Is clinical behavior of composite restorations placed in non-carious cervical lesions influenced by the application mode of universal adhesives? A systematic review and meta-analysis

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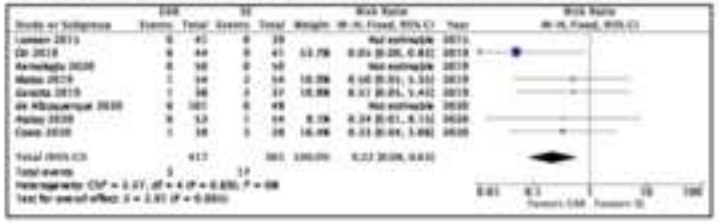
Background

PICOS question:

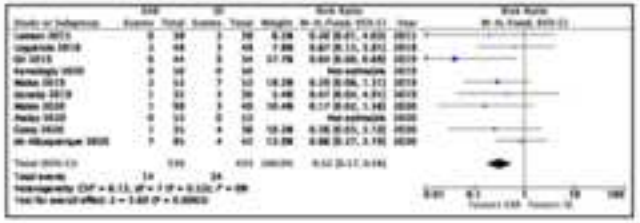
Is the risk of retention loss and postoperative sensitivity (POS) equal for etch-and-rinse (EAR) compared to self-etch (SE) or selective-enamel etch (SEE) mode when restoring non carious cervical lesions with universal adhesives?

Results

Retention at 12-months follow-up (favors EAR over SE)



Retention at 18/24-months follow-up (favors EAR over SE)



Postoperative sensitivity at baseline (favors SE over EAR)

Conclusion

More predictable retention when using universal adhesives in EAR compared to SE mode

Higher risk for postoperative sensitivity when using universal adhesives in EAR mode

Is clinical behavior of composite restorations placed in non-carious cervical lesions influenced by the application mode of universal adhesives? A systematic review and meta-analysis.

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Is clinical behavior of composite restorations placed in non-carious cervical lesions influenced by the application mode of universal adhesives? A systematic review and meta-analysis.

Abstract

Objective: To answer the following PICOS question: "Is the risk of retention loss, marginal discoloration, marginal adaptation and postoperative sensitivity (POS) equal for etch-and-rinse (EAR) compared to self-etch (SE) or selective-enamel etch (SEE) mode when restoring non carious cervical lesions (NCCLs) with universal adhesives?".

Methods: PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, Scientific Electronic Library Online, LILACS, OpenGrey and Google Scholar™ were searched. Randomized controlled clinical trials in which resin composites and universal adhesives were used for restoration of NCCLs were considered. Cochrane Risk of Bias Tool was used to assess the risk of bias. Meta-analyses were performed using Revman; random-effects models were applied, and heterogeneity was tested using the I^2 index. The significance level was set at $p<0.05$. Certainty of evidence was assessed by GRADE tool.

Results and significance: After screening, 20 articles were included in qualitative, while 14 articles were used for quantitative synthesis. Twelve studies ranked as "low", while 8 studies scored as "unclear" for risk of bias. At 12- and 18/24-months the risk for retention loss was higher for SE than for EAR groups ($p=0.005$; RR=0.22, 95% CI [1], moderate certainty of evidence) and $p=0.0002$; RR=0.32, 95% CI [0.17, 0.58], moderate certainty of evidence, respectively). No significant differences were observed for marginal discoloration and adaptation ($p>0.05$). The probability of POS occurrence was less in SE than in EAR groups (RR=2.12, 95% CI [1.23, 3.64], moderate certainty

of evidence). The certainty of evidence for other outcomes was scored as “low” or “moderate”, depending on the follow-up period. Using universal adhesives in EAR or SEE mode provides more predictable retention, while SE strategy reduces the risk of POS occurrence.

1. Introduction

Resin-based dental composites are the most commonly used restorative materials in everyday dental practice due to their good mechanical and esthetic characteristics and handling properties [1, 2]. In order to achieve long term bonding to enamel and dentin, composite materials require the use of adhesive systems [3]. Based on their interaction with the smear layer and number of steps used during bonding procedures, dental adhesives can be classified into etch-and-rinse (EAR) systems (3- and 2-step) and self-etch (SE) systems (2- and 1-step) [4, 5]. In an attempt to overcome problems related to technique sensitivity and provide a more user-friendly approach within clinically acceptable time frame, one bottle universal (or multi-mode) adhesives have been introduced. These materials represent the latest generation of dental adhesives and, according to manufacturers' claims, can be used successfully in EAR, SE or selective enamel etch (SEE) mode [6]. They are referred to as "universal" due to the addition of functional monomers, such as 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP), which can bond chemically to dental tissues as well as to metal/composite/ceramic restorations. Lastly, when used in EAR mode, the need for moisture control for successful bonding is considered to be less critical when compared to previous adhesive systems [7-9].

Many *in vitro* studies focused on investigating the bonding performances of universal adhesives to dental substrates [10-16]. Improved bond strength to enamel has been observed when universal adhesives were used in the EAR mode (13). On the contrary, bonding to dentin did not show the same benefits (13). Further, a recent systematic review of *in vitro* studies found that performance of universal adhesives can be improved by selective enamel etching (SEE) and that, in general, mild universal adhesives showed good stability over time, regardless of the application mode [17].

Results obtained from *in vitro* research represent a solid and irreplaceable tool in the early screening of dental materials' performance. Conclusions drawn from well-designed randomized clinical trials (RCTs) are at the top of the pyramid of evidence-based medicine, with only well conducted systematic reviews being a more powerful tool which can examine treatment effects that were not or could not be apparent in individual RCTs [18, 19]. Recently, the clinical behavior of composite restorations placed in non-carious cervical lesions (NCCLs) using EAR or SE adhesive systems has been evaluated in two systematic reviews [1, 20]. It was reported that composite restorations placed in NCCLs with either of the adhesive strategies have similar clinical behaviors, with EAR adhesive systems performing better in terms of marginal discoloration [1]. When restoring NCCL with SE adhesives, higher restoration longevity was reported when they were used in SEE mode [20].

Considering that universal adhesives were the last to be introduced to the market, RCTs investigating the clinical behavior of composite restorations placed using different adhesive protocols have recently become available in the literature. So far, no clear consensus exists on the most appropriate adhesive strategy in which these adhesives should be used. Therefore, the aim of this systematic review was to answer the following PICOS question: "Is the risk of failure rate, marginal discoloration, marginal adaptation and postoperative sensitivity (POS) equal for EAR compared to SE or SEE mode when restoring NCCLs with universal adhesives?"

2. Methods

2.1. Study protocol and registration

This study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under the number CRD42020184666. The

reporting of this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21].

2.2 Eligibility criteria and search strategy

The PICOS [22] strategy that guided the choice of the inclusion criteria and the search strategy, is described herein:

Population (P) - adult patients with the need of NCCL restoration;

Intervention (I) – composite restoration placed using universal adhesive in EAR mode;

Comparison (C) - composite restoration placed using universal adhesive in SE or SEE mode;

Outcome (O) - clinical parameters used to evaluate direct composite restorations (retention, marginal adaptation/discoloration, POS) for different follow-up periods;

Study design (S) – randomized controlled clinical trials.

A comprehensive literature search was performed with no language restriction through several international and national databases. To identify relevant RCTs investigating the clinical behavior of NCCL composite restorations placed using universal adhesives in EAR, SE, or SEE modes, Clarivate Analytics' Web of Science (including Web of Science Core Collection—WoS, Korean Journal Database — KJD, Russian Science Citation Index — RSCI, SciELO Citation Index — SciELO) [1980-2021], Scopus [1960-2021], PubMed [1964-2021], Cochrane Central Register of Controlled Trials (CENTRAL) [1996-2021], and Latin American & Caribbean Health Sciences Literature (LILACS) through the Virtual Health Library (VHL) portal [1982-2021], were explored up to January 11, 2021. Preliminary searches of mentioned key sources were conducted to identify potential previously published systematic reviews and relevant RCTs in the field, as well as terms and synonyms related to the main concepts of interest (*non-carious cervical lesions* and *universal adhesives*). Test

searches were also used to develop and evaluate various information retrieval strategies, maximize sensitivity, and obtain the most optimal search structure. Various combinations of previously identified free keywords, relevant controlled vocabulary terms (Medical Subject Headings — MeSH descriptors, https://www.ncbi.nlm.nih.gov/mesh), Boolean, truncation, and proximity operators were used, depending on the database being searched. Details on the number of identified articles and complete representation of applied strategies for all searched databases, including the search terms employed, are given in Supplementary Table 1. Furthermore, complementary searches through OpenGrey, Google Scholar™ (first 100 returns), and other available digital repositories (e.g., Networked Digital Library of Theses and Dissertations, Open Access Theses and Dissertations, DART-Europe E-theses Portal – DEEP, Opening access to UK theses – EThOS) were performed to identify unpublished manuscripts, research reports, conference papers, doctoral dissertations, and other grey literature. Finally, reference lists of included studies and relevant reviews were also examined to assure the reliability of obtained data and inclusion of relevant studies that may not have been identified through database and grey literature searches. Additional search during the final drafting of the paper performed up to July 12, 2021, indicated no new relevant studies had been published after completion of the literature search.

The exclusion criteria were as follows: (1) *In vitro* or *ex vivo* studies; (2) reviews (narrative or systematic); (3) case reports; (4) conference abstracts; (5) studies that did not involve at least two groups of direct restorations within the same patient comparing EAR with SE or SEE mode; (6) studies that compared outcomes between vital and non-vital teeth; (7) studies on primary dentition; (8) experiments carried out on animal subjects; (9) materials other than resin composite used as restorative material; (10)

cavities other than NCCLs. No minimum follow-up period threshold was established for this systematic review and meta-analysis, since POS, which is very likely to occur in the first hours or days after the restorative procedure, was one of the main outcomes of interest.

2.3 Study selection and data extraction

All literature search results were imported into the Rayyan QCRI environment [23] for duplicate removal and further analysis. In this systematic review, the study selection process was performed in two stages. To select studies eligible for inclusion, two independent investigators (U.J. and F.D.B.) completed the initial screening of titles and abstracts. Articles that did not meet the eligibility criteria were excluded and full texts of initially selected studies were retrieved for further evaluation. In the second stage, three investigators (U.J., C.M. and T.M.) independently assessed full texts of studies identified as possibly being relevant in the initial screening stage. All disagreements were resolved by consensus or discussion with a senior investigator (L.B.).

