

**PREDICTION OF BISPHOSPHONATE-ASSOCIATED  
OSTEONECROSIS OF THE JAWS IN BULGARIAN  
PATIENTS USING LOGISTIC REGRESSION**

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**Abstract:** Bisphosphonates are a group of drugs that are widely used in the treatment of osteoclast-mediated diseases related to bone loss. Since 2003 the problem of bisphosphonate-associated osteonecrosis of the jaws (BAONJ) has been raised, and many authors have published the cases they have observed. BAONJ is a multifactorial disease, and the risk factors for the development of the disease can be divided into those related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors. The aim of the present study is to determine the effect of the duration of bisphosphonate (BF) intake and the period of time from the surgical intervention (TPSI) on the outcome of BAONJ treatment using logistic regression. The obtained models allow to estimate the predicted probability of the occurrence of this complication. The models were based on experimental data from 44 patients who received medical and diagnostic care in the University Hospital “St. Anna” - Sofia, as well as patients treated in an outpatient setting in the Dental Medicine Faculty - Sofia, Bulgaria.

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## 1. Introduction

Bisphosphonates are a group of drugs that are widely used in the treatment of osteoclast-mediated diseases related to bone loss, such as osteoporosis [1], [2], [3], multiple myeloma [4], bone cancer and metastases in malignant tumors [5], [6], fibrous dysplasia, osteogenesis imperfecta [7].

In 2003, Marx first described “painful exposure of the bone” of the jaws in patients taking pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ) and zoledronate (Zometa; Novartis Pharmaceuticals) [8]. Since then, the problem of bisphosphonate-associated osteonecrosis of the jaws has been raised, and many authors have published the cases they have observed [9], [10], [11], [12]. BAONJ is a multifactorial disease, and the risk factors for the development of the disease can be divided into those related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors [9]. The treatment of BAONJ can be divided into conservative and surgical, and there is no unanimity in the literature about the effectiveness of one or the other method of treatment. There is a lack of systematic data on the impact of risk factors for the development of BAONJ on the outcome of BAONJ treatment [13], [14], [15].

The aim of the present study is to determine the effect of the two risk factors duration of BF intake and the period of the surgical intervention (TPSI) on the outcome of BAONJ treatment. For statistical analysis of the data, a specialized package STATISTICA 11 [16] was used. The obtained models allow to estimate the predicted probability of the occurrence of this complication.

## 2. Materials and methods

In the present study we included 44 patients diagnosed with Bisphosphonate-associated osteonecrosis of the jaw (BAONJ). In the sample data we include patients who received medical and diagnostic care in the department of Oral and Maxillofacial Surgery at the University Hospital “St. Anna” - Sofia, as well as patients treated in an outpatient setting in the Faculty of dental medicine -Sofia. For each patient included in the study, information on the anamnesis, general and local status and results of clinical and paraclinical studies is recorded in an

individual card 20 (45.5%) of the patients included in our survey were women and 24 (54.5%) were men, minimum age 36 years, maximum age 88 years, mean value of age 62 years.

The present study shows that in 40 (90.9%) of the patients the main diagnosis was malignant disease, and in 4 patients (9.1%) the intake of BF was indicated by osteoporosis. Our study showed a maximum value of the duration of BF intake 108 (in months), a minimum of 8 months, an average of 41.75 months.

The factor duration of BF intake is defined as the time from the start of BF therapy (first intake of BF-oral or intravenous) to the time the BAONJ is diagnosed. We used the second factor - the period of time from the surgical intervention (TPSI) to denote the time from the surgical intervention (tooth extraction, dental implant placement) to the time of diagnosis of BAONJ, measured in months.

The results of the treatment are reported on the 30th day and on the 6th month. Periodic follow-up examinations were performed with a frequency determined by clinical symptoms and indications for treatment. In the present study the results were reported according to the following criteria:

- progression - transition to a more advanced stage of BAONJ;
- stationing - the patient is in the same stage of BAONJ at different intervals of documentation.

### *Logistic regression model*

Logistic regression model is used to relate a categorical response (dependent variable  $y$ ) to the explanatory variable (predictor)  $x$ . We interested of the presence (coded by 1) or the absent (coded by 0) of the response - appearance of BAONJ. The explanatory variables are duration of BF intake and the period of time from the surgical intervention (TPSI). The factor duration of BF intake is defined as the time from the start of BF therapy (first intake of BF-oral or intravenous) to the time the BAONJ is diagnosed.

