Submitted: 26 June, 2024 Accepted: 23 August, 2024 Published: 03 May, 2026 DOI:10.22514/jocpd.2026.060

Journal of Clinical Pediatric Dentistry

SYSTEMATIC REVIEW

Assessment of the efficacy of platelet-rich plasma in treatment of immature permanent teeth in children: a systematic review and meta-analysis

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Abstract

Background: Platelet-rich plasma (PRP) has been proposed as an adjunct scaffold for regenerative endodontic treatment (RET) in immature permanent teeth. The aim of this study is to evaluate whether PRP improves (i) overall clinical efficacy, (ii) periapical regeneration, and (iii) root canal healing in children with immature permanent teeth compared with conventional blood-clot scaffolds. **Methods**: A systematic search of six electronic databases was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Clinical trials assessing PRP in RET of immature permanent teeth were included. Pooled effects were calculated as relative risks (RR) with 95% confidence intervals (Mantel-Haenszel model). **Results**: Seven clinical trials were included. PRP was associated with a lower risk of unfavorable overall outcomes (RR 0.76, 95% CI 0.62–0.93; I^2 = 0%) and a lower risk of unfavorable periapical outcomes (RR 0.54, 95% CI 0.43–0.67; I^2 = 0%). No significant effect was observed for root canal healing (RR 1.01, 95% CI 0.83–1.23; I^2 = 0%). **Conclusions**: PRP may improve periapical outcomes in RET of immature permanent teeth in children, but it does not appear to affect root canal healing. Given clinical and methodological variability across studies, further well-designed trials with standardized protocols are warranted. **The PROSPERO Registration**: CRD42024563068.

Keywords

Platelet-rich plasma; Apexogenesis; Root canal treatment; Permanent teeth

1. Introduction

Pulp necrosis is typically an illness caused by the withdrawal of dental pulp from its essential blood and nutritional source, causing interference with cellular physiological function and the development of necrotic tissue as a result [1]. The development of pulp necrosis in an immature permanent tooth is a multifaceted and complex process, often caused by extreme dental trauma, dental caries, or developmental pulp conditions that cause interruption of the blood supply to the pulp [2]. The effect of pulp necrosis in an immature permanent tooth is far-reaching. First, the interference with blood supply and the consequent tissue necrosis impedes the normal physiological function of the dental pulp, including dentin formation and maintenance, responsible for the protection of the tooth [3]. Interference like this may detrimentally affect the structural integrity of the tooth, causing breakages and other anomalies in dental structures [4].

There are four main types of platelet concentrates depending on their utilization; these types include: Platelet-Rich Plasma (PRP), Platelet-Rich Fibrin (PRF), Platelet-Leukocyte Gel (PLG), and Platelet-Rich Growth Factor (PRGF). These are divided based on their method of preparation and composition characteristics. PRP is obtained by centrifugation of anticoagulant-treated whole blood, whereas PRF is prepared without using anticoagulants, thereby making it possible to form a fibrin matrix. PRP and PRF have been extensively researched, and they are presently applied to a range of dental procedures. Research indicates that PRP and PRF promote bone growth and healing of soft tissues and, therefore, improve success in bone grafting, sinus augmentation, and socket preservation [5–7]. Platelet concentrates have also been found to have beneficial effects on periodontal tissue regeneration, with the outcome of reduced pocket depth and increased attachment level gain. PRP and PRF have also been used to enhance implant success and osseointegration [6]. By the use of these platelet concentrates in the implant site, the release of the growth factors initiates angiogenesis and bone formation, permitting the implant to become integrated with the bone [7]. PRP has also shown promise for use in regenerative treatment to revascularize non-vital or immature teeth with open apices. The growth factors secreted from these concentrates of platelets have the ability to stimulate stem cell recruitment and differentiation to form new pulp-like tissue inside the root canal.

Despite numerous investigations examining PRP effects, certain knowledge gaps have not yet been addressed in the literature. These gaps occur due to the heterogeneity of factors, including heterogeneity in study design and methodology [8–12]. The studies differ in sample sizes, follow-up durations, outcome measures accepted, and treatment protocols, and therefore, direct comparisons and synthesis of the findings are impossible. Furthermore, some studies that compare PRP treatment with control treatments or with conventional treatments may have deficiencies in control groups. Adequate control groups, for instance, placebos or control treatments, are necessary for a proper evaluation of the specific effects of PRP and to differentiate them from natural healing processes or effects due to other causes. Moreover, selection and documentation of the outcome measures in the existing studies differ widely. While some studies employ radiographic parameters, some employ clinical parameters or patient-based outcomes. This variability in standardized outcome measures makes combining and comparing the findings of the studies challenging, and therefore, gaining a comprehensive understanding of the overall efficacy of PRP treatment becomes challenging. Despite these knowledge gaps, this study had two main aims: to evaluate the effectiveness of PRP for immature permanent teeth in children. PRP was selected in comparison to other platelet concentrates in this study due to its extensive research background, promising results in dental procedures, and its ability to recruit and differentiate stem cells. Furthermore, PRP preparation is relatively simple and can be performed using commercially obtained kits, and therefore, it becomes more convenient for clinical application compared with other platelet concentrates. Also, PRP has a longer shelf life than PRF, and therefore, more flexibility is achieved in treatment planning and implementation. Specifically, we aimed to assess the effect of PRP on periapical regeneration and root canal healing. The primary goal was to ascertain whether the treatment with PRP showed evident proof of efficacy in improving periapical regeneration and root canal healing in immature permanent teeth in children. The secondary goal was to ascertain any difference in efficacy between PRP treatment and conventional treatment methods or control treatments.

2. Materials and methods

2.1 Study protocol and design

This review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist; **Supplementary material**) [13]. PRISMA is a globally recognized set of guidelines that outlines a comprehensive methodology for the performance and reporting results of systematic reviews and meta-analyses, enhancing methodological rigor and transparency. The review was registered with the interim PROSPERO identifier CRD42024563068. Transparency as well as clear documentation of the process of study selection, data extraction, assessment of risk of bias, and statistical analysis have been increased with the use of the PRISMA reporting guideline. The correct framework is presented in Fig. 1.

An accurately phrased PICOS framework was employed to form the research question and guide the study design. PICOS is an acronym used to denote Population, Intervention, Comparison, Outcome, and Study Design. Application of the PICOS framework assisted in guiding the systematic review, thus establishing a clear and specific research question and assist in identifying and selecting relevant studies.