Data extraction was performed by three independent investigators (U.J., C.M. and T.M.) using customized extraction forms in MS Word. We extracted details of the study (author, year, location, and study design), participants (number and age range), direct restoration (number, type, and material used for indirect restorations, and type of teeth restored), adhesive strategy (type of adhesive system used during restorative procedures, number of restorations placed with EAR, SE or SEE approach), methodology (evaluation criteria, follow-up periods), and results (success and failure rates, as well as statistical analyses). If essential data were not reported in a certain study, the corresponding author of that paper was contacted by e-mail in an attempt to retrieve the necessary information.

When more than one universal adhesive was used in a trial, the data were combined and assigned to the adhesive strategy investigated in the study. Since an earlier systematic review [24] found that the isolation method (rubber dam or cotton rolls) and enamel bevel [25] did not influence retention and marginal discoloration, we collected data from all the studies, regardless of these two variables. However, since roughening of dentin can lead to improved retention [24], the data from the studies which had groups with roughened dentin was not considered suitable to be included in the meta-analysis. Similarly, the data from the groups that used nanoparticle-doped universal adhesives, as well as studies in which more than one layer of adhesive was applied during adhesive procedure and where dentin was pretreated with a primer (i.e. cross-linking agents), were not included in quantitative synthesis. Since the study results were reported in several periods of follow-ups, the data for 18/24 months was pooled in order to obtain sufficient data to run the meta-analysis. Lastly, when multiple publications with different follow-up periods were detected, the data from the latest publication were taken into consideration for performing the meta-analysis.

2.4. Risk of bias assessment

Two independent reviewers (I.R. and U.J.) performed the risk of bias assessment of the trials using the Cochrane Collaboration's tool for assessing risk of bias in RCTs. [26] Six domains of bias were evaluated: selection bias - random sequence generation and allocation concealment; performance bias - blinding of participants and personnel; detection bias - blinding of outcome assessment; attrition bias - incomplete outcome data; reporting bias - selective outcome reporting; other

possible sources of bias. In case of disagreements between the reviewers, a consensus was reached through discussion, and if needed, by consulting a third reviewer (A.M.).

At the study level, the study was at "low" risk of bias if the two domains considered most relevant for clinical studies in dentistry (selection and detection bias) were at "low" risk of bias. If one or more key domains were judged as at "unclear" risk, the study was considered at "unclear" risk of bias. Finally, if at least one domain was judged at "high" risk of bias, the study was considered at "high" risk of bias.

2.5. Meta-analysis

The extracted data were analyzed using Revman (Review Manager 5.4, The Cochrane Collaboration, Copenhagen, Denmark). Data for all outcomes (retention, marginal discoloration, marginal adaptation, POS) of the eligible studies were dichotomous. To summarize the risk of the mentioned outcomes for each study, the relative risk with a 95% confidence interval (CI) was calculated. Random-effects models were applied, and heterogeneity was tested using the I^2 index.

2.6. Certainty of evidence assessment

The overall quality of clinical evidence (certainty in the estimates of effect) for each of the outcomes was critically assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [27], evaluating individual risk for bias, inconsistency, indirectness, imprecision, and publication bias. Based on these indicators, the certainty of the estimated effect was rated as *high quality of evidence* (the true effect lies close to that of the effect estimate), *moderate quality of evidence* (the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different), *low quality of evidence* (the true effect may be substantially different from the effect estimate), and *very low quality of evidence* (the true effect is likely to be substantially different from the effect estimate) [28]. The

quality assessment was conducted by two independent investigators (U.J. and A.M.) and any disagreements were resolved through discussion.

3. Results

3.1. Study selection

Figure 1 shows a PRISMA flow diagram of the study selection process based on the presented eligibility criteria. The initial search of the chosen databases and other relevant sources retrieved 434 references for potential inclusion in this systematic review. In the next step, 171 duplicates were identified and removed from the database. Following the initial screening of titles and abstracts, 240 records did not satisfy the inclusion criteria and were therefore excluded, while 23 studies were eligible for full-text assessment. In total, 3 studies were excluded after the full-text examination due to the missing EAR group [29, 30] or data reported only in percentages, and no answer was obtained after writing to the authors for additional information [31]. Finally, 20 RCTs were included in this systematic review.

3.2. Descriptive analysis of the selected studies

Detailed information about 20 articles selected for this review is shown in Supplementary Table 2. All studies that were included were conducted as RCTs with split-mouth design in University settings, with majority of them carried out in Brazil [8, 11, 32-43], followed by Turkey [44, 45], USA [46], Spain [47], Germany [48] and Portugal [49]. The studies were published between 2013 and 2020 and included a total number of 1.890 NCCL restorations placed in both anterior and posterior teeth of 527 patients older than 18 years. The follow-up periods included 1-week, 6-, 12-, 18-, 24-

to 36-months for most of the studies, and only one study [8] evaluated the restorations after 5 years of clinical service.

Before placing composite restorations, prophylaxis was performed on NCCLs with pumice and water, whereas in only two studies a cervical bevel was created [46]. Several studies [8, 36-38, 46, 50] reported using rubber dam during restorative procedures, while no information on NCCL pretreatment or rubber dam placement was available in one study [45]. A universal adhesive was modified by adding Cu nanoparticles in one study [38] and in 3 publications two different brands of universal adhesives that were used for restoration of the lesions were compared [39-41]. The clinical outcomes were assessed using either the FDI World Dental Federation (FDI) or modified United Stated Public Health Service (USPHS) criteria. Interestingly, POS, which was one of the main outcomes analyzed in this review, was assessed in two ways: by applying a stimulus in dental office [8, 11, 32, 35, 37, 38, 43, 44, 46, 48, 49, 51] or via questionnaire (asking the patient if he/she experienced any pain within the week following the restorative procedure) [33, 36]. One study [47] employed both methods in assessing POS, whereas two studies did not asses POS [40, 45]. In 2 studies the method of POS evaluation was not reported, and after writing to the authors it was not possible to obtain this information [42, 52].

3.3. Risk of bias of the included studies

Figure 2 summarizes the risk of bias judgment for each of the included studies. Overall, the reviewed studies had no major problems regarding the study design and reporting of results. The raised concerns were related to: selection bias – not clearly stated if the allocation concealment was kept hidden until the moment of restorative procedure [32, 42, 46, 48, 49]; performance bias – not reported if the participants were blinded [39, 45, 53]; detection bias – not mentioned if the evaluators were blinded [40,

45, 47]; attrition bias – patient drop out led to the loss of follow up greater than 20% [40, 41, 47]. Consequently, eight studies [32, 40-42, 46-49] were considered to be at "unclear" risk of bias, while the remaining twelve were judged as "low" risk of bias.

3.4. Quantitative synthesis: meta-analyses

Based on data extraction, 14 studies [8, 32, 34, 36-38, 42, 44-46, 48-50, 54] were suitable for the inclusion in the meta-analyses for the outcomes of interest. The data from some studies [31] could not be used for meta-analysis since the authors reported their results in percentages, and we received no response after contacting the corresponding author.

3.5. Loss of retention

The forest plots of meta-analyses for loss of retention at different follow-up periods for EAR and SE mode are shown in Figures 3 - 6. No significant differences between the groups were observed at 6- and 36- months (p=0.36; p=0.14, respectively) recall (Figures 3 and 6). However, there was a statistically significant difference for 12- (p=0.005; RR=0.22, 95% CI [0.08, 0.63]) and 18/24- (p= 0.0002; RR=0.32, 95% CI [0.17, 0.58]) months follow-up between the two groups, favoring the EAR groups (Figures 4 and 5). Data from 12- and 18/24-months follow up were not heterogeneous (I^2=0%), while the data from 6- (chi^2 test; p=0.02; I^2=66%) and 36-months (chi^2 test; p=0.13, I^2=56%) follow-up showed substantial heterogeneity.

Figures 7 - 10 illustrate the forest-plots for meta-analyses for loss of retention at different follow-up periods for EAR and SEE mode. No statistically significant difference was observed at 6-, 12-, 18/24- and 36- months follow-up (p=0.97; p=0.15; p=0.49; p=0.99, respectively). The data for 6- (chi^2 test; p=0.68, I^2=0%), 12- (chi^2 test;

p=0.56, I^2=0%), 18/24- (chi^2 test; p=0.44, I^2=0%) and 36-months (chi^2 test; p=0.98, I^2=0%) follow-up were not heterogeneous.

3.6. Marginal discoloration

Forest plots of the meta-analyses for risk of marginal discoloration for EAR and SE groups are presented in Figures 11 - 13. No statistically significant differences were seen at 6-, 12- and 18/24- months follow-up period (p=0.40; p=0.34; p=0.73, respectively). The data for 6- and 18/24- months follow up showed no heterogeneity, while substantial heterogeneity was observed at 12- months (chi^2 test; p=0.07, I^2=70%). No events were observed when comparing EAR with SEE adhesive strategy and therefore the meta-analyses could not be performed.

3.7. Marginal adaptation

Forest plots of the meta-analyses for marginal adaptation for EAR and SE groups are seen in Figures 14 - 16. No statistically significant differences were seen at 6-, 12- and 18/24-months follow up periods (p=0.88; p=0.21; p=0.34, respectively). The data for 6- (chi^2 test; p=0.59, I^2=0%), 12- (chi^2 test; p=0.83, I^2=0%), 18/24- months (chi^2 test; p=0.43, I^2=0%) were not heterogeneous.

Similar to marginal discoloration, no events were observed when comparing EAR to SEE strategy.

3.8. POS

Three meta-analyses were performed for POS, taking into account the method of the assessment and the adhesive strategy for this clinical outcome. Figure 17 demonstrates the forest plot for the risk of POS for EAR and SE modes, analyzed Based on the data derived from questionnaires (subjective POS) which was given to patients one week within the restorative procedure, no significant difference was seen for subjective POS (p=0.55, Figure 17). The second meta-analysis (Figure 18), which

included studies that assessed POS by applying stimuli during recall (objective POS) after one week of the restorative procedure demonstrated significantly increased likelihood for POS occurring in the EAR groups (p=0.007, RR=2.12, 95% CI [1.23, 3.64]).

Lastly, no significant difference was observed (p=0.80) when comparing EAR to SEE groups in terms of stimulated POS (Figure 19).

3.9. Certainty of evidence assessment

The certainty of evidence for each of the outcomes evaluated in our meta-analyses was assessed by the GRADE tool [27].

