Received: 17 August 2021 | Accepted: 22 March 2022

DOI: 10.1111/iej.13736

INTERNATIONAL ENDODONTIC JOURNAL | WILEY

REVIEW ARTICLE

Outcomes of primary root canal therapy: An updated systematic review of longitudinal clinical studies published between 2003 and 2020

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Abstract

Background: A comprehensive effort to evaluate outcomes of primary root canal therapy (RCT) between 1966 and 2002 was published by Ng et al. (2007, *International Endodontic Journal*, 40, 921; 2008, *International Endodontic Journal*, 41, 6). Changes in endodontic materials and treatment methods warrant an updated analysis of outcomes.

Objectives: This study aimed to (1) quantify the success rates of primary RCT published between 2003 and 2020; and (2) investigate the influence of some characteristics known/suspected to be associated with treatment outcomes.

Methods: An electronic search was performed in the following databases (01-01-2003 to 12-31-2020): Pubmed, Embase, CINHAL, Cochrane and Web of Science. Included study designs were longitudinal clinical studies (randomized control trials, cohort studies, retrospective observational studies). Studies with at least twelve-months of post-operative review and success rates based on clinical and radiographic criteria were analysed. The terms 'strict' (complete resolution of periapical lesion) or 'loose' (reduction in size of existing periapical lesion) were used to describe the outcome criteria. Weighted, pooled success rates were calculated. Random effects meta-regression models were used to investigate potential sources of statistical heterogeneity. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to evaluate for quality assessment of the included studies.

Results: Forty-two studies were included in the review. Meta-analyses showed that the weighted pooled success rates were estimated to be 92.6% (95% CI: 90.5%–94.8%) under 'loose criteria' and 82.0% (95% CI: 79.3%–84.8%) under 'strict' criteria. The most significant areas of study heterogeneity were year of publication and qualification of operator. The majority (64.29%) of studies were considered to be of low quality of evidence.

Discussion: Biological factors continue to have the most significant impact on RCT outcomes. The technological method of instrumentation had no significant effect.

The quality of evidence was based primarily on study design and only randomized control trials were considered to be 'high' quality of evidence.

Conclusions: The reported success rates show improvement over time. Weighted success rates for studies with a minimum of four-years follow-up had better outcomes, compared to those with less than four years, when 'strict criteria' were used.

Registration: PROSPERO database (CRD42021226311).

KEYWORDS

primary root canal therapy, systematic review, treatment outcomes

INTRODUCTION

The goal of root canal therapy, the prevention or elimination of apical periodontitis of endodontic origin, is closely coupled with the interest to quantify endodontic treatment success. Several endodontic scholars have sought to summarize the outcomes of primary root canal therapy, including but not limited to Lewsey et. al (2001), Basmadjian-Charels et al. (2002), Friedman (2002), Chugal et al. (2001) and Sathorn et al. (2005). One of the most comprehensive, systematic efforts to evaluate the outcomes of primary root canal treatment, the effect of study characteristics and the influence of treatment factors on the probability of success was published in two parts by Ng et al. (2007, 2008). As a result of her group's evaluation of 63 longitudinal clinical studies, published between 1922 and 2002, the estimated pooled success rates of primary root canal treatment with at least 1 year follow-up, ranged between 68% and 85% (Ng et al., 2007). When applying a 'strict' success criterion, that required complete healing of periapical pathology, 40 analysed studies indicated an overall success rate of 74.7% (Ng et al., 2007). Evaluations using a 'loose' criterion of success, where reduction in the size of radiolucency was also considered successful, the success increased to 85.2%, based on 36 studies (Ng et al., 2007).

The systematic reviews by Ng et al. have been influential in changing the landscape of outcome studies in endodontics (Ng et al., 2007, 2008). Noting that the quality of evidence for treatment factors affecting primary root canal treatment outcomes was suboptimal, the findings of her group's work called for standardization in the aspects of study design, data recording and presentation of outcome data. This included: (1) mandatory reporting of the definition for the criteria for success as part of the methodology, preferably stratified by loose and strict outcome criteria; (2) the good practice of having at least two pre-calibrated observers, reporting intra and inter observer agreement rates by kappa score to reduce variability in radiographic assessment; (3) standardization of the duration of follow-up for all patients or, at least, the inclusion of the duration as a covariate into the statistical model to account for variations in the success rate based on different follow-up times; (4) the use of survival analysis techniques to analyse the time to healing (success), understanding that this method would require regular follow-up of all patients; (5) A minimum follow-up period of 1 year and preferably, at least three years after completion of treatment (Ng et al., 2007, 2008).

Aware that root canal treatment consists of a cumulative series of interdependent steps, several researchers including Strindberg (Strindberg, 1956) and Ng's group (Ng et al., 2007, 2008) have acknowledged that the probability of treatment factors interacting and therefore influencing treatment outcomes is extremely high. They found that the statistical methods used for analysing the association between potential influencing factors and treatment outcomes did not account for all of the effects of potential confounders. The findings of Ng's group, in agreement with other outcome studies (Ng et al., 2007; Sjogren et al., 1990), concluded that the following conditions significantly influenced the outcome of primary root canal treatment: (1) pre-operative presence of periapical lesion; (2) apical extent of root canal filling; (3) quality of root canal filling; (4) post-treatment restorative status.

Guided by the methodology of Ng et al. (2007) the aims of this study were: (1) to conduct an updated systematic review of the literature on the outcome of primary (initial or first time) root canal treatment published between 2003 and 2020; (2) to investigate the influence of some characteristics known or suspected to significantly impact the outcome of primary root canal treatment: year of treatment, length of follow-up, geographic location of treatment, qualification of operators, pre-operative presence of periapical lesion and method of instrumentation.

METHODS

A detailed protocol of this systematic review and meta-analysis was defined and agreed to by all authors, in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols statement (PRISMA-P; Page et al., 2021; Shamseer et al., 2015). This protocol of the review was registered in the international prospective register of systematic previews: PROSPERO database (CRD42021226311). The PRISMA checklist is included as Table S1.

Literature search

Longitudinal clinical studies investigating the outcome of primary root canal treatment published between January 1, 2003 and December 31, 2020 were identified using electronic databases: Pubmed, Embase, CINHAL, Cochrane CCTR and Web of Science (Figure 1). There were no language restrictions applied. Electronic database searches were supplemented by hand searching the last 10 years of the Journal of Endodontics, International Endodontic Journal, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, and Dental Traumatology. Keywords and search strategies identified by Ng et al. (2007) were used to develop the search strategy for this study (Table S2). For duplicate removal and further analysis, all records were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at: www.covidence.org).

Inclusion criteria

Clinical studies (randomized control trials (RCT), cohort studies, retrospective observational studies) were selected based on modifications to the inclusion criteria used by Ng et al. (2007):

1. Data allowed for tooth-level outcome assessment.
2. Stratified analysis of primary root canal therapy available, if other treatment types had been included.
3. Sample size provided.
4. At least 12-months post-operative review.