Population: The population of interest for this review included children with immature permanent dentition that required treatment. The age range and specific population characteristics were clearly defined to encompass studies that were deemed eligible.

Intervention: The review topic was the use of PRP as a treatment protocol in immature permanent teeth. PRP is a treatment protocol that involves the use of the patient's own concentrated blood platelets, which are considered to have growth factors and bioactive molecules that will stimulate tissue regeneration.

Comparison: The comparison group for this review consisted of either a new treatment regimen or a control group with no PRP treatment. Comparison interventions consisting of the therapeutic benefit of PRP with other treatment interventions or therapeutic controls/placebo were included to compare the relative advantage of PRP; however, since the therapeutic review was exploratory, the inclusion of this group was not necessary.

Outcome: The main outcomes of interest were those related to the efficacy of PRP treatment in relation to clinical outcomes. The outcomes were periapical healing, formation of dentinal wall, root development, and other such indicators of treatment success. The review aimed to determine the influence of PRP on these outcomes and its efficacy in relation to other interventions or to controls.

Study Designs: The current study included not only randomized controlled trials (RCTs), but other study types such as retrospective case-control studies and prospective cohorts. By including a broad range of study designs, the review tried to gather evidence of varied sources to create an overall assessment of the effectiveness of PRP in treating immature permanent teeth.

2.2 Database search protocol

The process of conducting the literature review involved the use of six individual databases (see Table 1). The strategy used a blend of Medical Subject Headings (MeSH) terms and Boolean operators to cover all relevant literature. The MeSH terms used in the search were those associated with PRP,

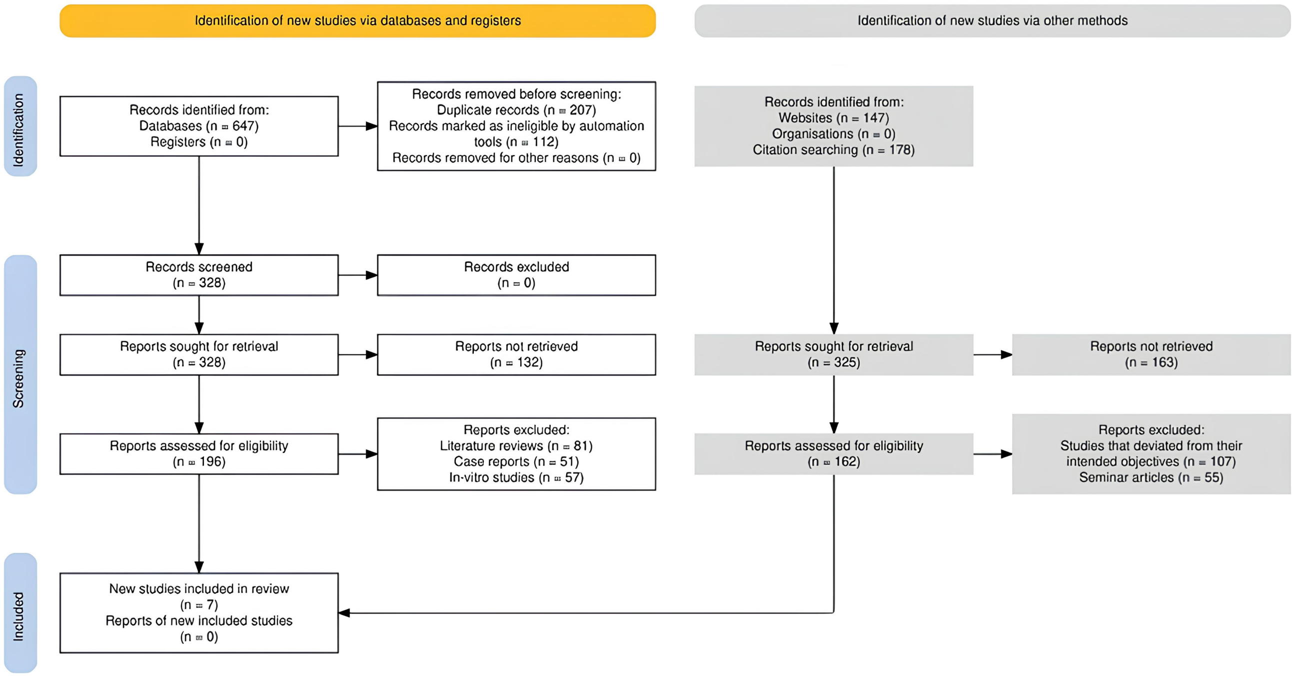


FIGURE 1. Study selection protocol documenting the PRISMA guideline utilization for the selected studies.

TABLE 1. Search strategy across six different databases utilized for the review.

Database	Search Strategy
PubMed	((“Platelet-Rich Plasma”[MeSH]) OR PRP OR “Platelet-Rich Fibrin”[MeSH] OR PRF) AND (“Permanent Dentition”[MeSH] OR “Permanent Teeth” OR “Young Adult”[MeSH] OR “Child”[MeSH])
Embase	(“platelet-rich plasma”/exp OR PRP OR “platelet-rich fibrin”/exp OR PRF) AND (“permanent dentition”/exp OR “permanent teeth” OR “young adult”/exp OR “child”/exp)
Scopus	(TITLE-ABS-KEY (Platelet-Rich Plasma OR PRP OR “Platelet-Rich Fibrin” OR PRF) AND TITLE-ABS-KEY (“Permanent Dentition” OR “Permanent Teeth” OR “Young Adult” OR Child))
Web of Science	TOPIC: (Platelet-Rich Plasma OR PRP OR Platelet-Rich Fibrin OR PRF) AND TOPIC: (Permanent Dentition OR Permanent Teeth OR Young Adult OR Child)
Cochrane Library	(Platelet-Rich Plasma OR PRP OR Platelet-Rich Fibrin OR PRF) AND (Permanent Dentition OR Permanent Teeth OR Young Adult OR Child)
CINAHL	(MH “Platelet-Rich Plasma” OR PRP OR MH “Platelet-Rich Fibrin” OR PRF) AND (MH “Permanent Dentition” OR “Permanent Teeth” OR “Young Adult” OR “Child”)

MeSH: Medical Subject Headings.

immature permanent teeth, and pedodontic age groups. The chosen terms were modified to fit the controlled vocabularies of the individual databases to ensure a uniform process in the search strategy. The research used free-text keywords and MeSH headings to cover for linguistic differences and to thoroughly cover the literature. The main goal of the search strategy was to capture all relevant literature on the subject by combining synonyms, related terms, and misspellings. The Boolean operators were utilized wisely to combine the distinct concepts of PRP, immature permanent teeth, and children while at the same time excluding irrelevant studies through the utilization of proper exclusion criteria. Besides the database searching, the reference lists of applicable articles and reviews were screened for additional studies that would have been overlooked in the initial search. It should be mentioned that the utilization of gray literature and unpublished studies were not included in the search plan.

