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Efficacy of concentrated growth factor combined with coronally advanced flap in the treatment of gingival recession: a systematic review and meta-analysis

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Abstract

Objectives This study aims to evaluate the efficacy of combining the coronally advanced flap (CAF) technique with concentrated growth factor (CGF) in the treatment of gingival recession (GR), and to compare this approach with other alternative treatments.

Methods This systematic review and meta-analysis included randomized controlled trials (RCTs) comparing CAF combined with CGF to other treatments for root coverage procedures. Included studies evaluated systemically healthy adults (> 18 years) with Miller Class I/II or Cairo RT1 gingival recessions. Primary outcomes were complete root coverage (CRC) and mean root coverage (MRC); secondary outcomes included changes in keratinized tissue width (KTW), gingival thickness (GT), clinical attachment level (CAL), recession width (RW), recession depth (RD), and probing depth (PD). A comprehensive search was conducted across multiple databases, including PubMed, Scopus, Cochrane Library, Web of Science, and Embase, up to November 9, 2024. The study protocol was prospectively registered in PROSPERO (CRD42024556815). Statistical analyses were performed using Review Manager 5.4.1.

Results Eight studies were included in the meta-analysis. Compared to CAF alone, the combination of CAF and CGF significantly improved CRC (OR = 1.79, $P = 0.04$), MRC (MD = 10.38%, $P = 0.04$), KTW (MD = 0.40 mm, $P = 0.02$), GT (MD = 0.26 mm, $P < 0.00001$), and CAL (MD = 0.36 mm, P = 0.03). CAF combined with connective tissue graft (CTG) showed superior efficacy for CRC compared to CAF + CGF (OR = 0.25, $P = 0.009$). However, no significant differences were found between CAF + CTG and CAF + CGF for MRC, CAL, KTW, RD, RW, or PD. Additionally, no significant differences were observed when comparing CAF + CGF with CAF + PRF across all clinical parameters (all $P > 0.05$).

Conclusions The findings of this meta-analysis indicate that CAF/CGF improves clinical outcomes in treating GR compared to CAF alone, and CGF may be a viable alternative to CTG when CTG is not applicable. Further studies are needed to validate the efficacy of CAF/CGF in the treatment of GR.

Clinical significance In cases where CTG is not applicable, CGF may serve as a viable alternative for the treatment of Miller class I and II GR.

Keywords Concentrated growth factor, Root coverage, Coronally advanced flap, Gingival recession, Meta-analysis

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Introduction

Gingival recession (GR) refers to the downward shift of the gingival margin past the cementoenamel junction [1]. This condition is commonly observed in adults and

increases with age [2]. Recent research has identified several potential causes of GR, such as traumatic toothbrushing, a thin gingival biotype, periodontal disease, and orthodontic tooth movement [3, 4]. Furthermore, GR is often associated with aesthetic concerns, frequently compelling patients to seek treatment. It is also linked to other issues, including tooth sensitivity, dental decay, and non-carious cervical lesions (NCCL) [2, 5].

The primary aims of treating GR are to achieve root coverage, arrest the progression of recession, improve aesthetics, and preserve oral functions such as prevention of dentinal hypersensitivity and mastication efficiency [6, 7]. GR defects can be treated with multiple techniques, such as guided tissue regeneration (GTR) [8], connective tissue graft (CTG) [9], coronally advanced flap (CAF) [10], and tunnel technique (TUN) [11]. The gold standard for treating GR is widely recognized as the combination of CTG and CAF [9]. Nevertheless, the CTG technique's disadvantages include the need to harvest grafts from the donor site, postoperative pain, and limited tissue availability [12, 13]. Consequently, alternative biomaterials and autologous platelet concentrates (APCs) are increasingly recognized as viable substitutes and adjunct therapeutic strategies, including platelet-rich fibrin (PRF) [14], amniotic membrane (AM) [15], and xenogeneic collagen matrix (XCM) [16].

Concentrated Growth Factor (CGF), introduced by Sacco in 2006, is generated through variable-speed centrifugation [17]. Compared to PRF, CGF exhibits superior tensile strength and higher levels of growth factors. Its interwoven fibrous structure provides relatively stiffer texture and a denser fibrin matrix, which enhances structural support and contributes to the formation of a durable biological scaffold. This scaffold supports the regeneration of both soft tissue and bone tissue [18, 19]. Additionally, it has a greater potential to promote the proliferation of osteoblasts and gingival fibroblasts [17, 20]. Recently, CGF has been widely applied in various dental procedures, such as extraction sockets, maxillary sinus lifting, and the treatment of gingival recession, yielding favorable results [21–23].

Several studies indicate that CGF enhances cell adhesion, migration, proliferation, differentiation, and induces angiogenesis [17, 24]. CGF also exhibits antimicrobial properties, regulates inflammation, and reduces the risk of infection, thereby accelerating wound healing and tissue repair [17, 25, 26]. Additionally, CGF elicits macrophage-driven immunomodulation, further enhancing its regenerative potential and establishing it as an effective therapeutic avenue for tissue regeneration [27]. Despite CGF's promising properties, there is limited evidence evaluating its clinical efficacy for managing gingival recession, particularly regarding root coverage and overall periodontal outcomes. Therefore, this research aims to assess the effectiveness of CAF combined with CGF for managing GR, compared to other available treatment modalities.

Materials and methods

The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024556815. Additionally, this systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28].

Focused PICOS questions

The Participants, Intervention, Comparison, Outcomes, and Study design (PICOS) framework for this study was applied as follows:

P – Individuals with gingival recession on maxillary or mandibular teeth.
I – Root coverage surgical technique using CAF in combination with CGF.
C – Using CAF without adjuncts or in conjunction with other treatment modalities for root coverage procedures.
O –– The primary outcomes were complete root coverage (CRC) and mean root coverage (MRC), while the secondary outcomes included increases in keratinized tissue width (KTW), gingival thickness (GT), and clinical attachment level (CAL), as well as reductions in recession width (RW), recession depth (RD), and probing depth (PD).
S – Randomized controlled trials (RCTs).

Search strategy

A comprehensive search was conducted in the following databases: PubMed/Medline, Scopus, Web of Science, EMBASE, and Cochrane Library, from their inception to November 9, 2024. The following MeSH terms and free-text keywords were used in the search strategy: "gingival recession", "gingival atrophy", "atrophy of gingiva", "concentrated growth factor", and "CGF". The search strategy involves using a combination of MeSH terms and free-text keywords, connected by 'OR' and 'AND', to search the electronic databases. The details of the search strategy for PubMed are provided in Table 1. In addition, gray literature was retrieved from databases such as Google Scholar, Open Grey, and ClinicalTrials. Furthermore, manual literature searches were carried out by reviewing relevant systematic reviews and the reference lists of

Table 1 Search strategy details for PubMed

No	Query
#1	Gingival Recession [MeSH Terms]
#2	(Gingival Recessions) OR (Recession, Gingival) OR (Recessions, Gingival) OR (Gingival Atrophy) OR (Gingival Atrophies) OR (Atrophy of Gingiva) OR (Gingiva Atrophies) OR (Gingiva Atrophy) OR (Miller class I) OR (Miller class II)
#3	#1 OR #2
#4	(Concentrated Growth Factor) OR (CGF)
#5	#3 AND #4

included studies. Each database's detailed search strategies are described in Supplementary Material 1.

Eligibility criteria

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs); (2) studies involving systemically healthy adults (> 18 years) with Miller's Class I or II (Cairo Class I) gingival recession on maxillary or mandibular teeth; (3) the intervention involved the combination of CAF and CGF for treating gingival recession; (4) the control group received CAF alone or with other root coverage treatments; (5) studies that reported relevant clinical outcomes; and (6) studies published in English.

The exclusion criteria were as follows: (1) Animal and in vitro research, retrospective studies, study protocols, review articles, and case reports. (2) Clinical trials that did not meet the study design criteria, such as those where the intervention was not the combination of CAF and CGF or lacked a relevant control group. (3) Studies that excluded participants with systemic diseases affecting oral health or other significant confounding factors (e.g., smoking, poor oral hygiene). (4) Studies with incomplete data (e.g., missing standard deviations, unreported follow-up periods). (5) Studies published in non-English languages.

