

Systematic Reviews and Meta-Analysis

## Impact of platelet-rich fibrin on pain after mandibular third molar extraction: A systematic review and meta-analysis

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### ABSTRACT

Platelet rich fibrin (PRF) is an autologous biomaterial and has many clinical applications. It is produced without the addition of anticoagulant and with no gelling agent, through the immediate centrifugation of blood after collection. The effect of PRF on post-surgical pain is unclear. Thus the aim of this systematic review was to assess whether PRF was effective in controlling pain after the extraction of bilateral mandibular third molars. A comprehensive literature search was performed for articles published from January 2000 to January 2021 in the PubMed, PubMed Central, Directory of Open Access Journals (DOAJ), Campbell systematic review, Scopus, Cochrane review, Embase and Google scholar. Randomized clinical trials with PRF used as one of the comparison groups PRF after extraction and articles assessing pain as an outcomes measure were included for the systematic review. Results: A total of 160 records were found by preliminary screening through database search and 30 records were retrieved by additional sources, of which eleven were selected for qualitative analysis and four for quantitative analysis. A meta-analysis was performed only for pain, due to the considerable heterogeneity among studies for the other outcome variables. The overall quality of evidence was low for all outcomes of included studies. In these studies pain was assessed using a visual analog scale ranging from 0 (no pain) to 10 (most severe pain) point scale. Post-operative pain on day 1, 3 and 7 showed statistically significant difference between the PRF and non-PRF groups. In conclusion PRF administered after third molar extraction significantly reduced pain. But, further randomized controlled trials with larger cases and well-designed models are essential to validate the current findings.

**Keywords:** Mandibular third molar, Pain, Platelet-rich fibrin

### INTRODUCTION

Third molar (M3) extraction is one of the most common operations in oral and maxillofacial surgery. The literature on M3 removal consequences is vast.<sup>[1]</sup>

After the third molar tooth is removed, pain, edema, inflammation, alveolar osteitis (dry socket), and bleeding are all possible post-operative consequences. To prevent post-operative problems, oral and maxillofacial surgeons are continuously working to enhance their surgical technique.<sup>[2]</sup>

Inflammatory pain is caused by tissue damage and inflammation, neuropathic pain is caused by damage to the central nervous system, and functional pain is caused by changes in the normal function of the nervous system.<sup>[3]</sup> Pain is a key issue that might discourage patients from obtaining dental treatment in clinical settings.<sup>[4,5]</sup>

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The extraction of an impacted molar may cause severe agony to the patient. It begins when the anesthetic wears off and peaks on the first day following surgery. If a dry socket or infection arises, inflammation can make it more difficult to alleviate post-operative discomfort.<sup>[6,7]</sup>

This is classified as being of short to moderate duration, with the peak severity occurring during the first 12 h after surgery.<sup>[8,9]</sup> As a result, oral and maxillofacial surgeons are continuously refining their surgical techniques to reduce post-operative problems.

Using a centrifuge to produce a platelet-rich fibrin (PRF) clot from autogenous whole blood, Dr. Joseph Choukroun of France was the first to discuss the use of PRF in oral and maxillofacial surgery.<sup>[10]</sup> To accelerate socket repair and reduce post-operative discomfort, he suggested utilizing a platelet concentrate autogenous substance (PRF) in tooth extraction sites.<sup>[11]</sup> PRF is part of a new class of platelet concentrates that are simple to prepare and do not need biological blood processing. PRF is a kind of autologous tissue that may be employed in a number of therapeutic applications. It is created without anticoagulants or gelling chemicals, and it is made by centrifuging blood just after it has been processed.<sup>[11]</sup> One of the main benefits of PRF over first-generation platelet concentrate platelet-rich plasma (PRP) is the complex and resilient structure of the fibrin matrix, which stores a considerable number of cytokines inside its structure and releases them slowly during healing (PRP).<sup>[12]</sup> The fibrin matrix's particular design, in combination with the leukocyte material it contains, may have a healing impact, lowering surgery-related morbidity. PRF had demonstrated good outcomes in the treatment of bony deformities, maxillary sinus augmentation, dental implant surgery, periodontal tissue engineering, post-extraction socket repair, and third molar surgery.<sup>[13]</sup> Some researchers have discovered that PRF can help reduce discomfort following mandibular third molar surgery in particular.<sup>[14]</sup>

The real impact of PRF on post-operative problems, however, is unclear. The goal of this systematic study was to see if PRF was effective in controlling pain after bilateral mandibular third molar extractions. The hypothesis for this review was that applying PRF locally to the extraction site of the lower third molars would minimize post-operative pain.

