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MEDICATION INDUCED OSTEONECROSIS OF JAWS: A SYSTEMATIC REVIEW

DR. CHANDRASEKARAN KRITHIKA[1], DR. ASHWINI DESHPANDE[2], DR. CHITATHOOR SRIDHAR[3], DR. MANJU. J[4], DR. PONNULAKSHMI[5], DR. SELVARAJ JAYARAMAN[6]

[1]BDS, MDS, PHD, PRO VICE-CHANCELLOR AND PROFESSOR OF ORAL MEDICINE AND RADIOLOGY, MEENAKSHI AMMAL DENTAL COLLEGE, MEENAKSHI ACADEMY OF HIGHER EDUCATION AND RESEARCH, CHENNAI, INDIA.
[2]BDS, MDS, ADJUNCT PROFESSOR, DEPARTMENT OF RESEARCH, MEENAKSHI ACADEMY OF HIGHER EDUCATION AND RESEARCH, CHENNAI, INDIA.
[3]MBBS, MD, VICE CHANCELLOR AND PROFESSOR OF INTERNAL MEDICINE, MEENAKSHI ACADEMY OF HIGHER EDUCATION AND RESEARCH, CHENNAI, INDIA.
[4]MDS, PH.D, READER, THAI MOOGAMBIGAI DENTAL COLLEGE AND HOSPITAL, DR. M.G.R EDUCATIONAL AND RESEARCH INSTITUTE, CHENNAI, INDIA.
[5]SCIENTIST GRADE-III, CENTRAL RESEARCH LABORATORY, MEENAKSHI AMMAL DENTAL COLLEGE AND HOSPITAL, MEENAKSHI ACADEMY OF HIGHER EDUCATION AND RESEARCH, CHENNAI, INDIA.
[6]PROFESSOR, CENTRE OF MOLECULAR MEDICINE AND DIAGNOSTICS (COMMAND), DEPARTMENT OF BIOCHEMISTRY, SAVEETHA DENTAL COLLEGE & HOSPITALS, SAVEETHA UNIVERSITY, CHENNAI-600077, INDIA.

ABSTRACT

Background: Medication-Related Osteonecrosis of the Jaw (MRONJ) is a severe condition associated with antiresorptive and antiangiogenic therapies, primarily affecting patients with osteoporosis and metastatic bone disease. Despite extensive research, optimal treatment strategies remain uncertain due to variability in clinical management and outcomes.

Aim: This systematic review evaluates the comparative effectiveness of surgical, non-surgical, and pharmacological treatment modalities for MRONJ in achieving optimal healing, symptom relief, and disease prevention.

Methodology: A systematic search was conducted across PubMed, Embase, Cochrane Library, Scopus, Web of Science, and CINAHL, adhering to PRISMA 2020 guidelines. Studies published between January 2017 and June 2024, including randomized controlled trials, cohort, and case-control studies, were included. Data extraction was performed by two independent reviewers, and study quality was assessed using the Newcastle-Ottawa Scale and the Cochrane Risk of Bias Tool. A narrative synthesis identified treatment trends and clinical outcomes. Fourteen studies met the inclusion criteria, providing insights into MRONJ management strategies.

Results: This review analysed 14 studies involving 1,539 MRONJ patients. Surgical treatments, such as sequestrectomy and resection, showed superior healing, with success rates of 100% in Stage I & II and 86.5% in Stage III. Conservative approaches, including antiseptics, antibiotics, and laser therapy, had limited effectiveness, with 79.8% disease progression. Teriparatide improved bone healing ($p=0.013$), while early antiresorptive discontinuation accelerated recovery ($p=0.01$). Zoledronic acid and denosumab posed the highest MRONJ risk, often following extractions (55.8%–73%). Surgical interventions had higher remission rates, while non-surgical methods stabilized disease progression.

Conclusion: Surgical interventions demonstrated superior healing outcomes in MRONJ management, particularly in early-stage cases, while conservative approaches primarily stabilized disease progression. Given the variability in treatment success, individualized management strategies and further research are essential to establish standardized protocols for optimizing patient outcomes and preventing MRONJ-related complications.

Key words: Antiresorptive Agents, Bisphosphonates, Bone Diseases, Osteonecrosis, Bone Regeneration, Drug-Related Side Effects

INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a serious condition characterized by necrosis of the jawbone in patients exposed to antiresorptive and antiangiogenic medications. Researchers initially identified MRONJ in bisphosphonate users, and they have also linked it to denosumab and tyrosine kinase inhibitors; it primarily affects individuals with osteoporosis, metastatic bone disease, and multiple myeloma undergoing long-

term therapy to prevent skeletal complications[1,2,3]. The pathophysiology of MRONJ is multifactorial, involving suppressed bone remodelling, impaired angiogenesis, immune dysfunction, and microbial infections, all contributing to delayed healing and persistent necrosis [3-6]. The condition is staged based on severity, with symptoms ranging from asymptomatic bone exposure to severe necrosis with pathological fractures [2,7].

Improved preventive and therapy techniques are necessary since MRONJ is still a major clinical issue because of its refractory nature, unexpected course, and detrimental effects on oral function and quality of life [3,8, 9]. Over time, the diagnosis, and criteria for medication-related osteonecrosis of the jaw (MRONJ) have changed. The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines MRONJ in patients who have received antiresorptive or antiangiogenic therapy without prior jaw irradiation as exposed oral cavity bone persisting for more than eight weeks. [7]. The stages of MRONJ range from severe osteonecrosis with pathological fractures and the production of extraoral fistulas to asymptomatic bone exposure [2,10] .

Clinical signs include discomfort, swelling, infection, and difficulties masticating, and the maxilla may also be impacted, however the mandible is most afflicted [8,11]. Though mild early symptoms frequently result in delayed detection, causing more advanced disease at presentation, early diagnosis is crucial to preventing progression [12]. Early diagnosis and timely intervention are crucial for improving patient outcomes. Several risk factors, such as those connected to drugs, patients, and procedures, can lead to the development of MRONJ. MRONJ is closely linked to denosumab and bisphosphonates, especially when used in high dosages and for extended periods of time [1,13]. The danger of intravenous injection is much higher than that of oral formulations used to treat osteoporosis, as observed in cancer patients. Immunosuppression, diabetes mellitus, poor oral hygiene, and advanced age are patient-related variables that further increase susceptibility [3,9]. Invasive dental operations such as implants, extractions, and periodontal surgeries are also known to be significant contributors to the development of MRONJ [5,14]. Dental evaluation before to starting high-risk drugs, oral hygiene education for patients, and avoiding needless invasive dental operations are all key components of preventive measures [13,15]. The treatment of MRONJ is still debatable; options range from severe surgical intervention to conservative therapy. To control infection and preserve function without worsening necrosis, conservative measures include antibiotic therapy, pain management, and minimally invasive debridement [16,17]. Surgeons only treat late stages or unresponsive cases with surgery, such as sequestrectomy or resection [18,19]. Studies with varied outcomes have explored adjuvant therapies including laser therapy, platelet-rich plasma, and hyperbaric oxygen [20,21,22]. There is still uncertainty on the best course of treatment, therefore more research is essential to create standardized procedures.

