals (CIs) for genetic models; and (5) studies with no deviation of HWE in their control groups.

Exclusion criteria were (1) studies without the required data regarding genotype distributions, (2) animal studies, meta-analyses, review articles, book chapters, and letters to the editors; and (3) studies including less than 10 cases in each group (case and control groups).

The second author (H.M.) screened all the titles and abstracts based on the eligibility criteria and included/excluded studies for full-text review. Another author (D.S.B.) rechecked the relevant articles. In the event of low agreement, a third reviewer (S.B.) took a final solution.

2.4. Data Extraction

One author (M.S.) independently extracted the information or data from each study and another author (J.T.) rechecked them. If there was a disagreement between the authors, a third author (H.M) took the final decision.

2.5. Quality of Assessment

Two authors (M.S. and H.M.) independently evaluated the quality of each included article using the modified Newcastle-Ottawa Scale (NOS) questionnaire (a maximum total score of 9 was possible for each study) [25].

2.6. Statistical Analyses

We used Review Manager 5.3 (RevMan 5.3) to calculate crude OR and 95% confidence intervals (CI) as an estimate of the association between IL−1 polymorphisms and PID risk in the five genetic models. To assess the pooled OR significance, the Z-test was applied with a \( p < 0.05 \). The \( I^2 \) statistic showed the heterogeneity, we used the random-effect model, if there was a statistically significant heterogeneity (\( p < 0.1 \) or \( I^2 > 50\% \)); if there was no significant heterogeneity, the fixed-effect model was used. Ethnicity, PID outcome, and sample size were criteria for subgroup analyses.

We used Chi-square tests to calculate the \( p \)-value of the HWE in the control group of each study; in such cases, a \( p < 0.05 \) was considered as a deviation from the HWE.
We used Egger’s and Begg’s tests to plot and analyze the funnel plots; if a \( p < 0.05 \), then this was interpreted as publication bias. To evaluate the stability of pooled data, we used sensitivity analyses (“one study removed” and “cumulative analysis”). We used the Comprehensive Meta-Analysis version 2.0 (CMA 2.0) to calculate publication bias tests and sensitivity analyses.

We performed a meta-regression to survey the impact of publication year, ethnicity, PID outcome, and sample size on the pooled results. We used SPSS® version 22.0 (IBM Corporation, Armonk, NY; USA) to perform the meta-regression.

To conduct the trial sequential analysis (TSA) we used the TSA software (version 0.9.5.10 beta) (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark). Running TSAs reduce these statistical errors [26], because each meta-analysis may create a false-positive or negative conclusion [27]. Based on an alpha risk of 5%, a beta risk of 20%, and a two-sided boundary type we computed the required information size (RIS). Studies were considered to have adequate sample sizes and lead to valid results, if the analyses of the Z-curve reached the RIS line, or monitored the boundary line or futility area. Otherwise, the amount of information was considered not to be large enough, suggesting the need for more evidence. A threshold of futility area showed no effect before reaching the information size.

3. Results

3.1. Study Selection

“Of the 212 papers retrieved in the databases, 112 were duplicates, and thus removed, leaving 100 titles and the abstracts for further evaluation. It turned out that 61 papers were irrelevant records, and thus excluded. At the end, 39 full-text articles were evaluated for eligibility” (Figure 1). Then, 23 articles were excluded with reasons (5 were systematic reviews, 3 were meta-analyses, 5 were reviews, 2 had no control groups, 1 was book chapter, 2 included less than 10 cases, 1 had a control group demonstrating HWE deviation, and 4 had insufficient data to estimate the odds ratios). At last, 16 articles were entered in the analysis.

3.2. Characteristics of the Studies

Supplementary Table S1 provides the characteristics of sixteen articles [16–42] included in the meta-analysis. Nine articles [16–42] included Caucasians, three [29–41] Asians, and four [30–37] had participations with mixed ethnicity. Eighty studies reported IL−1A (−889) polymorphism [16,28–31,37,39,41], eight [16–41] IL−1B (−511), three [28,30,39] IL−1B (+3953) polymorphism, seven [16–42] IL−1B (+3954), two [30–40] IL−1RN (VNTR) polymorphism, three [28–38] composite genotype of IL−1A (−889) and IL−1B (+3953), and three [31–36] composite genotype of IL−1A (−889) and IL−1B (+3954) polymorphisms. Of the 16 articles, the outcomes were as follows: seven articles [16–39]: implant failure; six articles [31–42]: peri-implantitis; three articles [29–41]: marginal bone loss. Supplementary Table S1 provides the quality scores of each study: 14 out of 16 studies were considered to be of high quality (score ≥ 7).

3.3. Pooled Analyses

As Table 1 shows, the pooled ORs for the association between alleles and genotypes of IL−1A (−889) polymorphism and the risk of dental PID were 1.19 (95% CI: 0.92, 1.55; \( p = 0.19 \); \( I^2 = 0\% \)) for allelic, 1.18 (95% CI: 0.62, 2.55; \( p = 0.61 \); \( I^2 = 0\% \)) for homozygous, 1.45 (95% CI: 0.97, 2.16; \( p = 0.07 \); \( I^2 = 0\% \)) for heterozygous, 1.43 (95% CI: 0.98, 2.10; \( p = 0.07 \); \( I^2 = 0\% \)) for recessive, and 1.02 (95% CI: 0.64, 1.63; \( p = 0.94 \); \( I^2 = 0\% \)) for dominant models. There was no association between IL−1A (−889) polymorphism and the risk of dental PID.
Table 2 shows the pooled analyses for the association between alleles and genotypes of IL−1B (−511) polymorphism and the dental PID risk. The pooled ORs were 1.10 (95% CI: 0.69, 1.75; \( p = 0.70; I^2 = 75\% \)) for allelic, 1.20 (95% CI: 0.59, 2.42; \( p = 0.61; I^2 = 54\% \)) for homozygous, 1.72 (95% CI: 0.52, 1.01; \( p = 0.06; I^2 = 18\% \)) for heterozygous, 1.84 (95% CI: 0.61, 1.14; \( p = 0.25; I^2 = 48\% \)) for recessive, and 1.45 (95% CI: 1.00, 2.09; \( p = 0.05; I^2 = 42\% \)) for dominant models. There was no association between IL−1B (−511) polymorphism and the risk of dental PID.
Table 1. Pooled analysis of the association between alleles and genotypes of IL-1A (−889) polymorphism and the risk of dental PID.

| Genetic Model | First Author, Publication Year | Case | Control | Weight | Odds Ratio |
|---------------|--------------------------------|------|---------|--------|------------|
|               |                                | Events | Total | Events | Total | M-H, Fixed, 95% CI |
| **T vs. C**   | Rogers, 2002 [28]              | 10    | 38     | 16     | 62     | 8.8% 1.03 [0.41, 2.57] |
|               | Shimpuku, 2003 [29]            | 4     | 34     | 4      | 44     | 3.0% 1.33 [0.31, 5.77] |
|               | Campos, 2005 [30]              | 17    | 56     | 21     | 68     | 12.9% 0.98 [0.45, 2.10] |
|               | Laine, 2006 [31]               | 49    | 142    | 33     | 98     | 25.0% 1.04 [0.60, 1.79] |
|               | Melo, 2012 [37]                | 25    | 32     | 51     | 62     | 7.4% 0.77 [0.27, 2.23] |
|               | Jacobi-Gresser, 2013 [39]      | 28    | 82     | 32     | 136    | 15.5% 1.69 [0.92, 3.08] |
|               | Cosyn, 2016 [16]               | 10    | 24     | 4      | 26     | 2.2% 3.93 [1.03, 14.99] |
|               | Agrawal, 2021 [41]             | 98    | 136    | 89     | 126    | 25.2% 1.07 [0.63, 1.83] |
| **Subtotal (95% CI)** |                          | 241   | 544    | 250    | 622    | 100.0% 1.19 [0.92, 1.55] |
| **TT vs. CC** | Rogers, 2002 [28]              | 0     | 9      | 3      | 21     | 12.2% 0.28 [0.01, 5.96] |
|               | Shimpuku, 2003 [29]            | 1     | 15     | 0      | 18     | 2.4% 3.83 [0.14, 101.07] |
|               | Campos, 2005 [30]              | 4     | 19     | 5      | 23     | 21.0% 0.96 [0.22, 4.23] |
|               | Laine, 2006 [31]               | 2     | 26     | 3      | 22     | 17.6% 0.53 [0.08, 3.49] |
|               | Melo, 2012 [37]                | 9     | 9      | 21     | 22     | 3.8% 1.33 [0.05, 35.60] |
|               | Jacobi-Gresser, 2013 [39]      | 3     | 19     | 3      | 42     | 9.2% 2.44 [0.44, 13.38] |
|               | Cosyn, 2016 [16]               | 2     | 6      | 0      | 9      | 1.6% 10.56 [0.41, 268.69] |
|               | Agrawal, 2021 [41]             | 37    | 44     | 32     | 38     | 32.1% 0.99 [0.30, 3.25] |
| **Subtotal (95% CI)** |                          | 147   | 195    | 67     | 195    | 100.0% 1.18 [0.62, 2.25] |
| **CT vs. CC** | Rogers, 2002 [28]              | 10    | 19     | 10     | 28     | 9.6% 2.00 [0.61, 6.55] |
|               | Shimpuku, 2003 [29]            | 2     | 16     | 4      | 22     | 7.4% 0.64 [0.10, 4.03] |
|               | Campos, 2005 [30]              | 9     | 24     | 11     | 29     | 15.6% 0.98 [0.32, 3.00] |
|               | Laine, 2006 [31]               | 45    | 69     | 27     | 46     | 28.3% 1.32 [0.61, 2.84] |
|               | Melo, 2012 [37]                | 7     | 7      | 9      | 10     | 1.3% 2.37 [0.08, 66.88] |
|               | Jacobi-Gresser, 2013 [39]      | 22    | 38     | 26     | 65     | 20.3% 2.06 [0.91, 4.65] |
|               | Cosyn, 2016 [16]               | 6     | 10     | 4      | 13     | 3.5% 3.38 [0.60, 19.01] |
|               | Agrawal, 2021 [41]             | 24    | 31     | 25     | 31     | 14.2% 0.82 [0.24, 2.80] |
| **Subtotal (95% CI)** |                          | 214   | 244    | 116    | 244    | 100.0% 1.45 [0.97, 2.16] |

