

# EFFECTIVENESS OF LEUKOCYTE- AND PLATELET-RICH FIBRIN IN THE MANAGEMENT OF MEDICATION-RELATED OSTEONECROSIS OF THE JAWS – A SYSTEMATIC REVIEW

Efectividad de la fibrina rica en leucocitos y plaquetas en el tratamiento de osteonecrosis mandibular relacionada con medicamentos: Una revisión sistemática

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## ABSTRACT

**Background:** Medication-related osteonecrosis of the jaw (MRONJ) is a rare, but significant adverse event primarily associated with the intake of antiresorptive and antiangiogenic medications. Although antiresorptive and antiangiogenic therapies improve life expectancy, particularly in cancer patients, MRONJ may hamper the patient's quality of life due to pain, discomfort, anxiety, depression, speech impairment, difficulty in swallowing and eating, frequent medical and dental evaluations and treatments, and the possibility of treatment discontinuation. Leukocyte- and Platelet-rich Fibrin (L-PRF) is an autologous platelet aggregate that promotes wound healing by stimulating re-epithelialization, angiogenesis, and extracellular matrix production. **Aim:** The present systematic review aimed to compare the results in the published literature on whether L-PRF is an effective and predictable adjuvant to surgical debridement of necrotic bone for improving the healing efficacy in patients with MRONJ.

**Materials and Methods:** The *PubMed*, *Scopus*, *Cochrane*, *Science Direct*, *LILACS*, and *Web of Science* databases were searched using the predetermined *MeSH* terms and eligibility criteria, and the search yielded a total of five articles. Two studies were retrospective, and three studies were case series.

**Results:** Seventeen participants received a combination of surgical debridement, L-PRF membrane, and antibiotics. Complete wound healing was observed in 70% of the participants, and most of them healed without any complications.

**Conclusions:** L-PRF as an adjuvant to surgical debridement of necrosed bone appears to have a positive association with the healing outcome in patients with MRONJ.

**Keywords:** Jaw; Osteonecrosis; Bisphosphonate-Associated Osteonecrosis of the Jaw; Wound healing; Guided tissue regeneration; Platelet-rich Fibrin.

## RESUMEN

**Introducción:** La osteonecrosis mandibular relacionada con medicamentos (ONMRM) es un evento adverso raro pero significativo asociado principalmente con la ingesta de medicamentos antirresortivos y antiangiogénicos. Aunque las terapias antirresortivas y antiangiogénicas mejoran la esperanza de vida, particularmente en pacientes con cáncer, la ONMRM puede obstaculizar la calidad de vida del paciente debido a dolor, incomodidad, ansiedad, depresión, discapacidad del habla, dificultad para tragar y comer, evaluaciones y tratamientos médicos y dentales frecuentes, y la posibilidad de interrupción del tratamiento. La fibrina rica en plaquetas y leucocitos (L-PRF) es un agregado de plaquetas autólogo que promueve la curación de heridas al estimular la reepitelización, la angiogénesis y la producción de la matriz extracelular. **Objetivo:** La presente revisión sistemática tuvo como objetivo comparar los resultados en la literatura publicada sobre si L-PRF es un adyuvante efectivo y predecible al desbridamiento quirúrgico del hueso necrótico para mejorar la eficacia curativa en pacientes con ONMRM.

**Materiales y Métodos:** Las bases de datos de *PubMed*, *Scopus*, *Cochrane*, *ScienceDirect*, *LILACS* y *Web of Science* se registraron utilizando los términos *DeCS/MeSH* predeterminados y los criterios de elegibilidad, y la búsqueda arrojó un total de cinco artículos. Dos estudios fueron retrospectivos, y tres estudios fueron series de casos.

**Resultado:** Diecisiete participantes recibieron una combinación de desbridamiento quirúrgico, membrana L-PRF y antibióticos. Se observó curación completa de heridas en el 70% de los participantes, y la mayoría de ellos se curaron sin ninguna complicación.

**Conclusión:** L-PRF como adyuvante para el desbridamiento quirúrgico del hueso necrótico parece tener una asociación positiva con el resultado de curación en pacientes con ONMRM.

**Palabras Clave:** Maxilares; Osteonecrosis; Osteo-necrosis de los Maxilares Asociada a Difosfonatos; Cica-trización de heridas; Regeneración tisular dirigida; Fibrina rica en plaquetas.

