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SYSTEMATIC REVIEW

Pocket resolution in regenerative treatment of intrabony defects with papilla preservation techniques: A systematic review and meta-analysis of randomized clinical trials

Mario Aimetti[1] | Adriano Fratini[1] | Valeria Manavella[2] | Marta Giraudi[1] | Filippo Citterio[1] | Francesco Ferrarotti[1] | Giulia Maria Mariani[1] | Francesco Cairo[3] | Giacomo Baima[1] | Federica Romano[1]

[1]Department of Surgical Sciences, C.I.R. Dental School, Section of Periodontology, University of Turin, Turin, Italy

[2]Private practice, Turin, Italy

[3]Department of Experimental and Clinical Medicine, Research Unit in Periodontology and Periodontal Medicine, University of Florence, Florence, Italy

Correspondence
Mario Aimetti, C.I.R. Dental School, Section of Periodontology, Via Nizza 230, Turin 10126, Italy.
Email: mario.aimetti@unito.it

Abstract

Aim: To systematically assess the clinical performance of different approaches for periodontal regeneration of intrabony defects in terms of pocket resolution compared to access surgery with papilla preservation techniques (PPTs).

Material and Methods: Systematic literature searches were conducted on PubMed, EMBASE, and CENTRAL up to April 2020 to identify RCTs on regenerative treatment [guided tissue regeneration (GTR) or enamel matrix derivative (EMD) with or without biomaterials] of intrabony defects using PPTs. Results were expressed as weighted mean percentages (WMP) or risk ratios of pocket resolution at 12 months (considering both final PD ≤ 3 mm and ≤4 mm).

Results: A total of 12 RCTs were included. Based on a final PD ≤ 3 mm or PD ≤ 4 mm, the WMP of pocket resolution was 61.4% and 92.1%, respectively. EMD and GTR obtained comparable results. Pairwise meta-analysis identified a greater probability of achieving pocket resolution for GTR compared to PPTs. The number needed to treat for GTR to obtain one extra intrabony defect achieving PD ≤ 3 mm or PD ≤ 4 mm over PPTs was 2 and 4, respectively.

Conclusion: Regenerative surgery represents a viable approach to obtain final PD ≤ 4 mm in the short-term.

KEYWORDS
enamel matrix derivative, guided tissue regeneration, intrabony defect, meta-analysis, periodontitis, pocket closure

Clinical Relevance

Scientific rationale for the study: Due to the paucity of data in literature, this systematic review analysed the performance of regenerative therapy in terms of percentage of pocket resolution (PD ≤ 3 mm or ≤4 mm).

Principal findings: The use of membrane barriers with papilla preservation techniques significantly increased the probability of pocket resolution compared to access flap alone at 12 months, while for the application of EMD the evidence is inconclusive.

Practical implications: Pocket resolution combined with absence of BoP should be considered as endpoint in RCTs in order to apply the treat-to-target approach in periodontal regenerative treatment.

1 | INTRODUCTION

Intrabony (angular) defects are the anatomical sequelae of the apical spread of periodontitis in which the base of the pocket is apical to the alveolar crest and surrounded by one, two, three residual bony walls or their combination (Lang & Tonetti, 2003). After the completion of initial periodontal therapy, persistent pathological pockets associated with an intrabony pattern of bone resorption have an increased risk for disease progression and usually require further surgical treatment (Papapanou & Wennstrom, 1991; Papapanou & Tonetti, 2000; Rams et al., 2018). Many randomized controlled trials and systematic reviews have shown that periodontal regenerative therapies can achieve better treatment outcomes compared to access flap surgery in the treatment of such angular bony defects (Pagliaro et al., 2008; Esposito et al., 2009; Tu et al., 2010; Cortellini & Tonetti, 2011). While access flap surgery reduces probing depth (PD) by forming a long junctional epithelium attached to a previously diseased root surface (Caton et al., 1980), periodontal regenerative procedures aim to restore the lost attachment apparatus (periodontal ligament, cementum and bone) (Karring et al., 1993). To this regard, there is clinical and histological evidence that guided tissue regeneration (GTR) and enamel matrix derivatives (EMD) are the two most effective approaches in obtaining periodontal regeneration (Cortellini et al., 1993; Sculean et al., 1999; Sanz et al., 2004; Needleman et al., 2006; Bosshardt, 2008).

Although the true endpoint of periodontal regeneration can be demonstrated only histologically, PD reduction and clinical attachment level (CAL) gain are the surrogate treatment outcomes more commonly assessed in the clinical practice. However, changes in these parameters may be not clinically relevant and may not reflect disease remission (Chambrone & Armitage, 2016). Accordingly, pocket resolution has been proposed as an appropriate endpoint for applying the treat-to-target concept in trials evaluating the efficacy of active periodontal treatment (Feres et al., 2020).

Recently, Trombelli et al. (2020) proposed a composite outcome measure to assess the effect of regenerative treatment of intrabony defects in which they incorporated CAL gain and pocket resolution, defined as a post-surgery PD ≤ 4 mm. There is significant evidence that residual PD > 4 mm after non-surgical and regenerative periodontal treatments represents a risk factor for long-term disease progression/recurrence at site level (McGuire & Nunn, 1996; Matuliene et al., 2008). However, considering the final goal of periodontal regenerative treatment that is to restore the architecture of lost periodontal tissues, PD reduction on a physiological level of up to 3 mm would have clinical relevance for the success of periodontal regenerative surgery.

Despite the publication of several systematic reviews on the clinical effects of regenerative therapy in the treatment of intrabony defects (Needleman et al., 2006; Esposito et al., 2009; Nibali et al., 2020), a systematic assessment of the percentage of pocket resolution is still lacking. Thus, the aim of this research was to systematically review the literature on the clinical performance of GTR and EMD in terms of pocket resolution (considering both final PD ≤ 3 mm and ≤4 mm) of intrabony defects in periodontitis patients compared to access flap surgery with papilla preservation techniques (PPTs).

2 | MATERIALS AND METHODS

This systematic review was conducted according to the Cochrane Handbook (Higgins & Green, 2011) and reported according to the PRISMA statement recommendations (Moher et al., 2009). The PRISMA checklist is included in Table S1. The protocol was registered with PROSPERO (available from ID: CRD42020133658).

2.1 | PICOS question

The systematic review was developed to answer the following two focused questions:

- "In patients with periodontitis, what is the clinical performance of GTR or EMD with PPTs for regeneration of intrabony defects in terms of pocket resolution?"
- Do regenerative procedures provide additional benefit in terms of pocket resolution compared to access flap surgery with PPTs?

Eligibility criteria used in this systematic review were based on the PICOS framework as follow (Forrest & Miller, 2002):

(P) Patient/Population**:** Systemically healthy adult patients affected from periodontitis who at the completion of the cause-related periodontal therapy presented full mouth plaque score (FMPS) and full mouth bleeding score (FMBS) values <20% [or in alternative Plaque index (PI) and Gingival Index (GI) <1], and at least one residual periodontal intrabony defect in need of regenerative treatment (defect with a base apical to the interdental alveolar crest, surrounded by one, two, three walls or a combination, PD ≥5 mm and a radiographic intrabony component ≥3 mm).

Intervention: regenerative periodontal therapy consisting in GTR using resorbable or non-resorbable membranes either alone or in

combination with bone grafts or bone substitutes or induced tissue regeneration using EMD either alone or in combination with bone grafts or bone substitutes. All regenerative procedures should employ PPTs.

C (Comparison): access flap surgery with PPTs.

O (Outcome measures): the primary outcome was the percentage of pocket resolution at 12 months. It was identified as the percentage of treated sites that converted to PD ≤3 mm or PD ≤ 4 mm, on the total number of treated pockets. Secondary outcomes were mean change in PD, mean change in CAL, patient-reported outcome measures (PROMs) and adverse events.

S (Type of Study): only Randomized Controlled Clinical Trials (RCT) in humans, with parallel or split-mouth design, were considered.