Heterogeneity: Chi² = 4.11, df = 7 (p = 0.77); I² = 0% Test for overall effect: Z = 1.81 (p = 0.07)
### Table 1. Cont.

| Genetic Model | First Author, Publication Year | Case | Control | Weight | Odds Ratio |
|---------------|--------------------------------|------|---------|--------|------------|
|               |                                | Events | Total | Events | Total | M-H, Fixed, 95% CI | |
| TT + CT vs. CC | Rogers, 2002 [28] | 10 | 19 | 13 | 31 | 10.7% | 1.54 [0.49, 4.85] |
|               | Shimpuku, 2003 [29] | 3 | 17 | 4 | 22 | 6.6% | 0.96 [0.18, 5.03] |
|               | Campos, 2005 [30] | 13 | 28 | 16 | 34 | 17.7% | 0.97 [0.36, 2.66] |
|               | Laine, 2006 [31] | 47 | 71 | 30 | 49 | 27.4% | 1.24 [0.58, 2.64] |
|               | Melo, 2012 [37] | 16 | 16 | 30 | 31 | 1.4% | 1.62 [0.06, 42.12] |
|               | Jacobi-Gresser, 2013 [39] | 25 | 41 | 29 | 68 | 19.4% | 2.10 [0.95, 4.63] |
|               | Cosyn, 2016 [16] | 8 | 12 | 4 | 13 | 2.9% | 4.50 [0.84, 24.18] |
|               | Agrawal, 2021 [41] | 61 | 68 | 57 | 63 | 13.9% | 0.92 [0.29, 2.89] |
| Subtotal (95% CI) | 272 | 311 | 100.0% | 1.43 [0.98, 2.10] |
| Total events | 183 | | 183 | | |
| TT vs. CC + CT | Rogers, 2002 [28] | 0 | 19 | 3 | 31 | 7.7% | 0.21 [0.01, 4.27] |
|               | Shimpuku, 2003 [29] | 1 | 17 | 0 | 22 | 1.2% | 4.09 [0.16, 106.89] |
|               | Campos, 2005 [30] | 4 | 28 | 5 | 34 | 11.3% | 0.97 [0.23, 4.01] |
|               | Laine, 2006 [31] | 2 | 71 | 3 | 49 | 10.1% | 0.44 [0.07, 2.76] |
|               | Melo, 2012 [37] | 9 | 16 | 21 | 31 | 18.3% | 0.61 [0.18, 2.12] |
|               | Jacobi-Gresser, 2013 [39] | 3 | 41 | 3 | 68 | 6.1% | 1.71 [0.33, 8.90] |
|               | Cosyn, 2016 [16] | 2 | 12 | 0 | 13 | 1.1% | 6.43 [0.28, 148.77] |
|               | Agrawal, 2021 [41] | 37 | 68 | 32 | 63 | 44.2% | 1.16 [0.58, 2.30] |
| Subtotal (95% CI) | 272 | 311 | 100.0% | 1.02 [0.64, 1.63] |
| Total events | 58 | 67 | | |

Heterogeneity: Chi² = 4.21, df = 7 (p = 0.76); I² = 0% Test for overall effect: Z = 1.83 (p = 0.07)

Abbreviation: CI: confidence interval; F: heterogeneity.
Table 2. Pooled analysis of the association between alleles and genotypes of IL−1B (−511) polymorphism and the risk of dental PID.

| Genetic Model | First Author, Publication Year | Event | Total | Event | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---------------|--------------------------------|-------|-------|-------|-------|--------|-------------------------------|
| **T vs. C**   |                                |       |       |       |       |        |                               |
| Shimpuku, 2003 [29] |                                | 22    | 34    | 19    | 44    | 10.6%  | 2.41 [0.96, 6.07]             |
| Campos, 2005 [30]  |                                | 21    | 56    | 30    | 68    | 12.6%  | 0.76 [0.37, 1.57]             |
| Laine, 2006 [31]   |                                | 51    | 142   | 35    | 98    | 14.6%  | 1.01 [0.59, 1.73]             |
| Lin, 2007 [33]     |                                | 37    | 58    | 19    | 60    | 12.2%  | 3.80 [1.77, 8.16]             |
| Dirschnabel, 2011 [35] |                            | 83    | 184   | 144   | 370   | 16.4%  | 1.29 [0.90, 1.84]             |
| Melo, 2012 [37]    |                                | 25    | 32    | 51    | 62    | 9.4%   | 0.77 [0.27, 2.23]             |
| Cosyn, 2016 [16]   |                                | 16    | 28    | 18    | 28    | 9.2%   | 0.74 [0.25, 2.17]             |
| Agrawal, 2021 [41] |                                | 40    | 136   | 61    | 126   | 14.9%  | 0.44 [0.27, 0.74]             |
| **Subtotal (95% CI)** |                            | 670   | 856   |       |       | 100.0% | 1.10 [0.69, 1.75]             |
| **Total events**  |                                | 295   |       | 377   |       |        |                               |
| **TT vs. CC**     |                                |       |       |       |       |        |                               |
| Shimpuku, 2003 [29] |                                | 8     | 11    | 3     | 9     | 8.8%   | 5.33 [0.78, 36.33]            |
| Campos, 2005 [30]  |                                | 7     | 21    | 7     | 18    | 13.4%  | 0.79 [0.21, 2.92]             |
| Laine, 2006 [31]   |                                | 10    | 40    | 5     | 24    | 14.4%  | 1.27 [0.37, 4.28]             |
| Lin, 2007 [33]     |                                | 14    | 20    | 6     | 15    | 12.6%  | 3.50 [0.86, 14.30]            |
| Dirschnabel, 2011 [35] |                            | 21    | 51    | 28    | 97    | 20.1%  | 1.73 [0.85, 3.51]             |
| Melo, 2012 [37]    |                                | 2     | 6     | 3     | 13    | 7.6%   | 1.67 [0.20, 14.05]            |
| Cosyn, 2016 [16]   |                                | 5     | 8     | 6     | 8     | 7.5%   | 0.56 [0.06, 4.76]             |
| Agrawal, 2021 [41] |                                | 7     | 42    | 13    | 28    | 15.6%  | 0.23 [0.08, 0.69]             |
| **Subtotal (95% CI)** |                            | 199   |       | 212   |       | 100.0% | 1.20 [0.59, 2.42]             |
| **Total events**  |                                | 74    |       | 71    |       |        |                               |
| **CT vs. CC**     |                                |       |       |       |       |        |                               |
| Shimpuku, 2003 [29] |                                | 6     | 9     | 13    | 19    | 3.4%   | 0.92 [0.17, 5.00]             |
| Campos, 2005 [30]  |                                | 7     | 21    | 16    | 27    | 11.4%  | 0.34 [0.10, 1.13]             |
| Laine, 2006 [31]   |                                | 31    | 61    | 25    | 44    | 17.5%  | 0.79 [0.36, 1.71]             |
| Lin, 2007 [33]     |                                | 9     | 15    | 15    | 24    | 5.6%   | 0.90 [0.24, 3.38]             |
| Dirschnabel, 2011 [35] |                            | 41    | 71    | 88    | 157   | 28.3%  | 1.07 [0.61, 1.89]             |
| Melo, 2012 [37]    |                                | 10    | 14    | 18    | 28    | 4.2%   | 1.39 [0.34, 5.60]             |
| Cosyn, 2016 [16]   |                                | 6     | 9     | 6     | 8     | 2.6%   | 0.67 [0.08, 5.54]             |
| Agrawal, 2021 [41] |                                | 26    | 61    | 35    | 50    | 27.0%  | 0.32 [0.14, 0.70]             |
| **Subtotal (95% CI)** |                            | 136   |       | 216   |       | 100.0% | 0.72 [0.52, 1.01]             |
| **Total events**  |                                | 136   |       | 216   |       |        |                               |