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## INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is a rare, but significant adverse event primarily associated with the intake of anti-resorptive and antiangiogenic medications.<sup>1</sup> The occurrence of MRONJ is linked to the therapeutic indications and the type, duration, and mode of administration of the medications.<sup>2</sup> MRONJ has been reported in 1% to 9% of advanced cancer patients who are on injectable bone-modifying drugs.<sup>3</sup> On the contrary, the prevalence of MRONJ was approximately 0.21% in patients on oral bisphosphonate therapy for managing osteoporosis after at least four years of exposure.<sup>4</sup>

Despite the fact that antiresorptive and antiangiogenic therapies improve life expectancy in cancer patients, MRONJ may impair the patient's quality of life due to pain, discomfort, anxiety, depression, speech impairment, difficulty swallowing and eating, frequent medical and dental evaluations and treatments, and the possibility of treatment discontinuation.<sup>5</sup> The current regimen for the management of MRONJ is restricted to surgical debridement and symptomatic relief. However, aggressive surgical modalities may not be suitable in medically compromised patients, considering the morbidity of such patients.<sup>2</sup>

Hence, the search for newer, less invasive therapeutic alternatives to aid in the management of MRONJ is ongoing. However, currently, no therapy is universally accepted.<sup>6</sup> Joseph Choukroun developed leukocyte- and platelet-rich fibrin (L-PRF) in 2007, as an adjuvant to intraoral surgical procedures to enhance wound healing and tissue regeneration.<sup>7</sup> L-PRF is easy-to-prepare and devoid of any additives.<sup>8</sup>

It is largely made up of a dense fibrin scaffold, which allows platelets and leukocytes to enmesh and release cytokines and growth factors, aiding

wound healing and tissue regeneration.<sup>9</sup> Because of their high density, the L-PRF fibres are resistant to frequent mechanical stresses in the oral cavity and can tolerate proteolytic destruction for a longer duration.<sup>10</sup> It promotes wound healing by stimulating extracellular matrix production, re-epithelialization, and angiogenesis.<sup>11</sup> L-PRF has been shown to release more growth factors when compared to other platelet aggregates.<sup>12</sup> Additionally, animal and clinical trials have reported improved wound healing and tissue regeneration using L-PRF as an adjuvant treatment modality.<sup>13</sup>

In recent years, an increasing trend in incidence of MRONJ has been noted among patients on antiresorptive and antiangiogenic medications. Hence, it is the need of the hour to stay updated on its diagnosis and management, particularly with L-PRF. Thus the present systematic review aimed to compare the results in the published literature on whether L-PRF is an effective and predictable adjuvant to surgical debridement of necrotic bone for improving the healing efficacy in patients with MRONJ.

## MATERIALS AND METHODS

The current systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.<sup>14</sup>

### Protocol registration

The review was registered in the PROSPERO database (the International Prospective Register of Systematic Reviews hosted by the National Institute of Health Research, University of York, Centre for Reviews and Dissemination) according to the guidelines, with the identification number CRD42023427069.

### Review question

What is the effect of L-PRF on the healing outcomes of patients with MRONJ? PICO analysis:

P. Patients with MRONJ.

I. L-PRF alone or as an adjunct to conventional therapy.

C. Not applicable.

O. Healing outcome of MRONJ.

### Search strategy

Two authors (RM and SM) conducted a thorough literature search to evaluate the efficacy of L-PRF in improving the healing outcome of patients with MRONJ. Online electronic databases like *PubMed*, *Scopus*, *Cochrane*, *LILACS*, *ScienceDirect*, and *Web of Science* were searched from the earliest available data until 31<sup>st</sup> May 2023. A combination of appropriate keywords and Medical Subject Heading (MeSH) terms like “*leukocyte-rich, platelet-rich fibrin*”, “*L-PRF*”, “*medication-related osteonecrosis of jaws*”, “*MRONJ*”, and “*healing outcome*”, were used with “OR” and “AND”, Boolean operators. The search string is as follows:

(((((“Leukocyte-rich and platelet-rich fibrin”) OR (L-PRF)) AND (((MRONJ) OR (medication-related osteonecrosis of the jaws)) OR (medication-induced osteonecrosis of the jaws)))) AND ((humans[Filter])))

Manual search was done using these three methods: firstly, two authors (RM and SM) searched the reference lists of included articles; secondly, citation tracking was performed by RM and MS in which they tracked all the articles that cited each one of the included articles, and thirdly, SM and MS searched all “related to” or “similar” articles. In the case of unpublished articles, the authors were contacted. A detailed search strategy is illustrated in Figure 1.

