https://doi.org/10.5272/jimab.2025311.5989

Journal of IMAB
ISSN: 1312-773X
https://www.journal-imab-bg.org

Journal of IMAB. 2025 Jan-Mar;31(1)

Original article

EPIDEMIOLOGICAL INVESTIGATION OF THE CLINICAL MANIFESTATION OF BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAWS IN 112 ONCOLOGY PATIENTS

Meri Hristamyan[1], Ralitsa Raycheva[2], Veselka Hristamyan[3]
1) Department of Epidemiology and Disaster Medicine, Faculty of Public Health, Medical University of Plovdiv, Bulgaria;
2) Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Bulgaria;
3) Clinic of Maxillo-facial Surgery, UMHAT St. George - Plovdiv, Bulgaria.

ABSTRACT

Background: Bisphosphonate-associated osteonecrosis of the jaws (BAONJ) is a condition linked to the intake of Bisphosphonates (BP) and clinically manifesting in mucosal ulceration and exposure of underlying necrotic bone. The aim of the study is to analyze the clinical manifestation, paraclinical methods for diagnosis, and treatment methods of BAONJ in oncology patients.

Methods: A prospective epidemiological study of 112 oncology patients diagnosed with BAONJ was conducted in the Clinic of maxillo-facial surgery of UMHAT "St. George", Plovdiv, Bulgaria. SPSS Statistics v.24 was used for statistical analysis at a significance level of $p<0.05$.

Results: The main diagnostic methods were clinical examination and history taking, with X-rays in 91.96% (n=103). Half of the patients were diagnosed at stage II, 29.46% at stage I, 17.86% at stage III, and 1.79% at stage 0. The highest proportion of patients (71.41%, n=80) reported pain in the jaws, about 2/3 - exposed bone (65.18%, n=73), and swelling/edema (60.71%, n=68). Treatment included an antibiotic in 54.45% (n=61) of the ²-lactam antibiotics group. Debridement was performed in 32.14% (n=36) of cases, followed by other surgical manipulation in 18.75% (n=21) and resection in 4.56% (n=5).

Conclusion: BAONJ is diagnosed late, which leads to the necessity of surgical treatment.

Keywords: bisphosphonates, osteonecrosis, jaw, clinical manifestation, oncology, epidemiology,

INTRODUCTION

Bisphosphonates (BP) are stable synthetic analogs of pyrophosphate with high affinity to calcium crystals, which allows them to inhibit osteoclast-mediated cross-resorption [1]. In clinical practice, BP have been used for several decades for the treatment of multiple myeloma, bone metastases, osteoporosis, Paget disease, and others [2]. In recent years, reports of Bisphosphonate-associated osteonecrosis of the jaws (BAONJ), also extendedly named Medication-associated osteonecrosis of the jaws(MAONJ), a condition manifesting in mucosal ulceration and exposure of underlying necrotic bone, have been constantly increasing [3, 4]. It is an extremely complex and multifactorial process, and most patients develop the condition after dental manipulations. However, BRONJ may also occur spontaneously [5]. This leads to the need for careful monitoring and an individual approach to each patient, and efforts should be directed to prevention and early diagnosis, and minimally invasive therapy since it can lead to debilitating clinical sequelae with limited treatment options [4]. Epidemiological and clinical studies summarize many discussions of different groups of specialists about the problem, with some of the most discussed and controversial aspects being the specifics of the clinical presentation, diagnosis, and treatment of the condition.

This article aims to study the clinical manifestation, paraclinical methods for diagnosis, and treatment methods of BAONJ in oncology patients.

MATERIAL AND METHODS

Population surveyed and procedure

A prospective epidemiological study, applying a non-random convenience sampling method, was conducted in the Clinic of maxillo-facial Surgery of UMHAT "St. George", Plovdiv, Bulgaria, between 2016 and 2017. We analyzed the anamnesis, clinical examination, and hospital documentation, including data from imaging studies - conventional radiographic examination, CT, MRI, and scintigraphy, and

paraclinical studies - complete blood count and biochemistry, pathophysiological examination, microbiological examination of 112 oncology patients diagnosed with Bisphosphonate-associated Osteonecrosis of the jaw.

Participants and eligibility criteria

Inclusion criteria: patients diagnosed with BAONJ with bony exposure in the maxilla and/or mandible persisting for more than 8 weeks who have received or continue to receive bisphosphonates. Exclusion criteria: patients who underwent head and neck radiotherapy; patients who did not take bisphosphonates; refusal of the patient to participate in the study. The data was listed in 0 specially created for the purpose epidemiological study card.

Statistical analysis

Standard descriptive statistics were used to summarize demographic characteristics. Kolmogorov-Smirnov test was used to examine if variables are normally distributed, and based on the sample distribution, quantitative variables were presented as mean ± standard deviation (mean ± SD) or median (Interquartile (IQ) range 25th percentile; 75th percentile). Categorical variables were presented as absolute numbers and totals (n), as well as percentages (%). Variables were compared with the use of two proportions z-test. The chi-squared test was used to probe for associations between explanatory and outcome variables. The p-value<0.05 was considered statistically significant for all statistical tests. The systematization, processing and analysis were performed using SPSS Statistics v. 26 software (IBM Corp. Released 2019. Armonk, NY: USA).

Ethical considerations

The study was carried out in accordance with accepted standards and as a part of a dissertation titled" Bisphosphonate-associated Osteonecrosis of the Jaws - Epidemiological and Clinical Research" was submitted to the Ethical Committee of the Medical University of Plovdiv with ID number P-3911 (29.05.2018) and approved with protocol No.4/28.06.2018. Informed consent was obtained from all subjects involved in the study.