Heterogeneity: Tau² = 0.32; Chi² = 27.86, df = 7 (p = 0.0002); I² = 75% Test for overall effect: Z = 0.38 (p = 0.70)

Heterogeneity: Tau² = 0.51; Chi² = 15.17, df = 7 (p = 0.03); I² = 54% Test for overall effect: Z = 0.50 (p = 0.61)

Heterogeneity: Chi² = 8.58, df = 7 (p = 0.28); I² = 18% Test for overall effect: Z = 1.91 (p = 0.06)
| Genetic Model   | First Author, Publication Year | Events | Total | Events | Total | Weight | Odds Ratio          |
|----------------|-------------------------------|--------|-------|--------|-------|--------|---------------------|
| TT + CT vs. CC | Shimpuku, 2003 [29]           | 14     | 17    | 16     | 22    | 2.8%   | 1.75 [0.37, 8.33]   |
|                | Campos, 2005 [30]             | 14     | 28    | 23     | 34    | 11.7%  | 0.48 [0.17, 1.34]   |
|                | Laine, 2006 [31]              | 41     | 71    | 30     | 49    | 16.8%  | 0.87 [0.41, 1.82]   |
|                | Lin, 2007 [33]                | 23     | 29    | 21     | 30    | 4.8%   | 1.64 [0.50, 5.40]   |
|                |Dirschnabel, 2011 [35]         | 62     | 92    | 116    | 185   | 28.2%  | 1.23 [0.73, 2.08]   |
|                | Melo, 2012 [37]               | 12     | 16    | 21     | 31    | 4.0%   | 1.43 [0.37, 5.56]   |
|                | Cosyn, 2016 [16]              | 11     | 14    | 14     | 31    | 2.9%   | 0.61 [0.09, 4.37]   |
|                | Agrawal, 2021 [41]            | 33     | 68    | 48     | 63    | 28.8%  | 0.29 [0.14, 0.62]   |
|                |Subtotal (95% CI)              | 335    | 428   |        |       | 100.0% | 0.84 [0.61, 1.14]   |
|                |Total events                   | 210    | 287   |        |       |        |                     |

Heterogeneity: $\chi^2 = 13.40$, df = 7 ($p = 0.06$); $I^2 = 48\%$ Test for overall effect: $Z = 1.15$ ($p = 0.25$)

| TT vs. CC + CT | Shimpuku, 2003 [29]           | 8      | 17    | 3      | 22    | 3.0%   | 5.63 [1.20, 26.41]  |
|                | Campos, 2005 [30]             | 7      | 28    | 7      | 34    | 10.2%  | 1.29 [0.39, 4.24]   |
|                | Laine, 2006 [31]              | 10     | 71    | 5      | 49    | 11.0%  | 1.44 [0.46, 4.52]   |
|                | Lin, 2007 [33]                | 14     | 29    | 6      | 30    | 6.6%   | 3.73 [1.18, 11.83]  |
|                |Dirschnabel, 2011 [35]         | 21     | 92    | 28     | 185   | 31.0%  | 1.66 [0.88, 3.12]   |
|                | Melo, 2012 [37]               | 2      | 16    | 3      | 31    | 3.9%   | 1.33 [0.20, 8.92]   |
|                | Cosyn, 2016 [16]              | 5      | 14    | 6      | 14    | 8.3%   | 0.74 [0.16, 3.39]   |
|                | Agrawal, 2021 [41]            | 7      | 68    | 13     | 63    | 26.1%  | 0.44 [0.16, 1.19]   |
|                |Subtotal (95% CI)              | 335    | 428   |        |       | 100.0% | 1.45 [1.00, 2.09]   |
|                |Total events                   | 74     | 71    |        |       |        |                     |

Heterogeneity: $\chi^2 = 12.03$, df = 7 ($p = 0.10$); $I^2 = 42\%$ Test for overall effect: $Z = 1.95$ ($p = 0.05$)

Abbreviation: CI: confidence interval; $I^2$: heterogeneity. Fixed-effects model was used for homozygous (CT vs. CC), recessive (TT plus CT vs. CC), and dominant (TT vs. CC plus CT) models.
The pooled analyses for the association between alleles and genotypes of \(IL−1B\) (+3953) polymorphism and the dental PID risk are shown in Table 3. The pooled ORs were 1.45 (95% CI: 0.93, 2.27; \(p = 0.10\); \(I^2 = 0\%\)) for allelic, 2.03 (95% CI: 0.54, 7.55; \(p = 0.29\); \(I^2 = 0\%\)) for homozygous, 1.53 (95% CI: 0.87, 2.70; \(p = 0.14\); \(I^2 = 0\%\)) for heterozygous, 1.58 (95% CI: 0.91, 2.74; \(p = 0.10\); \(I^2 = 0\%\)) for recessive, and 1.78 (95% CI: 0.49, 6.42; \(p = 0.38\); \(I^2 = 0\%\)) for dominant models. There was no association between \(IL−1B\) (+3953) polymorphism and the risk of dental PID.

The pooled analyses for the association between alleles and genotypes of \(IL−1B\) (+3954) polymorphism and the dental PID risk are illustrated in Table 4. The pooled ORs were 2.04 (95% CI: 1.02, 4.08; \(p = 0.04\); \(I^2 = 73\%\)) for allelic, 1.73 (95% CI: 0.45, 6.58; \(p = 0.42\); \(I^2 = 52\%\)) for homozygous, 1.68 (95% CI: 0.18, 2.39; \(p = 0.004\); \(I^2 = 49\%\)) for heterozygous, 2.27 (95% CI: 1.11, 4.64; \(p = 0.03\); \(I^2 = 65\%\)) for recessive, and 1.19 (95% CI: 0.58, 2.45; \(p = 0.63\); \(I^2 = 42\%\)) for dominant models. Significant associations were observed between the T allele, CT genotype of \(IL−1B\) (+3954) polymorphism, and the susceptibility to dental PID.

The pooled analyses for the association between alleles and genotypes of \(IL−1RN\) (VNTR) polymorphism and the dental PID susceptibility are shown in Table 5. The pooled ORs were 0.91 (95% CI: 0.34, 2.49; \(p = 0.86\); \(I^2 = 74\%\)), 0.40 (95% CI: 0.01, 23.82; \(p = 0.66\); \(I^2 = 82\%\)), 0.86 (95% CI: 0.26, 2.81; \(p = 0.80\); \(I^2 = 66\%\)), 0.81 (95% CI: 0.19, 3.45; \(p = 0.77\); \(I^2 = 79\%\)), and 0.74 (95% CI: 0.26, 2.09; \(p = 0.57\); \(I^2 = 32\%\)) for allelic, homozygous, heterozygous, recessive, and dominant models, respectively. There was no association between \(IL−1RN\) (VNTR) polymorphism and the risk of dental PID.

Table 6 reports the pooled analyses for the association of the composite genotype of \(IL−1A\) (−889)/\(IL−1B\) (+3953) and \(IL−1A\) (−889)/\(IL−1B\) (+3954) with the risk of dental PID (genotype-positive vs. -negative). The pooled ORs were 1.73 (95% CI: 1.03, 2.92; \(p = 0.04\); \(I^2 = 0\%\)) for the composite genotype of \(IL−1A\) (−889)/\(IL−1B\) (+3953) and 2.31 (95% CI: 0.65, 8.17; \(p = 0.20\); \(I^2 = 82\%\)), 0.86 (95% CI: 0.26, 2.81; \(p = 0.80\); \(I^2 = 66\%\)), 0.81 (95% CI: 0.19, 3.45; \(p = 0.77\); \(I^2 = 72\%\)) for the composite genotype of \(IL−1A\) (−889)/\(IL−1B\) (+3954). An association was only observed between the composite genotype of \(IL−1A\) (−889)/\(IL−1B\) (+3953) and the risk of dental PID.