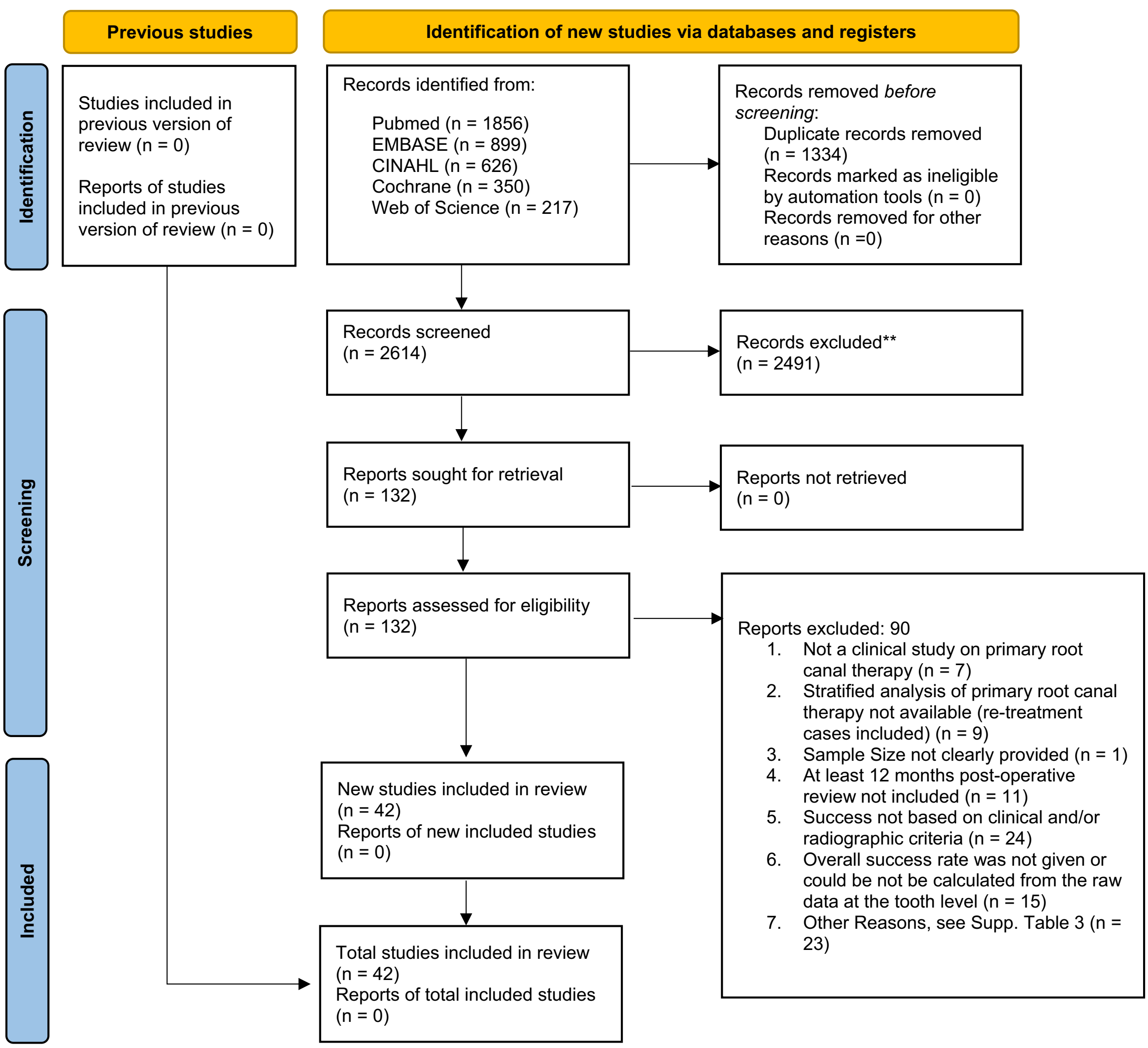

FIGURE 1 Prisma 2020 Flow Diagram

5. Success determined based on clinical and radiographic criteria.
   a. Clinical success was defined as the absence of clinical symptoms, as defined by the individual study.
   b. Radiographic success was characterized by either 'strict' or 'loose' criteria.
      (i) 'Strict' radiographic criteria of success: the absence of apical radiolucency at follow-up examination
      (ii) 'Loose' radiographic criteria of success: reduction in the size of apical radiolucency at follow-up examination
6. Overall success rate given or could be calculated from the raw data provided.
7. Other reasons specified: authors could translate study to English; clinical protocol was described; data was not already reported in a previously included study; appropriate study quality

Study selection and data extraction

Title and abstract screening were performed independently by 2 reviewers (LEB, and either RA, or JK). A third reviewer (AS) was consulted to resolve any conflicts. Two reviewers (LEB and JK) independently evaluated the full-texts of the studies that passed the title and abstract screening and extracted relevant data from the included studies utilizing a custom-designed data collection form in RedCap (Harris et al., 2009). The data extracted included: general information (author, year, title, journal, geographic location); study design (years of treatment, treatment setting, qualification of operators, sample size, follow-up period, outcome criteria and assessment); noted medical conditions of patients; and pre-, intra- and postoperative factors.

Quality of evidence

The quality of evidence for each study was appraised with guidance from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Handbook (Schünemann et al., 2013). In the GRADE approach to quality of evidence, randomized trials without important limitations provide 'high' quality evidence and observational studies without special strengths or important limitations provide 'low' quality evidence. Thus, the determined quality of the evidence of the studies in this review was predominately driven by study design. According to GRADE, factors that can reduce the quality of the evidence (1 or 2 levels) include the following: limitations in study design or execution (risk of bias); inconsistency of results; indirectness of evidence; imprecision; publication bias. An assessment of factors that may impact the quality of evidence for the included studies were guided by the findings of Ng et al. (2007) and Wu et al. (2009). The following were considered to be study limitations: a single radiographic observer (risk of bias); calibration of radiographic observers not documented (risk of bias); re-examination rates under 50% (risk of bias) and inconsistencies, indirectness, imprecision or publication bias in the reporting of outcomes. The overall quality of evidence level was adjusted when more than one factor considered to have a negative impact on quality of evidence was identified. GRADE's quality of evidence levels include: 'high', 'moderate', 'low' and 'very low' (Schünemann et al., 2013).

Data synthesis and statistical analysis

All statistical analyses were performed in R version 4.0.3 for Windows (R Core Team, 2020). Un-weighted pooled success rates by each factor were calculated by dividing the total number of successful units with the total number of units (excluding uncertain units) within the respective category according to Hepworth and Friedman (Hepworth & Friedman, 1997). The weighted pooled success rates were estimated using random effects meta-analysis with DerSimonian and Larid's methods (DerSimonian & Laird, 1986). Statistical heterogeneity across different subgroups of the studies was assessed by Cochran's (Q) test (Cochran, 1954).

The weighted effect of pre-operative periapical lesion on success rate was estimated and expressed as odds ratios (OR) for the dichotomous outcomes (success or failure) using a random-effect meta-analysis. This analysis was restricted to studies providing partitioned data on success rates, enabling direct comparison of sub-categories of characteristics investigated in the same study.

Meta regression models (Thompson & Higgins, 2002) were used to investigate the potential sources of statistical heterogeneity. The following study characteristics were considered in the meta-regression analyses as covariates: year of publication (2003–2010 and 2011–2020), geographical location (USA or Canada, Asia, Europe, South/Central America, and Other), qualification of operators (general dentist, endodontist, dental students, post-graduate student, mixed), treatment setting (private practice, academic and hospital), tooth type (single rooted, multiple rooted, both), method of instrument (hand, rotary, both), presence of pre-operative periapical lesion (present or absent), number of observers and observer calibration. Studies with any missing data on these covariates were excluded from meta-regression analyses. Different aspects of data were missing from different studies; thus, when individual factors' effect on the success rates across studies was assessed, the pool of studies could vary. When investigating potential sources of heterogeneity, only studies with no missing covariates were included in the analysis. Covariates were considered as a potential source of heterogeneity if: (1) the estimated proportion of total variation due to heterogeneity across studies (I^2) was reduced substantially (>10%) when a covariate was included into the model or (2) the estimated between-study variance (τ^2) from the meta-regression model without any covariate in the model was reduced substantially (>10%) when a covariate was included into the model.