## MATERIALS AND METHODS

The parameters for this systematic review were based on the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis declaration.<sup>[15]</sup> A detailed protocol was developed prior and was registered in the PROSPERO database (Registration number CRD42020187688).

Multiple electronic databases such as PubMed, PubMed Central, Directory of Open Access Journals (DOAJ), Campbell systematic review, Scopus, Cochrane review, Embase, and Google Scholar were used to conduct a conventional literature search. This review covered all English-language articles that were published between January 2000 and January 2021.

### The articles with following criteria were included for the review

- Randomized and controlled trials assessing bilateral mandibular third molars impaction requiring surgical extraction
- Randomized and controlled trials with at least two comparison groups: One group receiving PRF after extraction and the other group receiving control treatment without PRF after extraction
- Articles published in the English language
- Articles assessing pain as an outcomes measure.

### The exclusion criteria were as follows

- Randomized and controlled trials with PRF placed at the extraction sites of maxillary third molars
- Randomized and controlled trials without comparison group
- Letter to editor, case report, personnel proceedings, personal communications, and any types of reviews were excluded from the study
- Systematic reviews and meta-analysis
- Studies published in language other than English.

### Search strategy

PubMed, PubMed Central, EMBASE, Google Scholar, DOAJ, Scopus, Campbell systematic review, and Cochrane were

**Table 1:** Method of PRF preparation in the included studies.

Author, Year	Volume of blood drawn, in ml	Centrifugation parameters speed and time
Sybil <i>et al.</i> , <sup>[17]</sup> 2020	10 ml	3000 rpm for 10 min
Bhujbal <i>et al.</i> , <sup>[18]</sup> 2020	6 ml	3000 rpm for 10 min
Surekha <i>et al.</i> , <sup>[19]</sup> 2019	10 ml	3000 rpm for 10 min
Kapse <i>et al.</i> , <sup>[20]</sup> 2019	10 ml	2700 rpm for 12 min
Singha <i>et al.</i> , <sup>[21]</sup> 2019	10 ml	3000 rpm for 15 min
Dar <i>et al.</i> , <sup>[22]</sup> 2018	10 ml	3000 rpm for 12 min
Unakalkar <i>et al.</i> , <sup>[23]</sup> 2018	NR	NR
Gulsen <i>et al.</i> , <sup>[24]</sup> 2017	10 ml	3000 rpm for 10 min
Asutay <i>et al.</i> , <sup>[25]</sup> 2017	12 ml	2700 rpm for 12 min
Kumar <i>et al.</i> , <sup>[26]</sup> 2015	5 ml	3000 rpm for 10 min
Ozgul <i>et al.</i> , <sup>[27]</sup> 2015	10 ml	3000 rpm for 10 min