RESULTS

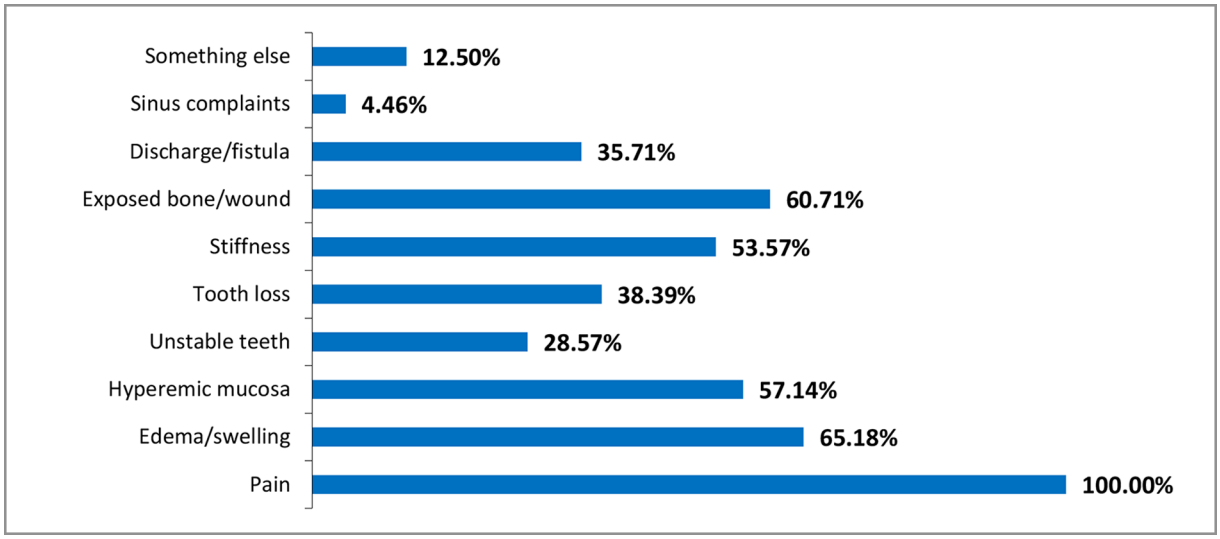
The median age of the 112 oncology patients was 68; 16 years, with no statistically significant difference between the relative parts of men (51.79%, n=58) and women (48.21%, n=54) (p>0.05).

Half of those diagnosed were in stage II of BAONJ (according to the American Association of Oral and Maxillofacial Surgeons (AAOMS)) (50.89%, n=57). Significantly less in stage I (29.46% (n=33) (p<0.05)) and stage III (17.86%, n=20). Only two (1.79%) patients fall in the stage 0 category at the time of hospitalization, which indicates the lack of prophylaxis and monitoring of those receiving BP.

In addition to taking the history of the present illness, the main method of diagnosis in all patients was a clinical examination. In 91.96% (n=103) of cases, conventional radiography was the additional radiological examination used to confirm the diagnosis, and in nearly one-third (n=35), data from computed tomography (CT) or magnetic resonance imaging (MRI) were also required. Other methods to confirm BAONJ were used on 22 patients (19.64%), mainly scintigraphy.

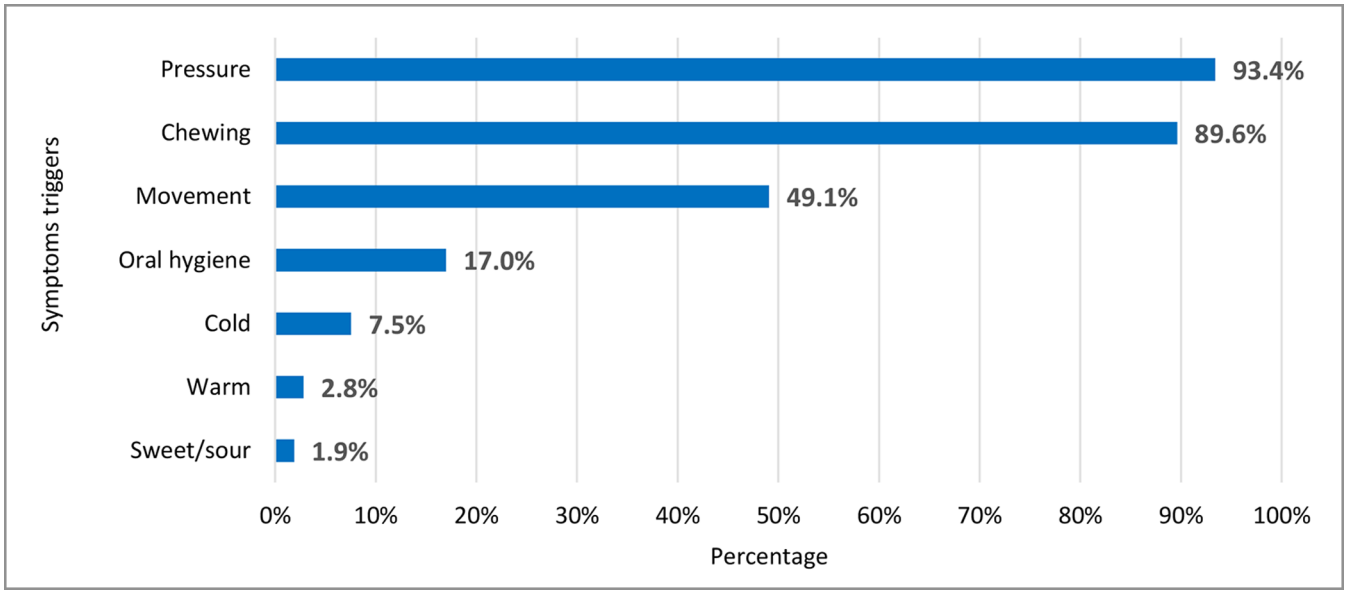
The highest proportion of patients (71.41%, n=80) reported pain in the jaw bones as their main complaint, and about 2/3 – exposed bone/wound (65.18%, n=73) and swelling/edema (60.71%, n=68). This was followed by 57.14% (n=64) who indicated a hyperemic mucosa and 53.57% (n=60) who noted stiffness as the reason for their discomfort. Significantly lower (p<0.05) were the proportions of those complaining of tooth loss (38.39%, n=43), unstable teeth (28.57%, n=32), and secretion (35.71%, n=40). The proportion of those who indicated other complaints, including mainly subjective sensations, as well as difficulty eating and/or speaking, was 31.25% (n=35), and only 4.46% (n=5) had complaints from the maxillary sinus probably due to the specificity of the localization of the osteonecrotic lesion (Figure 1).

