

Original Article

Evidence for platelet-rich fibrin in combination with other regenerative materials for treatment of periodontal furcation defects: a systematic review and meta-analysis

Xiaoming Lou^{1,2}, Yingjie Lou³

¹Department of Stomatology, Shangguan Township Community Health Service Center, Fuyang District, Hangzhou 311415, Zhejiang, China; ²Shangguan Branch of The Medical and Health Service Community of Hangzhou Fuyang District First People's Hospital, Hangzhou 311415, Zhejiang, China; ³Department of Stomatology, Jingshan Town Community Health Service Center, Yuhang District, Hangzhou 311116, Zhejiang, China

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Abstract: This study aimed to examine the effects of platelet-rich fibrin (PRF), alone or in combination with other regenerative materials, for periodontal furcation defects and to evaluate the quality of existing evidence. A systematic search was performed for studies published up to October 2025 in several databases, such as PubMed/MEDLINE, Embase, Scopus, and Cochrane Central Register of Controlled Trials. This meta-analysis included only randomized controlled trials (RCTs) that used PRF for Class II furcation defects with a follow-up period of more than 6 months. Main outcomes included probing depth (PD) and clinical attachment level (CAL), while secondary outcomes included radiographic bone fill. Twenty RCTs involving 786 participants were included. The use of PRF with open flap debridement (OFD) significantly improved PD reduction, vertical CAL gain, and horizontal CAL gain compared to OFD alone ($P < 0.00001$). PRF combined with bone grafts (BG) yielded comparable or slightly superior clinical outcomes to BG alone. The adjunctive use of small biomolecules with PRF demonstrated significant additional benefits in improving clinical findings compared to PRF monotherapy. The evidence was characterized by a high heterogeneity ($I^2 > 85\%$ for many comparisons), and the majority of studies were assessed as having 'some concerns' regarding the risk of bias. Compared to OFD alone, its combination with PRF greatly improved periodontal regeneration in Class II furcation defects, with results comparable to those of existing biomaterials such as BG. The most convincing evidence indicates that PRF together with osteopromotive biomolecules have a synergistic effect.

Keywords: Platelet-rich fibrin, furcation defects, periodontal regeneration, systematic review, meta-analysis, bone grafts, biomolecules

Introduction

Periodontal disease is a chronic, multifactorial inflammatory condition that affects the tissues supporting the teeth, such as alveolar bone, cementum, and the periodontal ligament [1]. About 47%-50% of adults worldwide suffer from periodontal disease [2]. Approximately 38.5% of them are in moderate or severe stages (Stage III or IV) [3]. As the condition progresses, alveolar bone resorption may result in both vertical and horizontal bone defects. Among them, furcation defects are characterized by complex anatomic structure and limited accessibility, posing a major challenge for treatment and representing a key risk factor for tooth loss [4-6].

Open flap debridement (OFD), guided tissue regeneration (GTR), bone grafts (BG), and enamel matrix derivatives (EMD) are commonly used treatments [7]. However, regenerative outcomes in furcation areas remain inconsistent. Platelet-rich fibrin (PRF), a second-generation autologous platelet concentrate, has been widely used in periodontal regeneration in recent years. PRF is simple to prepare, absent of anticoagulants, rich in growth factors and leukocytes, and capable of sustained release of bioactive molecules [7, 8].

Although PRF has been investigated for the treatment of furcation defects in several randomized controlled trials (RCTs), its efficacy alone or with BG, bioactive molecules, or barri-

er membranes has not been fully explored. Comprehensive evidence and quality evaluation of key clinical data, such as probing depth (PD), clinical attachment level (CAL), and bone regeneration outcomes, remain limited [7, 8].

Therefore, the objective of this meta-analysis was to evaluate the efficacy of PRF used either alone or with other biomaterials in the treatment of periodontal furcation defects. Subgroup analyses of PD, CAL, and bone fill findings were conducted to clarify their clinical value and the strength of the available evidence. This meta-analysis may provide useful evidence in periodontal regeneration.

Materials and methods

Search strategy

This systematic review and meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD-420261284302. The literature in databases such as PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were thoroughly retrieved from the start of the databases up to October 2025, with no restrictions on languages. The reference lists of relevant literature were manually screened to identify all potentially eligible studies. The search strategy combined both free-text terms with controlled vocabulary. Key terms included “platelet-rich fibrin”, “PRF”, “furcation defect”, “periodontal regeneration”, “guided tissue regeneration”, “bone graft”, “clinical attachment level”, “probing depth”, and “radiographic bone fill”. The search syntax was adapted according to the requirements of each database. The study selection process is presented in **Figure 1**.

Eligibility criteria

The PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework was employed to define the study eligibility.

Population: Systemically healthy patients diagnosed with chronic periodontitis presenting Class II furcation defects in maxillary or mandibular molars, confirmed clinically and radiographically.

Intervention: Surgical therapy involving OFD with adjunctive application of PRF. This included the use of PRF alone, PRF in combination with BG (e.g., demineralized freeze-dried bone [DFDBA], β -tricalcium phosphate [β -TCP], hydroxyapatite), PRF with bioactive molecules (e.g., statins, metformin, alendronate), or PRF with barrier membranes.

Comparison: OFD alone or OFD in conjunction with other established regenerative methods (e.g., BG, collagen membranes, enamel matrix derivatives [EMD]).

Outcomes: Primary outcomes: Probing Depth/ Probing Pocket Depth (PD/PPD): The distance from the gingival margin to the base of the periodontal pocket.

CAL: The distance from the cemento-enamel junction (CEJ) to the base of the periodontal pocket. Subgroup analysis was performed for Vertical CAL/Relative Vertical CAL (VCAL/RVCAL) and Horizontal CAL/Relative Horizontal CAL (HCAL/RHCAL).

Secondary outcomes: Bone regeneration effects: Assessed radiographically, including bone fill percentage, defect depth reduction (vertical defect fill [VDF]/horizontal defect fill [HDF] reduction), and radiographic bone fill (RBF). In addition, vertical bone fill (VBF) and horizontal bone fill (HBF) were assessed.

Study design: Only RCTs with at least a 6-month follow-up period were selected.

Studies meeting any of the following criteria were excluded: non-randomized studies, animal studies, case reports, reviews, conference abstracts, studies with unavailable data or full text, and studies involving patients with systemic conditions known to severely impair bone metabolism or wound healing (e.g., uncontrolled diabetes, osteoporosis). Studies involving smokers were excluded unless separate data for non-smokers were provided.

Quality assessment

Two reviewers independently assessed the quality of the included RCTs [10-29] using the Cochrane Risk of Bias tool (RoB 2) [9]. Any discrepancies were resolved through discussion or consultation with a third reviewer. Five domains were assessed, including bias from

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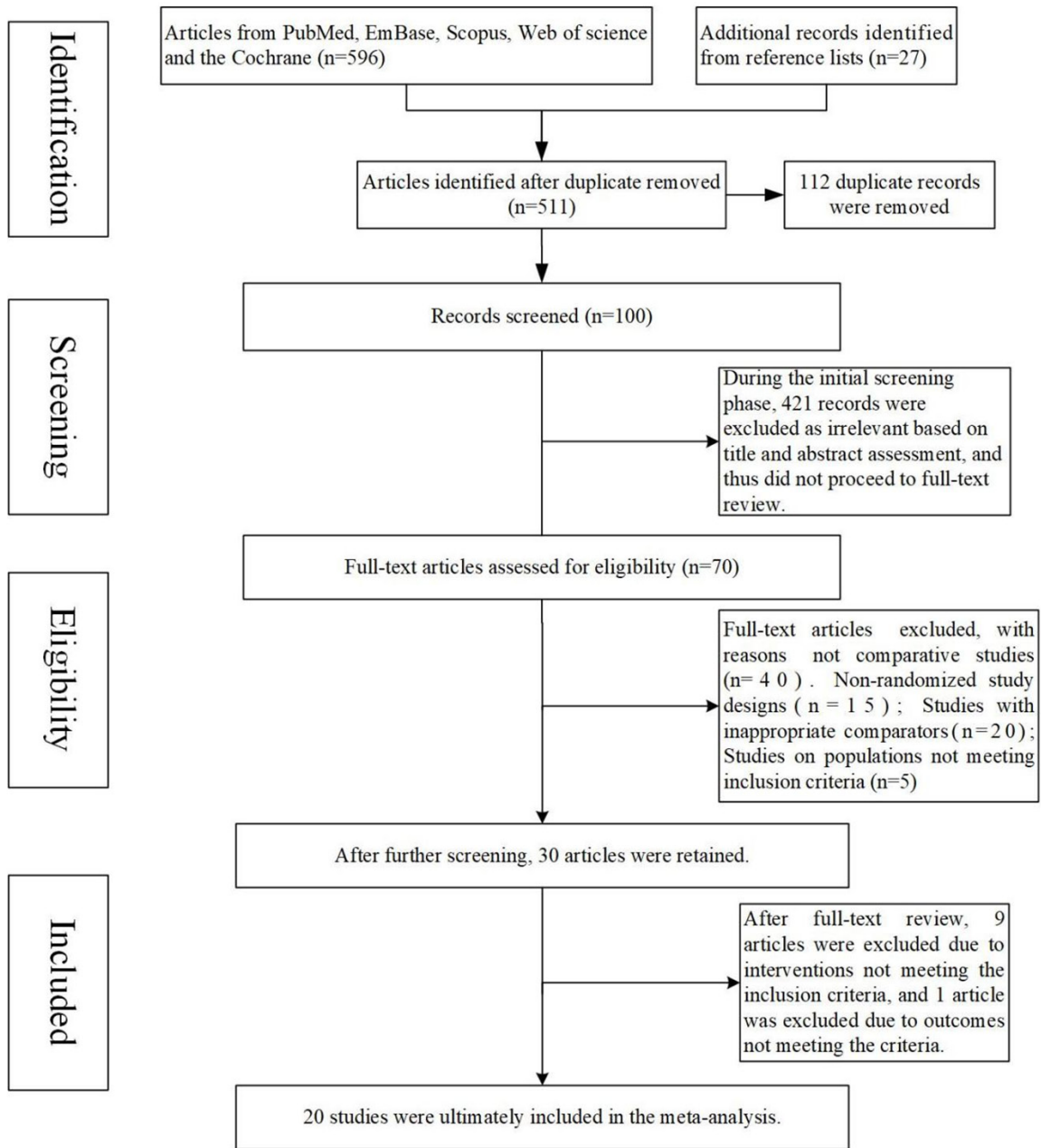


Figure 1. Study selection flow diagram.

the randomization process, bias due to deviations from intended interventions, bias caused by missing outcome data, bias in outcome measurement, and bias in the selection of the reported results.

