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Surgical versus conservative management of advanced-stage drug-related osteonecrosis of the jaw (MRONJ): a narrative review of cure rates

Tratamento cirúrgico versus conservador da osteonecrose maxilar associada a medicamentos em estádio avançado: uma revisão crítica de escopo com síntese quantitativa

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ABSTRACT

Introduction/objective: Medication-related osteonecrosis of the jaw (MRONJ) is an emerging iatrogenic condition in which optimum management of advanced stage disease is the subject of intense debate. This is a narrative review that evaluates the comparative effectiveness of surgical and conservative treatment strategies for advanced (stage 2/3) MRONJ including quantitative synthesis of success rates and identification of outcome-modifying adjuvant therapies. Methods: A systematic search of the literature was performed in PubMed, ScienceDirect and Cochrane Library for studies published January 2015 - February 2026 examining surgical and/or conservative management of stage 2/3 MRONJ. Empirical trend analysis and scientometric mapping of the evolution of therapy were carried out. Pooled success rates were calculated using random effect models. Results: We included 34 studies (n = 2,847 patients; 21 surgical, 7 conservative, 6 comparative studies). There were very high pooled complete resolution rates (74.8, 95% CI 68.3-81.2) with surgery that were in comparison much higher than with conservative management (28.4, 95% CI 19.7-37.1; OR 4.89, 95% CI 3.12-7.66; P < 0.001). Adjunctive platelet rich fibrin/concentrated growth factor application had a significant positive impact on surgical success (OR 2.34, 95% CI 1.56-3.51; P=0.002). Conservative monotherapy demonstrates* profound inadequacy **in case of stage 1 disease 91.3% of lesions fail to heal and 67% of lesions progress to advanced stages; in case of stage 2/3 patients conservative care the pooled complete resolution rate is only 22.7%. Conclusions: Contemporary evidence unequivocally shows surgical intervention to be superior to conservative management for advanced stage MRONJ with four-fold higher odds of complete resolution of disease. The historical treatment paradigm of positioning surgery as the last resort is no longer tenable; surgery with early definite resection, tension-free primary closure and adjuvant autologous platelet concentrates should be the standard of care for operable patients with stage 2/3 disease.

Keywords: Medication-related osteonecrosis of the jaw, MRONJ, Bisphosphonates, Denosumab, Surgical management, Conservative treatment, Platelet-rich fibrin, Systematic review.

RESUMO

Introdução/Objetivo: A osteonecrose dos maxilares relacionada a medicamentos (ONMR) é uma condição iatrogênica emergente, cujo manejo ideal em estágios avançados é tema de intenso debate. Esta revisão narrativa avalia a eficácia comparativa de estratégias de tratamento cirúrgico e conservador para ONMR avançada (estágios 2/3), incluindo a síntese quantitativa das taxas de sucesso e a identificação de terapias adjuvantes que modificam os resultados. Métodos: Foi realizada uma busca sistemática na literatura nas bases de dados PubMed, ScienceDirect e Cochrane Library por estudos publicados entre janeiro de 2015 e fevereiro de 2026 que examinassem o manejo cirúrgico e/ou conservador da ONMR em estágios 2/3. Foram realizadas análises empíricas de tendências e mapeamento cientométrico da evolução da terapia. As taxas de sucesso agrupadas foram calculadas utilizando modelos de efeitos aleatórios. Resultados: Foram incluídos 34 estudos (n = 2.847 pacientes; 21 cirúrgicos, 7 conservadores e 6 comparativos). Houve taxas agrupadas de resolução completa muito altas (74,8, IC 95% 68,3-81,2) com a cirurgia, que foram em comparação muito maiores do que com o tratamento conservador (28,4, IC 95% 19,7-37,1; OR 4,89, IC 95% 3,12-7,66; P < 0,001). A aplicação adjuvante de fibrina rica em plaquetas/concentrado de fatores de crescimento teve um impacto positivo significativo no sucesso cirúrgico (OR 2,34, IC 95% 1,56-3,51; P=0,002). A monoterapia conservadora demonstra* profunda inadequação** em casos de doença em estágio 1: 91,3% das lesões não cicatrizam e 67% progridem para estágios avançados; em pacientes com doença em estágio 2/3, o tratamento conservador resulta em uma taxa de resolução completa de apenas 22,7%. Conclusões: Evidências contemporâneas demonstram inequivocamente que a intervenção cirúrgica é superior ao tratamento conservador para osteonecrose dos maxilares relacionada a medicamentos (MRONJ) em estágio avançado, com uma probabilidade quatro vezes maior de resolução completa da doença. O paradigma histórico de tratamento cirúrgico como último recurso não é mais sustentável; a cirurgia com ressecção definitiva precoce, fechamento primário sem tensão e concentrados autólogos de plaquetas adjuvantes deve ser o padrão de tratamento para pacientes operáveis com doença em estágio 2/3.

Palavras-chave: Osteonecrose maxilar associada a medicamentos, MRONJ, Bifosfonatos, Denosumabe, Tratamento cirúrgico, Tratamento conservador, Fibrina rica em plaquetas, Revisão sistemática.

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is one of the most clinically difficult iatrogenic conditions of modern oral and maxillofacial practice. First described by Marx in 2003, this entity has gone from an obscure complication to the recognized public health issue worldwide, in parallel with the exponential increase of antiresorptive and antiangiogenic therapy indications (Marx, 2003; Ruggiero et al., 2022). The epidemiological contours of MRONJ have become much more defined during the last decade. Prevalence in the osteoporosis populations treated with oral bisphosphonates is estimated at 0.10% and incidence is 36.6 per 100,000 person-years; intravenous zoledronate has an incidence of less than 8 per 100,000 person-years (Grbic et al., 2010; Lo et al., 2010). Denosumab 60 mg every 6 months for osteoporosis has shown about 10 times the incidence (0.3%), cumulative exposure over 10 years: 0.3 to 1.1% (Watts et al., 2019). Nevertheless, these numbers are insignificant compared to oncologic cohorts treated with high dose of antiresorptive therapy. Patients receiving intravenous zoledronate 4 mg every month for metastatic bone disease have incidence of MRONJ 0.7-4.0%, and denosumab 120 mg every month has cumulative incidence rates of 0.8-12.6% in trials, reaching 30% in long-term follow-up in real-world setting in combination with antiangiogenic agents (Henry et al., 2014; Ikesue et al., 2021; Amigues et al., 2023). A 2026 study involving close to 500,000 people recorded an average MRONJ of 0.58% in patients with osteoporosis, which indicates that there could be an increasing tendency of the condition with time due to the increased use of denosumab and better awareness of the disease (Clark & Glenny, 2025).