Study selection

To ensure objectivity and reduce bias, the study selection process was independently carried out by two reviewers (Y.Y. and L.O.). Initially, the reviewers reviewed the titles and abstracts of all retrieved studies. At this stage, studies not meeting the pre-defined inclusion criteria were excluded. Following the preliminary screening, the remaining articles' full texts were carefully assessed for eligibility. Any discrepancies regarding whether to include or exclude the selected articles were settled through constructive dialogue with one of the reviewers (B.J.) to reach a consensus.

Data collection

Data extraction was conducted independently by two reviewers (Y.Y. and L.O.), while the accuracy of the extracted data was subsequently verified by the third reviewer (C.C.). The extracted information included year, author, sample size, study design, recession type, intervention and control groups, age, sex, follow-up, and study outcomes. Study outcomes, including means and standard deviations (SD), were either directly extracted or calculated from baseline and endpoint data for CRC, MRC, CAL, KTW, GT, PD, RW, and RD.

Risk of bias and quality assessment

The Cochrane Risk of Bias 2 (RoB 2) tool [29] was applied to evaluate the risk of bias in the included RCTs. The assessment covered five domains: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Based on the evaluation of these domains, each study was categorized into one of three risk levels: "high risk," "some concerns," or "low risk" of bias. Two reviewers (Y.Y. and L.O.) independently evaluated the risk of bias for each included RCT. Any differences were addressed by discussion with a third reviewer (B.J.).

Data analysis

In this systematic review and meta-analysis, the data analysis was conducted using Review Manager 5.4.1 (The Cochrane Collaboration, Copenhagen, Denmark). The intervention's effect on dichotomous outcomes (CRC) was presented as odds ratios (OR) with 95% confidence intervals (CI), whereas for continuous variables, mean differences (MD) with 95% CIs were calculated. Heterogeneity was assessed using the Cochran-Q test and the I^2 statistic. A random-effects model was applied when high heterogeneity ($I^2 \geq 50\%$) was present. When heterogeneity was low ($I^2 < 50\%$), a fixed-effects model was used. Results with substantial heterogeneity underwent sensitivity and subgroup analyses. Funnel plots and Egger's tests were employed to evaluate publication bias, with a p-value of < 0.05 considered statistically significant.

Results

Study search

The initial search process identified 512 articles for inclusion in this study, including 509 from electronic database searches and 3 additional articles through manual searching. After removing 92 duplicates, 409 articles were eliminated during title and abstract evaluation, while 3 articles were further eliminated after full-text review due to irrelevant categorization and non-English articles.

Finally, 8 studies [23, 30–36] were selected for inclusion, and Fig. 1 presents a flowchart outlining the literature search and screening process.

Characteristics of included studies

A total of eight (RCTs) [23, 30–36] were selected, consisting of two studies with a parallel design [32, 36] and six studies with a split-mouth design [23, 30, 31, 33–35]. These studies involved 131 participants, comprising 479 cases of gingival recessions treated. The follow-up periods spanned from 3 to 6 months (mean = 5.6 months), and participants' ages ranged from 18 to 65 years. Four studies compared CAF/CGF vs. CAF [23, 31, 32, 34], three studies compared CAF/CGF vs. CAF/CTG [30, 33, 36], and a single study compared CAF/CGF vs. CAF/PRF [35]. Study characteristics are presented in Table 2.

Risk of bias

According to the use of the RoB 2 tool to assess the included studies, five were classified as high risk [23, 31, 33, 35, 36], three as low risk [30, 32, 34], and none showed some concerns. (Figs. 2 and 3). The risk of bias primarily stemmed from the allocation concealment issues during the randomization process. Since the trials involved surgical procedures for GR, blinding the treatment to the surgeons was not feasible. Surgeons were aware of the interventions being administered, which made it particularly challenging to achieve proper allocation concealment.

Meta-analysis

According to the different treatment approaches, eight studies were divided into three subgroups, which included the following comparisons: (a) CAF/CGF vs. CAF, (b) CAF/CGF vs. CAF/CTG, (c) CAF/CGF vs. CAF/PRF. The data extracted from the included studies are summarized in Table 3.

Complete root coverage (CRC)

Six studies [23, 31, 32, 34–36] on CRC outcomes demonstrated high heterogeneity ($P = 0.03$; $I^2 = 59\%$) thus a random-effect model was applied. Subgroup analysis showed, compared to CAF alone, CAF/CGF significantly improved CRC (OR = 1.79, 95% CI: [1.03, 3.13],

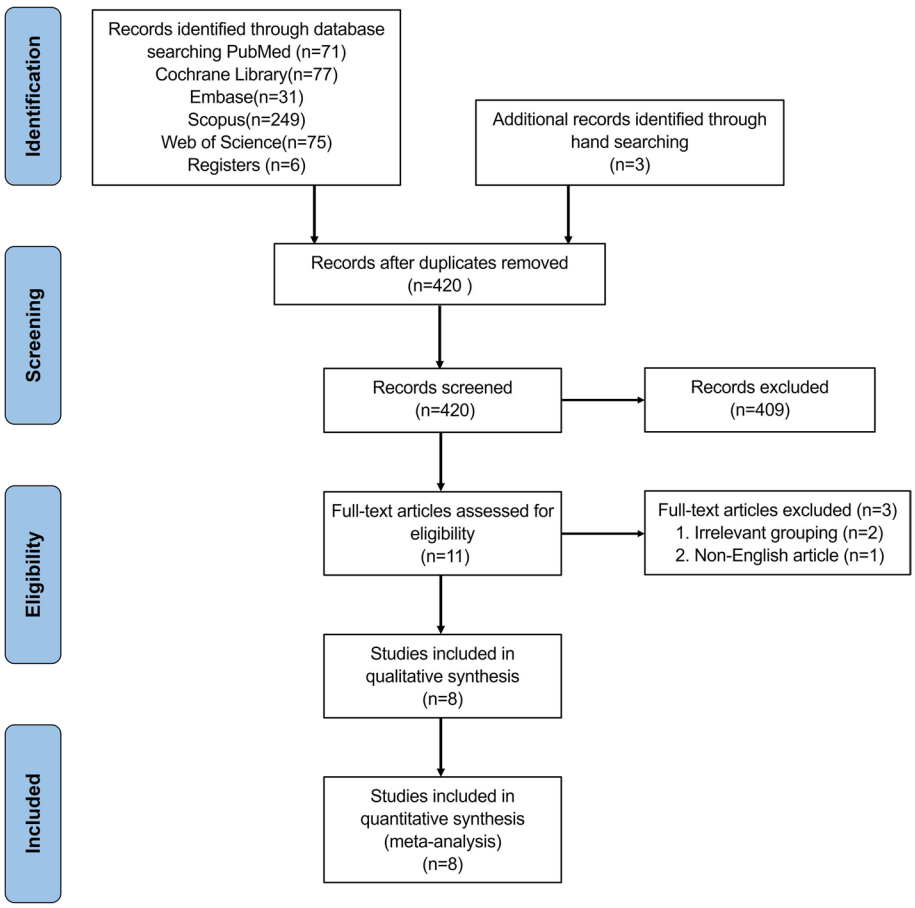

Fig. 1 The PRISMA flowchart of study selection

Table 2 General characteristics of the included studies

Author (Year)	Study Design	Follow-up (Months)	No. of Patients	Defects (Test/ Control)	Age range M/F	smokers	Recession type	Site of recessions	Surgical technique	
									Control (sites)	Test (sites)
Doğan et al, (2015) [23]	RCT (split-mouth)	6	20	119	20–45 7/13	excluded	Miller's I or II	maxillary	CAF (59)	CAF + CGF (60)
Akcan et al, (2020) [30]	RCT (split-mouth)	3,6	19	74	20–63 11/8	excluded	Miller's I	maxillary and mandibular	CAF + CTG (37)	CAF + CGF (37)
Cader et al, (2022) [31]	RCT (split-mouth)	3	10	60	18–50	excluded	Miller's I	maxillary	CAF (30)	CAF + CGF (30)
El-kholy et al, (2022) [33]	RCT (split-mouth)	1,3,6	10	20	20–45 3/7	excluded	Miller's II	maxillary and mandibular	CAF + CTG (10)	CAF + CGF (10)
Mitra et al, (2022) [34]	RCT (split-mouth)	1,3,6	15	30	18–60	excluded	Miller's I or II	NR	CAF (15)	CAF + CGF + sticky bone (15)
Tazegül et al, (2022) [35]	RCT (split-mouth)	6	18	76	>18 10/8	excluded	Miller's I	maxillary	CAF + PRF (37)	CAF + CGF (39)
Xue et al, (2022) [36]	RCT (parallel)	6	28	70	18–65 17/11	excluded	Cairo Class I	maxillary and mandibular	CAF + CTG (36)	CAF + CGF (34)
Dede et al, (2023) [32]	RCT (parallel)	6	11	30	25–45 6/5	excluded	Cairo Class I	maxillary	CAF (15)	CAF + CGF (15)