EAR versus SE groups

Low certainty of evidence was observed for retention at 6- and 36-months follow-up with serious inconsistency and imprecision, while moderate certainty was seen at 12-, 18/24- months follow-up (Table 1). Similarly, low certainty with serious imprecision was seen for marginal discoloration at 6- and 12-months follow-up, while moderate certainty was observed for 18/24- months (Table 2). Moderate certainty was observed for marginal adaptation for all follow-up periods (Table 3). As for POS, low certainty with very serious imprecision was seen for subjective POS, whereas moderate certainty of evidence was observed for objective POS evaluation (Table 4).

EAR versus SEE groups

Moderate certainty of evidence was noted for retention at 6-, 12- and 18/24-months, while low certainty with very serious imprecision was detected at 36-months

follow-up (Table 5). Our assessment revealed moderate certainty of evidence for the outcome POS when comparing EAR to SEE groups (Table 6).

4. Discussion

Organizing RCTs to evaluate clinical behavior of resin-based restorations placed in NCCLs using different adhesive strategies is considered to be state of the art [1, 20, 55]. Only results from carefully conducted, homogenous systematic reviews with meta-analyses can be considered equally, or even more important for decision making in every day practice [18]. Earlier systematic reviews analyzed the clinical performance NCCLs restored with EAR or SE adhesive systems and SE adhesives in two different etching modes (SE or SEE) [1, 20]. However, to the best of our knowledge, no systematic reviews analyzing clinical trials in which universal adhesives were used for restoring NCCLs have been published so far. Therefore, by conducting a systematic review with meta-analyses, we synthetized the data from the available RCTs and sought to investigate which adhesive strategy should be employed in order to optimize clinical performances of composite restorations placed with this category of adhesive systems.

The results of our study revealed that the loss of retention is not significantly influenced by the adhesive strategy at 6-months follow-up (low certainty of evidence). On the contrary, significant difference was observed for 12- and 18/24- months with a moderate certainty of evidence, with SE group being exposed to increased likelihood for loss of retention when compared to EAR group. Even though the trend towards increased risk of retention loss was expected to be found with a longer follow-up period, no difference was observed at 36-months recall. However, this result must be interpreted with caution since low certainty of evidence was present at 36-months

evaluation, meaning that the true effect might be markedly different from the estimated one (Table 3) [27].

The fact that higher retention rates were observed when universal adhesives were used in EAR compared to SE mode may be explained by the morphology and configuration of NCCLs. The margins, or at least a part of NCCLs is located in enamel [55], and it is well known that it is easier to achieve predictable bonding to enamel compared with dentin, due to the differences in the composition of these two tissues [56]. Indeed, previous *in vitro* studies reported increased bond strengths of universal adhesives to enamel that had previously been etched with phosphoric acid [17, 57]. The conclusion is confirmed by our results which revealed that, in clinical settings, the risk for loss of retention can be decreased when using universal adhesives in EAR mode rather than in SE mode. Furthermore, our meta-analysis results showed no differences for the risk of retention loss between EAR and SEE groups. This suggests that SEE mode may be an alternative approach to EAR mode, since the application of phosphoric acid is limited to enamel only, therefore leaving behind mineralized dentin. This strategy enables Ca-salts to be embedded within the hybrid layer, and when using adhesives that contain 10-methacryloyloxydecyl dihydrogen phosphate (10-MDP) as a functional molecule, common for universal adhesives used in the present systematic review [15, 34, 37, 39, 44], it may lead to the formation of stable MDP-Ca salts which provide clinical durability of the hybrid layer [58].

Contrary to what might have been expected, the results of our meta-analysis revealed that the choice of the adhesive strategy (EAR *vs.* SE) did not have an influence on marginal discoloration at any of the follow-up periods. Moreover, no events related to marginal discoloration were found during the data extraction process from studies that compared EAR to SEE groups and, consequently, meta-analysis was not run. On

the contrary, a recent systematic review and meta-analysis reported that restorations placed in NCCLs with EAR adhesive systems tend to achieve more satisfactory long-term results for marginal discoloration than SE systems. [1] However, our review cannot be fully compared to the previous one, since the former review compared EAR and SE adhesive systems, which often differ considerably in the composition. However, comparison of the universal adhesives used in the EAR and SE modes, entails the employment of the same material in different adhesive strategies, and therefore the material composition cannot account for the differences in the clinical behavior. Furthermore, although it seems that applying universal adhesives in EAR mode offers no advantage over SE mode, closer look should be given to the certainty of evidence tool and the length of the follow-up periods. Low certainty was seen for 6- and 12-months follow-up, while moderate level with very few events was observed for 18/24 months. Besides low and moderate certainty of evidence observed at these short- and medium-term follow-ups, the literature suggests that it may take more than 5 years to observe a significant number of events between the treatment groups in clinical settings [59]. Unfortunately, we could not run a meta-analysis for long-term follow-ups since only one study [8] evaluated the NCCL restorations after 5 years of clinical function, and found superior clinical performance for EAR and SEE compared to SE strategy. Another factor to be considered is that marginal discoloration, assessed by the FDI and USPHS criteria, was not evaluated separately between dentin and enamel margins, as suggested by Cieplik et al. (2017), thus potentially masking differences between different adhesive strategies [60].

POS is a clinical parameter widely discussed among clinicians since it can cause patients' dissatisfaction and difficulties in resolving [61]. Despite the large interest, this clinical parameter has not always been studied in previous systematic reviews that

analyzed different types of adhesives employed in resolving the problem of NCCLs [62, 63], and neither was it addressed in a recent systematic review which evaluated the influence of etching mode (SE vs. SEE) for NCCLs restored with SE adhesives [20]. As far as the authors of this paper are aware, the only systematic review that analyzed POS after placing composite restorations in NCCLs found no differences when EAR were compared to SE adhesive systems [1]. However, unlike the previous review [1] in which dichotomous data from 19 studies, irrespective of the POS assessment method, were used to run a single meta-analysis, we performed separate meta-analyses, distinguishing the data based on the way in which POS was estimated and taking into account the adhesive strategy. We opted to investigate POS only at baseline, since this it clinically most often occurs only within the first week following the intervention. Our results for subjective POS are in line with earlier conclusions [1], since no difference was observed when universal adhesives were employed in the EAR and SE mode for restoration of cervical lesions. However, an interesting finding from our study was that EAR groups had higher risk for objective POS occurrence than SE groups. Contrary, no differences in terms of POS when EAR and SE adhesives were used for restoration of posterior cavities has been reported in the literature [64], and the choice of the adhesive strategy (EAR or SE) seemed to play no role in POS occurrence in NCCLs restorations [1]. Therefore, this may be the first systematic review which reported, with moderate level of evidence, that the choice of adhesive strategy could influence objective POS when universal adhesives are used for NCCLs restoration, suggesting that SE approach could be more appropriate than EAR when aiming to reduce POS sensitivity during NCCLs restoration.

One of the main remarks of evaluating POS by applying a stimulus is that it serves rather as pulp vitality indicator and that the absence of preoperative POS may

change due to the adhesive procedure and become detectable on stimulus after the restoration has been placed [65]. However, the primary studies included in our meta-analysis involved (in various percentage) NCCLs which already exhibited baseline preoperative sensitivity, thus it is not likely that the reported POS sensitivity occurred due to the restorative procedure. Regardless of potential drawbacks for POS assessment by applying a stimulus, we observed higher risk for POS occurrence in EAR groups, most probably due to the fact that phosphoric acid partially or even completely dissolved the hypermineralized layer within NCCLs [66].

Generally, RCTs included in this systematic review demonstrated no major concerns considering the risk of bias assessment. The random allocation sequence took place in all reviewed RCTs, but the lack of clear reporting of allocation concealment, blinding of participants and/or evaluators led to classifying some domains as "unclear" (Figure 2). Furthermore, we ranked 3 articles [40, 41, 47] as "unclear" for attrition bias, since more than 20% of patients were lost and no intention-to-treat analysis was reported to had been performed. Traditional understanding suggests that patient drop-out rate higher than 20% may represent a serious threat to study's validity. [67] Despite this belief, our decision to score attrition bias domain as "unclear" instead of "high" was based on the fact that the split-mouth design was employed in all RCTs, and consequently, the patient drop-out led to the balanced loss of restorations across the groups [68].

Lastly, one of the novelties of this review compared to the previous ones [1, 20, 64] was the implementation of certainty of evidence that was assessed according to the GRADE tool. The benefits of introducing GRADE assessment is that it provides assessments about the quality of evidence for each outcome in a transparent manner, and may differ for the same outcome at various follow-up periods depending on

inconsistency, indirectness and imprecision. One of the limitations of this review is that our conclusions are drawn from meta-analysis performed for short- and medium-term follow-up periods (the longest follow-up was 36 months). Another limitation is that direct comparison between SE and SEE strategy was not performed, as it would have led to a less focused PICOS question. The rationale for comparing EAR with SE or SEE mode lies in the fact that when using universal adhesives in EAR mode dentin is etched, while it is left unetched in both SE and SEE strategy. In future, it would be of interest to conduct systematic reviews that compare the influence of SE and SEE strategy on clinical performance of composite restorations placed in NCCLs with universal adhesives and include RCTs with follow-ups longer than 5 years.

5. Conclusions

Based on the results of this systematic review and meta-analyses on clinical data available so far, we could recommend with a moderate certainty of evidence that the application of universal adhesives in the EAR mode could lead to better medium-term retention of composite restorations of NCCLs compared to the SE application strategy, while the use of the SE adhesives could lead to less immediate POS and therefore better short-term patient satisfaction. The SEE approach was comparable with the EAR approach in terms of retention (moderate level of evidence at 6 and 18/24 months) and POS (moderate level of evidence).