### 3.4. Subgroup Analysis

The subgroup analyses (based on the ethnicity, PID outcome, and the sample size) of the association between \(IL−1A\) (−889) polymorphism and the risk of dental PID are shown in Supplementary Table S2. The results showed that the ethnicity and the outcome were two significant factors that could affect the pooled estimates for the association between alleles, genotypes of \(IL−1A\) (−889) polymorphism and the risk of dental PID in heterozygous and recessive models.

The subgroup analyses (the ethnicity, the outcome, and the sample size) of the association between \(IL−1B\) (−511) polymorphism and the dental PID risk are shown in Supplementary Table S3. The findings reveal that the ethnicity, the outcome, and the sample size were significant factors influencing the pooled analysis for the association between \(IL−1B\) (−511) polymorphism and the risk of dental PID in the heterozygous model. For the dominant model, ethnicity, PID outcome, and sample size influenced the pooled estimates.

Supplementary Table S4 shows the subgroup analyses (the ethnicity, the outcome, and the sample size) of the association between \(IL−1B\) (+3954) polymorphism and the dental PID risk. The results suggest that sample size was a significant factor influencing the pooled analysis for the association between \(IL−1B\) (+3954) polymorphism and the risk of dental PID in allelic, heterozygous, and dominant models.
### Table 3. Pooled analysis of the association between alleles and genotypes of IL−1B (+3953) polymorphism and the risk of dental PID.

| Genetic Model | First Author, Publication Year | Events | Control | Weight | Odds Ratio |
|---------------|--------------------------------|--------|---------|--------|------------|
|               |                                | Case   |         |        |            |
|               |                                | Total  |         |        |            |
|               |                                | Events | Total   |        |            |
|               |                                |        |         |        |            |
| T vs. C       | Rogers, 2002 [28]              | 11     | 38      | 13     | 62         | 22.2% | 1.54 [0.61, 3.89] |
|               | Campos, 2005 [30]              | 13     | 56      | 14     | 68         | 30.7% | 1.17 [0.50, 2.74] |
|               | Jacobi-Gresser, 2013 [39]      | 24     | 82      | 28     | 136        | 47.1% | 1.60 [0.85, 3.00] |
|               | Subtotal (95% CI)              | 48     | 176     | 55     | 266        | 100.0%| 1.45 [0.93, 2.27] |
|               | Total events                   |        |         |        |            |
|               | Rogers, 2002 [28]              | 0      | 8       | 1      | 20         | 27.8% | 0.76 [0.03, 20.74] |
|               | Campos, 2005 [30]              | 3      | 21      | 2      | 24         | 52.4% | 1.83 [0.28, 12.19] |
|               | Jacobi-Gresser, 2013 [39]      | 2      | 21      | 1      | 42         | 19.8% | 4.32 [0.37, 50.58] |
|               | Subtotal (95% CI)              | 5      | 50      |        | 86         | 100.0%| 2.03 [0.54, 7.55] |
|               | Total events                   |        |         |        |            |
|               | Rogers, 2002 [28]              | 11     | 19      | 11     | 30         | 18.7% | 2.38 [0.73, 7.69] |
|               | Campos, 2005 [30]              | 7      | 25      | 10     | 32         | 32.8% | 0.86 [0.27, 2.70] |
|               | Jacobi-Gresser, 2013 [39]      | 20     | 39      | 26     | 67         | 48.5% | 1.66 [0.75, 3.68] |
|               | Subtotal (95% CI)              | 38     | 83      |         | 129        | 100.0%| 1.53 [0.87, 2.70] |
|               | Total events                   |        |         |        |            |
|               | Rogers, 2002 [28]              | 11     | 19      | 12     | 31         | 19.0% | 2.18 [0.68, 6.96] |
|               | Campos, 2005 [30]              | 10     | 28      | 12     | 34         | 34.5% | 1.02 [0.36, 2.90] |
|               | Jacobi-Gresser, 2013 [39]      | 22     | 41      | 27     | 68         | 46.6% | 1.76 [0.80, 3.85] |
|               | Subtotal (95% CI)              | 43     | 88      |         | 133        | 100.0%| 1.58 [0.91, 2.74] |
|               | Total events                   |        |         |        |            |
|               | Rogers, 2002 [28]              | 0      | 19      | 1      | 31         | 32.6% | 0.52 [0.02, 13.46] |
|               | Campos, 2005 [30]              | 3      | 28      | 2      | 34         | 46.7% | 1.92 [0.30, 12.38] |
|               | Jacobi-Gresser, 2013 [39]      | 2      | 41      | 1      | 68         | 20.7% | 3.44 [0.30, 39.13] |
|               | Subtotal (95% CI)              | 5      | 88      |         | 133        | 100.0%| 1.78 [0.49, 6.42] |
|               | Total events                   |        |         |        |            |

Heterogeneity: $\chi^2 = 0.35$, $df = 2$ ($p = 0.84$); $I^2 = 0\%$ Test for overall effect: $Z = 1.64$ ($p = 0.10$)

Heterogeneity: $\chi^2 = 0.71$, $df = 2$ ($p = 0.70$); $I^2 = 0\%$ Test for overall effect: $Z = 1.05$ ($p = 0.29$)

Heterogeneity: $\chi^2 = 1.56$, $df = 2$ ($p = 0.46$); $I^2 = 0\%$ Test for overall effect: $Z = 1.47$ ($p = 0.14$)

Heterogeneity: $\chi^2 = 1.04$, $df = 2$ ($p = 0.59$); $I^2 = 0\%$ Test for overall effect: $Z = 1.64$ ($p = 0.10$)

Abbreviation: CI: confidence interval; $I^2$: heterogeneity.
Table 4. Pooled analysis of the association between alleles and genotypes of IL−1B (+3954) polymorphism and the risk of dental PID.

| Genetic Model | First Author, Publication Year | Case | Control | Weight | Odds Ratio |
|---------------|--------------------------------|------|---------|--------|------------|
|               |                                | Events | Total | Events | Total | M-H, Random, 95% CI |
| T vs. C       | Shimpuku, 2003 [29]            | 1     | 34     | 2      | 44     | 6.0% 0.64 [0.06, 7.33] |
|               | Laine, 2006 [31]               | 40    | 142    | 30     | 98     | 20.6% 0.89 [0.51, 1.56] |
|               | Lin, 2007 [33]                 | 7     | 58     | 2      | 60     | 10.4% 3.98 [0.79, 20.03] |
|               | Montes, 2009 [34]              | 40    | 180    | 78     | 352    | 21.8% 1.00 [0.65, 1.55] |
|               | Melo, 2012 [37]                | 13    | 32     | 16     | 62     | 16.9% 1.97 [0.79, 4.87] |
|               | Cosyn, 2016 [16]               | 10    | 28     | 1      | 28     | 7.3% 15.00 [1.76, 127.54] |
|               | Saremi, 2021 [42]              | 20    | 100    | 7      | 178    | 17.0% 6.11 [2.48, 15.03] |
|               |                                |       | 574    |        | 822    | 100.0% 2.04 [1.02, 4.08] |
|               | Subtotal (95% CI)              | 574   | 131    | 100.0% | 2.04   |
|               | Total events                   | 574   | 131    | 100.0% | 2.04   |
|               | Heterogeneity: Tau² = 0.53; Chi² = 22.46, df = 6 (p = 0.0010); I² = 73% Test for overall effect: Z = 2.01 (p = 0.04) |
| TT vs. CC     | Shimpuku, 2003 [29]            | 0     | 16     | 0      | 20     | Not estimable |
|               | Laine, 2006 [31]               | 4     | 39     | 5      | 29     | 27.7% 0.55 [0.13, 2.26] |
|               | Lin, 2007 [33]                 | 0     | 22     | 0      | 28     | Not estimable |
|               | Montes, 2009 [34]              | 2     | 54     | 8      | 114    | 25.7% 0.51 [0.10, 2.49] |
|               | Melo, 2012 [37]                | 2     | 7      | 3      | 21     | 20.7% 2.40 [0.31, 18.55] |
|               | Cosyn, 2016 [16]               | 2     | 8      | 0      | 13     | 13.6% 10.38 [0.43, 249.04] |
|               | Saremi, 2021 [42]              | 4     | 38     | 0      | 82     | 13.6% 21.52 [1.13, 410.64] |
|               | Subtotal (95% CI)              | 184   | 307    | 100.0% | 1.73   |
|               | Total events                   | 184   | 307    | 100.0% | 1.73   |
|               | Heterogeneity: Tau² = 1.16; Chi² = 8.40, df = 4 (p = 0.08); I² = 52% Test for overall effect: Z = 0.80 (p = 0.42) |
| CT vs. CC     | Shimpuku, 2003 [29]            | 1     | 17     | 2      | 22     | 3.5% 0.63 [0.05, 7.53] |
|               | Laine, 2006 [31]               | 32    | 67     | 20     | 44     | 26.7% 1.10 [0.51, 2.35] |
|               | Lin, 2007 [33]                 | 7     | 29     | 2      | 30     | 3.2% 4.45 [0.84, 23.61] |
|               | Montes, 2009 [34]              | 36    | 88     | 62     | 168    | 53.2% 1.18 [0.70, 2.01] |
|               | Melo, 2012 [37]                | 9     | 14     | 10     | 28     | 5.0% 3.24 [0.85, 12.36] |
|               | Cosyn, 2016 [16]               | 6     | 12     | 1      | 14     | 1.0% 13.00 [1.27, 133.28] |
|               | Saremi, 2021 [42]              | 12    | 46     | 7      | 89     | 7.5% 4.13 [1.50, 11.40] |
|               | Subtotal (95% CI)              | 273   | 395    | 100.0% | 1.68   |
|               | Total events                   | 273   | 395    | 100.0% | 1.68   |
|               | Heterogeneity: Chi² = 11.73, df = 6 (p = 0.07); I² = 49% Test for overall effect: Z = 2.89 (p = 0.004) |
| Genetic Model | First Author, Publication Year | Events | Total | Events | Total | Weight | Odds Ratio |
|---------------|--------------------------------|--------|-------|--------|-------|--------|------------|
| TT + CT vs. CC | Shimpuku, 2003 [29] | 1      | 17    | 2      | 22    | 6.3%   | 0.63 [0.05, 7.53] |
|               | Laine, 2006 [31]        | 36     | 71    | 25     | 49    | 20.6%  | 0.99 [0.48, 2.05]  |
|               | Lin, 2007 [33]          | 7      | 29    | 2      | 30    | 10.8%  | 4.45 [0.84, 23.61] |
|               | Montes, 2009 [34]       | 38     | 90    | 70     | 176   | 23.1%  | 1.11 [0.66, 1.85]  |
|               | Melo, 2012 [37]         | 11     | 16    | 13     | 31    | 14.3%  | 3.05 [0.85, 10.90] |
|               | Cosyn, 2016 [16]        | 8      | 14    | 1      | 14    | 7.1%   | 17.33 [1.75, 171.66]|
|               | Saremi, 2021 [42]       | 16     | 50    | 7      | 89    | 17.7%  | 5.51 [2.08, 14.60] |
|               | **Subtotal (95% CI)**   | 287    | 411   |        |       | 100.0% | 2.27 [1.11, 4.64]  |