CGF concentrated growth factor, *CAF* coronally advanced flap, *RCT* randomized clinical trial, *PRF* platelet-rich fibrin, *CTG* connective tissue graft, *M* male, *F* female, *NR* not reported

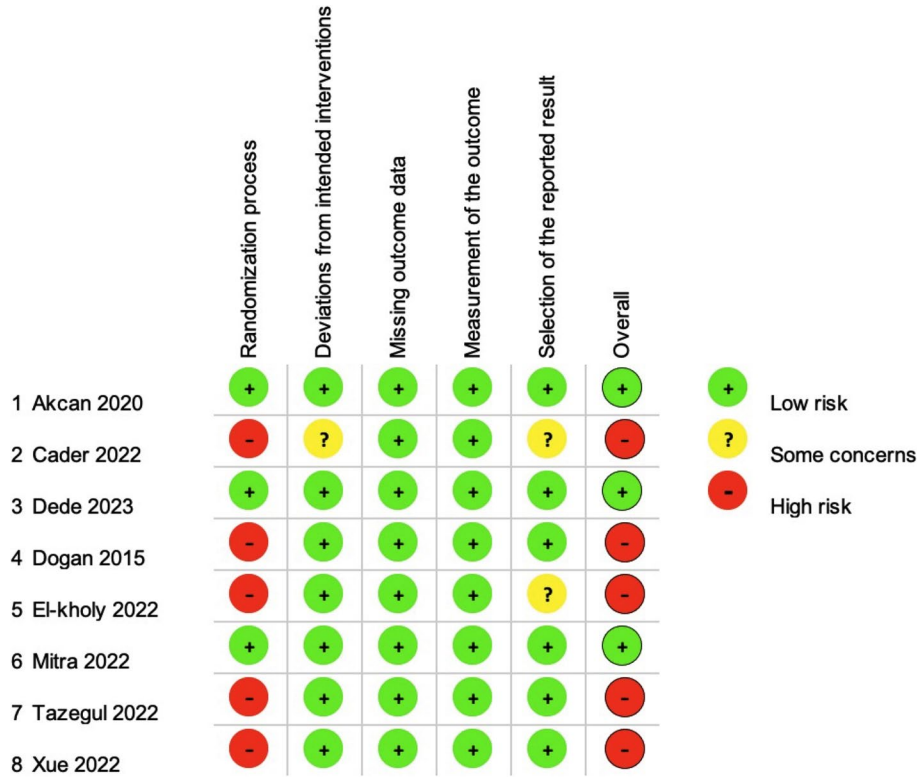

Fig.2 Summary of the risk of bias assessment

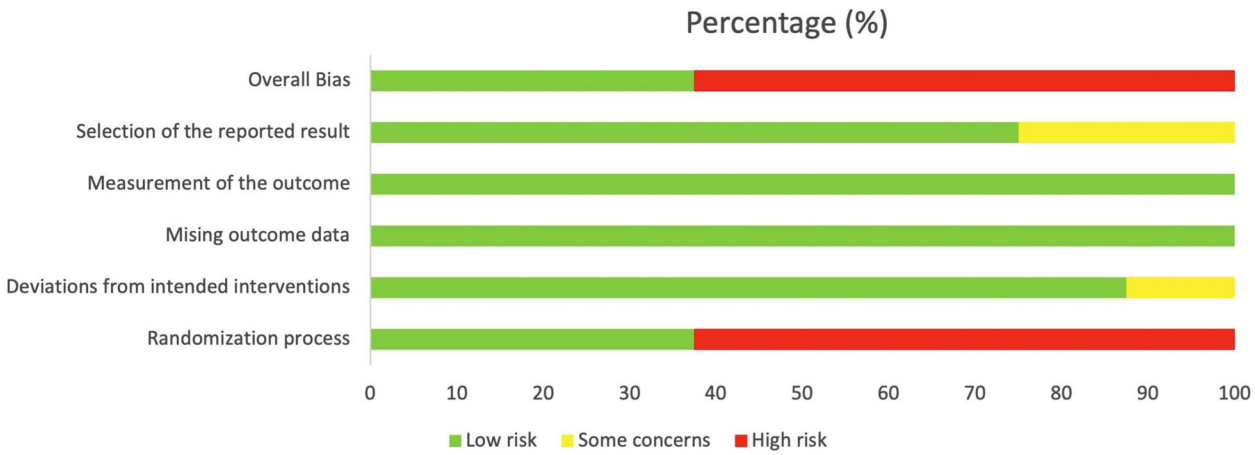

Fig. 3 Risk of bias graph

$P=0.04$). However, in achieving CRC, CAF/CTG demonstrated superior efficacy over CAF/CGF (OR = 0.25, 95% CI: [0.09, 0.71], $P=0.009$). When comparing CAF/CGF with CAF/PRF, no significant difference was observed between the two groups (OR = 1.52, 95% CI: [0.61, 3.77], $P=0.37$) (Fig. 4).

Mean root coverage (MRC)

Six studies [23, 30–33, 36] on MRC outcomes showed high heterogeneity ($P<0.00001$; $I^2=87\%$) thus a random-effect model was applied. Subgroup analysis showed that, compared to CAF alone, CAF/CGF significantly improved MRC (MD = 10.38%, 95% CI: [0.41, 20.35],

Table 3 Data extracted from the included studies

Author (Year)	Group	CRC (n/N)	MD in MRC between baseline and final follow-up (%)	MD in CAL between baseline and final follow-up (mm)	MD in KTW between baseline and final follow-up (mm)	MD in GT between baseline and final follow-up (mm)	MD in PD between baseline and final follow-up (mm)	MD in RD between baseline and final follow-up (mm)	MD in RW between baseline and final follow-up (mm)
Doğan et al, (2015) [23]	T	34/60	86.67 ± 15.59	2.83 ± 0.62	0.58 ± 0.53	0.32 ± 0.1	0.37 ± 0.49	2.47 ± 0.54	3.15 ± 0.88
	C	27/59	82.06 ± 17.49	2.58 ± 0.62	0.14 ± 0.63	0.06 ± 0.09	0.29 ± 0.46	2.29 ± 0.56	2.92 ± 1.02
Akcan et al, (2020) [30]	T	NR	52.54 ± 33.97	1.3 ± 0.96	0.14 ± 1.02	NR	0.03 ± 0.54	1.25 ± 0.82	0.95 ± 1.18
	C		72.45 ± 22.92	1.73 ± 0.93	0.98 ± 1.14		-0.03 ± 0.55	2.05 ± 0.87	1.38 ± 1.45
Cader et al, (2022) [31]	T	7/30	67.77 ± 20.84	1.5 ± 0.82	1.9 ± 0.79	NR	NR	2 ± 0.69	1.57 ± 0.76
	C	2/30	49.16 ± 23.4	0.83 ± 0.83	1.07 ± 0.85			1.4 ± 0.6	0.9 ± 0.79
El-kholy et al, (2022) [33]	T	NR	80 ± 4.83	2.3 ± 0.54	NR	NR	NR	1.7 ± 0.58	1.85 ± 0.53
	C		81.6 ± 2.46	2.4 ± 0.6				1.6 ± 0.58	1.95 ± 0.55
Mitra et al, (2022) [34]	T	9/15	NR	NR	0.77 ± 0.65	NR	NR	1.15 ± 0.63	1.89 ± 0.86
	C	7/15			0.67 ± 0.55			1.6 ± 0.69	1.98 ± 1.05
Tazegül et al, (2022) [35]	T	24/39	NR	2.51 ± 0.82	0.69 ± 0.77	0.27 ± 0.2	0.18 ± 0.39	2.33 ± 0.74	2.79 ± 0.92
	C	19/37		2.51 ± 0.96	0.62 ± 0.76	0.31 ± 0.22	0.22 ± 0.58	2.3 ± 0.78	2.86 ± 0.86
Xue et al, (2022) [36]	T	16/34	80.55 ± 22.03	NR	0.964 ± 0.87	NR	-0.071 ± 0.42	NR	NR
	C	28/36	96.18 ± 7.66		0.62 ± 0.79		-0.16 ± 0.4		
Dede et al, (2023) [32]	T	10/15	85.66 ± 22.68	1.8 ± 1.29	1.54 ± 1.42	0.64 ± 0.28	0.06 ± 0.62	1.73 ± 1.08	2.7 ± 1.41
	C	8/15	75.1 ± 32.37	1.8 ± 1.17	1.67 ± 1.07	0.29 ± 0.29	-0.2 ± 0.49	1.8 ± 1.01	2.54 ± 1.68