2.3 Selection process

The inclusion criteria were to identify relevant clinical trials and cohort studies for this systematic review. The population of interest was children with immature permanent teeth that required treatment with PRP. The intervention of interest was the use of PRP for the treatment of immature permanent teeth. Comparisons of PRP with other interventions or control groups, such as placebo or conventional treatments, were included. This review focused on outcomes that were specific to the efficacy of PRP treatment, including pulp vitality, periapical healing, dentinal wall regeneration, and overall clinical as well as radiographic success. Moreover, only English-language publications were included to ensure accessibility and comprehensibility of literature. Conversely, the specific exclusion criteria were as follows: Studies published in languages other than English were excluded because of limitations in translation skills. Animal studies were not included in this review because the interest was only in studies with human subjects. Single case reports and case series were excluded in order to give priority to the selection of controlled studies with large sample sizes. Review articles, editorials, letters, and conference abstracts were excluded from the analysis in order to maintain the integrity of primary studies. Finally, studies with missing data or with incomplete reporting of outcomes were also excluded to ensure proper analysis and reliable conclusions. Using these strict inclusion and exclusion criteria, this study attempted to identify high-quality studies that addressed the research question, had relevant data, and provided in-depth analysis of the efficacy of PRP in the treatment of immature permanent teeth in children.

2.4 Data extraction protocol

The process of data extraction involved the systematic and uniform extraction of the data points from all the included studies. The study utilized a pre-designed form to extract data, which required all critical study elements, demographics, intervention variables, and results to be included. The data extraction process was performed by two reviewers independently to ensure accuracy and minimize bias. The extracted data consisted of information on the studies, *e.g.*, the names of authors, year of publication, study design, sample sizes, and study duration. Participant characteristics, *e.g.*, age range and gender distribution, were also extracted. Detailed data on the PRP intervention were extracted, including the specific protocol, concentration, and method of administration. Outcomes regarding pulp vitality, periapical healing, dentinal wall regeneration, and success were extracted. In addition to qualitative data presented in study results tables, quantitative data such as means and standard deviations were gathered to be used in the subsequent meta-analysis. In case of inconsistencies in data extracted from articles by the two researchers, these were resolved by consensus via discussion. In the case where consensus could not be reached, a third reviewer was involved to make the final decision. In addition to this, efforts were made to reach out to authors of studies cited in the paper for additional information. Through the application of a rigorous and systematic data extraction process, the systematic review ensured that pertinent information from the selected studies was accurately captured.

2.5 Bias assessment protocol

The bias assessment process enabled a global evaluation of studies included according to the specific risks of bias specific to their respective study design. Utilizing the Risk of bias (RoB) 2.0 tool [14, 15] for RCTs and the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) tool [14, 16, 17] for cohort studies as shown in Figs. 2,3 respectively, a systematic and transparent approach was utilized to assess the possible sources of bias and conclude the overall quality and reliability of the evidence. The process enabled a stronger interpretation of the study findings and an in-depth appreciation of the weaknesses and possible biases of the included studies.

2.6 Statistical analysis

The meta-analysis for the present study was performed using RevMan 5 software version 5.4.1 (The Cochrane Collaboration, London, UK). The data were synthesized using a fixed effects model. The data of the included studies were first extracted and tabulated, including respective outcome measures and effect sizes. The effect sizes were calculated based on the outcome measure of RR, along with respective 95% confidence interval (CI). Then the fixed effects model was applied to pool the effect sizes of the included studies. The fixed effects model assumes that there is a common true effect size for all the included studies and the observed variability is a sampling error artifact. The fixed-effects model carries greater weight for larger studies and provides a better approximation of the true study effect. Heterogeneity between the included studies was assessed using the chi-squared test as well as the I^2 statistic. In case of extreme heterogeneity ($I^2 > 50\%$ or significant chi-squared test), then a random effects model would have been applied. But in the current study, a fixed effects model was applied since no significant heterogeneity was observed ($I^2 = 0\%$, $p > 0.05$). The pooled effect sizes were provided with respective 95% CIs to provide an idea about the precision of the estimates. Forest plots were generated to visually depict the individual study effect sizes, along with the overall pooled effect. Besides, a test for overall effect (Z-test) was obtained to assess the statistical significance of the pooled effect estimate.

The meta-analysis method using RevMan 5 (5.4.1) and the fixed effects model allowed for the statistical pooling of data from the eligible studies to generate an estimate of the overall effect size and its statistical significance. This allowed systematic and objective evaluation of the effectiveness of platelet-rich plasma for the treatment of immature permanent teeth in children based on cumulative evidence from several studies.

3. Results

3.1 Baseline characteristics

Table 2 (Ref. [18–24]) provides collective information from the 7 studies conducted in different countries and years. Sample size, age, and gender distribution were quantified across the studies. The pooled data show that sample sizes varied across the studies, with sample sizes ranging from 13 to 77 participants. The ages also varied, with the participants being 7 to 14 years or less than the age of 20. In terms of gender distribution, the majority of the studies over-represented the males, with male-to-female ratios of 8:0 to 44:0.

3.2 Inferences observed

Table 3 (Ref. [18–24]) encompasses a collective analysis of different studies, focusing on various aspects of regenerative endodontic treatment. The protocols used in the studies included RCTs and retrospective case-control designs. The tooth types and numbers assessed varied across the studies, with a range of incisors and premolars examined.