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Figure legends

Figure 1: PRISMA flowchart of study identifications

Figure 2: Risk of bias of the included studies

Figure 3: Forest plot for retention at 6-months follow-up (EAR vs.SE)

Figure 4: Forest plot for retention at 12-months follow-up (EAR vs.SE)

Figure 5: Forest plot for retention at 18/24-months follow-up (EAR vs.SE)

Figure 6: Forest plot for retention at 36-months follow-up (EAR vs.SE)

Figure 7: Forest plot for retention at 6-months follow-up (EAR vs.SEE)

Figure 8: Forest plot for retention at 12-months follow-up (EAR vs.SEE)

Figure 9: Forest plot for retention at 18/24-months follow-up (EAR vs.SEE)

Figure 10: Forest plot for retention at 36-months follow-up (EAR vs.SEE)

Figure 11: Forest plot for marginal discoloration at 6-months follow-up (EAR vs.SE)

Figure 12: Forest plot for marginal discoloration at 12-months follow-up (EAR vs.SE)

Figure 13: Forest plot for marginal discoloration at 18/24-months follow-up (EAR vs.SE)

Figure 14: Forest plot for marginal adaptation at 6-months follow-up (EAR vs.SE)

Figure 15: Forest plot for marginal discoloration at 12-months follow-up (EAR vs.SE)

Figure 16: Forest plot for marginal discoloration at 18/24-months follow-up (EAR vs.SE)

Figure 17: Forest plot for subjective POS at baseline (EAR vs.SE)

Figure 18: Forest plot for objective POS at baseline (EAR vs.SE)

Figure 19: Forest plot for objective POS at baseline (EAR vs.SEE)

Figure 1

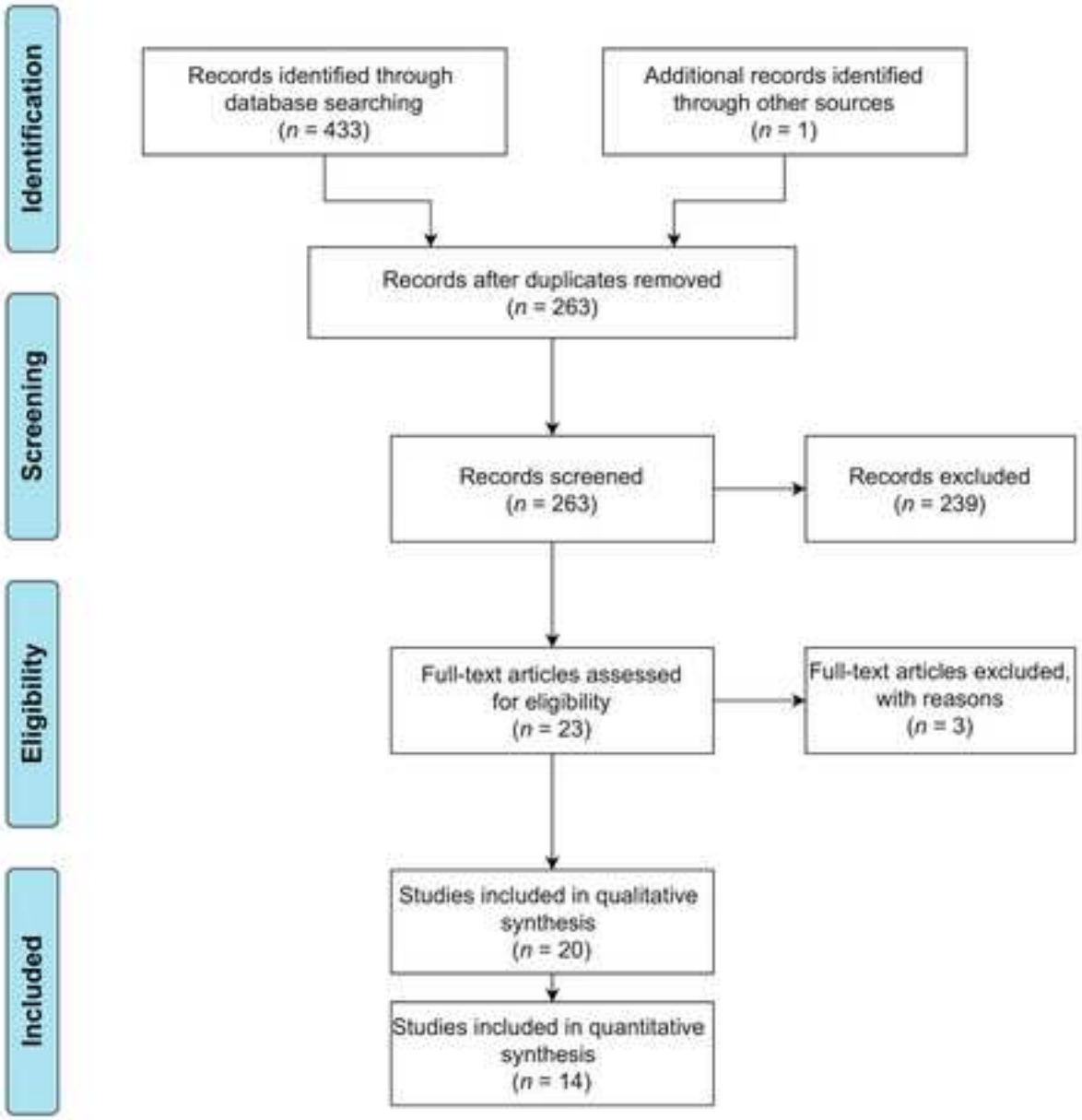

Figure 2

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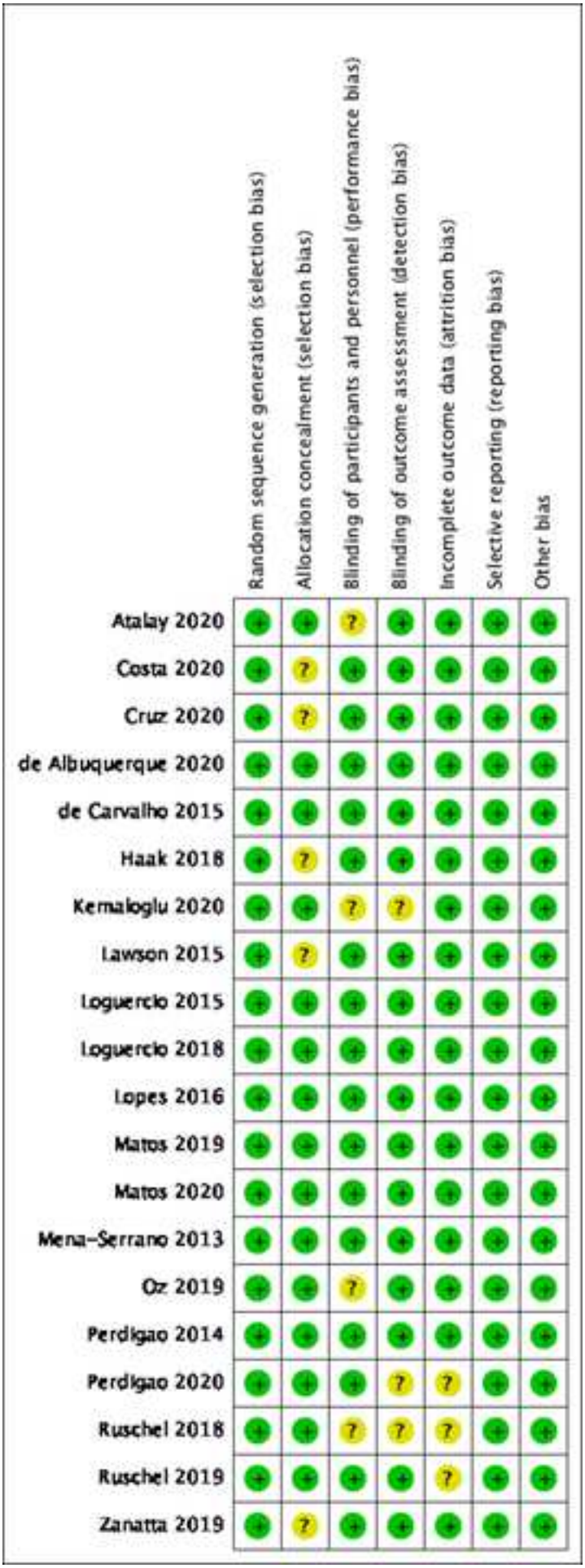

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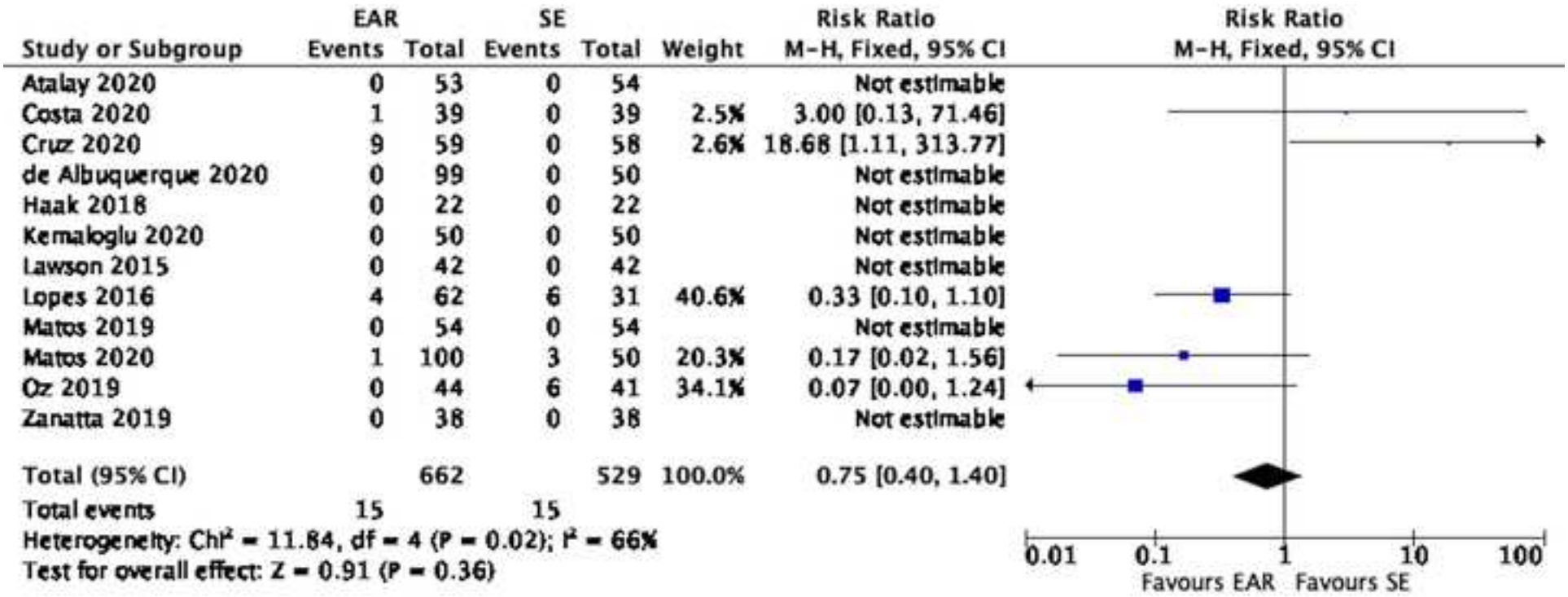