The following additional inclusion criteria were applied: (1) RCTs published in English language; (2) with a minimum follow-up time of 12 months after surgery; (3) including at least 10 patients per arm; (4) reporting clinical outcomes in terms of PD changes. Exclusion criteria included: (1) RCTs with unclear type of treated intrabony defects; (2) including teeth with furcation involvement.

2.2 | Literature search

Electronic search was performed independently by two authors (A.F. and V.M.) until 30 April 2020 in the database of the National Library of Medicine (MEDLINE by PubMed), in the Excerpta Medica dataBASE (EMBASE), and in the Cochrane Central Register of Controlled Trials (CENTRAL) using a combination of medical subject headings (MeSH) terms and free text words. The search strategy was first designed for the MEDLINE database and was then modified for the other databases as reported in Table S2.

The references of all included studies and relevant reviews were manually crosschecked and additional search was also performed in indexes of relevant dental journals (*International Journal of Periodontics & Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Periodontal Research and Journal of Periodontology*) in the previous 3 years.

Two independent reviewers (A.F. and V.M.) screened all articles based on titles and abstracts for adherence to the eligibility criteria. Relevant articles were analysed in full text, and any disagreement was resolved by discussion with a third examiner (M.A.). Agreement between reviewers was assessed by means of Cohen's K-score. When deemed necessary, the authors of the original studies were contacted to request further information or clarification. If no reply was received within 3 weeks, the study was excluded.

2.3 | Data extraction and risk of bias assessment

Data of the included studies were independently extracted by two reviewers (A.F. and V.M.) and entered into a database. Study design, patient characteristics, type of intervention, clinical outcomes and PROMs were recorded. When the percentage of pocket resolution was not provided, calculations were performed based on the raw data reported in the paper or collected by the authors. In case of several articles reporting different follow-up durations on the same study population, 12-month data were extracted for the meta-analysis from the first published study.

The Cochrane Collaboration's tool (Higgins & Green, 2011) was used for assessing the risk of bias (low, high and unclear) of the selected studies.

2.4 | Statistical analysis

Data on treatment effect in terms of percentage of pocket resolution, PD reduction and CAL gain at 12 months were combined in the meta-analysis and expressed as weighted means and 95% confidence intervals (CI). The risk ratios (RR) and corresponding 95% CIs of pocket resolution were calculated from the event rates in regenerative and access flap surgery groups of each of the studies and pooled. Studies not reporting mean differences and standard deviation between baseline and 12-month examination for PD and CAL were excluded from the meta-analysis unless data of each patient were provided.

Heterogeneity was quantified using the Q test and the I^2 index (Higgins et al., 2003). Values over 70% were classified as substantial heterogeneity. A random-effect model was applied when the heterogeneity among studies was statistically significant.

Subgroup analyses were performed on the selected outcome variables to explore the effect of biomaterials and type of membrane in tissue regenerative surgery. A forest plot was created to illustrate the effects of the different studies and the global estimation. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using statistical software package OpenMeta [Analyst].

3 | RESULTS

3.1 | Search results

The study selection process is presented in the flow diagram (Figure 1). From the initial search, 2324 records were identified, 1202 of which were screened after duplicates removal and 72 articles were analysed in the full text. Finally, 35 met the inclusion criteria. The inter-examiner agreement was excellent for the screening of both the abstracts and full texts (*K*-score = 0.87 and *K*-score = 0.94, respectively).

As data on pocket resolution were available only in 2 papers for PD ≤ 3 (Aimetti et al., 2017; Aslan et al., 2020), and in one paper for both PD ≤ 3 mm and PD ≤ 4 (Cortellini & Tonetti, 2011), the corresponding authors of the included studies were contacted to request the row data. Lastly, 12 articles (Cortellini, Pini Prato, & Tonetti,

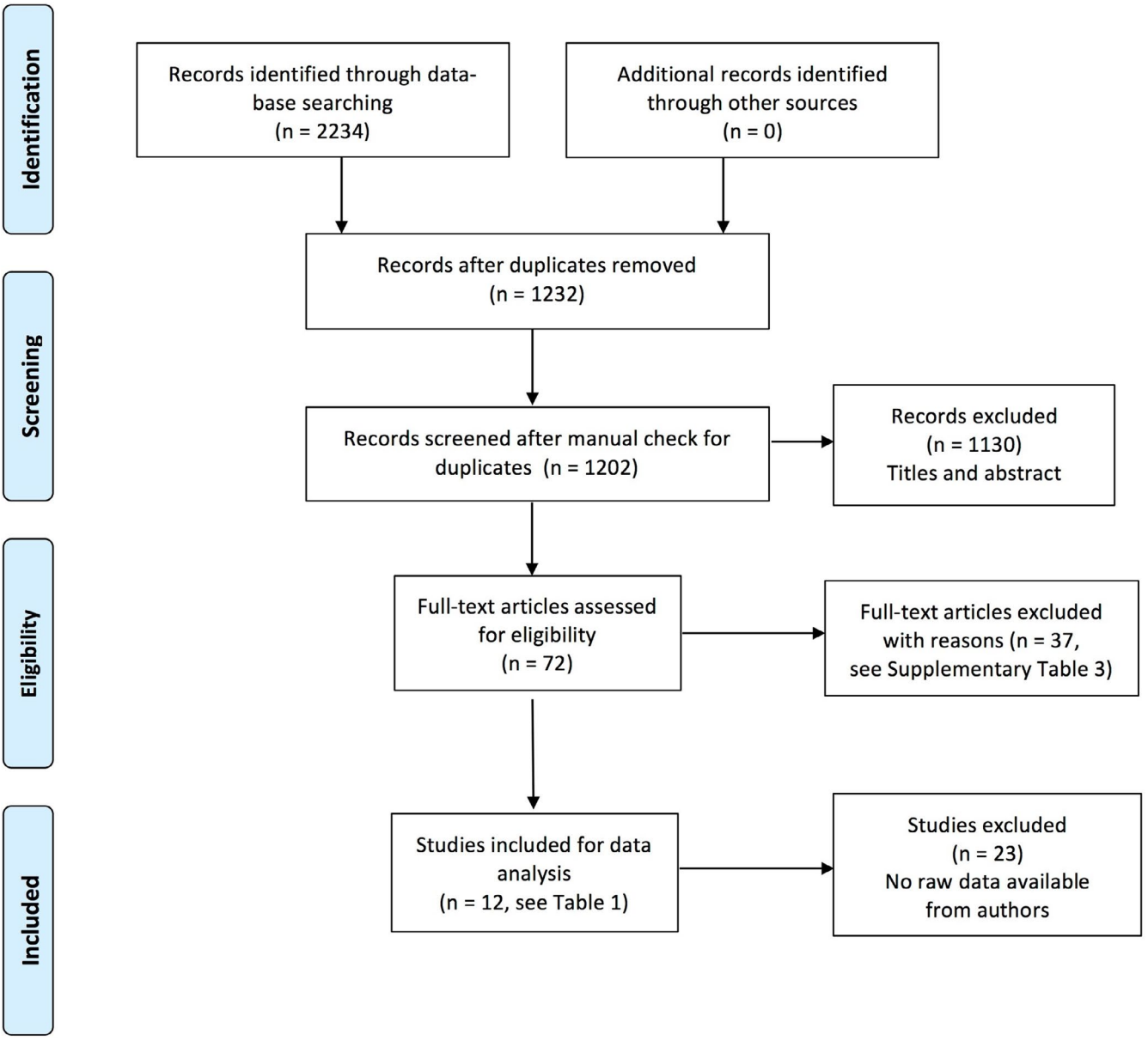

FIGURE 1 Prisma flow chart of selection process

1995, 1996; Cortellini et al., 2001; Christgau et al., 2002; Eickholz et al., 2000; Guida et al., 2007; Crea et al., 2008; Cortellini & Tonetti, 2011; Ghezzi et al., 2016; Aimetti et al., 2017; Aslan et al., 2020; Paolantonio et al., 2020) were included in the final analysis. Data from both the experimental groups in 7 articles (Cortellini et al., 1996; Cortellini et al., 2001; Christgau et al., 2002; Eickholz et al., 2000; Guida et al., 2007; Crea et al., 2008; Ghezzi et al., 2016) were considered separately in the analysis. A list of the excluded studies with the reason of exclusion is available in Table S3.