Fig. 1. Distribution of complaints in patients with BAONJ.



On a ten-point scale, the median pain intensity of hospitalized BAONJ patients was 7; 1. Regarding spontaneity, the pain was provoked in the majority of patients (96.25%, n=77). The most common reasons for provoking or intensifying pain were pressure (93.51%, n=72) and chewing (89.61%, n=69). A significantly lower proportion was pain during movement (49.35%, n=38) ($p<0.05$), followed by provoking a painful sensation during oral hygiene (16.88%, n=13). With low relative shares was pain that occurs after cold, hot, and sweet/sour foods/drinks (Figure 2).

Fig. 2. Distribution of causes provoking and/or intensifying pain in patients with BAONJ.



In two-thirds (n=71) of the patients with BAONJ, the necrotic lesion was localized in the lower jaw (mandibula), followed by 31.25% (n=35) in which the upper jaw (maxilla) was affected, and 5.36% (n=6) with lesions in both jaws.

In slightly more than half of the patients (n=58), the lesion was located in the left half of the jaw. This was followed by a significantly lower proportion of those in whom the necrotic area was on the right (32.14%, n=36). Only 11.61% (n=13) had lesions on both sides. The frontal area was affected in 4.46% (n=5).

The median lesion size along its longest diameter was 21 mm (IQR=15), with a minimum of 1 mm and a maximum of 69 mm. In stage I patients, the average size was 14 mm, in stage II – 27 mm, and in stage III – 44 mm.

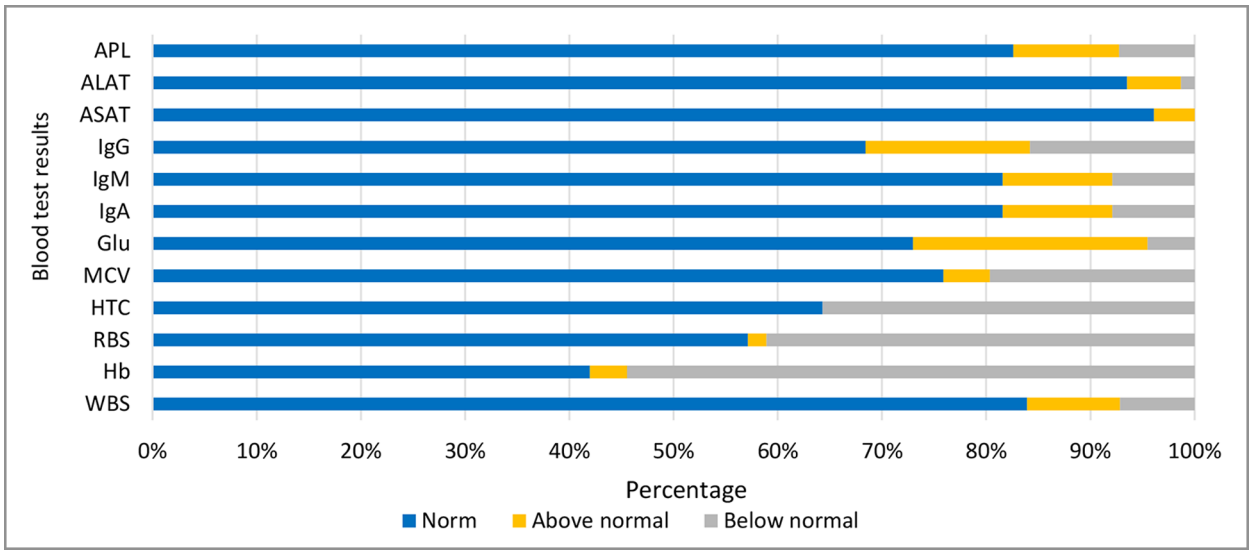
In 70.54% (n=79) of the examined patients, the presence of concomitant soft tissue infection was found, the color of the mucosa was erythematous in 95.54% (n=107), nearly two-thirds (59.62%, n=67) had soft tissue edema. An association between the presence of concomitant soft tissue infection and the diagnosed BAONJ stage was established ($\chi2=22.10$, $p<0.05$).

Almost half (47.33%, n=53) of the patients had mobile teeth in and adjacent to the lesion, with a median number of affected teeth being 1 (ICR=1), with a minimum of 1 and a maximum of 5 teeth. In two-thirds (n=71), tooth loss in the lesion area was found, with a median number of affected teeth being 1 (ICR=1), with a minimum of 1 and a maximum of 3 teeth. An association between the presence of mobile teeth ($\chi2=13.22$, $p<0.05$), tooth loss ($\chi2=15.96$, $p<0.05$), and the stage of the disease were established.

No fistulas were found in 78.1% (n=89), while 19 (16.7%) of the patients had intraoral and 6 (5.3%) – extraoral fistulas, mostly singular.

Except for hemoglobin (Hb), most patients ($p<0.05$) had results within the normal range for the respective blood test (Figure 3). All 112 patients were tested for WBS (White blood cells); Hb; RBS (Red blood cells); HTC (Hematocrit); MCV (Mean corpuscular volume) Glu (blood glucose), 38 (33.92%) for IgA, IgM, IgG, and 77 (68.75%) for ASAT (Aspartate aminotransferase); ALAT (Alanine Transaminase); APL (Alkaline phosphatase).

