Systematic Review

Evaluation of various therapeutic approaches in treating Medication-related osteonecrosis of the jaw: A Systematic Review

ABSTRACT

Background and Aims: Medication-related osteonecrosis of the jaws (MRONJ) is a significant and potentially debilitating side effect caused by antiresorptive and antiangiogenic drugs, which can lead to bone exposure in the oral cavity. However, the management of this condition remains controversial, with adjuvant therapies being employed despite limited scientific evidence. This systematic review aimed to identify effective therapeutic procedures for treating MRONJ.

Methodology: A literature search was conducted without any temporal limitations. The PRISMA protocol was followed. To identify relevant studies, we developed electronic search strategies for various bibliographic databases, as Cochrane, Embase, PubMed, Scopus, and Web of Science. It was conducted a comprehensive analysis of 30 studies involving 2,079 patients from 35 countries to evaluate the effectiveness of various treatment approaches for MRONJ.

Results: The systematic review revealed that long-term use of Zoledronic acid for approximately 452.04 months (±27.41; 12-102) exposed many patients (n=772) to the risk of MRONJ. Similarly, Alendronate use for approximately 104.4 months (±60.16; 6-180) also posed a risk, affecting 650 patients, while Pamidronate use for about 20.74 months (±4.94; 6-96) was associated with MRONJ risk in 121 patients. Among the treatment approaches, conservative surgical management was the most frequently employed (27.92%), followed by local debridement (13.57%) and conservative treatment (11.21%). Treatment complications were observed in 13.03% of cases, with the most frequent complications being resistant or worsening clinical stage of osteonecrosis, followed by incomplete mucosal healing or dehiscence and mental nerve injury.

Conclusion: While conservative surgical management, local debridement, and conservative treatment are commonly utilized approaches, the treatment of MRONJ lacks a standardized consensus due to the scarcity of scientific evidence. Further research and comprehensive studies are imperative to establish effective therapeutic strategies for managing this condition.

Keywords: Osteonecrosis; Bisphosphonates; Jaw; Treatment

1. INTRODUCTION

Drug-related jaw osteonecrosis is an oral lesion that affects the jawbone and the jawbone. This condition is currently characterized by exposed bone or bone that can be probed through an intra or extraoral fistula in the maxillofacial region. It is caused by an insufficiency of blood in the bone that can have various origins, such as bisphosphonates, trauma, infections, or radiation therapy. Medication-related osteonecrosis of the jaws (MRONJ) represents a significant and concerning adverse outcome linked to the use of antiresorptive and/or antiangiogenic medications, specifically bisphosphonates. Initially, it was characterized as avascular osteonecrosis triggered by Pamidronate and Zoledronate, as delineated by Marx [1]. Subsequently, due to the escalating occurrence of osteonecrotic lesions, the term evolved to bisphosphonate-related osteonecrosis of the jaws (BRONJ), and the last M.R.O.N.J [1,2,3].

MRONJ is typified by necrosis of bone tissue and oral cavity exposure, arising from a metabolic imbalance in the mineral bone matrix induced by these medications. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has meticulously established specific criteria for MRONJ diagnosis, encompassing a history of bisphosphonate treatment, prolonged bone exposure exceeding eight weeks, and the absence of radiotherapy or metastatic disease within the maxillofacial region [4].

1.1 Staging

1.1.1 Stage 0 (Nonexposed Bone Variant)

Patients with no clinical evidence of necrotic bone but who present with non-specific symptoms or clinical and radiographic findings, such as: odontalgia not explained by an odontogenic cause; dull, loosening of teeth not explained by chronic periodontal disease, intraoral or extraoral swelling, alveolar bone loss or resorption not attributable to chronic periodontal disease, changes to trabecular pattern sclerotic bone and no new bone in extraction sockets, regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone, thickening/obscuring of periodontal ligament (thickening of the lamina dura, sclerosis, and decreased size of the periodontal ligament space).

These non-specific findings, which characterize this variant of OMRM without bone exposure, may occur in patients with a prior history of Stage 1, 2, or 3 disease who have been healed and have no clinical evidence of exposed bone. Progression to Stage 1 disease has been reported in up to 50 percent of patients with Stage 0 disease 41 percent; therefore, AAOMS deems it prudent to consider Stage 0 disease as a potential precursor to OMRM.

1.1.2 Stage 1

Exposed and necrotic bone or fistula that probes to the bone in asymptomatic patients with no evidence of infection/inflammation. These patients may also present with radiographic findings mentioned for Stage 0 localized to the alveolar bone region.