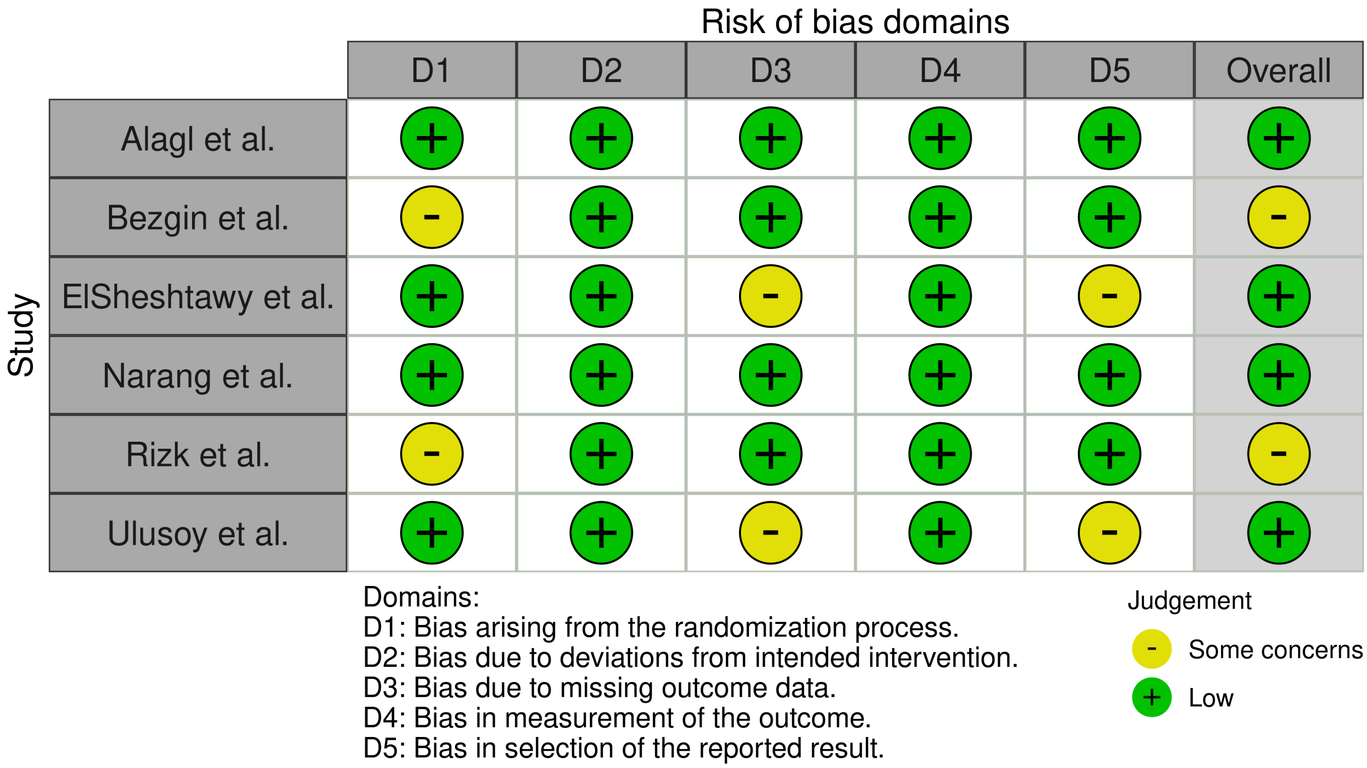


FIGURE 2. Bias evaluation of the RCTs included in the review.

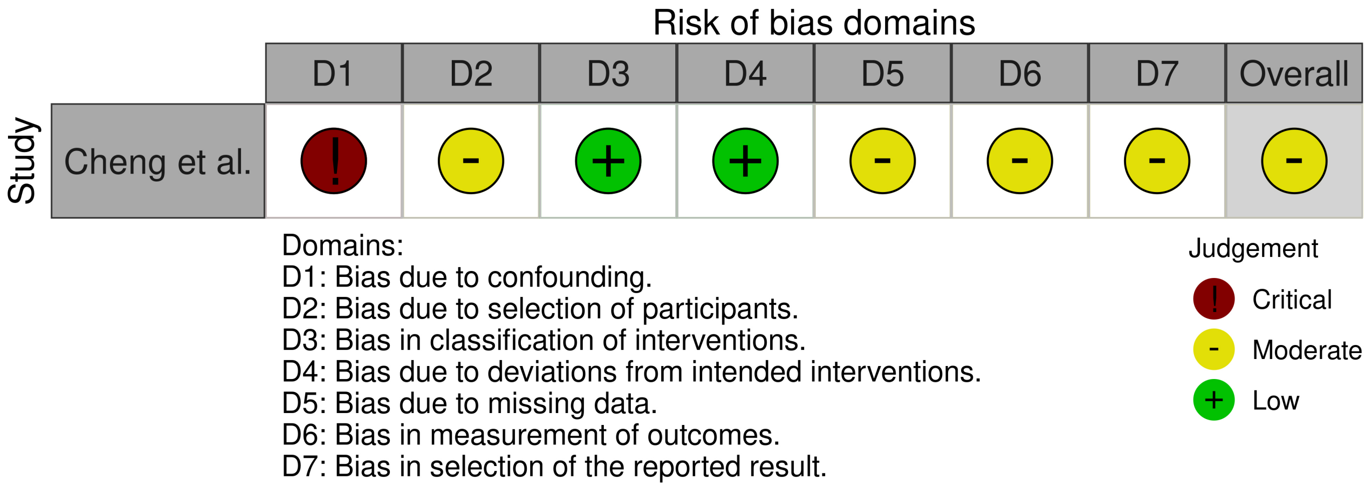


FIGURE 3. Bias evaluation of the retrospective study included in the review.

TABLE 2. Assessment of demographic variables pertaining to sample size, age, and gender of the included clinical trials.

Study ID	Year of study	Country	Sample size (n)	Age range (yr)	Gender ratio
Alagl *et al.* [18]	2017	Saudi Arabia	15	7–12	9 males
Bezgin *et al.* [19]	2015	Turkey	20	7–13	12 males
Cheng *et al.* [20]	2022	China	62	8.6 ± 1.4 (mean)	34 males
ElSheshtawy *et al.* [21]	2020	Egypt	26	12.66 ± 4.47 (mean)	15 males
Narang *et al.* [22]	2015	India	20	<20	Unspecified
Rizk *et al.* [23]	2019	Egypt	13	8–14	8 males
Ulusoy *et al.* [24]	2019	Turkey	77	8–11	44 males

TABLE 3. Technical characteristics of included studies pertaining to PRP and its related outcomes.