### Inclusion criteria

- Studies comparing the healing outcomes of L-PRF as primary or adjuvant therapy in the management of MRONJ.

- Articles published from the earliest available date to 31<sup>st</sup> May 2023.

- Studies conducted on adults above the age of 18 years, with no gender restriction.

- Study design: Randomized controlled trials, non-randomized interventional studies, non-experimental studies, case reports, case series.

### Exclusion criteria

- Articles using any other adjunct therapy to yield better treatment outcomes for MRONJ.

- Letters to the editor, review articles, animal studies, technical notes, and correspondence were excluded.

### Screening and selection

All the searched data was imported to an Excel spreadsheet (MS Excel 2020). The titles and abstracts of the included studies were screened from the above-mentioned databases independently by two reviewers (RM and SM).

If the search terms appeared in the title and abstract, the papers were chosen for full-text reading. Articles lacking abstracts but titles related to this review’s objectives were also chosen to screen the full text for eligibility. After selection, two reviewers read the full-text papers in detail (RM and SM). Studies that fulfilled all selection criteria were processed for data extraction. Discussion was used to settle disagreements between the two reviewers. If the conflict persisted, the decision of a third reviewer (SK) was regarded as final.

### Data extraction

The relevant data was extracted on to a standardized form by two reviewers (RM and SM). Data extraction included information like author/year of publication, patient characteristics like mean age, gender and number of patients, study design, condition for antiresorptive or bisphosphonate therapy, duration of medication intake, drug regimen, clinical presentation of MRONJ, site of involvement, MRONJ stage, triggering factor, management of MRONJ, healing outcome

and follow-up data. Disagreements between individual judgments in data extraction were resolved by taking the third reviewer's opinion (SK). The extracted data were recorded using an excel spreadsheet (MS Excel 2020).

### Risk of Bias and Level of Evidence

Case reports and case series are typically biased. However, standardized tools to assess their methodological quality in systematic reviews have been formulated. Two reviewers (RM and SM) independently assessed the quality of the included case series using a standardized tool by Murad *et al.*,<sup>15</sup> The included case series were rated as having low, moderate, or high risk of bias. The Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool was applied to assess the risk of bias among the included observational studies (16). The level of evidence was assigned according to the Agency for Health Research and Quality (AHRQ), 2016 classification of the level of evidence.<sup>17</sup>

## RESULTS

### Search Selection

The *PubMed*, *Scopus*, *Cochrane*, *Science Direct*, *Lilac*, and *Web of Science* databases using the predetermined MeSH terms and hand-searched articles yielded a total of 27 articles, of which 11 were duplicates. 13 titles and abstracts were related to the inclusion criteria. After analysis, 7 publications were finalized for full article screening. Finally, five articles were acknowledged to meet the review criteria (18–22). PRISMA flowchart (figure 1) was developed to summarise the selection of included studies (23).

### Place of study

Among the five included studies, two were conducted in Brazil (18, 19); while one each

was conducted in Belgium,<sup>22</sup> Turkey,<sup>21</sup> and Switzerland,<sup>20</sup> (Table 1).

### Characteristics of Included Studies

The total number of participants in the five included studies was 34. The sample size varied from 2 to 15. Two studies were retrospective, and three studies were case series (Table 1). Among the included studies, 38.23 % of the participants were males, and 61.77% were females. All the studies included adult participants, with the mean age ranging from 56.5 years to 77 years. (Table 2)

### Study findings

#### A. Underlying condition and Causative Medication

The most common underlying condition for medication intake was osteoporosis (35.3%), followed by breast cancer and prostate cancer (26.4%), multiple myeloma (5.8%), lung cancer (2.9%) and melanoma (2.9%). The most common causative medication was zoledronate (52.9%), followed by denosumab (14.7%), alendronate (11.8%), and ibandronate (8.8%). The maximum drug intake duration was one to five years (50%).