RESULTS

The electronic searches produced 3948 results: Pubmed (1856), Embase (899) and CINAHL (626), Cochrane CCTR (350) and Web of Science (217). One article was added from hand searching the last 10 years of the Journal of Endodontics, International Endodontic Journal, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, and Dental Traumatology. After duplicates were removed 2614 abstracts remained. After abstract screening, 132 studies were selected for full text review. After full text review, 90 studies were excluded for the reasons given in Table S3. Forty-two studies fulfilled the inclusion criteria for this review and underwent statistical analysis. The search and review processes are outlined in Figure 1. The years of publication of the selected studies ranged from 2003 to 2020, 69% were published between 2011 and 2020 (Table 1).

Methodological characteristics of included studies

Of the 42 included studies, 15 (35.7%) were RCTs, 14 (33.3%) were prospective cohort studies and 13 (31%) were retrospective studies (Table 1). Although five studies (Chybowski et al., 2018; Cotton et al., 2008; Imura et al., 2007; Pirani et al., 2015; Prati et al., 2018) included other treatment procedures in their protocols, they provided stratified analysis for primary root canal therapy. Teeth were used as the unit of evaluation and the reported sample sizes ranged from 27 to 1376 teeth with a median of 107 teeth. Re-examination rates were reported for 36 studies, at either the tooth or patient level, and ranged from 23% to 100% with a median of 76%.

The majority, (38, 90.5%) of studies determined the treatment outcome by clinical and radiographic assessment. Four studies additionally used CBCT evaluation in their outcome assessment (Tables 1 and 2). The terms 'strict' (complete resolution of peri-apical lesion) or 'loose' (reduction in the size of existing peri-apical lesion) were used to describe the outcome criteria. For 18 studies, outcomes could be calculated using both the 'strict' and 'loose' criteria. It was noted that at least two observers conducted radiographic assessment outcome in 36 (85.7%) studies (Table 2). The radiographic observers were reported to be calibrated and/or inter-observer reliability calculations were performed in 33 (78.6%) studies (Table 2).

The reported success rates from the included studies ranged from 73.3% to 100% based on 'loose' criteria and from 29.8% to 97.3% based on 'strict' criteria. The weighted pooled success rates from studies using 'strict' criteria (data available from 39 studies) were about 10% lower than that from studies using 'loose' criteria (data available from 21 studies). Meta-analyses showed that the weighted pooled success rates were estimated to be 92.6% (95% CI: 90.5%–94.8%) under 'loose' criteria and 82% (95% CI: 79.3%–84.4%) under 'strict' criteria. Figures 2 and 3 present estimated success rates by individual studies as well as the weighted pooled success rates by the two radiographic criteria, respectively. The weighted success rates of the subgroups differed substantially (Cochran's (Q) test: $p < .001$) in the mixed-effect model. Therefore, statistical analyses of potential source of heterogeneity caused by individual factors were conducted separately for data based on the use of 'strict' or 'loose' criteria. Table 2 reports unweighted pooled success rates and weighted pooled success rates by study characteristics and outcome criteria.

Success rates by study characteristics

Year of publication

The weighted pooled success rates based on 'loose' outcome criteria were 90.9% for studies published between 2003 and 2010 compared to 93.1% for studies published between 2011 and 2020. The weighted success rates based on 'strict' outcome criteria were 82.6% for studies published between 2003 and 2010 compared to 81.5% for studies published between 2011 and 2020.

Years of treatment

Whilst the years of publication of the selected studies ranged from 2003 to 2020, the treatment periods ranged from 1971 to 2019. Years of treatment were not reported by 12 studies (Angerame et al., 2017; Arya et al., 2017; Demirci & Çalışkan, 2016; Dorasani et al., 2013; Molander et al., 2007; Verma et al., 2019, 2020; Wong et al., 2015; Zavattini et al., 2020). When evaluated as a categorical

TABLE 1 Study characteristics

Author (year)	Location	Study design[a]	Reexam rate	≥4 year follow-up	Year of treatment	Sample size	Outcome assessment[b]	Radiographic criteria of success[c]	Operator	Treatment Setting	Tooth type	Method of instrument[d]	Number of observers	Calibration	Pre-op pulpal diagnosis	Pre-op PARL[e]	Presence of restoration at follow-up noted
Angerame et al. (2017)	Europe	RCT	100%	No	Missing	Missing	C & R	S/L	Missing	Missing	Single rooted	R	2	Missing	Non-Vital	Y-All	No
Aqrabawi (2006)	Other (Jordan)	R	Missing	Yes	Before 2000	340	C & R	S	Endodontist	Academic	Both	H	1	Yes	Missing	Y-All	No
Arya et al. (2017)	Asia	P	77%	No	Missing	60	C & R	S/L	Missing	Academic	Multiple rooted	R	2	Yes	Non-Vital	Y- All	No
Chu et al. (2005)	Asia	P	84%	Yes	Before 2000	85	C & R	S	General Dentist	Academic	Both	H	1	Yes	Both	Y+N	Yes
Chybowski et al. (2018)	USA or Canada	P	Missing	No	After 2000	235	C & R	S/L	Endodontist	Private practice	Both	R	2	Yes	Both	Missing	Yes
Cotton et al. (2008)	USA or Canada	R	42%	No	After 2000	67	C & R	S	Endodontist	Private practice	Both	R	2	Yes	Both	Y+N	Yes
Craveiro et al. (2015)	South/ Central America	P	23%	Yes	After 2000	523	C & R	S	Endodontist	Hospital	Both	Both	1	Yes	Non-Vital	Y+N	Yes
de Chevigny et al. (2008)	USA or Canada	P	24%	Yes	Cross 2000	582	C & R	S	Post-graduate student	Academic	Both	R	1	Yes	Both	Y+N	Yes
de-Figueiredo et al. (2020)	South/ Central America	RCT	73%	No	After 2000	120	C & R	S/L	Endodontist	Hospital	Single rooted	Both	2	Yes	Non-Vital	Y-All	No
Demirci and Çalışkan (2016)	Other (Turkey)	RCT	93%	No	Missing	120	C & R	S	Endodontist	Missing	Single rooted	H	2	Yes	Non-Vital	Y-All	No
Dorasani et al. (2013)	Asia	P	69%	No	Missing	64	C & R	S/L	Missing	Missing	Single rooted	R	Missing	Yes	Non-Vital	Y-All	No
Eyuboglu et al. (2020)	Other (Turkey)	R	66%	Yes	After 2000	137	C & R	S	Endodontist	Academic	Both	R	2	Yes	Non-Vital	Y+N	Yes
Farzaneh et al. (2004)	USA or Canada	P	35%	Yes	Before 2000	442	C & R	S	Post-graduate student	Academic	Both	H	1	Yes	Both	Y+N	Yes
Friedman et al. (2003)	USA or Canada	P	35%	Yes	Before 2000	405	C & R	S	Post-graduate student	Academic	Both	H	2	Yes	Both	Y+N	Yes
Galani et al. (2017)	Asia	RCT	89%	No	After 2000	27	C & R	S	Post-graduate student	Academic	Multiple rooted	R	2	Yes	Vital	N	Yes
Gill et al. (2016)	Asia	P	74%	No	After 2000	81	C & R	S/L	Post-graduate student	Academic	Single rooted	H	More than 2	Yes	Non-Vital	Y-All	No
Hale et al. (2012)	USA or Canada	R	Missing	No	After 2000	71	C & R	L	dental student	Academic	Both	R	2	Missing	Both	Y+N	Yes