1.1.3 Stage 2

Exposed and necrotic bone, or fistula that probes to the bone, with evidence of infection/inflammation. These patients are symptomatic. These patients may also present with radiographic findings mentioned for Stage 0 localized to the alveolar bone region.

1.1.4 Stage 3

Exposed and necrotic bone or fistulae that probe to the bone, with evidence of infection, and one or more of the following: exposed necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla), pathologic fracture, extraoral fistula, oral antral/oral-nasal communication, osteolysis extending to the inferior border of the mandible or sinus floor [4].

Bisphosphonates are pivotal as antiresorptive agents in managing malignancies and fractures related to osteoporosis. Efficacious fracture reduction has been demonstrated in both orally administered forms (Alendronate and Residronate) and parenteral agents (Zoledronic acid and iodronate) for osteoporosis patients [5,6]. However, it gradually became evident that other antiresorptive, as well as other classes of medications, were also involved in the MRONJ, such as the Denosumab, an antiresorptive human antibody that exhibited promising fracture risk reduction for osteoporosis patients [7].

MRONJ is associated with several risk factors, including tooth extractions, chemotherapy, steroid use, periodontal disease, and various medical conditions [8]. To diagnose MRONJ accurately, advanced imaging techniques like cone-beam computed tomography (CT) are often necessary to assess the extent of bone involvement comprehensively [9]. In human patients, MRONJ is classified based on clinical presentation. Stage 0 signifies the absence of clinical evidence of necrotic bone, but the patient may exhibit non-specific symptoms or radiographic findings. In such cases, the treatment approach typically involves pain management and, if necessary, antibiotics. Conversely, Stage 3 represents the most severe manifestation, where the patient presents with an infection and maxillary sinus involvement. The prognosis of osteonecrosis of the jaws related to drugs in stage 3 is variable. It depends on several factors, such as the extent of the lesion, the presence of infection, the response to treatment, and the patient's general health [10].

Thus, the therapeutic landscape for MRONJ comprises nonoperative and operative modalities. Nonoperative strategies emphasize patient education, pain management, infection control, and the facilitation of necrotic bone sequestration [11]. Conversely, operative interventions have shown encouraging outcomes and are increasingly acknowledged as practical approaches across various stages of osteonecrosis [11]. However, the efficacy of specific therapies like hyperbaric oxygen or ozone therapy remains limited by insufficient evidence, warranting further exploration [12,13]. Supplementary treatments such as vitamin E and Pentoxifylline have been primarily reported in case studies, with ongoing research exploring their potential efficacy [14].

Despite the array of treatment options, a definitive consensus on the optimal MRONJ management protocol remains elusive. The AAOMS advocates a multidisciplinary approach involving dental, oncological, and maxillofacial specialists. Conservative management is endorsed for early-stage MRONJ, concentrating on infection control, necrosis management, and pain alleviation [15]. Proactive measures, encompassing optimization of oral health and dental care before initiating antiresorptive therapy, have been underscored in multiple studies. These preventive strategies mitigate the risk of MRONJ and contribute to the overall enhancement of oral health [16-19]. Thus, this systematic review provides a comprehensive overview of the primary therapies currently employed in treating MRONJ, shedding light on the evolving landscape of its management. This systematic review aims to identify forms of treatment for OMRM by treating current infection, controlling pain associated with the injury and promoting healing in the affected area.

2. METHODOLOGY

2.1 Protocol

The authors of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [20,21] to ensure the thoroughness and transparency of the review process. The review encompassed a comprehensive literature search strategy, a meticulous selection process that relied on pre-established inclusion and exclusion criteria, meticulous data extraction, and a rigorous assessment of the quality of the studies included.

2.2 Study Design and Eligibility Criteria

A literature search was conducted without any temporal limitations. The patient, intervention, comparison, outcome (PICOS) strategy was employed to formulate the research question, incorporating the following inclusion criteria: (i) population - patients diagnosed with medication-related osteonecrosis of the jaw, (ii) intervention - identification of clinical treatments administered, (iii) comparison - none, (iv) outcome - identification of clinical treatments implemented in patients with medication-related osteonecrosis of the jaw and their respective outcomes, and (v) study design - observational studies (cohort and case-control studies).

Studies were excluded based on the following criteria: i) studies involving patients unaffected by medication-related osteonecrosis of the jaw, ii) studies lacking reporting on clinical treatment of medication-related osteonecrosis of the jaw, or iii) reviews, letters, conference summaries, or personal opinions.