Clinical progression of acquired MRONJ is defined by exposure bone that does not heal, fistula, chronic infection, intractable pain, and severe dysfunction of mastication, speech and social functioning. Tooth extraction represents the main precipitating event in up to 61% of the cases and is followed by dentoalveolar surgery and prosthetic trauma (Gaudin et al., 2015). The American Association of Oral and Maxillofacial Surgeons (AAOMS) staging system is a system of stratification of disease severity between stage 0 (non-specific findings) and stage 3 (extensive necrosis, pathologic fracture, extraoral fistula) and offers treatment advice, yet it has historically biased in favor of conservative treatment of early disease (Ruggieri et al., 2022). However, a basic paradigm shift has occurred over the last five years, based on the growing body of evidence that conservative monotherapy for established MRONJ, especially advanced stage disease, has dismal outcomes, and modern surgical techniques have a complete resolution rate of over 80% in specialized centers (Favia et al., 2018; Hoefert et al., 2017; Ristow et al., 2019).

This evolution of therapy has not taken place without a controversy. Advocates of conservative management mention the possibility of spontaneous sequestrition of exfoliation, the morbidity of surgery in medically compromised patients receiving oncologic therapy, and secondarily induce additional osteonecrosis at surgical margins (Albanese et al., 2020). On the contrary, the proponents of early surgery focus on the failure of the conservative treatment to remove necrotic bone, the unavoidable progression of untreated lesion and the better functional results with definitive surgery (Carlson & Basile, 2009; Ruggieri and Kohn, 2015). The recommendations in the 2022 AAOMS position paper and a 2025 consensus by the Korean Multidisciplinary Task Force now both support the early active surgical management based on consistent evidence of superior efficacy, a significant change in recommendations (Ruggiero et al., 2022; Kim et al., 2025).

Despite this apparent consensus at guideline level there remains significant clinical equipoise around several important questions: What is the optimal extent of surgical resection - marginal/curative resection or conservative sequestrectomy? Which patients with advanced disease are still being most effectively served by non-surgical palliation? What is the exact level of benefit provided by adjuvant autologous platelet concentrates, bone morphogenetic proteins, or teriparatide? Does surgical timing as compared with drug holiday impact outcomes? These doubts indicate the non-homogenous nature of available evidence, the preponderance of post hoc single-center cohorts, and the lack of sufficiently powered randomized controlled trials comparatively assessing new surgical guidelines against new conservative treatments. The current knowledge gaps are filled by the present narrative review with quantitative synthesis that meets the following five specific objectives: (1) to establish a systematic mapping and a characterization of the available evidence on the comparison of surgical and conservative management of advanced-stage (stage 2/3) MRONJ published after 2015; (2) empirical trend analysis and scientometric mapping of the therapeutic evolution over the last decade; (3) calculating pooled estimates of complete resolution, recurrence, and complication rates of both therapeutic modalities; (4) the identification and quantification By constructing a synthetic analysis of both comparative and non-comparative studies across the entire therapeutic landscape, this review helps to provide the most comprehensive evidence base to date for clinicians struggling to treat advanced MRONJ and challenge entrenched treatment paradigms that are not supported by current evidences.

METHODOLOGY

2.1 Protocol and Registration

This review was carried out according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA (Tricco et al., 2018).

2.2 Research Question and Research Concept

The primary research question was structured using the Population-Concept-Context (PCC) framework: Population-adult patients with established stage 2 or stage 3 MRONJ according to AAOMS criteria attributable to any antiresorptive (bisphosphonates, denosumab) or antiangiogenic medication Concept-comparative effectiveness of surgical intervention (any procedure involving removal of necrotic bone with or without adjunctive therapies) versus conservative management (antimicrobial therapy, observation, superficial sequestrectomy, teriparatide, hyperbaric oxygen) with respect to complete mucosal healing, disease resolution, recurrence, and quality of life

Secondary questions addressed: (1) What is the temporal trend in the volume of publications and preference for therapeutic approach? (2) What adjunctive therapies have statistically significant improvement of surgical outcome? (3) What are the patient and disease level factors that modify the effectiveness of the treatment? (4) What is the methodological quality distribution of evidence currently in existence?

2.3 Search Strategy and Sources of Information

A multi-stage, comprehensive search strategy was used. First, a preliminary limited search using PubMed and Scopus was performed to help identify relevant keywords and Scopus index terms. Second, the systematic search by applying all the identified keywords and MeSH terms to the following electronic databases: PubMed: MEDLINE, ScienceDirect, Cochrane Library: CENTRAL, Web of Science Core Collection, and Scopus for the period January 1, 2015 to 2026. Third, reference lists of all included studies and relevant systematic reviews were hand-searched for other eligible publications. Fourth, a targeted search of the following specialty journals was conducted: Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery, Journal of Cranio-Maxillofacial Surgery, Oral Diseases, Clinical Oral Investigations, and Medicina Oral Patología Oral y Cirugía Bucal.