NR: Not reported, PRF: Platelet-rich fibrin

**Table 2:** Characteristics of included studies.

Author, Year	Place of study	Mean age, (Range)	Number of participants		Follow-up visits (Post-operative visits)	Outcome assessed
			Test	Control		
Sybil <i>et al.</i> , <sup>[17]</sup> 2020	India	32.3 (18–55)	25	25	Pain, tenderness, and edema – 1 <sup>st</sup> , 3 <sup>rd</sup> day, 1 week, and 1 month. Sensitivity – 1 week, 1, 3, and 6 months. Area-specific SBI and Plaque Index – 1 week and 1, 3, and 6 months. Area-specific CAL, probing depth, and radiographic bone height – 3 and 6 months.	Pain, edema, tenderness, sensitivity, SBI, Plaque Index, CAL, probing depth, and bone height
Bhujbal <i>et al.</i> , <sup>[18]</sup> 2020		22	20	20	Soft-tissue healing, pain, and swelling – 1 <sup>st</sup> day, 3 <sup>rd</sup> day, and 7 <sup>th</sup> day. Radiological bone density – 3 <sup>rd</sup> and 6 <sup>th</sup> month.	Soft-tissue healing, pain, and swelling
Surekha <i>et al.</i> , <sup>[19]</sup> 2019			15	15	Pain, facial swelling, soft-tissue healing, – 1 <sup>st</sup> , 3 <sup>rd</sup> , and 7 <sup>th</sup> day. Bone density – 1 <sup>st</sup> and 3 <sup>rd</sup> month.	Pain, facial swelling, soft-tissue healing, and bone density
Kapse <i>et al.</i> , <sup>[20]</sup> 2019	India	25.47±0.90 years 18–40	30	30	Pain and swelling – 1, 3, 7, and 14 day. Bone healing – 8 <sup>th</sup> and 16 <sup>th</sup> post-operative week.	Pain, swelling and bone healing.
Singha <i>et al.</i> , <sup>[21]</sup> 2019	Madhya Pradesh, India.	18–30 years	100	100	Pain, Facial measurements, mouth opening, dry socket, and infection – 1 <sup>st</sup> , 3 <sup>rd</sup> , and 7 <sup>th</sup> day. Wound dehiscence – 3 <sup>rd</sup> and 7 <sup>th</sup> day Soft tissue healing – 7 <sup>th</sup> day	Pain, facial measurements, mouth opening, dry socket, infection and wound dehiscence, and soft-tissue healing.
Dar <i>et al.</i> , <sup>[22]</sup> 2018	Srinagar, Jammu and Kashmir, India.	18–50	60	60	Pain – 1 <sup>st</sup> , 3 <sup>rd</sup> , 7 <sup>th</sup> , and 14 <sup>th</sup> day. Swelling – 1 <sup>st</sup> , 3 <sup>rd</sup> , 7 <sup>th</sup> , and 14 <sup>th</sup> day Bone healing – 4 <sup>th</sup> and 12 <sup>th</sup> week	Pain, swelling, periodontal health, and bone healing.
Unakalkar <i>et al.</i> , <sup>[23]</sup> 2018	India	18–40	25	25	Pain – 1 <sup>st</sup> , 3 <sup>rd</sup> , 7 <sup>th</sup> , and 14 <sup>th</sup> day. Trismus – 1 <sup>st</sup> , 3 <sup>rd</sup> , 7 <sup>th</sup> , and 14 <sup>th</sup> day. Swelling – 1 <sup>st</sup> , 3 <sup>rd</sup> , 7 <sup>th</sup> , and 14 <sup>th</sup> day. Periodontal heal <sup>th</sup> – 8 <sup>th</sup> and 16 <sup>th</sup> week. Bone healing – 8 <sup>th</sup> and 16 <sup>th</sup> week.	Pain, swelling, trismus, periodontal health, and bone healing.
Gulsen <i>et al.</i> , <sup>[24]</sup> 2017	Turkey	17–27	30	30	Edema – 2 <sup>nd</sup> and 7 <sup>th</sup> day. Pain – 6 h, 12 h, 1 <sup>st</sup> , 2 <sup>nd</sup> , 3 <sup>rd</sup> , and 7 <sup>th</sup> day.	Edema and pain
Asutay <i>et al.</i> , <sup>[25]</sup> 2017	Turkey	20.32 (18–29 years)	30	30	Pain – 6 h, 12 h, and 1, 2, 3, 4, 5, 6, and 7 days after surgery. Trismus and mouth opening 2 <sup>nd</sup> and 7 <sup>th</sup> Post-operative days.	Pain, trismus, and mouth opening
Kumar <i>et al.</i> , <sup>[26]</sup> 2015	India	19–35 years	16	15	Pain, swelling, and mouth opening – 1 <sup>st</sup> , 1, and 3 month. Periodontal pocket depth and bone formation – 1 and 3 month.	Pain, swelling, maximum mouth opening, periodontal pocket depth and bone formation.
Ozgul <i>et al.</i> , <sup>[27]</sup> 2015	Turkey	18–28 years	56	56	Pain and facial swelling – 1, 3, and 7 days.	Pain and facial swelling

CAL: Clinical attachment level, SBI: Sulcus bleeding index

used to conduct a complete electronic search. The search was conducted using medical subject heading phrases as well as free text words. To identify the relevant papers, researchers used keywords such as platelet-rich plasma, PRF, pain, tooth extraction, mandibular third molar, impaction, and post-operative problems. This evaluation covered studies that were published up through January 2021. The reference lists

of the eligible paper as well as review articles were manually searched.