Medication-related osteonecrosis of the jaw (MRONJ) remains a significant clinical challenge despite extensive research efforts. While numerous studies have explored its pathophysiology, risk factors, and management strategies, inconsistencies persist in understanding its precise mechanisms and optimal treatment approaches [2,3,10]. The interplay between suppressed bone remodelling, microbial infection, immune dysfunction, and angiogenesis inhibition is well-documented; however, their exact contribution to disease progression remains unclear. There is ongoing debate regarding the most effective preventive measures and therapeutic interventions, particularly in high-risk patient populations. Variability in diagnostic criteria and staging further complicates standardized clinical management. Given these gaps in knowledge, a systematic review is essential to consolidate existing data, address inconsistencies, and provide evidence-based recommendations. This study aims to critically evaluate the literature on MRONJ, focusing on its epidemiology, risk factors, prevention, and treatment strategies to improve patient outcomes and clinical practice.

METHODOLOGY

Research Question: The research question guiding this systematic review was: "What is the comparative effectiveness of surgical, non-surgical, and pharmacological treatment modalities for Medication-Related Osteonecrosis of the Jaw (MRONJ) in achieving optimal healing outcomes, symptom relief, and preventing disease progression?" The PICOS framework was utilized to structure this review:

- **Population:** Patients diagnosed with Medication-Related Osteonecrosis of the Jaw (MRONJ).
- **Intervention:** Surgical and non-surgical treatment approaches for MRONJ.
- **Comparator:** Different treatment modalities compared to each other or standard care.
- **Outcome:** Healing rates, symptom reduction, and complication rates.
- **Study Design:** Randomized controlled trials, retrospective and prospective studies, and case-control studies.

Search strategy: The study timeline (January 2017–June 2024) was selected to incorporate recent advancements in MRONJ research, addressing emerging treatment modalities, updated diagnostic criteria, and evolving clinical guidelines. A comprehensive search strategy, adhering to PRISMA 2020 guidelines (Figure 1), was implemented to identify relevant studies. Systematic searches were conducted across PubMed, Embase, Cochrane Library, Scopus, Web of Science, and CINAHL. Both key terms and MeSH terms were used to optimize retrieval. Key terms included “Medication-Related Osteonecrosis of the Jaw,” “MRONJ treatment,” “bisphosphonates,” “denosumab,” “osteonecrosis management,” and “oral cancer treatment.” MeSH terms such as “Osteonecrosis,” “Bisphosphonates,” “Antineoplastic Agents,” and “Bone Diseases, Metabolic” were applied. Boolean operators

(AND, OR, NOT) refined search combinations, ensuring high-quality evidence selection based on study relevance, design, and publication date.

Selection criteria: This review included case-control, cohort, and clinical trials focusing on MRONJ treatment approaches to ensure a comprehensive evaluation. Only studies published in English within the specified timeline were considered for consistency and relevance. Exclusion criteria included studies not addressing MRONJ treatment, lacking treatment outcomes, animal studies, laboratory research, insufficient data, or no full-text access. Publications in languages other than English were also omitted to maintain uniformity in interpretation and accessibility of findings.

Data Extraction, Synthesis, and Quality Assessment: A total of 648 articles were screened, with 14 meeting the inclusion criteria. Two independent reviewers, AD and KC, conducted data extraction: AD extracted research features and patient demographics, while KC focused on treatment procedures and outcomes. CS assessed study quality and bias. Extracted data included author details, study design, sample size, interventions, results, and follow-up duration. A narrative synthesis approach identified trends. Study quality was evaluated using the Newcastle-Ottawa Scale [23] for observational studies and the Cochrane Risk of Bias Tool for RCTs [24].

Risk of Bias Assessment: The Cochrane Risk of Bias Tool was used to assess selection, performance, detection, and reporting bias among other domains in randomized controlled trials. The Newcastle-Ottawa Scale was used to evaluate selection bias, comparability, and outcome evaluation in observational research. To guarantee the validity and dependability of the review's conclusions, the risk of bias findings was incorporated into the overall study.

RESULTS

Table 1 summarizes experimental and clinical studies on MRONJ treatment strategies, analyzing 1,539 patients. Surgical interventions (sequestrectomy, resection) showed superior healing, with 100% success in Stage I & II and 86.5% in Stage III [27]. Conservative therapies, including antiseptics, antibiotics, and laser therapy, had limited success, with 79.8% disease progression in non-surgical cases [30]. Teriparatide improved MRONJ resolution (45.4% vs. 33.3%; p=0.013) and bone volume (80% vs. 31.3%; p=0.017) [32]. Early antiresorptive discontinuation accelerated healing (p=0.01) [26]. Nasolabial flap procedures enhanced wound closure [29], and piezoelectric bone surgery with Nd:YAG laser achieved complete mucosal healing [38]. Most MRONJ cases were Stage 2 (54.93%) [37], with the mandible affected in 64-68.5%. Zoledronic acid and denosumab posed higher risks [35]. Surgical approaches had better remission rates, while non-surgical methods stabilized disease. Adverse effects included delayed healing, infection, and pain.

Table 2 highlights bisphosphonates (Zoledronate, Alendronate, Ibandronate, Pamidronate), denosumab, and antiangiogenic drugs as major MRONJ risk factors. Drug use ranged from 33.9 months to over 10 years [30,37], with Zoledronate IV for >3 years [34]. MRONJ followed extractions (55.8%–73%), denture wear (9%–20.8%), poor hygiene, cancer therapy, steroids (14.3%), and diabetes. Spontaneous cases occurred in 19.5%–36%. MRONJ rates varied from 100% [25] to 1.9% [29]. Prevention includes pre-therapy dental evaluations, hygiene, and reduced drug exposure [27,28,32]. Severe cases required surgery [38], while non-surgical therapies (antibiotics, chlorhexidine, pentoxifylline + tocopherol, teriparatide) showed success [32,36]. Follow-ups ranged from 8 weeks [32] to 10 years [30], emphasizing individualized management.

Table 3 evaluates the quality of 13 prospective and retrospective MRONJ studies using the Newcastle-Ottawa Scale (NOS) across three domains: Selection (S1-S4), Comparability, and Exposure (E1-E3). Studies were classified as Good, Fair, or Poor based on their scores. Seven studies were rated as "Good" due to strong selection criteria, robust comparability, and effective exposure assessment. These studies offer high methodological quality. Few studies received a "Fair" rating, often due to missing selection criteria or limited comparability [25,27,29,31,33]. Despite some methodological weaknesses, these studies provided valuable insights into MRONJ. Table 4 assesses the only RCT included Sim IW et al. (2020) [32] which received a "Good" rating. This study demonstrated strong selection criteria, adequate comparability, and thorough exposure assessment, making it a high-quality source of evidence on MRONJ treatment strategies.