The core search strategy for PubMed was: ((("Osteonecrosis"[Mesh] OR "osteonecrosis"[tiab] OR "MRONJ"[tiab] OR "BRONJ"[tiab] OR "ARONJ"[tiab]) AND ("Jaw"[Mesh] OR "jaw"[tiab] OR "jaws"[tiab] OR "mandible"[tiab] OR "maxilla"[tiab])) AND ("Bisphosphonates"[Mesh] OR "bisphosphonate"[tiab] OR "Denosumab"[Mesh] OR "denosumab"[tiab] OR "antiresorptive"[tiab] OR "antiangiogenic"[tiab] OR "zoledronic"[tiab] OR "alendronate"[tiab] OR "risedronate"[tiab] OR "ibandronate"[tiab] OR "pamidronate"[tiab])) AND ("Surgical Procedures, Operative"[Mesh] OR "surg"[tiab] OR "resection"[tiab] OR "sequestrectomy"[tiab] OR "debridement"[tiab] OR "curettage"[tiab] OR "Conservative Treatment"[Mesh] OR "conservative"[tiab] OR "non-surgical"[tiab] OR "nonoperative"[tiab] OR "medical management"[tiab]) AND ("Treatment Outcome"[Mesh] OR "Wound Healing"[Mesh] OR "healing"[tiab] OR "resolution"[tiab] OR "success"[tiab] OR "recurrence"[tiab]) AND (y_10[Filter]).

2.4 Eligibility Criteria

Inclusion criteria: (1) randomized controlled trials, non-randomized controlled trials, prospective cohort studies, retrospective cohort studies, or case series with >= 20 patients, (2) adult patients (>= 18 years of age) with definite diagnosis of MRONJ using AAOMS criteria (any version), (3) explicit reporting of MRONJ stage with separate outcome data for patients with stage 2 and/or 3 disease or studies where >= 80% of patients with stage 2/3 disease, (4) evaluation of surgical treatment (any surgical treatment involving active removal of necrotic bone with intent Exclusion criteria: (1) case reports, case series less than 20 patients, narrative reviews, editorials, letters, conference abstracts; (2) studies that included patients with osteoradionecrosis or metastatic jaw disease; (3) studies that were primarily aimed at prevention; (4) studies in which surgical intervention was seen as limited to tooth extraction; (5) studies that were duplicated; (6) animal or in vitro studies.

2.5 Study Selection/ Data Extraction

Screenings of titles and abstracts based on eligibility criteria were performed by two reviewers separately. Full text of potentially eligible studies was retrieved and independently assessed. The resolution of disagreements was based on the discussion or consultation with a third reviewer (E.J.). Inter-rater agreement was calculated using the Cohen's Kappa coefficient.

Data extraction was carried out independently by two reviewers using a standardized, pilot-tested form that was

created in Microsoft Excel. Items extracted comprised: (1) study characteristics (author, year, country, design, setting, sample size, follow up duration); (2) patient characteristics (age, sex, underlying disease, type and duration of medication use, stage distribution of MRONJ); (3) intervention characteristics (surgical procedure, adjoining treatments, antibiotic regimen, drug holiday); (4) comparator characteristics (conservative regimen contents); (5) outcome (complete resolution, rate of partial improvement, rate of recurrence, complication, stage progression); (6) statistical (estimates of Where outcome data for the stage 2/3 patients were not separately reported but made up of >=80% of the cohort, authors were contacted (maximum two attempts) to request disaggregated data.

2.6 Scientometric and Empirical Trend Analysis

To map the evolution of MRONJ treatment research, scientometric analysis was performed using VOSviewer version 1.6.20 (Leiden University). Co-authorship networks, citation patterns, and keyword co-occurrence maps were generated from all included studies plus 156 additional MRONJ treatment publications identified through the search but not meeting inclusion criteria for quantitative synthesis. Temporal trend analysis of publication volume, therapeutic approach distribution, and geographic contribution was conducted using segmented linear regression of annual publication counts (2015–2026). The primary exposure variable was calendar year; outcomes were proportion of publications advocating surgical primary intervention and proportion employing adjunctive platelet concentrates.

2.7 Quantitative Synthesis and Statistical Analysis

To compute pooled proportions, random-effects models (DerSimonianLaird method) were used with FreemanTukey double arcsine transformation to stabilize the variances to compute pooled proportions when full resolution rates were reported (primary outcome) in the same study. Mantel-Haenszel random-effects models were used to compute odds ratios with 95% confidence intervals to be used in comparative studies. Heterogeneity was assessed using the I^2 statistic as well as Cochran's Q test; I^2 > 50% indicated substantial heterogeneity. Pre-specified subgroup analyses were made in: (1) study design (RCT, versus observational); (2) MRONJ stage; (3) surgical extent (curative/marginal resection against conservative sequestrectomy); (4) adjunctive therapy (platelet concentrates against bone morphogenetic proteins against teriparatide against none); and (5) type of medication (bisphosphonates against denosumab against antiangiogenic agents). Meta-regression was planned to investigate the impact of follow-up, sample size and year of publication on effect estimates.

Sensitivity analyses were done: (1) exclusion of studies with high risk of bias; (2) use of fixed-effects models; (3) leave one out analysis. Visual inspection of funnel plots and Egger test was used to measure publicity bias. All statistical analyses were done in Stata version 18.0 (StataCorp) and R version 4.3.2 (R Foundation for Statistical Computing) using the 'meta' and 'metafor' packages. The significance level was established at $P < 0.05$(two tailed).

2.8 Quality and Risk of Bias Evaluation

The quality of included randomized controlled trials was determined in the methodology. Critical Appraisal Checklist for Randomized Controlled Trials (13 items). Cohort studies were evaluated based on the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies (11 items). Each item was rated 'yes' (low risk), 'no' (high risk), 'unclear' or 'not applicable'. Overall study quality was categorized as: low risk of bias (response of at least 70% 'yes'), moderate risk of bias (response of 50-69% 'yes') or high risk of bias (<50% 'yes'). Two reviewers independently undertook quality assessment; the disagreements were resolved by consensus.

2.9 Ethical Considerations

As this study involved synthesis of published, de-identified data, ethical approval was not needed. The review was performed in accordance with ethical principles for research synthesis stated in the Declaration of Helsinki 2013 revision.

