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A scoping review of Root Canal Revascularization: relevant aspects for clinical success and tissue formation

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Abstract

The aim of this Scoping Study was to evaluate the survival rate and nature of tissue formed inside root canals of human Necrotic Immature Permanent Teeth (NIPT) under root canal revascularization (RCR). The search was performed in SciVerse Scopus®, PubMed/Medline, Web of Science®, BIREME and in grey literature up to November 2015. The keywords were selected using MeSH terms and DECs. Two independent reviewers scrutinized the records obtained considering specific inclusion criteria. The included studies were evaluated in accordance with a modified Arksey and O' Malley's framework. From 375 studies that were evaluated 75 were included. A total of 367 NIPT were submitted to RCR, from which only 21 needed endodontic treatment. The weighted mean follow-up time was 17.6 months. The data were derived mainly from case reports (69%) or small case series (15%). NaOCl [0.5% to 6%] was applied as the disinfecting solution in almost all studies. Triple Antibiotic Paste was as effective as $Ca(OH)_2$ as on intracanal medicament. *De novo* tissue was cementum and poorly mineralized bone positive to Bone Sialoprotein (BSP) but negative to Dentine Sialoprotein (DSP). Failures were associated mainly with reinfection of the root canal. The majority of included studies reported a significant increase in both, root length and width. However, since most of these data came from case reports, they must be interpreted with care, as most case reports were focused on treatment successes (not failures). Therefore, well-designed randomized controlled trials comparing RCR with available apexification treatments are needed to address this gap in the literature.

Introduction

Immature permanent teeth with necrotic pulps (NIPT) have thin root walls associated with incomplete root apices, characterized by a wide apical foramen (Wigler *et al.* 2013). Such characteristics are challenging to treat (Andreasen & Bakland 2012). Traditionally, NIPT use treated by apexification involve the insertion of $Ca(OH)_2$-based medicaments inside the root canal to establish favorable conditions for subsequent conventional root canal treatment (Rafter 2005). Even though in these cases traditional root canal treatment has a success rate of 74% (Kleier & Barr 1991, Cvek 1992, Andreasen *et al.* 2002) the need for multiple treatment appointments, as well as increased brittleness of root dentine (Andreasen *et al.* 2002), raises the risk of tooth fracture (Cvek 1992). Placing an apical plug of MTA has been reported as an alternative treatment option, but it does not regenerate the physiology of the pulp-dentine complex (Jeeruphan *et al.* 2012, Simon & Goldberg 2014), nor does it allow for further root formation.

Root canal revascularization (Wigler *et al.* 2013), was proposed to overcome the obstacles related to the clinical management of NIPT (Iwaya *et al.* 2001, Banchs & Trope 2004). RCR aims to fill the root canal with pulp-like tissue after the induction of a blood clot inside the root canal system, which will serve as an anchorage site for cells from the apical region (Fig. 1). Since then, evidence regarding stimulating ingrowth of tissues into the root canal system following RCR has been provided (Murray *et al.* 2007, Nosrat *et al.* 2011, Garcia-Godoy & Murray 2012). In addition, the application of blood venous derivatives, such as Platelet-Rich Plasm (PRP) and Platelet-Rich Fibrin (PRF), could be performed in specific cases aiming to accelerate tissue formation (Mittal & Narang 2012).

Disinfection of the root canal system is a crucial step in RCR since mechanical instrumentation is contraindicated due to the presence of thin walls, which could increase further the risk of root fracture (Andreasen & Bakland 2012). Rather, disinfection solutions, such as NaOCl, and a triple antibiotic paste (TAP) containing ciprofloxacin, metronidazole, and minocycline (Hoshino *et al.* 1996) are applied.

Despite the promising results observed in several published case series, RCR is not a well-established therapy (Wigler *et al.* 2013) due to the lack of well-designed clinical trials evaluating its prognosis. Furthermore, little is known about the exact nature of the tissue growing into the canal after RCR is performed in humans. Taking these aspects in consideration, the aim of this study was to carry out a scoping review evaluating the performance of human NIPT submitted to RCR as well as the nature of tissue formed inside the root canal system of such teeth.

Material and Methods

Conceptual Definition: The American Association of Endodontists Guide to Current Dental Terminology (AAE 2013) describes a biological-based procedure named "Pulpal regeneration, which aims to replace damaged tooth structures in NIPT. The process is based on root canal disinfection and subsequent induction of periapical tissue bleeding (AAE 2013). The first report describing the term "revascularization" for NIPT (Iwaya *et al.* 2001) used a case study on the application of Hoshino's TAP (Hoshino *et al.* 1996) inside a root canal to treat an abscess (Iwaya *et al.* 2001). However, the term revascularization is not well accepted (Wigler *et al.* 2013); some authors claim that revascularization is more applicable to events related to dental trauma (Huang & Lin 2008). In such a context, the term "maturogenesis" has been reported to better describe the clinical and radiographic data depicting the apical maturation in NIPT (Weisleder & Benitez 2003). As mentioned by Wigler *et al.* (2013), "*procedures designed to promote continued root development in NIPT should be described as* *maturogenesis, rather than revascularization*". The present authors believe that "Maturogenesis" is a general term for the promotion of root development by different treatments and is not limited to vital pulp therapy. Therefore, the term "Root Canal Revascularization – RCR" was applied by researches for protocols aiming to treat apical periodontitis, to induce radiographic evidence of apical root closure, and to promote root development, after the induction of blood clot.

The clinical definition of the success of RCR varies between studies and methodologies. In general, the most frequently used method is the evaluation of root lengthening and root wall thickening, as well as the absence of pain or sinus tract, resulting in periapical healing. Aside from this, the follow-up periods vary largely in the published studies, making it difficult to define parameters to compare all cases. As a result, the ultimate goal of RCR is to increase tooth survival in the mouth with minimal intervention. In this scoping review, the clinical success of RCR was considered when there was no report indicating extraction or conventional root canal treatment for the treated tooth.

Exploratory Search: An exploratory search was performed in PubMed/Medline up to August 2015. To construct the search strategy, the terms "root canal revascularization", "maturogenesis", "dental pulp necrosis", "dental pulp regeneration", and "infected teeth" were applied. The initial search resulted in 1297 initial records corresponding to 517 studies. Such an exploratory search was relevant to identify that the first studies relating to the importance of the blood clot over the healing of periapical tissues (Torneck & Smith 1970). A remarkable methodological heterogeneity among studies was observed; most of the data obtained were derived from case reports or relatively small case series. A systematic review is a key element to produce evidence-based clinical protocols but based on the resultant evidence, a systematic review was not considered appropriate. Therefore, a Scoping Study (SS) was designed under a modified five-stage framework proposed by Arksey & O'Malley (2005) (Daudt *et al.* 2013). According to the applied framework (Daudt *et al.* 2013): "A scoping review, or scoping study, is a form of knowledge synthesis that addresses an exploratory research question aimed at mapping key concepts, types of evidence and gaps in research related to a defined area or field by systematically searching, selecting and synthesizing existing knowledge".