The search for suitable research was conducted until January 30, 2021. During the search process, if any relevant publications were discovered without full text, the respective authors were contacted through email to obtain the article. Duplicate articles were initially eliminated. The study's titles

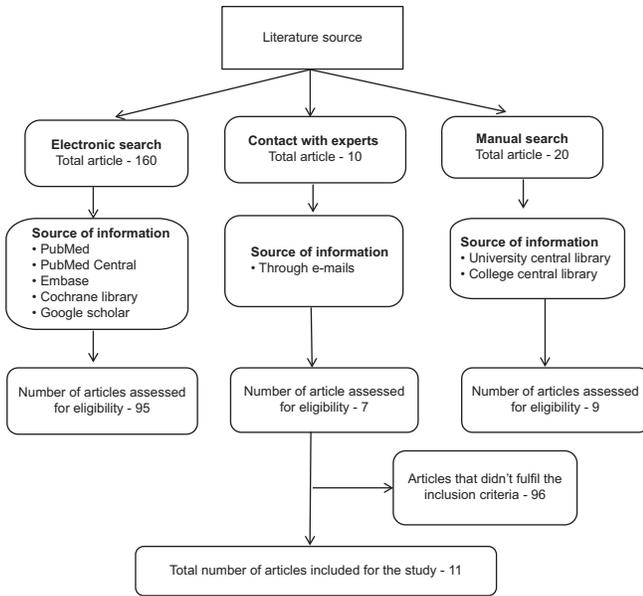


Figure 1: Search strategy.

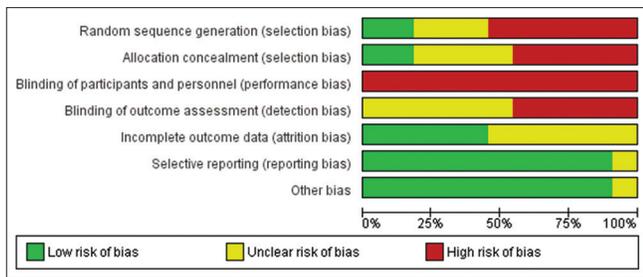


Figure 2: Review author's judgments about each risk of bias item presented as percentages across all included studies.

and abstracts were then evaluated separately by two writers using the eligibility criteria.

Finally, the inclusion and exclusion criteria were applied to the entire text of the articles that were initially included in the study. If the two author's options differed during the process, they came to an agreement through conversation. The inter examiner reliability was measured using Cohen's kappa.

**Extraction of data**

The first author used a data extraction form to obtain data from the included studies, which was then confirmed by consensus with the second author. The following information was gathered from each article: For PRF sample collection, volume of blood drawn and centrifugation parameters such as speed and time were gathered from included studies [Table 1]. For description of included studies: The first author's surname, the year, the article was published, the location of the study, the mean age or range, the number of participants in the test and control groups, the number of follow-up visits, and the

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Asudry F et al, 2017	Red	Red	Red	Yellow	Green	Green	Green
Bhujbal R et al, 2020	Red	Red	Red	Yellow	Green	Green	Green
Dar MM et al, 2018	Red	Red	Red	Yellow	Green	Green	Green
Gulsen U et al, 2017	Red	Red	Red	Yellow	Green	Green	Green
Kapso S et al, 2019	Red	Red	Red	Yellow	Green	Green	Green
Kumar et al, 2015	Red	Red	Red	Yellow	Green	Green	Green
Oguzi et al, 2015	Red	Red	Red	Yellow	Green	Green	Green
Singha et al, 2019	Red	Red	Red	Yellow	Green	Green	Green
Suresha K et al, 2019	Red	Red	Red	Yellow	Green	Green	Green
Soni D et al, 2020	Red	Red	Red	Yellow	Green	Green	Green
Unnikrishnan et al, 2018	Red	Red	Red	Yellow	Green	Green	Green

Figure 3: Risk of bias overview for evaluating the judgments of the author on each risk of bias items for each study included. Green stands for a low bias risk, yellow reflects an unknown bias risk, and red suggests a high bias risk.

outcome measured. Two authors independently derived these results. Any disagreements were handled between them, and in the end, they came to an agreement [Table 2].