C control group, *T* test group, *NR* not reported, *MD* mean difference, *CRC* complete root coverage, *MRC* mean root coverage, *KTW* width of keratinized tissue, *GT* gingival thickness, *PD* probing depth, *RD* recession depth, *RW* recession width

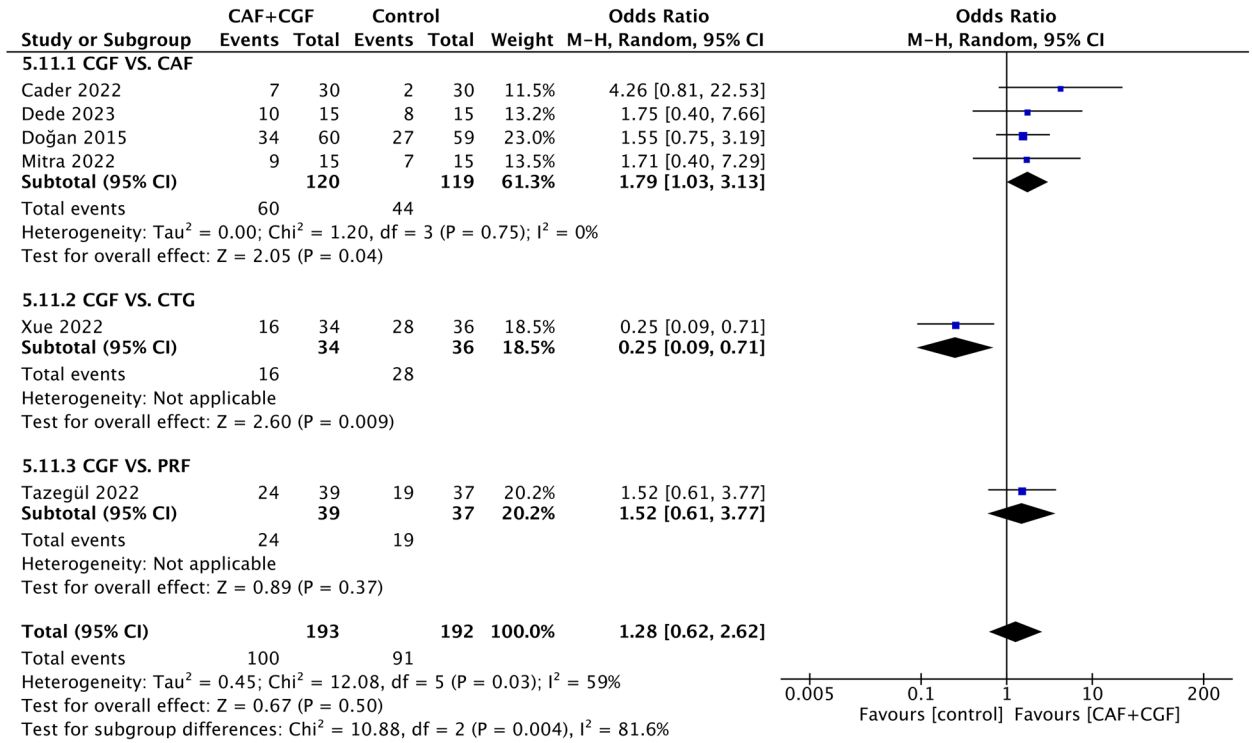

Fig. 4 Forest plot of the complete root coverage

$P=0.04$). When comparing CAF/CGF with CAF/CTG, no significant difference was observed between the two groups (MD = -11.37%, 95% CI: [-23.58, 0.83], $P=0.07$) (Fig. 5).

Increases in keratinized tissue width (KTW)

Seven studies [23, 30–32, 34–36] on KTW outcomes demonstrated high heterogeneity ($P<0.0001$; $I^2=81\%$) thus a random-effect model was applied. Subgroup analysis showed, compared to CAF alone, CAF/CGF significantly increased KTW (MD = 0.40 mm, 95% CI: [0.07, 0.72], $P=0.02$). However, no significant differences were observed when comparing CAF/CGF with CAF/CTG (MD = -0.24 mm, 95% CI: [-1.40, 0.92], $P=0.69$) and CAF/CGF with CAF/PRF (MD = 0.07 mm, 95% CI: [-0.27, 0.41], $P=0.69$) (Fig. 6).

Increases in Gingival Thickness (GT)

Three studies [23, 32, 35] on GT outcomes showed high heterogeneity ($P<0.00001$; $I^2=94\%$) thus a random-effect model was applied. Subgroup analysis showed that CAF/CGF significantly increased GT compared to CAF