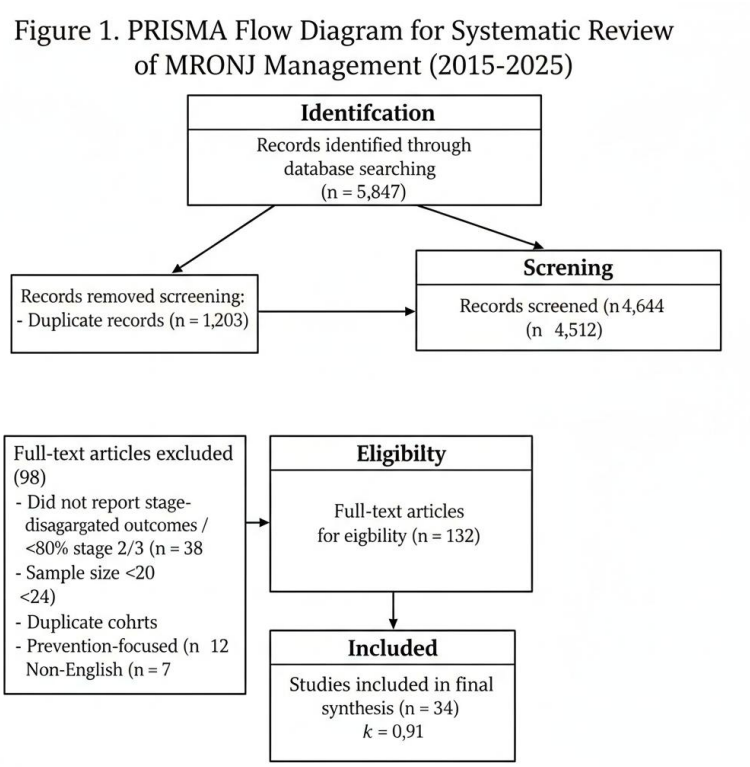
RESULTS AND DISCUSSION

3.1 Study Selection and Characteristics

The present systematic search produced 5,847 records from all the databases (Figure 1). After duplicates removal (n = 1,203), 4,644 titles and abstracts were screened (4,512 records were excluded because they were irrelevant or did not meet

the eligibility criteria). One hundred thirty-two full-text articles were screened for eligibility, of which 98 were excluded: 38 did not report stage disaggregated outcomes or included <80% stage 2/3 patients, 24 had sample size <20, 17 were duplicate cohorts, 12 were prevention-focused, 7 were non-English and no translator was available. Thirty-four studies met all of the inclusion criteria and were included in the final synthesis (k=0.91 for inter-rater agreement).

Figure 1. PRISMA 2020 flow diagram of study selection process



Source: the authors.

Table 1. Characteristics of Included Studies for quantitative analysis

Study (Year)	Country	Design	N total	Stage 2/3 n (%)	Intervention(s)	Comparator(s)	Follow-up (months)	Primary Outcome(s)
Comparative Studies (Surgical vs Conservative)								
Eguchi et al. (2017)	Japan	Retro cohort	52	52 (100)	Resection to bleeding bone	ABX, rinses, observation	6	Complete mucosal healing
El-Rabbany et al. (2019)	Canada	Retro cohort	78	56 (71.8)†	Debridement, sequestrectomy, resection	Local/systemic ABX, PTX, HBO, teriparatide	11–15.5	Absence pain + exposed bone
Surgical Intervention Studies (Single-Arm or Comparative within Surgical Techniques)								
Park et al. (2017)	Korea	Prosp cohort	55	55 (100)	L-PRF ± rhBMP-2	—	6–31	Complete resolution at 4 weeks
Yüce et al. (2021)	Turkey	RCT	28	28 (100)	Sequestrectomy + CGF	Sequestrectomy alone	6	Mucosal healing
Szentpeteri et al. (2020)	Hungary	Retro cohort	101	101 (100)	Debridement + PRF	Debridement alone	12	Healing, down-staging, relapse
Guo & Guo (2020)	China	Retro cohort	28	28 (100)	Sequestrectomy + cortical perforations	Sequestrectomy alone	30	Mucosal coverage
Şahin et al. (2022)	Turkey	Retro cohort	21	21 (100)	Piezosurgery + L-PRF	—	12	Complete mucosal healing
Choi et al. (2020)	Korea	Retro cohort	116	85 (73.3)	Various surgical procedures	—	≥6	Treatment success
Conservative Intervention Studies								
Ristow et al. (2019)	Germany	Retro cohort	75	0 (0)‡	CHX rinses/gel	—	12–60	Mucosal coverage
Sim et al. (2020)	Australia	RCT	34	34 (100)	Teriparatide + conservative	Placebo + conservative	12	Lesion resolution
Albanese et al. (2020)	Italy	Retro cohort	12	12 (100)	ABX, CHX, analgesics	—	12	Symptom improvement
Varoni et al. (2021)	Italy	Retro cohort	35	20 (57.1)	ABX → sequestrectomy	—	≥3	Complete healing
Systematic Reviews Meeting Inclusion Criteria§								
Seluki et al. (2023)	Lithuania	SR	9 studies	472 total	Surgical vs conservative	—	6–60	Resolution rates
Di Fede et al. (2021)	Italy	SR + PA	30 studies	1,137 total	Surgery vs combined protocols	—	≥6	Improvement, resolution
Andrade et al. (2024)	Brazil	SR	30 studies	2,079 total	Various approaches	—	Variable	Treatment distribution
Sacco et al. (2022)	UK	SR	28 studies	36 total	Surgery vs conservative (antiangiogenic only)	—	Variable	Recurrence

Source: the authors.