Information sources, literature search and inclusion criteria: A structured search was performed in SciVerse Scopus™, PubMed/Medline, ISI Web of Science™, and BIREME up to November 2015. The keywords were selected based on the two pre-specified questions:

1. What is the performance of Necrotic Immature Permanent Teeth under RCR?

2. What is the nature of tissue formed inside the root canal of Necrotic Immature Permanent Teeth?

The relevant MeSH terms were considered, as well as the relevant entry terms (Table 1), and then combined (Table 2) to search the studies. The retrieved records were uploaded into EndNote™ software (Thomson Reuters, Rochester, New York, USA), aiming to delete duplicates and to build up a virtual library (VL). Two independent reviewers (MCMC and LAC) read the titles and abstracts of all reports, under the following inclusion criteria:

- Studies: Clinical studies, without language restriction
- Subjects: NIPT from humans
- Diagnosis: Any classification of Pulp Necrosis
- Regenerative procedures carried out: induced-bleeding from periapical region (classical RCR); application of blood venous derivatives (PRF and/or PRP); application of scaffolds over the clot formed after the induced-bleeding of periapical region
- Clinical follow-up: any follow-up period

To confirm if the selected studies met the inclusion criteria, the same reviewers independently judged their full text. If any disagreement was found, the reviewers attempted to reach a consensus through discussions. Persistent disagreements were resolved by intervention from the third reviewer (FFD). After that, MCMC and LAC evaluated manually all references reported in each selected studies. Twenty percent of the studies were randomly selected, and the data were again checked.

The grey literature in the annals of International Association for Dental Research (IADR), European Society of Endodontology, and AAE were searched. In order to identify registered clinical trials the following database were consulted: International Clinical Trials Registry Platform (ICTRP), Clinical trials.gov, Clinical Trials Registry-India (CTRI), EU Clinical Trials Register, Australian Clinical Trials, Pan African Clinical Trials Registration, and Brazilian Clinical Trials Registration (*Registros Brasileiros de Ensaios Clínicos*) by using the following free terms: “root canal revascularization”, “maturogenesis”, and “dental pulp necrosis”.

Strategy for data synthesis: The selected studies were charted in accordance with the fourth and fifth stages of the applied framework (Daudt *et al.* 2013). Data analysis was carried out at the level of an individual tooth. The Kaplan-Meier was built simply to illustrate an overview of the evaluated follow-up time (Figure 3). Each tooth submitted to RCR was inserted individually in the test with their respective follow-up. Initial failures due to impossibility of establishing bleeding or control infection were not submitted to the Kaplan-Meier analysis.

Moreover, due to the impossibility of accessing the follow-up period for each tooth, studies reporting only the mean follow-up time were not included. Thus, 326 teeth were included in the Kaplan-Meier survival curve. The follow-up time was calculated by weighted average, considering weights proportional to the study size.

Results

The search resulted in 998 initial records, but only 375 of them were considered unique studies. After evaluation of titles and abstracts, 84 studies were selected for full-text assessment, from which 75 were included (Fig. 2). The reasons for exclusion are outlined in Table 3. In total, 367 teeth were submitted to RCR, from which 21 failed. The evaluated teeth had a weighted (according to study's follow-up time) mean follow-up time of 17.6 months. The Kaplan-Meier curve was built to illustrate the follow-up times reported by the selected studies (Fig. 3).

Studies: The oldest included publication dates from 2004 (Banchs & Trope 2004); the majority of the included studies were published from 2012 up to November 2015 (Figure 4). Most studies were case reports (69%) or relatively small case series (15%). Stronger evidence was provided by three pilot randomized clinical studies (4%), four prospective clinical studies (5%) and two retrospective studies (Table 4).

Grey literature: Four abstracts about RCR were found and only one had been published (Bezgin *et al.* 2015). Seven clinical trials registration were found; two reporting status as completed (NCT00881491 and NCT00881907) and five as "recruiting participants" (NCT01827098, NCT01976065, NCT01799187, NCT01817413, CTRI/2012/11/003086).

Disinfection Solutions: NaOCl (0.5% to 6%) was applied as the disinfecting solution in almost all cases (Table 4), often associated mainly with chlorhexidine (CHX) – 0.12 - 2% (Banchs & Trope 2004, Reynolds *et al.* 2009, Shin *et al.* 2009, Petrino *et al.* 2010, Shivashankar *et al.* 2012, Chen *et al.* 2013, McTigue *et al.* 2013, Becerra *et al.* 2014, Bezgin *et al.* 2014, Kaya-Buyukbayram *et al.* 2014, Nagata *et al.* 2014, Saoud *et al.* 2014a, Bezgin *et al.* 2015, Nevins & Cymerman 2015, Solomon *et al.* 2015) and hydrogen peroxide (Cotti *et al.* 2008, Shah *et al.* 2008, Santiago *et al.* 2015).

Intracanal Medication: Hoshino's TAP, and its modifications (Table 4), were applied as the intracanal medicament in 86% of the studies while $Ca(OH)_2$ was registered in 13.5% (Cotti *et al.* 2008, Aggarwal *et al.* 2012, Cehreli *et al.* 2012, Chen *et al.* 2012, Rudagi & Rudagi 2012, Shimizu *et al.* 2012, Paryani & Kim 2013, Shimizu *et al.* 2013, Soares *et al.* 2013, Alobaid *et al.* 2014, Kaya-Buyukbayram *et al.* 2014, Lin *et al.* 2014, Nagata *et al.* 2014, Yadav *et al.* 2015). Two cases performed RCR in one-single appointment and so did not apply TAP or $Ca(OH)_2$;

rather systemic antibiotics (Shin *et al.* 2009) or NaOCl were used as the sole disinfectant (McCabe 2015). A microbiological analysis revealed that TAP, as well $Ca(OH)_2$, did not reduce significantly the number of microorganisms after the application of disinfecting solutions (Nagata *et al.* 2014).

Histological features of the new-formed tissue inside root canals: Studies carrying out histological analysis (Torabinejad & Faras 2012, Martin *et al.* 2013, Shimizu *et al.* 2013, Becerra *et al.* 2014, Lin *et al.* 2014, Lei *et al.* 2015) did not report the presence of both polarized cells resembling odontoblasts or pulp-like tissue. Continued root development was provided, mostly, by cellular/acellular cementum and poor mineralized bone (Shimizu *et al.* 2013, Becerra *et al.* 2014). Immunohistochemical analysis showed that the tissue formed inside the root canal was positive to Bone Sialoprotein (BSP) but negative to Dentine Sialoprotein (DSP) (Shimizu *et al.* 2013).