3.2 | Characteristics of the included studies

The main characteristics of selected studies are described in Table 1. All included studies were published between 1995 and 2020 and accounted for 419 patients with an age range between 21 and 70 years. Smokers were enrolled in 7 studies (Cortellini et al., 1995; Cortellini et al., 1996; Cortellini et al., 2001; Christgau et al., 2002; Guida et al., 2007; Cortellini & Tonetti, 2011; Ghezzi et al., 2016) for a total of 54 patients. Two of the included studies had a split-mouth design and were commercially funded (Christgau et al., 2002; Eickholz et al., 2000).

In total, 465 intrabony defects were treated. Regarding defect localization, Cortellini et al. (2001) selected only anterior and premolar teeth, while the other studies included all types of teeth. Concerning defect type, Crea et al. (2008) included only three-wall intrabony defects, Guida et al. (2007) and Paolantonio et al. (2020) only one- to two-wall intrabony defects. Eickholz et al. (2000) and Aslan et al. (2020) selected only two- and three-wall defects.

The regenerative surgery included the application of resorbable barriers (polylactide (PLA), polydioxanon (PDS) or

poly-D,L-lactide-co-glycolide) in 5 studies (Cortellini et al., 1996; Cortellini et al., 2001; Christgau et al., 2002; Eickholz et al., 2000; Ghezzi et al., 2016), non-resorbable membranes (expanded polytetrafluoroethylene (ePTFE) or titanium-reinforced membranes) in 3 studies (Cortellini et al., 1995; Cortellini et al., 1996; Crea et al., 2008), EMD alone in 4 studies (Guida et al., 2007; Crea et al., 2008; Cortellini & Tonetti, 2011; Aimetti et al., 2017) and in combination with grafting materials (bone mineral-derived xenograft or autogenous cortical bone) in 5 studies (Guida et al., 2007; Cortellini & Tonetti, 2011; Ghezzi et al., 2016; Aslan et al., 2020; Paolantonio et al., 2020). Five studies and 7 datasets compared regenerative treatment with PPTs (Cortellini et al., 1995; Cortellini et al., 1996; Cortellini et al., 2001; Cortellini & Tonetti, 2011; Aslan et al., 2020).

All patients received antibiotics during the first 6–7 days after treatment to prevent post-operative infection in 9 studies (Cortellini et al., 1995; Cortellini et al., 1996; Cortellini et al., 2001; Christgau et al., 2002; Guida et al., 2007; Crea et al., 2008; Ghezzi et al., 2016; Aslan et al., 2020; Paolantonio et al., 2020). Maintenance care was set on a 2–3 month interval, except in three studies (Cortellini et al., 1995, 1996; Aslan et al., 2020) in which professional prophylaxis was scheduled monthly.

3.3 | Results from meta-analysis

3.3.1 | Pocket resolution (PD ≤ 3 mm or PD ≤ 4 mm)

The percentage of pocket resolution considering a final PD ≤ 3 mm ranged from 28.6% (Guida et al., 2007) to 93.3% (Cortellini et al., 1995) after regenerative surgery and from 11.1% (Cortellini et al., 2001) to 80% (Aslan et al., 2020) using PPTs. Random-effects meta-analysis (Figure 2a) showed a weighted mean percentage (WMP) of pocket resolution of 61.4% (95% CI: 51.8–71.0) after regenerative procedures with considerable heterogeneity (I^2 = 75.21%). The application of non-resorbable membranes (Figure 3a) obtained a WMP of 74.9% of pocket resolution (95% CI: 47.4–99.6), while resorbable barriers achieved a WMP of 59.2% (95% CI: 47.2–71.2). Moreover, the combination of EMD and grafting material (Figure 3b) yielded a 61.5% of pocket resolution (95% CI: 42.0–80.9), which was higher than EMD alone (52.7%, 95% CI: 30.2–75.3).

As reported in Figure 4a, the use of regenerative procedures makes intrabony defects 1.65 times more likely to achieve a final PD ≤ 3 mm compared to PPTs (p = 0.040). The application of resorbable or non-resorbable membranes increased by 3.77-fold (95% CI: 1.99–7.12; p < 0.001) and 2.58-fold (95% CI: 1.51–4.42; p < 0.001), respectively, the probability of pocket resolution, while the application of EMD did not significantly improve the clinical outcome.

Considering a threshold of 4 mm (Figure 2b), 5 studies (Eickholz et al., 2000; Crea et al., 2008; Cortellini & Tonetti, 2011; Ghezzi et al., 2016; Aslan et al., 2020) with 7 data sets reported a percentage of pocket resolution of 100% after regenerative surgery and from 63.7% (Cortellini et al., 2001) to 100% (Cortellini & Tonetti, 2011) using PPTs. Random-effects meta-analysis showed an overall WMP of pocket resolution after regenerative treatment of 92.1% (95% CI: 88.9–95.4) with low heterogeneity (I^2 = 29.52%). GTR and EMD (89.5% *versus* 94.8%), as well as non-resorbable and resorbable barriers (93.3% *versus* 88.0%), were comparably effective in obtaining final PD ≤4 mm (Figures 3c,d). The application of a grafting material did not increase the clinical performance of EMD (95.3% *versus* 92.8%). When comparing regenerative procedures with PPTs (Figure 4b), the use of regenerative procedures resulted in a 1.15-fold higher probability of achieving a final PD ≤4 mm (95% CI: 1.01–3.31; p = 0.031); both resorbable (RR: 1.50, 95% CI: 1.19–1.90; p < 0.001) and non-resorbable barriers (RR: 1.36, 95% CI: 1.05–1.76; p = 0.020) performed better than PPTs with no heterogeneity among the studies. The number needed to treat (NNT) for GTR to obtain one extra intrabony defect achieving PD ≤ 3 mm or PD ≤ 4 mm over PPF was 2 and 4, respectively.

3.3.2 | Mean changes in PD and CAL

As reported in Figure 5, statistical heterogeneity was detected as significantly high in the analysis of both PD reduction and CAL gain. Overall, the weighted mean PD reduction (Figure 5a) and weighted mean CAL gain (Figure 5b) after regenerative treatment were 4.56 mm (95% CI: 4.14–4.99) and 3.89 mm (95% CI: 3.53–4.25). Similar PD reduction and CAL gain were obtained when applying a non-resorbable membrane (5.29 mm and 4.37 mm, respectively) or EMD combined with a grafting material (4.73 mm and 4.37 mm, respectively). Resorbable membranes performed as EMD alone for both PD reduction (4.29 mm, *versus* 4.21 mm) and CAL gain (3.54 mm *versus* 3.74 mm).

Statistically significant greater PD reduction and CAL gain were found for regenerative procedures compared with PPTs (Figures 5c,d) with a weighted mean difference (WMD) of 0.95 mm (95% CI: 0.31–1.59; p = 0.004) and 1.27 mm (95% CI: 0.28–2.27; p = 0.012), respectively. The application of a resorbable membrane achieved a WMD of 1.43 mm for PD and 1.59 mm for CAL and the use of a non-resorbable barrier of 1.64 mm for PD and 2.86 mm for CAL. The EMD application did not provide additional benefits to the use of PPTs alone.