| TT vs. CC + CT | Shimpuku, 2003 [29] | 0      | 17    | 0      | 22    | 22      | Not estimable |
|               | Laine, 2006 [31]     | 4      | 71    | 5      | 49    | 41.6%   | 0.53 [0.13, 2.06] |
|               | Lin, 2007 [33]       | 0      | 29    | 0      | 30    | Not estimable |
|               | Montes, 2009 [34]    | 2      | 90    | 8      | 176   | 39.5%   | 0.48 [0.10, 2.30] |
|               | Melo, 2012 [37]      | 2      | 16    | 3      | 31    | 13.3%   | 1.33 [0.20, 8.92] |
|               | Cosyn, 2016 [16]     | 2      | 14    | 0      | 14    | 3.1%    | 5.80 [0.25, 132.56]|
|               | Saremi, 2021 [42]    | 4      | 50    | 0      | 89    | 2.5%    | 17.32 [0.91, 328.70]|
|               | **Subtotal (95% CI)** | 287    | 411   |        |       | 100.0% | 1.19 [0.58, 2.45]  |

**Table 4. Cont.**

|               | **Total events** | 117    | 120   |
| Heterogeneity: Tau^2 = 0.51; Chi^2 = 17.02, df = 6 (p = 0.009); I^2 = 65% Test for overall effect: Z = 2.23 (p = 0.03) |

|               | **Total events** | 14     | 16    |
| Heterogeneity: Chi^2 = 6.85, df = 4 (p = 0.14); I^2 = 42% Test for overall effect: Z = 0.47 (p = 0.63) |

| Abbreviation: CI: confidence interval; I^2: heterogeneity. Fixed-effects model was used for homozygous (CT vs. CC) and dominant (TT vs. CC plus CT) models. |
Table 5. Pooled analysis of the association between alleles and genotypes of \textit{IL}–\textit{1RN} (VNTR) polymorphism and the risk of dental PID.

| Genetic Model | First Author, Publication Year | Case | Control | Weight | Odds Ratio |
|---------------|--------------------------------|------|---------|--------|------------|
|               |                                | Events | Total   | Events | Total      | M-H, Random, 95% CI |
| **A2 vs. A1** | Campos, 2005 [30]              | 19    | 54      | 17     | 66         | 47.5% 1.56 [0.71, 3.43] |
|               | Petkovic-Curcin, 2017 [40]     | 18    | 68      | 50     | 128        | 52.5% 0.56 [0.29, 1.07] |
|               | Subtotal (95% CI)              | 37    | 122     | 67     |            | 100.0% 0.91 [0.34, 2.49] |
| **A2A2 vs. A1A1** | Campos, 2005 [30]         | 3     | 14      | 2      | 20         | 53.4% 2.45 [0.35, 17.08] |
|               | Petkovic-Curcin, 2017 [40]     | 0     | 22      | 11     | 36         | 46.6% 0.05 [0.00, 0.88] |
|               | Subtotal (95% CI)              | 3     | 36      | 56     |            | 100.0% 0.40 [0.01, 23.82] |
| **A1A2 vs. A1A1** | Campos, 2005 [30]         | 13    | 24      | 13     | 31         | 46.7% 1.64 [0.56, 4.79] |
|               | Petkovic-Curcin, 2017 [40]     | 12    | 34      | 28     | 53         | 53.3% 0.49 [0.20, 1.18] |
|               | Subtotal (95% CI)              | 25    | 58      | 84     |            | 100.0% 0.86 [0.26, 2.81] |
| **A2A2 + A1A2 vs. A1A1** | Campos, 2005 [30]         | 16    | 27      | 15     | 33         | 48.1% 1.75 [0.62, 4.88] |
|               | Petkovic-Curcin, 2017 [40]     | 13    | 34      | 39     | 64         | 51.9% 0.40 [0.17, 0.93] |
|               | Subtotal (95% CI)              | 29    | 61      | 97     |            | 100.0% 0.81 [0.19, 3.45] |
| **A2A2 vs. A1A1 + A1A2** | Campos, 2005 [30]         | 3     | 27      | 2      | 33         | 18.7% 1.94 [0.30, 12.53] |
|               | Petkovic-Curcin, 2017 [40]     | 3     | 34      | 11     | 64         | 81.3% 0.47 [0.12, 1.80] |
|               | Subtotal (95% CI)              | 6     | 61      | 97     |            | 100.0% 0.74 [0.26, 2.09] |

Abbreviation: CI: confidence interval; I$^2$: heterogeneity. Fixed-effects model was used for dominant (A2A2 vs. A1A1 plus A1A2) model.
Table 6. Pooled analysis of the association between composite genotype of IL−1A (−889)/IL−1B (+3953) and IL−1A (−889)/IL−1B (+3954) and the risk of dental PID (genotype-positive vs. genotype-negative).

| The Composite Genotype | First Author, Publication Year | Case | Control | Weight | Odds Ratio |
|-------------------------|--------------------------------|------|---------|--------|------------|
| IL−1A (−889) and IL−1B (+3953) | Rogers, 2002 [28] | 9 | 19 | 11 | 31 | 20.7% | 1.64 [0.51, 5.23] |
|                          | Campos, 2005 [30] | 8 | 28 | 10 | 34 | 30.3% | 0.96 [0.32, 2.89] |
|                          | Vaz, 2012 [38] | 25 | 55 | 27 | 100 | 49.1% | 2.25 [1.13, 4.49] |
| Total (95% CI) | | 42 | 102 | | 165 | | 100.0% | 1.73 [1.03, 2.92] |
| Total events | | 42 | 48 | | | | | |
| Heterogeneity: Chi² = 1.67, df = 2 (p = 0.43); I² = 0% Test for overall effect: Z = 2.08 (p = 0.04) |

| IL−1A (−889) and IL−1B (+3954) | Laine, 2006 [31] | 34 | 71 | 22 | 49 | 40.5% | 1.13 [0.54, 2.34] |
| Lachmann, 2007 [32] | 6 | 11 | 8 | 18 | 28.1% | 1.50 [0.33, 6.77] |
| Hamdy, 2011 [36] | 17 | 25 | 5 | 25 | 31.4% | 8.50 [2.34, 30.91] |
| Total (95% CI) | | 57 | 107 | | 92 | | 100.0% | 2.31 [0.65, 8.17] |
| Total events | | 57 | 35 | | | | | |
| Heterogeneity: Tau² = 0.89; Chi² = 7.19, df = 2 (p = 0.03); I² = 72% Test for overall effect: Z = 1.29 (p = 0.20) |
3.5. Meta-Regression

Supplementary Table S5 provides the results of the meta-regression analysis to evaluate the effect of publication year, sample size, ethnicity, and PID outcome on the association between IL−1A (−889), IL−1B (−511), and IL−1B (+3954) polymorphisms and the risk of dental PID. The publication year predicted pooled results, and just for the dominant model of IL−1B (+3954) polymorphism.