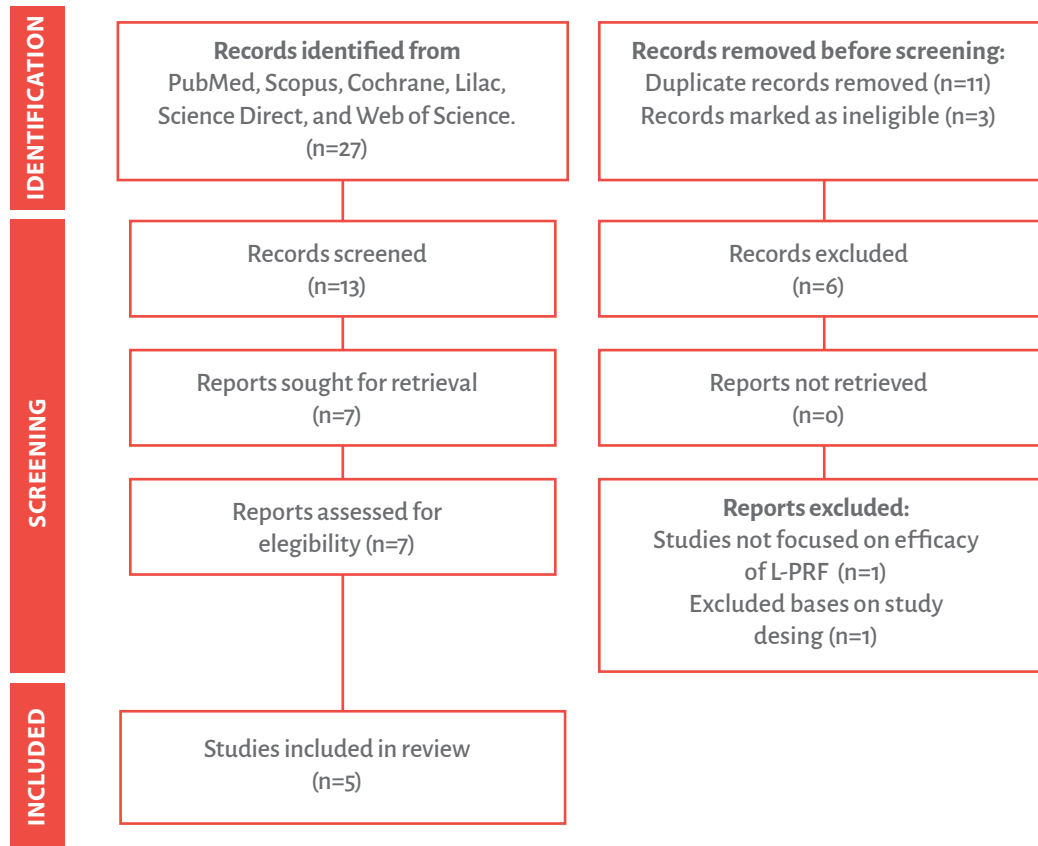
#### B. Clinical presentation of MRONJ

The most common site of presentation of MRONJ was the mandible (70.9%). In the study by Ozalp *et al.*,<sup>21</sup> the clinical presentation was not reported. Among the other four included studies (18-20, 22), the most common clinical presentation was bone exposure with purulent discharge (20.6%). Most participants belonged to MRONJ Stage 2 (50%), followed by Stage 3 (29.4%). In the majority of the cases, the most common triggering event for initiation of MRONJ was spontaneous (23.5%), closely followed by dental extraction (17.6%).

#### C. Management of MRONJ and Follow-up

Most of the included studies used a combination of surgical debridement, L-PRF membrane, and