3.4 | Adverse events

No authors reported serious adverse events. Flap dehiscence was observed in 7.5% of defects treated with PPTs alone (Cortellini et al., 2001). Infection requiring antibiotic administration occurred in two intrabony defects, one treated with PDS barrier (Eickholz et al., 2000) and the other one with PLA membrane (Crhristgau et al., 2002). The complication most frequently reported for GTR procedures was the membrane exposure with a rate of exposure ranging from 15% (Crea et al., 2008) to 41.7% for non-resorbable barriers (Cortellini et al., 1996) and from 6.5% (Christgau et al., 2002) to 80% (Eickholz et al., 2000) for resorbable membranes

TABLE 1 Characteristics of the included studies

First author, Publication year	Site and Funding	Study design	Defects (*N*)	Participants (*N*) Gender	Mean age (year) mean ± SD	Diagnostic criteria intrabony defect
Aimetti et al. (2017)	University of Turin (Italy)	Parallel RCT	15 (EMD group)	15 7 F, 8 M	42.2 ± 6.1	PD ≥ 6 mm, radiographic intrabony component ≥3 mm
Aslan et al. (2020)	Ege University, İzmir (Turkey)	Parallel RCT	15 (EMD group)	15 5 F, 10 M	44.9 ± 13.1	PD ≥7 mm, CAL ≥8 mm, radiographic intrabony component ≥4 mm, no one wall defects
			15 (PPT group) CTR	15 7 F, 8 M	43.9 ± 12.9	
Christgau et al. (2002)	University of Regensburg (Germany), Industry supported	Split-mouth RCT	31 (GTR group) a	31 17 F, 14 M	44 (range 28 to 62)	PD ≥6 mm, radiographic intrabony component ≥4 mm
			31 (GTR group) b			
Cortellini et al. (1995)	University of Siena (Italy), University of Berne (Switzerland)	Parallel RCT	15 (GTR group)	15 10 F, 5 M	39.3 + 6.4	Deep intrabony defect
			15 (PPT group) CTR	15 8 F, 7 M	45.4 + 9.7	
Cortellini et al. (1996)	University of Siena (Italy), University of Berne (Switzerland)	Parallel RCT	12 (GTR group) a	12 9 F, 3 M	42.6 ± 8.4	Deep intrabony defect
			12 (GTR group) b	12 8 F, 4 M	44.1 ± 7.2	
			12 (PPT group) CTR	12 6 F, 6 M	45.9 ± 8.4	
Cortellini et al. (2001)	Practice-based research network Belgium, Holland, Italy, United States	Parallel RCT	55 (GTR group)	56, 1 patient lost to follow-up 33 F, 23 M	46 ± 9.9	Deep intrabony defect (≥4 mm), anterior or premolar teeth
			54 (PPT group) CTR 3 patients lost to follow-up	57, 3 patients to follow-up 39 F, 18 M	46.6 ± 11.7	

during the first 6 post-operative weeks. The extent was always limited to a small portion of the interdental tissue. In the study by Christgau et al. (2002), the exposure of PDS membranes steadily increased up to 11 mm resulting in exfoliation between 5 and 6 weeks.

3.5 | PROMs

Four studies (Cortellini et al., 2001; Cortellini & Tonetti, 2011; Aimetti et al., 2017; Aslan et al., 2020) reported data on PROMs and

Type of Procedure	Smoking	Supportive Therapy	Outcomes	PD (mm) mean ± SD	CAL (mm) mean ± SD	FMPS (%) mean ± SD	FMBS (%) mean ± SD
EMD	No	2 months	PD, REC, CAL, INTRA, PROMs, FMPS, FMBS	Baseline 7.3 ± 0.8 1 Y 3.7 ± 0.9	Baseline 9.0 ± 1.7 1 Y 5.5 ± 1.5	Baseline 10.7 ± 2.4 1 Y 11.1 ± 2.1	Baseline 8.3 ± 2.1 1 Y 8.9 ± 1.8
EMD +DBBM	No	1 month	PD, REC, CAL PROMs, FMPS, FMBS	Baseline 9.3 ± 2.9 1 Y 2.8 ± 0.7	Baseline 11.7 ± 3.5 1 Y 5.4 ± 1.9	Baseline 13.9 ± 2.3 1 Y N.A.	Baseline 9.4 ± 1.9 1 Y N.A.
PPT	No			Baseline 9.3 ± 1.7 1 Y 3.1 ± 0.8	Baseline 11.4 ± 2.2 1 Y 5.6 ± 1.7	Baseline 13.1 ± 1.6 1 Y N.A.	Baseline 10.2 ± 1.3 1 Y N.A.
PDS membrane	5 smokers, 4 smoking >5 cigarettes/day	2 – 3 months	PD, REC, CAL, PBI	Baseline 9.4 ± 1.6 Y 5.7 ± 2.2	Baseline 10.9 ± 2.1 Y 7.5 ± 2.5	Baseline N.A. Y N.A.	Baseline N.A. Y N.A.
PLA membrane				Baseline 9.4 ± 1.5 Y 5.4 ± 1.6	Baseline 10.6 ± 2.0 Y 7.1 ± 2.6	Baseline N.A. Y N.A.	Baseline N.A. Y N.A.
Titanium-reinforced membrane	2 smokers (> 10 cigarettes/day)	1 month	PD, REC, CAL, FMPS, FMBS	Baseline 8.4 ± 2.5 Y 2.1 ± 0.5	Baseline 9.9 ± 3.2 Y 4.7 ± 1.8	Baseline 11.0 ± 2.3 Y 9.2 ± 3.0	Baseline 10.9 ± 3.2 Y 7.3 ± 2.8
PPT	2 smokers (> 10 cigarettes/day)			Baseline 8.3 ± 2.0 Y 3.7 ± 1.3	Baseline 9.5 ± 2.7 Y 7.1 ± 2.4	Baseline 12.2 ± 1.2 Y 9.1 ± 1.9	Baseline 10.5 ± 2.4 Y 7.1 ± 2.0
Poly-D,L-lactide-co-glycolide membrane	1 smoker (> 10 cigarettes/day)	1 month	PD, REC, CAL, FMPS, FMBS	Baseline 9.8 ± 2.4 Y 3.3 ± 0.9	Baseline 11.1 ± 2.0 Y 6.5 ± 1.5	Baseline 12.6 ± 4.0 Y 8.4 ± 2.4	Baseline 10.5 ± 2.6 Y 7.1 ± 2.1
ePTFE membrane	1 smoker (>10 cigarettes/day)			Baseline 8.8 ± 1.3 Y 2.9 ± 0.9	Baseline 10.8 ± 1.8 Y 5.6 ± 1.6	Baseline 14.4 ± 2.2 Y 9.5 ± 1.7	Baseline 11.8 ± 1.9 Y 7.4 ± 2.5
PPT	2 smokers (>10 cigarettes/day)			Baseline 8.5 ± 2.0 Y 4.2 ± 0.9	Baseline 10.3 ± 1.9 Y 8.0 ± 2.1	Baseline 14.2 ± 2.7 Y 10.8 ± 2.6	Baseline 12.2 ± 2.8 Y 8.7 ± 1.8
PLA membrane	15 smokers (< 20 cigarettes/day)	3 months	PD, REC, CAL, Mobility, PROMs FMPS, FMBS	Baseline 8.2 ± 1.9 Y 3.8 ± 1.5	Baseline 9.5 ± 2.1 Y 5.9 ± 1.9	Baseline 9.6 ± 6.2 Y 11.7 ± 7.9	Baseline 10.4 ± 5.8 Y 8.6 ± 5.0
PPT	17 smokers (< 20 cigarettes/day)			Baseline 8.2 ± 1.8 Y 4.7 ± 1.4	Baseline 9.5 ± 2.4 Y 6.9 ± 2.2	Baseline 10.0 ± 6.7 Y 10.3 ± 6.9	Baseline 9.7 ± 5.9 Y 8.1 ± 6.0

(Continues)

used the Visual Analogue Scale to score the degree of discomfort/pain during the first post-operative week. Pain was absent or moderate after both EMD and GTR procedures. No differences were observed between regenerative procedures and PPTs in terms of pain intensity and duration (Cortellini et al., 2001; Cortellini & Tonetti, 2011; Aslan et al., 2020). Pain lasted few hours after either PPT or PLA membrane positioning (Cortellini et al., 2001); four patients need pain control medication following treatment with EMD alone or in combination with grafting material and three patients following PPTs (Cortellini & Tonetti, 2011).