Figure 2 shows a summary of the risk of bias assessments for each study in all the domains.

Statistical analysis

All statistical analyses for this meta-analysis were performed using Stata 18.0 (StataCorp,

College Station, TX, USA). Continuous variables, including changes in PD, CAL, and bone regeneration measurements (e.g., bone fill percentage and defect depth reduction), were analyzed and presented as standardized mean differences (SMD) with 95% confidence intervals (CI), calculated according to Cohen's d. Forest plots were generated to visualize the effect estimates. For all outcomes, a negative SMD for PD and a positive SMD for CAL and bone regeneration indicated a beneficial effect of the PRF-based intervention relative to the comparator.

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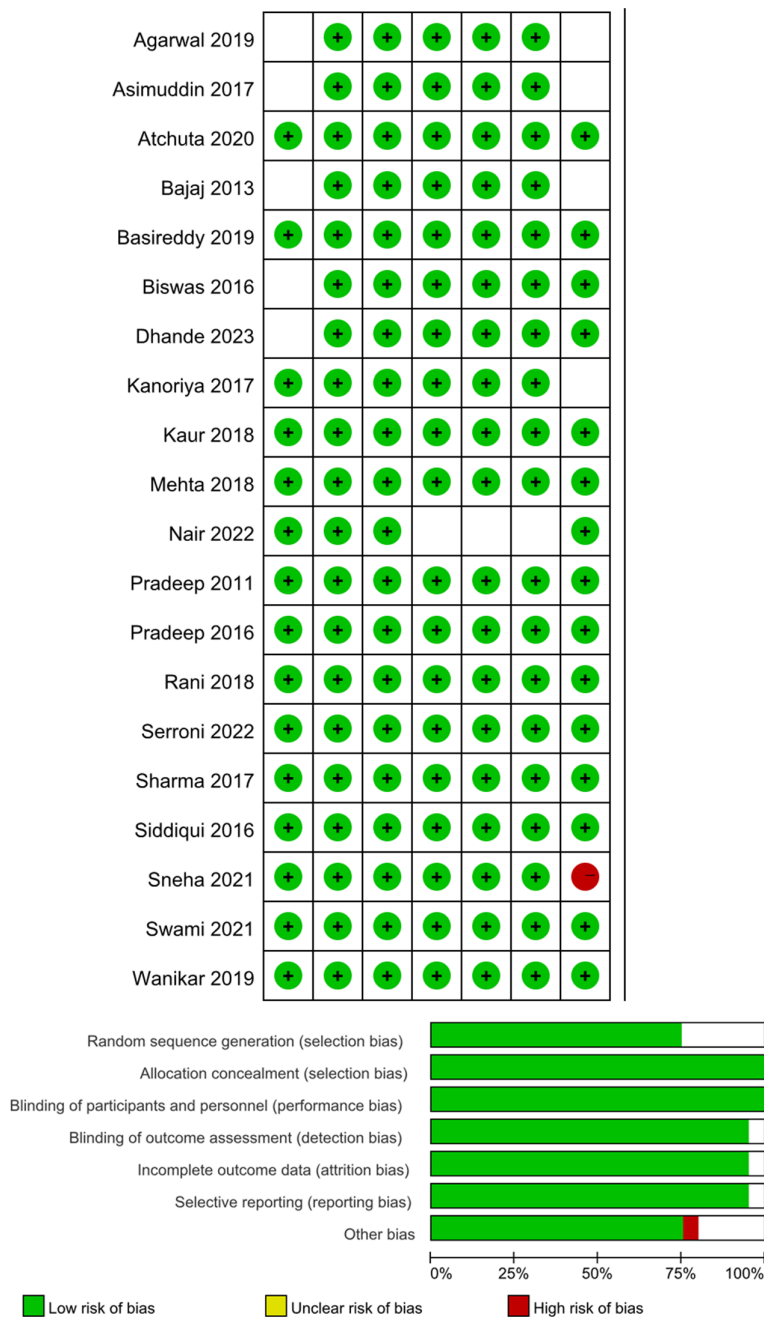


Figure 2. Risk of bias summary.

The SMD was calculated as the mean difference in the change from baseline between the intervention and control groups, divided by the pooled standard deviation. A random-effects model was employed for all meta-analyses to explain the anticipated clinical and methodologic heterogeneity among the included studies. Given the variability in radiographic assessment methods (e.g., cone-beam computed tomography [CBCT], digital subtraction

radiography, and conventional X-ray), bone regeneration outcomes were pooled using SMD. Due to the limited number of studies within each imaging category, subgroup analysis by detection method was not feasible.

The heterogeneity of studies was assessed using the I^2 and tau-squared (τ^2) statistics, together with the Chi-square test (Cochran's Q test). Heterogeneity was considered significant if $I^2 > 50\%$. To investigate the extent of heterogeneity and possible sources, pre-specified subgroup analyses were conducted according to intervention types, including PRF alone, PRF with BG (PRF + BG), PRF with medications (PRF + medications), and PRF with membrane materials (PRF + membrane). Since only one study investigated PRF + membrane, it was impossible to perform a quantitative synthesis for this subgroup. To determine the reliability of the pooled results, sensitivity analyses were carried out by sequentially removing individual studies. The Cochrane Risk of Bias tool (RoB 2) was used to assess the risk of bias in the included RCTs. Review Manager (RevMan version 5.3; The Cochrane Collaboration, Copenhagen, Denmark) was applied to generate the corresponding risk-of-bias summary figures. A p -value below 0.05 (two-sided) was deemed significant for all overall effect sizes.

Assessment of certainty of evidence (GRADE)

The certainty (quality) of the evidence for the pre-specified primary outcomes, including PD reduction, CAL gain, and radiographic bone regeneration, was assessed using the Grading of Recommendations Assessment, Develop-

ment and Evaluation (GRADE) framework. Two reviewers (X.L. and Y.L.) independently evaluated each outcome for each comparison of interest (e.g., PRF-based intervention vs. control). The evidence was initially rated as 'high' for randomized trials and then potentially downgraded by one or two levels across five domains: 1) Risk of bias (serious concerns regarding randomization, deviations, missing data, measurement, or selective reporting, as per RoB 2 assessment); 2) Inconsistency (unexplained heterogeneity in results, particularly high I^2 values with inconsistent direction of effects); 3) Indirectness (population, intervention, comparator, or outcome not directly applicable to the review question); 4) Imprecision (wide confidence intervals crossing a minimally important difference or small total sample size); and 5) Publication bias (assessed using funnel plot inspection when ≥ 10 studies were available). Disagreements were resolved by consensus. The final certainty ratings were categorized as high, moderate, low, or very low. A GRADE evidence profile (Summary of Findings) table summarizing the ratings, reasons for downgrading, and the magnitude of effects for each key comparison are provided as [Supplementary Table 1](#).

Results

Study selection

The systematic literature search identified 623 records from databases and additional sources. After removing 112 duplicates, 511 unique records remained for title and abstract screening. During this initial screening, 421 records were excluded as irrelevant. Subsequently, 100 records underwent further eligibility assessment, of which 30 were excluded, leaving 70 full-text articles for detailed evaluation. Following full-text review, 40 articles were excluded due to reasons such as interventions or outcomes not meeting the inclusion criteria. A total of 20 RCTs [10-29] were included in the meta-analysis. The study selection process is presented in the PRISMA flowchart (**Figure 1**).

Characteristics of the included studies

Table 1 presents the main characteristics of the 20 included RCTs [10-29]. These studies were published between 2011 and 2023. Sample sizes varied, with furcation defects ranging from 12 to 105. Most studies were con-

ducted in India (n = 19) [10-20, 22-27, 29], and one study was carried out in Italy [21].

Of the included studies, four [22, 25, 27, 29] involved both maxillary and mandibular molars, while the remaining studies focused on Degree II furcation defects in the mandibular molars. The follow-up durations ranged from 6 to 12 months, with eleven studies [13, 15, 16, 18-20, 22, 23, 25, 27, 29] at 6 months, eight studies [10-12, 14, 17, 24, 26, 28] at 9 months, and one study [25] at 12 months.

The intervention measures were classified into four categories for analysis: PRF alone: Compared to OFD alone [10-14, 17] or other active controls like PRP [11], BG [13, 15, 16], bioactive glass [15], recombinant human bone morphogenetic protein-2 (rhBMP-2) [26], or collagen membranes [23].

PRF + BG: Compared to BG alone [18-21, 24, 28] or as a combined treatment (PRF + BG) compared with PRF alone [17].

PRF + medications: This involved combining PRF with different topical medications, including 1% metformin gel [15, 25, 27], 1% alendronate gel [14, 22], 1% melatonin gel [29], and 1.2% rosuvastatin gel [28].

PRF + membrane: PRF compared to a collagen membrane [23], or combined with an amniotic membrane [19].

PD, VCAL/RVCAL, and HCAL/RHCAL were the main outcomes assessed across the studies. The radiographic results (e.g., bone fill percentage, defect depth reduction) were frequently evaluated.

Due to the limited number of studies investigating PRF with membrane, a meta-analysis could not be performed for this specific subgroup.

PD/PPD

The effect of PRF alone, PRF + BG, and PRF + medications on PD in patients with periodontal furcation defects was evaluated through the meta-analysis. PRF combined with membrane materials could not be included in the meta-analysis due to limited numbers of studies.