**Figure 1.** Detailed search strategy using PRISMA flowchart.



**Table 1.** Search strategies carried out in each search engine.

Number	Title	Author, year	Place of study	Study design	Level of Evidence
1	Use of leukocyte- and patelet-rich fibrin in the treatment of medication-related osteonecrosis of the jaws.	Maluf <i>et al.</i> , <sup>18</sup> 2018	Brazil	Case series	Level 5
2	Case reports of medication-related osteonecrosis of the jaw (MRONJ) treated with uncultured stromal vascular fraction and L-PRF.	Bouland <i>et al.</i> , <sup>22</sup> 2020	Belgium	Case series	Level 5
3	Promising results of surgical management of advanced medication related osteonecrosis of the jaws using adjunctive leukocyte and platelet rich fibrin	Ozalp <i>et al.</i> , <sup>21</sup> 2021	Turkey	Retrospective study	Level 4
4	Medication-related osteonecrosis of the Jaw: The use of leukocyte-platelet-rich fibrin as an sdjunct in the treatment	Valente <i>et al.</i> , <sup>20</sup> 2019	Switzerland	Retrospective study	Level 3
5	Surgery combined with LPRF in denosumab osteonecrosis of the jaw: Case Report	Maluf <i>et al.</i> , <sup>19</sup> 2016	Brazil	Case series	Level 5

**Table 2.** Detailed description of included studies depicting demographic details, underlying medical condition, details of medication intake, MRONJ presentation, and management and follow-up details

Author, year		Maluf et al, <sup>18</sup> 2018	Bouland et al, <sup>19</sup> 2020	Ozalp et al, <sup>21</sup> 2021	Valente et al, <sup>20</sup> 2019	Maluf et al, <sup>19</sup> 2016	Total number (n)
<b>Gender</b>	Male	0	0	6	6	1	13
	Female	2	2	7	9	1	21
<b>Mean age</b>	years	77	76.5	72.4	64	56.5	NA
<b>Condition</b>	Breast cancer	2	1	3	2	1	9
	Prostate cancer	--	--	6	3	--	9
	Lung cancer	--	--	--	-	1	1
	Multiple myeloma	--	--	1	1	--	2
	Melanoma	--	--	--	1	--	1
	Osteoporosis	--	1	3	8	--	12
	<b>Medication</b>	Zoledronate	--	2	11	5	--
	Denosumab	--	--	--	4	1	5
	Alendronate	--	--	1	3	--	4
	Ibandronate	--	--	--	3	--	3
	Bevacizumab + Denosumab	--	--	--	--	1	1
	Ibandronate + Zoledronate + Denosumab	--	--	1	--	--	1
	Fulvestrant + Zoledronate	1	--	--	--	--	1
	Fulvestrant + Zoledronate + Denosumab	1	--	--	--	--	1
<b>Duration</b>	Less than 1 year	--	--	--	--	2	2
	1 year - 5 years	2	1	--	14	--	17
	More than 5 years	--	1	--	1	--	2
	Not specified	--	--	--	--	--	13
<b>Site</b>	Maxilla	1	1	2	6	--	10
	Mandible	1	1	11	9	2	24
<b>Clinical presentation</b>	Pain	--	--	--	1	--	1
	Fistula	--	--	--	1	--	1
	Exposed bone	--	--	--	3	--	3
	Exposed bone + purulent discharge	1	--	--	6	--	7
	Purulent discharge + fistula	1	--	--	--	--	1
	Pain + purulent discharge + oroantral communication	--	1	--	--	--	1
	Pain + purulent discharge + exposed bone	--	1	--	--	2	3
	Pain + swelling + exposed bone	--	--	--	1	--	1
	Pain + bone exposure	--	--	--	3	--	3
	Not specified	--	--	--	--	--	13
<b>MRONJ Stage</b>	Stage 0	--	--	--	1	--	1
	Stage 1	1	--	--	4	--	5
	Stage 2	1	1	4	9	2	17
	Stage 3	--	1	9	--	--	10
	Not specified	--	--	--	--	--	1
<b>Trigger</b>	Dental extraction	1	--	--	5	--	6
	Implant surgery	1	--	--	1	1	3
	Endodontic surgery	--	--	--	-	1	1
	Unfitting prosthesis	--	--	--	3	--	3
	Spontaneous	--	2	--	6	--	8
	Not specified	--	--	--	--	--	1