Table 1 (Continued)

First author, Publication year	Site and Funding	Study design	Defects (*N*)	Participants (*N*) Gender	Mean age (year) mean ± SD	Diagnostic criteria intrabony defect
Cortellini & Tonetti (2011)	Private Practice, Florence, Genova (Italy) ERGOPerio, Berne (Switzerland)	Parallel RCT	15 (EMD group) a	15 8 F, 7 M	47.2 ± 8.5	Deep intrabony defect
			15 (EMD group) b	15 7 F, 8 M	53.5 ± 11.9	
			15 (PPT group) CTR	15 6 F, 9 M	48.9 ± 7.9	
Crea et al. (2008)	Catholic University of Sacred Heart, Rome (Italy)	Parallel RCT	19 (EMD group) a	19 11 F, 8 M	46.0 ± 7.2	Angular intrabony defect ≥4 mm, radiographic intrabony component ≥3 mm, only 3-wall defect
			20 (GTR group) b	20 10 F, 10 M	45.6 ± 8.6	
Eickholz et al. (2000)	University Hospital Heidelberg (Germany), Industry supported	Split-mouth RCT	15 (GTR group)a	15 N.A.	N.A.	Intrabony defect
			15 (GTR group) b			
Ghezzi et al. (2016)	Private Practice (Italy)	Parallel RCT	10 (EMD group) a	10 5 F, 5 M	56.0 ± 8.15	PD ≥6 mm, intrabony component ≥3 mm
			10 (GTR group) b	10 6 F, 4 M	52.9 ± 10.25	
Guida et al., (2007)	University of Naples (Italy)	Parallel RCT	14 (EMD group) a	14 7 F, 7 M	48.4 ± 9.9	PD ≥6 mm, radiographic intrabony component ≥4 mm.
			13 (EMD group) b	13 7 F, 6 M	44.1 ± 6.9	
Paolantonio et al. (2020)	University Chiero-Pescara (Italy)	Parallel RCT	(EMD group) 22	22 N.A.	N.A.	PD ≥5 mm, radiographic intrabony component ≥4 mm, predominantly 1-, combined 1–2, and 2 wall defects

Abbreviations: AB, autologous bone; BMDX, Bone marrow-derived xenograft; BOP, Bleeding on probing; CAL, Clinical attachment Level; CAL-V, Vertical attachment level; CEJ-AC, Distance from cemento-enamel Junction to alveolar crest; CEJ-BD, Distance from cemento-enamel junction to bony defect; CTR, control group; DBBM, Deproteinized bovine bone mineral; EMD, enamel matrix derivatives; ePTFE, Expanded polytetrafluorethylene; FMBS, Full Mouth Bleeding Score; FMPS, Full Mouth Plaque Score; GI, Gingival Index; INTRA, radiographic intrabony defect depth; LBS, Local bleeding score; LPS, Local plaque score; N.A., not available; PBI, Papillary Bleeding Index; PD, Probing depth; PDS, polydioxanon; PI, Plaque Index; PLA, polylactic-acid; PPT, Access flap with Papilla preservation technique; PROMs, Patient-related outcomes; RCT, Randomized clinical Trial; Rec, Gingival recession; SD, Standard Deviation; VBL-V, Vertical probing bone level.

Type of Procedure	Smoking	Supportive Therapy	Outcomes	PD (mm) mean ± SD	CAL (mm) mean ± SD	FMPS (%) mean ± SD	FMBS (%) mean ± SD
EMD	2 smokers	3 months	PD, REC, CAL, Mobility, PROMs, FMPS, FMBS	Baseline 7.8 ± 0.9 Y 3.4 ± 0.6	Baseline 9.9 ± 1.3 Y 5.7 ± 1.7	Baseline 12.5 ± 3.7 Y 9.9 ± 4.0	Baseline 10.4 ± 3.4 Y 5.7 ± 3.0
EMD + BMDX	2 smokers			Baseline 7.3 ± 1.2 Y 3.3 ± 0.6	Baseline 10.1 ± 1.4 Y 6.4 ± 2.4	Baseline 14.4 ± 6.0 Y 10.6 ± 4.8	Baseline 10.7 ± 4.1 Y 7.0 ± 3.6
PPT	1 smoker			Baseline 7.5 ± 1.6 Y 3.1 ± 0.6	Baseline 9.6 ± 2.0 Y 5.5 ± 1.6	Baseline 13.6 ± 4.9 Y 10.2 ± 4.4	Baseline 10.3 ± 4.4 Y 7.0 ± 5.2
EMD	No	3 months	PD, REC, CAL, PI, BoP	Baseline 6.6 ± 0.9 Y 3.2 ± 0.8	Baseline 7.5 ± 1.3 Y 4.7 ± 1.4	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
ePTFE membrane				Baseline 7.2 ± 1.2 Y 3.6 ± 0.7	Baseline 8.7 ± 1.7 Y 6.0 ± 1.4	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
PDS membrane	No	3 months	PD, VBL-V, CAL-V, CEJ-AC, CEJ-BD, PI, GI	Baseline 6.17 ± 2.34 Y 3.08 ± 1.19	Baseline 7.19 ± 2.15 Y 4.75 ± 1.36	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
PLA membrane				Baseline 6.31 ± 2.42 Y 2.79 ± 1.21	Baseline 7.32 ± 2.41 Y 4.53 ± 1.67	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
EMD + DBBM	Non-smokers, former smokers, light smokers (< 10 cigarettes/day)	N.A.	PD, REC, CAL	Baseline 8.2 ± 1.3 Y 3.3 ± 0.48	Baseline 9.2 ± 1.9 Y 4.8 ± 1.4	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
Collagen membrane + DBBM				Baseline 7.8 ± 2.4 Y 3.1 ± 0.57	Baseline 8.5 ± 2.0 Y 4.5 ± 1.27	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
EMD	2 smokers	3 months	PD, REC, CAL, INTRA, LPS, LBS	Baseline 9.6 ± 1.7 Y 3.9 ± 0.7	Baseline 10.6 ± 1.3 Y 6.1 ± 0.9	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
EMD + AB	2 smokers	3 months		Baseline 9.1 ± 1.6 Y 4.0 ± 1.4	Baseline 10.3 ± 1.5 Y 5.4 ± 1.7	Baseline N.A. Y N.A..	Baseline N.A. Y N.A.
EMD + AB	No	N.A.	PD, REC, CAL, FMPS, FMBS, INTRA	Baseline 7.64 ± 1.09 Y 3.68 ± 0.67	Baseline 8.46 ± 1.26 Y 5.18 ± 0.77	Baseline 14.0 ± 1.6 Y 14.0 ± 2.3	Baseline 13.0 ± 2.0 Y 14.0 ± 5.0

3.6 | Risk of bias assessment

The risk of bias assessment for the included RCTs is summarized in Figure 6. Seven papers have a low risk of bias (Aimetti et al., 2017; Aslan et al., 2020; Cortellini et al., 2001; Crea et al., 2008; Ghezzi et al., 2016; Eickholz et al., 2000; Paolantonio et al., 2020) and one paper (Guida et al., 2007) showed a high risk of performance bias due to the lack of blinding of the examiners.

4 | DISCUSSION

The present systematic review investigated the clinical performance of GTR or EMD alone or in combination with grafting materials in terms of pocket resolution in the treatment of deep intrabony defects based on existing RCTs. The obtained results from the included studies indicate how this endpoint of clinical success has been assessed only by a few clinical studies, while most provided mean and standard deviation of PD and/or CAL at 12 months. This mode of data presentation makes it difficult for clinicians to estimate the efficacy of treatment in changing the prognosis at the tooth and site level (Lang & Tonetti, 2003). In view of the impossibility to have histological evidence of periodontal tissue regeneration, pocket resolution remains an important parameter in clinical success estimation as forecaster of long-term tooth retention (Westfelt et al., 1988; Badersten et al., 1990; Claffey & Egelberg, 1995; Lang & Tonetti, 2003).