Figure 2 assesses the risk of bias in prospective and retrospective MRONJ studies using the ROBINS-I tool across seven domains. Most studies show low to moderate risk, with critical bias (red) observed in Yazdi PM et al. (2015) [25], Hadaya D et al. (2018) [28], and Giudice A et al. (2020) [31], particularly in participant selection (D2) and missing data (D5). Figure 3 provides an overall risk summary, showing low risk (green) in classification (D3) and deviations from intended interventions (D4), while moderate risk (yellow) is prevalent in confounding (D1) and selection (D2). Critical risk (red) appears in select studies, indicating methodological limitations. Some areas lack sufficient information (blue). Figure 4 evaluates the single RCT by Sim IW et al. (2020) [32] using the ROB2 tool, showing low risk (green) across most domains, with some concerns (yellow) in reported results selection (D5). This suggests high methodological rigor with minor reporting concerns. Figure 5 summarizes the RCT's overall bias risk, reinforcing its reliability with mostly low-risk assessments. However, minor concerns (yellow) in selective reporting highlight areas requiring careful interpretation.

DISCUSSION

MRONJ is a serious adverse effect that is seen in patients receiving antiangiogenic agents for diseases like multiple myeloma, osteoporosis, and metastatic cancer, and antiresorptive treatments like denosumab and bisphosphonates [1,2,39]. It is characterized by exposed necrotic bone that does not repair, and frequently occurs spontaneously or due to trauma or dental operations [3,7]. The complicated and multifaceted pathophysiology of MRONJ comprises of suppressed bone remodelling, poor angiogenesis, immunological dysfunction, and microbial infections [4,40].
Long-term use of antiresorptive drugs, intravenous delivery, poor dental hygiene, and systemic illnesses like diabetes and cancer therapy are among the risk factors that have been documented [8,14]. Anatomically, the mandible is more commonly affected than the maxilla owing to its comparatively lesser vascularization (64%–68.5%) [34.42]. Preventive measures and early diagnosis are essential for reducing the chances of MRONJ. New management strategies including both surgical and non-surgical measures have been adopted along with developments in molecular and pharmacogenetic research [4,43]. A multidisciplinary approach is necessary, as treatment is still highly customized to improve patient results [6,19].
The Newcastle-Ottawa Scale (NOS) and the ROBINS-I instrument were used in this review's quality evaluation to guarantee the validity of the results. Non-randomized studies were assessed by the NOS according to selection criteria, comparability, and outcome assessment; "Good" ratings indicated sound technique, while "Fair" ratings drew attention to possible constraints that could compromise internal validity [23]. Study reliability could have been impacted by bias, which was evaluated by the ROBINS-I method in seven categories, such as participant selection, confounding, and missing data [24]. Utilizing the ROB2 method, which reduces bias through rigorous design and enhances the credibility of systematic reviews, high-quality randomized controlled trials (RCTs) were evaluated. RCTs and carefully executed observational studies together offered a fair, fact-based evaluation that considered the limitations of MRONJ therapy research.
The risk of MRONJ is greatly increased by prolonged exposure to antiresorptive agents, such as denosumab and bisphosphonates (zoledronate, alendronate, ibandronate, and pamidronate), especially when administered intravenously over an extended period [1,2]. After three years of treatment, the cumulative risk is significantly higher, according to a systematic review [6]. The risk is increased when antiangiogenic drugs are used concurrently [39]. Trauma from poorly fitting dentures (9%–20.8%) is the second most common recorded precipitating event, after dental extractions, which account for 55.8%–73% of cases [8,14]. Systemic variables that greatly increase MRONJ vulnerability include diabetes, corticosteroid therapy, and cancer-related treatments [3]. Significantly, spontaneous cases those that happen without a clear triggering event make up 19.5% to 36% of recorded occurrences, highlighting the complex character of MRONJ pathophysiology [7].
Strategies such as pre-therapy dental evaluations, oral hygiene education, and minimizing drug exposure play a crucial role in reducing MRONJ incidence. Studies suggest that early discontinuation of antiresorptive medications can accelerate healing [44], reinforcing the need for interdisciplinary collaboration among oncologists, dentists, and endocrinologists. Interdisciplinary collaboration enhances patient outcomes, reinforcing the need for proactive risk assessment and tailored treatment approaches [15].
Surgical vs. Non-Surgical Approaches: The best course of treatment for MRONJ is still surgery, especially in cases that are early and advanced. According to Favia et al. (2018), sequestrectomy and resection result in full healing in 86.5% of Stage III cases and 100% of Stage I and II cases. [27]. Better clinical results are achieved with surgical debridement, which efficiently eliminates necrotic bone, lowers the microbial load, and promotes tissue regeneration [30]. In contrast to conservative management, vigorous surgical intervention leads to superior healing, according to Nicolatou-Galitis et al. (2019) [5]. Cutting-edge surgical methods have shown better healing and fewer postoperative problems, such as piezoelectric bone surgery in conjunction with Nd:YAG laser therapy [20,38]. Nasolabial flap restoration was used to successfully heal the mucosa in severe cases, according to Lemound et al. (2018) [29]. Combining autologous platelet concentrates, including platelet-rich fibrin (PRF), with surgical procedures improves bone repair even more [21]. Antibiotics, laser therapy, and antiseptic rinses are examples of non-surgical methods that are mostly used for palliative purposes. Varoni et al. (2021) [36] showed that while antibiotics and mouthwash containing chlorhexidine can help manage symptoms, they seldom result in total remission. 79.8% of patients that were conservatively managed advanced, according to Ristow et al. (2015) [30], underscoring the drawbacks of non-surgical treatments. Conservative approaches, on the other hand, may help stabilize lesions and slow the course of early-stage MRONJ [22].
Adjunctive and Preventive Strategies: Pharmacological adjuncts are essential for enhancing MRONJ results. According to Sim et al. (2020) [32], teriparatide has been demonstrated to considerably increase bone volume (80% vs. 31.3%; p=0.017) and healing rates (45.4% vs. 33.3%; p=0.013). Early antiresorptive medication termination speeds up MRONJ recovery, according to Martins et al. (2017) [26], while new research indicates that pentoxifylline and tocopherol may improve results by regulating inflammation and bone turnover [31,45]. Preventive measures are essential. It has been demonstrated that regulated drug exposure, oral hygiene education, and pre-therapy dental assessments reduce risk to reduce the occurrence of MRONJ [26]. It has been shown that early antiresorptive medication termination significantly speeds up healing (p=0.01). The most successful MRONJ management plan combines pharmaceutical treatments, surgical intervention, and adjuvant procedures in a multimodal approach. Especially in more advanced cases, this largescale treatment plan maximizes healing,

reduces complications, and enhances patient outcomes [12,15,19]. Beth-Tasdogan et al. (2022) [45], reported about the standardized protocols to improve treatment efficacy which should be the main emphasis of future research.