Fig. 3. Distribution of blood test results of patients with BAONJ.



Pathogenic microorganisms were isolated in 29 (25.89%) patients, most often – E.coli (n=9), E. cloacae (n=6) and Klebsiella pneumoniae (n=5). The absence of pathogens or a sterile culture was found in slightly more than half of the patients, and in 18.75% (n=21) of cases, no microbiological examination was performed.

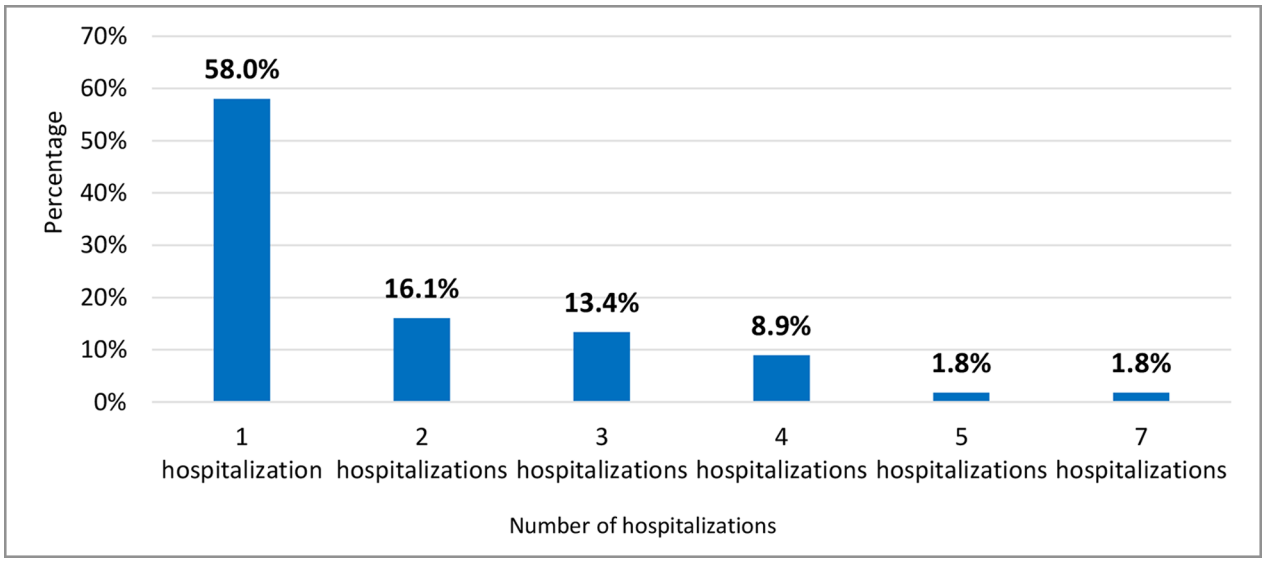
Only 24.10% (n=27) of the patients hospitalized with BAONJ underwent a histological examination, and the presence of necrotic areas in the bone structures of the jaws was confirmed. Actinomycetes were also isolated in 4 of these patients. A significantly higher proportion of patients with BAONJ stage III had a histological sample taken than those with stage I.

All patients received drug treatment, including an antibiotic, in combination with various symptomatic agents appropriate for the specific cases. The most frequently administered antibiotics were from the group of β-lactam penicillins (54.45%, n=61), followed by a reliably low proportion of patients taking Lincosamides (31.25%, n=34) ($p<0.05$). Antibiotics from the groups of Cephalosporins (8.04%, n=9) and Tetracyclines (6.25%, n=7) were less frequently used.

During the study period, 44.64% (n=50) of patients did not undergo surgical treatment, while one-third underwent debridement/sequestrectomy. Another surgical procedure underwent 18.75% (n=21) of the patients, most commonly incision (13.39%, n=15), followed by incision and tooth/s extraction (3.57%, n=4). Resection of the jaw was performed on only 5 (4.46%) individuals, and most often, these were patients in stage III BAONJ ($\chi 2=24.96$, $p<0.05$).

During the two-year period of the study, the patients were admitted for treatment in a hospital most often once (58.04%, n=65). The remaining over 40% of patients with BAONJ needed multiple hospitalizations (between 2 (16.07%, n=18) and 7 (1.79% (n=2)) due to more frequent exacerbation of complaints (Figure 4).

Fig. 4. Distribution of patients with BAONJ according to the number of hospitalizations in the period 2016-2017.



DISCUSSION

Our studies on the clinical presentation, methods of diagnosis, and applied treatment in patients with BAONJ generalize many results observed by other authors who have worked on the problem, as well as point to differences in other aspects of the clinical and treatment-diagnostic profile of this complication.

In the present study, the largest proportion of patients was diagnosed with stage II of BAONJ. Klingelhöffer et al. found that of 76 patients, 34 were at stage I, 36 were at stage II, and only 6 were at stage III [6]. Wang et al. reported 9 patients at stage III, 17 patients at stage II, and only one at stage I, while three patients were at stage 0, with maxillary lesions being observed mainly at a more advanced stage [7]. In Turkey, stage I was diagnosed in 17.1% of cases, stage II in 60.0%, and stage III in 22.9% of cases [8]. Other authors also reported that the majority of patients in their studies were in stage II [9-12]. Pelaz et al. found bone exposure in 89.2% of cases, while 12 patients developed stage 0 BAONJ (no bone exposure) [13]. The higher rate of stage 0 findings in most of these studies compared to our data indicates better prophylaxis and monitoring of patients taking BP.