Overall effect analysis: The random-effects model meta-analysis included 18 studies (**Figure 3**). Compared to control groups, PRF

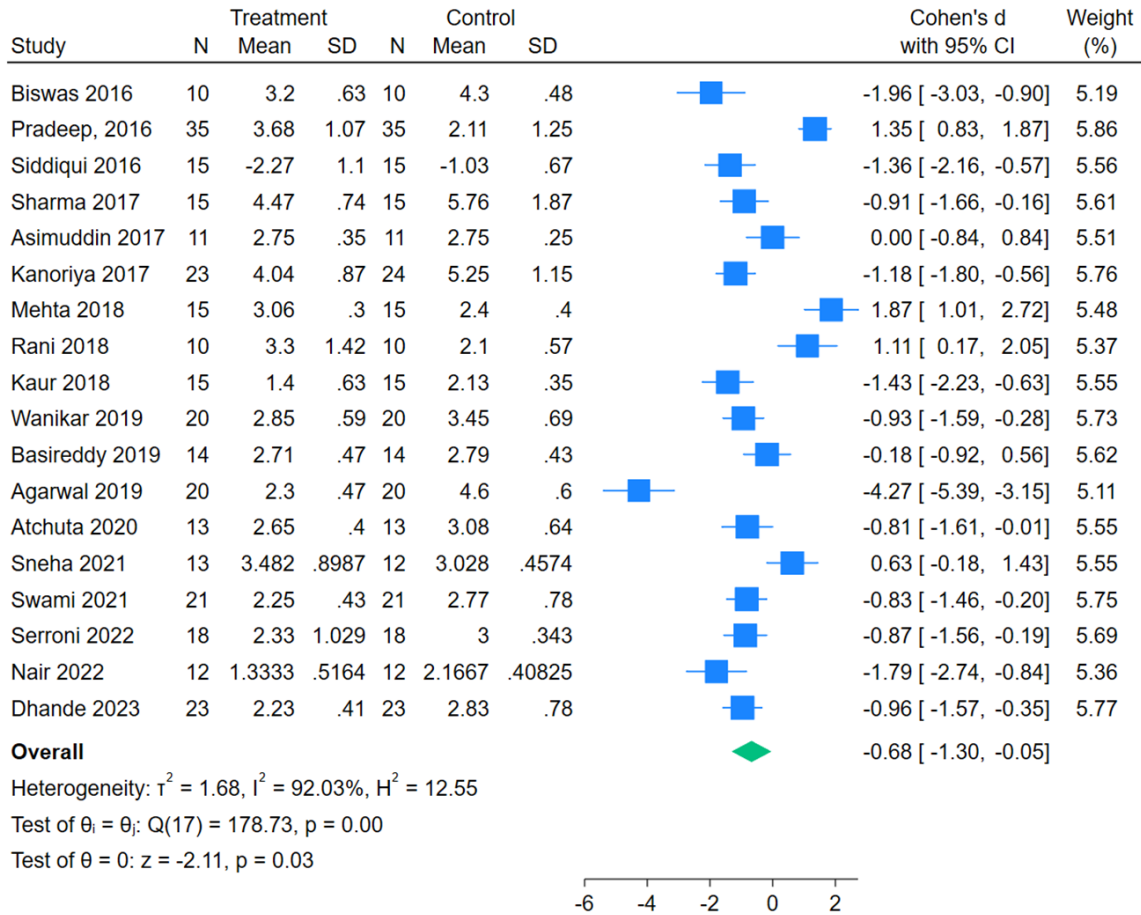
Platelet-rich fibrin for periodontal furcation defect

Table 1. Main characteristics of the 20 RCTs included in this study investigating furcation defects treated with PRF

No.	First Author/Year	Country	Study Design	Sample Size (Patients/ Defects)	Furcation Site	Staging/ Grading	Follow-up	Intervention	Group (I)	Control Group (C)	Primary Outcome Variables
1	Sharma 2011 [10]	India	Split-mouth, double-blind RCT	18/36	Mandibular molars	Degree II	9 months	PRF + OFD		OFD	RVCAL, RHCAL, bone defect depth
2	Bajaj 2013 [11]	India	Three-arm parallel RCT	42/72	Mandibular molars	Degree II (Hamp)	9 months	PRF + OFD		PRP + OFD; OFD	RVCAL, RHCAL, bone fill %
3	Biswas 2016 [12]	India	Two-arm parallel RCT	15/20	Mandibular molars	Degree II (Glickman)	9 months	PRF		Bioactive glass putty	VPD, HPD, CAL, bone density
4	Pradeep 2016 [13]	India	Three-arm, double-blind RCT	105/105	Mandibular molars	Degree II	9 months	1.2 mg RSV gel + PRF + Porous HA bone graft + OFD		OFD + Placebo gel; PRF + HA + OFD	Bone fill %, PD, RVCAL, RHCAL, IDD
5	Siddiqui 2016 [14]	India	Three-arm parallel RCT	31/45	Mandibular molars	Degree II	6 months	PRF		β-TCP; OFD	PPD, VCAL, HCAL, CBCT
6	Sharma 2017 [15]	India	Two-arm parallel RCT	22/30	Mandibular molars	Degree II	6 months	PRF + 1% metformin gel		PRF	PD, RVAL, RHAL, IDD
7	Asimuddin 2017 [16]	India	RCT	22/22	Mandibular molars	Degree II	9 months	PRF (graft + membrane)		Allograft + GTR	PI, PD, RVCAL, RHCAL, GML, RVGBF
8	Kanoriya 2017 [17]	India	RCT	72/72	Mandibular molars	Degree II	9 months	PRF + 1% ALN gel		PRF alone, OFD	PD, RVAL, RHAL, bone fill %
9	Mehta 2018 [18]	India	Split-mouth RCT	18/36	Mandibular molars	Degree II	6 months	DFDBA + PRF		DFDBA + Collagen membrane	PD, RVCAL, RHCAL, bone fill
10	Rani 2018 [19]	India	RCT	20/20	Mandibular molars	Degree II	6 months	β-TCP + PRF membrane		β-TCP alone	PPD, CAL, GR, VDD, HDD
11	Kaur 2018 [20]	India	Split-mouth RCT	15/30	Mandibular molars	Degree II	6 months	PRF + Amnion membrane		PRF alone	PI, GI, PPD, RAL, defect depth, bone fill
12	Wanikar 2019 [21]	India	Split-mouth RCT	20/40	Maxillary & mandibular molars	Degree II	6 months	PRF + 1% alendronate gel		PRF	PPD, CAL, HPD, CBCT-DV
13	Basireddy 2019 [22]	India	Split-mouth RCT	14/28	Mandibular molars	Degree II	6 months	DFDBA + PRF		DFDBA alone	PD, RVCAL, RHCAL, GML, VDD, HDD
14	Agarwal 2019 [23]	India	RCT	46/60	Mandibular molars	Degree II	9 months	PRF + DFDBA + OFD		OFD, PRF + OFD	VPD, VCAL, GML, HPD, VBF, HBF
15	Atchuta 2020 [24]	India	RCT	39 sites	Intrabony	Chronic periodontitis	6 months	DFDBA + PRF		OFD, DFDBA alone	PPD, RAL, RBF
16	Sneha 2021 [25]	India	Two-arm parallel RCT	25/32	Maxillary & mandibular molars	Degree II	6 months	PRF		rhBMP-2 + collagen sponge	PPD, CAL, digital subtraction bone area
17	Swami 2021 [26]	India	Split-mouth, double-blind RCT	21/42	Maxillary & mandibular molars	Degree II	12 months	PRF + 1% metformin gel		PRF	CAL, HPD, CBCT-DV
18	Serroni 2022 [27]	Italy	Three-arm parallel RCT	54/54	Mandibular molars	Degree II	6 months	ABG + L-PRF		ABG; OFD	HCAL, VCAL, PD, VBL
19	Nair 2022 [28]	India	RCT	12/12	Mandibular molars	Degree II	9 months	Nano-HA + i-PRF		Nano-HA alone	PI, GI, PPD, CAL, HPD, VPD, BAF
20	Dhande 2023 [29]	India	Split-mouth, double-blind RCT	23/46	Maxillary & mandibular molars	Degree II	6 months	PRF + 1% melatonin gel		PRF	PPD, CAL, HPD, CBCT-DV

ABG: autogenous bone graft; ALN: alendronate; BAF: bone area fill; β-TCP: β-tricalcium phosphate; CAL: clinical attachment level; CBCT: cone-beam computed tomography; DFDBA: demineralized freeze-dried bone; DV: defect volume; GI: gingival index; GML: gingival marginal level; GTR: guided tissue regeneration; HA: hydroxyapatite; HBF: horizontal bone fill; HCAL: horizontal clinical attachment level; HDD: horizontal defect depth; HPD: horizontal probing depth; IDD: intrabony defect depth; i-PRF: injectable-platelet-rich fibrin; L-PRF: leukocyte and platelet-rich fibrin; OFD: open flap debridement; PD: probing depth; PPD: probing pocket depth; PRF: platelet-rich fibrin; RBF: radiographic bone fill; RCT: randomized controlled trials; rhBMP-2: recombinant human bone morphogenetic protein-2; RHCAL: relative horizontal clinical attachment level; RSV: rosuvastatin; RVCAL: relative vertical clinical attachment level; RVGBF: bone fill using radio-visiography; VBL: vertical bone level; VCAL: vertical clinical attachment level; VBF: vertical bone fill; VPD: vertical probing depth. Controls were heterogeneous across studies and included both passive surgical controls (e.g., OFD alone) and active regenerative comparators (e.g., bioactive glass putty, β-TCP, PRF alone, or PRP). Sample size was reported as patients and analyzed sites/defects whenever available. For split-mouth or site-based studies, the second number refers to the number of sites/defects rather than the number of individual patients.