Study ID	Protocol	Tooth type and number assessed	Irrigant utilized	Pulp vitality response assessed (cold/heat/electric)	Intracanal compounds utilized	Follow-up period (in years)	Results assessed
Alagl *et al.* [18]	RCT	24 incisors and 6 premolars	NaOCl and CHX	Positive in 19 teeth and negative in 11 teeth	TAP	1	PRP demonstrated significant efficacy in reducing overall size of incident lesion, enhancement in periapical bone density and overall root development as well as growth.
Bezgin *et al.* [19]	RCT	14 incisors and 6 premolars	NaOCl, CHX and EDTA	Positive in 7 teeth and negative in 13 teeth	TAP	1.5	There were no appreciable differences in treatment outcomes between PRP and traditional clot scaffold in terms of overall regenerative efficacy.
Cheng *et al.* [20]	Retrospective case-control	32 incisors	NaOCl and EDTA	Unspecified	TAP and $Ca(OH)_2$	1.85 (mean)	After utilizing PRP, a substantial difference was seen in the apical diameter, which decreased, and the root area, which increased. The success rates of PRP across different injury types were as follows (in descending order): fracture, luxation, and avulsion.
ElSheshtawy *et al.* [21]	RCT	14 incisors	NaOCl	Negative	TAP	1	There were no significant improvements between the PRP and control groups in terms of changes assessed in terms of root length, width, apical diameter and periapical bone density.
Narang *et al.* [22]	RCT	15 (type unspecified)	NaOCl	Unspecified	TAP	1.5	In comparison to PRP and blood clot, PRF significantly improved the growth properties of immature necrotic permanent teeth.
Rizk *et al.* [23]	RCT	13 incisors	NaOCl	Negative	TAP	1	Root length, width, apical diameter and periapical bone density were significant improved in teeth that had received PRP treatment when assessed radiographically.
Ulusoy *et al.* [24]	RCT	73 incisors	NaOCl and CHX	Positive in 65 teeth and negative in 8 teeth	TAP	2.35 (mean)	Without antecedent apical bleeding and with considerably less risk of root canal obliteration than blood clot, PRP and PRF produced clinical and radiographic results that are comparable to those of blood clot.

PRP: Platelet-Rich Plasma; RCT: randomized controlled trial; NaOCl: sodium hypochlorite; CHX: chlorhexidine gluconate; TAP: triple antibiotic paste; EDTA: ethylenediaminetetraacetic acid; $Ca(OH)_2$: calcium hydroxide; PRF: Platelet-Rich Fibrin.

The agents used for irrigation were sodium hypochlorite (NaOCl), chlorhexidine gluconate (CHX), and ethylenediaminetetraacetic acid (EDTA). The response to pulp vitality tests to heat, electric currents, and cold stimuli were assessed. Intracanal compounds, such as triple antibiotic paste (TAP; typically ciprofloxacin–metronidazole–minocycline) and calcium hydroxide ($Ca(OH)_2$), were employed in the studies. The follow-up periods ranged from 1 to 2.35 years, allowing for the observation of long-term outcomes. In terms of results, the efficacy of PRP was highlighted in reducing the size of incident lesions, enhancing periapical bone density, and promoting overall root development and growth. There were no major differences in regenerative ability detected between PRP and traditional clot scaffold approaches. The utilization of PRP showed a positive impact on apical diameter reduction and root area increase, with varying success rates across different types of dental injuries. The PRP group did not show any marked differences from the control group in terms of root dimensions and periapical bone density. The values for changes in root length did not differ significantly. The changes in width were not significantly different. However, PRF demonstrated significant improvements in the growth properties of immature necrotic permanent teeth compared with PRP and blood clot treatments. At the same time, evaluation by radiography demonstrated PRP to have resulted in marked increases in values related to root length, width, apex diameter, and bone density.

3.3 Assessed clinical efficacy of PRP

Table 3 summarizes a more integrated analysis of different studies in terms of different parameters of regenerative endodontic treatment. The studies had different protocols that included RCTs and retrospective case-control designs. The nature and number of teeth included ranged from incisors to premolars in studies. NaOCl, CHX, and EDTA were some of the irrigants used for the treatments. The pulp vitality response was measured in terms of the response to cold, heat, and electric stimuli. Intracanal compounds such as TAP and $Ca(OH)_2$ were used in the studies. Follow-up ranged from 1 to 2.35 years, and thus the long-term effects could be seen. In terms of results, the efficacy of PRP was observed in reducing the lesion size of incident lesions, increasing the periapical bone density, and stimulating root growth and development in total. The PRP treatments, however, did not show any differences from conventional clot scaffold treatments in terms of regenerative efficacy. The application of PRP more often showed positive effects on reduction in apical diameter and the increase in root area, more often with different success rates for different types of dental injury. There were no differences between PRP and controls regarding root length, width, apical diameter, and periapical bone density. However, PRF showed significant improvements in the growth properties of immature necrotic permanent teeth compared with PRP and blood clot treatments. However, the result of radiographic evaluation confirmed that PRP promoted significant increments in the length, width, apical diameter, and periapical density.

3.4 Assessment of clinical efficacy of PRP

The forest plot of Fig. 4 provides the results of the pooled studies included in this review [18–24]. Fig. 4 summarizes study-specific risk ratios (RRs) for overall clinical efficacy comparing PRP with the conventional blood-clot scaffold. The percentage values shown in the forest plot represent the study weights (6.3%–39.3%), reflecting differences in precision and sample size. The pooled RR was 0.76 (95% CI 0.62–0.93; $Z = 2.67$, $p = 0.008$), indicating a lower risk of unfavorable overall outcomes with PRP. No statistical heterogeneity was detected ($\chi^2 = 5.28$, $df = 6$, $p = 0.51$; $I^2 = 0\%$). This shows that the observed difference between the studies in the effect estimates is by chance and not by true heterogeneity in the treatment efficacy. The test for overall effect, in the form of the Z-statistic, is 2.67 with a p-value of 0.008. This shows that there is a statistically significant overall effect of PRP treatment on immature permanent teeth in children. So, in essence, the forest plot shows that the overall efficacy of PRP for the treatment of immature permanent teeth in children is visible, with an RR of 0.76 and with a significant overall effect. More studies and more research are needed in order to have stronger views regarding the efficacy of PRP in this regard.