Alternative strategies to improve the RCR: From the selected studies, 17 (22%) applied alternative strategies in an attempt to improve RCR. Thereby, blood venous derivatives, such as PRP (Jadhav *et al.* 2012, Jadhav *et al.* 2013, Guven Polat *et al.* 2014, Jadhav *et al.* 2014, Bezgin *et al.* 2015, Nagaveni *et al.* 2015, Narang *et al.* 2015, Wang *et al.* 2015) and PRF (Torabinejad & Turman 2011, Rudagi & Rudagi 2012, Shivashankar *et al.* 2012, Keswani & Pandey 2013, Mishra *et al.* 2013, Bezgin *et al.* 2014, Jadhav *et al.* 2015, Nagaveni *et al.* 2015, Narang *et al.* 2015, Ray *et al.* 2015, Solomon *et al.* 2015, Yadav *et al.* 2015) were the most commonly applied. It was reported that PRP slightly improved the results of periapical healing, dentinal walls thickening, root lengthening (Jadhav *et al.* 2013, Narang *et al.* 2015), and apical closure (Jadhav *et al.* 2013).

Failures and Adverse events: Failures were associated mainly with reinfection of the root canal system (Alobaid *et al.* 2014, Lin *et al.* 2014), root resorption (Nagata *et al.* 2014, Santiago *et al.* 2015) and failure to induce periapical bleeding (Ding *et al.* 2009, Bezgin *et al.* 2015). Critical crown fractures occurred in cases considered successful (Shimizu *et al.* 2012, Martin *et al.* 2013, Shimizu *et al.* 2013). Inadequate removal of biofilm, presence of bacteria in dentinal tubules or defective restoration were also related to failures (Torabinejad & Turman 2011, Torabinejad & Faras 2012, Yadav *et al.* 2015).

Discussion

The studies included in this scoping review reported a high success rate for the 367 teeth under RCR. The survival of teeth under RCR was based on an increase in root length and width (apical closure), resolution of apical periodontitis, and the absence of clinical signs and symptoms. By comparing radiographic outcomes in NIPT submitted to $Ca(OH)_2$ apexification, MTA apical plugs, and RCR (Jeeruphan *et al.* 2012) those treated with RCR increased an average of 28.2% in root width and 14.9% in root length, while those receiving an MTA plug increased only 6% in root length (Chen *et al.* 2012, Jadhav *et al.* 2012). The survival rate in the revascularized group was 100%, against MTA (95%) and $Ca(OH)_2$ apexification (77.2%).

The main objective of RCR is to generate pulp-like tissue to reduce the risk of tooth loss (Wigler *et al.* 2013). Knowledge regarding the nature of tissue formed inside the root canal is fundamental in forecasting tooth survival as well as treatment prognosis (Conde et al. 2016). However, there is a lack of histological and biomolecular data on the tissues responsible for apical closure, canal narrowing, and even the recovery of pulp sensibility. Selected studies (Martin *et al.* 2013, Shimizu *et al.* 2013, Becerra *et al.* 2014, Lin *et al.* 2014, Lei *et al.* 2015) reported that continued root development was provided, mainly by cellular/acellular cementum and poorly mineralized bone. Tissues formed after PRP application were histologically similar to those without PRP; deprived of odontoblast-like polarized cells (Martin *et al.* 2013). Furthermore, a fibrous non-mineralized connective tissue with different degrees of inflammation and dystrophic calcifications was observed (Becerra *et al.* 2014). The evaluated teeth had closed apices in radiographic evaluation; meanwhile, cone-bean analysis, together with the morphological and histological findings, depicted that root elongation was achieved only in the lingual portion. This observation highlights the difficulty in establishing parameters to confirm clinical success after RCR.

To perform RCR, decontamination is carried out by applying disinfecting solutions without conventional mechanical instrumentation (Wigler *et al.* 2013). In the present scoping review, almost 100% of the included studies applied NaOCl. However, an histological/bacteriological analysis related the presence of necrotic debris, comprising a thick bacterial biofilm, in the apical portion of NIPT. In addition, bacterial clusters were found on root walls and in dentinal tubules (Lin *et al.* 2014). Alobaid *et al.* (2014) suggested that passive disinfection with NaOCl may not be sufficient to reduce/eliminate contamination. However, a greater bacterial reduction was observed after the irrigation of root canal system with NaOCl compared to TAP or $Ca(OH)_2$ placement (Nagata *et al.* 2014). Due to its extended residual antimicrobial properties, CHX has been successfully associated with NaOCl as a disinfecting agent (Reynolds *et al.* 2009, Shin *et al.* 2009, Petrino *et al.* 2010, Shivashankar *et al.* 2012, Chen *et al.* 2013, McTigue *et al.* 2013) and to $Ca(OH)_2$ as intracanal medicaments (Soares *et al.* 2013, Nagata *et al.* 2014).

When RCR was performed in traumatized teeth, TAP was as effective as $Ca(OH)_2$ in reducing spontaneous and induced pain as well as for repairing periapical lesions (Nagata *et al.* 2014). However, a high incidence of crown discoloration (83%) was associated with TAP

(Gelman & Park 2012, Nagata *et al.* 2014). In fact, the main concern related to TAP is the potential for tooth discoloration, derived from the contact between minocycline and the root walls during the time needed to eradicate the infection in RCR (Kim *et al.* 2010). Attempts to substitute minocycline by amoxicillin (Petrino *et al.* 2010, Thomson & Kahler 2010, Kahler *et al.* 2014), doxycycline (Jadhav *et al.* 2012, Nagy *et al.* 2014, Raju *et al.* 2014), clindamycin (McTigue *et al.* 2013, Kumar *et al.* 2014), tetracycline (Guven Polat *et al.* 2014), or cefaclor (Thibodeau & Trope 2007, Thibodeau 2009, Kim *et al.* 2012, Amit *et al.* 2014, Bezgin *et al.* 2014, Bezgin *et al.* 2015) have been reported. No discoloration was observed after the application of TAP containing cefaclor in a randomized clinical trial following-up 20 teeth for 18 months (Bezgin *et al.* 2015). Unaesthetic results were also associated with MTA, with crown discoloration being observed in 12 out of 20 cases (60%) (Bezgin *et al.* 2015). Nevertheless, RCR was considered successful by the authors since the teeth were suitable for root canal treatment and the patient referred to prosthodontists for tooth restoration.