Clinical Implications: This systematic review highlights the significance of tailored management approaches for medication-related osteonecrosis of the jaw (MRONJ), with a focus on treatment goals, patient-specific variables, and disease stage. According to current data, surgical procedures are the gold standard for advanced MRONJ patients because they have better long-term results and healing rates than non-surgical methods [19,22,31]. Antimicrobial therapy and local wound care, on the other hand, are still effective conservative therapeutic techniques for stabilizing early-stage MRONJ, especially in patients who have serious comorbidities or are not candidates for surgery [16,28,41,46]. Teriparatide and other adjuvant treatments have shown promise in promoting bone regeneration and improving MRONJ resolution, especially when bone remodeling is compromised [20,32]. Medication suspension procedures might help slow the advancement of MRONJ and enhance surgical results, but their effectiveness is still stage-dependent [27,47,48]. Reducing the incidence of MRONJ requires the implementation of preventive measures. MRONJ risk among at-risk groups has been demonstrated to be considerably decreased by pre-treatment dental examinations, periodontal disease therapy, and patient education on oral hygiene [5,15,37]. Identifying and reducing precipitating variables, such as invasive dental treatments and dentoalveolar trauma, are crucial elements of MRONJ prevention [25,49,50]. Early discovery, adequate treatment, and long-term follow-up of MRONJ patients depend on interdisciplinary coordination between oral surgeons, oncologists, endocrinologists, and primary care physicians. Improved patient quality of life, optimal therapy results, and prompt intervention are all made possible by a multidisciplinary approach [13,30,35]. Future studies should keep investigating new therapeutic approaches and improving management procedures to improve the effectiveness of MRONJ treatment and lower the illness burden.

Strengths and Limitations: A major strength of this study is its comprehensive evaluation of MRONJ management, incorporating data from 1,539 patients and assessing both surgical and non-surgical approaches. The use of validated assessment tools, such as NOS, ROBINS-I, and ROB2, enhances methodological reliability. The inclusion of randomized controlled trials (RCTs) strengthens the evidence base for therapeutic strategies. However, certain limitations exist. Variability in diagnostic criteria, treatment protocols, and follow-up durations across studies may contribute to heterogeneity. The retrospective nature of some data limits the ability to establish causality. Differences in drug exposure and patient comorbidities could influence treatment outcomes. Future research should prioritize standardized diagnostic frameworks and long-term prospective trials to refine and optimize MRONJ management strategies.

CONCLUSION

The clinical importance of tailored MRONJ management is emphasized in this comprehensive review, which also shows the possible advantages of supplementary medications such as teriparatide and the superiority of surgical procedures in advanced instances. Stage-specific treatment techniques are necessary since conservative approaches can effectively stabilize early-stage illness. Reducing the occurrence of MRONJ still requires preventive interventions, such as patient education and pre-treatment dental assessment. Standardized diagnostic standards, long-term prospective studies, and innovative regenerative medicines should be the main topics of future research to improve treatment effectiveness. There is hope for better MRONJ prevention and management thanks to developments in biomaterials, tissue engineering, and targeted medication changes. For long-term treatment plans and patient results to be optimized, a multidisciplinary strategy comprising orthopaedic specialists, oncologists, and dentists is essential.

Ethical Consideration and Informed Consent: This systematic review is based on previously published studies and does not involve direct human or animal subjects. Therefore, ethical approval and informed consent were not required. The included studies were reviewed for compliance with ethical guidelines, and all data used were obtained from publicly available sources.

Data availability – Data will be made available on request

Conflict of Interest: The authors have no competing interests to declare that are relevant to the content of this article.

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Figure 1: PRISMA 2020 Flowchart for the review

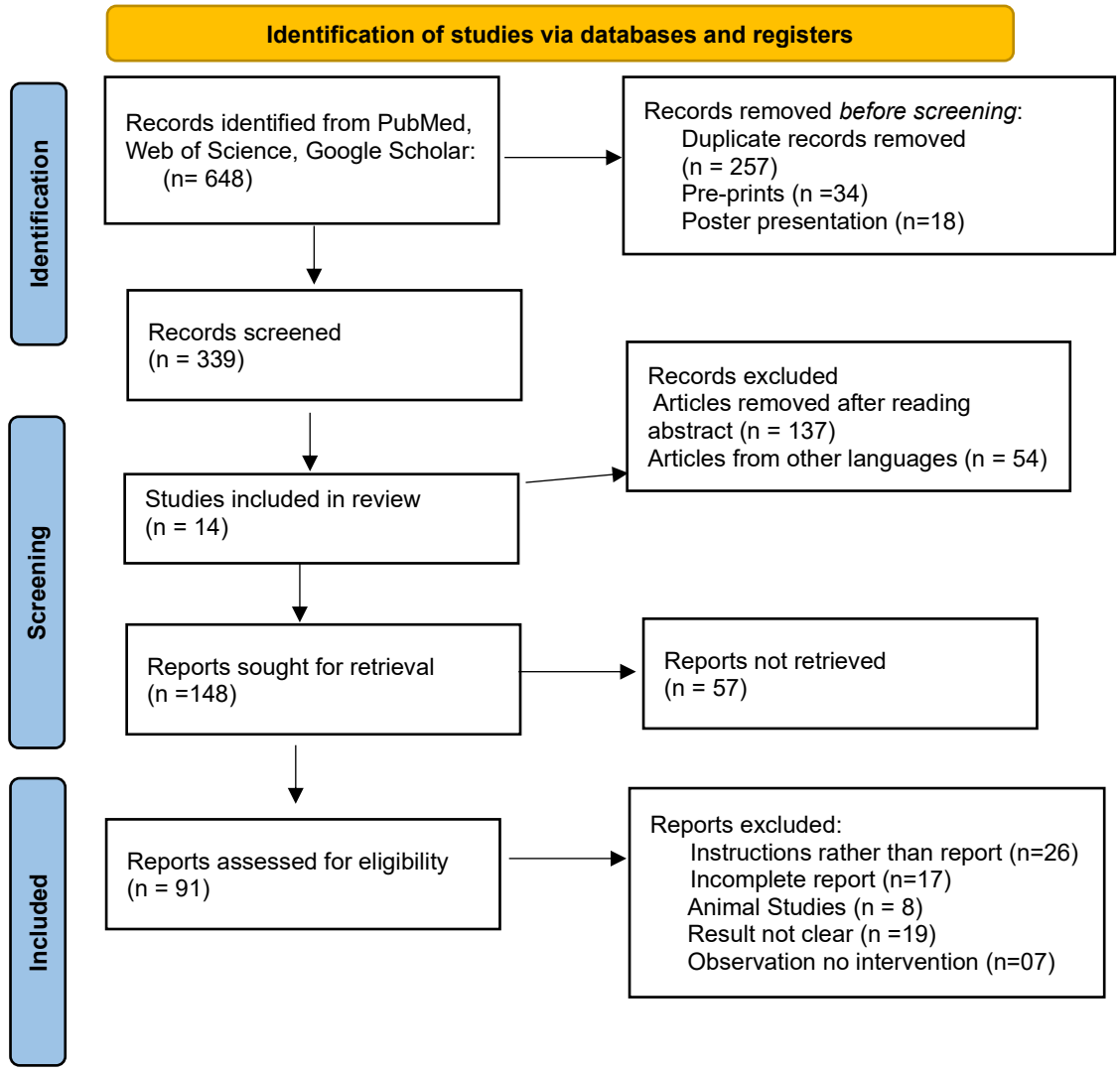

Table 1: Summary of Experimental and Clinical Studies on Treatment Strategies for Medication-Related Osteonecrosis of the Jaw (MRONJ)