3.5 Impact of PRP across different parameters of tooth healing

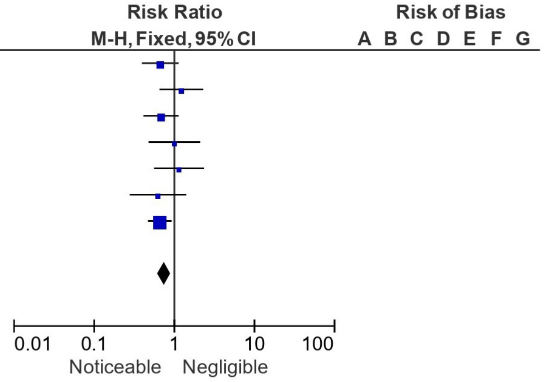
Fig. 5's first forest plot indicates the results for the effect of PRP on periapical regeneration by the RR measure. The individual results of the studies are indicated in the forest plot by the event numbers and the sample sizes. Events were defined as unfavorable periapical outcomes as reported in the included trials (therefore RR <1 favors PRP). The forest plot shows study weights ranging from 4.0% to 21.7%. The RR estimates derived, with their 95% CI, indicate the overall effect of PRP treatment for periapical regeneration. The overall RR estimate is 0.54, indicating a reduction in the risk of poor periapical regeneration with PRP treatment. The 95% CI for the RR is 0.43 to 0.67. The heterogeneity analysis, done by the Chi-square test (χ^2) and I^2 statistic, indicates no heterogeneity between the studies ($\chi^2 = 3.56$, $df = 6$, $p = 0.74$; $I^2 = 0\%$). This indicates that the variation in effect estimates between the studies is most likely due to chance and not due to variation in effect of PRP treatment. The overall effect test, as indicated by the Z-statistic, has a value of 5.58 and its corresponding p-value of less than 0.00001. This indicates a highly significant overall effect of PRP treatment for periapical regeneration for improved outcomes. This forest plot, therefore, indicates a seeming overall effect of PRP treatment for periapical regeneration as indicated by the RR estimate of 0.54 and the significant overall effect test. The component studies contributed different weights (4.0%–21.7%). These findings indicate that PRP therapy is promising in the reduction of risk for poor periapical regeneration. Future studies will be needed to verify these findings and identify possible variables that will influence the efficacy of PRP in this use.

The second forest plot in Fig. 5 shows the effect of PRP on healing of the root canal. Individual study findings are plotted in the forest plot with sample size and number of events.

Study or Subgroup	Noticeable Events	Noticeable Total	Negligible Events	Negligible Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alagl et al 2017	12	30	18	30	16.1%	0.67 [0.39, 1.13]
Bezgin et al 2015	11	20	9	20	8.0%	1.22 [0.65, 2.29]
Cheng et al 2022	13	32	19	32	17.0%	0.68 [0.41, 1.14]
El Sheshtawy et al 2020	7	14	7	14	6.3%	1.00 [0.48, 2.10]
Narang et al 2015	8	15	7	15	6.3%	1.14 [0.56, 2.35]
Rizk et al 2019	5	13	8	13	7.1%	0.63 [0.28, 1.41]
Ulusoy et al 2019	29	73	44	73	39.3%	0.66 [0.47, 0.92]
Total (95% CI)		**197**		**197**	**100.0%**	**0.76 [0.62, 0.93]**
Total events	85		112			

Heterogeneity: Chi² = 5.28, df = 6 (p = 0.51); I² = 0%

Test for overall effect: Z = 2.67 (p = 0.008)



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

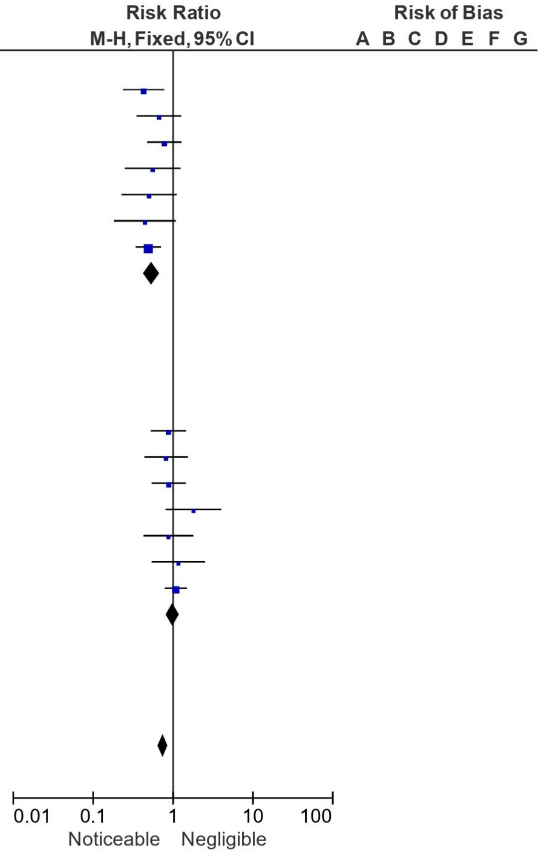
FIGURE 4. Overall clinical efficacy of PRP as observed in the selected studies represented in terms of RR. M-H: Mantel-Haenszel; CI: Confidence interval.

Study or Subgroup	Noticeable Events	Noticeable Total	Negligible Events	Negligible Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Impact of PRP on periapical regeneration						
Alagl et al 2017	9	30	21	30	9.3%	0.43 [0.24, 0.78]
Bezgin et al 2015	8	20	12	20	5.3%	0.67 [0.35, 1.27]
Cheng et al 2022	14	32	18	32	8.0%	0.78 [0.47, 1.28]
El Sheshtawy et al 2020	5	14	9	14	4.0%	0.56 [0.25, 1.24]
Narang et al 2015	5	15	10	15	4.4%	0.50 [0.22, 1.11]
Rizk et al 2019	4	13	9	13	4.0%	0.44 [0.18, 1.08]
Ulusoy et al 2019	24	73	49	73	21.7%	0.49 [0.34, 0.71]
Subtotal (95% CI)		**197**		**197**	**56.6%**	**0.54 [0.43, 0.67]**
Total events	69		128			
Heterogeneity: Chi² = 3.56, df = 6 (p = 0.74); I² = 0%						
Test for overall effect: Z = 5.58 (p < 0.00001)						
2.1.2 Impact of PRP on root canal healing						
Alagl et al 2017	14	30	16	30	7.1%	0.88 [0.53, 1.45]
Bezgin et al 2015	9	20	11	20	4.9%	0.82 [0.44, 1.53]
Cheng et al 2022	15	32	17	32	7.5%	0.88 [0.54, 1.44]
El Sheshtawy et al 2020	9	14	5	14	2.2%	1.80 [0.81, 4.02]
Narang et al 2015	7	15	8	15	3.5%	0.88 [0.43, 1.80]
Rizk et al 2019	7	13	6	13	2.7%	1.17 [0.54, 2.53]
Ulusoy et al 2019	38	73	35	73	15.5%	1.09 [0.78, 1.50]
Subtotal (95% CI)		**197**		**197**	**43.4%**	**1.01 [0.83, 1.23]**
Total events	99		98			
Heterogeneity: Chi² = 3.49, df = 6 (p = 0.75); I² = 0%						
Test for overall effect: Z = 0.10 (p = 0.92)						
Total (95% CI)		**394**		**394**	**100.0%**	**0.74 [0.64, 0.86]**
Total events	168		226			