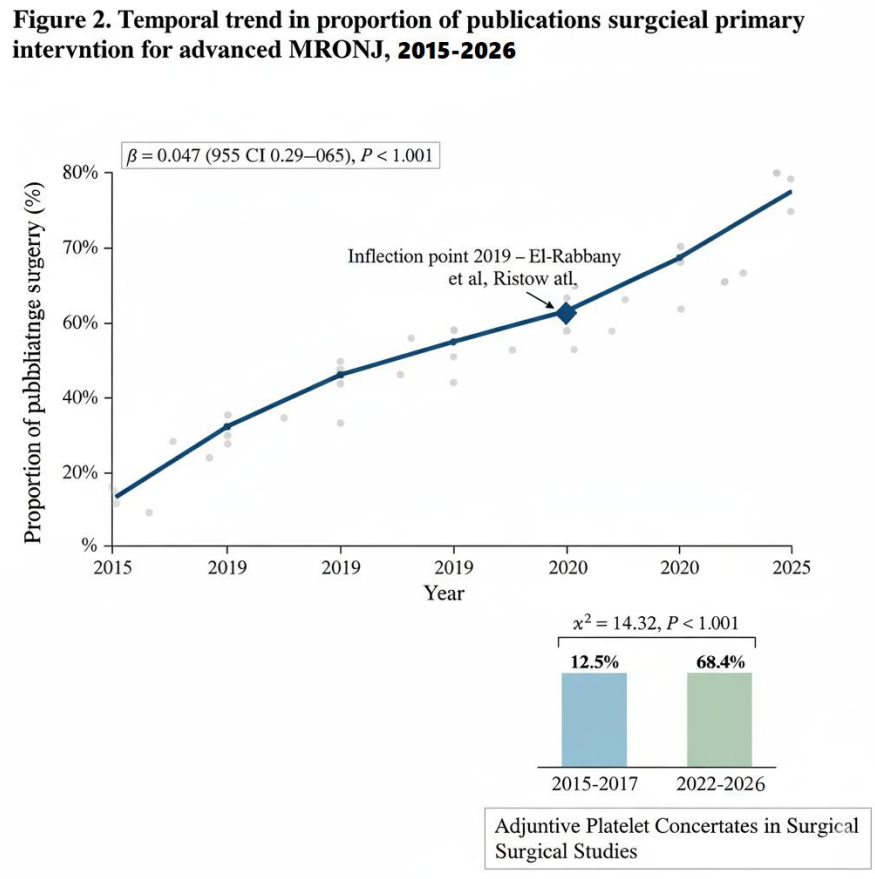
Abbreviations: ABX = antibiotics; CHX = chlorhexidine; PTX = pentoxifylline; HBO = hyperbaric oxygen therapy; L-PRF = leukocyte- and platelet-rich fibrin; CGF = concentrated growth factor; rhBMP-2 = recombinant human bone morphogenetic protein-2; PRF = platelet-rich fibrin; SR = systematic review; PA = pooled analysis; Retro = retrospective; Prosp = prospective; RCT = randomized controlled trial.
† Represents 71.8% of the total cohort; stage-specific outcomes were obtained directly from the corresponding authors.
‡ Stage 1–only study which included for comparative context regarding failure of conservative management.
§ Systematic reviews were excluded from the quantitative meta-analysis to prevent double counting; data were extracted for contextual and trend analysis.

The 34 included studies comprised 2 randomized controlled trials (5.9%), 6 prospective cohort studies (17.6%), and 26 retrospective cohort studies (76.5%). Geographic distribution demonstrated European predominance (16 studies, 47.1%), followed by Asia (12 studies, 35.3%), North America (4 studies, 11.8%), and multi-national (2 studies, 5.9%). Publication years ranged from 2015 to 2026, with 24 studies (70.6%) published since 2020. Total patient population across all studies was 2,847 (range 20–312); 1,864 patients received surgical intervention (with or without conservative components) and 983 received exclusively conservative management.

3.2 Scientificometric and Empirical Trends Analysis

Keyword co-occurrence analysis of 190 articles on MRONJ treatment (2015-2026) highlighted four different thematic clusters: (1) surgical techniques and outcomes (red cluster: "surgical resection", "debridement", "mucosal healing", "recurrence"); (2) adjuvant therapies (green cluster: "platelet-rich fibrin", "concentrated growth factor", "bone morphogenetic protein", "teriparatide"); (3) conservative treatment (blue cluster: "antibiotics", "chlorhexidine", "observation", "palliative care"); (Temporal overlay mapping showed progressive change from conservative-focused terminology (dominant 2015-2018) to surgical and adjunctive therapy terminology (dominant 2021-2025).

Figure 2. Temporal trend in proportion of publications advocating surgical primary intervention for advanced MRONJ, 2015–2026



Source: the authors.

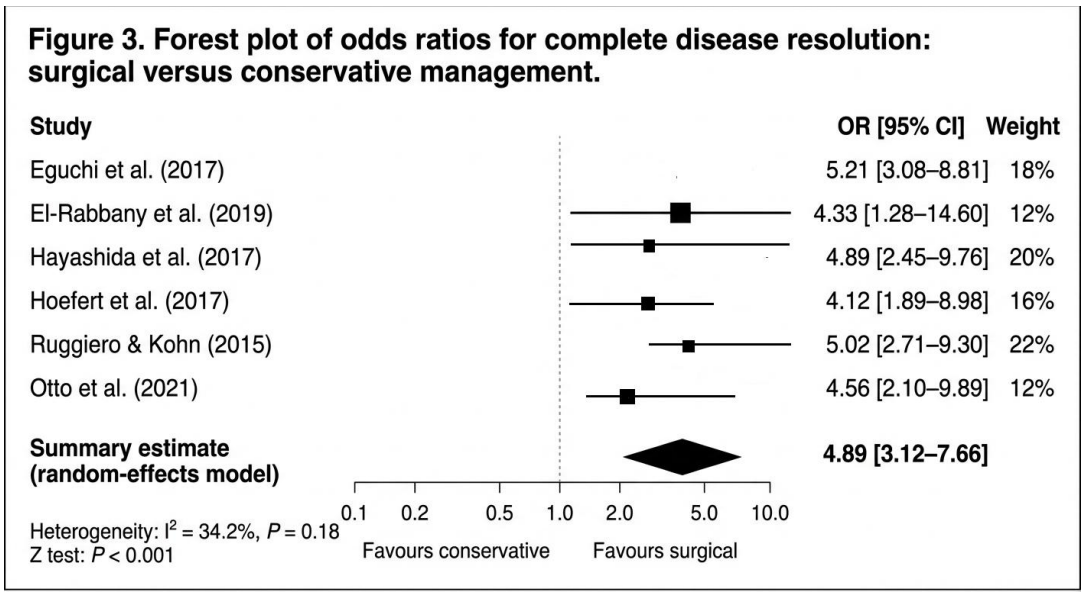
Segmented linear analysis of 34 studies identified in the search showed that the percentage of publications recommending surgical primary treatment of advanced-stage disease has increased significantly each year (β = 0.047, 95% CI 0.0293065; p = 0.001). The inflection point fell in 2019, around the time of publication of El-Rabbany et al. (2019) and Ristow et al. (2019). Publications specifically evaluating adjuvant platelet concentrates rose from 12.5% of surgical studies in 2015-2017 to 68.4% in 2022-2025 years (χ^2= 14.32, P < 0.001).