TABLE 1 (Continued)

Author (year)	Location	Study design[a]	Reexam rate	≥4 year follow-up	Year of treatment	Sample size	Outcome assessment[b]	Radiographic criteria of success[c]	Operator	Treatment Setting	Tooth type	Method of instrument[d]	Number of observers	Calibration	Pre-op pulpal diagnosis	Pre-op PARL[e]	Presence of restoration at follow-up noted
Imura et al. (2007)	South/ Central America	R	Missing	Yes	Before 2000	1376	C & R	S	Endodontist	Private practice	Both	H	2	No	Both	Missing	Yes
Kist et al. (2017)	Europe	RCT	72%	No	After 2000	60	C & R	S/L	General Dentist	Academic	Both	R	2	Yes	Non-Vital	Y-All	Yes
Knight et al. (2020)	Europe	P	74%	No	After 2000	88	C & R & CBCT	S/L	Post-graduate student	Academic	Both	R	2	Yes	Both	Y+N	Yes
Kumar et al. (2020)	Asia	RCT	92%	No	After 2000	120	C & R	S	Missing	Academic	Multiple rooted	R	2	Missing	Non-Vital	Y-All	Yes
Llena et al. (2020)	Europe	R	71%	Yes	After 2000	820	C & R	S/L	Post-graduate student	Academic	Both	Both	2	Missing	Both	Y+N	Yes
Marquis et al. (2006)	USA or Canada	P	27%	Yes	Before 2000	532	C & R	S	Post-graduate student	Academic	Both	R	2	Yes	Both	Y+N	Yes
Molander et al. (2007)	Europe	RCT	88%	No	Missing	101	C & R	S/L	Endodontist	Hospital	Both	R	2	Yes	Non-Vital	Y-All	No
Ozer and Aktener (2009)	Other (Turkey)	RCT	82%	No	After 2000	98	C & R	S	Missing	Academic	Multiple rooted	R	2	Missing	Non-Vital	Y-All	No
Paredes-Vieyra and Enriquez (2012)	South/ Central America	RCT	94%	No	After 2000	300	C & R	S/L	Endodontist	Academic	Both	R	2	Yes	Non-Vital	Y-All	No
Penesis et al. (2008)	USA or Canada	RCT	68%	No	After 2000	97	C & R	S/L	Post-graduate student	Academic	Both	R	More than 2	Yes	Non-Vital	Y-All	No
Pirani et al. (2015)	Europe	R	70%	Yes	Before 2000	209	C & R	S	Endodontist	Private practice	Both	H	2	Yes	Both	Y+N	Yes
Prati et al. (2018)	Europe	R	55%	Yes	Before 2000	173	C & R	S	Endodontist	Private practice	Both	H	2	Yes	Both	Y+N	Yes
Restrepo-Restrepo et al. (2019)	South/ Central America	R	75%	Yes	After 2000	166	C & R & CBCT	S/L	Post-graduate student	Academic	Both	Missing	2	Yes	Non-Vital	Y-All	Yes
Ricucci et al. (2011)	Europe	P	60%	Yes	After 2000	Missing	C & R	S	General Dentist	Private practice	Both	H	2	Yes	Both	Missing	Yes
Saini et al. (2012)	Asia	RCT	78%	No	After 2000	167	C & R	S	Post-graduate student	Academic	Multiple rooted	H	More than 2	Yes	Non-Vital	Y-All	Yes
Sarin et al. (2016)	Asia	R	Missing	No	After 2000	146	C & R	S	Endodontist	Academic	Both	Missing	2	No	Non-Vital	Missing	No

TABLE 1 (Continued)

Author (year)	Location	Study design[a]	Reexam rate	≥4 year follow-up	Year of treatment	Sample size	Outcome assessment[b]	Radiographic criteria of success[c]	Operator	Treatment Setting	Tooth type	Method of instrument[d]	Number of observers	Calibration	Pre-op pulpal diagnosis	Pre-op PARL[e]	Presence of restoration at follow-up noted
Sigurdsson et al. (2016)	USA or Canada	P	84%	No	After 2000	89	C & R	S/L	Endodontist	Private practice	Multiple rooted	R	2	Yes	Both	Missing	Yes
Sigurdsson et al. (2018)	USA or Canada	P	98%	No	After 2000	45	C & R	S/L	Endodontist	Private practice	Multiple rooted	R	2	Yes	Non-Vital	Y-All	No
Siqueira et al. (2008)	South/ Central America	P	33%	No	Cross 2000	307	C & R	S/L	dental student	Academic	Both	Both	More than 2	Yes	Non-Vital	Y-All	Yes
Tang et al. (2015)	Asia	RCT	100%	No	After 2000	360	C & R	S	Endodontist	Hospital	Both	R	2	Yes	Non-Vital	Y-All	No
Verma et al. (2019)	Asia	RCT	86%	No	Missing	100	C & R	S/L	Missing	Academic	Multiple rooted	R	2	Missing	Non-Vital	Y-All	Yes
Verma et al. (2020)	Asia	RCT	83%	No	Missing	69	Clinical + CBCT	S/L	Missing	Academic	Single rooted	R	2	Missing	Non-Vital	Y-All	Yes
Wong et al. (2015)	Asia	RCT	86%	No	Missing	256	C & R	S	General Dentist	Academic	Both	R	2	Yes	Both	Missing	Yes
Zavattini et al. (2020)	Europe	P	83%	No	Missing	125	C & R & CBCT	L	mixed	Hospital	Both	R	2	Yes	Both	Missing	Yes
Zmener and Pameijer (2004)	South/ Central America	R	81%	No	After 2000	180	C & R	L	Endodontist	Private practice	Both	H	2	Yes	Both	Y+N	No

[a]R, retrospective cohort study or retrospective observational; C, prospective cohort study; RCT, randomized controlled trial.
[b]C&R, combined clinical and radiographic examination.
[c]S, strict criteria; L, loose criteria.
[d]H, hand instrumentation; R, Rotary instrumentation.
[e]Y, yes; N, no.

variable, studies with treatment periods before the year 2000 (8 studies) were compared to studies with treatment years in 2000 (23 studies) or later. Two studies (De Chevigny et al., 2008; Siqueira et al., 2008) were excluded from the comparison because years of treatment in this study occurred both before and after 2000). The weighted success rates based on 'strict' outcome criteria for treatment conducted before 2000 was 82.1%, compared to 84.1% for treatment performed after 2000.

Length of follow-up

Follow-up after completion of treatment ranged from 12-months to 19 years. Fourteen studies reported at least 48 months of follow-up. Outcomes for studies with a minimum of four-year follow-up period had a weighted success rate of 83.5% when 'strict' criteria were used, compared to 80.8% for studies that followed-up all of the cases for less than 4 years.