RCR relies on the mechanical irritation of the periapical tissues to initiate bleeding into the canal to produce a blood clot, which is expected to act as a matrix where the migrating responsive cells will possibly adhere and differentiate to reestablish the physiological activities of the pulp-dentine complex (AAE 2013, Wigler *et al.* 2013). The impossibility of inducing initial bleeding comprises one of the main causes of failure of RCR (Ding *et al.* 2009). In multi rooted teeth, after observing an inadequate level of haemorrhage in some canals, transferring blood between canals comprised an effective strategy (Cehreli *et al.* 2011). Bleeding and fibrin clot formation are the initial stage of wound healing after tissue injury. Fibrin is a biopolymer critical for haemostasis and wound healing (Mittal & Narang 2012), and it is responsible for blood clot formation and stabilization, acting as a “trap” to retain the unknown cells enrolled in healing (Lovelace *et al.* 2011).

Based on tissue engineering principles (Langer & Vacanti 1993), a range of strategies has been proposed by incorporating artificial scaffolds, after the initial bleeding. The application of a gelatin hydrogel charged with basic Fibroblast Growth Factor (bFGF) over the blood clot (Nagy *et al.* 2014) or injection of PRP into the apical third of the canal (Martin *et al.* 2013) did not appear to improve healing since both pulp-like tissue and odontoblastic cells were not observed in the revascularized teeth. However, when a collagen sponge soaked with PRP was applied over the blood, a slight improvement in periapical healing, apical closure, root wall thickening, and root lengthening was observed (Jadhav *et al.* 2013, Conde *et al.* 2016). The utilization of PRP and PRF has been reported more frequently in recent years (2012 - 2015), and they were feasible adjuncts to obtain clinical success over more than 30 months follow-up (Ray *et al.* 2015, Wang *et al.* 2015). PRP and PRF possess important differences regarding their properties to deliver growth factors (Mittal & Narang 2012). The releasing peak of growth factors from PRP takes place in the first day, decreasing significantly in the third day, while the releasing-GF peak of PRF, mainly for TGF-β1 and alkaline phosphatase, ensues on the 14th day (He *et al.* 2009). These properties can justify the better response of periapical healing, root lengthening, and root wall thickening of PRF over PRP and conventional blood clots observed in studies comparing these techniques (Narang *et al.* 2015). The main disadvantages of PRP and PRF are related to the need for centrifugation, mainly to obtain the PRP (Mittal & Narang 2012), and the need to collect venous blood from young patients. One reported failure occurred after application of blood venous derivatives (Yadav *et al.* 2015).

The periapical region of NIPT's possesses a population of MSC, named Stem Cells of the Apical Papilla – SCAPs – (Sonoyama *et al.* 2008), which are odontoblastic-progenitor cell thought to be enrolled in healing during RCR (Wigler *et al.* 2013). However, histological and immunohistochemical analysis performed after RCR identified structures staining positively for Bone Sialoprotein (BSP) but negatively for Dentine Sialoprotein (DSP), which are a protein enrolled in dentinogenesis (Martin *et al.* 2013, Shimizu *et al.* 2013, Becerra *et al.* 2014, Lin *et al.* 2014, Lei *et al.* 2015). It has been speculated that both, the inherent bacterial contents of necrosed pulp as well as the application of $Ca(OH)_2$ as a temporary filling could be harmful for these cells (Nagata *et al.* 2014). In such a context, EDTA has been suggested to be applied in RCR since it can solubilize the growth factors fossilized in the dentine matrix (Graham *et al.* 2006), which semms to be essential for pulp regeneration (Conde et al. 2016). However, only 14 from the selected studies applied EDTA during RCR (Paryani & Kim 2013, Soares *et al.* 2013, Alobaid *et al.* 2014, Amit *et al.* 2014, Jadhav *et al.* 2014, Nagata *et al.* 2014, Bezgin *et al.* 2015, Jadhav *et al.* 2015, Lei *et al.* 2015, McCabe 2015, Nagata *et al.* 2015, Nevins & Cymerman 2015, Ray *et al.* 2015).

Conclusion

Most of the cases reported a significant gain in root length and width in NIPT. Histological analysis revealed cementum-like tissue inside the root canal suggesting that RCR in NIPT provides repair instead regeneration. NaOCl and TAP were the most frequently used intracanal medicaments. However, such results must be carefully interpreted since most of them are derived from case reports and uncontrolled clinical trials. Besides, it is unclear if the motivation to submit and publish cases of RCR failure is as high as the motivation to publish RCR successes. Therefore, the results of this analysis are likely to overestimate the actual success rate of RCR. Thus, well-designed randomized controlled trials comparing RCR with available apexification treatments are needed to address this important gap knowledge.

Conflict of Interest statement

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Table 1 Structured search strategy carried out in MEDLINE/PubMed database.

		Search Syntaxes
PubMed	#1	("Immature Permanent Teeth" OR "Immature Permanent Tooth" OR "Young Permanent Teeth" OR "Young Permanent Tooth")
	#2	("Root Canal Revascularization" OR Revascularization OR Maturogenesis)
	#3	(“Dental pulp necrosis” [Mesh] OR “Dental Pulp Necroses” OR ”Necroses, Dental Pulp” OR ”Pulp Necroses, Dental” OR ”Pulp Necrosis, Dental” OR ”Pulp Necroses” OR ”Pulp Necrosis” OR “Necrosis, Pulp” OR “Necroses, Pulp” OR ”Necrosis, Dental Pulp” OR “Gangrene, Dental Pulp” OR “Dental Pulp Autolysis” OR ”Autolyses, Dental Pulp” OR ”Dental Pulp Autolyses” OR “Pulp Autolyses, Dental” OR “Pulp Autolysis, Dental” OR “Autolysis, Dental Pulp” OR “Infected Teeth”)
	#4	(“Platelet-Rich AND Fibrin”)
	#5	("Platelet-Rich Plasma" [Mesh] OR "Plasma, Platelet-Rich" OR "Platelet-Rich AND Plasma")

* Searches in SciVerse Scopus™ (SS), ISI web of a science™ and BVS were adapted according to the database.

Table 2 Keywords combination and records recovered in each database.