It is important to establish a threshold value for pocket resolution, because cut-off points impact on the definition of successful therapy (Tomasi et al., 2007), and therefore, we considered two distinct cut-off values of ≤3 mm and ≤4 mm PD. As the goal of periodontal regeneration is to restore the lost periodontal attachment, PD ≤3 mm represents the physiological depth of the gingival sulcus. On the other hand, periodontal stability in successfully treated periodontitis patients has been characterized by the absence of sites with PD > 4 mm or PD = 4 mm that bleed on probing (Chapple et al., 2018). BoP was associated to the risk of further disease progression with odds ratio of 2.79 (95% CI: 1.03–7.57) in a treated and well-maintained population (Armitage, 1996). Subjects presenting residual pockets with PD ≥4 mm and BoP have an incidence of tooth loss almost twice those not showing gingival inflammation during a supportive periodontal treatment (Tonetti et al., 1998). It is noteworthy that none of the included studies reported results in terms of composite outcome (residual PD and absence/presence of BoP).

In the present meta-analysis, only intrabony defects treated with GTR and EMD were selected based on the histological evidence of regeneration in humans (Cortellini et al., 1993; Sculean et al., 1999; Sanz et al., 2004; Needleman et al., 2006). Furthermore, previous systematic reviews (Murphy & Gunsolley, 2003; Graziani et al., 2012) highlighted the effect of the flap design on the clinical outcomes. Therefore, we included only studies in which PPTs were performed to manage interdental soft tissues.

Based on final PD ≤ 3 mm, the percentage pocket of resolution at 12 months after regenerative treatment was largely variable across the studies ranging from 28.6% to 93.3%. The WMP was 61.4%, with a high heterogeneity probably attributable to differences in defect characteristics, biomaterials applied, years of publication, learning curve and skill of the operators. In the subgroup analysis, the addition of a bone filler material to EMD increased the WMP of pocket resolution from 52.7% to 61.5%. In parallel, a trend for non-resorbable membranes to perform better than resorbable barriers was observed (74.9% and 59.2% respectively), although no direct comparison could be made. It should be underlined that the studies with the greatest weight in the meta-analysis achieved 83.3% and 93.3% probability of pocket resolution (Cortellini et al., 1995, 1996). Interestingly, these studies were the oldest reports included and belonged to the same research group. Their results may have been influenced by the skill of the clinician and by the technique employed (e.g. non-resorbable membrane).

The overall results improved when considering 4 mm PD as cut-off value. The included studies reported percentages ranging from 71.4% to 100%. The WMP of pocket resolution increased to 92.1% with low heterogeneity. In contrast to what we observed for PD ≤ 3 mm, the application of a grafting material did not increase the clinical performance of EMD (95.3% *versus* 92.8%) and the differences between non-resorbable and resorbable membranes were small (93.3% *versus* 88.0%). It should be kept in mind that in the present meta-analysis, a heterogeneous group of biomaterials was considered and applied into predominantly two- to three-walled defects accessed with different PPTs techniques. The limited flap extension and the minimal elevation of the interdental tissue in more recently introduced minimally invasive procedures may have improved wound stability, and thus questioned the additional benefit of using any supporting biomaterial for regeneration (Cortellini & Tonetti, 2009; Liu et al., 2016). Furthermore, the present results corroborate the decreasing use of non-resorbable membranes over the last 15 years, also in consideration of the high number of complications and the need of second surgery.

It is noteworthy that about 30% and 11.0% of deep pockets treated with regeneration procedures had residual PD of 4 mm and ≥5 mm, respectively, at 12 months. Unfortunately, we did not have data on BoP positive sites. Considering that the treated and stable periodontitis patients remain at increased risk of recurrence of periodontitis, it could be envisaged additional treatments.

When comparing regenerative procedures with PPTs in the pairwise meta-analysis, the probability of pocket resolution was higher for the formers for both thresholds of treatment outcomes. However, statistically significance was only obtained for GTR and not for EMD, with clinically relevant NNT values. It is relevant to underline how surgical techniques were not the same across the selected studies, with the application of MIST in Cortellini et al. (1995, 1996, 2001), M-MIST in Cortellini et al. (2011) and entire papilla preservation in Aslan et al. (2020). Among PPTs, the employment of a specific flap design represents a variable significantly affecting the final clinical results, with the raising of a single flap performing better than a double flap (Graziani et al., 2012).

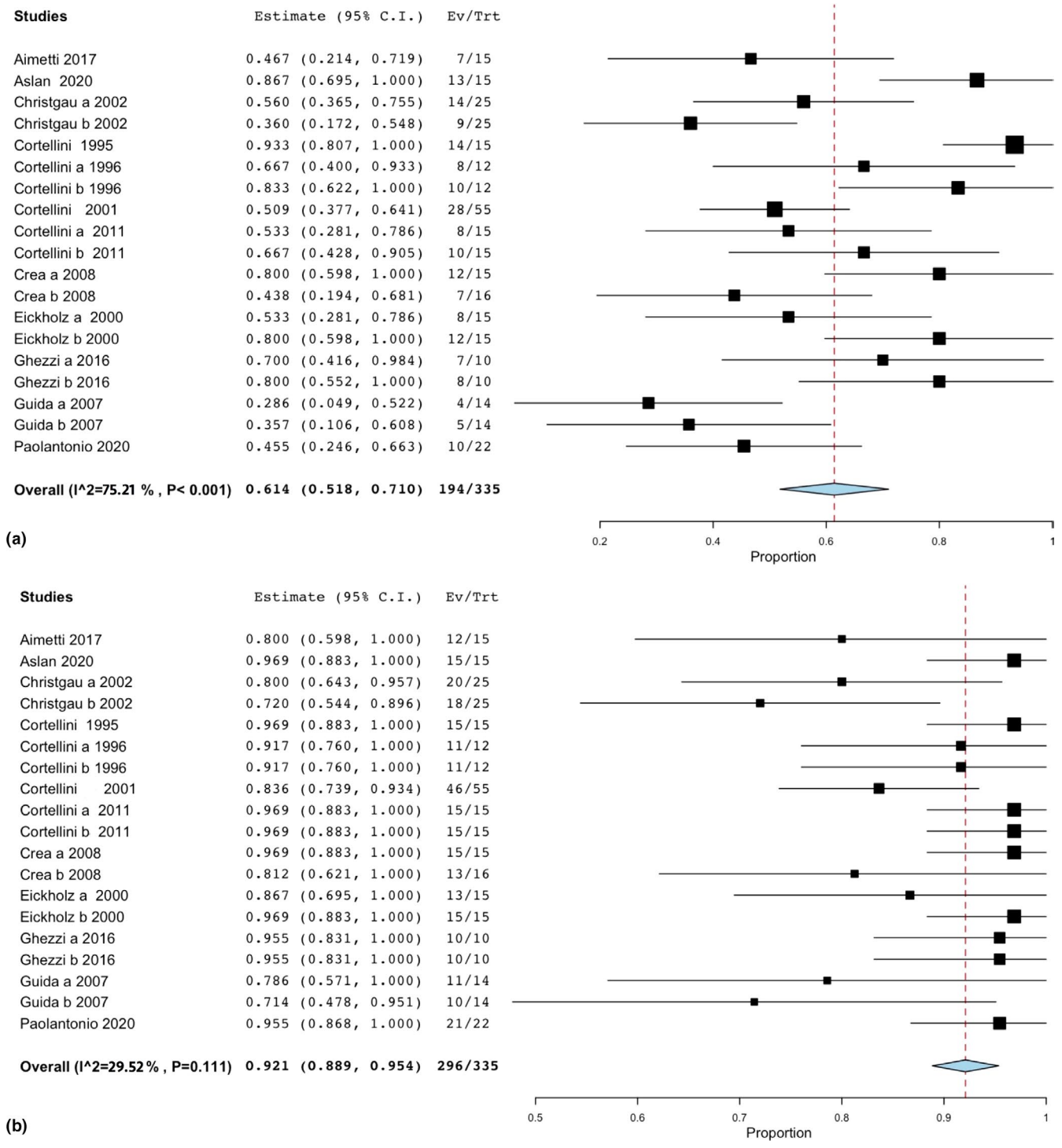

FIGURE 2 Forest plots from random effects of meta-analysis on the percentage of pocket resolution considering final PD ≤ 3 mm (a) and PD ≤ 4 mm (b) 12 months after regenerative surgery

Cost-effectiveness data would provide essential information for making clinical decisions, although none of the included RCTs reported it. When evaluating the few data present in the literature, EMD in conjunction with biomaterials was more effective than EMD alone, while the additional benefit of a membrane only came at relatively high costs (Listl et al., 2011). It should be underlined how flap operation employed in that study did not comprise more modern minimally invasive procedures.