The main imaging studies used to confirm the diagnosis in the contingent studied by us are in association with the methods applied by other authors. In a study by Wang et al., all patients with BAONJ were studied with a dental panoramic radiography or CT [7]. Some authors suggest that MRI and CT, although methods with a high potential for visualization of lesions far exceeding that of panoramic radiographs, both show problems with an accurate assessment of the extent of lesions in individual patients [14]. Studies by other authors have shown that CT detects changes that cannot be detected by plain radiography in patients with osteonecrosis [15,16]. According to some researchers, CBCT (cone beam computed tomography), in combination with clinical examination, can be effectively used to define the boundaries of affected areas, especially in advanced cases [17]. Another study found that scintigraphy showed increased bone metabolism, and MRI and CT showed abnormalities in all symptomatic patients in correlation with orthotomographic features [18]. Another team of specialists reported that of 38 patients who under-went 99Tc bone scintigraphy, 23 (67.5%) had positive marker uptake in areas that subsequently developed BAONJ, which proves the benefit of using the method for early diagnosis.10 Several publications on the subject also indicate methods other than conventional radiography used successfully in the diagnosis of BAONJ [19, 20].

The findings observed in this study mirror those of the previous studies that have examined the complaints and clinical presentation of BAONJ. According to Otto et al., the most common clinical feature was the exposure of necrotic bone (93.9%) in the oral cavity, which was accompanied in 78.8% of cases with pain [21]. All symptomatic patients in a study on the clinical aspects of BAONJ complained of edema consistent with the area of bony exposure, accompanied by constant dull pain aggravated by palpation/pressure and inflammation of the surrounding soft tissues [18]. Wang et al. reported that the patient's symptoms were: edema (18, 60%), pus (17, 56.7%), trismus (8, 26.7%), paresthesia (5, 16.7%), oral fistula (7, 23.3%), skin fistula (4, 13.3%), halitosis (2, 6.7%), hemorrhage (2, 6.7%).7 Other studies have also shown that patients presented mainly with pain and recurrent infection with involvement of the surrounding soft tissue, often with purulent exudate and necrotic exposed bone [22]. In another study, the mean score of the visual analog scale for jaw pain in patients with stage I and II BAONJ was 4.0 [23]. The difference in the degree of pain, which in our case was an average of 7 on the ten-point system, is due to the small sample in the aforementioned study, the stratification by stages, as well as the different assessment methods.

The lesion in the largest proportion of patients with BAONJ studied by us was localized in the lower jaw, which is consistent with the data of other authors, as well as the lesion being more often located distally and on the left side, as data regarding the side of localization was not found in our literature search. The affected area in those studied by Klingelhöffer et al. was located in the maxilla in 21 (27.6%) patients, 55 had an affected mandible (72.3%), and while the lesions were evenly distributed in the maxilla, 79.9% were located in the distal part of the mandible [6]. In China, specialists reported 11 patients with lesions located in the maxilla, as opposed to 19 in the mandible, and no patient had both jaws affected [7]. In another study, 30 (60%) patients had lesions in the mandible, 17 (34%) – in the maxilla, and 3 (6%) – in both jaws [9]. Other authors reported 10 cases of bone necrosis of the lower jaw, 3 cases of the upper, and 1 case of the upper and lower jaw affected simultaneously [24]. According to data from a study in Turkey, the osteonecrotic lesions were localized in the lower jaw (20 patients, 57.1%), upper jaw (11 patients, 31.4%), and in both jaws (4 patients, 11.4%) [8]. Another team reported that 75% of the lesions were mandibular [10]. Panya et al. discovered that the mandible was more commonly impacted than the maxilla in terms of jaw involvement [12]. Vescovi et al. reported that the maxilla was affected in 42 patients (27.8%), the mandible in 95 patients (63%), and in 14 patients (9.2%) both were affected [25]. In a national study in France, 357 patients (57%) had osteonecrosis of the mandible, 166 patients (26%) had osteonecrosis of the maxilla, and 19 patients

(3%) both, with data missing for 87 patients (14%) [26]. Otto et al. reported preferential involvement of the mandible and particularly the molar and premolar regions in both jaws [21].

The mean size of the lesion in our study was 21 mm, and it varied according to the stage, which corroborates the findings of Klingelhöffer et al., in which in patients who had no recurrence for 6 months, the value of the diameter of exposed bone was 23 mm, compared with a mean diameter of 28 mm measured in the group with early recurrence [6]. There are similarities in the results of other authors, in which the mean largest lesion diameter was 2 cm (0.5-5 cm), and patients who did not relapse had significantly smaller mean lesion diameters than those who did (1.2 and 2, respectively 5 mm) [8]. Another study reported mean diameter values from 25 mm before therapy to 4.5 mm after [27].

In the present study, the majority of patients had at least one loose and/or missing tooth in the lesion area. A study of the periodontal status of patients with BAONJ also found that patients with necrosis had more missing teeth (7.8 vs. 3.1, P=0.002) than controls [28]. Missing and loose teeth are associated with extraction, which is a major risk factor. Dental manipulation is also responsible for the emergence of BAONJ, followed by periodontal diseases [28,29,30].

We found low proportions of patients with intra- and extra-oral fistula courses, with intra-oral fistulas being more common. The present findings seem to be consistent with Wang et al., who reported the presence of an oral fistula in 7 (23.3%) and a cutaneous fistula in 4 (13.3%) patients [7]. Another team indicated the presence of extraoral fistulas in stage 3 patients and intraoral fistulas in stage 0 patients [25].

In general, blood tests are not considered pathognomonic and have not been widely applied in other studies on the subject, although the presence of anemia has been considered a risk factor for the development of BAONJ. Koth et al. found that in patients with BAONJ, the levels of alkaline phosphatase (p=0.005) and ESR (p=0.041) were significantly higher compared to the control group, while serum glucose (fasting) (p=0.331), calcium (p=0.892) and phosphorus (p=0.859) showed no significant difference between groups [31]. For other authors, low levels of alkaline phosphatase are associated with a higher incidence of incomplete recovery after surgery intervention [32].