Key words applied to develop the search strategy	Records found			
	PubMed™	Scopus™	ISI web of science™	BVS™
#1 and #2 and #3	25	37	31	20
#1 and #2	64	107	107	52
#1 and #4	7	18	2	5
#1 and #5	8	6	41	5
#2 and #4	11	93	10	5
#2 and #5	38	188	84	34

Table 3 Excluded studies and reasons for exclusion

Reason	Studies
Periapical bleeding was not induced; neither PRF or PRP was applied	Iwaya *et al.* 2001, Chueh *et al.* 2006, Akgun *et al.* 2009, Iwaya *et al.* 2011, Fujita *et al.* 2013, Kumar *et al.* 2014, Saeki *et al.* 2014
Follow-up was not reported or carried out	Nagata *et al.* 2014

Table 4 Characteristics of included studies

Study	Type of Study	Teeth/ Success	Follow-up (months)	Disinfection Agent [%] / Intracanal Medication	Blood Derivatives
Banchs and Trope (2004)	Case Report	1/1	24	NaOCl [5.25]+Peridex™ / TAP	-
Thibodeau and Trope (2007)	Case Report	1/1	24	NaOCl [1.5] / TAP(CEF)	-
Cotti *et al.* (2008)	Case Report	1/1	30	NaOCl [5.25] + H_2O_2 [3] / $Ca(OH)_2$	-
Jung *et al.* (2008)	Small Case Series	4/4	33	NaOCl [2.25] / TAP	-
Shah *et al.* (2008)	Small Case Series	11/11	19	NaOCl [2.25] and H_2O_2 [3] / -	-
Ding *et al.* (2009)	Small Case Series	9/3	16	NaOCl [5.25] / TAP	-
Reynolds *et al.* (2009)	Case Report	2/2	18	NaOCl [6] and CHX [2] / TAP Hoshino	-
Shin *et al.* (2009)	Case Report	1/1	19	NaOCl [5.25] and CHX [2] / Systemic AB	-
Thibodeau (2009)	Case Report	1/1	41	NaOCl [1.25] / TAP(CEF)	-
Kim *et al.* (2010)	Case Report	1/1	8	NaOCl [3] / TAP	-
Petrino *et al.* (2010)	Small Case Series	6/6	11	NaOCl [5.25] and CHX [0.2] / TAP	-
Thomson and Kahler (2010)	Case Report	1/1	18	NaOCl [1] / TAP(AMXI)	-
Cehreli *et al.* (2011)	Small Case Series	6/6	9.5	NaOCl [2.25] / $Ca(OH)_2$	-
Nosrat *et al.* (2011)	Case Report	2/2	16.5	NaOCl [5.25] / TAP	-
Torabinejad and Turman	Case Report	1/1*	5.5	NaOCl [5.25]	

(2011)*					TAP	
Aggarwal *et al.* (2012)	Case Report	1/1	24	NaOCl [5.25]	TAP	-
Cehreli *et al.* (2012)	Case Report	1/1	18	NaOCl [2.5]	$Ca(OH)_2$	-
Chen *et al.* (2012)	Large Case Series	20/20	11.45	NaOCl [5.25]	$Ca(OH)_2$	-
Dabbagh *et al.* (2012)	Large Case Series	18/18	24	NaOCl [5]	TAP	-
Gelman and Park (2012)	Case Report	1/1	11	NaOCl [6]	TAP	-
Jadhav *et al.* (2012)	Randomized Clinical Study	20/20	12	NaOCl [2.25]	TAP(DOXI)	-
Jeeruphan *et al.* (2012)	Retrospective Study	20/20	21.15	NaOCl [2.5]	TAP	-
Kottoor and Velmurugan (2012)	Case Report	1/1	60	NaOCl [5.25]	TAP	-
Kim *et al.* (2012)	Small Case Series	3/3	38	NaOCl [3]	TAP(CEF)	-
Lenzi and Trope (2012)	Case Report	2/2	21	NaOCl [2.5]	TAP	-
Narayana *et al.* (2012)	Case Report	1/1	12	NaOCl [5.25]	TAP	-
Nosrat *et al.* (2012)	Case Report	2/2	72	NaOCl [5.25]	TAP	-
Rudagi and Rudagi (2012)	Case Report	1/1	12	NaOCl [1]	$Ca(OH)_2$	PRF
Shimizu *et al.* (2012)	Case Report	1/0	0.75	NaOCl [5.25]	$Ca(OH)_2$	-
Shivashankar *et al.* (2012)	Case Report	1/1	12	NaOCl [5.25] and CHX [0.12]	TAP	PRF
Torabinejad and Faras (2012)*	Case Report	1/0	14	NaOCl [5.25]	TAP	PRP
Chen *et al.* (2013)	Case Report	1/1	12	NaOCl [3] and CHX [DNR]	TAP	-
Farsi *et al.* (2013)	Small Case Series	3/3	18	NaOCl [2.5]	TAP	-
Forghani *et al.* (2013)	Case Report	1/1	18	NaOCl [5]	TAP	-
Jadhav *et al.* (2013)	Small Case Series	6/6	12	NaOCl [2.5]	TAP	PRP

Kalaskar and Kalaskar (2013)	Case Report	1/1	15	NaOCl [0.5] TAP	-
Keswani and Pandey (2013)	Case Report	1/1	15	NaOCl [5.25] TAP	PRF
McTigue *et al.* (2013)	Large Case Series	32/32	51	NaOCl [3] and CHX [2] TAP(CLIN)	-
Martin *et al.* (2013)	Case Report	1/0	25	NaOCl [5.25] TAP	-
Mishra *et al.* (2013)	Case Report	1/1	12	NaOCl [2.5] TAP	PRF
Paryani and Kim (2013)	Case Report	2/2	20	NaOCl [5.25] $Ca(OH)_2$	-
Shimizu *et al.* (2013)	Case Report	1/0	26	NaOCl 2.6% $Ca(OH)_2$	-
Soares *et al.* (2013)	Case Report	1/1	24	CHX [2] $Ca(OH)_2$ and CHX	-
Sonmez *et al.* (2013)	Small Case Series	3/3	24	NaOCl [5.25] TAP	-
Wang *et al.* (2013)	Case Report	2/2	18	NaOCl [3] TAP	-
Yang *et al.* (2013)	Case Report	1/1	24	NaOCl [5.25] TAP	-
Abduljabbar *et al.* (2014)	Case Report	1/1	36	NaOCl [5.25] TAP	-
Alobaid *et al.* (2014)	Retrospective Study	19/15	17	¥NaOCl and CHX TAP vs. DAP (ciprofloxacin, metronidazole) vs. $Ca(OH)_2$	-
Amit *et al.* (2014)	Case Report	1/1	18	NaOCl [5.25] TAP(CEF)	-
Becerra *et al.* (2014)	Case Report	1/1	24	NaOCl [5.25] and CHX [2] TAP	-
Bezgin *et al.* (2014)	Case Report	1/1	12	NaOCl [2.5] and CHX [0.12] TAP(CEF)	PRP
Chandran *et al.* (2014)	Case Report	1/1	12	NaOCl [5.25] TAP	-
Jadhav *et al.* (2014)	Case Report	1/1	12	NaOCl [2.5] TAP	PRP
Kahler *et al.* (2014)	Prospective Clinical Studies	16/16	18	NaOCl [1] TAP(AMXI)	-
Kaya-Buyukbayram *et al.* (2014)	Case Report	1/1	20	NaOCl [2.5] $Ca(OH)_2$ and TAP	-

