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Association of apical maturity with clinical and biological outcomes after regenerative endodontic procedures: a systematic review, meta-analysis, dose-response meta-analysis and trial sequential analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202640005

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 1 April 2026 and was last updated on 1 April 2026.

INTRODUCTION

Review question / Objective This study is aimed to systematically evaluate the outcomes of regenerative endodontic procedures (REPs) in teeth with varying degrees of root maturity and investigate how initial apical diameter influences clinical success, tooth survival, complete apical closure and pulp vitality recovery rates.

Condition being studied Patients receiving regenerative endodontic treatment include immature and mature permanent teeth (with pulp necrosis).

METHODS

Search strategy A systematic electronic search is conducted up to July 2025, with no date restrictions applied. The search is extended to July 2025 to provide the most current evidence available at the time of analysis and was conducted with no lower date limit to capture the

full historical development of regenerative endodontic evidence. Five electronic databases are searched: PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE) (<https://pubmed.ncbi.nlm.nih.gov/>), Embase via Ovid (<https://www.embase.com/>), Web of Science Core Collection (<https://www.webofscience.com/>), Scopus (<https://www.scopus.com/>) and Cochrane Central Register of Controlled Trials (CENTRAL) (<https://www.cochranelibrary.com/>). Search terms will combine controlled vocabulary (medical subject heading [MeSH] terms, where applicable) and free-text keywords. The full electronic search strategies use for all databases are provided in Supplementary Appendix S1.

For PubMed (MEDLINE), the search strategy is: (('REP*' OR 'pulp revascularisation' OR revascularisation [MeSH])) AND (('immature permanent teeth' OR 'root development' OR 'apical closure' OR apexification)) AND (('treatment outcome' [MeSH] OR 'clinical outcome*' OR success OR survival OR 'pulp vitality')).

Participant or population The population (P) comprised the immature and mature permanent teeth (with necrotic pulps) of patients undergoing Regenerative endodontic procedures.

Intervention Intervention refers to the regenerative endodontic treatments/materials used, including blood clot (BC) formation, platelet-rich fibrin (PRF), triple antibiotic paste (TAP), calcium hydroxide (CaOH), mineral trioxide aggregate (MTA), fibroblast growth factor (FGF) and other regenerative materials.

Comparator Comparison denotes conventional apexification (e.g. MTA apexification) or comparisons among different regenerative techniques (single-arm observational studies and case series of ≥ 5 teeth were also eligible).

Study designs to be included Randomised controlled trials (RCTs), prospective and retrospective cohort studies and case series involving ≥ 5 teeth will be included.

Eligibility criteria Studies are excluded if they were animal or in vitro studies, reviews, letters, commentaries, single case reports, case series with < 5 teeth or conference abstracts or protocols without published full-text results.

Information sources PubMed/Medical Literature Analysis and Retrieval System Online (MEDLINE) (<https://pubmed.ncbi.nlm.nih.gov/>), Embase via Ovid (<https://www.embase.com/>), Web of Science Core Collection (<https://www.webofscience.com/>), Scopus (<https://www.scopus.com/>) and Cochrane Central Register of Controlled Trials (CENTRAL) (<https://www.cochranelibrary.com/>).

Main outcome(s) Outcomes include clinical success rate (primary outcome) and tooth survival, complete apical closure and pulp vitality recovery rates (secondary outcomes).

Quality assessment / Risk of bias analysis Study quality was evaluated independently by two reviewers according to study design. Randomised controlled trials were assessed using the Cochrane Risk of Bias tool 2 (RoB 2.0). Five domains were evaluated (randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes and selective reporting), and each study's risk of bias was classified as 'low', 'some concern' or 'high'. Observational studies (cohort and case series) were evaluated using the Newcastle–Ottawa scale (NOS), covering three main domains (selection of study groups, comparability of groups and

ascertainment of outcomes). Studies were classified as being of low (0–4 stars), moderate (5–6 stars) or high (7–9 stars) quality. Consensus discussions or arbitration by a third reviewer resolved any disagreements.

Strategy of data synthesis Meta-analyses are performed using R (version 4.3.0, R Foundation) with the meta and metafor packages. Proportions and 95% confidence intervals (CIs) are calculated using random-effects models (the DerSimonian–Laird method). Heterogeneity among studies is quantified using Cochran's Q statistic (with $P < 0.10$ indicating significant heterogeneity) and the I^2 statistic (with 60% as substantial). Forest plots are generated to visualise pooled effect estimates for each outcome.

Dose–response meta-analysis between apical maturity (represented as apical diameter in millimetres or approximated from Cvek classification) and outcomes is evaluated using two-stage generalised least squares regression models in R (the dosresmeta package). Restricted cubic splines (three knots) are employed to model potential nonlinear relationships. It should be noted that methods of measuring and reporting apical diameters varied across the included primary studies (e.g. radiographic measurement, Cvek stage estimation, clinical estimation), and Cvek classification stages were approximated to continuous apical diameter values based on published reference standards. This heterogeneity in apical diameter assessment is acknowledged as a potential source of bias and increased statistical heterogeneity in the DRMA. Subgroup analyses by regenerative materials are also conducted as exploratory analyses.

Trial sequential analyses are conducted to assess the robustness and sufficiency of evidence for the primary outcome (clinical success) and a secondary outcome (tooth survival) and performed using R (the RTSA package). Conventional boundaries ($\alpha = 0.05$, $\beta = 0.20$, power = 80%) and required information size (RIS) are calculated using the O'Brien–Fleming α -spending function to generate trial sequential monitoring boundaries. Publication bias is assessed visually using funnel plots for each outcome.

Subgroup analysis Subgroup analyses by regenerative materials are also conducted as exploratory analyses.

Sensitivity analysis Sensitivity analyses are pre-specified to examine the robustness of meta-analysis findings by excluding studies with a high or unclear risk of bias, evaluating fixed effect versus random-effects models and conducting

leave-one-out analyses to assess individual study influence.

Country(ies) involved China - Shaoxing Stomatological Hospital.

Keywords dental pulp necrosis, endodontics, regeneration, root canal therapy, tooth apex, treatment outcome.

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