Platelet-rich fibrin for periodontal furcation defect



Random-effects REML model

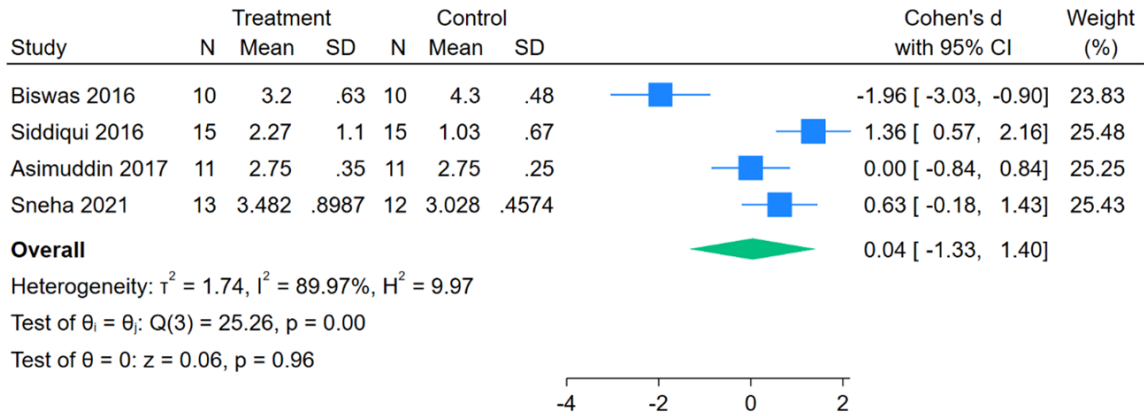
Figure 3. Forest plot of the overall effect of PRF and its combinations on PD. Note: This figure summarizes all included studies, showing the standardized mean difference (Cohen's d) and 95% confidence intervals for PD improvement in the PRF intervention groups compared to controls. PRF: platelet-rich fibrin; PD: probing depth.

and its combinations were associated with a significant reduction in PD (overall effect size: Overall Cohen's d = -0.68, $P = 0.03$). The studies exhibited high heterogeneity ($I^2 = 92.03\%$, $\tau^2 = 1.68$, $P < 0.001$), indicating the need for subgroup analyses to explore sources of variability. Notably, the magnitude of the overall effect (Cohen's d = -0.68) was smaller than that observed in the PRF combined therapy subgroup (Cohen's d = -0.97). This discrepancy can be attributed to the inclusion of PRF monotherapy studies in the overall analysis, which demonstrated minimal or non-significant effects and therefore diluted the pooled effect size. In contrast, PRF combination therapies, particularly those involving bioactive molecules or BG, consistently showed stronger clinical efficacy, thereby driving the larger effect size observed in subgroup analyses.

PRF alone: The effect of PRF alone on PD was investigated in four studies (Figure 4). According to the pooled analysis finding, PD was not significantly reduced in the PRF (Cohen's d = 0.04, 95% CI: -1.33 to 1.40, $P = 0.96$). Significant heterogeneity was observed ($I^2 = 89.97\%$, $\tau^2 = 1.74$, $P < 0.001$), indicating that the findings should be interpreted with caution. The high heterogeneity likely stems from the limited number of studies, their generally small sample sizes, and the clinical diversity introduced by varying control interventions. Consequently, these findings should be interpreted with considerable caution, and no definitive conclusion regarding the efficacy of PRF monotherapy for PD reduction can be drawn from this subset of data.

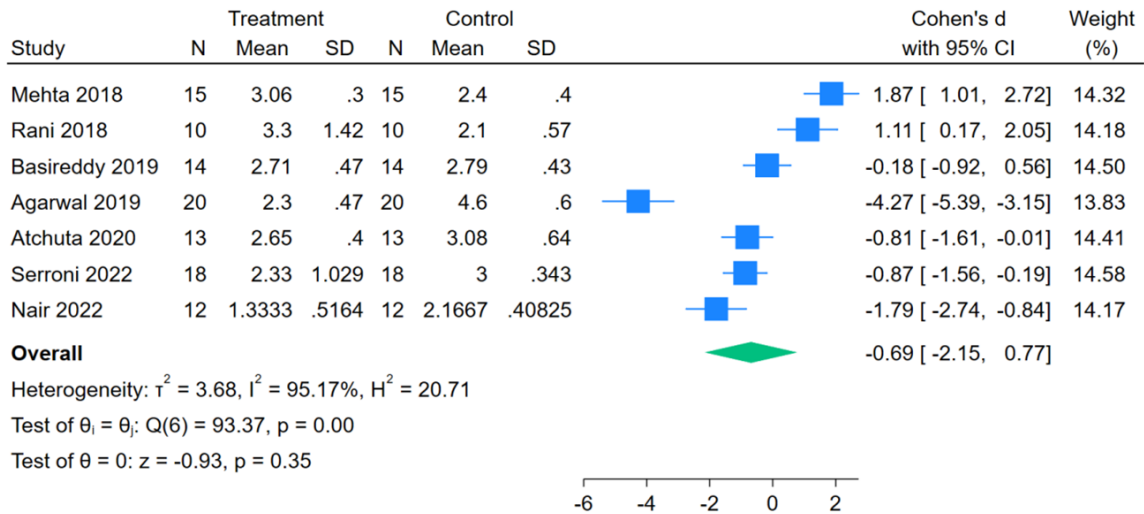
PRF combined with BG: The effect of PRF combined with BG on PD was studied in seven arti-

Platelet-rich fibrin for periodontal furcation defect



Random-effects REML model

Figure 4. Forest plot of the effect of PRF alone on PD. Note: This subgroup analysis compares PRF alone versus control groups in terms of PD improvement. PRF: platelet-rich fibrin; PD: probing depth.



Random-effects REML model

Figure 5. Forest plot of the effect of PRF combined with bone grafts on PD. Note: This figure presents the effect of combining PRF with bone grafts on PD reduction compared to control groups. PRF: platelet-rich fibrin; PD: probing depth.

cles (**Figure 5**). The pooled effect size was Cohen's $d = -0.69$ (95% CI: -2.15 to 0.77). This indicated that PD was significantly decreased ($P < 0.05$). Heterogeneity was moderate to high ($I^2 = 95.17\%$, $\tau^2 = 3.68$, $P < 0.001$), possibly due to variations in graft materials and surgical technique.

PRF combined with medications: Five studies analyzed the effect of PRF combined with medications (e.g., statins, bisphosphonates) on PD (**Figure 6**). The results showed a significant reduction in PD (Cohen's $d = -0.97$, 95% CI: -1.26 to -0.68, $P < 0.001$) with low heterogeneity

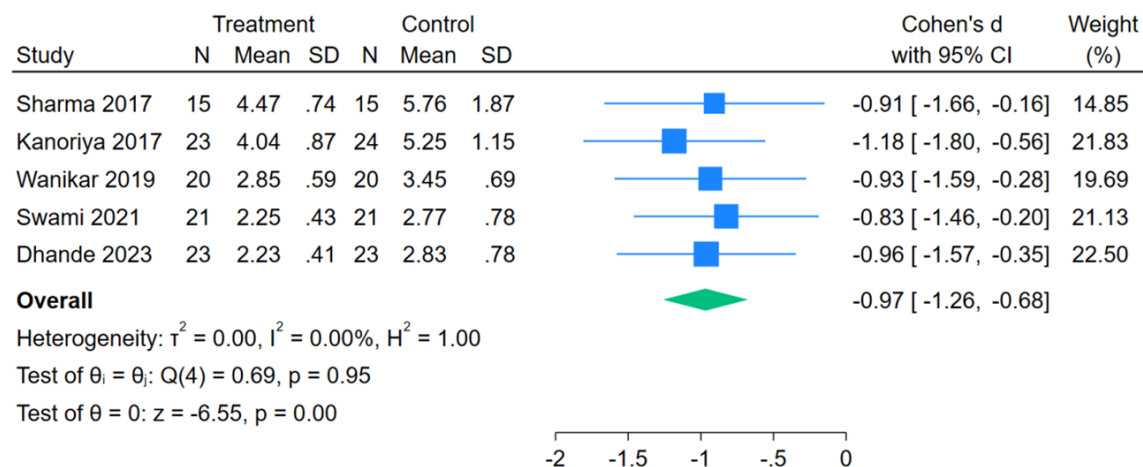
($I^2 = 0.00\%$, $\tau^2 = 0.00$, $P = 0.95$), indicating consistent findings across studies.

PRF combined with membrane materials: Only one study reported the effect of PRF combined with membrane materials on PD, precluding meta-analysis. Although this study suggested a possible benefit in PD reduction, evidence remains limited and requires further validation.

CAL, VCAL/RVCAL, and HCAL/RHCAL

This section evaluates the effects of PRF alone or in combination with various biomaterials on

Platelet-rich fibrin for periodontal furcation defect



Random-effects REML model

Figure 6. Forest plot of the effect of PRF combined with drugs on PD. Note: This subgroup displays the standardized mean difference and confidence intervals for PD improvement with PRF and drug combinations. PRF: platelet-rich fibrin; PD: probing depth.

CAL in patients with periodontal furcation defects. Seventeen studies were included in the random-effects meta-analysis (**Figure 7**). The pooled results showed that PRF interventions significantly improved CAL (Cohen's $d = 0.94$, 95% CI: 0.46-1.41, $P < 0.001$). Significant heterogeneity was observed among the included studies ($I^2 = 85.70\%$, $\tau^2 = 0.85$, $P < 0.001$), indicating the need for subgroup analysis to investigate the effects of various intervention strategies.