Author(s)/Year	Study Design & Sample Size	MRONJ Stage	Treatment Protocol & Follow-up Duration	Key Findings	Outcome Measures	Adverse effects
Yazdi PM et al. (2015) [25]	Retrospective study, 149 patients	Stages 1–3	Surgical intervention (block resection for severe cases), conservative management, prosthodontic referral; follow-up duration not specified	ONJ triggered by dentoalveolar trauma (64%) and spontaneous factors (36%); fistula to skin more common in spontaneous cases; significant male-to-female ratio difference	ONJ location (mandible: 65%, maxilla: 26%, both: 9%), pain (VAS 3.4), abscess formation (28%), fistula (8%), referral delay (8 months)	Delayed healing, infection, pain, abscess, purulent discharge
Martins AS et al. (2017) [26]	Retrospective longitudinal cohort study, 77 patients	Stage 0 (3.9%), Stage 1 (36.4%), Stage 2 (55.8%), Stage 3 (3.9%)	Surgery (sequestrectomy, marginal resection with closure), nonsurgical (antibiotics, chlorhexidine). Mean follow-up: 25.48 ± 24.51 months (3–118 months)	Primary disease and route of administration significantly influenced outcomes. Early discontinuation of antiresorptives reduced healing time ($p = 0.01$).	67.5% healed/improved, 32.5% stable/worse. Mean healing time: 15.07 ± 16.94 months. Late discontinuation delayed healing ($p = 0.013$).	24.68% had complications (paraesthesia, cutaneous fistula). 11.7% needed reintervention.
Favia G et al. (2018) [27]	Retrospective study; 106 patients with 131 lesions	Stage I: 11 lesions (9 in G1, 2 in G2) Stage II: 65 lesions (61 in G1, 4 in G2) Stage III: 55 lesions (37 in G1, 18 in G2)	G1 (Surgical, 85 patients, 107 lesions): Anti-resorptive drug cessation, pre-op antibiotics, necrotic bone removal, mucoperiosteal flap closure, and follow-up at 1, 3, 6, 12 months. G2 (Non-surgical, 21 patients, 24 lesions): Antiseptic rinse, periodic dental checks, monthly antibiotics, low-level laser therapy, and 18-month follow-up.	Surgical group (G1): - 100% complete healing in Stage I & II - 86.5% complete healing in Stage III - 13.5% Stage III lesions downstaged to Stage I Non-surgical group (G2): - No complete healing - 87.5% lesions remained stable	Complete healing: Full mucosal coverage Partial healing: Downstaging per AAOMS criteria Stable disease: No change in staging Progressive disease: Upstaging	Surgical group: No major complications Non-surgical group: One lesion worsened (Stage II → III)

				- One lesion upstaged from Stage II to III		
Hadaya D et al. (2018) [28]	Retrospective analysis of 106 patients with 117 MRONJ sites	Predominantly Stage 1; includes Stage 2 and Stage 3 lesions (small sample size for Stage 3)	Local wound care (antibiotics, chlorhexidine, cotton swabs, small toothbrush for cleaning exposed bone); Follow-up 1-3 months for stage 1, 9 months for stage 2/3	71% complete resolution, 22% improvement; better wound care scores correlated with faster healing. Lesions with higher scores (>3) showed slower healing.	Disease resolution, time to resolution, wound care score, radiographic healing	No significant adverse effects; poor compliance noted in some cases
Lemound J et al. (2018) [29]	Prospective study, n = 32	Various stages, Stage I & II, Stage I, II, III, Stage I & II.	Decortication with/without nasolabial flap, follow-up 15-17 months	- Nasolabial flap significantly improved healing and reduced relapse rates in MRONJ cases. - Control group showed poorer healing.	Success rate of wound healing, MRONJ relapse	No significant adverse effects reported; some cases had complications related to wound closure and healing.
Ristow O et al. (2019) [30]	Long-term, single-center cohort study, 92 MRONJ lesions	Stage I (according to AAOMS)	Conservative non-surgical treatment, follow-up duration of 10 years	8.7% mucosal rehabilitation, 91.3% exposed bone or fistula, 79.8% worsened to higher stages, 32% stable stage I with antibiotics, 68% required surgery	Mucosal healing, stage progression, need for surgery.	Silent disease progression, bone loss, no resolution of necrotic bone
Giudice A et al. (2020) [31]	Prospective observational study with 129 patients (90 women, 39 men); mean age: 71.2 ± 12.7 years.	Stage 1 and Stage 2 MRONJ	Surgical treatment, follow-up every month for clinical evaluation (mean follow-up duration: 71.6±67.7 days)	Surgical treatment showed mucosal integrity in 71.6±67.7 days and downstaging of lesions in 43.6±38.4 days. Stage 2 had slower mucosal healing than stage 1.	Time to mucosal integrity and downstaging	Pain, swelling, relapse (in 4 patients)
Sim IW et al. (2020) [32]	Randomized placebo-controlled trial, 34	Various stages, similar between groups	Teriparatide 20 µg/day SC for 8 weeks vs. placebo, 52-week follow-up	MRONJ resolution in 45.4% (Teriparatide) vs. 33.3% (Placebo) (P	MRONJ resolution rate, bone defect size reduction, P1NP, CTX,	Similar adverse event rates in both groups (P = .43). GI symptoms:

	participants (Teriparatide: 15, Placebo: 19)			= .013). Bone volume increase in 80% (Teriparatide) vs. 31.3% (Placebo) (P = .017). P1NP increased by ≥10 mg/L in 85.7% (Teriparatide). Increased PET-CT uptake in Teriparatide group.	PET-CT uptake, OHIP-14 quality of life scores (no significant difference)	Nausea (Teriparatide: 33.3%, Placebo: 21.1%). Injection site reactions (Teriparatide: 20%, Placebo: 5.3%). Musculoskeletal pain at similar rates. Three serious adverse events per group, including one death and one new malignancy in the placebo group. No hypercalcemia or new malignancies in Teriparatide group.
Choi NR et al. (2020) [33]	Retrospective study with 116 patients comparing surgical and conservative treatments for MRONJ.	All stages (1, 2, 3)	Surgical treatment (curettage, saucerization, sequestrectomy); Follow-up at 10 days, 3 months, 6 months	Zoledronate (OR 21.40, p=0.005) and IV administration (OR 4.99, p=0.044) significantly affected treatment results. 83% healed within 6 months; 6% failure rate.	Lesion exacerbation (AAOMS stage change); Treatment completion time	6 patients progressed from stage 2 to 3; Stage 3 lesions enlarged
Albanese M et al. (2020) [34]	Retrospective analysis, 12 patients (7F, 5M, mean age 81.5 years)	Stage II & III (SIPMO/SICMF staging)	Conservative non-surgical protocol: dental hygiene every 4 months, chlorhexidine mouthwash (0.12%) first 7 days of each month, antibiotics (amoxicillin + clavulanic acid + metronidazole) for 7 days/month if infection or pain occurred, follow-up at t0, t1, t2, t3, t4 (12 months total)	Improvement in mucosal inflammation, pain reduction (VAS score), complete mucosal healing in some cases, potential to avoid surgery in high-risk patients	Significant reduction in clinical symptoms like bone exposure, edema, rubor, and fistula presence; pain reduced; improved quality of life	No reported
Fusco V et al. (2021) [35]	Retrospective (2009-2015) & Prospective (2016-2018); 459	All stages (I-III)	Non-surgical therapy; follow-ups at major oral care centers; drug exposure median 17-42 months	MRONJ incidence: 11.6/million/year (2009-2015), 7.5/million/year	MRONJ cases recorded; drug exposure duration; site of occurrence	Tooth extractions, peri-implantitis, poor-fitting dentures; higher risk