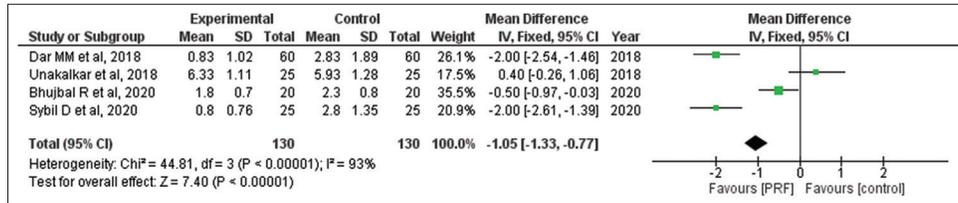
**Quality assessment**

The studies included in the review were analyzed using the Cochrane collaboration method driven by the Cochrane Handbook for Systematic Intervention Reviews (RevMan, version 5.3 The Cochrane Collaboration, Copenhagen, Denmark).<sup>[16]</sup> The risk of bias in the studies that were included was rated as “low,” “unclear,” or “high.” Method of sequence creation, allocation sequence concealment, blinding of care providers and participants, blinding of outcome assessors, inadequate outcome data, selective outcome reporting, and other forms of bias were all examined to determine the risk of bias in each research. Any discrepancies between the writers were worked out through communication. Review manager version 5.3 software was used for performing the analysis.

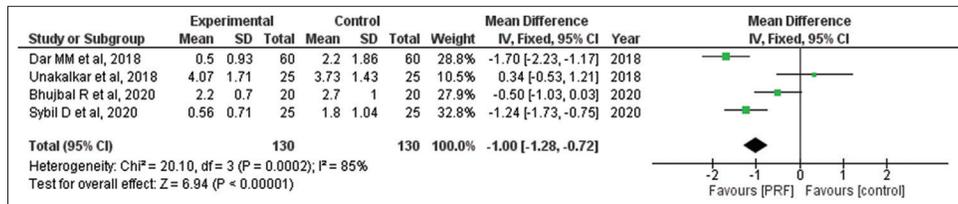
**RESULTS**

A first database search yielded 160 entries and further sources yielded 30 more records. Out of the 190 papers, 111 were evaluated for eligibility, with 96 articles failing to fulfill the inclusion criteria and just 11 being included in the review. The flow diagram for the selection of articles included in this study is shown in [Figure 1]. [Table 1] shows method of PRF preparation for all included studies.<sup>[17-27]</sup>

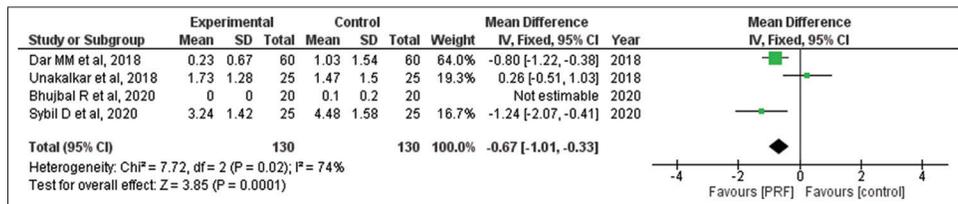
The overall quality of evidence was low for all outcomes. The risk of bias was evaluated as unclear in most studies, except for selective reporting, because of lack of detail in the reports. The assessments of risk of bias for included studies are given in [Figures 2 and 3]. Only two studies (5/14) described the random sequence generation and allocation concealment while detailed information was deficient in the other nine trials. None of the trials (0/11) described blinding of participants and personnel clearly being judged to be “high”



**Figure 4:** Forest plot and meta-analysis comparing day-1 post-operative pain for 10 point VAS scale. SD: Standard deviation



**Figure 5:** Forest plot and meta-analysis comparing day-3 post-operative pain for 10 point VAS scale. SD: Standard deviation



**Figure 6:** Forest plot and meta-analysis comparing day-7 post-operative pain for 10 point VAS scale. SD: Standard deviation

in this domain. The majority of trials (5/11) provided no details related to blinding of outcome assessment and for five (5/11) judged to be “unclear” due to lack of details. Only five trials (5/11) showed low risk of bias for incomplete outcome data according to the reports of the drop-outs or intention-to-treat analysis. Majority of the studies (11/12) had low risk of bias for selective reporting and other bias.