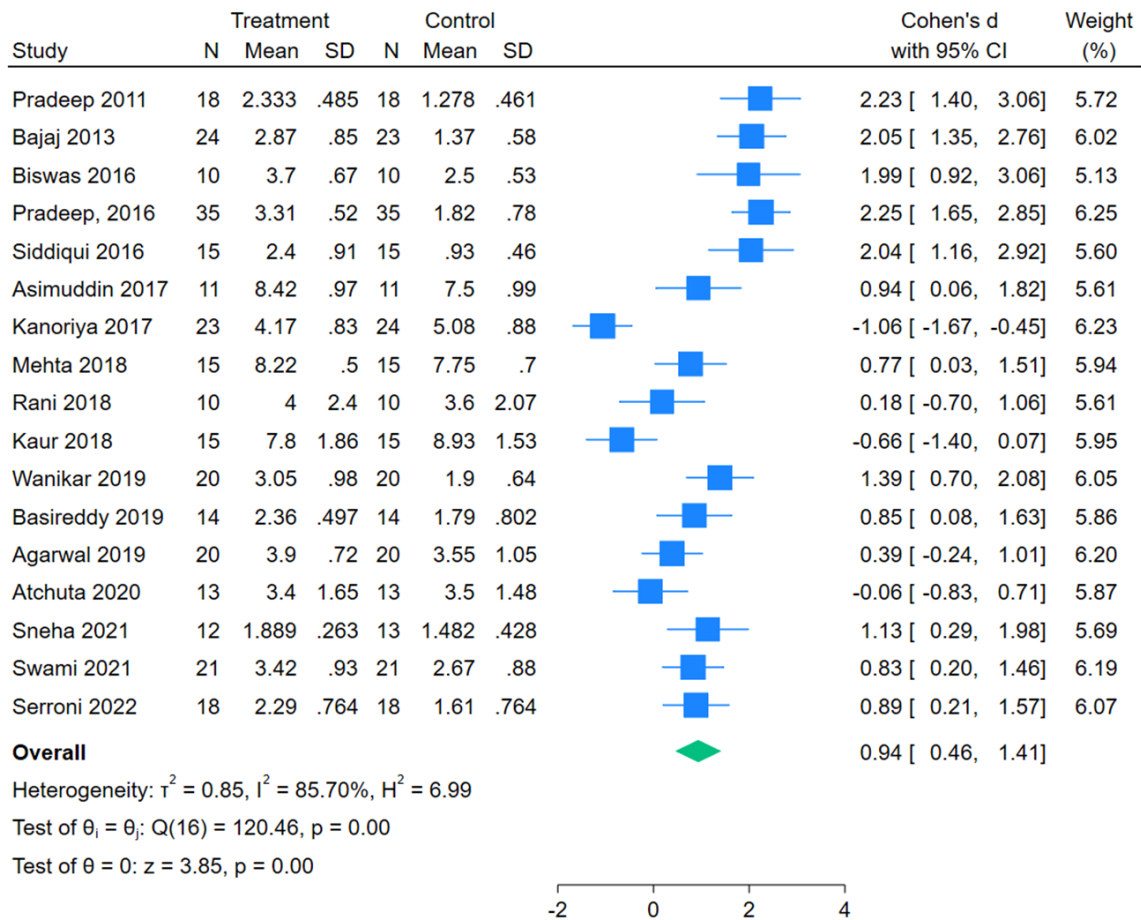
PRF alone: The effect of PRF alone on CAL was evaluated in four studies (**Figure 8**). The pooled analysis showed no significant difference in CAL gain between the PRF and control groups (Cohen's $d = 1.49$, 95% CI: 0.93-2.05, $P = 0.96$). Significant heterogeneity was observed among the studies ($I^2 = 33.61\%$, $\tau^2 = 0.11$, $P = 0.21$). The heterogeneity observed in the PRF monotherapy subgroup is likely attributable, at least in part, to differences in comparator type across the included studies. Specifically, PRF alone was compared not only with passive surgical controls such as OFD alone, but also with active regenerative controls such as bioactive glass putty and β -TCP. Because these control interventions differ markedly in biological activity and clinical efficacy, the pooled estimate for the PRF-alone subgroup should be interpreted with caution.

PRF with BG: The effect of PRF with BG on CAL was explored in seven studies (**Figure 9**). The

pooled effect size showed no significant difference (Cohen's $d = 0.33$, 95% CI: -0.13 to 0.79, $P = 0.16$). Moderate heterogeneity was observed ($I^2 = 61.68\%$, $\tau^2 = 0.24$, $P = 0.02$), which may be due to changes in graft materials and defect configurations.

PRF combined with medications: The effect of PRF combined with medications (e.g., alendronate, metformin) on CAL was investigated in four studies (**Figure 10**). The pooled effect size showed no significant difference (Cohen's $d = 0.56$, 95% CI: -0.53 to 1.64, $P = 0.32$). This subgroup showed high heterogeneity ($I^2 = 91.44\%$, $\tau^2 = 1.13$, $P < 0.001$). Notably, the direction of the effect size varied across studies. For instance, Kanoriya et al. (2017) [17] reported a negative effect size, whereas the other three studies showed positive effects. This apparent discrepancy is methodologic rather than clinical. In the study by Kanoriya et al. [17], the intervention (PRF + 1% alendronate gel) was compared to an active control (PRF alone), rather than with OFD alone. In this context, a negative effect size indicates that the combination therapy was superior to PRF monotherapy for CAL gain. In contrast, the other studies compared PRF + drug to OFD alone, where a positive effect size favors the combination therapy. Therefore, the opposing signs in the forest plot reflect differences in comparator selection and do not imply contradictory clinical outcomes. The high heterogeneity likely stems from these methodologic variations, in addition to differ-

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Random-effects REML model

Figure 7. Forest plot of the overall effect of PRF and its combinations on CAL. Note: This figure presents the standardized mean difference (Cohen's d) and 95% confidence intervals for CAL improvement in the PRF intervention groups compared to control groups across all included studies. PRF: platelet-rich fibrin; CAL: clinical attachment level.

ences in drug types, concentrations, and delivery methods.

PRF integrated with membrane materials: The effect of PRF integrated with an amnion membrane on CAL was reported in one study (Kaur and Bathla 2018). This study suggested a positive trend toward CAL gain with the combination therapy. However, quantitative synthesis was not feasible due to the limited number of studies available, and this preliminary finding should be verified by more high quality work.

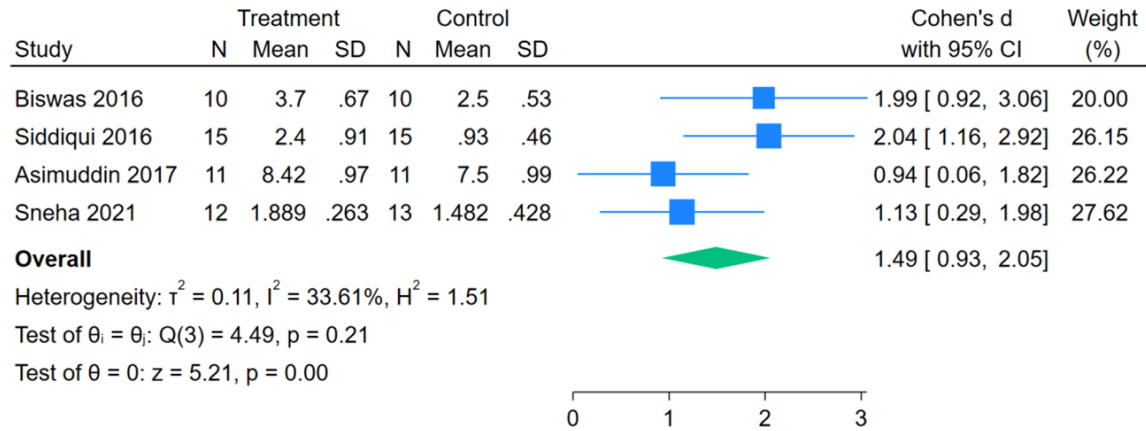
Bone regeneration effect (Bone Fill %/Defect Depth Reduction/RBF)

This meta-analysis assessed the effect of PRF on bone regeneration outcome in periodontal furcation defects. Bone regeneration was eval-

uated using bone fill percentage, defect depth reduction, and RBF. The subgroup analyses were performed based on intervention types, including PRF alone, PRF with BG, and PRF with medications. Since only one study (Kaur and Bathla 2018) explored PRF combined with membrane materials, this subgroup was not included in the meta-analysis.

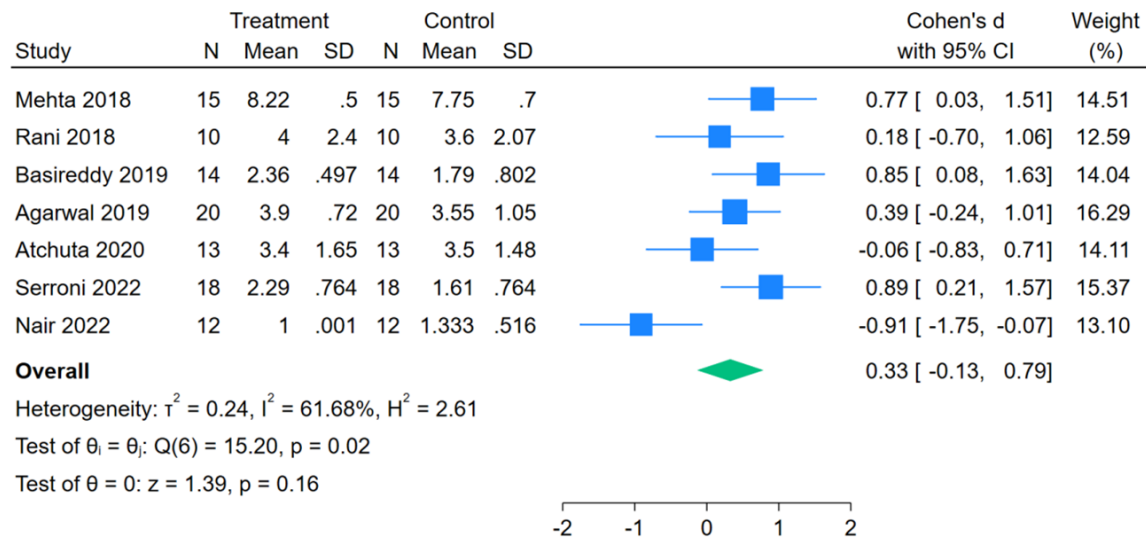
Overall effect analysis: The meta-analysis of random-effects model included 17 studies (Figure 11). The results showed that PRF and its combinations were associated with significantly better bone regeneration outcomes compared with the control groups (overall effect size: Cohen's $d = 2.04$, 95% CI: 0.51-3.56, $P = 0.01$). Significant heterogeneity was observed among the studies ($I^2 = 98.42\%$, $\tau^2 = 10.03$, $P < 0.001$), indicating the need for sub-

Platelet-rich fibrin for periodontal furcation defect



Random-effects REML model

Figure 8. Forest plot of the effect of PRF alone on CAL. Note: This subgroup analysis compares PRF alone versus control groups in terms of CAL gain. PRF: platelet-rich fibrin; CAL: clinical attachment level.