In this subsection we describe dichotomous regression model used for prognostic purposes [17] and [18]. The model describes the dependence of the phenomenon presence/absence of a certain complication (including disease) as a function of various factors which are accepted as independent continuous variables. The response, or the dependent binary variable  $y$ , takes two values:  $y = 0$  when the complication is absent, and  $y = 1$  when the complication occurs. In the univariate model it is supposed that the probability  $p$  of appearance of a

complication depends on the values of an affine function of the factor

$$d(x, \beta_0, \beta_1) = \beta_0 + \beta_1 x. \quad (1)$$

Here  $x$  is the factor, or independent explanatory, and  $\beta_0, \beta_1$  are coefficients which are to be estimated by the experimental data for  $x$  and for the complications. Usually  $n$  observations for the factor  $x$  are known (in our case  $n=44$  is the number of patients). For each complication a separate dependence on each factor is considered. The estimates  $\hat{\beta}_0$  and  $\hat{\beta}_1$  for  $\beta_0, \beta_1$  are obtained using the method of maximum likelihood estimation [19] and [20]. If the response  $y$  does not depend (or depend very weakly) on  $x$  than  $\beta_1 = 0$ .

To be able to relate value of  $y$  to the value of  $d$ , the specific assumption about the form of  $p(d)$  is required. In so called logit or logistic model the distribution function of logistic density is [17]:

$$p(d) = \frac{e^d}{1 + e^d}. \quad (2)$$

The shape of  $p(d)$  (logistic distribution) is quite similar to the shape for normal distribution. The odds ratio of a dichotomous response is given by

$$\text{odds ratio} = \left[ \frac{p(d)}{1 - p(d)} \right]. \quad (3)$$

The logit transformation

$$\ln \left[ \frac{p(d)}{1 - p(d)} \right] = d = \beta_0 + \beta_1 x \quad (4)$$

gives an important advantage of the model because (4) is the linear function of the explanatory variables. The Newton-Raphson iterative procedure is used to make maximal likelihood estimators  $\hat{\beta}_0$  and  $\hat{\beta}_1$  of coefficients in the logistic model. The procedure is based on a preliminary estimator of vector  $\beta(\beta_0, \beta_1)$  given by  $\hat{\beta}(X^T X)^{-1} X^T Y$ . where  $Y$  is the vector of response values  $y_i$  ( $i = 1, \dots, n$ ) and  $X(n \times 1)$  is the vector of observations. The estimator  $\hat{\beta}(\hat{\beta}_1, \hat{\beta}_2)$  can be used to obtain the estimator  $\hat{p}_i$  for each of  $n$  observations. In comparison to the linear regression model, the coefficient vector  $\hat{\beta}$  must be interpreted differently:

- The coefficients  $\hat{\beta}$  were interpreted as estimates of *log odds*.
- A marginal one unit increase in  $x_j$  brings an increase in  $d$  (i.e. in *log odds*) of the amount of  $\hat{\beta}_1$ .

- The confidence intervals were calculated for the odds estimates by taking the exponent of upper and lower endpoints of the asymptotic confidence interval for the *log odds*.

Testing of hypothesis concerning the regression parameters is usually constructed with a large sample Wald test, with test statistic

$$Q_W = \hat{\beta}^T [Var(\beta)]^{-1} \hat{\beta}, \quad (5)$$

where  $Var(\beta)$  is the estimated covariance sub-matrix for the relevant parameters. This statistics is approximately distributed as a  $\chi^2(r)$  random variable with  $r$  degrees of freedom under the null hypothesis that  $r$ -dimensional vector  $\hat{\beta}$  is equal  $\vec{0}$ .

Values  $P < 0.05$  of Wald test statistics were adopted for statistically significant. In univariate analysis an important characteristic is the value of the factor  $x$  for which probability is  $\frac{1}{2}$  (the median of the values of the factor  $x$ ) which is given by  $x_n = \frac{\hat{\beta}_0}{-\hat{\beta}_1}$ . This value is an inflection point of the probability curve.