3.6. Sensitivity Analysis

Both “one study removed” and “cumulative analysis” were performed for the sensitivity analyses that included at least three studies; results remained stable.

3.7. Trial Sequential Analysis

Supplementary Figure S1 shows the TSA based on recessive model for the association of IL−1A (−889), IL−1B (−511), and IL−1B (+3954) polymorphisms with the risk of dental PID. The Z-curve did neither reach the RIS line, nor monitor the boundary line or futility area; as a result, there was inadequate evidence and therefore, more information was needed.

3.8. Publication Bias

We plotted the funnel plots (Supplementary Figure S2) and calculated the p-values of Egger’s and Begg’s tests to evaluate the publication bias across the studies in the analyses that included at least three studies. There was no publication bias across the studies, except homozygous (p-value of Egger’s test: 0.007) and dominant models (p-value of Egger’s test: 0.013) of IL−1B (+3954) polymorphism.

4. Discussion

The main findings of the present meta-analysis showed that there was no association between IL−1A (−889), IL−1B (−511), IL−1B (+3953), and IL−1RN (VNTR) polymorphisms and the risk of dental PIDs. In contrast, there was an increased risk of IL−1B (+3954) in the patients with PIDs. In addition, an association was observed between the composite genotype of IL−1A (−889)/IL−1B (+3953) and PIDs, but not between the composite genotype of IL−1A (−889)/IL−1B (+3954) and PIDs. Further, the subgroup analysis showed that ethnicity and PID outcomes influenced the association of IL−1A (−889) polymorphism and the risk of PID. Ethnicity, PID outcome, and sample sizes were significant factors for IL−1B (−511) polymorphism, while the sample size influenced the IL−1B (+3954) polymorphism. Further, based on meta-regression, the publication year was a significant predictor of the pooled results of IL−1B (+3954) polymorphism. Last, the TSA showed that there were inadequate sample sizes among the studies included in the analyses.

Three published meta-analyses [10–22] investigated the association between the IL−1 polymorphisms and the risk of PIDs. Junior et al. [21] reported just two articles and reported that there was no association between IL−1B (−511) polymorphism and the risk of implant failure based on the allelic model. Liao et al. [10] included 13 articles reporting IL−1A (−889), IL−1B (−511), IL−1B (+3954), and IL−1RN (VNTR) polymorphisms and the risk of dental PIDs and also mixing the patients with peri-implantitis, implant loss, and marginal bone loss based on the allelic model. This study [10] included both IL−1B (+3953) and IL−1B (+3954) in a similar analysis. The authors found that IL−1B (−511) polymorphism and the composite genotype of IL−1A (−889)/IL−1B (+3954) on risk for implant failure and peri-implantitis. Third, meta-analysis [22] included two articles to check the association of IL−1 polymorphisms (IL−1A (−889), IL−1B (−511), and IL−1B (+3954)) with early crestal bone loss around submerged dental implants that there was just an association between IL−1B (−511) polymorphisms and early crestal bone loss. Our meta-analysis included 16 articles to investigate the association between the IL−1
polymorphisms and the risk of PIDs. In addition, we included peri-implantitis, implant loss, and marginal bone loss as PIDs and mixed them in the first analysis such as the meta-analysis of Liao et al. [10], but in subgroup analysis, we separately analyzed them for each polymorphism. Unlike the previously mentioned meta-analyses, we used five genetic models, meta-regression, and TSA, as well as removed studies with a deviation from HWE in their control group to reduce bias and heterogeneity.

IL−1A (−889) polymorphism was found to be related to chronic periodontal disease in Brazilian cases [43]. Further, for IL−1A (−889) polymorphism, T allele compared to C allele induced a four times higher expression of IL−1 alpha [44] and also TT genotypes compared to CC genotype [45]. Similarly, Cosyn et al. [16] presented the association between IL−1A (−889) polymorphism and the risk of implant failure. In contrast and unlike previous studies [28–41], we were unable to identify an association between this polymorphism and the risk of PID. However, our subgroup analysis showed that the association between IL−1A (−889) polymorphism and the risk of implant failure was statistically significant. Therefore, PID outcomes appeared to be important factors to explain the association between IL−1A (−889) polymorphism and PID risk.

IL−1B (−511) polymorphism is similar to IL−1B (+3954) polymorphism, which was found to have a strong role in chronic periodontitis and inflammation [46]. With regards to the association of IL−1B (−511) polymorphism with the risk of PID, one study [33] showed an elevated risk, while another study [41] reported a protective role of this polymorphism. In this view, the present meta-analysis was unable to confirm the association between IL−1B (−511) polymorphism and the risk of PID, and this zero association was already observed elsewhere [16–37]. However, the subgroup analysis showed that TC genotype has a protective role on marginal bone loss in Asian individuals. Therefore, the role of ethnicity should be considered when focusing on the association between IL−1B polymorphisms and the risk of PID.

The IL−1 gene polymorphism may have a negative effect on the results of peri-implantitis treatment in genotype-positive individuals, and the combination of IL−1A (−889)/IL−1B (+3954) in peri-implant tissues may act as a risk factor that elevates tissue destruction [36]. In this view, polymorphisms may be involved in osseointegration through the cumulative effect of multiple polymorphisms [47]. In our meta-analysis, the pooled results showed that the combination of IL−1A (−889)/IL−1B (+3953) could act as a risk factor for PID, while this was not the case for the combination of IL−1A (−889)/IL−1B (+3954). Further, the prevalence of these combinations varied among ethnic groups [36]. Therefore, in future studies, and due to the different results between the combination of IL−1 polymorphisms and the risk of PID, the combination of IL−1 polymorphisms with emphasis on ethnicity demand special attention. In addition, the functional genetic polymorphisms of IL−1B (+3954) and IL−1RN (VNTR) may diversify the production of IL−1b and IL−1ra proteins [48,49]. IL−1B and IL−1RA may act as regulators of the inflammatory immune system [50]; as a result, polymorphisms in these genes can affect inflammation and cause implant failure [31,32]. Given this background, two studies reported that IL−1B (+3954) polymorphism could play a role in the pathogenesis of peri-implantitis and increase its risk [16,42]. In accordance, our meta-analysis confirmed the result that IL−1B (+3954) polymorphism caused an increased risk of PID, but not for individuals with peri-implantitis. In the same vein, our meta-analysis and several other individual studies [30–40] did not confirm the association of IL−1RN (VNTR) polymorphism with the risk of PID.

The success of dental implants is determined by several factors such as clinical, biomechanical, and genetic risk [51,52]. Further, the synergistic effect of smoking and the positive IL−1 genotype significantly increase the risk of implant failure [17]. Regardless of the status of the IL−1 genotype, smoking was associated with elevated peri-implant bone loss and implant failure [53,54]. In our meta-analysis, several studies did not report the smoking status, or data on smoking prevalence among case and control groups were not reported; as such, smoking status was not entered as a further factor in the present meta-
analysis. However, future studies should consider the smoking status and its correlation with implant failure and the prevalence of IL−1 polymorphisms.

Despite the new results, several limitations should be considered. First, based on TSA, there was a lack of sufficient sample sizes in the included studies. Second, only a very few studies were available for the two polymorphisms (IL−1B (+3953) and IL−1RN (VNTR)), given this, subgroup analyses and meta-regression analyses for these polymorphisms were not possible. Third, a high heterogeneity across the studies in several analyses was observed. Fourth, several confounding factors were observed in the pooled results.

In contrast, the strengths of the meta-analysis were first, the lack of publication bias across the studies in most analyses; second, the stability of the results; and third, studies with a deviation from HWE in their control group were removed.