Geographic location of study

Published studies were conducted globally: 10 (23.8%) were conducted in the United States or Canada; 12 (28.6%) were conducted in Asia; 9 (21.4%) were conducted in Europe; 7 (16.7%) were conducted in Central or South America. The rest of the studies (4, 9.5%) were conducted in the countries Jordan and Turkey. Weighted success rates varied by geographic region: 91.2% USA or Canada, 90.6% Asia, 92.2% Europe, 94.1% in Central or South America when 'loose' evaluation criteria were used; 85.9% USA or Canada, 76.5% Asia, 80.7% Central or South America, 81.9% Europe and 89.5% other countries when 'strict' evaluation criteria were used.

Qualification of operators (undergraduate, postgraduate, general practitioner and specialist)

The reviewed studies classified operator qualification as (Table 2): undergraduate students (2 studies), general dentist (4 studies), post-graduate student (11 studies) and endodontist (17 studies). In Zavattini et al. (2020), treatment was performed by a mixed group of operators and 7 studies did not provide this information. There was only 1 study (Siqueira et al., 2008) reporting the use of undergraduates as operators under 'strict' outcome criteria and only 1 study (Kist et al. 2016) reporting the use of general dentists as operators under 'loose' outcome criteria. Meta-regression analyses showed that qualification of operators had no significant effect on the success rates ($p = .135$ under loose criteria and $p = .256$ under strict criteria, by the Cochran's (Q) test).

Effects of clinical characteristics on success rates

Presence of pre-operative periapical lesion

Eleven studies provided outcome data stratified by presence of pre-operative periapical lesion. The weighted success rates for teeth with pre-operative periapical lesions were lower than that for teeth without pre-operative periapical lesions, regardless of the use of 'loose' or 'strict' criteria (Table 3). This was consistent with the pooled estimate of effect of pre-operative presence of periapical lesion on the odds of success (OR = 2.75; 95% CI: 1.73, 4.41, Table 3). Teeth with pre-operative periapical lesions were used as the reference group.

Method of instrumentation

This study evaluated the effect of the method of instrumentation (hand vs. rotary) on study outcomes. Rotary instrumentation was used in 24 (57.1%) of studies, hand instrumentation was used in 12 (28.6%) of studies, 4 studies (9.5%) used both hand and rotary instrumentation methods and 2 studies (4.8%) did not report their method of instrumentation. There was no statistically significant difference in outcomes across studies by method of instrumentation ($p = .133$ for 'loose' criteria outcome, $p = .924$ for 'strict' criteria outcome, by the Cochran's (Q) test).

Restoration at follow-up

Data were collected regarding the type of restoration placed at the completion of treatment: permanent restorations in 19 studies (45.2%), temporary restorations in 12 studies (28.6%), a combination of permanent and temporary restorations in 4 studies (9.5%). Seven studies (16.7%) did not report the type of restoration placed at the completion of endodontic treatment. In studies where temporary restorations were placed after the completion of primary RCT, 62.5% confirmed presence of permanent restorations at follow-up visits. Although the majority of studies did make note of the type of restoration placed at the completion of treatment and the presence of a permanent restoration at follow-up, the reporting was varied. For example, for studies that placed a temporary restoration after completion of root canal treatment, some placed

TABLE 2 Estimated success rates by study characteristics

	Loose radiographic criteria				Strict radiographic criteria			
			Pooled success rates				Pooled success rates	
Categories	No. studies	No. teeth	Un-weighted success rates (%)[a]	Weighted success rates[b]	No. studies	No. teeth	Un-weighted success rate (%)[a]	Weighted success rate[b]
Total	21	2466	92	92.6 (90.5-94.8)	39	7432	85.4	82.0 (79.3-84.8)
Outcome criteria								
Clinical + Radiographic	17	2115	92	93.1 (90.7-95.5)	36	7185	86.5	84.4 (82.1-86.7)
Clinical + CBCT	1	57	93	93 (86.4-99.6)	1	57	29.8	29.8 (17.9-41.7)
Clinical + CBCT + Radiographic	3	294	90	89.5 (86-93)	2	190	59.5	61.8 (45-78.6)
At least 4 years follow-up								
No	19	1756	92	92.9 (90.6-95.2)	25	2684	82.5	80.8 (76.6-84.9)
Yes	2	710	92	91.5 (88.9-94.1)	14	4748	87	83.5 (79.6-87.4)
Year of publication								
2003–2010	4	397	90	90.9 (86.7-95)	12	2697	87.8	82.6 (77.6-87.7)
2011–2020	17	2069	92	93.1 (90.7-95.5)	27	4735	84	81.5 (78-85.1)
Year of treatment								
Before 2000	0	NA	NA	NA	8	2543	87.4	82.1 (75.2-89)
After 2000	13	1880	92	91.9 (89.1-94.7)	21	3938	85.4	84.1 (81-87.2)
Location								
USA or Canada	5	488	90	91.2 (85.8-96.7)	9	995	85.4	85.9 (82.6-89.2)
Asia	5	293	90	90.6 (82.9-98.3)	12	1353	79.7	76.5 (69.7-83.2)
Europe	6	946	91.9	92.2 (90.5-93.9)	8	1969	85	81.9 (76.4-87.4)
Central South America	5	739	94.5	94.1 (90.6-97.7)	6	2493	88.6	80.7 (73.2-88.2)
Other	0	NA	NA	NA	4	622	86	89.5 (80.7-98.4)
Treatment settings								
Private practice	4	499	92	94.2 (90.4-98)	8	2924	89.1	85.7 (80.8-90.6)
Academic	12	1583	92	92.2 (89.1-95.3)	24	3233	82.6	80 (75.8-84.1)
Hospital	3	280	91	92.1 (88-96.2)	4	1059	82.6	80.4 (75.1-85.7)
Qualification of operators								
General Dentist	1	43	95	95.3 (89.1-100)	4	1079	87.9	88 (86.1-90)
Endodontist	7	957	94	94.7 (91.9-97.5)	16	4208	87.1	85.2 (81.5-89)
Dental student	2	171	90	89 (76-100)	1	100	76	76 (67.6-84.4)
Post-graduate student	5	898	90	87.3 (82.1-92.4)	11	1562	82.7	79.8 (73.8-85.9)
Mixed	1	104	89	89.4 (83.5-95.3)	0	NA	NA	NA
Tooth types								
Single rooted	5	308	89	89.8 (83.5-96)	6	420	78.3	75.6 (59.6-91.5)
Multiple rooted	4	251	98	98.8 (97-100)	8	594	81.5	82.1 (75.9-88.3)
Both	12	1907	92	91.3 (88.5-94.1)	25	6418	86.2	83.1 (80.1-86)
Pre-operative pulpal diagnosis								
Vital	0	NA	NA	NA	1	24	87.5	87.5 (74.3-100)
Non-Vital	14	1186	93	93.5 (91-96.1)	22	2736	81.1	78.8 (73.8-83.7)
Both	7	1280	91	91.5 (88.9-94.2)	15	4332	88.5	85.6 (82.5-88.7)
Method of instrument								
Hand	2	205	86	82.9 (65.7-100)	11	3457	87.5	83.7 (79-88.4)

TABLE 2 (Continued)

	Loose radiographic criteria				Strict radiographic criteria			
			Pooled success rates				Pooled success rates	
Categories	No. studies	No. teeth	Un-weighted success rates (%)[a]	Weighted success rates[b]	No. studies	No. teeth	Un-weighted success rate (%)[a]	Weighted success rate[b]
Rotart	15	1364	93	93.4 (90.9-95.9)	22	2409	84	82.1 (78-86.3)
Both	3	772	93	93.4 (91.3-95.6)	4	1295	86.3	83.2 (77.1-89.3)
Restoration at follow up								
Yes	11	1546	92	92.8 (89.7-95.9)	25	5619	86.3	82.3 (78.9-85.7)
No	10	920	92	92.1 (88.5-95.6)	14	1813	82.7	81.2 (76.1-86.4)
Number of observers								
1	0	NA	NA	NA	5	1193	84	84.4 (81.4-87.4)
2	17	2199	93	93.7 (91.6-95.8)	29	5843	86.4	82.6 (79.4-85.8)
More than 2	3	223	86	84.4 (71.1-97.6)	4	352	75.9	76.6 (70.5-82.6)
Observer calibration								
No	0	NA	NA	NA	2	1522	92.4	86.4 (70.8-100)
Yes	16	1607	92	92.3 (89.8-94.8)	31	4932	83.2	82.1 (79.1-85.1)

Abbreviations: USA, United States; CBCT, cone-beam computed tomography; NA, not applicable.