In our study, a histological examination was performed mainly on the patients who underwent surgical manipulation to confirm the diagnosis. This also accords with Hinson et al., who found a necrotic bone in 375 (85.1%) of the histological samples and Badros et al., who observed a necrotic bone in 20 of the 22 patients they studied, as well as inflammatory infiltrates in 4 patients [33,34]. Histological analysis in another study on the subject again demonstrated that all study subjects had predominant areas of necrotic bone and surrounding inflammatory process [22].

Due to the specificity of the test, in our study, *actinomycetes* were not isolated in the microbiological samples but rather only in histological examinations in only 4 out of the 27 patients tested. In a study conducted by Klingelhöffer et al., *actinomycetes* were diagnosed in 38% of cases [6]. *Actinomycetes* were observed in 17 (60.7%) of resected patients in another study [9]. Other authors found *actinomycete* colonies in 86% of the cases and in 63.3% of the 371 cases presented in the literature [22]. In another study they found *actinomycetes* (n=7) and mixed flora (n=9) [34]. For Panya et al., the most common microorganisms are, again, both *actinomycetes* and mixed flora [12]. We found a mixed flora in 6 of the 29 patients from whom m.o. was isolated, and most often, these were *Enterobacteriaceae* and *Klebsiella pneumoniae*. In contrast to our study, a microbiological analysis showed pathogenic microorganisms in most patients, including *Bacteroides fragilis, Enterobacteriaceae (*incl. *Klebsiellae*), *Beta-haemolytic Streptococcus Group F, and Haemophilus influenza* [18]. Hinson et al. reported the presence of *actinomycetes* in 248 patients (68.8%). Of the remaining m.o*., streptococci* are the most common isolated pathogen (54.7%). Other colonies (although much less common) include *Candida (4), Staphylococcus (3), Klebsiella (3), Eikenella (3), Haemophilus (1), Fusobacterium (1), and Escherichia*. Mixed oral flora (not otherwise specified) was reported in a further 43 cases [33].

Similar to the results in our study regarding the antibiotic therapy administered, others have reported the use of lincosamides (Clindamycin, Lincomycin) and broad-spectrum penicillins (Amoxicillin) in the treatment of patients with BAOHN [35]. For some specialists, penicillins are recommended as the empiric agent of choice, and quinolones, Metronidazole, Clindamycin, Doxycycline, and Erythromycin – as alternatives [36]. Pelaz et al. also reported the use of Amoxicillin in 77.1% of cases, followed by Clindamycin in 4.3% [13]. In their study, Vescovi et al. again emphasize the use of oral Amoxicillin (1 g three times a day) in the drug therapy of patients [25]. Other authors argue that antibiotic therapy may have limited efficacy on lesions since bacterial level in osteonecrosis patients was reportedly higher even when treated with systemic antibiotics [37].

Regarding the treatment of BAONJ, there are disputes among many clinicians as to whether affected individuals should receive symptomatic therapy, with pain and infection control and possible minimally invasive debridement of the superficial necrotic bone, or whether more invasive surgical methods should be applied, with the greater part of specialists supporting the first thesis. For Klingelhöffer et

al., patients in more advanced stages of the condition may be treated surgically, while those diagnosed as stage 1 may be treated conservatively [6]. Others also believe that surgical treatment can improve the condition ($p>0.05$), with 81.3% of advanced-stage patients in their series showing improvement after such intervention [7]. In the patients we studied, the main surgical treatment was debridement, and nearly half of the subjects received only medical therapy, which is consistent with data from a study in Turkey, where half of the patients were treated conservatively (51.4%) and one third – surgically (31.4%) [8]. In another study, the initial treatment was non-surgical, with performing debridement at follow-up visits if necessary [11]. Vescovi et al. applied different treatment, with 28 lesions treated only with medication; 32 lesions were treated with drug therapy and low-frequency laser therapy (LLLT); 17 lesions were treated with medication and traditional surgical therapy; 33 lesions were treated with medication, conventional surgical therapy, and LLLT; and 29 lesions received drug therapy, Er: YAG laser surgical therapy, and LLLT [25]. Of the 14 patients in another study, 10 received surgical treatment.24 A Danish study reported that 28 out of 506 patients underwent surgical treatment, with a 96.4% healing rate and no exposed bone after the first or second revision surgery [38]. According to a retrospective study in Japan, patients had a poor prognosis with conventional treatment applied according to the stage and primary disease and separation of sequestrum had favorable outcomes [39]. Other experts believe that conservative treatment remains the first line of defense up to stage II, and surgical intervention is recommended for persistent stage 3 that does not respond to medication [40]. These findings are mostly consistent with the data from our study, which included only a small number of resections, mainly in stage III patients.

CONCLUSION

There are many discussions and disputes among specialists regarding the specifics of the clinical manifestation, as well as the methods of diagnosis and treatment of BAONJ. The obtained results are in accordance with those of other specialists, with the predominant left-sided localization of the lesions being of interest in the clinical manifestation. The number of diagnosed patients remains high, and the majority of them are diagnosed at a more advanced stage of the disease, which in some cases leads to the need for more aggressive surgical treatment and indicates gaps in the prevention and early recognition of this complication.