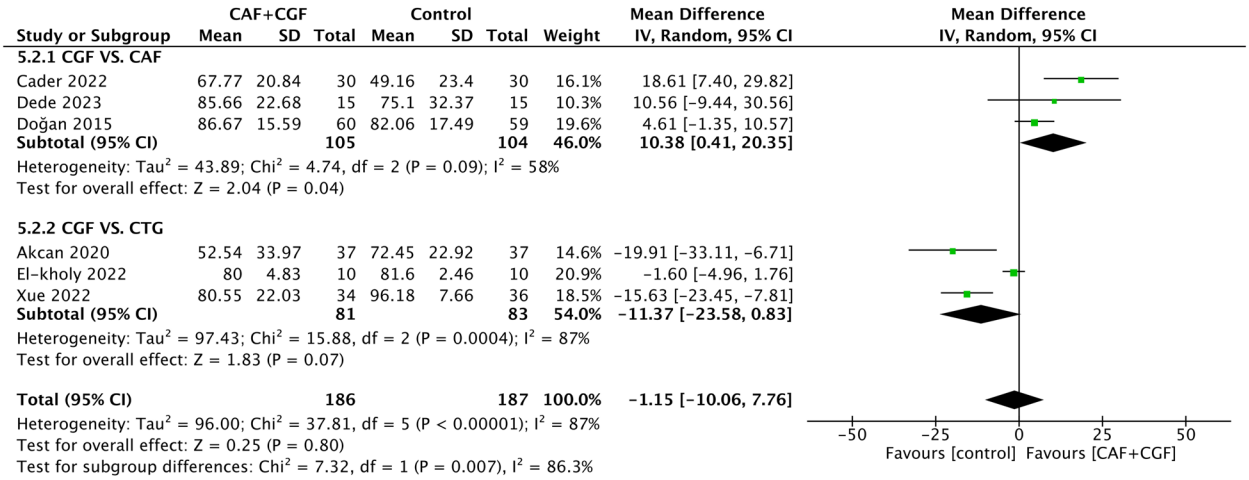

Fig. 5 Forest plot of the mean root coverage

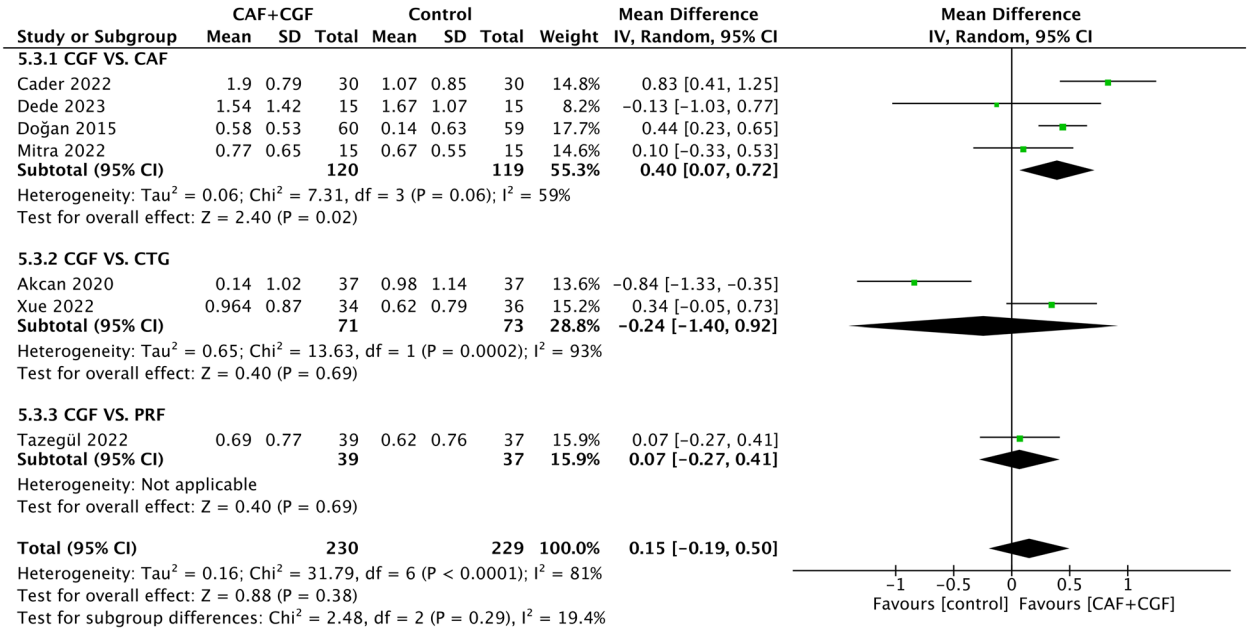

Fig. 6 Forest plot of the keratinized tissue width increases

alone (MD = 0.26 mm, 95% CI: [0.23, 0.30], $P < 0.00001$). When comparing CAF/CGF with CAF/PRF, no significant difference was observed between the two groups (MD = -0.04 mm, 95% CI: [-0.13, 0.05], $P = 0.41$) (Fig. 7).

Gain in clinical attachment level (CAL)

Six studies [23, 30–33, 35] on CAL outcomes demonstrated high heterogeneity ($P = 0.009$; $I^2 = 67\%$) thus a random-effect model was applied. Subgroup analysis showed that CAF + CGF significantly improved CAL gain compared to CAF alone (MD = 0.36 mm, 95% CI: [0.04, 0.69], $P = 0.03$). However, no significant differences were observed when comparing CAF/CGF with CAF/CTG (MD = -0.29 mm, 95% CI: [-0.62, 0.04], $P = 0.08$) and CAF/CGF with CAF/PRF (MD = 0.00 mm, 95% CI: [-0.40, 0.40], $P = 1.00$) (Fig. 8).

Reduction in probing depth (PD)

Five studies [23, 30, 32, 35, 36] on PD outcomes demonstrated no heterogeneity ($P = 0.76$; $I^2 = 0\%$) thus a fixed-effect model was used. Subgroup analysis showed that no significant differences were observed when comparing CAF/CGF with CAF alone (MD = 0.11 mm, 95% CI: [-0.05, 0.26], $P = 0.18$), CAF/CGF with CAF/CTG (MD = 0.08 mm, 95% CI: [-0.07, 0.23], $P = 0.31$), or CAF/