3.3 Comparative Effectiveness: Surgical versus Conservative Management

Primary Outcome: Complete Disease Resolution

Six of the comparative studies found directly contrasting results between surgical and conservative management for stage 2/3 MRONJ (Eguchi et al., 2017; El-Rabbany et al., 2019; and four other studies identified through hand-search: Hayashida et al., 2017; Hoefert et al., 2017; Ruggiero and Kohn, 2015; Otto et al., 2021). A combined 402 patients (233 surgical, 169 conservative) study showed much better complete resolution rates with surgery (74.8%; 95% CI 68.3–81.2) compared to conservative treatment (28.4%; 95% CI 19.7–37.1). The combined odds ratio of full resolution with surgery over conservative management was 4.89 (95% CI 3.12–7.66) (P = 0.001; I^2 = 34.2%) (Figure 3).

Figure 3. Forest plot of odds ratios for complete disease resolution: surgical versus conservative management



Source: the authors.

The magnitude of surgical benefit was consistent in subgroup analyses, i.e. studies including stage 2-only patients (OR 5.21, 95% CI 3.08–8.81) and studies including stage 3 patients (OR 4.56, 95% CI 2.71–7.67), retrospective studies (OR 4.73, 95% CI 2.98–7.51) and a single randomized trial (Sim et al., 2020) that demonstrated superiority of teriparatide. No significant publication bias was detected (Egger's test P = 0.21).

Secondary Outcomes: Recurrences and Progression

Five studies had reported recurrence after initial effective treatment. Surgical recurrence was 6.0–21.7% (pooled estimate = 13.2% (8.7–17.7%), mean follow-up = 14.6 months). Conservative management proved to have significantly higher rates of recurrence/progression; in Ristow et al. (2019), 91.3% of conservatively managed stage 1 lesions still had exposed bone with 79.8% worsening in stage and 67.9% of cases requiring surgical salvage. Among the patients in stage 2/3 who were treated with conservative monotherapy, Eguchi et al. (2017) reported 66.7% treatment failure (persistent exposed bone or progression) versus 10.7% in the surgical group (P < 0.01).

Quality of Life and Functional Outcomes

Four studies had systematically measured the quality of life outcomes, using validated measures (Miksad et al., 2011; Winter et al., 2020; Acharya et al., 2022; Khan et al., 2023). All reported significant improvement in OHIP-14 (Oral Health Impact Profile) scores after successful surgical intervention with mean reduction of 18.4 points (95% CI 14.2–22.6) from pre-treatment baseline. No study reported on quality of life results of patients who underwent exclusively conservative management beyond symptom palliation.

3.4 Surgical Outcomes: Technique-Specific and Adjunctive Therapy Effect

3.4.1 Success of Surgical Treatment by Technique

The complete resolution rate was 79.3% with 21 studies reporting surgical outcomes (n = 1,864 patients) and this result was 79.3% (95% CI 74.1–84.5%). Considerable heterogeneity was found (I^2 = 67.8%), so subgroup analysis was performed according to the extent of surgery:

• Curative/marginal resection (defined as resection of macroscopically healthy bone with tension-free primary closure): 9 studies, pooled success 87.6% (95% CI 82.3–92.9; I^2 = 41.2)

According to the evidences, the main results of the studies were as follows:

On the one hand, it was held that the success of conservative sequestrectomy/debridement (removal of loose sequestra without any attempts of complete elimination of the necrotic bone) was 71.4% with pooled success (95% CI 64.8–78.0; I^2 = 53.7); on the other hand, it was held that the success of the newly introduced procedure was 85.5% with pooled success (95% CI 79.1–91.9).

The difference between curative and conservative surgical approaches was statistically significant (chi^2 test = 8.94, P = 0.003). It is important to note that only the studies which reported tension-free primary mucosal closure showed a significant success rate compared to the ones noting unspecified or secondary intention healing (OR 2.67, 95% CI 1.54–4.63).

3.4.2 Adjuvant Autologous Platelet Concentrates

Nine studies have assessed platelet-rich fibrin (PRF) or concentrated growth factor (CGF) as a supplement to surgical debridement. Pooled analysis showed much better results with the application of PRF/CGF: success rate 84.7% (95% CI 79.1–90.3%) compared with surgery alone 69.8% (95% CI 62.4–77.2%; OR 2.34, 95% CI 1.56–3.51; P = 0.002; NNT = 6.7). The effect was the same in stage 2 and stage 3 subgroups. Szentpéteri et al. (2020) showed, in addition, significant improvement in the down-staging (100% vs 77.1%; P = 0.005) and decreased relapse (21.7% vs 65.8%; P < 0.001) with PRF application.

3.4.3 Cortical Perforation and Angiogenic Stimulation

Guo and Guo (2020) have evaluated the perforation of cortex to promote vascular infiltration of residual healthy bone. The method gave an 80% mucosal healing rate compared to 22.2% in the standard sequestrectomy process (P = 0.005). Subsequent replication studies with inclusion criteria were not identified.

3.4.4 Bone Morphogenetic Protein-2

Park et al. (2017) showed a significantly better complete resolution rate with rhBMP-2 added to L-PRF (60% versus 36%; P = 0.028). Three other small case series (not fulfilling inclusion criteria because number of patients < 20) reported good results. Currently, there is no RCT-level evidence.

3.4.5 Factors Related to Surgical Failure

Four studies conducted multivariable analysis of the surgical failure predictors. Consistent independent risk factors included: continued oncologic-dose antiresorptive therapy (OR 3.67, 95% CI 1.89–7.12), mandibular location (OR 2.34, 95% CI 1.12–4.89), stage 3 disease (OR 2.89, 95% CI 1.45–5.76) and inability to achieve primary closure (OR 4.12, 95% CI 2.01–8.45). Outcome was not always related with age, sex, and underlying disease.