Random-effects REML model

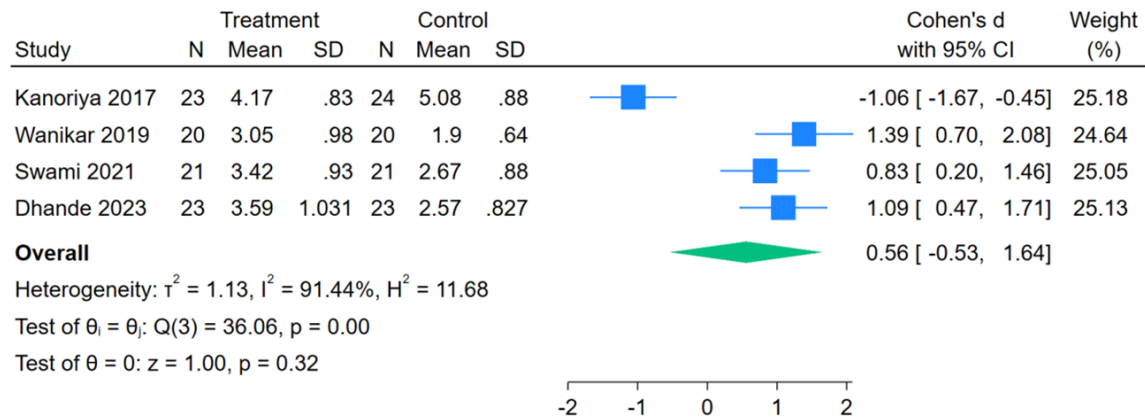
Figure 9. Forest plot of the effect of PRF combined with bone grafts on CAL. Note: This figure shows the effect of combining PRF with bone grafts on CAL gain compared to control groups. PRF: platelet-rich fibrin; CAL: clinical attachment level.

group analyses to explore potential sources of variability. This extremely high heterogeneity may be attributed partly to differences in imaging modalities and measurement protocols across studies.

PRF alone: The effect of PRF alone on bone regeneration outcomes was reported in two studies (Figure 12). The pooled analysis result showed no significant difference in bone regeneration between the PRF and control groups (Cohen's $d = 1.67$, 95% CI: -1.30 to 4.63, $P =$

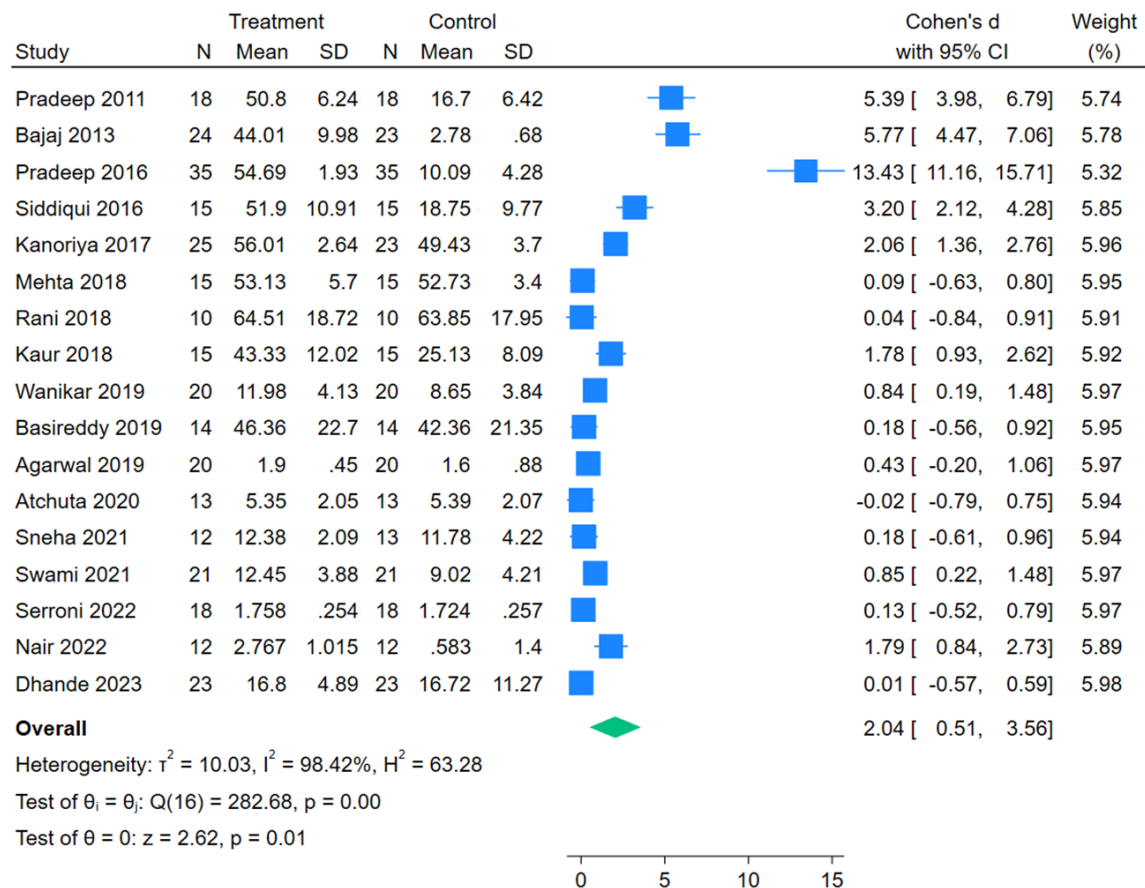
0.27). This subgroup showed significant heterogeneity ($I^2 = 94.91\%$, $\tau^2 = 4.34$, $P < 0.001$). It is critical to emphasize that this pooled result is highly unstable and exploratory due to the following reasons: First, the analysis was underpowered and vulnerable to outlier influence, being based on only two studies with limited sample sizes. Second, the two studies employed different radiographic assessment methods, which may have substantially influenced bone fill measurements. Third, variations in initial defect morphology and depth between

Platelet-rich fibrin for periodontal furcation defect



Random-effects REML model

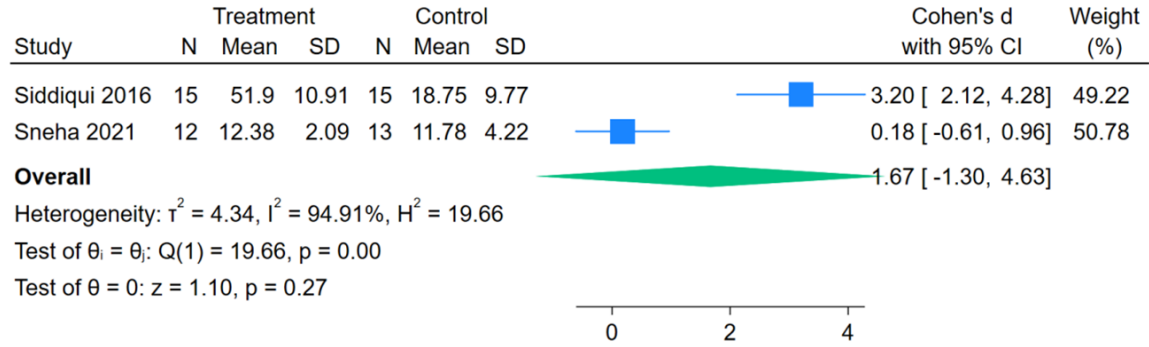
Figure 10. Forest plot of the effect of PRF combined with drugs on CAL. Note: This subgroup displays the standardized mean difference and confidence intervals for CAL improvement with PRF and drug combinations. Comparator types were heterogeneous across studies: Kanoriya et al. (2017) used PRF alone as an active control, whereas the remaining studies used OFD alone as passive controls. PRF: platelet-rich fibrin; CAL: clinical attachment level.



Random-effects REML model

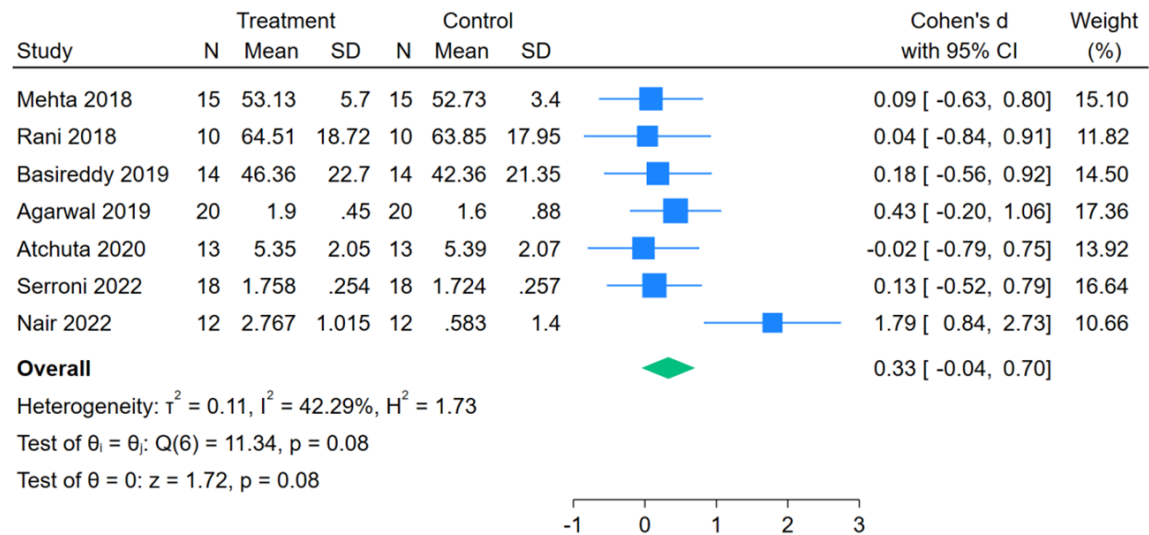
Figure 11. Forest plot of the overall effect of PRF and its combinations on bone regeneration outcomes. Note: This figure summarizes the standardized mean difference (Cohen's d) and 95% confidence intervals for the improvement in bone regeneration outcomes in PRF intervention groups compared to control groups across all included studies. PRF: platelet-rich fibrin.