Heterogeneity: Chi² = 23.50, df = 13 (p = 0.04); I² = 45%

Test for overall effect: Z = 4.01 (p < 0.0001)

Test for subgroup differences: Chi² = 17.53, df = 1 (p < 0.0001), I² = 94.3%



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

FIGURE 5. Impact of PRP across different parameters of tooth healing as observed in the selected studies represented in terms of RR. M-H: Mantel-Haenszel; CI: Confidence interval; PRP: Platelet-rich plasma.

Events are the effect of PRP on healing of the root canal observed. Study weights ranged from 2.2% to 15.5%. The RR measures with their 95% CI provide a summary estimate of the effect of PRP treatment on healing of the root canal. The summary RR estimate is 1.01 with no significant effect of PRP on outcome. The 95% CI for RR is between 0.83 and 1.23, and includes the null value of 1. Test for heterogeneity, based on the Chi-square test (χ^2) and I^2 statistic, reveals no significant heterogeneity of the studies ($\chi^2 = 3.49$, $df = 6$, $p = 0.75$; $I^2 = 0\%$). This implies that the observed heterogeneity of effect measures among the studies is by chance and not by true heterogeneity of the effect of PRP treatment on healing of the root canal. The test for overall effect, based on the Z-statistic, is 0.10 with a corresponding p-value of 0.92. This result shows a non-significant overall effect of PRP treatment on healing of the root canal, further revealing the negligible effect observed. This second forest plot, thus, shows a null overall effect of PRP treatment on healing of the root canal, as evidenced by the RR estimate of 1.01 and the non-significant test for overall effect. The patient studies range between 2.2% and 15.5% by event rate. These findings show that PRP treatment is not effective on success of healing of the root canal. It is, however, important to add that additional studies must be conducted to confirm the findings and examine possible factors affecting the efficacy of PRP in the above context.

4. Discussion

The results reported in this review are of particular significance. The meta-analysis reveals a significant overall effect of PRP treatment on regeneration of the periapical area, as reported by the RR estimate of 0.54 and the significantly different test of overall effect. The individual studies used in the analysis contained different event rates, which implies that PRP treatment leads to reduced risk of adverse periapical regeneration. These results imply the potential of PRP as a therapeutic agent to induce favorable outcomes of periapical regeneration. The meta-analysis also reveals, however, a trivial overall effect of PRP treatment on this root canal healing, as reported by the RR estimate of 1.01 and the non-significant test of overall effect. The individual studies also contained different event rates, which implies that PRP treatment has no significant influence on the outcome of root canal healing. These results imply that PRP may not have significant effects on root canal healing. The role of these results lies in the potential implications of the findings for clinical practice. The significant overall effect of PRP treatment on regeneration of the periapical area implies that the use of PRP in addition to treatment protocols for immature permanent teeth in children may yield favorable outcomes and lower risk of adverse regeneration. The restricted impact observed in root canal healing, nonetheless, indicates that PRP is not going to be of significant value in this particular case. The findings also indicate the requirement of further research to confirm the findings and determine possible factors that may affect the efficacy of PRP treatment. These would encompass factors like variation in PRP preparation protocols, patient, and treatment protocols that may be accountable for heterogeneity of the results reported. Future studies will need to consider such factors in order to offer more concrete evidence for the efficacy of PRP treatment in the management of permanent immature teeth in children.

Clinical evidence of pulp regeneration is generally confirmed by a positive response to the pulp sensitivity test [21]. While the determination of root development in mature teeth is challenging to assess, application of the pulp sensitivity test can still receive positive responses due to biological repair mechanisms. The studies that formed the basis of this review utilized predominantly temperature tests or electric tests for pulp sensitivity. However, take note that the tests could give false positive symptoms, particularly in injured and immature permanent teeth [22]. Previous researches on pulp activity indicated that blood supply, rather than the nervous system, is a more accurate predictor of pulp vitality [23, 24]. In disinfection of the root canal and obturation of the crown, application of minocycline and other disinfection materials has been suspected to be associated with crown discoloration [25–32]. For instance, a TAP study utilizing minocycline as a root canal disinfectant reported subsequent tooth discoloration [26, 33]. In an *in vitro* study, it was demonstrated that of three antimicrobial agents, minocycline alone caused crown discoloration [26, 31]. A study of the influence of mineral trioxide aggregate (MTA) on crown discoloration indicated that gray MTA and white MTA caused discoloration *in vitro* [34]. Bismuth oxide, a component of MTA, has been suspected to be the causative agent for staining since it reacts with the collagen present in the dentin matrix [35–37]. Gasparro *et al.* [38] found that application of leukocyte- and platelet-rich fibrin (L-PRF) after third molar impacted extraction resulted in greater gain of clinical attachment level (CAL) and probing depth reduction compared with control sites, and suggested that L-PRF might facilitate prevention of clinical attachment loss as a result of third molar malposition. A subsequent literature review by the same author [39], discussed the ability of non-transfusional hemocomponents, autogenous products obtained from a patient's blood sample, to regenerate tissues and heal wounds. These novel tools are widely used in many medical and surgical procedures involving tissue regeneration or repair, and the authors also emphasized the need for additional research and clinical trials for effective use of the products in regenerative therapy.

Recent advances also extend to digital health and computational tools. Light gradient boosting models have been successfully applied to predict quality of life in oral cancer survivors, suggesting that artificial intelligence may soon support personalized prognostic evaluation in regenerative therapies as well [40–42]. Furthermore, genetic and syndromic conditions, such as hereditary gingival fibromatosis linked to KCNK4 (Potassium Two Pore Domain Channel Subfamily K Member 4) mutations, remind us that biological variability must be carefully considered when evaluating tissue healing potential [43–45].