	MRONJ cases in cancer/myeloma patients			(2016-2018); Mandible affected in 64.5% of cases		with zoledronic acid & denosumab
Varoni EM et al. (2021) [36]	Retrospective study, n = 35	Stage I: 6 (17.1%) Stage II: 28 (80%) Stage III: 1 (2.9%)	Topical chlorhexidine; Systemic amoxicillin ± metronidazole; Pentoxifylline + Tocopherol (9 patients); Surgical sequestrectomy (57 interventions) Follow-up: Mean: 23.86 ± 18.14 months (Range: 1–74 months)	- MRONJ more common in females (68.6%) - Most patients (48.5%) on zoledronate - Mandible most affected (68.5%) - Stage II most frequent (80%) - 7 cases of spontaneous sequestrum exfoliation	- Clinical improvement after pharmacological therapy and/or surgery - Bone sequestrum removal effective	None
Bacci C et al. (2022) [37]	Retrospective study, 71 patients (50 females, 21 males)	Stage 1: 25.35% (18 patients) Stage 2: 54.93% (39 patients) Stage 3: 19.72% (14 patients)	51 patients (71.83%) received antibiotics 46 (64.78%) used painkillers 62 (87.32%) used antiseptic therapy 27 (38.02%) underwent resection 9 (12.67%) had spontaneous sequestration Biopsy in 24 cases; Actinomyces found in 13 (54.17%) Follow-up duration not specified	Preventive dental care reduces MRONJ risk if patients comply with recommendations. Most MRONJ cases were stage 2 (54.93%). No significant statistical difference between groups.	40 patients (56.33%) achieved remission 28 (39.43%) relapsed 3 (4.22%) had new MRONJ site	Not reported
Şahin O et al. (2022) [38]	Retrospective cohort study, 21 patients	Stage 2-3	Surgical resection, ultrasonic piezoelectric bone surgery, L-PRF application, Nd:YAG laser therapy; Follow-up: 9–28 months	Complete mucosal healing achieved in all patients using a combined treatment approach	Healing rate, pain reduction, mucosal integrity, absence of infection	None

Table 2: Summary of Patient-Related and Treatment-Related Risk Factors for MRONJ

Author/ year	Primary Medication (Bisphosphonates/ Denosumab/ Others)	Duration of Drug Exposure	Contributing Factors (e.g., Dental Extractions, Poor Hygiene)	MRONJ Development Rate (%)	Preventive Measures Applied	Treatment Modality	Treatment Duration	Treatment Frequency
Yazdi PM et al. (2015) [25]	Bisphosphonates (BPs) / Denosumab (Low-dose for osteoporosis, High-dose for cancer)	Mean duration not specified (42 months in one case)	Dental extractions (54%), denture-related sore mouth (9%), minor trauma (intubation, impression tray) (1%), spontaneous (36%)	100% (149 patients)	Caution during dental procedures, meticulous mucosal closure post-extraction, close monitoring	Conservative management, surgical intervention (block resection in severe cases), prosthodontic referral	Not mentioned	Not mentioned
Martins AS et al. (2017) [26]	Zolendronic acid (59.7%) Alendronic acid (22.1%) Ibandronic acid (14.3%) Pamidronate (2.6%) Denosumab (5.2%) Sunitinib + bisphosphonate (5.2%)	47.91 ± 60.59 months (Mean)	Tooth extraction (55.8%) Denture wear (20.8%) Chronic steroids (14.3%) No traumatic factors (19.5%)	Not reported	Minimal dental care before antiresorptive therapy	Surgery (63.6%) Non-surgical: antibiotics, chlorhexidine	Mean: 15.07 ± 16.94 months	Varied, based on patient response
Favia G et al. (2018) [27]	Bisphosphonates (88 cases) Denosumab (13 cases) Bisphosphonates + Denosumab (6 cases)	Not reported	Oral surgery (73 cases in G1, 14 in G2) Spontaneous (34 cases in G1, 10 in G2)	Not reported	Cessation of BPs/antiresorptives (≥3 months before surgery in G1) Antibiotics before surgery (G1) Antiseptic mouth rinse, periodic	Surgical removal of necrotic bone (G1, 107 lesions, 85 patients) Non-surgical: antibiotics, antiseptic rinse, laser therapy	Follow-up: 18 months (range 12-28 months)	G1: Weekly in first month, then at 1, 3, 6, 12 months G2: Monthly antibiotic

					dental checks (G2)	(G2, 24 lesions, 21 patients)		and laser therapy
Hadaya D et al. (2018) [28]	Bisphosphonates (majority), Denosumab (15%)	Varied (long-term use for bone malignancies/osteoporosis)	Dental extractions, poor hygiene	Dental extractions, poor hygiene	Pre-treatment dental evaluation, hygiene improvement	Local wound care (antibiotics, chlorhexidine, cotton swabs, small toothbrush)	9 months for stage 2/3, 1-3 months for stage 1	Follow-up every 1-3 months for stage 1, 9 months for stage 2/3
Lemound J et al. (2018) [29]	Bisphosphonates, Denosumab, Antiangiogenic drugs	Varies	Dental extractions, other surgical procedures, poor mucosal perfusion	1.9% (general MRONJ rate from meta-analysis)	Not mentioned	Decortication with or without nasolabial flap	15-17 months follow-up	Single surgical intervention, follow-up care
Ristow O et al. (2019) [30]	Bisphosphonates, Denosumab, Anti-resorptive drugs	Varies, long-term use (10 years average in study)	Dental extractions, poor oral hygiene, cancer treatments	Not mentioned	Antibiotics, anti-inflammatory rinses	Conservative non-surgical therapy (antibiotics, oral rinses)	Follow-up duration of 10 years	Regular follow-up visits, conservative management unless surgery required
Giudice A et al. (2020) [31]	Bisphosphonates, Anti-resorptive drugs	Long-term (average 71.2±12.7 years for patients)	Tooth extractions, periodontal disease, dental trauma, cancer treatment	Not mentioned	Oral hygiene, post-surgical care	Surgical treatment (including sequestrum removal and soft tissue coverage)	Mean time for mucosal integrity: 71.6±67.7 days	Monthly clinical follow-up
Sim IW et al. (2020) [32]	Bisphosphonates and Denosumab (for malignant bone disease in 79.4% of participants)	Not mentioned	Poor oral hygiene (gingival index ≥2 associated with lower resolution rate),	Not reported	Optimized oral hygiene, minimized antiresorptive exposure	Teriparatide 20 µg/day + calcium & vitamin D	8 weeks	Daily