5. Conclusions

The main findings of the meta-analysis showed that there was no association between IL−1A (−889), IL−1B (−511), IL−1B (+3953), and IL−1RN (VNTR) polymorphisms, the composite genotype of IL−1A (−889)/IL−1B (+3954) and the risk of dental PID. In contrast, the composite genotype of IL−1A (−889)/IL−1B (+3953) and IL−1B (+3954) polymorphism was associated with an elevated risk for PID. Further, other factors such as the publication bias, ethnicity, PID outcome, and sample size affected the pooled results. In addition, small sample sizes and high heterogeneity across the studies showed that the power and accuracy of the results appeared to be low. Clinicians should pay attention to the effects of these polymorphisms on the outcomes of treatment. Given this, further larger and well-designed studies among people of different ethnicities and with detailed individual information (age, sex, and smoking status) are needed to confirm the present results.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/pathogens10121600/s1, Figure S1: Trial sequential analysis of the association between genotypes of three polymorphisms and the risk of dental PID based on recessive model (TT + CT vs. CC). (A) IL-1A (−889) [D2 = 0%; RIS = 1027]; (B) IL-1B (−511) [D2 = 57%; RIS = 8814]; and (D) IL-1B (+3954) [D2 = 76%; RIS = 2205]. Figure S2: Funnel plot analysis of the association between alleles, genotypes of IL-1 polymorphisms and the risk of dental PID. (A) IL-1A (−889); (B) IL-1B (−511); (C) IL-1B (+3953); (D) IL-1B (+3954); (E) composite genotype of IL-1A (−889)/IL-1B (+3953); and (F) composite genotype of IL-1A (−889)/IL-1B (+3954). Table S1: Characteristics of the studies included in the meta-analysis. Table S2: Subgroup analysis of the association between alleles, genotypes of IL-1A (−889) polymorphism and the risk of dental PID. Table S3: Subgroup analysis of the association between alleles, genotypes of IL-1B (−511) polymorphism and the risk of dental PID. Table S4. Subgroup analysis of the association between alleles, genotypes of IL-1B (+3954) polymorphism and the risk of dental PID. Table S5. Meta-regression analysis of the association between alleles and genotypes of IL-1A (−889), IL-1B (−511), and IL-1B (+3954) polymorphisms and the risk of dental PID.

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References

1. Karoussis, I.K.; Kotsovillis, S.; Fourmousis, I. A comprehensive and critical review of dental implant prognosis in periodontally compromised partially edentulous patients. Clin. Oral Implant. Res. 2007, 18, 669–679. [CrossRef] [PubMed]

2. Bornstein, M.M.; Halbritter, S.; Harnisch, H.; Weber, H.-P.; Buser, D. A retrospective analysis of patients referred for implant placement to a specialty clinic: Indications, surgical procedures, and early failures. Int. J. Oral Maxillofac. Implant. 2008, 23, 1109–1116. [PubMed]

3. Dereka, X.; Mardas, N.; Chin, S.; Petrie, A.; Donos, N. A systematic review on the association between genetic predisposition and dental implant biological complications. Clin. Oral Implant. Res. 2012, 23, 775–788. [CrossRef] [PubMed]

4. Kowalski, J.; Lapinska, B.; Nissan, J.; Lukomska-Szymanska, M. Factors Influencing Marginal Bone Loss around Dental Implants: A Narrative Review. Coatings 2021, 11, 865. [CrossRef]

5. Heitz-Mayfield, L.J. Peri-implant diseases: Diagnosis and risk indicators. J. Clin. Periodontol. 2008, 35, 292–304. [CrossRef]

6. Jamshidy, L.; Tadakamadla, S.K.; Choubsaz, P.; Sadeghi, M.; Tadakamadla, J. Association of IL-10 and TNF-α Polymorphisms with Dental Peri-Implant Disease Risk: A Meta-Analysis, Meta-Regression, and Trial Sequential Analysis. Int. J. Environ. Public Health 2021, 18, 7697. [CrossRef]

7. Mo, Y.-Y.; Zeng, X.-T.; Weng, H.; Cen, Y.; Zhao, Q.; Wen, X. Association between tumor necrosis factor-alpha G-308A polymorphism and dental peri-implant disease risk: A meta-analysis. Medicine 2016, 95, e4425. [CrossRef] [PubMed]

8. Nichols, J. The management of periodontal and peri implant disease. BDJ Team 2020, 7, 34–36. [CrossRef]

9. Insua, A.; Monje, A.; Wang, H.L.; Inglehart, M. Patient-centered perspectives and understanding of peri-implantitis. J. Periodontol. 2017, 88, 1153–1162. [CrossRef] [PubMed]

10. Liao, J.; Li, C.; Wang, Y.; Ten, M.; Sun, X.; Tian, A.; Zhang, Q.; Liang, X. Meta-analysis of the association between common interleukin-1 polymorphisms and dental implant failure. Mol. Biol. Rep. 2014, 41, 2789–2798. [CrossRef] [PubMed]

11. Zhang, F.; Finkelstein, J. The relationship between single nucleotide polymorphisms and dental implant loss: A scoping review. Clin. Cosmet. Investig. Dent. 2019, 11, 131. [CrossRef] [PubMed]

12. Casado, L.P.; Villas-Boas, R.; de Mello, W.; Duarte, L.M.E.; Granjeiro, M.J. Peri-implant disease and chronic periodontitis: Is interleukin-6 gene promoter polymorphism the common risk factor in a Brazilian population? J. Int. Maxillofac. Implant. 2013, 28, 35–43. [CrossRef] [PubMed]

13. e Silva, R.C.; Reis, M.B.L.; Arid, J.; Flores, E.K.B.; Cruz, G.V.; Maraño-Vásquez, G.A.; de Souza, L.K.F.; Novaes, A.B., Jr.; de Queiroz, A.M.; Küchler, E.C. Association between Genetic Polymorphisms in RANK, RANKL and OPG and Peri-Implant Diseases in Patients from the Amazon Region. Braz. Dent. J. 2020, 31, 63–68. [CrossRef]

14. Kornman, K.S. Interleukin-1 genetics, inflammatory mechanisms, and nutrigenetic opportunities to modulate diseases of aging. Am. J. Clin. Nutr. 2006, 83, 475S–483S. [CrossRef] [PubMed]

15. Graves, D.T.; Cochran, D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. J. Periodontol. 2003, 74, 391–401. [CrossRef] [PubMed]

16. Cosyn, J.; Christiaens, V.; Koningveld, V.; Coucke, P.; De Coster, P.; De Paepe, A.; De Bruyn, H. An exploratory case-control study on the impact of IL-1 gene polymorphism on early implant failure. Clin. Implant. Dent. Relat. Res. 2016, 18, 123–240. [CrossRef]

17. Andreiotelli, M.; Koutayas, S.-O.; Madianos, P.N.; Strub, J.-R. Relationship between interleukin-1 genotype and peri-implantitis: A literature review. Quintessence Int. 2008, 39, 289–298. [PubMed]

18. Huynh-Ba, G.; Lang, N.P.; Tonetti, M.; Zucchero, M.; Salvi, G. Association of the composite IL-1 genotype with peri-implantitis: A systematic review. Clin. Oral Implant. Res. 2008, 19, 1154–1162. [CrossRef] [PubMed]

19. Bormann, K.-H.; Stühmer, C.; Z’Graggen, M.; Kochmoller, H.; Rücker, M.; Gellrich, N.-C. IL-1 polymorphism and perimplantitis. A literature review. Schweiz. Mon. Fur Zahnmed. 2010, 120, 510–520. [PubMed]

20. Kadkhodazadeh, M.; Tabari, Z.A.; Poursayediyani, T.; Najafi, K.; Amid, R. Relationship between Genetic Polymorphisms with Periodontitis and Peri-Implantitis in the Iranian Population: A Literature Review. J. Long-Term Eff. Med Implant. 2016, 26, 183–190. [CrossRef] [PubMed]

21. Junior, J.F.S.; Biguetti, C.C.; Matsumoto, M.A.; Kudo, G.A.H.; da Silva, R.B.P.; Saraiva, P.F.; Fakhouri, W.D. Can genetic factors compromise the success of dental implants? A systematic review and meta-analysis. Genes 2018, 9, 444. [CrossRef] [PubMed]

22. Agrawal, K.K.; Anwar, M.; Gupta, C.; Chand, P.; Singh, S.V. Association of interleukin-1 gene polymorphism and early crestal bone loss around submerged dental implants: A systematic review and meta-analysis. J. Indian Prosthodont. Soc. 2021, 21, 116. [CrossRef]

23. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int. J. Surg. 2010, 6, 336–341. [CrossRef] [PubMed]

24. Morgan, R.L.; Whaley, P.; Thayer, K.A.; Schüneemann, H.J. Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ. Int. 2018, 121, 1027. [CrossRef] [PubMed]

25. Wells, G.A.; Shea, B.; O’Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Appl. Eng. Agric. 2014, 18, 727–734. [CrossRef]

26. Wetterslev, J.; Jakobsen, J.C.; Gluud, C. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res. Methodol. 2013, 17, 39. [CrossRef] [PubMed]

27. Imberger, G.; Thorlund, K.; Gluud, C.; Wetterslev, J. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: An empirical review. BMJ Open 2016, 6, e011890. [CrossRef] [PubMed]
28. Rogers, M.A.; Figliomeni, L.; Baluchova, K.; Tan, A.E.; Davies, G.; Henry, P.J.; Price, P. Do interleukin-1 polymorphisms predict the development of periodontitis or the success of dental implants? J. Periodontal Res. 2002, 37, 37–41. [CrossRef] [PubMed]