REFERENCES:

1. Zhang J, Bai H, Bai M, Wang X, Li Z, Xue H, et al. Bisphosphonate-incorporated coatings for orthopedic implants functionalization. *Mater Today Bio*. 2023 Jul 22;22:100737. [PubMed]

2. Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws-2022 Update. *J Oral Maxillofac Surg*. 2022 May;80(5):920-943. [PubMed]

3. Martins LHI, Ferreira DC, Silva MT, Motta RHL, Franquez RT, Bergamaschi CC. Frequency of osteonecrosis in bisphosphonate users submitted to dental procedures: A systematic review. Oral Dis. 2023 Jan;29(1):75-99. [PubMed]

4. Dunphy L, Salzano G, Gerber B, Graystone J. Medication-related osteonecrosis (MRONJ) of the mandible and maxilla. *BMJ Case Rep*. 2020 Jan 5;13(1):e224455. [PubMed]

5. Chien HI, Chen LW, Liu WC, Lin CT, Ho YY, Tsai WH, et al. Bisphosphonate-Related Osteonecrosis of the Jaw. *Ann Plast Surg*. 2021 Feb 1;86(2S Suppl 1):S78-S83. [PubMed]

6. Klingelhöffer C, Zeman F, Meier J, Reichert TE, Ettl T. Evaluation of surgical outcome and influencing risk factors in patients with medication-related osteonecrosis of the jaws. *J Craniomaxillofac Surg*. 2016 Oct;44(10):1694-1699. [PubMed]

7. Wang Q, Liu J, Qi S, Liao X, Liu D, Pan J. Clinical analysis of medication related osteonecrosis of the jaws: A growing severe complication in China. *J Dent Sci*. 2018 Sep;13(3): 190-197. [PubMed]

8. Aksoy M, Kocer G, Kocer M, Baykul T. Medication related osteonecrosis of the jaws. A case serial study. *Int J Clin Exp Med*. 2017 Nov;10(11):15672-15679. [Internet]

9. Matsuda S, Yoshimura H, Sano K. Risk factors and treatments for medication-related osteonecrosis of the jaw: A 10-year single-institution experience. Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology. *J Oral Maxillofac Surg Med Pathol*. 2018 Jan;30(1):10-16. [Crossref]

10. O'Ryan FS, Khoury S, Liao W, Han MM, Hui RL, Baer D, et al. Intravenous Bisphosphonate-Related Osteonecrosis of the Jaw: Bone Scintigraphy as an Early Indicato. *J Oral Maxillofac Surg*. 2009 Jul;67(7): 1363-72. [PubMed]

11. Thumbigere-Math V, Sabino MC, Gopalakrishnan R, Huckabay S, Dudek AZ, Basu S, et al. Bisphosphonate-related osteonecrosis of the jaw: clinical features, risk factors, management, and treatment outcomes of 26 patients. *J Oral Maxillofac Surg*. 2009 Sep; 67(9):1904-13. [PubMed]

12. Panya S, Fliefel R, Probst F, Tröltzsch M, Ehrenfeld M, Schubert S, et al. Role of microbiological culture and polymerase chain reaction (PCR) of actinomyces in medication-related osteonecrosis of the jaw (MRONJ). *J Craniomaxillofac Surg*. 2017 Mar; 45(3):357-363. [PubMed]

13. Pelaz A, Junquera L, Gallego L, García-Consuegra L, García-Martínez L, Cutilli T, et al. Epidemi-

ology, pharmacology and clinical characterization of bisphosphonate-related osteonecrosis of the jaw. A retrospective study of 70 cases. *Acta Otorrinolaringol Esp.* 2015 May-Jun; 66(3):139-47. [PubMed]

14. Stockmann P, Hinkmann FM, Lell MM, Fenner M, Vairaktaris E, Neukam FW, et al. Panoramic radiograph, computed tomography or magnetic resonance imaging. Which imaging technique should be preferred in bisphosphonate-associated osteonecrosis of the jaw? A prospective clinical study. *Clin Oral Investig.* 2010 Jun; 14(3):311-7. [PubMed]

15. Guo Y, Wang D, Wang Y, Peng X, Guo C. Imaging features of medicine-related osteonecrosis of the jaws: comparison between panoramic radiography and computed tomography. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016 Aug; 122(2):e69-76. [PubMed]

16. Baba A, Goto TK, Ojiri H, Takagiwa M, Hiraga C, Okamura M, et al. CT imaging features of antiresorptive agent-related osteonecrosis of the jaw/medication-related osteonecrosis of the jaw. *Dentomaxillofac Radiol.* 2018 May;47(4): 20170323. [PubMed]

17. Demir A, Pekiner FN. Radiographic findings of bisphosphonate-related osteonecrosis of the jaws: Comparison with cone-beam computed tomography and panoramic radiography. *Niger J Clin Pract.* 2017 Mar;20(3):346-354. [PubMed]

18. Biasotto M, Chiandussi S, Dore F, Rinaldi A, Rizzardi C, Cavalli F, et al. Clinical aspects and management of bisphosphonates-associated osteonecrosis of the jaws. *Acta Odontol Scand.* 2006 Nov;64(6):348-54. [PubMed]

19. Watanabe S, Nakajima K, Kinuya S. &Symposium: Imaging modalities for drug-related osteonecrosis of the jaw (5), utility of bone scintigraphy and 18F-FDG PET/CT in early detection and risk assessment of medication-related osteonecrosis of the jaw (secondary publication). *Jpn Dent Sci Rev.* 2019 Nov;55(1):76-79. [PubMed]

20. Moridera K, Kitajima K, Yoshikawa K, Takaoka K, Tsuchitani T, Noguchi K, et al. Usefulness of quantitative bone SPECT/CT for medication-related osteonecrosis of the jaw in clinical settings. *Jpn J Radiol.* 2022 May;40(5):492-499. [PubMed]

21. Otto S, Schreyer C, Hafner S, Mast G, Ehrenfeld M, Stürzenbaum S, et al. Bisphosphonate-Related Osteonecrosis of the Jaws-Characteristics, Risk Factor, Clinical Features, Localization and Impact on Oncological Treatment. *J Craniomaxillofac Surg.* 2012 Jun;40(4):303-9. [PubMed]