A total of 260 cases from four RCTs were included in the meta-analysis of pain. In these studies, pain was assessed using a visual analog scale ranging from 0 (no pain) to 10 (most severe pain) point scale. For day-1 post-operative pain, there was statistically significant differences (Weighted Mean Difference [WMD], -1.05; 95% CI, -1.33 to -0.77; P = 0.00001) between the PRF and non-PRF groups [Figure 4]. Similarly, significant difference was observed for day-3 post-operative pain between the PRF and non-PRF groups (WMD, -1.00; 95% CI, -1.28 to -0.72; P = 0.00001) [Figure 5]. Day-7 also showed significant difference between the PRF and non-PRF groups (WMD, -0.67; 95% CI, -1.01 to -0.33; P = 0.0001) [Figure 6].

**DISCUSSION**

Slow polymerization occurs throughout preparation, resulting in a fibrous protein network that promotes cell

motility and proliferation, similar to that observed in natural cells. PRF is widely utilized as a direct graft or in combination with allograft or xenograft in the oral and maxillofacial areas.<sup>[28]</sup> In addition, without the use of a flap, PRF clots are utilized to repair acute sinus perforations.<sup>[29]</sup> Socket retention, infrabony flaws, and periodontal issues are among the other indications for PRF usage.<sup>[11]</sup> The present meta-analysis looked at the influence of PRF on a mandibular third molar in 260 cases from four studies, with the goal of evaluating the effect of PRF on post-operative pain following mandibular third molar surgery.

This might aid the oral and maxillofacial surgeon in giving a better post-operative outcome for his/her patients. Only pain was used as an outcome measure in this meta-analysis. The meta-analysis for these additional factors was not possible due to methodological heterogeneity across the included studies.

The findings of this meta-analysis revealed that when PRF was used, pain was reduced on the 1<sup>st</sup>, 3<sup>rd</sup>, and 7<sup>th</sup> days following surgery, with a statistically significant difference between the PRF and non-PRF groups. These findings point to PRF having a therapeutically positive effect on post-operative pain, as well as confirming the notion that applying PRF following lower third molar extraction reduces post-operative

discomfort. Although these findings are encouraging, due to the significant possibility of bias in the studies included, care is advised to avoid misunderstanding of the real data.

Our findings matched those of Xiang *et al.*,<sup>[30]</sup> who found that applying PRF locally during the extraction of the lower third molar considerably reduced discomfort on the 3<sup>rd</sup> post-operative day. Canellas *et al.*<sup>[13]</sup> and Al-Hamed *et al.*<sup>[14]</sup> both show that PRF has a clinically positive impact on post-operative pain.

A meta-analysis could be performed only for pain. The lack of a meta-analysis for various additional variables, such as edema, trismus, soft-tissue healing, and bone density, was due to the high methodological heterogeneity across the included studies. The randomized procedure and allocation concealment are the most essential components of a clinical trial in terms of risk of bias analysis. Only two of the 11 publications included in this study explained the process for generating the allocation sequence in sufficient depth, as well as the strategy for concealing the allocation sequence. Inadequate allocation concealment can lead to incorrect treatment effect estimates. The current meta-analysis has the following drawbacks: To begin with, the number of research included was limited, potentially reducing statistical power. Second, only studies that used the same measuring scale were considered. Third, only papers published in English were considered. Finally, the length of follow-up in the four trials differed significantly, making it difficult to determine the long-term clinical effects of PRF on the mandibular third molar.

## CONCLUSION

Despite the limitations, this study shows that PRF given after third molar extraction considerably reduces discomfort. To corroborate the current findings, more study with larger instances and well-designed models is required.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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