Lin *et al.* (2014)	Case Report	1/0	16	NaOCl [5.25]; / $Ca(OH)_2$ and TAP	-
Nagata *et al.* (2014)	Prospective Clinical Studies	23/22	15	NaOCl [6] and CHX [2] / TAP vs. $Ca(OH)_2$:Endogel^{TM} (1:1)	-
Nagy *et al.* (2014)	Prospective Clinical Studies	20/17	18	NaOCl [2.6] / TAP(DOXI)	-
Guven Polat *et al.* (2014)	Case Report	1/1	24	NaOCl [5] / TAP(TETRA)	PRP
Raju *et al.* (2014)	Case Report	1/1	12	NaOCl [2.25] / TAP(DOXI)	-
Saoud *et al.* (2014b)	Case Report	2/2	12	NaOCl [2.5] / TAP	-
Saoud *et al.* (2014a)	Prospective Clinical Studies	20/20	12	NaOCl [2.5] / TAP	-
Bezgin *et al.* (2015)	Randomized Clinical Study	20/19	18	NaOCl [2.5] and CHX [0.12%] / TAP(CEF)	PRP
Jadhav *et al.* (2015)	Case Report	1/1	18	NaOCl [2.5] / TAP	PRF
Lei *et al.* (2015)	Case Report	1/1	24	NaOCl [1] / TAP(CEF)	-
McCabe (2015)	Case Report	1/1	18	NaOCl [5.25] / -	-
Nagata *et al.* (2015)	Case Report	1/1	16	NaOCl [6] / $Ca(OH)_2$:Endogel^{TM} (1:1)	-
Nagaveni *et al.* (2015)	Case Report	1/1	12	NaOCl [5.25] / TAP	PRF
Narang *et al.* (2015)	Randomized Clinical Study	15/15	18	NaOCl [2.5] / TAP	PRP **vs.** PRF
Nevins and Cymerman (2015)	Small Case Series	5/5	10.5	NaOCl [6] / DAP	-
Ray *et al.* (2015)	Case Report	1/1	36	NaOCl [0.5] / DAP	PRF
Santiago *et al.* (2015)	Small Case Series	6/4	21	NaOCl [2.5/5.25%]; H_2O_2[3]; CHX[2] / TAP	-
Solomon *et al.* (2015)	Case Report	1/1	18	NaOCl [0.25] and CHX [2] / TAP	PRF
Wang *et al.* (2015)	Case Report	2/2	30	NaOCl [2.5] / TAP	PRP
Yadav *et al.* (2015)	Case Report	1/0	24	NaOCl [2.5] / $Ca(OH)_2$	PRF

*****both studies represent the same clinical case. The follow-up from Torabinejad and Turman (2011) was considered to calculate the clinical success; **¥**: data from retrospective study; AB: Antibiotic; **$Ca(OH)_2$**: Calcium Hydroxide; **CHX**: chlorhexidine; **DAP**: Double Antibiotic Paste containing ciprofloxacin and metronidazole; **H_2O_2**: hydrogen peroxide; **NaOCl**: Sodium Hypochlorite; **TAP**: Triple Antibiotic Paste developed by (1996); **TAP(AMXI)**: Triple Antibiotic Paste containing amoxicillin instead minocycline; **TAP(CEF)**: Triple Antibiotic Paste containing cefaclor instead minocycline; **TAP(CLIN)**: Triple Antibiotic Paste containing clindamycin instead minocycline; **TAP(DOXI)**: Triple Antibiotic Paste containing doxycycline instead minocycline; **TAP(TETRA)**: Triple Antibiotic Paste containing tetracycline instead minocycline; **™**: Trade Mark. The follow-up time has been calculated by weighted average with weights proportional to the study size.

Figure Legends

Figure 1 Schematic principle of Maturogenesis in necrotic immature permanent teeth. A: Immature permanent tooth; B: Necrotic immature permanent teeth; C: Pulp removal; D: Disinfection agent, E: Triple antibiotic paste; F: Irritating periapical tissue; G: Initial bleeding; H: Blood clot formation; I: MTA; J: Continued root development