[a]Un-weighted pooled success rates were estimated based on the Hepworth and Friedman (1997)'s approach.

[b]Weighted pooled success rates were estimated using random effects meta-analysis (where there was only one study, its reported success rate and confident intervals were presented).

composite orifice barriers, and a variety of temporary materials were used. Additionally, time to final restoration could not be accounted for in these cases. Due to the variations in reporting, we were unable to reliably analyse the influence of coronal restorations on the treatment outcomes at the level of meta-analysis.

Sources of heterogeneity

Meta regression models (Thompson & Higgins, 2002) were used to investigate the potential sources of statistical heterogeneity. The following study characteristics were considered in the meta-regression analyses as co-variates: year of publication (2003–2010 and 2011–2018), geographical location (USA or Canada, Asia and Other), qualification of operators (general dentist, endodontist, dental students, post-graduate student, mixed), treatment setting (private practice, academic and hospital), tooth type (single rooted, multiple rooted, both), method of instrumentation (hand, rotary, both), pre-operative pulpal diagnosis (vital, non-vital and both), number of observers and observer calibration. The analytic sample for the meta-regression analysis included 17 studies under 'loose' criteria and 27 studies under 'strict' criteria. Thirteen studies were excluded due missing data on the analysed co-variates (Angerame et al., 2017; Aqrabawi et al. 2006; Arya et al., 2017; Dorasani et al., 2013; Demirci & Çalışkan, 2016; Hale et al., 2012; Kumar et al., 2020; Llena et al., 2020; Ozer & Aktener, 2009; Restrepo-Restrepo et al., 2019; Sarin et al., 2016; Verma et al., 2019; Verma et al., 2020). Table 4 presents results of the meta-regression analysis to account for sources of heterogeneity. For success rates based on 'loose' criteria, potential sources of heterogeneity were geographical location and qualification of operators. For success rates based on 'strict' criteria, none had significant effects on the success rates reported by the studies or could account for the heterogeneity (Table 4).

Quality of evidence

The quality of evidence, guided by the GRADE approach (Schünemann et al., 2013), of the 42 clinical studies included in this review are presented in Table S4. Fifteen (35.71%) studies, randomized control trials, were considered to be 'high' quality of evidence. They investigated different aspects of root canal treatment procedures on treatment outcomes, including the effects of: single-visit versus multiple-visit root canal treatment (Molander et al., 2007; Paredes-Vieyra & Enriquez, 2012; Penesis et al., 2008; Wong et al., 2015); partial versus complete pulpal tissue removal (Galani et al., 2017); different

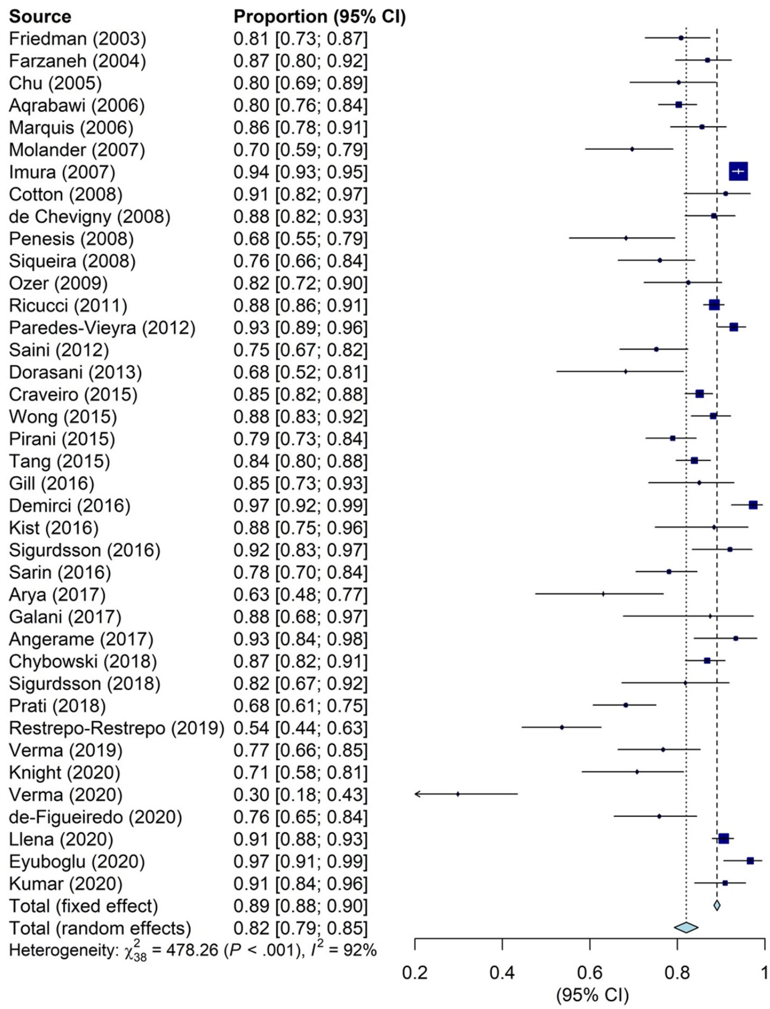

FIGURE 2 Estimated rates of success by study, based on strict radiographic criteria

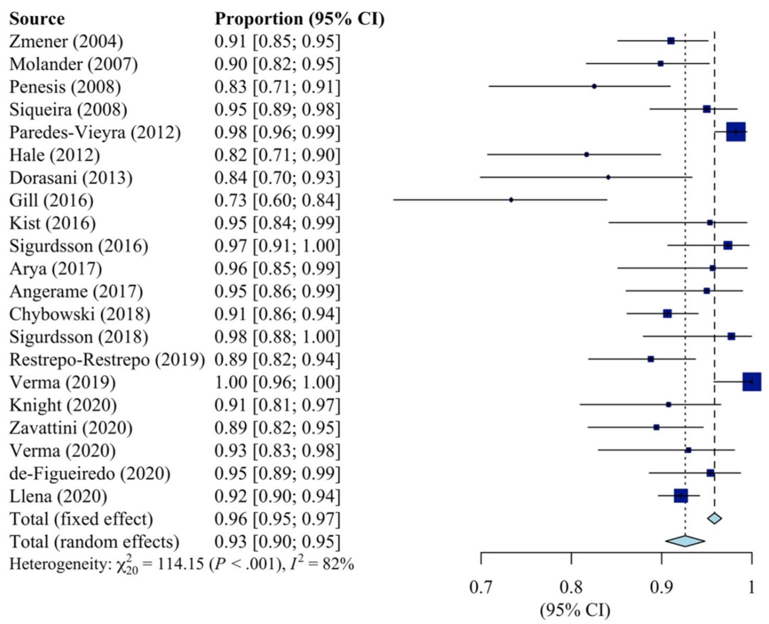

FIGURE 3 Estimated rates of success by study, based on loose radiographic criteria

obturation techniques (Ozer & Aktener, 2009); different apical preparation sizes (Saini et al., 2012); irrigation activation (Verma et al., 2020); types of irrigation (Kist et al., 2017; Tang et al., 2015); root filling materials (Demirci & Çalışkan, 2016); instrumentation type (Angerame et al., 2017; de-Figueiredo et al., 2020); concentration of irrigation solutions (Verma et al., 2019); intraorifice barrier (Kumar et al., 2020). Eighteen (42.86%) studies were 'low'