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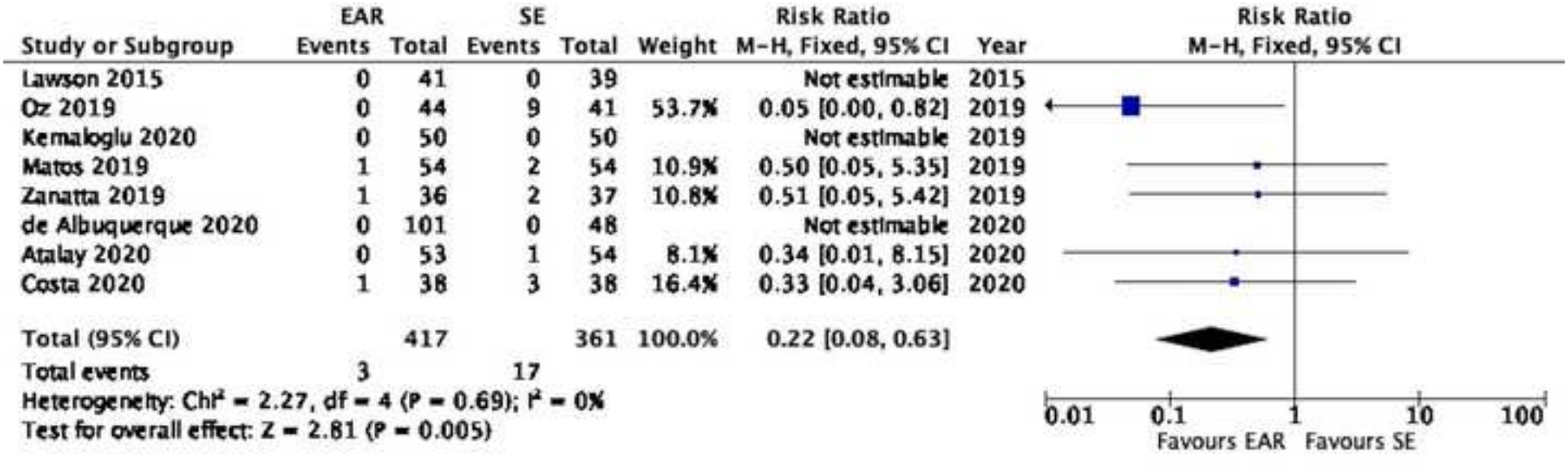

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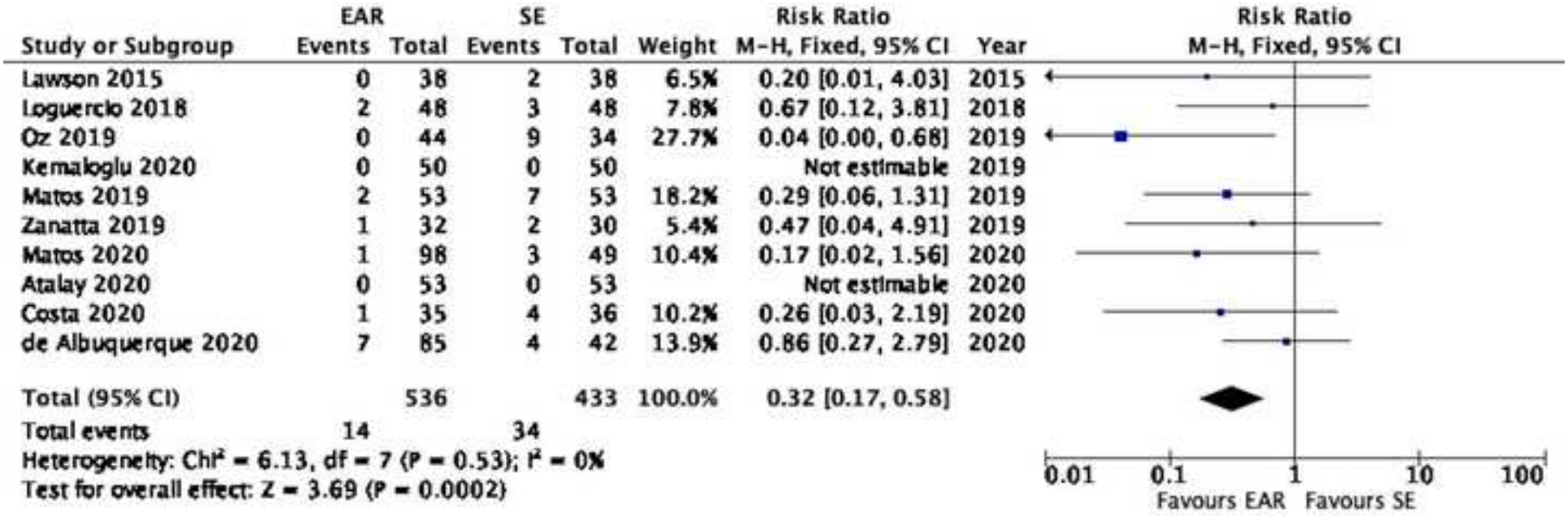

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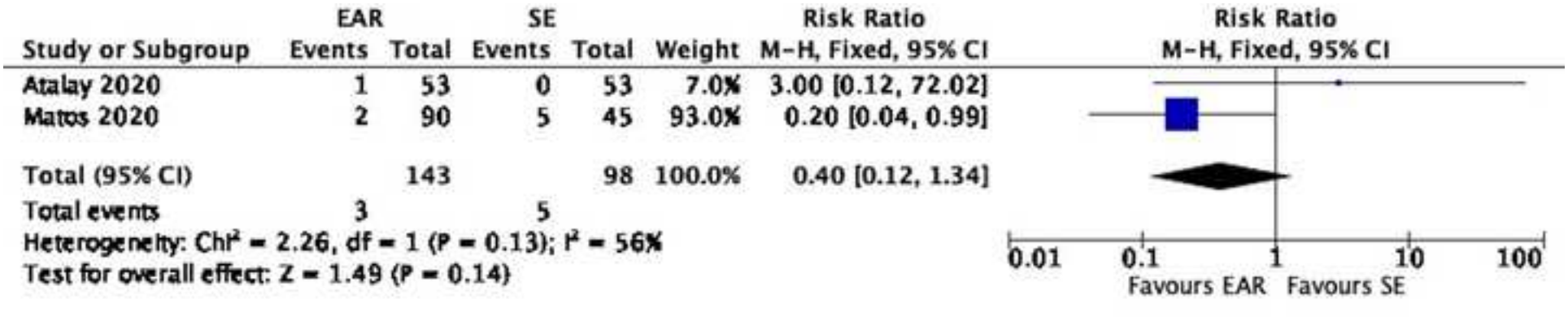

Figure 7

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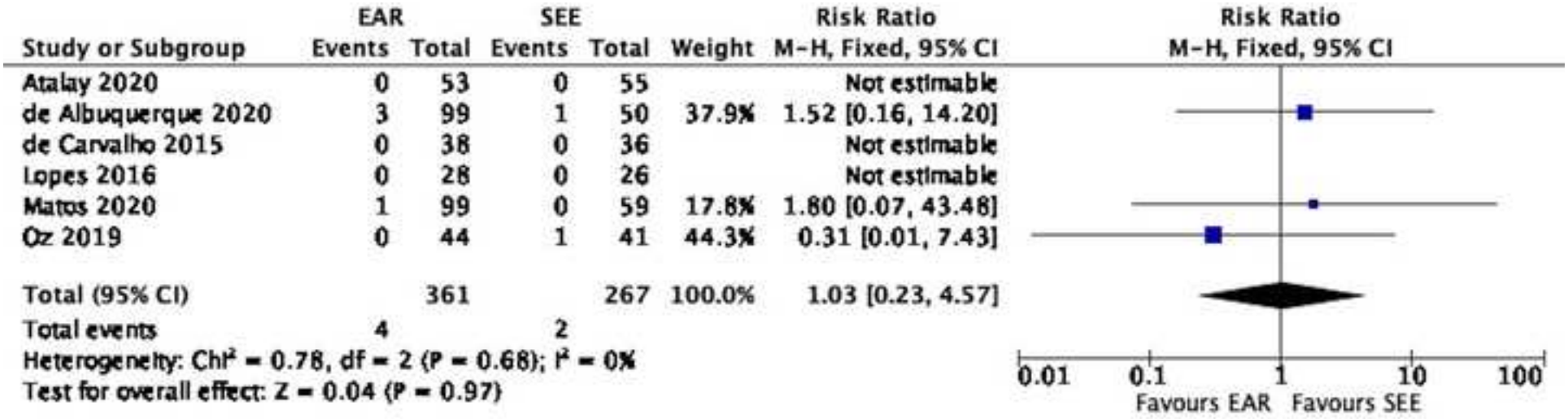

Figure 8

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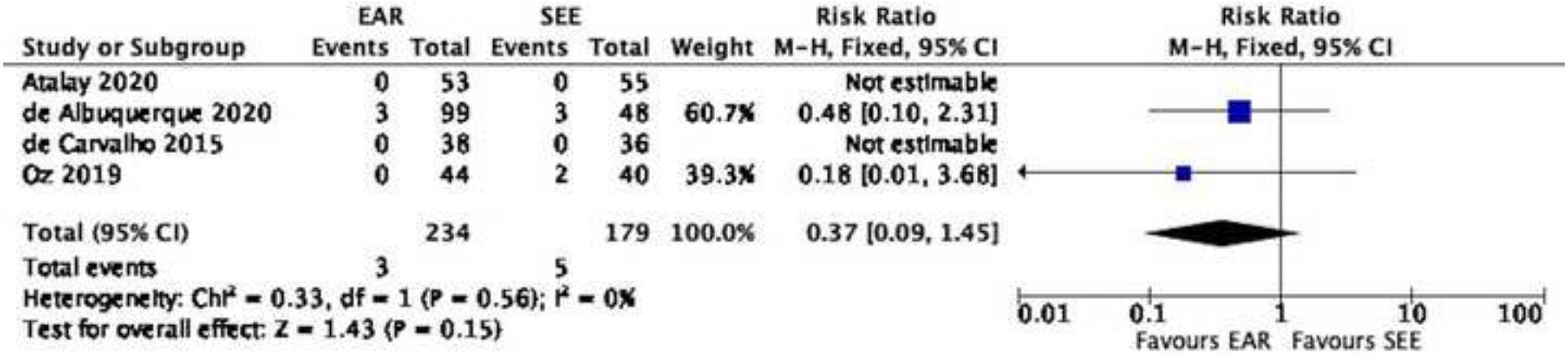