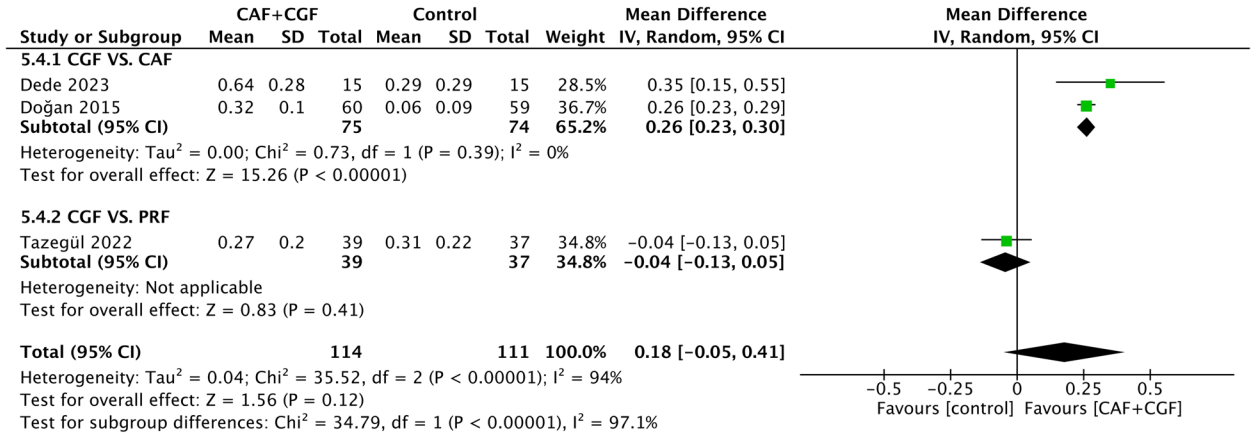

Fig. 7 Forest plot of the gingival thickness increase

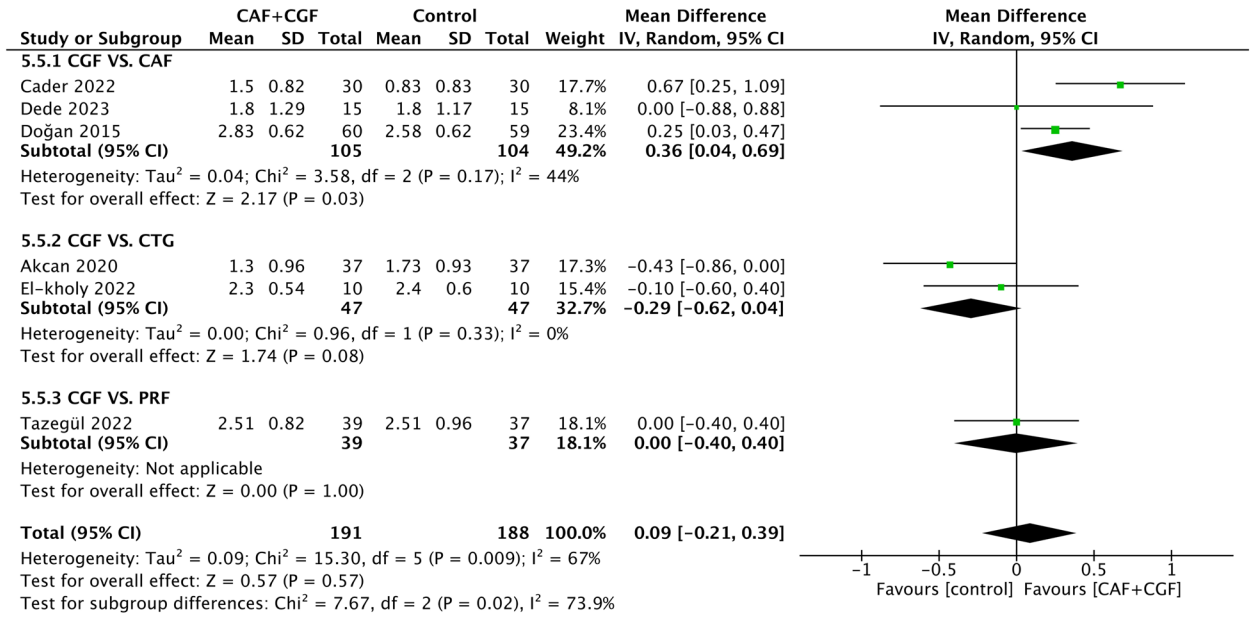

Fig. 8 Forest plot of the clinical attachment level gain

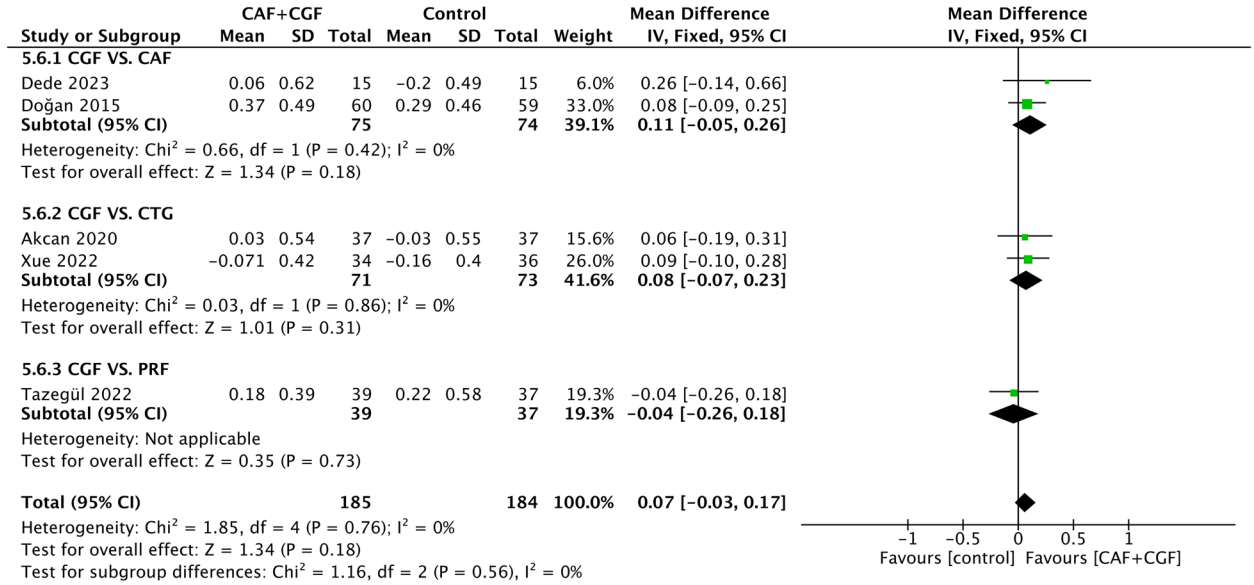

Fig. 9 Forest plot of the probing depth reduction

CGF with CAF/PRF (MD = -0.04 mm, 95% CI: [-0.26, 0.18], $P = 0.73$) (Fig. 9).

Reduction in recession depth (RD)

Seven studies [23, 30–35] on RD outcomes demonstrated high heterogeneity ($P < 0.00001$; $I^2 = 83\%$) thus a random-effect model was applied. Subgroup analysis showed that no significant differences were found when comparing CAF/CGF with CAF alone (MD = 0.11 mm, 95% CI: [-0.29, 0.51], $P = 0.59$), CAF/CGF with CAF/CTG (MD = -0.37 mm, 95% CI: [-1.25, 0.52], $P = 0.42$), or CAF/CGF with CAF/PRF (MD = 0.03 mm, 95% CI: [-0.31, 0.37], $P = 0.86$) (Fig. 10).

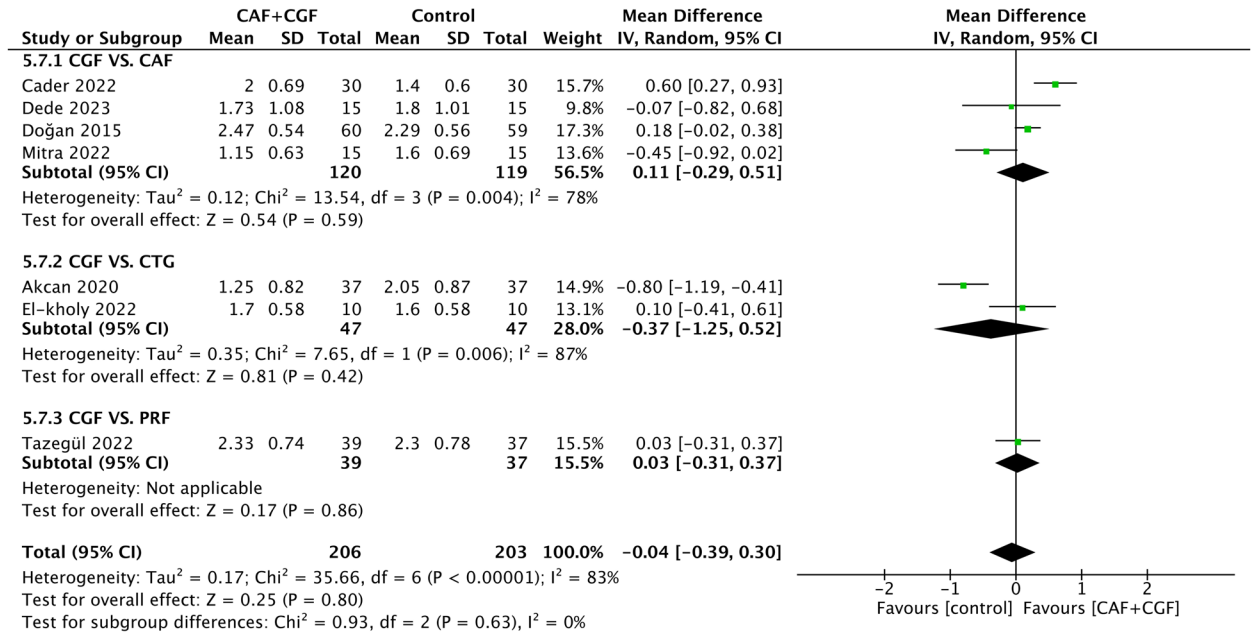

Fig. 10 Forest plot of the recession depth reduction

Reduction in recession width (RW)

Seven studies [23, 30–35] on RW outcomes demonstrated high heterogeneity ($P=0.04$; $I^2=55\%$) thus a random-effect model was applied. Subgroup analysis showed that no significant differences were found when comparing CAF/CGF with CAF alone (MD = 0.32 mm, 95% CI: [-0.00, 0.65], $P=0.05$), CAF/CGF with CAF/CTG (MD = -0.23 mm, 95% CI: [-0.60, 0.15], $P=0.23$), or CAF/CGF with CAF/PRF (MD = -0.07 mm, 95% CI: [-0.47, 0.33], $P=0.73$) (Fig. 11).

Sensitivity analysis

To evaluate the reliability of the synthesized outcomes, a sensitivity analysis was performed through sequential exclusion of one study at a time. The results showed that the synthesized outcomes remained stable, with no significant changes.

Publication bias analysis

No publication bias was observed across all assessed outcomes, based on Egger's tests ($P > 0.05$). In addition, the