Continued Table 2 ↘

Author, year		Maluf et al, <sup>18</sup> 2018	Bouland et al, <sup>19</sup> 2020	Ozalp et al, <sup>21</sup> 2021	Valente et al, <sup>20</sup> 2019	Maluf et al, <sup>19</sup> 2016	Total number (n)
<b>Management</b>	Surgical debridement + L-PRF + Antibiotics	2	--	--	13	2	17
	Only Antibiotics	--	--	--	1	--	1
	Surgical debridement + antibiotics + LPRF containing uncultured stromal vascular fraction	--	2	-	--	--	2
	Sequestrectomy with peripheral osteotomy + L-PRF	--	--	9	--	--	9
	Marginal resection + L-PRF	--	--	3	--	--	3
	Curettage + L-PRF	--	--	1	--	--	1
	Sequestrectomy + L-PRF	--	--	--	1	--	1
	<b>Follow-up</b>	Less than 1 year	--	--	--	1	2
1 year - 3 years		2	--	12	6	--	20
More than 3 years		--	--	1	8	--	9
Not specified		--	--	--	--	--	2
<b>Healing outcome</b>	Complete wound healing	2	2	9	11	--	24
	Partial wound healing	--	--	4	4	2	10
<b>Complications</b>	Additional surgeries	--	--	4	--	--	4
	Recurrence	--	--	--	4	--	4
	Discomfort	--	1	--	--	--	1
	Not specified	--	--	--	--	--	25

L-PRF: Leukocyte-rich, plasma-rich fibrin.

**Table 3.** ROBINS-E tool for risk of bias of observational studies.

Domains	Ozalp et al, <sup>21</sup>	Valente et al, <sup>20</sup>
Risk of bias due to confounding	No	No
Risk of bias arising from measurement of exposure	No	No
Risk of bias in selection of participants	No	No
Risk of bias due to post exposure intervention	No	No
Risk of bias due to missing data	No	No
Risk of bias arising from measurement of outcome	No	No
Risk of bias in selection of reported result	No	No
<b>Judgement</b>	<b>Low risk of bias</b>	<b>Low risk of bias</b>

**Table 4.** Risk of Bias Tool for Case Series.

Study	Maluf et al, <sup>19</sup> 2016	Maluf et al, <sup>18</sup> 2018	Bouland et al, <sup>22</sup> 2020
Is the patient selection method clear?	Not applicable	Not applicable	Not applicable
Was the exposure adequately ascertained?	Yes	Yes	Yes
Was the outcome adequately ascertained?	Yes	Yes	Yes
Were other alternative causes that may explain the observation ruled out?	Yes	Yes	Yes
Was there a dose-response effect?	Not applicable	Not applicable	Not applicable
Was follow-up long enough for outcomes to occur?	Yes	Yes	Yes
Can the case be replicated?	Yes	Yes	Yes
Risk of bias	Low	Low	Low

antibiotics (50%), followed by sequestrectomy with peripheral osteotomy combined with L-PRF (26.5%). Complete wound healing was observed in 70% of the participants (70.6%). The majority of patients were followed up for a period of one to three years (50.8%).

The majority of the participants healed without any complications. Recurrence was reported in four patients, and four patients required an additional surgical correction to facilitate healing.

### Risk of Bias and Level of Evidence

Three of the included studies were case series.<sup>18,19,22</sup> All three studies had a low risk of bias and were assigned a level of evidence as Level 5.

Two studies were retrospective studies.<sup>20,21</sup> Both the studies had a low risk of bias and were assigned a level of evidence as Level 4, (Table 3 and Table 4).

## DISCUSSION

Platelet concentrates are autologous products with high concentrations of different growth factors, such as transforming growth factor, platelet-derived growth factor, and vascular endothelial growth factor. These concentrates stimulate and accelerate bone healing and tissue regeneration.<sup>24</sup>

L-PRF is a leukocyte concentrate that allows sustained release of the growth factors, resulting in accelerated wound healing, and decreased risk of contamination, edema, and post-operative pain.<sup>25</sup> L-PRF can be obtained using a blood sample taken in 9 ml tubes without anticoagulant and immediately centrifuged at 2700 rpm during 12 minutes.

At the end of the process, a large L-PRF clot can be collected in the middle of each tube, that can be used directly to fill a cavity, or mixed with a bone material, or compressed into a membrane, or a fibrin cylinder.<sup>26</sup>

Among the included studies, the majority of the participants (61.77%) were females, with the mean age ranging from 56.5 years to 77 years.