29. Shimpuku, H.; Nosaka, Y.; Kawamura, T.; Tachi, Y.; Shinozaka, M.; Ohura, K. Genetic polymorphisms of the interleukin-1 gene and early marginal bone loss around endosseous dental implants. Clin. Oral Implant. Res. 2003, 14, 423–429. [CrossRef]

30. Campos, M.I.; Santos, M.C.; Trevilatto, P.C.; Sarell-Caminaga, R.M.; Bezerra, F.J.; Line, S.R. Evaluation of the relationship between interleukin-1 gene cluster polymorphisms and early implant failure in non-smoking patients. Clin. Oral Implant. Res. 2005, 16, 94–201. [CrossRef]

31. Laine, M.L.; Leonhardt, A.; Roos-Jansäker, A.M.; Peña, A.S.; Van Winkelhoff, A.J.; Winkel, E.G.; Renvert, S. IL-1RN gene polymorphism is associated with peri-implantitis. Clin. Oral Implant. Res. 2006, 17, 380–385. [CrossRef]

32. Lachmann, S.; Kimmerle-Müller, E.; Axmann, D.; Scheideler, L.; Weber, H.; Haas, R. Associations between peri-implant crevicular fluid volume, concentrations of crevicular inflammatory mediators, and composite IL-1A–889 and IL-1B+ 3954 genotype: A cross-sectional study on implant recall patients with and without clinical signs of peri-implantitis. Clin. Oral Implant. Res. 2007, 18, 212–223.

33. Lin, Y.-H.; Huang, P.; Lu, X.; Guan, D.-H.; Man, Y.; Wei, N.; Wang, Y.-Y.; Gong, P. The relationship between IL-1 gene polymorphism and marginal bone loss around dental implants. J. Oral Maxillofac. Surg. 2007, 65, 2340–2344. [CrossRef] [PubMed]

34. Montes, C.C.; Alvim-Pereira, F.; De Castilhos, B.B.; Sakurai, M.L.L.; Olandoski, M.; Trevilatto, P.C. Analysis of the association of IL1B (+ 3954T) and IL1RN (intron 2) polymorphisms with dental implant loss in a Brazilian population. Clin. Oral Implant. Res. 2009, 20, 208–217. [CrossRef]

35. Dirschnabel, A.J.; Alvim-Pereira, F.; Alvim-Pereira, C.C.; Bernardino, J.F.; Rosa, E.A.R.; Trevilatto, P.C. Analysis of the association of IL1B (C-511T) polymorphism with dental implant loss and the clusterization phenomenon. Clin. Oral Implant. Res. 2011, 22, 1235–1241. [CrossRef] [PubMed]

36. Hamdy, A.A.E.-M.M.; Ebrahem, M.A.E.-M. The Effect of Interleukin-1 Allele 2 Genotype (IL-1a-889 and IL-1b+ 3954) on the Individual’s Susceptibility to Peri-Implantitis: Case-Control Study. J. Oral Implantol. 2011, 37, 325–334. [CrossRef] [PubMed]

37. Melo, R.F.; Lopes, B.M.V.; Shibli, J.A.; Marcantonio, E., Jr; Marcantonio, R.A.C.; Galli, G.M.T. Interleukin-1ß and interleukin-6 expression and gene polymorphisms in subjects with peri-implant disease. Clin. Implant. Dent. Relat. Res. 2012, 14, 905–914. [CrossRef] [PubMed]

38. Vaz, P.; Gallas, M.; Braga, A.; Sampaio-Fernandes, J.; Felino, A.; Tavares, P. IL1 gene polymorphisms and unsuccessful dental implants. Clin. Oral Implant. Res. 2012, 23, 1404–1413. [CrossRef] [PubMed]

39. Jacobi-Gresser, E.; Huesker, K.; Schütt, S. Genetic and immunological markers predict titanium implant failure: A retrospective study. Int. J. Oral Maxillofac. Surg. 2013, 42, 537–543. [CrossRef] [PubMed]

40. Petkovic-Curcic, A.; Zeljic, K.; Cikota-Aleksic, B.; Dakovic, D.; Tatic, Z.; Magic, Z. Association of Cytokine Gene Polymorphism with Peri-implantitis Risk. Int. J. Oral Maxillofac. Implant. 2017, 32, e241–e248. [CrossRef]

41. Agrawal, K.K.; Chand, P.; Singh, S.V.; Singh, N.; Gupta, P.; Garg, R.K.; Chaurasia, A.; Anwar, M.; Kumar, A. Association of interleukin-1, interleukin-6, collagen type I alpha 1, and osteocalcin gene polymorphisms with early crestal bone loss around submerged dental implants: A nested case control study. J. Prosthet. Dent. 2021. [CrossRef]

42. Sarem, I.; Shafizadeh, M.; Esmaeilzadeh, E.; Ghaffari, M.E.; Mahdavi, M.H.; Amid, R.; Kadhkhodazadeh, M. Assessment of IL-10, IL-1ß and TNF-α gene polymorphisms in patients with peri-implantitis and healthy controls. Mol. Biol. Rep. 2021, 48, 2288–2290. [CrossRef] [PubMed]

43. Moreira, P.; Costa, J.; Gomez, R.; Gollob, K.; Dutra, W. The IL1A (– 889) gene polymorphism is associated with chronic periodontal disease in a sample of Brazilian individuals. J. Periodontal Res. 2007, 42, 23–30. [CrossRef]

44. Shirodaria, S.; Smith, J.; Mckay, I.; Kennett, C.; Hughes, F. Polymorphisms in the IL-1A gene are correlated with levels of interleukin-1α protein in gingival crevicular fluid of teeth with severe periodontal disease. J. Dent. Res. 2000, 79, 1864–1869. [CrossRef] [PubMed]

45. Dominici, R.; Cattaneo, M.; Mal ferrari, G.; Archi, D.; Mariani, C.; Grimaldi, L.; Biunno, I. Cloning and functional analysis of the allelic polymorphism in the transcription regulatory region of interleukin-1α. Immunogenetics 2002, 54, 82–86. [CrossRef]

46. Amirisetty, R.; Patel, R.P.; Das, S.; Saraf, J.; Jyothy, A.; Munshi, A. Interleukin 1ß (IL-1ß) gene polymorphism in early osseointegrated implant failure. Clin. Oral Implant. Res. 2013, 17, 311–316. [CrossRef] [PubMed]

47. Costa-Junior, F.; Alvim-Pereira, C.; Alvim-Pereira, F.; Trevilatto, P.; de Souza, A.; Santos, M.C.L. Influence of MMP-8 promoter polymorphism in early osseointegrated implant failure. J. Periodontol. 2001, 72, 396–402. [CrossRef] [PubMed]

48. Hu, S.; Song, Y.-B.; Yao, P.-F.; Hu, Q.-L.; Hu, P.-J.; Zeng, Z.-R.; Pang, R.-P. No relationship between IL-1B gene polymorphism and gastric acid secretion in younger healthy volunteers. World J. Gastroenterol. WJG 2005, 11, 6549. [CrossRef] [PubMed]

49. Bucis, N.; Di Giovine, E.; Silvestri, T.; Vannier, E.; Duff, G.W.; Miossec, P. IL-1B and IL-1RA gene polymorphisms and disease severity in rheumatoid arthritis: Interaction with their plasma levels. Genes Immun. 2001, 2, 222–228. [CrossRef] [PubMed]

50. Goiato, M.C.; Dos Santos, D.; Santiago, J.J.; Moreno, A.; Pellizzer, E.P. Longevity of dental implants in type IV bone: A systematic review. Int. J. Oral Maxillofac. Surg. 2014, 43, 1108–1116. [CrossRef] [PubMed]

51. Batista, V.E.d.S.; Junior, J.F.S.; Almeida, D.A.d.F.; Lopes, L.F.d.T.P.; Verri, F.R.; Pellizzer, E.P. The effect of offset implant configuration on bone stress distribution: A systematic review. J. Prosthodont. 2015, 24, 93–99. [CrossRef] [PubMed]
53. Wilson, T.G.W., Jr.; Nunn, M. The Relationship Between the Interleukin–1 Periodontal Genotype and Implant Loss. Initial Data. *J. Periodontol.* **1999**, *70*, 724–729. [CrossRef] [PubMed]

54. Strietzel, F.P.; Reichart, P.A.; Kale, A.; Kulkarni, M.; Wegner, B.; Küchler, I. Smoking interferes with the prognosis of dental implant treatment: A systematic review and meta-analysis. *J. Clin. Periodontol.* **2007**, *34*, 523–544. [CrossRef] [PubMed]