			glucocorticoid use, diabetes mellitus			supplementation		
Choi NR et al. (2020) [33]	Zoledronate, Alendronate, Risedronate, Ibandronate, Pamidronate (Bisphosphonates)	Not specified	Dental extraction, implantation, perioperative lesion, denture irritation	Not provided	Not mentioned	Curettage, saucerization, sequestrectomy	Follow-up at 10 days, 3 months, and 6 months	37 patients healed in 3 months, 53 in 6 months; 20 took >6 months
Albanese M et al. (2020) [34]	Zoledronate (IV), Alendronate (Oral), Denosumab (SC), Denosumab + Risedronate, Zoledronate + Alendronate, Trastuzumab	>3 years (Zoledronate IV), Not stated (others)	Tooth extraction, peri-implantitis, poorly fitting dentures	Not provided	Professional dental hygiene, chlorhexidine mouthwash, antibiotics	Non-surgical therapy	12 months	Regular follow-ups at t0, t1, t2, t3, t4
Fusco V et al. (2021) [35]	Zoledronate (IV), Denosumab (SC), Pamidronate (IV), Ibandronate (OS/IV), Antiangiogenics	Zoledronate: 17 (1-108), Denosumab: 19 (3-48), ZOL/DEN: 40 (11-80), Pamidronate: 20 (6-77), PAM/ZOL: 32 (10-227), ZOL/IBAN: 42 (7-85), Others: 36 (18-132), Ibandronate: 25 (6-77), Antiangiogenics: 18 (4-36)	Tooth extractions, peri-implantitis, poor-fitting dentures	11.6/million/year (2009-2015), 7.5/million/year (2016-2018)	Professional dental hygiene, chlorhexidine mouthwash, antibiotics	Non-surgical therapy	12 months	Regular follow-ups at t0, t1, t2, t3, t4
Varoni EM et al. (2021) [36]	**Zoledronate (48.5%)** Alendronate (25.7%) Denosumab (5.7%) Alendronate +	**Zoledronate:** 34.29 ± 33.42 months **Alendronate:** 79.42 ± 63.33 months	Cancer therapy (chemotherapy/steroids) Osteoporosis	Not reported	- Topical chlorhexidine - Systemic antibiotics	Pharmacological (antibiotics, antiseptics) - Surgical	Mean follow-up: 23.86 ± 18.14	57 surgical interventions

	Denosumab (5.7%) Alendronate + Risendronate (2.9%) Alendronate + Zoledronate (2.9%) Alendronate + Ibandronate (2.9%) Ibandronate + Clodronate (2.9%) Zoledronate + Denosumab (2.9%)	**Denosumab:** 15 ± 7.94 months	Diabetes Poor oral hygiene Dental extractions		- Pre-surgical dental scaling - Pentoxifylline + Tocopherol (9 patients)	(sequestrectomy)	months (Range: 1–74 months)	18 patients had one surgery 4 patients had two surgeries 5 patients had more than two surgeries
Bacci C et al. (2022) [37]	Bisphosphonates (Zoledronate) Denosumab Bevacizumab (IV)	Mean: 33.9 months Range: 1–300 months Zoledronate cycles: Mean 20.53 (4 mg/month) Switched to Denosumab: 25 patients (Mean 13.6 cycles, 120 mg/month)	Dental extractions Periodontal disease Peri-implant disease Ongoing inflammation	Not mentioned	Preventive dental visits (Group 1-4) No dental visit or oncologist assessment only (Group 0, 5)	Antibiotics (71.83%) Painkillers (64.78%) Antiseptic therapy (87.32%) Surgical resection (38.02%) Spontaneous sequestration (12.67%)	Not mentioned	Not mentioned
Şahin O et al. (2022) [38]	Bisphosphonates & Denosumab	39–96 months	Dental extractions, implants, prosthesis	Not mentioned	Not mentioned	Surgical resection, ultrasonic piezoelectric bone surgery, L-PRF, Nd:YAG laser	9–28 months	Single surgical procedure per patient

Table 3: Quality assessment done for prospective and retrospective studies using the Newcastle Ottawa Scale

S.no	Author (Year)	Selection (S1)	S2	S3	S4	Comparability	Exposure (E1)	E2	E3	Quality
1.	Yazdi PM et al. (2015) [25]	*	*	-	-	*	-	*	*	**Fair**
2.	Martins AS et al. (2017) [26]	*	*	*	*	*	*	*	-	**Good**
3.	Favia G et al. (2018) [27]	-	*	-	*	*	*	-	*	**Fair**
4.	Hadaya D et al. (2018) [28]	*	*	*	-	*	*	-	*	**Good**
5.	Lemound J et al. (2018) [29]	-	*	-	*	*	*	-	*	**Fair**
6.	Ristow O et al. (2019) [30]	*	*	*	*	*	*	*	-	**Good**
7.	Giudice A et al. (2020) [31]	-	*	-	*	*	*	-	*	**Fair**
8.	Choi NR et al. (2020) [33]	-	*	-	*	*	*	-	*	**Fair**
9.	Albanese M et al. (2020) [34]	*	-	*	*	*	*	*	-	**Good**
10.	Fusco V et al. (2021) [35]	*	*	-	*	*	*	*	-	**Good**
11.	Varoni EM et al. (2021) [36]	*	*	*	-	*	*	-	*	**Good**
12.	Bacci C et al. (2022) [37]	*	*	-	*	*	-	*	*	**Good**
13.	Şahin O et al. (2022) [38]	*	*	*	*	*	*	*	*	**Good**

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Table 4: Quality assessment done for RCT studies using the Newcastle Ottawa Scale

S.no	Author (Year)	Selection (S1)	S2	S3	S4	Comparability	Exposure (E1)	E2	E3	Quality
1.	Sim IW et al. (2020) [32]	*	*	-	*	*	*	-	*	**Good**

Figure 2: Risk of bias assessment for prospective and retrospective studies individual studies using ROBINS I tool.