### 3. Results

A dichotomous logistic regression analysis was performed to identify the exploratory variables (factors) independently associated with the result of treatment of BAONJ, which assumes a state of “stagnation” and “progression”. Two cases were considered for the dependence of the factor duration of BF: First, when the result of the of BAONJ was reported 1 month after treatment and second - when it was reported 6 months after treatment. The purpose of constructed models was to study the impact of two factors: duration of BF intake and the period of time from the surgical intervention (TPSI). Values  $P < 0.05$  were adopted for statistically significant. The statistical analysis of the data is made by a specialized software package STATISTICA [16].

#### *Identification of Prognostic Factors for the Progression of BAONJ one month after treatment*

Using Wald's test statistics and  $P$ -level  $< 0.05$  for significance we conclude that duration of BF intake ( $P = 0.0368$ ) and the period of time from the surgical intervention (TPSI) ( $P = 0.0302$ ) are prognostic for appearance progression of BAONJ. The results for estimated parameters and its standard error (S.E.) and odds ratio (O.R.) of these two logistics models are presented in Table 1.

Table 1: The estimated parameters of the logistic regression models for BAONJ first month after the treatment

| Estimated<br>Parameters | $\hat{\beta}_0 \pm \text{S.E.}$ | $\hat{\beta}_1 \pm \text{S.E.}$ | Wald's<br><i>P</i> -<br>level<br>$\hat{\beta}_1$ | O.R.<br>of $\hat{\beta}_0$ | O.R.<br>of $\hat{\beta}_1$ | 95% CL<br>for O.R.<br>of $\hat{\beta}_0$ | 95% CL<br>for O.R.<br>of $\hat{\beta}_1$ |
|-------------------------|---------------------------------|---------------------------------|--------------------------------------------------|----------------------------|----------------------------|------------------------------------------|------------------------------------------|
| Duration                | -0.892 $\pm$<br>0.728           | 0.032 $\pm$<br>0.015            | 0.037                                            | 0.409                      | 1.032                      | [0.092,0.781]                            | [1.001,1.064]                            |
| TPSI                    | -1.016 $\pm$<br>0. 631          | 0.122 $\pm$<br>0.056            | 0.030                                            | 0.362                      | 1.129                      | [0.101,1.294]                            | [1.008,1.266]                            |

The estimated positive models coefficient  $\hat{\beta}_1 = 0.0318$  indicated that the higher duration of BF first intake, the greater probability for progression of BAONJ. On Fig. 1 the distribution of the probabilities as a function of duration is presented. The critical abscissa (the Inflection point) corresponding to probability 0.5 is 28.06 months. The estimated models coefficient  $\hat{\beta}_1 = 0.1222$  indicated that the higher level of TPSI, the greater probability for progression of BAONJ. On Fig. 2 the distribution of the probabilities as a function of TPSI is presented. The inflection point corresponding to probability 0.5 is 8.31 months.

The logistic regression allows classification of the observed cases in the sample and predicted cases according to the model and the prognostic factor. For the model build using data of duration of BF first intake this classification is given in Table 2, and for TPSI – in Table 3.

Table 2: Classification of cases of progression (code 1) and stagnation (code 0) of treatment of BAONJ after 1 month using model factor duration of BF first intake

| Odds ratio: 5.4286    |                     |                     |                    |
|-----------------------|---------------------|---------------------|--------------------|
| Perc. correct: 70.45% |                     |                     |                    |
| Observed              | Predicted<br>code 0 | Predicted<br>code 1 | Percent<br>Correct |
| Code 0                | 12                  | 7                   | 63.16              |
| Code 1                | 6                   | 19                  | 76.00              |