22. Schipmann S, Metzler P, Rössle M, Zemann W, von Jackowski J, Obwegeser JA, et al. Osteopathology associated with bone resorption inhibitors - which role does Actinomyces play? A presentation of 51 cases with systematic review of the literature. *J Oral Pathol Med.* 2013 Sep;42(8):587-93. [PubMed]

23. Abel Mahedi Mohamed H, Nielsen CEN, Schiodt M. Medication related osteonecrosis of the jaws associated with targeted therapy as monotherapy and in combination with antiresorptives. A report of 7 cases from the Copenhagen Cohort. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018 Feb;125(2):157-163. [PubMed]

24. Guo YX, Wang DC, Wang Y, Peng X, Mao C, Guo CB. [Clinical features of osteonecrosis of jaws after bisphosphonates therapy for bone metastasis of breast cancer]. [in Chinese] *Beijing Da Xue Xue Bao Yi Xue Ban.* 2016 Feb 18;48(1):80-3. [PubMed]

25. Vescovi P, Merigo E, Meleti M, Manfredi M, Guidotti R, Nammour S. Bisphosphonatesrelated osteonecrosis of the jaws: a concise review of the literature and a report of a single-centre experience with 151 patients. *J Oral Pathol Med.* 2012 Mar;41(3): 214-21. [PubMed]

26. de Boissieu P, Gaboriau L, Morel A, Trenque T. Bisphosphonate-related osteonecrosis of the jaw: data from the French national pharmacovigilance database. *Fundam Clin Pharmacol.* 2016 Oct;30(5):450-8. [PubMed]

27. Alsehimy MM. Efficacy of a non-surgical treatment regimen in patients with bisphosphonate-related osteonecrosis of the jaws in Saudi Arabia. *SAGE Open Medicine.* 2017 Feb 14;2:2050312114522995. [PubMed]

28. Thumbigere-Math V, Michalowicz BS, Hodges JS, Tsai ML, Swenson KK, Rockwell L, et al. Periodontal disease as a risk factor for bisphosphonate-related osteonecrosis of the jaw. *J Periodontol.* 2014 Feb;85(2):226-33. [PubMed]

29. Dal Prá KJ, Lemos CA, Okamoto R, Soubhia AM, Pellizzer EP. Efficacy of the C-terminal telopeptide test in predicting the development of bisphosphonate-related osteonecrosis of the jaw: a systematic review. *Int J Oral Maxillofac Surg.* 2017 Feb;46(2):151-156. [PubMed]

30. Soutome S, Otsuru M, Hayashida S, Murata M, Yanamoto S, Sawada S, et al. Relationship between tooth extraction and development of medication-related osteonecrosis of the jaw in cancer patients. *Sci Rep.* 2021 Aug 26;11(1): 17226. [PubMed]

31. Koth VS, Figueiredo MA, Salum FG, Cherubini K. Interrelationship of clinical,radiographic and haematological features in patients under bisphosphonate therapy. *Dentomaxillofac Radiol.* 2017 Apr;46(4):20160260. [PubMed]

32. de Almeida AD, Leite FG, Chaud MV, Rebelo MA, Borges LCFS, Viroel FJM, et al. Safety and efficacy of hydroxyapatite scaffold in the prevention of jaw osteonecrosis in vivo. *J Biomed Mater Res B Appl Biomater.* 2018 Jul;106(5):1799-1808. [PubMed]

33. Hinson AM, Smith CW, Siegel ER, Stack BC Jr. Is bisphosphonate-related osteonecrosis of the jaw an infection? A histological and microbiological ten-year summary. *Int J Dent.* 2014;2014:452737. [PubMed]

34. Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, et al. Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. *J Clin Oncol.* 2006 Feb 20;24(6):945-52. [PubMed]

35. Janovska Z, Mottl R, Slezak R. Experience with the treatment of bisphosphonate-related osteonecrosis of the jaw. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2015

Jun;159(2):313-7. [PubMed]

36. Zadik Y. Clarithromycin as the empiric antibiotic therapy for medication-related osteonecrosis of the jaw in multiple myeloma patients. *Oral Oncol.* 2018 Sep;84:104-105. [PubMed]

37. De Bruyn L, Coropciuc R, Coucke W, Politis C. Microbial population changes in patients with medication-related osteonecrosis of the jaw treated with systemic antibiotics. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018 Mar;125(3):268-275. [PubMed]

38. Amin H, Andersen SWM, Jensen SS, Kofod T. Surgical and conservative treatment outcomes of medication-related osteonecrosis of the jaw located at tori: a retrospective study. *Oral Maxillofac Surg.* 2024 Sep;28(3):1117-1125. [PubMed]

39. Kaibuchi N, Hoshi K, Yamazaki A, Miyamoto-Sangu N, Akagi Y, Okamoto T. The progress of medication-related osteonecrosis of the jaw with conservative initial treatment: A 12-year retrospective study of 129 patients. *Bone Rep.* 2021 Apr 21;14:101072. [PubMed]

40. Coropciuc RG, Grisar K, Aerden T, Schol M, Schoenaers J, Politis C. Medication-relatedosteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2. *Br J Oral Maxillofac Surg.* 2017 Oct;55(8):787-792. [PubMed]

Please cite this article as: Hristamyan M, Raycheva R, Hristamyan V. Epidemiological investigation of the clinical manifestation of Bisphosphonate-associated Osteonecrosis of the jaws in 112 oncology patients. *J of IMAB.* 2025 Jan-Mar;31(1):5989-5997. [Crossref - https://doi.org/10.5272/jimab.2025311.5997]

Received: 18/07/2024; Published online: 10/02/2025

Address for correspondence:
Dr Meri Hristamyan, PhD
Department of Epidemiology and DM, Faculty of Public Health, Medical University - Plovdiv;
15A, Vasil Aprilov Str., Plovdiv, Bulgaria
E-mail: Meri.Hristamyan@mu-plovdiv.bg,