2.3 Information Sources and Search Strategy

To identify relevant studies, we developed electronic search strategies for various bibliographic databases,with terms in English, namely Cochrane (https://www.cochranelibrary.com), Embase (https://www.embase.com), PubMed (https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com), and Web of Science (https://www.webofscience.com/wos/woscc/basic-search). The search encompassed articles published across all databases until July 25, 2022, with a total of 3,253 articles identified. Rayyan software reference manager was employed to remove 438 duplicate articles. The search strategy was standardized and consistently applied for all subsequent updates. Supplementary Table 1 provides additional details regarding the search strategy employed for each database.

Supplementary Table 1. Search strategy in the databases.

Database	Search

PubMed (July 25, 2022)	"Diphosphonates"[Mesh] OR "Alendronate"[Mesh] OR "Etidronic Acid"[Mesh] OR "ibandronic acid" [Supplementary Concept] OR "pamidronate" [Supplementary Concept] OR "zoledronic acid" [Supplementary Concept] OR "risedronic acid" [Supplementary Concept] OR "denosumab" AND "Bisphosphonate-Associated Osteonecrosis of the Jaw"[Mesh] OR ("Osteonecrosis"[Mesh] AND "Jaw"[Mesh]) OR (osteonecrosis AND jaw) AND "Therapeutics"[Mesh]
Embase (July 25, 2022)	(('diphosphonates'/exp OR 'diphosphonates' OR 'alendronate'/exp OR 'alendronate' OR 'etidronic acid'/exp OR 'etidronic acid' OR 'ibandronic acid'/exp OR 'ibandronic acid' OR 'pamidronate'/exp OR 'pamidronate' OR 'zoledronic acid'/exp OR 'zoledronic acid' OR 'risedronic acid'/exp OR 'risedronic acid' OR 'denosumab'/exp OR 'denosumab') AND ('all fields' OR (all AND fields)) AND ('bisphosphonate-associated osteonecrosis of the jaw'/exp OR 'bisphosphonate-associated osteonecrosis of the jaw') OR (('osteonecrosis'/exp OR 'osteonecrosis') AND ('jaw'/exp OR 'jaw')) OR (('osteonecrosis'/exp OR osteonecrosis) AND ('jaw'/exp OR jaw))) AND ('therapeutics'/exp OR 'therapeutics')
Cochrane (July 25, 2022)	"Diphosphonates" OR "Alendronate" OR "Etidronic Acid" OR "ibandronic acid" OR "pamidronate" OR "zoledronic acid" OR "risedronic acid" OR "denosumab" in Title Abstract Keyword AND "Bisphosphonate-Associated Osteonecrosis of the Jaw" OR ("Osteonecrosis" AND "Jaw") in Title Abstract Keyword AND "Therapeutics" in Title Abstract Keyword - (Word variations have been searched)
Scopus (July 25, 2022)	(TITLE-ABS-KEY ("Diphosphonates" OR "Alendronate" OR "Etidronic Acid" OR "ibandronic acid" OR "pamidronate" OR "zoledronic acid" OR "risedronic acid" OR "denosumab") AND TITLE-ABS-KEY ("Bisphosphonate-Associated Osteonecrosis of the Jaw" OR ("Osteonecrosis" AND "Jaw") OR (osteonecrosis AND jaw)) AND TITLE-ABS-KEY ("Therapeutics"))
Web of Science (July 25, 2022)	"Diphosphonates" OR "Alendronate" OR "Etidronic Acid" OR "ibandronic acid" OR "pamidronate" OR "zoledronic acid" OR "risedronic acid" OR "denosumab" (All Fields) AND "Bisphosphonate-Associated Osteonecrosis of the Jaw" OR ("Osteonecrosis" AND "Jaw") OR (osteonecrosis AND jaw) (All Fields) AND "Therapeutics" (All Fields)

2.4 Study selection

The study selection process comprised two phases. During Phase 1, two authors (MJAA and MOCDL) independently screened the titles and abstracts of all references (n=2.815) using Rayyan software [22]. They identified 118 studies that fulfilled the inclusion criteria and excluded those that did not. Whenever necessary, the third author (R.A.M.) was consulted to reach a final decision regarding the inclusion or exclusion of a study. In Phase 2, the same two authors independently evaluated the full-text articles to verify data on medication-related osteonecrosis of the jaw, applying the same selection criteria. All three authors critically assessed the reference lists of all included articles, and any additional articles meeting the inclusion criteria were incorporated into the selection analysis. Any discrepancies during either phase were resolved through discussion and consensus among the three authors. The final selection was based on including 30 full-text articles, released from September 2008 through January 2022, that satisfied the predetermined criteria. From these articles, a population sample of 2,079 patients was obtained.