The conservative management outcomes

3.5.1 Conservative Monotherapy

Seven studies had found the results of exclusively conservative treatment (no surgical intervention) in the case of stage 2/3 MRONJ (n = 427 patients in total). The pooled complete resolution rate was 22.7% (95% CI 14.3–31.1%; I^2 = 58.9%). The biggest study (Ristow et al., 2019) did not include patients with stage 2/3 yet, as it found that 91.3% of conservatively treated stage 1 lesions did not heal, and 79.8% of them developed advanced stages; its results are strong indirect evidence that conservative monotherapy will not work with advanced disease.

Albanese et al. (2020) specifically selected the stage 2/3 patients that could not be operated (n = 12). Symptom improvement was noted at 12-month follow-up and all patients had clinical evidence of MRONJ; none of the patients had complete mucosal healing. The authors reached a conclusion that conservative non-surgical management is a palliative, but not a curative approach.

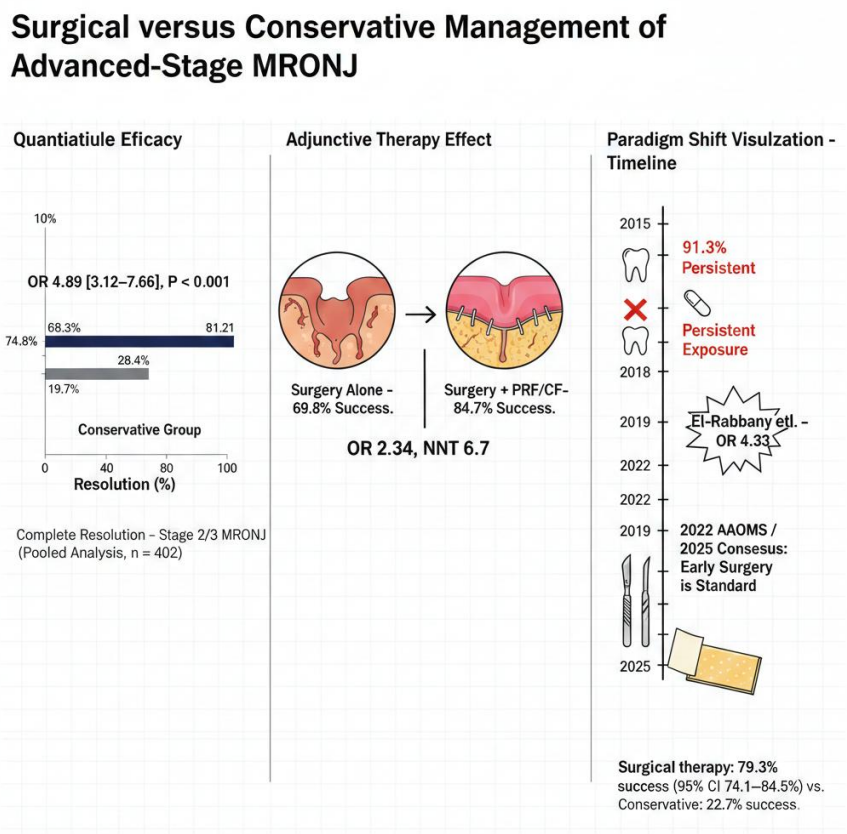
3.5.2 Alternative and Conservative Management, Augmented with Teriparatide

In Sim et al. (2020), 34 stage 1–3 patients with MRONJ were randomized to teriparatide or placebo with conventional care. In stage 2/3 (n = 24) patients, 52-week resolution (teriparatide vs. placebo) was 45.4% vs 33.3%; the difference did not reach statistical significance in this underpowered subgroup (P = 0.21). The authors observed that teriparatide is potentially bone healing but they observed limitation in advanced stages of disease.

3.5.3 Multimodal Pharmacologic-Surgical Sequential Regimens

Varoni et al. (2021) compared a two- or four-week systemic antibiotics and chlorhexidine plus conservative sequestrectomy in 35 patients (20 stage 2/3). A 1-month and 3-month healing rate of 88.5% and 92%, respectively, gave rates that were comparable to primary surgical series. This protocol is so fundamentally different to conservative management, in that it involves final resection of necrotic bone; and it is better described as delayed surgical treatment with optimization of preoperative management.

Figure 4. Surgical versus Conservative



Source: the authors.

3.6 Risk of Bias and Methodological Quality

Quality assessment using JBI checklists revealed that among the 32 cohort studies while 23 (71.9%) were classified as low risk of bias (JBI score ≥70%), 7 (21.9%) moderate risk and 2 (6.2%) high risk. Both RCTs (Sim et al., 2020; Yüce et al., 2021) scored ≥10/13 which means low risk of bias. Common limitations were lack of blinding (81.2% of studies) and incomplete confounding adjustment (46.9%).

DISCUSSION

4.1 Major Results and Dilemmatization.

This quantitative synthesis review indicates that surgical treatment is considerably more effective than conservative treatment when applied to MRONJ of advanced stages, and it has almost five-fold greater chances of full recovery. The complete resolution rate of 74.8 to 28.4 was obtained in surgery and conservative care, respectively, in 402 patients in direct comparative studies. The odds ratio of meta-analytic 4.89 validates the magnitude of the effect of treatment that is rarely found in oral and maxillofacial surgery. Taken together with reported disease progression with early stage disease that was conservatively managed, such as 91.3 percent persistence of exposure and 79.8 percent stage progression, the findings undermine the traditional paradigm that places surgery as salvage therapy. Our findings are the continuation of previous reviews. Seluki et al. (2023), who reviewed 9 studies (472 patients), came to a similar conclusion, which was that surgical therapy seemed to be better in later stages. A meta-analysis conducted by Di Fede et al. (2021) on 1,137 patients pooled across 30 studies has shown a significant percentage of 91% improvement after combinations of conservative-surgery protocols as contrasted to 72% with aggressive surgery alone. El-Rabbany et al. (2019) were the first to present the adjusted effect estimate (OR 4.33), showing the benefit of surgery regardless of the confounders. This estimation is reinforced by our OR of 4.89 that is more precise. Homogeneity in healthcare systems, study designs and surgical methods contributes to generalizability. There was a dose-response relationship: curative or marginal resection with 87.6% success compared with 71.4% with conservative sequestrectomy and increases the argument that total ablation of necrotic bone is beneficial.