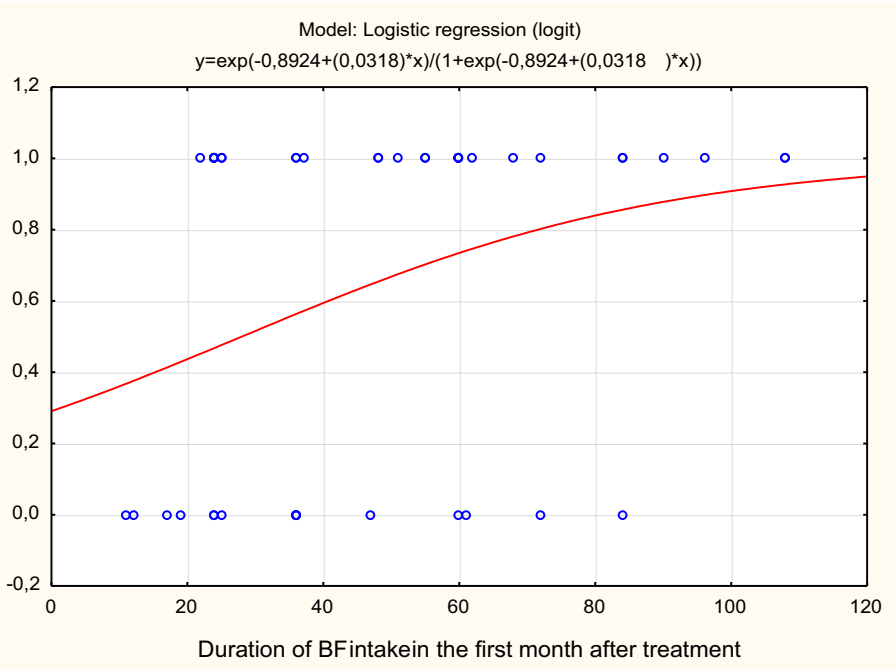


Figure 1: Estimated probability distribution for progression of BAONJ, reported in the first month of treatment, associated with duration of BF first intake

Table 3: Classification of cases of progression (code 1) and stagnation (code 0) of treatment of BAONJ after 1 month using model factor TPSI

|                       |                     |                     |                    |
|-----------------------|---------------------|---------------------|--------------------|
| Odds ratio: 6.4815    |                     |                     |                    |
| Perc. correct: 72.73% |                     |                     |                    |
| Observed              | Predicted<br>code 0 | Predicted<br>code 1 | Percent<br>Correct |
| Code 0                | 14                  | 5                   | 73.68              |
| Code 1                | 8                   | 17                  | 68.00              |

The obtained classification shows that the model built using duration of BF first intake truly predicted “progression” after first month of the treatment in 76% and using TPSI in 68.00%. The total percentage of correct predictions using the model associated with duration is 70.45% and with TPSI – 72.73%,

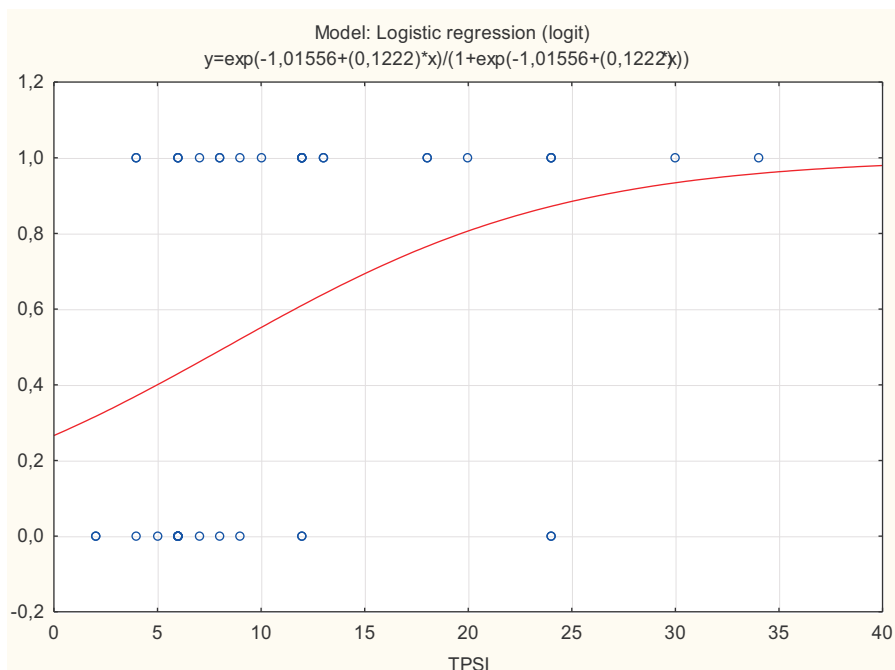


Figure 2: Estimated probability distribution for progression of BAONJ, reported in the first month of treatment, associated with TPSI

i.e. the predictions are reliable.

#### *Identification of Prognostic Factors for the Progression of BAONJ six month after treatment*

Using Wald's test statistics and  $P$ -level  $< 0.05$  for significance we conclude that duration of BF first intake ( $P = 0.0168$ ) and TPSI ( $P = 0.0218$ ) are prognostic for appearance progression of BAONJ six month after treatment. The results for estimated parameters and its standard error (S.E.) of these two logistics models are presented in Table 4.