2.5 Data collection

The relevant information from the selected articles was gathered by the first author (MJAA) and second author (MOCDL). The accuracy of the collected data was then verified through cross-checking by the third author (R.A.M.). Any discrepancies were addressed through discussion and consensus among the three authors. Additionally, experts were consulted when necessary to assist in making final decisions. In cases where the required data could not be obtained

from the selected articles, efforts were made to establish contact with the corresponding authors to acquire the missing information.

2.6 Risk of Bias Within Studies

To assess the risk of bias, two authors (MJAA and MOCDL) independently employed the Joanna Briggs Institute's Critical Appraisal Checklist for Studies Reporting Prevalence Data and the Critical Appraisal Checklist for Case Reports [23]. In instances of disagreement, the third author (R.A.M.) was consulted to facilitate consensus. Before conducting the critical appraisal assessments, all authors engaged in discussions and made decisions regarding the scoring criteria. Studies were categorized as having a high risk of bias if they received a "yes" score of up to 49%, moderate between 50% and 69%, and low above 70%.

3. RESULTS

3.1 Study Selection and Characteristics

The study was conducted in two phases. Initially, a total of 3,253 records were gathered from multiple databases. After removing duplicates, the remaining 2,815 records underwent screening based on their titles and abstracts. Subsequently, 118 articles were selected for the second phase, which involved thoroughly reading the full texts. Applying the predetermined eligibility criteria, 89 studies were excluded, resulting in 30 studies that were eligible for synthesis (Figure 1). Among these 30 studies, 23 were cohort studies, and 7 were case-control studies. The entire process is visually depicted in Figure 2 through a flowchart.

First authors, year [reference]	Country of study	Study design	Sample size (case/control)	Age years)		Sex		Site of injury	Mandible /Maxilla	Both mandible and maxilla	Evolution time (months)
				Case	control	case (M/F)	Control (M/F)				
Wutzi et al., 2008	Austria	Cohort	58	68.3 (±10.7; 32-92.2)	-		20/38	jaw	12/36	10	29.6-41.5
Scoletta et al., 2010	Italy	Cohort	20	71.3 (±9.86)	-		06/14	jaw	10/23	4	42.95 (±32.16)
Scolleta et al., 2010	Italy	Cohort	37	68 (±12.9)	-		11/26	jaw	10/23	4	25.5 (6-196)
Atalay et al., 2011	Peru	Case Control	10/10	55.4 (39-68)			07/13	jaw	9/11	-	32
Eckardt et al., 2011	Germany	Cohort	142	62 (38-94)	-		47/95	jaw	32/39	21	37 (5-130)
Freiberger et al., 2012	USA	Case-Control	25/21	66.1	66.3	13/12	06/15	jaw	-	-	3-24
Corviello et al., 2012	Italy	Case-Control	04/03	75.57			02/05	jaw	5/0	1	0.5
Graziani et al., 2012	Italy	Cohort	347	67 (±11; 34-92)	-		117/230	jaw	-	-	6
O'Ryan et al., 2012	USA	Cohort	30	77 (54-89)	-		04/26	jaw	6/11	-	52.8 (22.8-79.2)
Assaf et al., 2013	Germany	Cohort	20	74 (±6.4)	-		9/11	jaw	5/12	3	11 (±33; 9-84)
Lerman et al., 2013	USA	Cohort	120	63 (39-91)	-		60/60	jaw	85/21	14	36 (0-126)
Kim et al., 2016	South Korea	Cohort	325	75 (±10.0)	-		11/314	jaw	239/72	14	48
Otto et al., 2016	Germany	Cohort	54	71.4 (±9.2)	-		22/32	jaw	40/25	-	46.3 (±31.8)
Pichardo et al., 2016	Netherlands	Cohort	74	67.9 (26-91)	-		12/62	jaw	58/11	5	0.46-0.7
Blus et al., 2017	Italy	Cohort	18	69.1 (±8.3; 59-87)	-		13/05	jaw	4/14	-	30.4 (±41.9; 9-121)
Coropciuc et al., 2017	Belgium	Cohort	79	38 - 90	-		39/40	jaw	72/37	-	-
Jung et al., 2017	South Korea	Case-Control	07/10	75.11 (±8.11; 59-86)			01/16	jaw	17/0	-	3-4
Mauceri et al., 2017	Italy	Cohort	10	75.2 (±5.94)	-		03/07	jaw	01/09	-	12
Calvani et al., 2018	Italy	Case-Control	13/13	55-71			05/21	jaw	-	-	24-60
Hadaya et al., 2018	USA	Cohort	106	71.7	-		31/75	jaw	0/43	-	24
Nisi et al., 2018	Italy	Cohort	53	71.9 (±10.2; 41-87)	-		0/53	jaw	12/39	2	0.46
Ristow et al., 2018	Germany	Cohort	75	68.2 (±9.8)	-		33/42	jaw	68/24	-	44.5 (±34.0; 180)
El -Rabbany et al., 2019	Canada	Cohort	78	80.5 (71.8-87.5)	-		14/64	jaw	47/25	-	13
Giovannacci et al., 2019	Italy	Cohort	8	75.75 (62-85)	-		02/06	jaw	7/0	1	-
Petrovic et al., 2019	Serbia	Cohort	32	59 (±11.8)	-		11/21	jaw	9/23	1	108
Giudice et al., 2020	Italy	Cohort	129	71.2 (±12.7)	-		39/90	jaw	-	-	-
Sim et al., 2020	Australia	Case-Control	15/19	64 (59-71)	64 (5874)		18/16	jaw	-	-	-
Tenore et al., 2020	Italy	Case-Control	21/13	58.09			08/26	jaw	14/12	-	0.17-1
Varoni et al., 2021	Italy	Cohort	35	73.46 (±9.29; 51-93)	-		11/24	jaw	12/24	-	17-60
Blatt et al., 2022	Switzerland	Cohort	45	71.5 (±8.6)	-		18/27	jaws	-	-	0.17-1