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Random-effects REML model

Figure 12. Forest plot of the effect of PRF alone on bone regeneration outcomes. Note: This subgroup analysis compares PRF alone with heterogeneous control groups for bone regeneration outcomes. Controls included both passive surgical comparators and active regenerative materials; therefore, the pooled estimate should be interpreted cautiously. PRF: platelet-rich fibrin.



Random-effects REML model

Figure 13. Forest plot of the effect of PRF combined with bone grafts on bone regeneration outcomes. Note: This figure presents the effect of combining PRF with bone grafts on bone regeneration improvement compared to control groups. PRF: platelet-rich fibrin.

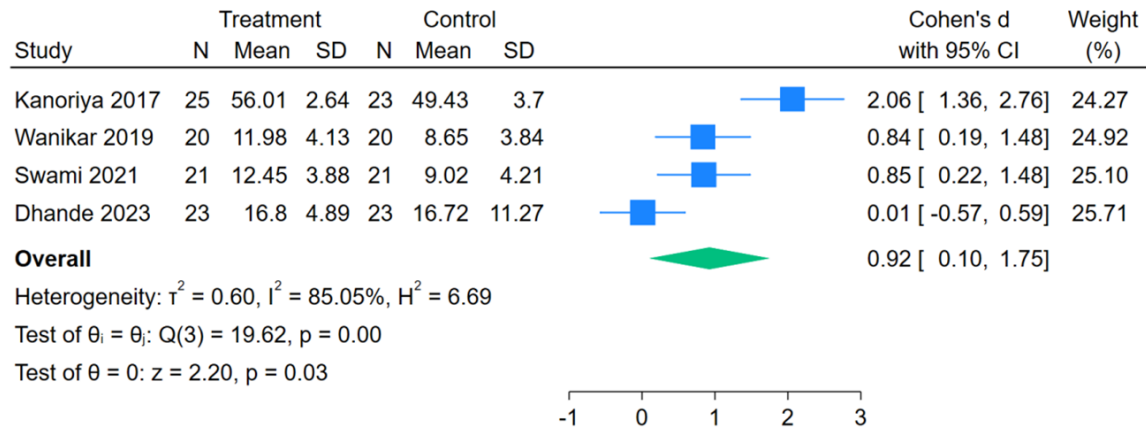
studies could have further contributed to the disparate treatment effects observed. Therefore, the enormous effect size should not be interpreted as a robust estimate of PRF monotherapy's efficacy for bone regeneration. Instead, these findings were purely hypothesis-generating. This finding warrants investigation in larger, methodologically uniform trials but provides no conclusive evidence regarding the superiority of PRF alone over the comparators used in these specific studies.

PRF integrated with BG: The effect of PRF integrated with BG on bone regeneration was

reported in seven studies (**Figure 13**). The pooled effect size exhibited a significant improvement in bone regeneration (Cohen's $d = 0.33$, 95% CI: -0.04-0.70, $P = 0.08$). Moderate heterogeneity was observed among the studies ($I^2 = 42.29\%$, $\tau^2 = 0.11$, $P = 0.08$), which may be caused by changes in graft materials and surgical methods.

PRF integrated with medications: The effect of PRF integrated with medications (e.g., statins, bisphosphonates) on bone regeneration was investigated in four studies (**Figure 14**). The findings revealed a significant improvement in

Platelet-rich fibrin for periodontal furcation defect



Random-effects REML model

Figure 14. Forest plot of the effect of PRF combined with drugs on bone regeneration outcomes. Note: This subgroup displays the standardized mean difference and confidence intervals for the improvement in bone regeneration with PRF and drug combinations. PRF: platelet-rich fibrin.

bone regeneration, with a Cohen's d of 0.92, 95% CI 0.10-1.75, and $P = 0.03$. The heterogeneity was low, with $I^2 = 85.05\%$, $\tau^2 = 0.60$, and $P = 0.00$. This indicated high consistency among the included studies.

PRF integrated with membrane materials: The effect of PRF integrated with an amnion membrane on bone regeneration was reported in only one study (Kaur and Bathla 2018). This study suggested a positive trend toward bone fill with the combined therapy. However, quantitative synthesis was not feasible due to the limited number of available studies, and this preliminary finding should be verified by more high quality work.

Sensitivity analysis

Leave-one-out sensitivity analyses were conducted to evaluate the influence of individual studies on the pooled effect estimates for the three primary outcomes: overall PD reduction, CAL gain, and bone regeneration. In summary, the direction and statistical significance of the pooled effect sizes for the primary outcomes were not substantially altered by the exclusion of any single study, supporting the robustness of our main findings. However, the consistently high I^2 values across all iterations confirm that the substantial statistical heterogeneity was an inherent feature of the dataset and not driven by an outlier study. A comprehensive table detailing the effect size and I^2 after each exclu-

sion is provided in [Supplementary Figures 1, 2, 3](#).

Discussion

This meta-analysis evaluated the effectiveness of PRF as a regenerative adjunct in the treatment of periodontal furcation defects. The pooled results confirm that PRF, particularly when combined with BG or specific biomolecules, significantly improved clinical and imaging outcomes compared to OFD alone. However, these findings should be interpreted in the context of substantial heterogeneity and complex underlying biological mechanisms. The seemingly simple benefits are actually the result of complex interactions between the inherent properties of biomaterial, defect configuration, and strategies for integrating it with other agents [7, 30]. This finding suggests that PRF alone may have limited efficacy, whereas its combination with other regenerative materials produces synergistic effects, highlighting the importance of adjunctive strategies in periodontal regeneration.

Interpretation of principal findings and biological plausibility

PRF is expected to provide better outcomes compared to OFD alone. While OFD promotes repair primarily through a long junctional epithelium, PRF introduces a fibrin scaffold enriched with platelets and leukocytes and

releases growth factors such as platelet-derived growth factor, transforming growth factor- β , and vascular endothelial growth factor over time [31]. This bioactive environment may facilitate angiogenesis, recruit stem cells, and modulate inflammatory responses, thereby enhancing regeneration [32]. It is critical to reconcile the seemingly contradictory findings between the overall analysis and subgroup analyses. The significant reduction in PD observed in the overall analysis is primarily attributable to the effects of PRF combination therapies, particularly with bone grafts and bioactive drugs. In contrast, the subgroup analysis of PRF alone demonstrated no significant benefit for PD reduction, a finding compounded by high heterogeneity. This indicates that while PRF serves as a valuable bioactive adjunct, its regenerative capacity in complex furcation defects may be maximized not through monotherapy but through strategic combination with osteoconductive scaffolds or osteopromotive agents. However, it should be noted that using PRF alone did not always significantly improve CAL and bone regeneration compared to other active controls. This means that although fibrin matrix effectively supports wound healing and soft tissue growth, it lacks osteoconductive rigidity and space-maintaining features necessary for regeneration within complex, debris-prone anatomical structures such as furcation defects [33]. This helps explain why combining PRF with BG like DFDBA or β -TCP is more effective. The graft maintains defect volume as a scaffold, while PRF provides osteoinductive and immunomodulatory signals, forming a synergistic “composite graft” system [33].

The findings should be interpreted with caution due to limited evidence quality derived from studies evaluating PRF integrated with metformin, statins, and bisphosphonates. The significant and homogeneous improvements are observed, indicating that it is a targeted, drug-enhanced regeneration strategy. Metformin, beyond its hypoglycemic effect, activates AMPK pathways, promotes osteoblastic differentiation, and inhibits osteoclastogenesis [34]. Similarly, statins stimulate BMP-2 expression and exert pleiotropic effects [35]. Local delivery of these agents by a PRF matrix allows high concentrations at the defect site, potentially overcoming the limitations of systemic delivery. This indicates a shift from passive, scaffold-

based PRF to active, drug-assisted regenerative therapy, and this concept gains attention in personalized periodontal medicine [7].

The apparent discrepancy between the significant overall effect and the unstable PRF monotherapy subgroup findings is likely explained by subgroup composition and comparator heterogeneity. While the overall analysis pooled all PRF-based interventions, the PRF-alone subgroup included studies using both passive surgical controls and active regenerative comparators, which are not clinically equivalent. This diversity of methods likely contributed to the substantial heterogeneity and limited the interpretability of the pooled monotherapy estimate.

Methodological consideration on effect direction in meta-analysis of active comparators

The interpretation of forest plots in this meta-analysis requires careful consideration of comparator types. As observed in the PRF-plus-drug subgroup for CAL outcomes, the direction of the standardized mean difference is contingent upon whether the experimental therapy is compared against a passive control or an active control. A negative d-value when compared to an active control may still represent clinical superiority, simply because the calculation yields a negative number if the intervention mean is lower (better) than the active control mean for CAL. This underscores a key challenge in synthesizing evidence from trials with varying control arms: the pooled effect size may be diluted or its direction obscured by these design differences, contributing to statistical heterogeneity. Our findings highlight the necessity of clear reporting of comparator types and cautious, context-driven interpretation of pooled estimates in regenerative periodontal therapy, where multiple bioactive strategies are often pitted against each other.