The estimated positive models coefficient  $\hat{\beta}_1 = 0.0593$  indicated that the higher duration of BF first intake, the greater probability for progression of BAONJ.

On Fig. 3 the distribution of the probabilities as a function of duration is presented. The critical abscissa (the Inflection point) corresponding to probability 0.5 now is 22.33 months.

The classification of the observed cases in the sample and predicted cases

Table 4: The estimated parameters of the logistic regression models for BAONJ first month after the treatment

| Estimated<br>Parameters | $\hat{\beta}_0 \pm \text{S.E.}$ | $\hat{\beta}_1 \pm \text{S.E.}$ | Wald's<br><i>P</i> -<br>level<br>of $\hat{\beta}_1$ | O.R.<br>of $\hat{\beta}_0$ | O.R.<br>of $\hat{\beta}_1$ | 95% CL<br>for O.R.<br>of $\hat{\beta}_0$ | 95% CL<br>for O.R.<br>of $\hat{\beta}_1$ |
|-------------------------|---------------------------------|---------------------------------|-----------------------------------------------------|----------------------------|----------------------------|------------------------------------------|------------------------------------------|
| Duration                | -1.324 $\pm$<br>0.716           | 0.059 $\pm$<br>0.025            | 0.037                                               | 0.266                      | 1.061                      | [0.063,1.129]                            | [1.009,1.115]                            |
| TPSI                    | -0.847 $\pm$<br>0.621           | 0.093 $\pm$<br>0.041            | 0.022                                               | 0.429                      | 1.098                      | [0.122,1.500]                            | [1.011,1.192]                            |

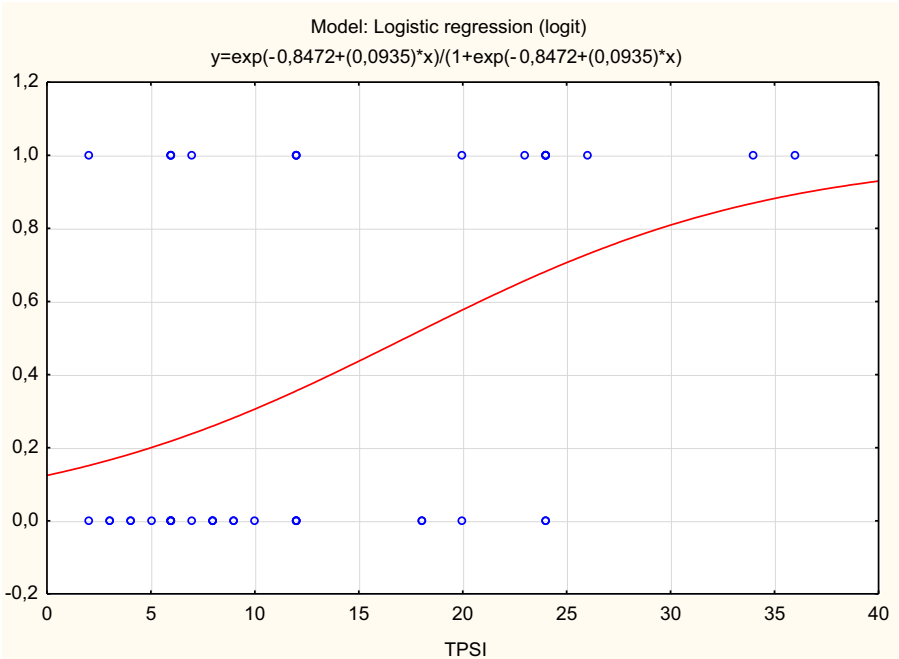


Figure 3: Estimated probability distribution for progression of BAONJ, reported six month after treatment, associated with duration of BF first intake

according to the model and the prognostic factor duration of BF first intake is given in Table 5, and for TPSI – in Table 6.