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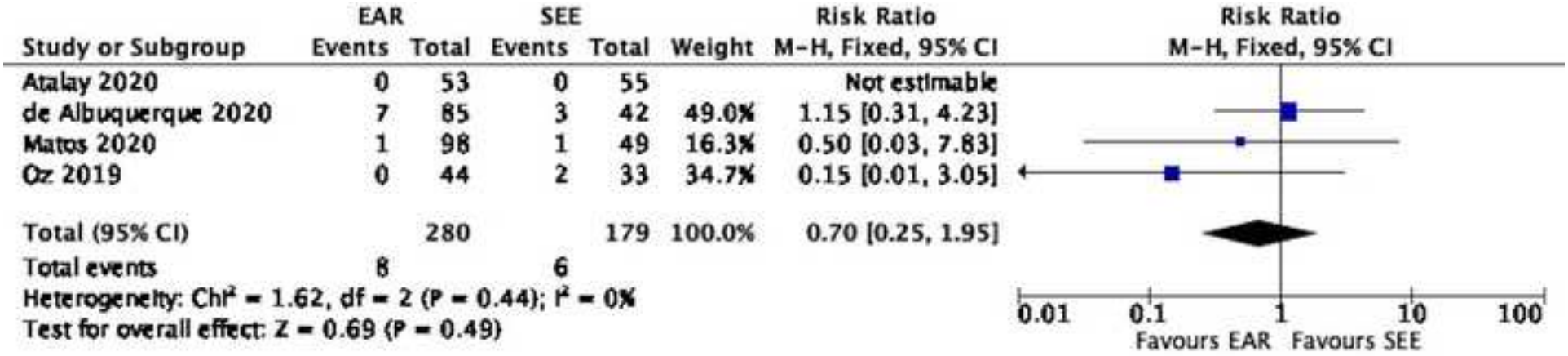

Figure 10

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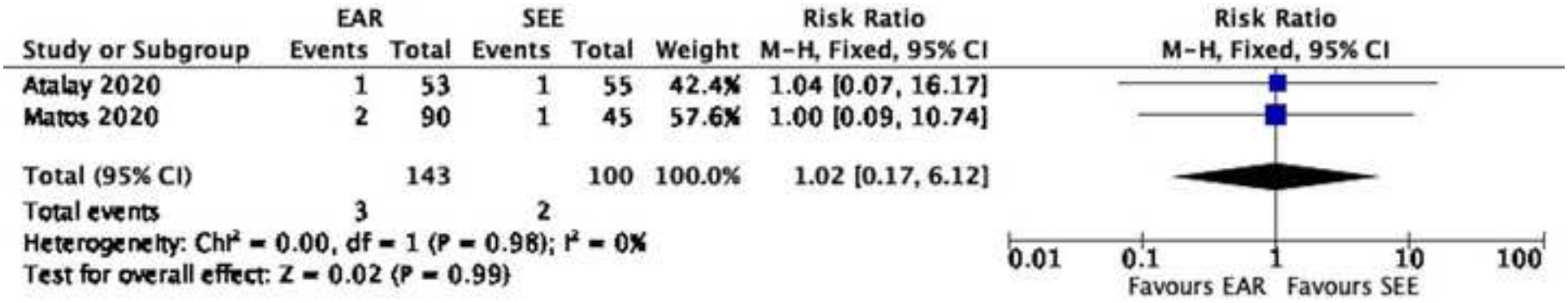

Figure 11

Study or Subgroup	EAR Events	EAR Total	SE Events	SE Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Atalay 2020	0	53	0	54		Not estimable
Costa 2020	0	38	0	38		Not estimable
Cruz 2020	1	50	3	58	100.0%	0.39 [0.04, 3.60]
de Albuquerque 2020	0	96	0	48		Not estimable
Haak 2018	0	22	0	22		Not estimable
Kemaloglu 2020	0	50	0	50		Not estimable
Lawson 2015	0	42	0	41		Not estimable
Loguercio 2018	0	48	0	46		Not estimable
Lopes 2016	0	59	0	25		Not estimable
Matos 2019	0	54	0	54		Not estimable
Matos 2020	0	100	0	50		Not estimable
Oz 2019	0	44	0	35		Not estimable
Zanatta 2019	0	38	0	38		Not estimable
Total (95% CI)		694		559	100.0%	0.39 [0.04, 3.60]
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)