Figure 2 Flowchart depicting the search strategy applied

Figure 3 Kaplan–Meier survival estimate

Figure 4 Studies grouped by year of publication

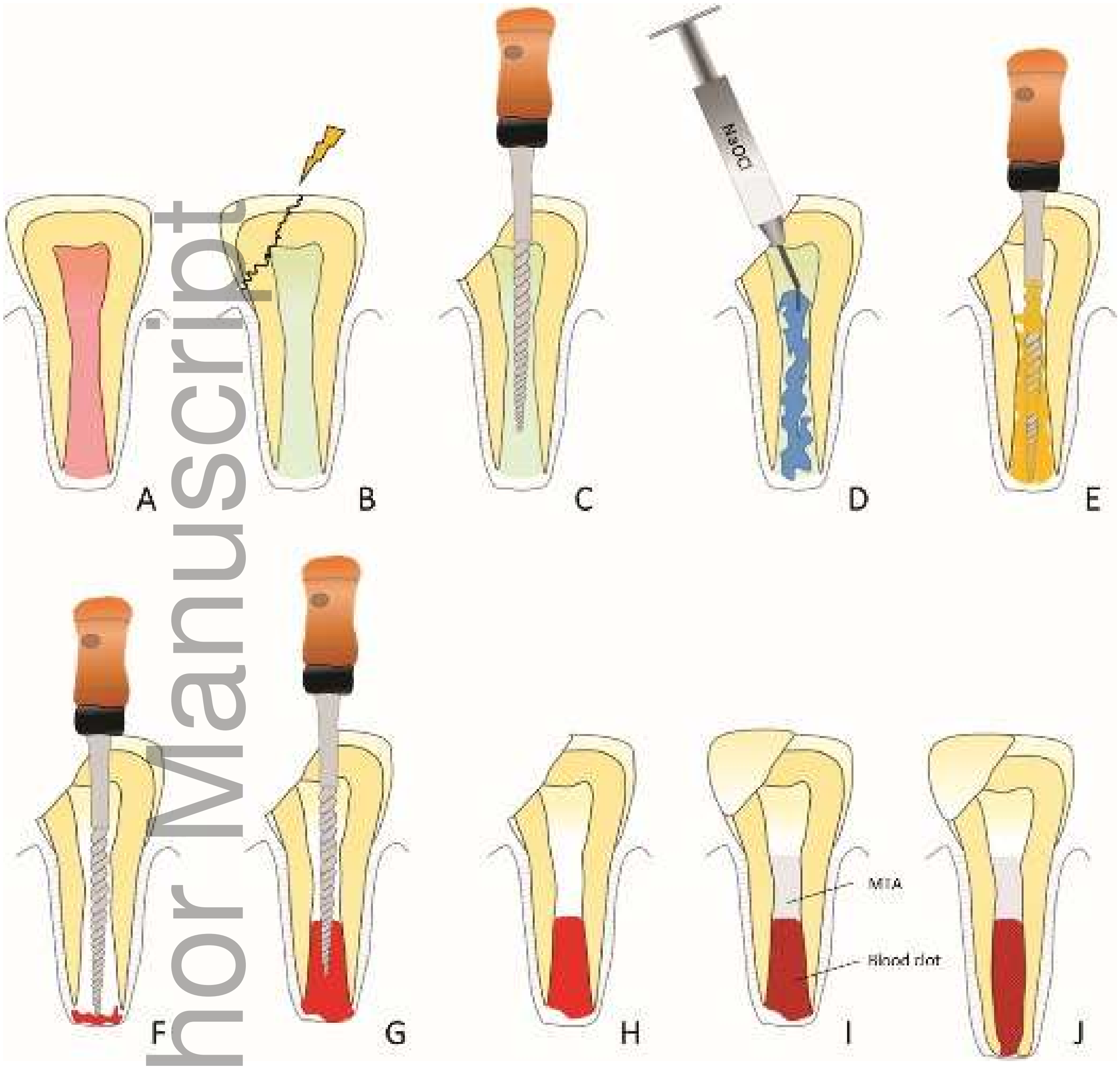

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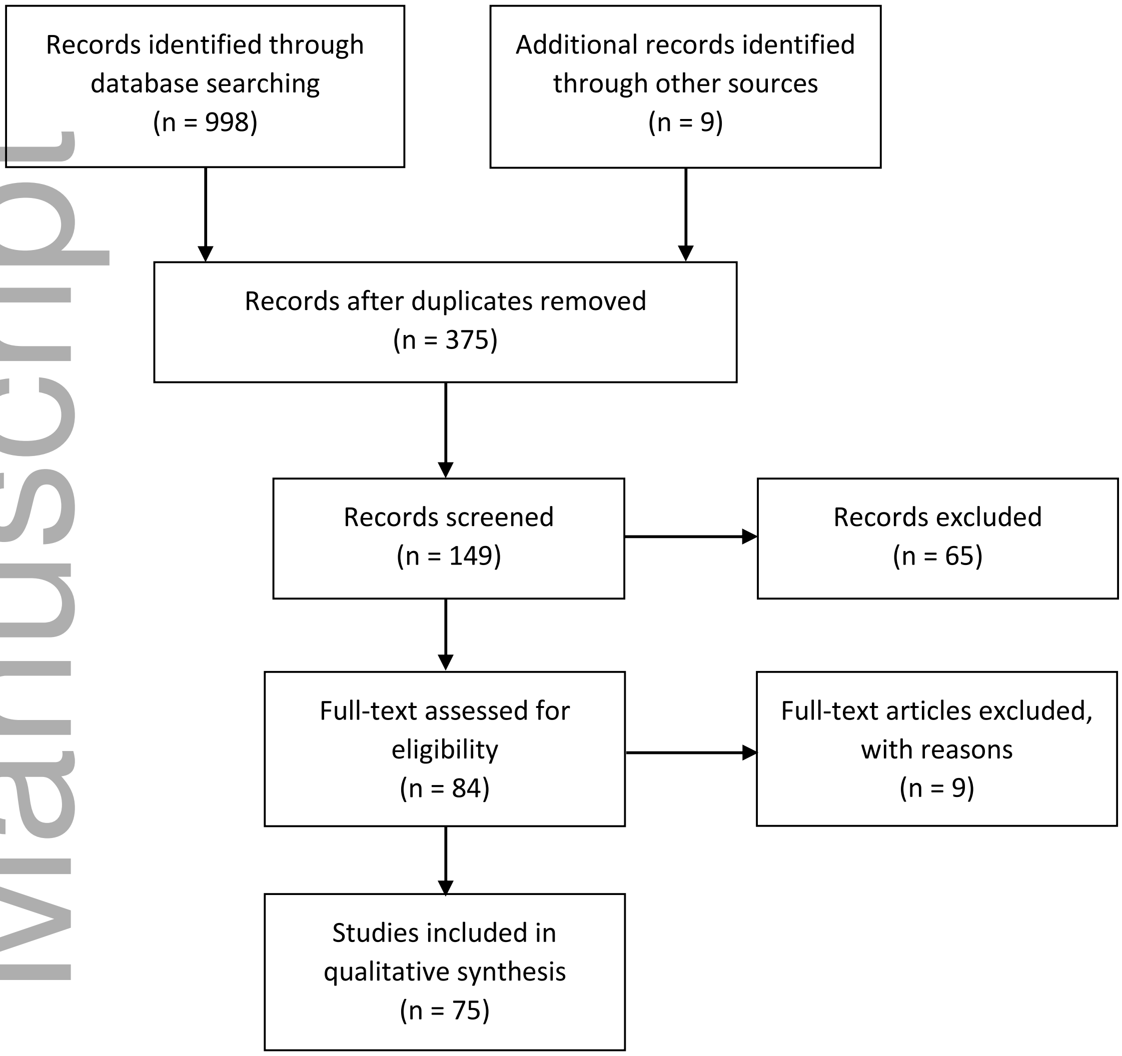
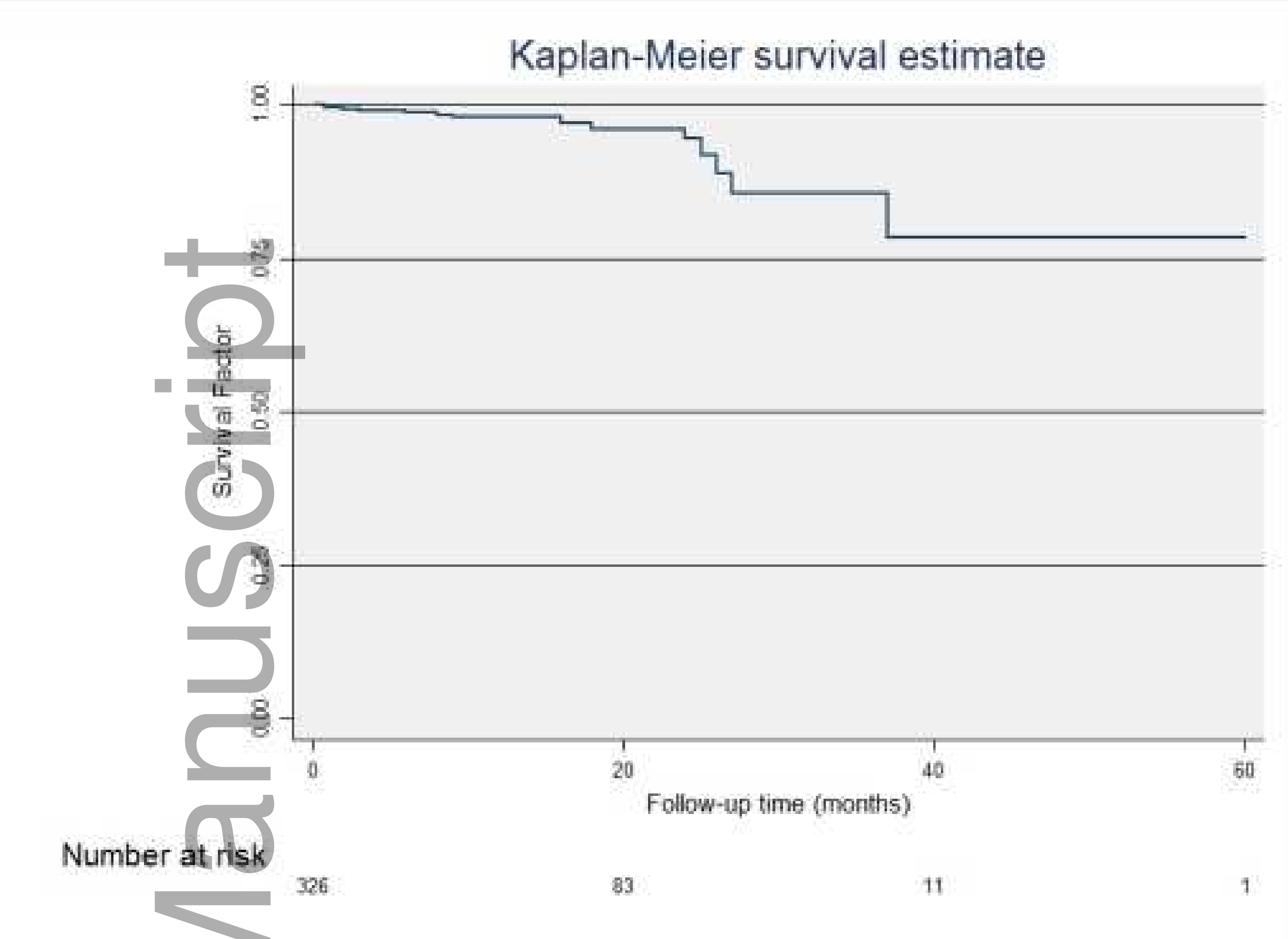
Figure 2. Flowchart depicting the search strategy applied