Fig. 1. The main characteristics of the selected articles focus on diagnosing medication-related osteonecrosis of the jaw.

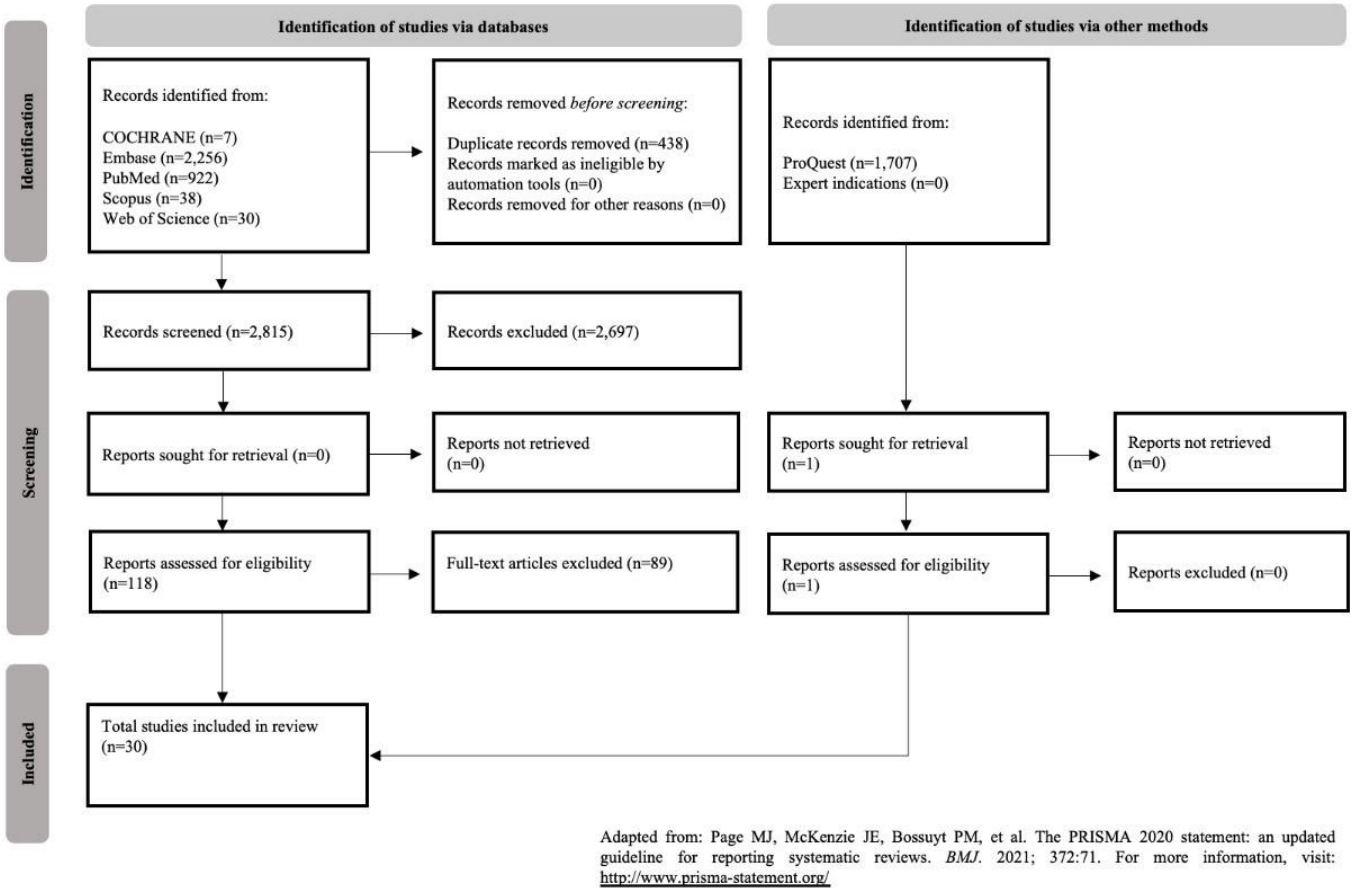

Fig. 2. PRISMA Flowchart

The selected studies encompassed a global perspective, with Europe contributing to 70.0% of the included studies, followed by North America with 16.7%, and Asia with 13.3% (Figure 1). These studies were published in the English language between September 2008 and January 2022.

3.2 Risk of Bias Within Studies

The risk-of-bias evaluations for each study are provided in Supplementary Table 2. For the assessment of cross-sectional studies, we utilized the specific checklist corresponding to the respective study design as outlined in the reference [23].

Supplementary Table 2. Risk of Bias assessed by the Joanna Briggs Institute Critical Appraisal Tools (A) for prevalence studies and (B) for case reports. Risk of bias was categorized as High when the study reaches up to 49% score "yes", Moderate when the study reached 50% to 69% score "yes", and Low when the study reached more than 70% score "yes". Checklist for case-control and cohort studies

First authors, year [reference]	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	% Yes / risk
Wutzi et al., 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Scoletta et al., 2010	Y	Y	N	Y	Y	Y	Y	Y	Y	88.9 / L
Scoletta et al., 2010	Y	Y	Y	Y	N	Y	Y	Y	Y	88.9 / L
Eckardt et al., 2011	Y	Y	Y	Y	Y	Y	Y	U	Y	88.9 / L
Mark et al., 2011	Y	Y	N	Y	Y	Y	Y	NA	Y	88.9 / L
Atalay et al., 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Freiberger et al., 2012	Y	Y	N	Y	Y	Y	NA	Y	Y	77.8 /L
Graziani et al., 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L

O'Rayan et al., 2012	Y	Y	N	Y	Y	Y	Y	Y	Y	88.9 / L
Coviello et al., 2012	Y	Y	N	Y	Y	U	U	N	Y	55.6 / M