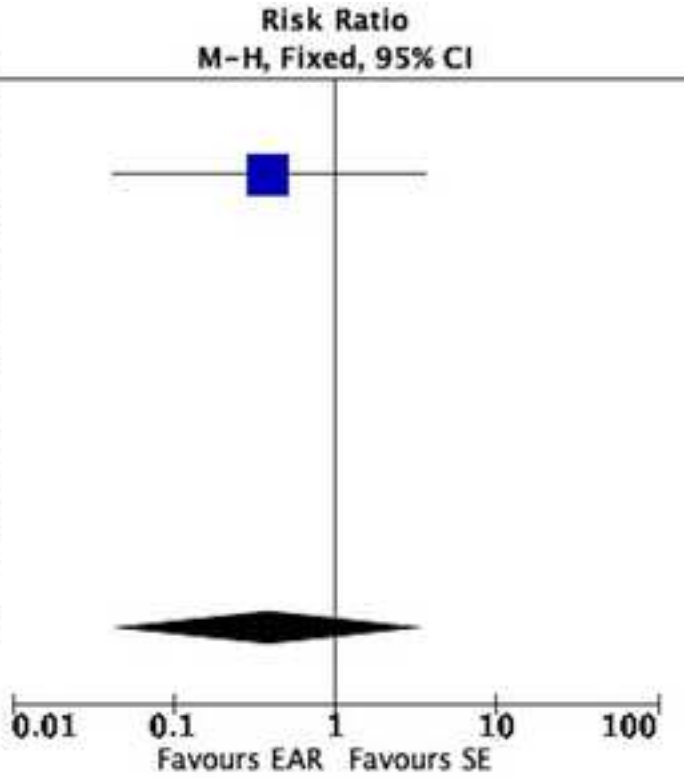

Figure 12

Click here to access/download;Figure;Figure 12.jpg

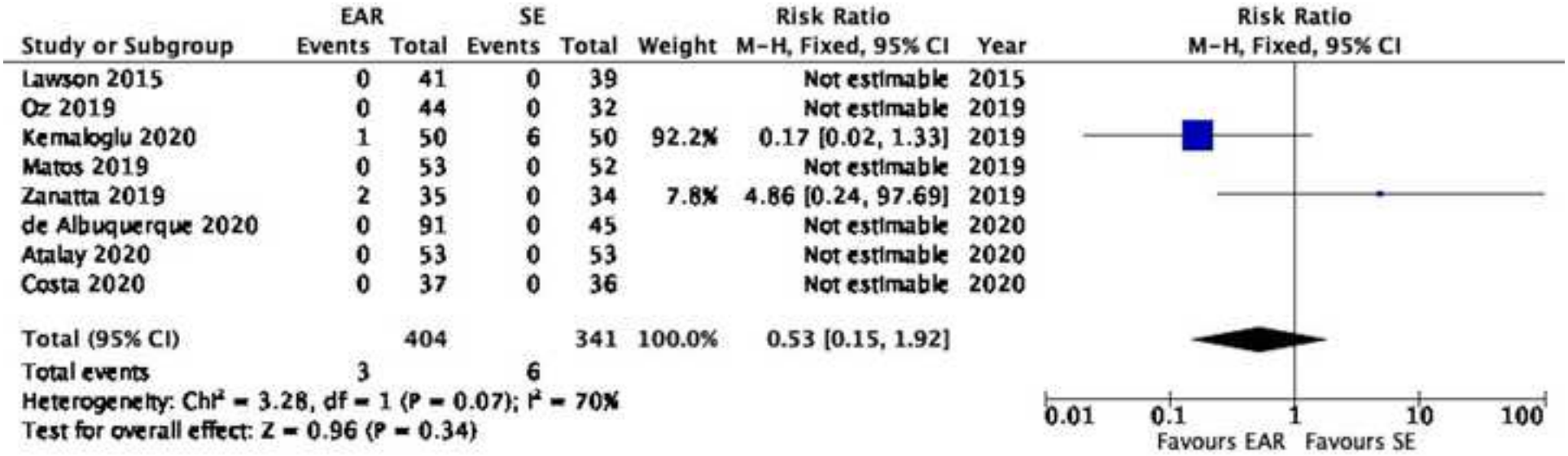

Figure 13

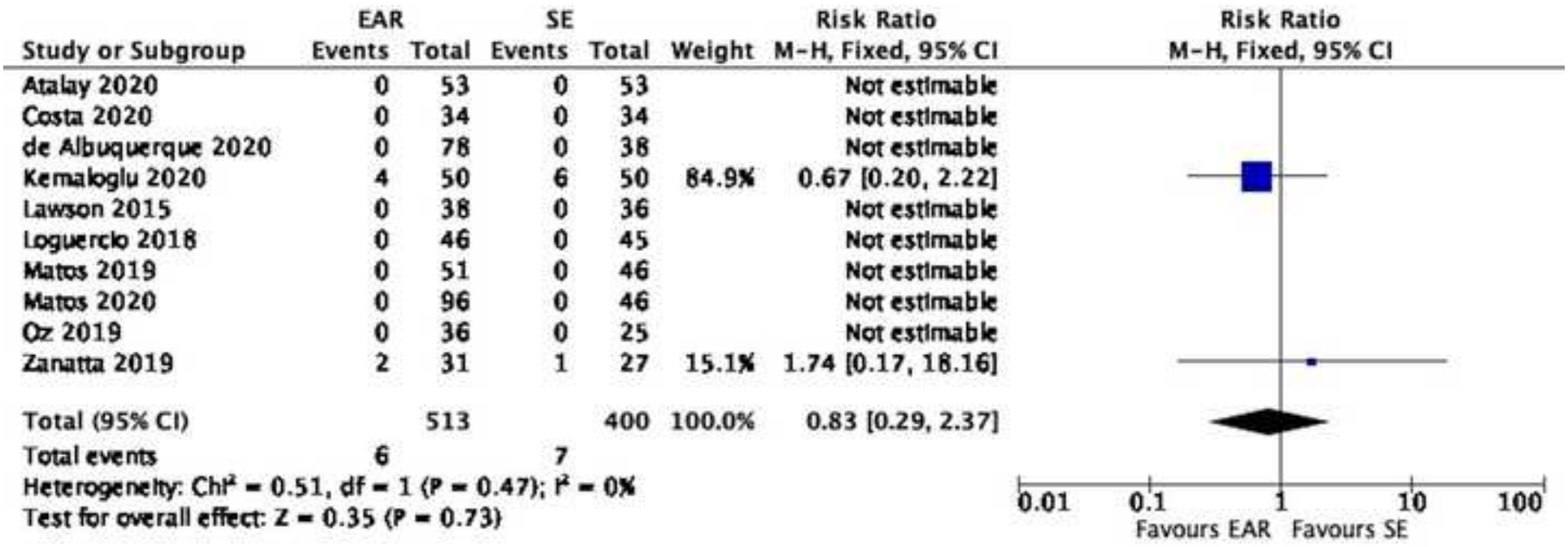

Figure 14

Click here to access/download;Figure;Figure 14.jpg

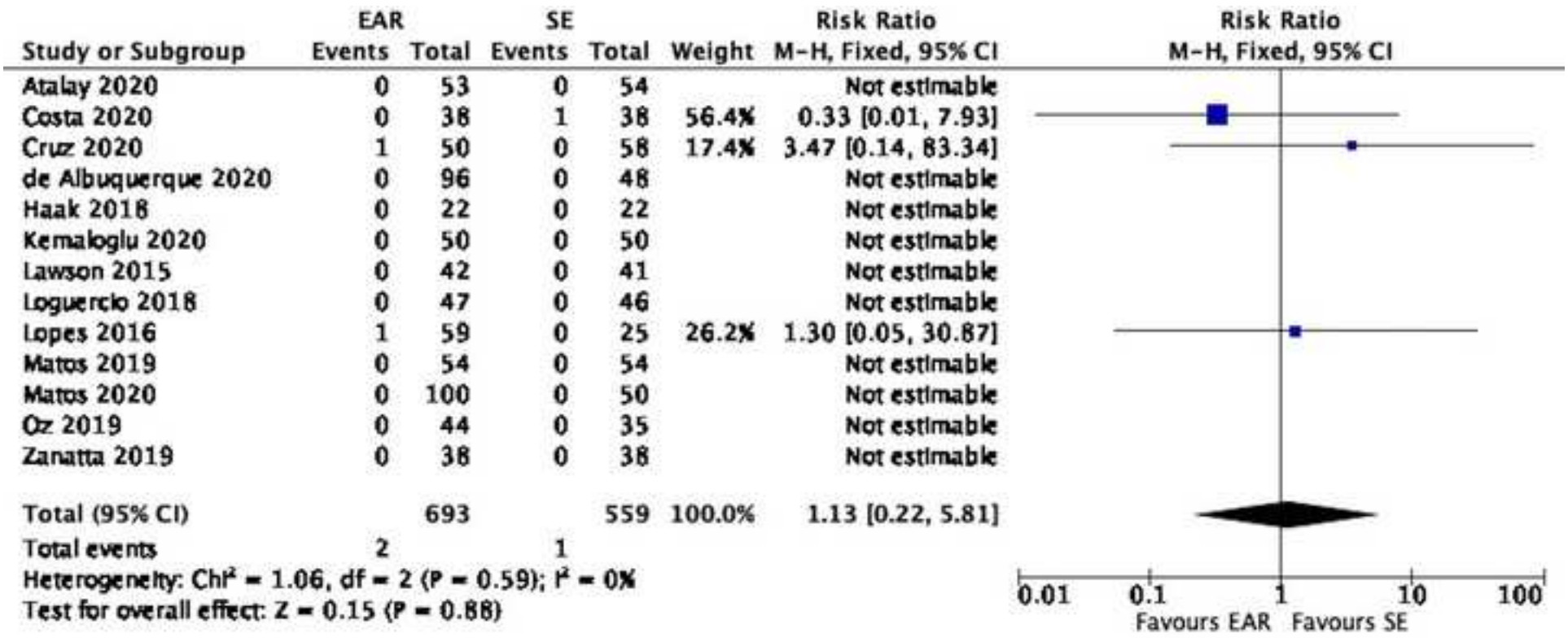

Figure 15

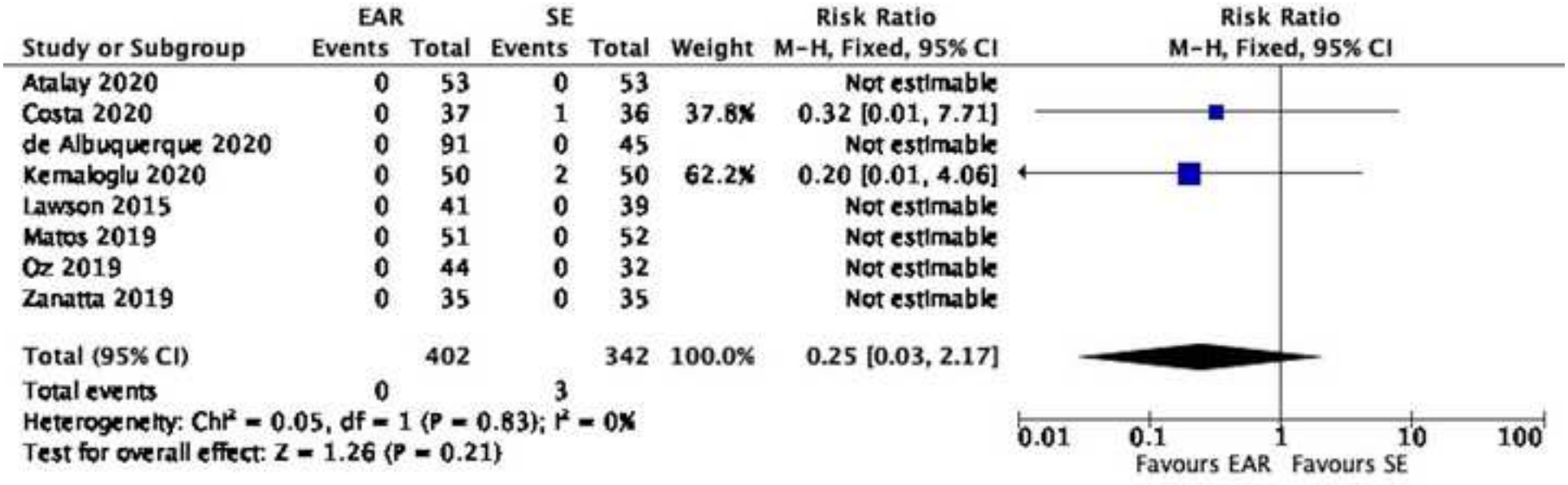

Figure 16

Click here to access/download;Figure;Figure 16.jpg

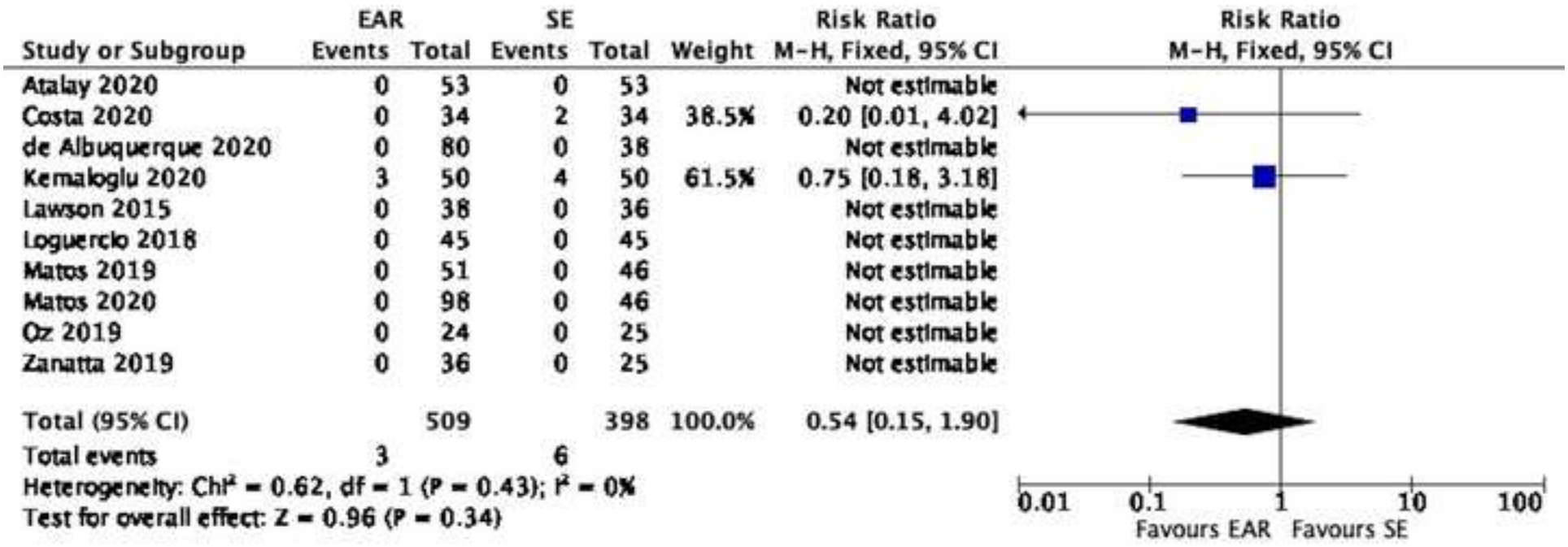

Figure 17

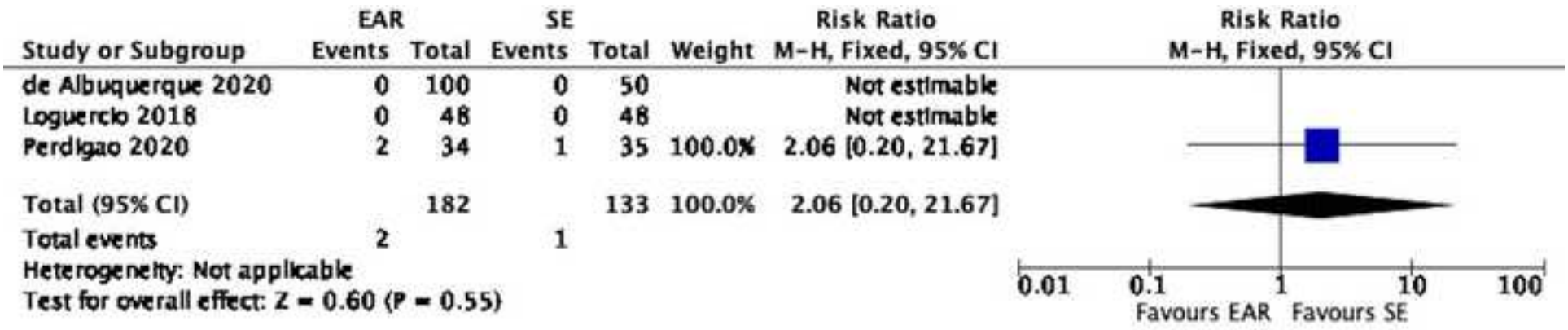

Figure 18

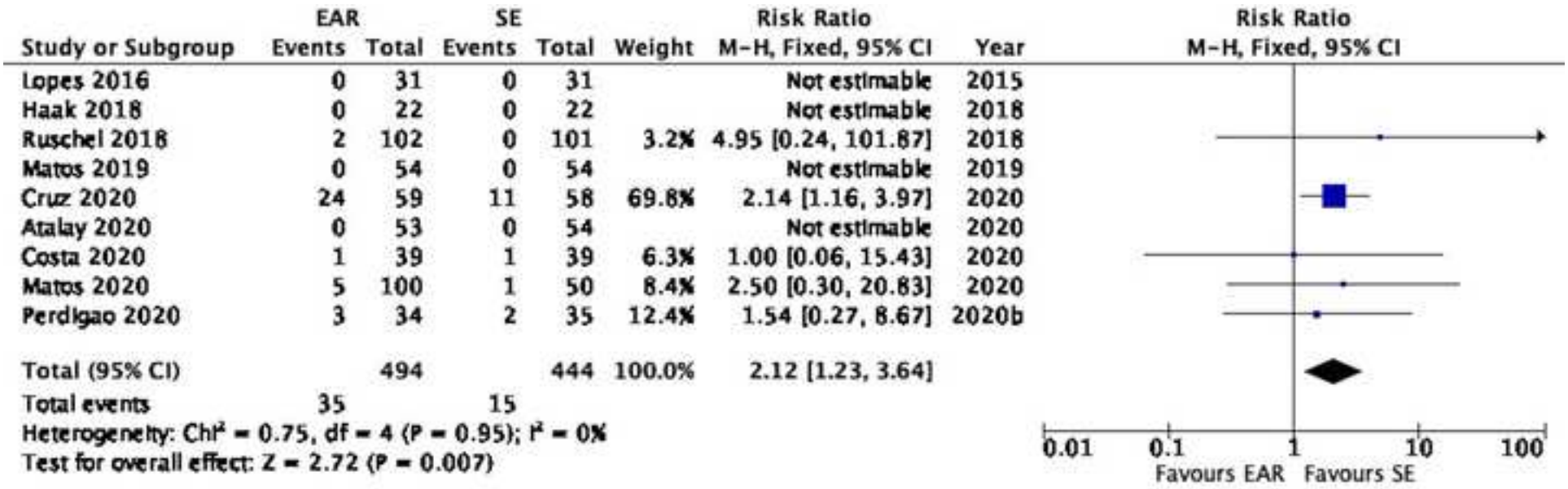

Figure 19

Click here to access/download;Figure;Figure 19.jpg

Study or Subgroup	EAR Events	EAR Total	SEE Events	SEE Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
de Carvalho 2015	3	38	2	36	33.9%	1.42 [0.25, 8.02]	2015
Lopes 2016	0	62	0	31		Not estimable	2015
Haak 2018	0	22	0	22		Not estimable	2018
Atalay 2020	0	53	0	55		Not estimable	2020
Matos 2020	5	100	3	50	66.1%	0.83 [0.21, 3.35]	2020
Total (95% CI)		275		194	100.0%	1.03 [0.35, 3.03]	
Total events	8		5				

Heterogeneity: $Chi^2 = 0.22$, $df = 1$ ($P = 0.64$); $I^2 = 0\%$

Test for overall effect: $Z = 0.06$ ($P = 0.95$)

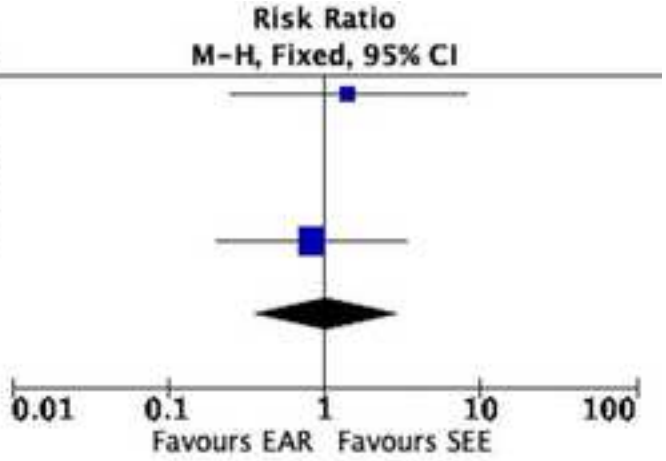

Table 1.

№ of studies	Study design	Certainty assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients: EAR	SE	Effect: Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Retention 6 months												
12	randomized trials	not serious	serious [a]	not serious	serious [b]	none	15/662 (2.3%)	15/529 (2.8%)	**RR 0.75** (0.40 to 1.40)	**7 fewer per 1,000** (from 17 fewer to 11 more)	⨁⨁◯◯ LOW	
Retention 12 months												
8	randomized trials	not serious	not serious	not serious	serious [c]	none	3/417 (0.7%)	17/361 (4.7%)	**RR 0.22** (0.08 to 0.63)	**37 fewer per 1,000** (from 43 fewer to 17 fewer)	⨁⨁⨁◯ MODERATE	
Retention 18/24 months												
10	randomized trials	not serious	not serious	not serious	serious [c]	none	14/536 (2.6%)	34/433 (7.9%)	**RR 0.32** (0.17 to 0.58)	**53 fewer per 1,000** (from 65 fewer to 33 fewer)	⨁⨁⨁◯ MODERATE	
Retention 36 months												
2	randomized trials	not serious	serious [a]	not serious	serious [d]	none	3/143 (2.1%)	5/98 (5.1%)	**RR 0.40** (0.12 to 1.34)	**31 fewer per 1,000** (from 45 fewer to 17 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Confidence intervals do not overlap; substantial heterogeneity
b. 95% CI includes appreciable benefit of harm (RR > 1.25)
c. Narrow confidence intervals, but few events.
d. 95% CI includes appreciable benefit of harm (RR>1.25); fairly small sample size;

Table 2. Certainty of evidence for the outcome Marginal adaptation (EAR vs. SE groups)

Table 2.

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EAR**	**SE**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Marginal adaptation 6 months												
13	randomized trials	not serious	not serious	not serious	serious [a]	none	2/693 (0.3%)	1/559 (0.2%)	**RR 1.13** (0.22 to 5.81)	**0 fewer per 1,000** (from 1 fewer to 9 more)	⨁⨁⨁◯ MODERATE	