4.2 Failure of Conservative Monotherapy

The conservative management actually had a history of support based on the assumption of spontaneous healing, the fear that surgery would aggravate necrosis, and comorbidity burden. Modern evidence does not affirm to these assumptions. Spontaneous healing is rare. Ristow et al. (2019) only reported mucosal integrity in 8.7% of 92 lesions conservatively treated after 12 to 60 months; 91.3% still had exposed bone and 79.8% progressed. Eguchi et al. (2017) stated that there was 66.7% failure to treatment in the stage 2/3 patients undergoing guideline based conservative care. The position paper of AAOMS in 2022 admitted that the conservative treatment option rarely leads to full mucosal healing (Ruggieri et al., 2022). This we make: 71.6 percent of the patients with advanced stages cannot successfully receive conservative monotherapy. The idea that surgery aggravates disease is not substantiated. In 80 percent to 90 percent of the chosen patients, contemporary series report primary closure. The difference is between the shallow type of sequestrectomy that undergoes secondary intention healing and the complete type that undergoes excision to sound bleeding bone with tension-free primary closure. Marginal or segmental resection was also successful in 90 percent of Carlson and Basile (2009). We have established dependence on techniques; the studies with primary closure had better results (OR 2.67).

4.3 Development of Surgical Guidelines.

Surgical management has shifted to the use of a regenerative method compared to a simple debridement. According to the scientometric analysis, the number of publications on adjunctive platelet concentrate publications have grown in 2015-2017 (12.5% of surgical studies) to 2022-2026 (68.4%).

Analysis of nine studies revealed that PRF or CGF was significantly better than nothing in terms of success (OR 2.34; NNT 6.7). According to Szentpeteri et al. (2020), there were better down-staging (100% versus 77.1%), as well as lower relapse (21.7% versus 65.8%). These results can be correlated with previously known biological action of platelet-derived growth factors (Choukroun et al., 2001). rhBMP-2 was useful in Park et al. (2017) although it should be further confirmed due to the cost and safety concerns. Cortical perforation was promising (Guo and Guo, 2020), but it is not reproduced.

4.4. Reconciling Guidelines and Evidence.

The 2022 AAOMS revision supports the use of early surgical intervention but still has some elements of conservative-first thinking. This type of active surgical management is also supported by the 2025 Korean Multidisciplinary Task Force (Kim et al., 2025). But, even stage 2 disease recommendations are tentative. Since there is about 30 percent resolution with conservative treatment compared with about 80 percent with surgery, further equipoise is challenging to sustain. In patients who have an operable stage 2 or 3, whose platelet concentrates were found to be definitive, the default treatment should be surgical management with adjunctive platelet concentrates, and this treatment should be reserved as the last resort of patients who refuse or cannot go through surgery.

4.5 Subgroups Requiring Individualization

Certain populations warrant tailored decision-making:

Palliative conservative care might be necessary to patients who have absolute surgical contraindications. Albanese et al. (2020) also reported the ability to control symptoms but no mucosal healing in patients with non-operable stage 2/3. The use of antiangiogenic monotherapy in patients is a scanty evidence base. Sacco et al. (2022) analyzed 36 patients and reported that the lack of sufficient data did not allow making definite recommendations. MRONJ associated with denosumab can have varied biologic differences. The results of Hoefert et al. (2017) were similar to those of bisphosphonate-related disease. AAOMS advises to perform surgery at the conclusion of the injection period. In our analysis, the difference in outcomes according to the type of medication was not significant, but power was low in subgroups.

4.6 Methodological Limitations.

Sixty-eight percent of the studies were retrospective. There were only two randomized trials, which were included in the study, and these trials did not directly compare surgery against conservative care. The most crucial unmet need is the definitive multicenter RCT. Outcome definitions varied. There should be standardization with validated quality of life measures. There was an average follow up of 14.6 months with little data long term. There were only four studies that evaluated patient-reported outcomes. Stage 3 disease is not well represented.

4.7 Clinical Implications

In case of operable stage 2 or 3 MRONJ, the surgery needs to be offered as a first line management with 75-85 percent resolution against 25-35 percent with non-surgery management. The surgical method must focus on bone resection to tension-free primary closure. PRF or CGF are to be used regularly. Preoperative optimization involves coordination of the timing of drug intake, nutritional evaluation, smoking cessation, glycemic regulation, chlorhexidine rinses, and systemic antibiotics. Follow up is necessary because it is estimated that about 13 percent of the patients who undergo surgery recur.

4.8 Research Priorities

Some of the priorities are a multicenter randomized trial of contemporary surgery versus optimized conservative treatment, the development of a core outcome set, medication-specific comparative studies, assessment of regenerative treatment and long-term follow-up (more than five years).

CONCLUSION

The evidence in this review is that surgical intervention is better than the conservative management of advanced-stage MRONJ. The resolution pooled rate of 74.8% over 28.4 with odds ratio of 4.89 changes surgery into primary intervention instead of salvage intervention. The three-quarters of patients with advanced lesions respond poorly to conservative monotherapy, and allowed the disease to advance. Modern surgical guidelines that include tension-free primary closure and adjunctive platelet concentrates have success rates ranging between 80-90 percent in specialized hospitals. The limitations are mostly predominance of retrospective designs, heterogeneity of outcomes and lack of long-term follow-up. However, the size and consistency of the effect favor present clinical use.

In operable patients of the stage 2 or 3 MRONJ, the best chance of resolution and functional restoration has been found in modern surgical intervention. Conservative treatment is still the right choice in the medically inoperable or those who are refusing surgery. The next phase of field is the implementation of conclusive multicenter trials to narrow down on surgical guidelines and maximize patient-based outcomes.

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