TABLE 3 Effect of preoperative Periapical Radiolucency

	Loose				Strict			
			Pooled success rates				Pooled success rates	
Categories	**No. studies**	**No. teeth**	**Un-weighted success rates (%)**	**Weighted success rates**	**No. studies**	**No. teeth**	**Un-weighted success rate (%)**	**Weighted success rate**
Preop PARL								
No	3	156	91.7	92.1 [87.8, 96.4]	8	1098	90.5	90.3 [85, 95.6]
Yes	3	125	86.4	87.3 [81.1, 93.5]	8	1126	80.6	80.3 [73.4, 87.1]

Comparisons (test versus reference categories)	**No. studies**	**Odds ratio**	**95% CI**	**Heterogeneity Q**	***p*-value**
Preop PARL No vs. Yes (ref)	11	2.75	1.73, 4.41	21.44 ($df = 10$)	.018

quality of evidence, and 9 (21.43%) studies were considered as 'very low' quality of evidence. Twenty-seven (64.28%) studies had identified study limitations: 14 studies had limitations in either the number or calibration of the radiographic observers; 6 studies had re-examination rates lower than 50%; 18 studies had determined limitations in their reporting of treatment outcomes (Table S4). There were 15 (35.71%) studies in which none of the considered areas of limitation were identified: 7 RCTs and 8 observational studies.

TABLE 4 Results of meta-regression analysis to account for the source of heterogeneity

	Loose ($N = 13$)		Strict ($N = 27$)	
Covariate included	I^2	τ^2	I^2	τ^2
No. covariate included	78.3%	0.0017	88.5%	0.0039
Year of publication	76.1%	0.0015	87.2%	0.0043
Geographical location	66.7%	0.0001	87.6%	0.0038
Qualification of operator	74.8%	0.0012	87.3%	0.0039
Treatment setting	78.6%	0.0021	86.9%	0.004
Tooth type	80.5%	0.0021	88.8%	0.0039
Method of instrument	77.1%	0.0016	88%	0.0045
Pre-op Pulpal Diagnosis	75.3%	0.0016	88.7%	0.0043
Number of observers	77.2%	0.0016	86.6%	0.0034
Calibration of observers	NA	NA	82.9%	0.0074

Note: I^2, proportion of total variation due to heterogeneity across studies; τ^2, estimate of between-study variance (if the I^2 and τ^2 values were reduced by 10% after including a covariate in the regression model as compared with the values estimated without any covariates entered, the respective covariate was considered to be a potential source of heterogeneity (indicated in gray shade).

DISCUSSION

In this systematic review and meta-analysis, the authors attempted to determine updated weighted, pooled success rates of primary root canal therapy based on longitudinal clinical outcome studies published between 2003 and 2020 and explore the effects of several study characteristics and clinical factors on treatment outcomes.

Previous systematic reviews by Paik et al. (2004) and Ng et al. (2007) highlighted the varying levels of evidence of endodontic outcomes studies as well as the limited number of high-quality studies in the outcome literature. Further, in *Outcome of Primary Root Canal Treatment: Systematic Review of the Literature* (Ng et al., 2007), it is noted that the quality of evidence for specific treatment factors affecting primary root canal therapy was suboptimal, and that there was substantial variation in study design. Calls for increased standardization in study design, data recording and the presentation format of outcome data followed.

The findings of the quality of evidence assessment in this systematic review, guided by the GRADE approach, suggests that the majority of outcomes studies on primary root canal therapy continue to be of low level of evidence. In this systematic review, 15 (35.71%) studies were randomized control trials, all considered to be of 'high' level of evidence. This can be compared to Ng et al.'s 2007 systematic review, in which only 6 (9.52%) of the included studies were RCTs. It should be noted that in both systematic reviews, the determination of level of evidence was based primarily on study design (RCT vs. cohort/observational). When assessing the quality of evidence in the endodontic literature, it should be considered that RCTs are not always the most appropriate study design for outcome studies in endodontics. In this review, particular focus was placed on evaluating the included studies for the presence of limitations related to standardization of study design. Based on the review of the included studies, it is clear that previous calls for study design standardization were heard throughout the endodontic community, at least to some extent.

Ng et al. (2007) suggested that it should be mandatory to state the criteria for success as part of the study methodology. In this updated systematic review, almost all of the studies reported their criteria of success but many studies did not clearly state if outcomes were based on 'loose' or 'strict' criteria, as suggested. Determining the outcomes by 'strict' and 'loose' criteria often took careful analysis of the reported results to see how they compared to the reported outcome criteria and occasionally required re-calculations to determine stratified success rates.

Another methodological conclusion made by Ng's group (Ng et al., 2007) was that studies had significant variability in radiographic assessment, resulting from not having at least two pre-calibrated observers. In the present systematic review, 83% of studies reported having two or more observers with 83% of studies reporting some method of observer calibration.

Further Ng's group (Ng et al., 2007) suggested standardization of the duration of follow-up for all patients or, at least, the inclusion of the duration as a covariate into the statistical model to account for variations in the success rate based on different follow-up times. In this updated systematic review, duration of follow-up after treatment was not standardized in the outcome reporting for many studies, thus variations in the success rates because of different follow-up times were not well accounted for. Further, several studies included cases evaluated during a range of follow-up times (e.g. 1–4 years) and failed to heed previous calls to include the follow-up times as a covariate in the statistical model to account for resulting variations in the success rate.

It would be remiss not to note the limitations of previously published systematic reviews evaluating the outcome of endodontic treatment identified by Wu et al. (2009) that may contribute to the overestimation of successful outcomes after root canal treatment: the use of two-dimensional periapical radiography to assess the outcome of root canal treatment; clinical studies that under record extractions and re-treatments as failures, and studies with re-examination rates lower than 50%.

Radiographic images represent a two-dimensional aspect of a three-dimensional anatomical structure (Huumonen et al., 2003). Three-dimensional representation of cone-beam computed tomography (CBCT) has been reported to have increased sensitivity compared to radiography in the detection of apical periodontitis (Patel et al., 2015). This increased sensitivity can result in the detection of apical periodontitis in cases where radiographic examination suggests complete resolution (strict criteria of success) or reveal enlarged lesions in cases where the reduction of the size of radiographic radiolucency (loose criteria of success) is considered. Despite Wu et al.'s call in 2009 for increased outcome reporting using CBCT imaging, in this updated review, only 4 of the 42 included studies used CBCT imaging for follow-up evaluation (Knight et al., 2020; Restrepo-Restrepo et al., 2019; Verma et al., 2020; Zavattini et al., 2020). For consistency, when both radiographic and CBCT outcomes were reported, only the outcomes based on radiographic evaluation were included for analysis in this review. Radiographic and CBCT outcomes were reported for 2 studies (Knight et al., 2020; Zavattini et al., 2020). For those studies, the success rates of CBCT analysis were lower than those reported after radiographic evaluation. When discussing the use of CBCT imaging in outcome studies, it is relevant to note that not all studies have confirmed the accuracy of CBCT when used for diagnosis of apical periodontitis (Kruse et al., 2019). Kruse et al. (2019) found in a cadaver study that the diagnosis of apical periodontitis was dependent on the treatment status of the tooth: for non-endodontically treated teeth, the diagnostic accuracy of CBCT was high, however, the diagnostic accuracy was lower for teeth with endodontic fillings. Their findings indicated that CBCT evaluation was less accurate for the diagnosis of apical periodontitis in endodontically treated teeth.