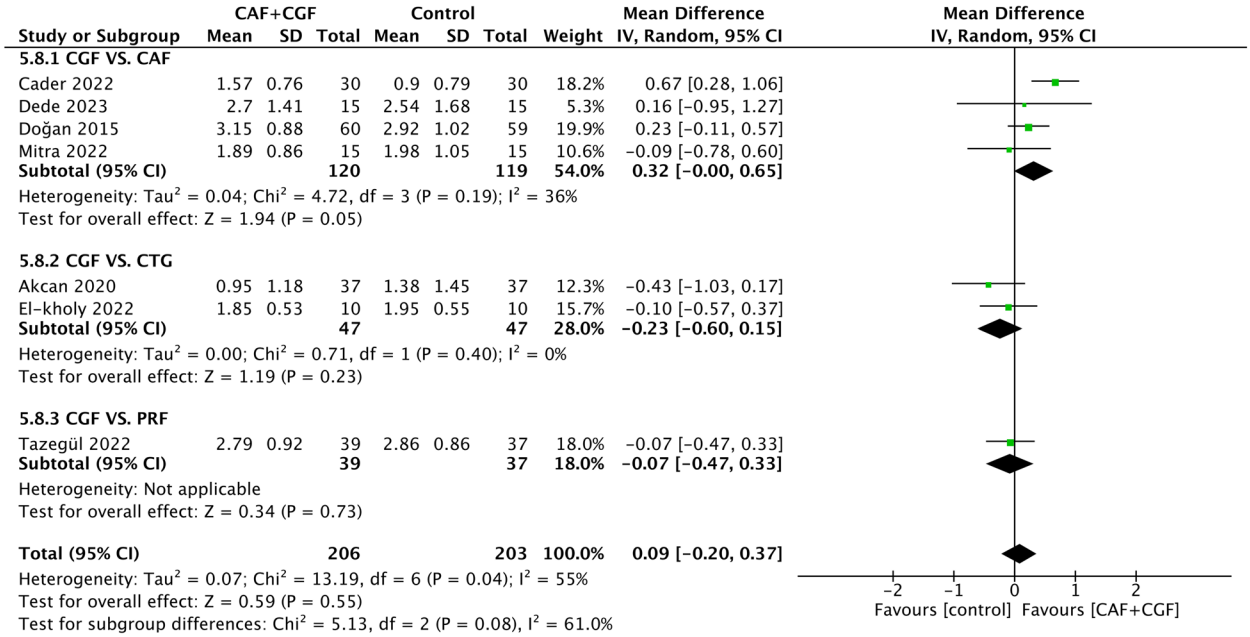

Fig. 11 Forest plot of the recession width reduction

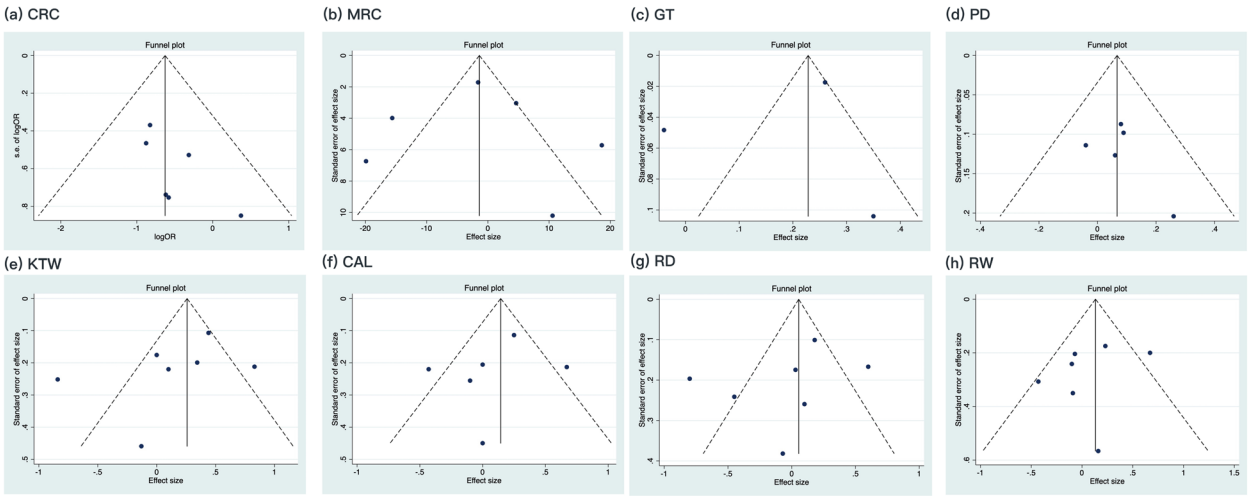

Fig. 12 Funnel plots comparing CAF + CGF versus CAF alone, CAF + CTG, and CAF + PRF for (**a**) CRC, (**b**) MRC, (**c**) GT, (**d**) PD, (**e**) KTW, (**f**) CAL, (**g**) RD, and (**h**) RW

symmetry observed in funnel plots (Fig. 12) further supports the reliability of the meta-analysis results.

Discussion

The study aimed to evaluate whether CAF combined with CGF yields superior clinical outcomes, including more effective root coverage and improvements in clinical parameters associated with aesthetic outcomes, compared to other treatment modalities. The findings could provide clinical evidence to guide the management of Miller Class I and II (or Cairo RT 1) gingival recessions and help refine treatment protocols for periodontal plastic surgery.

CAF/CGF vs. CAF

In the present study, a total of four studies [23, 31, 32, 34] were analyzed and compared to assess the effects of CAF/CGF combined treatment and CAF without adjunctive treatments in root coverage procedures. We observed that incorporating CGF membranes into the CAF procedure produced significant improvements in several clinical outcomes. Specifically, the use of CAF combined with CGF increased the odds of achieving CRC by 1.79 times ($P=0.04$) compared to CAF alone and resulted in a 10.38% higher MRC ($P=0.04$) compared to CAF alone.

Differing from the previous study of Li et al. [37], which reported no significant difference in MRC when comparing CAF and CAF/CGF, our results indicate an opposite outcome. Notably, Li et al.'s analysis was based primarily on a single study by Bozkurt et al. [23]. The discrepancy between their findings and ours could stem from the fact that they included only this one study, whereas our meta-analysis incorporated four studies, which likely accounts for variations in sample size and data diversity.

The primary goals of periodontal surgery for gingival recession are to achieve root coverage, prevent further recession, improve aesthetics, and preserve oral function [6, 7, 38]. The regenerative properties of CGF are primarily attributed to its high growth factor content, including vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), and CD34-positive cells, which play a key role in promoting cellular proliferation, angiogenesis, and tissue repair [17]. Additionally, CGF stimulates the regeneration of gingival tissue by modulating the AKT/Wnt/β-catenin and YAP signaling pathways. Specifically, CGF activates the AKT pathway, which functions upstream of the Wnt/β-catenin and YAP pathways, thereby promoting fibroblast proliferation and collagen synthesis [39]. This mechanism may play a crucial role in the enhanced soft tissue coverage observed in this study.

Moreover, our study demonstrates that the application of CAF/CGF also significantly improved KTW, GT, and CAL, compared to CAF alone, with statistically significant results. Specifically, CAF/CGF resulted increases of 0.40 mm in KTW ($P=0.02$), 0.26 mm in GT ($P<0.00001$), and 0.36 mm in CAL ($P=0.03$). These results support and extend previous meta-analysis by Chen et al. [40] and Li et al. [37], both of which showed a significant advantage for KTW and GT in CAF/CGF compared to CAF. Furthermore, the observed increase in GT and KTW following the CAF/CGF procedure may help enhance the enduring success of the treatment, as thicker gingiva and wider keratinized tissue are associated with better resistance to mechanical stresses and reduced risk of future recession. These factors are crucial for the long-term esthetic and functional outcomes of periodontal treatments for gingival recession [41–43]. Significant reductions in RW, PD, and RD were observed from baseline (pre-surgery) through 3–6 months post-surgery. However, no significant advantage was found for the CAF/CGF group in reducing these clinical parameters, with RW ($P=0.05$), RD ($P=0.59$), and PD ($P=0.18$) compared to the CAF alone group. The absence of significant differences may be attributed to individual variations in the healing response [44]. Additionally, PD, RD, and RW alone may not fully reflect the overall treatment success, as a comprehensive assessment of periodontal treatment outcomes typically requires combining clinical parameters with radiographic evaluation [45]. While clinical evaluation remains the primary method for assessing gingival graft outcomes, including root coverage and tissue augmentation, radiographic evaluation plays a complementary role by providing insight into underlying bone-level stability and helping rule out other periodontal conditions that may influence graft success. Other factors, such as differences in surgical techniques, postoperative care, and limited statistical power due to sample size constraints, may also have contributed to the absence of significant differences between the groups.

CAF/CGF VS. CAF/CTG

Over the years, for the management of GR, the gold standard is widely accepted as the combination of CTG and CAF [9]. This approach has been demonstrated to improve clinical outcomes including RC, KTW, and tissue contour and color [46, 47]. However, in the present study, three studies [30, 33, 36] were included that compared CAF/CGF and CAF/CTG for treating GR. Among the parameters analyzed, CRC showed a statistically significant improvement with the CAF/CTG technique compared to CAF/CGF ($P=0.009$), whereas other clinical outcomes did not show significant differences between the two techniques. These parameters included MRC ($P=0.07$), KTW increase ($P=0.69$), RW reduction

($P=0.23$), CAL gain ($P=0.08$), RD reduction ($P=0.42$), and PD reduction ($P=0.31$).

The results align with previous studies by Yerte et al. [48], which found no statistically significant differences regarding MRC, increase in KTW, gain in CAL, reductions in RW, RD, and PD between the CAF/CGF and CAF/CTG groups. Nevertheless, these results contrast with those of Chen et al. [40], who found that, in comparison to the CAF/CGF, the MRC and increase in GT showed significant improvement in the CAF/CTG. One possible explanation for this discrepancy is that Chen et al.'s [40] research included Korkmaz et al.'s [49] work within the CAF/CTG group, where the experimental group received TUN+CGF and the control group received TUN+CTG, rather than directly comparing CAF+CTG with CAF+CGF. This difference in study design may account for the observed variation in results.