Assaf et al., 2013	Y	Y	N	Y	Y	Y	Y	N	Y	77.8 / L
Kim et al., 2016	Y	Y	Y	Y	Y	Y	U	Y	Y	88.9 / L
Otto et al., 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Pichardo et al., 2016	Y	Y	Y	Y	Y	Y	Y	U	Y	88.9 / L
Jung et al., 2017	Y	Y	N	Y	Y	Y	Y	Y	Y	88.9 / L
Mauceri et al., 2017	Y	Y	N	Y	Y	Y	U	Y	Y	77.8 / L
Blus et al., 2017	Y	Y	N	Y	N	Y	Y	N	N	55.6 / M
Coropciuc et al., 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Hadaya et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Ristow et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	N	88.9 / L
Nisi et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Calvani et al., 2018	Y	N	N	U	Y	Y	Y	N	Y	55.6 / M
Giovannaci et al., 2019	Y	Y	N	Y	Y	Y	Y	N	N	66.7 / M
El – Rabbany et al., 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Petrovic et al., 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Giudice et al., 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Tenore et al., 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Sim et al., 2020	Y	Y	Y	Y	N	Y	Y	Y	Y	88.8/ L
Varoni et al., 2021	Y	Y	Y	Y	Y	Y	Y	Y	Y	100.0 / L
Blat et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	N	88.8 / L

Q1. Was the sample frame appropriate to address the target population? Q2. Were study participants sampled in an appropriate way? Q3. Was the sample size adequate? Q4. Were the study subjects and the setting described in detail? Q5. Was the data analysis conducted with sufficient coverage of the identified sample? Q6. Were valid methods used for the identification of the condition? Q7. Was the condition measured in a standard, reliable way for all participants? Q8. Was there appropriate statistical analysis? Q9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
Y - Yes; N - No; U – Unclear; NA – Not applicable; H – High, M – Moderate; L – Low.