With regards to secondary outcomes, higher weighted mean PD reduction and CAL gain were achieved in intrabony defects treated with EMD plus biomaterials or non-resorbable membranes compared to other regenerative strategies. Also, PPTs alone were less effective than GTR in obtaining PD reduction and CAL gain in the pairwise meta-analyses. These findings agree with data from previous systematic reviews (Esposito et al., 2009; Tu et al., 2010; Nibali et al., 2020), but it should be considered the high heterogeneity.

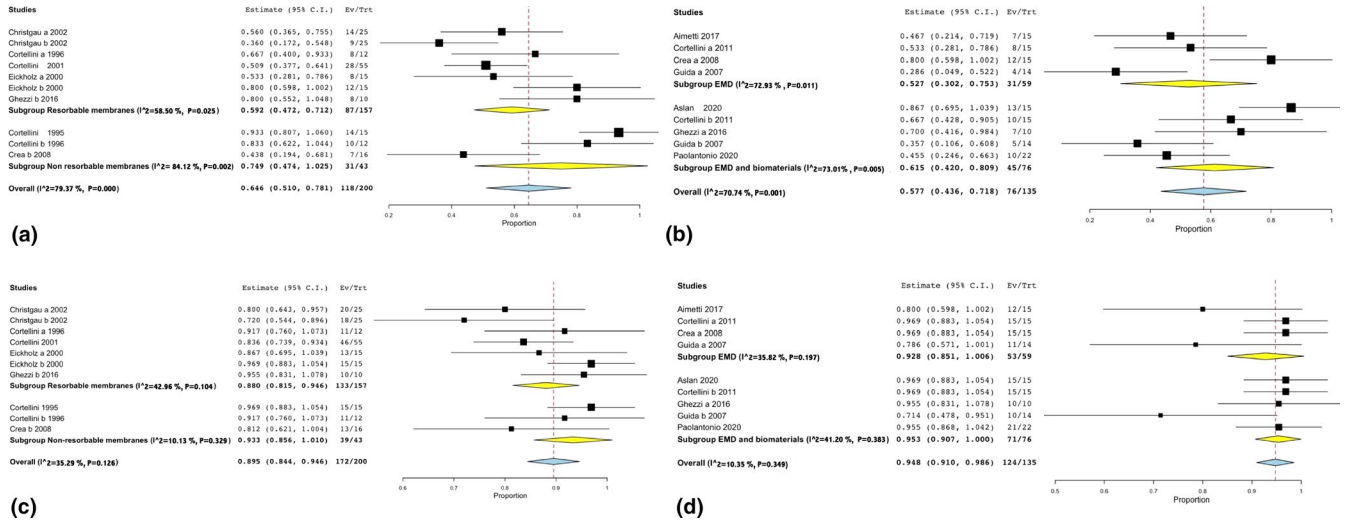

FIGURE 3 Forest plots from random effects of meta-analysis on the percentage of pocket resolution, subgroup analysis. Final PD ≤ 3 mm: effect of type of membrane (a) and effect of EMD and biomaterials (b). Final PD ≤ 4 mm: effect of type of membrane (c) and effect of EMD and biomaterials (d)

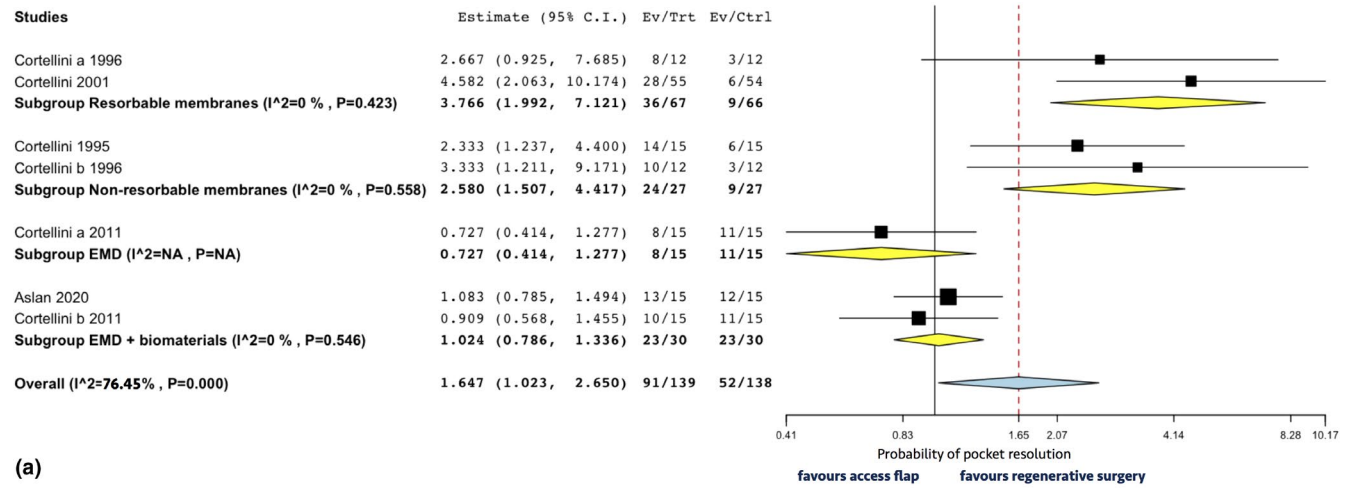

FIGURE 4 Forest plots from random effects of meta-analysis evaluating probability of pocket resolution (risk ratio, 95% CI) considering final PD ≤ 3 mm (a) and final PD ≤ 4 mm (b) after regenerative surgery compared to access flap alone with papilla preservation techniques