Our study, as well as the other reviews [11, 44, 46], also incorporated the use of PRP and/or PRF in this setting. The studies all agreed that teeth treated with PRP or PRF were clinically asymptomatic but showed improvement in most aspects of root development and periapical healing, such as apical closure, root lengthening, thickening of the dentin wall, and resolution of the periapical lesion, as in our study. Our study, as well as Tang *et al*. [11], Lolato *et al*. [42], and Murray *et al*. [46], concluded that PRP and PRF were superior to the traditional blood clot (BC) scaffold in a few aspects, such as periapical healing and apical closure. Saxena *et al*. [40], Metlerska *et al*. [41], Kiaipour *et al*. [43], and Li J *et al*. [45] studies also had favorable outcomes in pulp vitality and root development when PRP or PRF was employed.

There were some differences between our study and the others, however. Our study found statistically significant periapical regeneration improvements and a decrease in the risk of unfavorable periapical regeneration with PRP treatment, whereas some studies, *e.g.*, Tang *et al*. [11] and Lolato *et al*. [42], found non-statistically significant improvements. Our study also found an imperceptible effect of PRP on root canal healing, whereas other studies, *e.g.*, Metlerska *et al*. [41] and Kiaipour *et al*. [43], found positive outcomes for pulp vitality and root growth. Sabeti *et al*. [44] found that PRP and PRF were effective in the short term but not the long term, whereas our study did not find the long-term effectiveness of these treatments specifically. The study of Li J *et al*. [45] compared the effectiveness of concentrated growth factor (CGF) and PRF, and found comparable clinical performance between them, whereas our study compared PRP and did not include CGF.

4.1 Limitations

This study was also subject to a number of limitations that must be considered. First, data extraction, although stringent as it was conducted by two separate reviewers, is susceptible to human error and interpretative bias. In spite of the measures to reduce discrepancies through discussion to achieve consensus, the likelihood of discrepancies and misinterpretations during data extraction cannot be completely ruled out. Second, the use of reported data from included studies has the potential to introduce the risk of selective reporting and missing data. Third, analysis was conducted on some of the outcome measures, for instance, periapical regeneration and root canal healing, without consideration of other clinically relevant outcomes or long-term follow-up. This restricted the scope and potential to miss possible benefits or side effects of PRP treatment relevant to decision-making at the clinical level. Lastly, the generalizability of the findings may be influenced by the population under consideration and variations in PRP preparation protocols and treatment techniques between the included studies. The findings may not be universally applicable to other age groups or other dental diseases.

4.2 Clinical recommendations

Based on our evidence, some suggestions can be drawn about regenerative endodontic treatment of immature necrotic permanent teeth. PRF and PRP can be employed as possible scaffolds since they have demonstrated encouraging outcomes in root development, periapical healing, and tooth survival. The treatment protocol should include various irrigants, like NaOCl, CHX, and EDTA, for effective disinfection and root canal system conditioning. Intracanal medicaments, like TAP and $Ca(OH)_2$, can also be employed to further improve the disinfection process and provide tissue regeneration-favorable environment.

To assess the effectiveness of treatment by the regenerative treatment and the long-term prognosis of the tooth, pulp vitality response to cold, heat, and electric stimulation should be assessed. Radiographic examination should be performed to assess the changes in root length, width, apical diameter, and periapical bone density because these parameters are very revealing of the treatment effectiveness and subsequent dental development. Long-term follow-up, 1 to 2.35 years and more, is needed to monitor the stability of the treatment result and establish any potential complications or the need for further intervention.

In PRP versus PRF choice, we must keep in mind that PRF has been found to demonstrate significant gains in the parameters of growth when applied to immature permanent necrotic teeth compared with PRP and conventional blood clot therapies. Although PRP has indeed been found effective in reducing the size of lesions that have ocurred, activating periapical bone density, and activating root growth overall, its effectiveness may not be significantly higher than conventional blood clot scaffold therapy in some instances.

Further studies with more patients and standardized protocols are needed to provide firm guidelines for the application of PRP and PRF in regenerative endodontic treatment and to establish the ideal treatment parameters to use for the best clinical results. Practitioners need to stay current with the newest developments in regenerative endodontic research and modify their treatment protocols based on the new findings to offer the best and evidence-based treatment for immature necrotic permanent teeth patients.

5. Conclusion

Findings reveal a general significant effect of PRP treatment on periapical healing with reduced risk of adverse outcomes as evidenced by the meta-analysis. The analysis, however, reveals a small effect of PRP on the root canal healing with an RR estimate of 1.01. Findings reveal the potential of PRP as a valuable adjunctive therapy to enhance periapical healing in this patient population. Nevertheless, several issues have been identified in the current study which should be addressed in future research, such as bias in the selection of studies included in this research, restricted search techniques, variations in data collection, and limited criteria for study outcomes. Moreover, other factors that may be affecting the effectiveness of PRP treatment must be investigated. In general, the study contributes to the literature and presents strong evidence for clinical practitioners to make a well-informed decision regarding the use of PRP in the treatment of immature permanent teeth in children.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

AK, SA—conceptualization. SA—methodology. SAM—software; resources; data curation. AAB—validation; formal analysis. AAB, SAM—investigation. MMM, GM, AK—writing—original draft preparation. MC, GM—writing—review and editing; supervision. LA—visualization. AK, LA—project administration. AK—funding acquisition. MDB, GM, MC—writing, editing and supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

During the preparation of this manuscript, the authors used DeepL Translate for language checking/grammar correction. After its use, the authors thoroughly reviewed, verified, and revised all content to ensure accuracy and originality. The authors take full responsibility for the integrity and final content of the published article.

Moreover, the authors would like to acknowledge Luis Eduardo Almeida, a native English speaker at the Department of Surgical Sciences, School of Dentistry, Marquette University, Milwaukee, Wisconsin, USA, for reviewing and editing the manuscript to ensure proper scientific English. Moreover authors would like to acknowledge Mario Fordellone a professional statistic that revisioned the statistics of this paper.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Giuseppe Minervini was a member of the Editorial Board of this journal at the time of submission. We declare that Giuseppe Minervini had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to VB.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/2049724247289282560/attachment/Supplementary%20material.docx.

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How to cite this article: Ateet Kakti, Sarah A Mubaraki, Saeed Alamoudi, Lulya Alzain, Ahmed Abdullah Bahamid, Marco Di Blasio, Maria Maddalena Marrapodi, Marco Cicciù, Giuseppe Minervini. Assessment of the efficacy of platelet-rich plasma in treatment of immature permanent teeth in children: a systematic review and meta-analysis. Journal of Clinical Pediatric Dentistry. 2026; 50(3): 51-62. doi: 10.22514/jocpd.2026.060.