3.3 Synthesis of Studies

The systematic review comprised a study population of 2,079 patients. The sex distribution consisted of 1,495 (71.9%) women and 584 (28.1%) men, with an average age of 69.52 (±9.67; range: 26-94) years. Regarding the location of the condition, 905 (43.5%) cases were observed in the mandible, 403 (19.4%) in the maxilla, 80 (3.8%) in both areas, and the location was not reported in 691 (33.2%) cases. The average duration of disease progression was 31.68 months (±34.57; range: 0.17-196) (Figure 1).

The most frequently reported medical histories in the study population were breast cancer (n=344; 20%), multiple myeloma (n=330; 19.19%), hypertension (n=213; 12.38%), osteoporosis (n=191; 11.1%), and diabetes (n=161; 9.36%). These medical conditions were commonly associated with the use of specific medications, including Zoledronate [n=772, duration of 452.04 months (±27.41; range: 12-102)], Alendronate [n=650, duration of 104.4 months (±60.16; range: 6-180)], Pamidronate [n=121, duration of 20.74 months (±4.94; range: 6-96)], and Denosumab [n=107, duration of 15 months (±7.94)].

During the initial consultation, the stages of medication-related osteonecrosis of the jaw (MRONJ) were classified as follows: stage Osa (n=1; 0.09%), stage Oss (n=14; 1.31%), stage I (n=361; 33.68%), stage II (n=543; 50.65%), and stage III (n=153; 14.27%). In terms of treatment, the most commonly employed clinical therapies included conservative surgical management (n=578; 27.92%), local debridement (n=281; 13.57%), conservative treatment (n=232; 11.21%), sequestrectomy (n=224; 10.82%), surgical resection with auto-fluorescence guidance and low-level laser therapy (n=137; 6.62%), and a combination of chlorhexidine, antibiotics, analgesics, -and debridement (n=106; 5.12%).

Treatment complications were identified in 271 cases (13.03%). The most frequent complications were resistant or worsening clinical stage of osteonecrosis (n=184, 67.9%), followed by incomplete mucosal healing or dehiscence (n=47; 17.34%) and mental nerve injury (n=9; 3.32%), among others.

4. DISCUSSION

In this systematic review, we meticulously assessed and synthesized the findings of 30 studies encompassing a diverse global perspective, shedding light on the epidemiological and clinical aspects of MRONJ. Our comprehensive analysis has provided valuable insights into the prevalence, risk factors, treatment modalities, and associated complications of MRONJ. The study selection process followed a rigorous methodology, involving two distinct phases. A total of 3,253 records were initially identified, which were then meticulously screened and narrowed down to 30 studies meeting our predetermined eligibility criteria. The synthesis of the included studies revealed a study population of 2,079

patients, women (71.9%) with an average age of 69.52 years. The locations of MRONJ were observed in the mandible (43.5%) and the maxilla (19.4%), reflecting the areas most affected. Notably, the average duration of disease progression was approximately 31.68 months, indicating the chronic nature of MRONJ.

In all studies except those byLerman et al. [24] and Sim et al. [25], a consistently high prevalence of MRONJ was observed in women. Lerman et al. [24] reported an equal distribution of cases with 60 (50%) men and 60 (50%) women, whileSim et al. [25 showed 18 (52.9%) men and 16 (47.1%) women affected. The rate of age across the articles varied from 26 to 94 years, with the lowest mean age reported byAtalay et al. [26] of 55.4 years. Regarding the affected anatomical sites, the mandible was consistently identified as the most affected area in all articles, except for Atalay et al. [26], Eckardt et al. [27], Hadaya et al. [28], and Tenore et al. [29]. In Atalay et al. [26],11 cases were found in the maxilla and 9 in the mandible. Eckardt et al. [27]reported 39 cases in the maxilla and 32 in the mandible. Hadaya et al. [28]exclusively observed cases in the maxilla (n=43), and Tenore et al. [29]found 14 cases in the maxilla and 12 in the mandible. A recent study by Kuehn et al. [30]aimed to investigate the localizing factors that render the jawbone uniquely vulnerable to osteonecrosis with long-term anti-resorptive therapy. They noted that among patients receiving anti-resorptive medications, osteonecrosis was never reported in long bones. In Zoledronate-treated rats, traumatic bone exposure healed normally in areas where localized drug accumulation was like that in the jawbone [31]. On the contrary, Zoledronate treatment led to anabolic changes in cortical and trabecular areas in long bones, indicating that bone formation and remodeling remained active at normal levels in these regions. Additionally, levels of Wnt-3a and RANKL were significantly reduced in the jawbones of Zoledronate-treated animals, while iliac and tibial bones exhibited significantly increased levels [32]. Numerous factors have been explored as potential localizing factors, including dental trauma, particularly surgical extraction, periodontitis, impaired gingival healing, alterations in the oral bacteria biofilm profile, and compromised innate immune responses specific to the oral cavity [1,14,33-42].