Increased prevalence of osteoporosis and malignancies in older women could be the reason for this finding. The most common site of presentation of MRONJ was the mandible. This could be due to the fact that the mandible has a less intricate vascular network and a poor blood supply compared to maxilla. A study by Kang et al also reported that MRONJ is more common in the mandible in older women.<sup>27</sup> The most common underlying condition for medication intake was osteoporosis, followed by breast cancer and prostate cancer, multiple myeloma, lung cancer, and melanoma. This was in accordance with the findings of a study by Chang *et al.*,<sup>28</sup> who found that the most common diseases related to MRONJ were osteoporosis (47.92%), followed by breast cancer (29%), multiple myeloma (10%), and prostate cancer (10%).

The reason could be that postmenopausal osteoporosis commonly affects older women, and antiresorptive medications are frequently prescribed to reduce bone resorption effectively.<sup>29</sup> The most common causative medication was zoledronate, followed by denosumab, alendronate, and ibandronate. MRONJ has been linked to the medication-induced apoptosis of osteoclasts or the anti-angiogenic and suppressive effects that these drugs have on endothelial cells.<sup>30,31</sup> The majority of the participants belonged to advanced stages of MRONJ (Stage 2 and Stage 3), with the most common clinical presentation being bone exposure with purulent discharge. The lack of dental screening of such patients could have led to the diagnosis of MRONJ at advanced stages.<sup>32</sup>

In this review, we surprisingly noticed a high proportion of patients with a spontaneous onset of MRONJ. This raises the possibility that, in



comparison to other osteo-metabolic patients, specific systemic disorders may increase the susceptibility to the spontaneous development of MRONJ.<sup>33</sup>

Most of the included studies used a combination of surgical debridement, L-PRF membrane, and antibiotics, with complete wound healing observed in 70% of the participants. Also, the majority of the participants healed without any complications. It was found that the L-PRF matrix degrades gradually, enabling the gradual release of cytokines and platelet-derived growth factors. Thereby, it acts as an antimicrobial agent and plays a crucial role in immunological control. As a result, it encourages tissue vascularization, increases soft tissue regeneration, and hastens the healing of epithelial lesions.<sup>34</sup>

The majority of patients were followed up for a period of one to three years. Recurrence was reported in four patients, and four patients required an additional surgical correction to facilitate healing. This could be due to the presence of systemic comorbidities like diabetes mellitus, hypertension, or immunocompromised states.

### Limitations

Despite strict inclusion and exclusion criteria, this systematic review has a few limitations. All the included studies were either case series or retrospective studies that have a low level of evidence. Hence, it is not possible to confirm the validity and reliability of L-PRF in the management of MRONJ due to a lack of robust evidence. Secondly, the bulk of investigations was single-center case series or retrospective studies with wide disparities in follow-up time, had a very small sample size, and lacked a comparison arm. Hence, the number of studies included is insufficient to establish firm conclusions about the efficacy of L-PRF as an adjuvant in improving the healing outcome of patients with MRONJ.

Finally, due to the heterogeneity and inconsistency of the data from the included studies, a quantitative synthesis of the results was not achievable.

### Future directions

In the future, large multicenter trials with larger sample sizes, uniform sampling, proper randomization, and a longer follow-up time should be encouraged to arrive at conclusive evidence. The aim should be to develop a standardized treatment strategy by combining surgical intervention with L-PRF based on the stage and severity of MRONJ. A personalized treatment regimen needs to be formulated on a case-to-case basis, taking the clinical presentation and systemic comorbidities into account. Future research must focus on the comparison of L-PRF as an adjuvant to surgical debridement with the existing conventional treatment modalities for the management of MRONJ.

## CONCLUSION

L-PRF as an adjuvant to surgical debridement of necrosed bone appears to have a positive association with the healing outcome in patients with MRONJ. However, this conclusion is based only on reported case series and retrospective studies with a low level of evidence. For validation of the healing efficacy of L-PRF as an adjuvant to surgical debridement in patients with MRONJ, several high-powered, well-conducted randomized controlled trials with holistic evaluation criteria are necessary.

### CONFLICT OF INTERESTS

All authors declare that there are no potential conflicts of interest regarding the authorship and/or publication of this article.

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Does not apply.

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**Mohandas R:** Conceptualization, Data curation, Methodology, Writing – original draft.

**Mohapatra S:** Conceptualization, Data curation, Writing – original draft.

**Singh M:** Data curation, Writing – original draft.

**Kheur S:** Formal analysis, Manuscript review and editing.

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### PEER REVIEW

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