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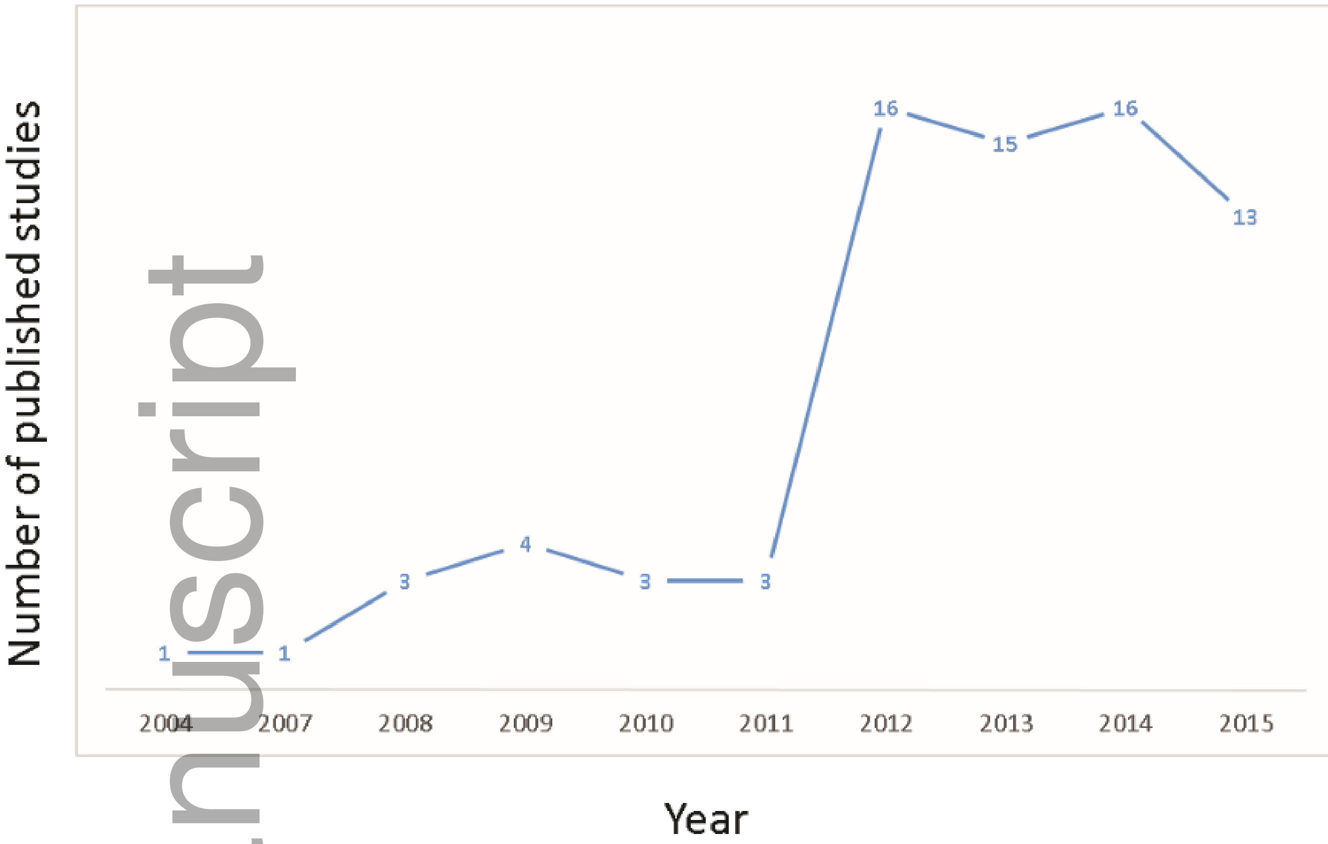

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