The CTG technique presents several limitations, including limited donor tissue availability and graft size due to the restricted donor area (typically the palate), additional risks from an additional surgical area, prolonged operative duration, and increased postoperative bleeding and pain, particularly when treating multiple or large recession areas, all of which justify the use of adjuvant techniques[12, 13, 50]. In contrast to the CTG technique, CGF offers several advantages, including ease of accessibility, low cost, excellent biocompatibility, no need for tissue donation, and rich content of growth factors. Beyond GR management, APCs have shown broader clinical potential. For example, a study by Bennardo et al. [51] showed that APCs, including platelet-rich plasma (PRP) and leukocyte- and platelet-rich fibrin (L-PRF), significantly enhance healing in medication-related osteonecrosis of the jaw (MRONJ), with complete healing rates of 83.7% for PRP and 86.9% for L-PRF. These results suggest that APCs may promote tissue regeneration not only in periodontal defects but also in complex osseous pathologies, highlighting their versatility as adjunctive therapies. The results of this study indicate that CGF could be a promising alternative for treating GR, especially in cases where CTG is not feasible, such as extensive recession sites, anatomical constraints, patient preferences, or insufficient availability of donor tissue.

CAF/CGF vs. CAF/PRF

In the present study, only one study [35] compared CAF/CGF with CAF/PRF. According to the meta-analysis, all assessed parameters, including CRC ($P=0.37$), KTW ($P=0.69$), GT ($P=0.41$), CAL ($P=1.00$), RW ($P=0.73$), RD ($P=0.86$), and PD ($P=0.73$), showed no statistically significant differences in both groups. These findings are consistent with recent studies by Azadi et al. [52], which found no statistically significant differences between CGF and PRF in terms of CRC, CAL, KTW, PD, RD, and RW. However, although there were no statistically significant differences, significant improvements in all assessed parameters were found from baseline (pre-surgery) to 6 months post-surgery in both the CGF and PRF groups. Notably, CAF/CGF demonstrated slightly better outcomes in CRC, KTW, and RD than CAF/PRF, while CAF/PRF showed slightly better results in GT, PD, and RW compared to CAF/CGF.

Differences in CGF preparation protocols, such as centrifugation speed, type of blood collection tubes, and the centrifuge used, can affect the distribution and concentration of platelets and growth factors, potentially contributing to variability in therapeutic outcomes. For example, low-speed centrifugation results in a more homogeneous distribution of platelets and a higher concentration of growth factors in certain regions, thereby enhancing regenerative effects. In contrast, high-speed centrifugation tends to produce less homogeneous platelet distribution and more diffuse release of growth factors [53]. Additionally, silica-coated tubes allow a more widespread distribution of platelets in the PRF matrix, regardless of centrifugal speed, whereas glass tubes result in platelet distribution that depends on centrifugal speed [54]. Moreover, stable centrifuges with low vibration levels produce clots with a highly polymerized fibrin matrix and a higher concentration of viable cells, enhancing regenerative outcomes, while those with higher vibration levels may damage cells, reducing regenerative outcomes [55].

Although CGF contains higher concentrations of growth factors than PRF, its clinical advantage was not apparent in this study, which raises an important question regarding why CGF did not show significant differences in treatment outcomes despite its seemingly advantageous biochemical profile. One possible explanation lies in the different growth factor release kinetics between CGF and PRF. According to the study by Kobayashi et al. [56], their research indicates that different platelet concentrates exhibit distinct release kinetics. PRP releases a significantly higher amount of growth factors at early time points (15 min) compared to PRF and A-PRF, making it suitable for clinical applications requiring rapid growth factor release, such as acute wound healing. In contrast, PRF and A-PRF demonstrate a more gradual and sustained release of growth factors over a 10-day period. Notably, A-PRF releases a significantly greater total amount of growth factors over this period compared to PRP and PRF, making it particularly well-suited for clinical scenarios that demand prolonged growth factor release, such as chronic wound healing and bone tissue regeneration. While CGF contains higher concentrations of growth factors, PRF exhibits a distinct

release pattern, with growth factors being released in a gradual and sustained manner. This gradual release may be particularly beneficial for maintaining cellular activity and promoting tissue regeneration over a longer period. The release of growth factors in CGF may not occur in a gradual and sustained manner, potentially limiting its overall clinical effectiveness. Another important factor to consider is the study design. Our analysis included only one study that directly compared CAF/CGF with CAF/PRF, and the limited sample size may have influenced the ability to detect statistically significant differences. It is possible that with a larger sample size or a broader range of studies, more significant effects of CGF could emerge.

Given the limitations of the current evidence, future research should investigate the relative effectiveness of CGF compared to PRF in greater detail. Moreover, further research into the release mechanisms of growth factors in CGF and their roles in tissue healing could help clarify why PRF may be more effective in certain clinical contexts and aid in optimizing the clinical application of platelet concentrates. Recent studies further suggest that second-generation platelet concentrates, such as PRF, may exert immunomodulatory effects beyond tissue regeneration. For example, a study by Dohle et al. [57] demonstrated that PRF, generated at low relative centrifugal forces (RCF), significantly decreased the viability of osteosarcoma and fibrosarcoma cells through upregulation of tumor-suppressive genes (e.g., p53) and downregulation of anti-apoptotic genes (e.g., BCL2). The increased release of growth factors, such as TGF-β1 and VEGF, supports PRF's potential in modulating the tumor microenvironment. These findings imply that PRF's immunomodulatory properties could extend to modulating tumor microenvironments, potentially serving as an adjunctive therapy for localized malignancies. While our study focused on PRF's regenerative role in GR, its dual functionality in immune regulation warrants further exploration to maximize therapeutic potential.

Limitations

Several limitations were observed in this study. Firstly, the small number of included RCTs (only eight) diminishes the overall strength of the evidence. Future research should include a greater number of RCTs. Moreover, several studies included in this review had only 6-month follow-up, which limited the assessment of the long-term effectiveness of CGF/CAF. Extended follow-up is required to assess whether the observed benefits are maintained in the long term. Therefore, future studies with longer follow-up periods are crucial for fully assessing the durability of CGF benefits. Another limitation is the lack of standardization in CGF preparation protocols. Variations in centrifugation speed, type of blood collection tubes, and the centrifuge used can lead to inconsistent results. Future studies should focus on standardizing key variables such as the type of blood collection tubes, centrifugation conditions (e.g., time, speed), and the centrifuge. This standardization will help ensure the reproducibility and reliability of future studies. Furthermore, the role of surgical techniques in influencing outcomes has been insufficiently explored in most of the included studies. Future research should focus on defining optimal surgical parameters, such as the size and thickness of the CGF membrane, tailored to various types of gingival recession. Finally, there was notable heterogeneity across certain outcomes; therefore, caution is advised when interpreting the findings.

Conclusions

Based on the findings of the present meta-analysis, the use of CAF/CGF improves clinical outcomes, including CRC, MRC, KTW, CAL, and GT in the treatment of GR compared to CAF alone. No significant differences were observed between CAF/CGF and CAF/PRF for all assessed outcomes. However, CAF/CTG demonstrated superior CRC results when compared with CAF/CGF. Therefore, in cases where CTG is not applicable, CGF may serve as a viable alternative to CTG for treating Miller class I and II GR. Considering the limitations of this meta-analysis, additional well-designed studies are needed to further validate the efficacy of CAF/CGF in the treatment of GR.

Abbreviations

CAF	Coronally Advanced Flap
CGF	Concentrated Growth Factor
GR	Gingival Recession
RCT	Randomized Controlled Trials
TUN	Tunnel Technique
CTG	Connective Tissue Graft
GTR	Guided Tissue Regeneration
APCs	Autologous Platelet Concentrates
PRF	Platelet-Rich Fibrin
AM	Amniotic Membrane
XCM	Xenogeneic Collagen Matrix
CRC	Complete Root Coverage
MRC	Mean Root Coverage
KTW	Keratinized Tissue Width
GT	Gingival Thickness
CAL	Clinical Attachment Level
RW	Recession Width
RD	Recession Depth
PD	Probing Depth
MD	Mean Difference
CI	Confidence Interval
PRP	Platelet-rich plasma
L-PRF	Leukocyte- and platelet-rich fibrin
MRONJ	Medication-related osteonecrosis of the jaw

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
Y.Y. contributed to the study's conception and design. Y.Y., L.O., and B.J. were responsible for data collection and analysis/interpretation. C.C., YQ.Y., and Q.C. contributed to the investigation and material preparation. Y.Y. wrote the manuscript. B.J. revised the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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