Underlying medical conditions were frequently associated with MRONJ, with breast cancer (20%), multiple myeloma (19.19%), hypertension (12.38%), osteoporosis (11.1%), and diabetes (9.36%) being commonly reported. These conditions often correlate with the use of specific medications, such as Zoledronate, Alendronate, Pamidronate, and Denosumab, with varying durations of usage. Studies have reported a prevalence rate of 0.3% to 0.4% for MRONJ in breast cancer patients using antiangiogenic inhibitors like Bevacizumab [43]. However, the prevalence increased to a range of 0.9% to 2.4% when both bevacizumab and bisphosphonates were used in combination [43]. The prevalence associated with Zoledronate or Denosumab treatment in osteoporotic patients was reported as 0.017% and 0.3%, respectively [44,45].

The classification of MRONJ stages revealed varying severity, with stage II being the most prevalent (50.65%), followed by stage I (33.68%) and stage III (14.27%). The therapeutic landscape for MRONJ was diverse, with commonly employed approaches including conservative surgical management, local debridement, sequestrectomy, and other methods. It is worth noting that complications in treatment were observed in 13.03% of cases, with the most frequent being resistance or worsening clinical stages, incomplete mucosal healing, and mental nerve injury.

Treatment modalities should primarily involve conservative surgical procedures, with elective procedures avoided as they may compromise additional areas of exposed bone necrosis and exacerbate symptoms [32, 33]. Non-surgical conservative therapy in stage I of MRONJ yielded low healing rates, leading to the conclusion that early surgical interventions should be considered across all stages to prevent progression [34]. Several studies have compared conservative surgical and non-surgical protocols [46-75]. A variety of surgical treatment options have been proposed, showing promising results [46,48-50,52,53,57-60,33,62-,64,66,68-71]. However, the absence of randomized controlled trials comparing nonsurgical and surgical treatment options has left the topic of surgical intervention in MRONJ still controversial [76]. Some less aggressive approaches have shown promise in reducing recurrences, such as autofluorescence/tetracycline-guided surgery, which enables the removal of all necrotic bone while preserving healthy bone [69]. The use of Piezoelectric in surgery is considered a less aggressive option and has been cited as a good choice in MRONJ cases [60,71]. To enhance surgical outcomes, various adjuvant therapies have been proposed in the literature, including parathyroid hormone (PTH), laser therapy, hyperbaric oxygen therapy, ozone therapy, and platelet-rich plasma (L-PRP/PRGF/PRP) [47,49,51,52,63,29,75]. These adjuvant therapies have shown faster and more comfortable postoperative healing. Additionally, studies have demonstrated the effectiveness of conservative management and antibiotics in MRONJ treatment [48,49,54,24,61,65,67,70,25]. Conservative surgery combined with adjuvant procedures (i.e., ozone, LLLT or blood component + Nd:YAG laser treatment) can contribute to partial or total healing in all stages of MRONJ, with improved results and variables (from symptoms to clinical and radiological signs). Adjuvant therapy associated with surgery (conservative or aggressive) may be the future for MRONJ treatment. This combination could lead to the most positive results, but it is also of the utmost importance for conducting further effectively controlled studies in order to arrive at conclusive statements for the effective treatment of MRONJ [76]. The results of this study suggest that the complete removal of the necrotic bone might have a higher impact on the success rates than the technique of the wound closure. Due to the fact that the mucoperiosteal wound closure technique offers a better overview of the extent of

the MRONJ lesion, the authors advise to use this technique. [77]. Moreover, worsening of clinical stages, especially in MRONJ lesions, often occurs within the initial six months of treatment [61].

It is crucial to acknowledge the limitations of our study, including its retrospective nature and potential selection bias. Additionally, the variations in study designs, patient populations, and treatment protocols may contribute to heterogeneity in the results. Furthermore, while we assessed the risk of bias within individual studies, we did not account for potential biases introduced during the synthesis process.

5. CONCLUSION

In conclusion, our systematic review has shed light on essential aspects of MRONJ, including its prevalence, risk factors, treatment strategies, and associated complications. The global distribution of the selected studies highlights the widespread impact of this condition. As further research continues to refine our understanding of MRONJ, a collaborative and multidisciplinary approach involving dental, oncological, and maxillofacial specialists remains essential to optimize patient outcomes and enhance our management strategies.

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