The estimated models coefficient  $\hat{\beta}_1 = 0.0089$  indicated that the highfigr level of TPSI, the greater probability for progression of BAONJ. On Fig. 4

Table 5: Classification of cases of progression (code 1) and stagnation (code 0) of treatment of BAONJ after 6 month using model factor duration of BF intake Classification of Cases: factor duration of BF first intake

|                       |                     |                     |                    |
|-----------------------|---------------------|---------------------|--------------------|
| Odds ratio: 6.4167    |                     |                     |                    |
| Perc. correct: 72.73% |                     |                     |                    |
| Observed              | Predicted<br>code 0 | Predicted<br>code 1 | Percent<br>Correct |
| Code 0                | 11                  | 6                   | 64.71              |
| Code 1                | 6                   | 21                  | 77.78              |

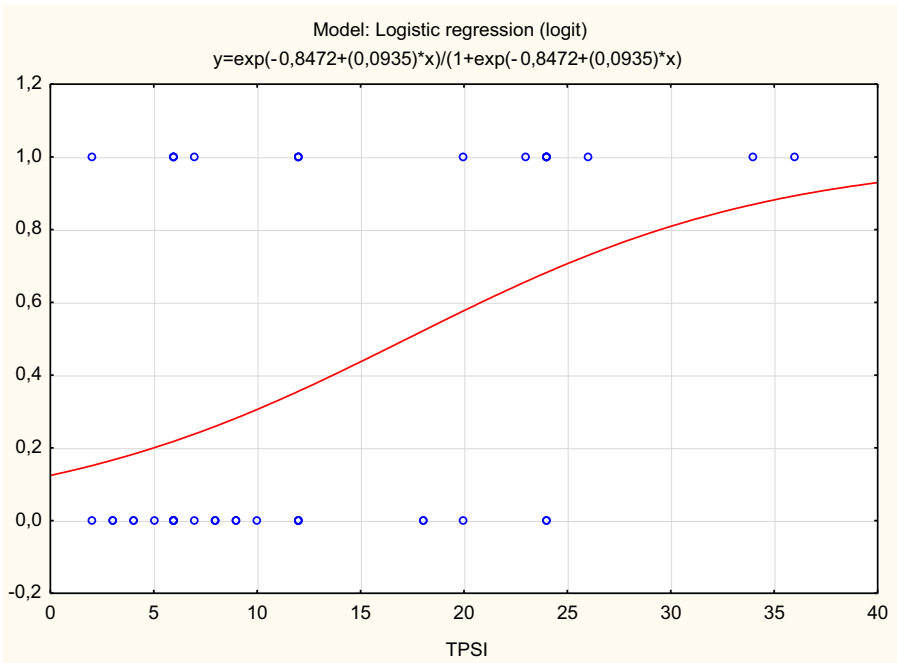


Figure 4: Estimated probability distribution for progression of BAONJ, reported six months after treatment, associated with TPSI

the distribution of the probabilities is presented and the critical point is 18.6 months.

The obtained classification shows that the model built using duration of

Table 6: Classification of cases of progression (code 1) and stagnation (code 0) of treatment of BAONJ after 6 month using model factor TPSI

| Odds ratio: 6.4167<br>Perc. correct: 72.73% |                     |                     |                    |
|---------------------------------------------|---------------------|---------------------|--------------------|
| Observed                                    | Predicted<br>code 0 | Predicted<br>code 1 | Percent<br>Correct |
| Code 0                                      | 9                   | 8                   | 52.94              |
| Code 1                                      | 5                   | 22                  | 81.48              |

BF first intake truly predicted “progression” of BAONJ in 77.78% of the cases using factor duration, and in 81.48% using factor TPSI. The total percentages of correct predictions using the models is over 70%, i.e. the prediction of the occurrence of “progression” of BAONJ is reliable.

#### 4. Conclusion

Our study shows that as the duration of BF first intake increases, so does the likelihood of disease progression, found in both the first and sixth months after treatment. As the values of the factor period from the surgical intervention increase, the probability of progression of BAONJ, established during the examination of the patient in the first and sixth month after the applied treatment, decreases. From the Wald’s statistics it can be concluded that the duration of bisphosphonate intake and the period from the surgical intervention are important factors that can lead to unfavorable clinical results in outpatient treatment of BAONJ. Therefore, we can conclude that both factors duration of BF intake and period from the surgical intervention can be used as predictors of the outcome of BAONJ treatment.

Reporting and monitoring statistically significant factors as soon as the patient is admitted for treatment will make it possible to predict (with over 70% accuracy) the probability of progression of BAONJ in the particular patient and apply the adequate treatment targetted at personalised medicine.

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