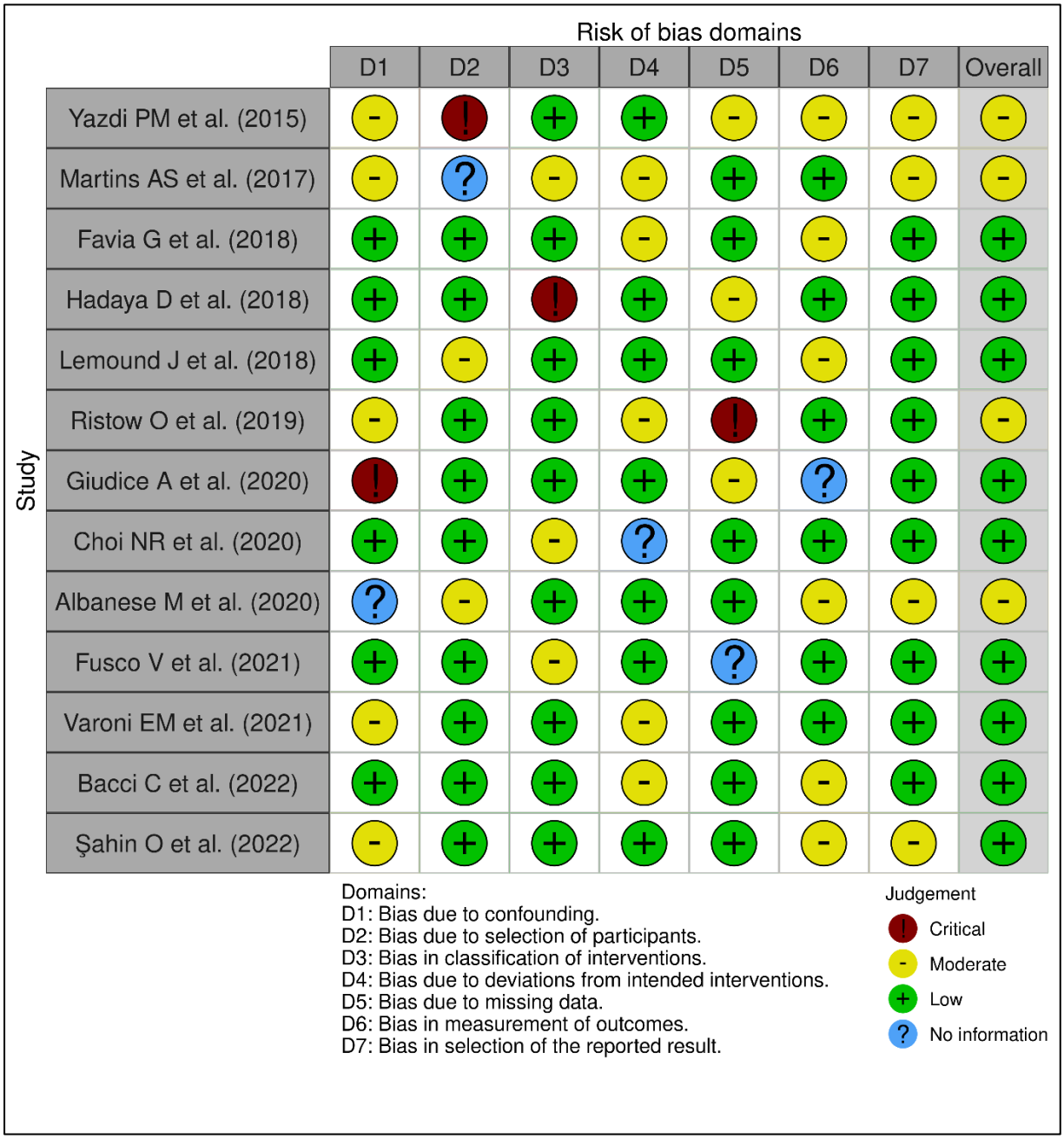

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Figure 3: Overall Risk of bias assessment for prospective and retrospective studies using ROBINS I tool.

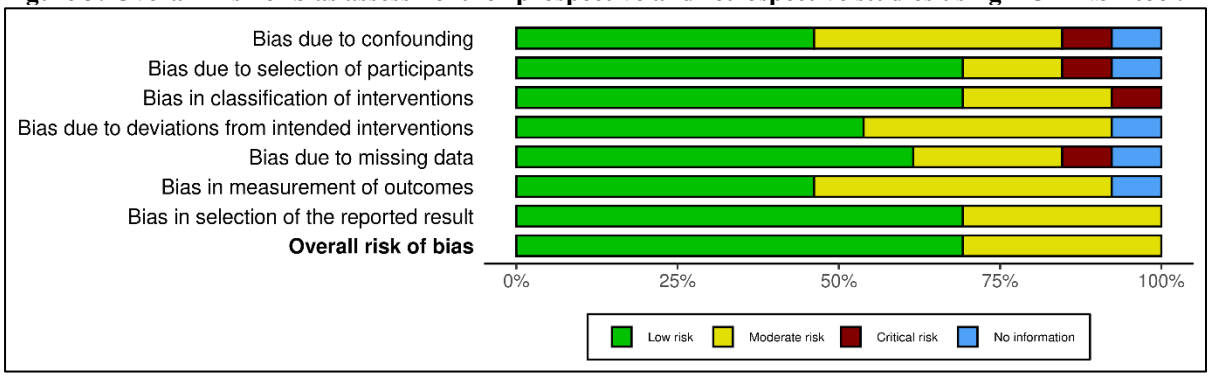

Figure 4: Individual assessment risk of bias assessment for RCT using ROB2 tool.

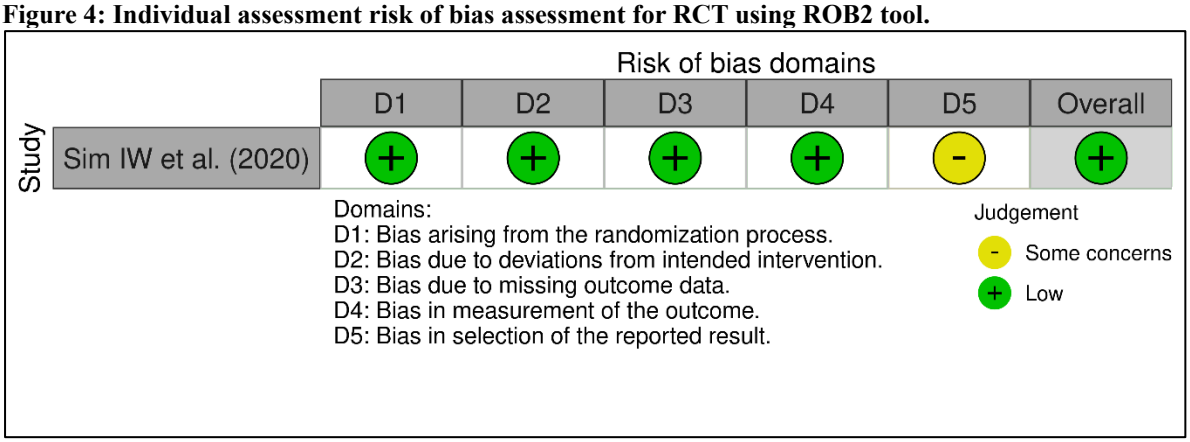

Figure 5: Overall risk of bias assessment for RCT using ROB2 tool.