It is understood that in studies with large percentages of patients lost to follow-up, the reported success rate may be an overestimation. Wu et al. (2009) suggested that 'recall' rates lower than 50% could further contribute to this overestimation. In Ng et al. (2007) study, only 62% of included studies reported rates of re-examination, with a median of 52.7%. In this review, 85.7% of studies reported re-examination rates, ranging from 23% to 100%, with 6 studies reporting rates <50%.

The unclear categorization of extractions and retreatment as failures is another limitation Wu et al. (2009) noted of previous systematic reviews on the outcome of endodontic treatment. In this review, outcomes were recorded as they were reported in the study; however, it was noted that 18 studies (Aqrabawi, 2006; Arya et al., 2017; Cotton et al., 2008; Craveiro et al., 2015; de Chevigny et al., 2008; Dorasani et al., 2013; Farzaneh et al., 2004; Friedman et al., 2003; Gill et al., 2016; Llena et al., 2020; Marquis et al., 2006; Molander et al., 2007; Penesis et al., 2008; Pirani et al., 2015; Ricucci et al., 2011; Saini et al., 2012; Siqueira et al., 2008; Zavanitti et al., 2020) excluded teeth from analysis that were extracted or required further endodontic treatment before the study endpoint, indicating that outcome rates reported in this review may be overestimated.

One of the criticisms of Ng's work (Ng et al., 2007, 2008) is that it includes data ranging over more than 5 or

6 decades (Setzer & Kim, 2014). This criticism notes that the focus of outcomes studies should be on the modern advances and techniques in the field. Whilst this criticism can be countered by the fact that Ng did not find improved success rates by year of publications, this study sought to update the pooled success rates on primary root canal therapy to reflect advancements in treatment made over the last 15 years. Ng et al. (2007) found that pooled success rates of treatment completed at least 1 year previously for studies published between 1922 and 2002, ranged between 68% and 85% when strict criteria were used, with a mean strict success rate of 74.7% (based on 40 studies) and a mean loose success rate of 85.3% (based on 36 studies). In the present systematic review of studies published between 2003 and 2020, weighted, pooled success rates of primary root canal treatments with at least 1 year of follow-up were 82% (based on 39 studies) when 'strict' criteria were applied and 92.6% (based on 21 studies) when 'loose' criteria were applied. It is important to note, that whilst included studies were published between 2003 and 2020, they included treatment years dated back to 1971 and 19% of studies included treatment performed before the year 2000. When analysing success rates by year of treatment the weighted, pooled success rates based on 'strict' outcome criteria were similar for treatment conducted before and after the year 2000.

Despite best efforts, this systematic review is not without limitations. The major limitation is that some clinical characteristics that have been considered to significantly impact the outcomes of root canal therapy were not evaluated in this systematic review: apical extent of root canal filling; quality of root canal filling; post-treatment restorative status. Similar to the findings of Ng's group, data heterogeneity related to these clinical characteristics and others was substantial between studies. Thus, analytic efforts were focused on conditions that were more consistently reported across the studies reviewed. Further, the generalizability of the reported treatment outcomes may be limited as most of the studies were conducted in educational/hospital settings.

Of the evaluated clinical characteristics in this systematic review and meta-analysis, the pre-operative presence of a periapical lesion had the strongest effect on the outcome of primary root canal therapy with a reported odds ratio 2.75. Further, one of the modern advancements in endodontics, the advent of 'rotary' instrumentation was not found to be a statistically significant factor effecting treatment outcomes when compared to 'hand' instrumentation. This can be viewed as a positive result, as technological aims to increase the efficiency and standardization of endodontic treatment have not sacrificed biologically measured outcomes. Meta-regression analyses showed that the qualification of operators had no significant effect on the success rates. However, this analysis was limited as 82% of the studies available for evaluation on this study characteristic reported post-graduate students and endodontists as operators. Regardless, it is relevant to note that the case selection of those specializing in endodontics is likely more complex compared to cases treated by general dentists and undergraduate dental students. This potential selection bias should be considered in any reporting of outcomes based on qualification of operators.

Outcome studies in endodontics have improved their standardization of study design and reporting of outcomes, but further standardization is needed. Research assessing the outcomes of root canal therapy should be required to report outcomes stratified by both 'loose' and 'strict' outcome criteria and standardize the follow-up period for all patients. Furthermore, there should a consensual protocol for placement of restorations after the completion of endodontic treatment in outcome studies so that this data can be more reliably analysed. Lastly, as many studies report 'uncertain' or 'healing' cases in their outcome assessment, the authors echo previous calls to analyse time to healing through the implementation of survival analyses statistical techniques. This effort will increase the ability of the specialty to compare the cumulative success rates of our endodontic procedures both over time and to other treatment modalities.

CONCLUSIONS

In conclusion, outcomes of primary root canal therapy remain high and endodontic treatment is, overall, a reliable and successful method of preserving the natural dentition no matter the outcome criteria used. Biological factors, such as the presence of a pre-operative periapical radiolucency, continue to be the most significant factors influencing the outcome of primary root canal therapy. Additionally, the findings of this research suggest that technological advancements in root canal instrumentation, such as nickel-titanium rotary instruments, aimed at increasing the efficiency and reproducibility of endodontic treatment, have not impacted treatment success rates. The results of the quality assessment highlight that randomized control trials are an infrequently utilized study design in the outcome assessment of primary root canal therapy and thus the level of evidence for these studies remain low, by GRADE standards.

ACKNOWLEDGEMENTS

The authors would like to acknowledge NYU Endodontics graduate, Dr. Sara Soumeeh, and NYU librarian, Dorice Vieira, for their contributions to this review.

CONFLICT OF INTEREST

The authors report no conflicts of interest related to this study.

ETHICAL APPROVAL

The study did not require ethical approval.

AUTHOR CONTRIBUTIONS

Study conception and design: Lorel E. Burns and Asgeir Sigurdsson. *Material preparation, data collection and analysis*: Lorel E. Burns, Jimin Kim, Yinxiang Wu, Rakan Alzwaideh, Richard McGowan, and Asgeir Sigurdsson. *First draft of the manuscript*: Lorel E. Burns and Asgeir Sigurdsson. *Final approval of the manuscript*: Lorel E. Burns, Jimin Kim, Yinxiang Wu, Rakan Alzwaideh, Richard McGowan, and Asgeir Sigurdsson.

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How to cite this article: Burns, L.E., Kim, J., Wu, Y., Alzwaideh, R., McGowan, R. & Sigurdsson, A. (2022) Outcomes of primary root canal therapy: An updated systematic review of longitudinal clinical studies published between 2003 and 2020. *International Endodontic Journal*, 55, 714–731. Available from: https://doi.org/10.1111/iej.13736