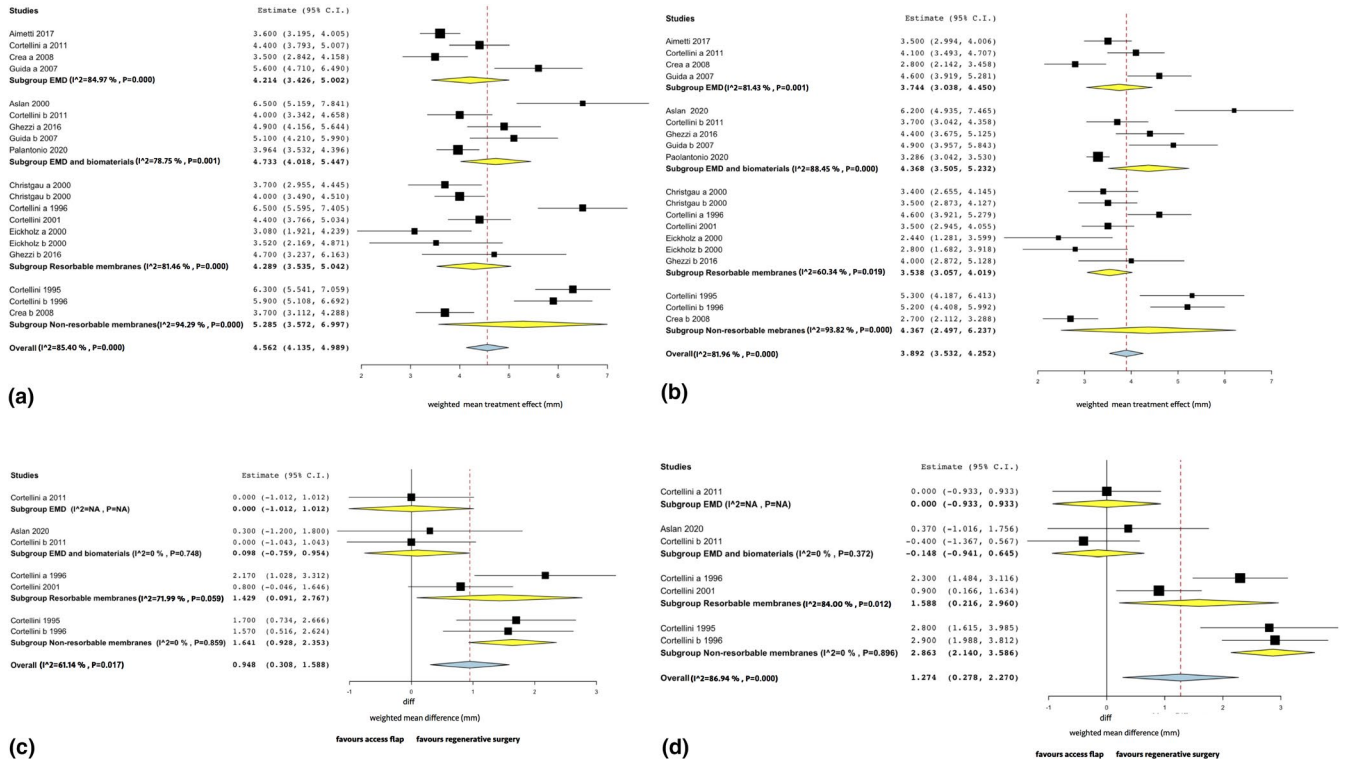

FIGURE 5 Forest plots from random effects of meta-analysis evaluating weighted mean changes in PD (a) and CAL (b) after regenerative surgery and weighted mean differences in PD reduction (c) and CAL gain (d) between regenerative surgery and access flap alone with papilla preservation techniques

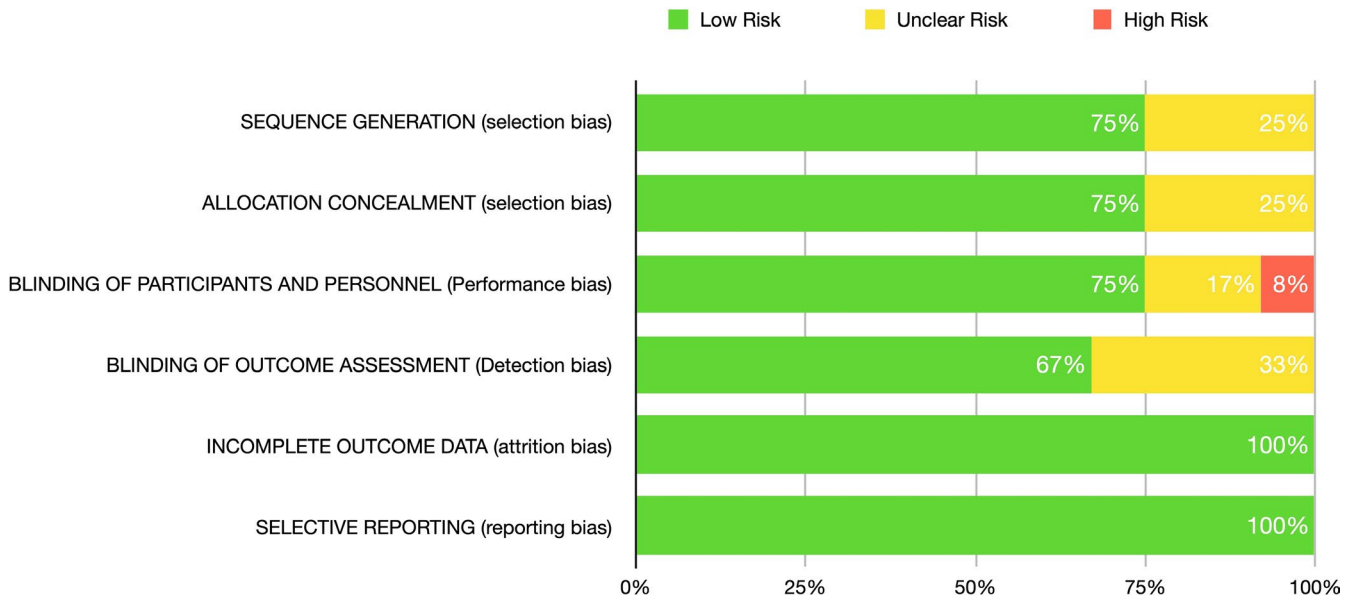

FIGURE 6 Risk of bias in the included studies

Because the number of studies available for pairwise comparisons is few, each meta-analysis may not have sufficient power to detect any genuine difference between treatments.

Data on adverse events were not consistently reported and there was a lack of information about PROMS, thus further studies on these aspects should be encouraged. No serious adverse effect was reported, and pain/discomfort experienced by patients was moderate and lasting few hours.

While these data are clinically promising, the high number of studies excluded from the final selection represents the major limitation of this study. Unfortunately, the majority of the authors were not able to provide raw data on pocket resolution and this

may have produced loss of potentially relevant information. The scarcity of data did not allow for a stratified analysis depending on pre-operative PD, which would have yielded an adjunctive clinical impact to our results. In addition, by complying with our inclusion criteria, we included only RCTs in English language and the results are short-term. The evaluation period of 12 months was selected because it is the follow-up time used in most studies. This limits the generalizability of the present conclusions. In addition, in some high-risk groups such as heavy smokers and subjects with poor plaque control the clinical benefit of periodontal regeneration procedures may be limited. We did not consider smoking habit as exclusion criterion. Thus, smokers were enrolled in 7 studies and represented about 13% of the overall sample included in the meta-analysis, although the number of cigarettes daily smoked was not specified in most of them. It should be considered that in the last 20 years, there has been an increasing awareness of the dose-dependent detrimental effect of cigarette smoking on the outcomes of periodontal regeneration (Cortellini & Tonetti, 2015). Consistently, the most recent papers included in this review enrolled only non-smokers and light smokers (<10 cigarettes/day). Finally, heterogeneity across the studies was high for PD < 3 mm and secondary outcomes.

5 | CONCLUSIONS

Within the limitations of the research, it can be concluded that EMD and GTR represent viable surgical approaches to achieve pocket resolution in the short-term considering final PD ≤ 4 mm. Non-resorbable membranes were associated with higher percentage of sites with final PD ≤ 3 mm at 12 months compared to PPTs. About 30% of treated intrabony defects presented residual PD of 4 mm regardless of the treatment applied. However, no information on persistence of BoP was provided. Due the low number of the included studies, the overall estimates from the meta-analyses should be interpreted with caution, despite representing best-available evidence. In addition, only half of the selected studies reported a low risk of bias for all the methodological aspects.

This review highlights the need of more trials that use pocket resolution combined with absence of BoP as clinical endpoint to evaluate the efficacy of regenerative treatment. Authors should be encouraged to report longitudinal results to provide more evidence on the long-term benefits of periodontal regenerative therapies.

CONFLICT OF INTEREST

The authors report no conflicts of interest related to this study. There was no external funding for this study.

ORCID

Mario Aimetti https://orcid.org/0000-0003-0657-0787
Adriano Fratini https://orcid.org/0000-0002-0562-2760
Filippo Citterio https://orcid.org/0000-0002-4513-7479
Francesco Cairo https://orcid.org/0000-0003-3781-1715
Giacomo Baima https://orcid.org/0000-0002-9395-4967
Federica Romano https://orcid.org/0000-0002-5172-299X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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