Comparison with existing systematic reviews

Our findings confirm and extend conclusions from recent authoritative reviews in this field. Miron et al. reported that PRF greatly improves the treatment of furcation defects, demonstrating effect comparable to other regenerative materials, while additionally providing biomolecular advantages [36]. Silva et al. reported that PRF is effective in managing intra-bony

defects [7]. In the present analysis, we quantitatively evaluated furcation defects and directly compared the effects of PRF alone, PRF with BG, and PRF with medication, thereby strengthening this evidence. These results further suggest that the main advantage of PRF may not lie in its use as a standalone material, but rather in its function as a multifunctional biological platform that enhances bone fill and serves as an effective carrier for osteopromotive agents.

The high heterogeneity observed in bone regeneration outcomes is likely driven by methodologic differences in imaging techniques. CBCT enables three-dimensional volumetric analysis, whereas conventional radiography provides two-dimensional measurements, leading to inconsistencies in outcome quantification. In addition, variations in defect morphology and measurement units may further contribute to heterogeneity.

Limitations and methodologic considerations

Statistical heterogeneity was high in this meta-analysis, with $I^2 > 90\%$ in several analyses. This is a key limitation, reducing the certainty of the pooled estimates. The heterogeneity reflects not only statistical variation but also marked differences in the clinical approach and method. These include variations in PRF preparation, such as different centrifugation speeds and times affecting fibrin structure and cell content [37], the use of various BG materials, including allografts, xenografts, and alloplasts, which differ in regenerative potentials, and the use of different types and concentrations of adjunctive biomolecules. Furthermore, most studies are mainly from a single region (India), which may limit the generalizability of the findings globally.

A specific and illustrative limitation concerns the meta-analysis of bone regeneration outcomes for PRF monotherapy. As presented in the results, the pooling of only two trials resulted in an implausibly large effect size with a confidence interval spanning from substantial harm to immense benefit, and extreme heterogeneity. This serves as a paradigmatic case of how meta-analyses with a very small number of component studies ($n \leq 2$) are methodologically frail. They are prone to produce unstable, exaggerated estimates that are disproportionately influenced by the specific characteristics and

results of each included study, such as differences in radiographic techniques and defect selection. Consequently, any quantitative estimate derived from this subgroup must be viewed as speculative. This confirms the principle that the reliability of a pooled effect size is not merely a function of statistical significance but fundamentally depends on the number, size, and methodological consistency of the contributing studies. Our decision to explicitly label these findings as “exploratory and hypothesis-generating” reflects this caution.

A clear gap in the current evidence system is the lack of human histologic data. While clinical and radiographic data are important, they cannot prove true regeneration of cementum, periodontal ligament, and alveolar bone. Theoretically, the clinical outcomes of PRF and its combinations are promising, reflecting an integration of repair and regeneration. Histomorphometric analysis of human biopsy specimens should be incorporated into future studies, thereby confirming their regenerative effects. Furthermore, the lack of subgroup analysis based on imaging modality represents a limitation and may have contributed to the observed heterogeneity.

Implications for clinical practice and future research

This meta-analysis shows that PRF serves as an effective adjunct in the treatment of periodontal furcation defects. The findings should be interpreted with caution due to limited evidence quality supporting its application in conjunction with BG or as a carrier for particular biomolecules. Additives should be selected based on the patient. For instance, local delivery of bisphosphonate, such as alendronate, through a PRF might be helpful for patients with periodontal disease and bone loss, since it has the ability to reduce bone resorption [38].

Future studies should change from testing whether PRF works to learning how it can be used in the best way. There is an urgent need for high-quality RCTs from multiple centers. These studies should use standardized PRF protocols and report relative centrifugal force rather than only RPM. The studies should directly compare different PRF combination therapies, include follow-up periods of 18-24 months to evaluate the stability of regenerated

tissue, and integrate biomarkers and histologic analyses to elucidate the underlying cellular and molecular mechanisms of observed clinical effects.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaoming Lou, Department of Stomatology, Shangguan Township Community Health Service Center, No. 301, Mu Village, Shanxi Village, Shangguan Township, Fuyang District, Hangzhou 311415, Zhejiang, China. Tel: +86-13868176235; E-mail: Dr_louxm@163.com

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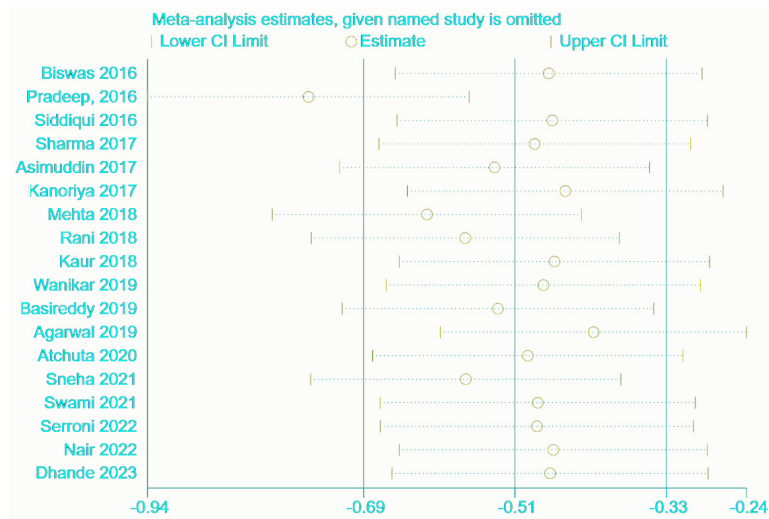
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Supplementary Table 1. GRADE evidence profile

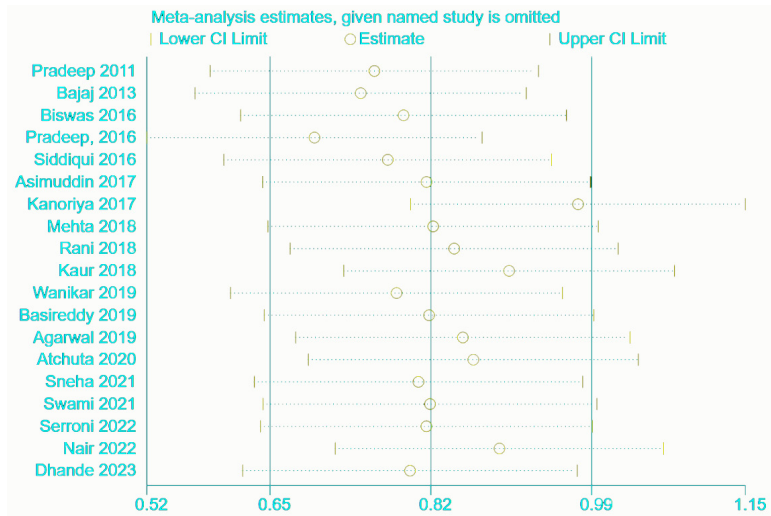
Outcome	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Probing depth reduction	SMD 0.97 lower	Cohen's d = -0.97 (-1.26-0.68)	606 (18)	⊕⊕○○	Downgraded for: 1. Inconsistency: Substantial heterogeneity that could not be fully explained by subgroup analyses.
Clinical attachment level gain	SMD 0.85 higher	Cohen's d = 0.85 (0.40-1.30)	659 (19)	⊕⊕○○	Downgraded for: 1. Inconsistency: Substantial heterogeneity ($I^2 = 85.70\%$). 2. Imprecision: The 95% CI is wide, indicating some uncertainty in the effect estimate.
Radiographic bone regeneration	SMD 1.20 higher	Cohen's d = 1.20 (0.69-1.70)	618 (17)	⊕⊕○○	Downgraded for: 1. Inconsistency: Considerable heterogeneity, indicating large variations in the measurement and/or magnitude of bone regeneration effects across studies. 2. Imprecision: Wide confidence interval. 3. Indirectness: Bone regeneration was assessed radiographically, which is an indirect surrogate measure for histological new attachment.

95% CI: 95% confidence intervals; GRADE: Grading of Recommendations Assessment, Development and Evaluation; SMD: standardized mean differences.

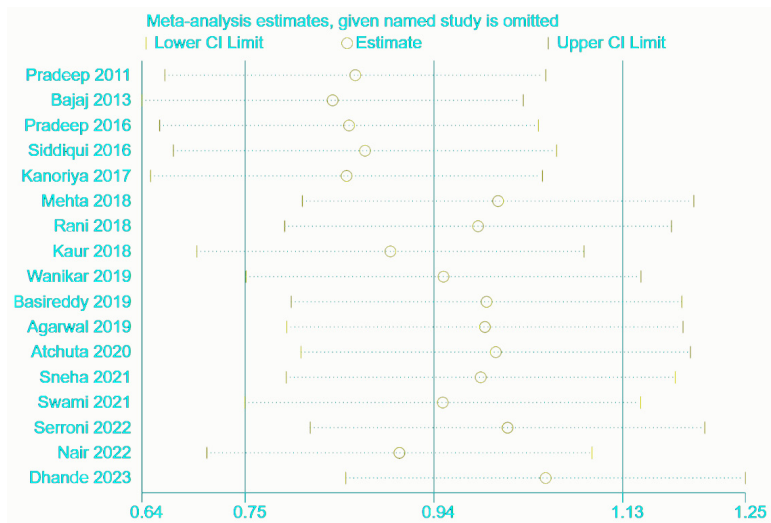


Supplementary Figure 1. Sensitivity analysis of probing depth (PD/PPD). PD: probing depth; PPD: probing pocket depth. Leave-one-out sensitivity analysis for the pooled effect size.

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Supplementary Figure 2. Sensitivity analysis of clinical attachment level. Leave-one-out sensitivity analysis for the pooled effect size.



Supplementary Figure 3. Sensitivity analysis of bone regeneration. Leave-one-out sensitivity analysis for the pooled effect size.