Marginal adaptation 12 months												
8	randomized trials	not serious	not serious	not serious	serious [b]	none	0/402 (0.0%)	3/342 (0.9%)	**RR 0.25** (0.03 to 2.17)	**7 fewer per 1,000** (from 9 fewer to 10 more)	⨁⨁⨁◯ MODERATE	
Marginal adaptation 18/24 months												
10	randomized trials	not serious	not serious	not serious	serious [b]	none	3/509 (0.6%)	6/398 (1.5%)	**RR 0.54** (0.15 to 1.90)	**7 fewer per 1,000** (from 13 fewer to 14 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Very wide 95% CI; few events
b. 95% CI includes appreciable benefit of harm (RR> 1.25); few events

Table 3. Certainty of evidence for the outcome Marginal discoloration (EAR vs. SE groups)

Table 3.

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EAR**	**SE**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Marginal discoloration 6 months												
13	randomized trials	not serious	not serious	not serious	very serious [c]	none	1/694 (0.1%)	3/559 (0.5%)	**RR 0.39** (0.04 to 3.60)	**3 fewer per 1,000** (from 5 fewer to 14 more)	⨁⨁◯◯ LOW	
Marginal discoloration 12 months												
8	randomized trials	not serious	serious [a]	not serious	serious [b]	none	3/404 (0.7%)	6/341 (1.8%)	**RR 0.53** (0.15 to 1.92)	**8 fewer per 1,000** (from 15 fewer to 16 more)	⨁⨁◯◯ LOW	
Marginal discoloration 18/24 months												
10	randomized trials	not serious	not serious	not serious	serious [d]	none	6/513 (1.2%)	7/400 (1.8%)	**RR 0.83** (0.29 to 2.37)	**3 fewer per 1,000** (from 12 fewer to 24 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Confidence intervals do not overlap; substantial heterogeneity
b. 95% CI includes appreciable benefit of harm (RR > 1.25)
c. Very wide 95% CI; few events
d. 95% CI includes appreciable benefit of harm (RR> 1.25); few events

Table 4.

№ of studies	Study design	Certainty assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients: EAR	SE	Effect: Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Postoperative sensitivity (baseline, subjective)												
3	randomized trials	not serious	not serious	not serious	very serious [a]	none	2/182 (1.1%)	1/133 (0.8%)	**RR 2.06** (0.20 to 21.67)	**8 more per 1,000** (from 6 fewer to 155 more)	⨁⨁◯◯ LOW	
Postoperative sensitivity (objective, baseline)												
9	randomized trials	not serious	not serious	not serious	serious [b]	none	35/494 (7.1%)	15/444 (3.4%)	**RR 2.12** (1.23 to 3.64)	**38 more per 1,000** (from 8 more to 89 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Very wide 95% CI; few events
b. Few events

Table 5.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EAR**	**SEE**	**Relative (95% CI)**	**Absolute (95% CI)**		
Retention 6 months												
6	randomized trials	not serious	not serious	not serious	serious [a]	none	4/361 (1.1%)	2/267 (0.7%)	**RR 1.03** (0.23 to 4.57)	**0 fewer per 1,000** (from 6 fewer to 27 more)	⨁⨁⨁◯ MODERATE	
Retention 12 months												
4	randomized trials	not serious	not serious	not serious	serious [b]		3/234 (1.3%)	5/179 (2.8%)	**RR 0.37** (0.09 to 1.45)	**18 fewer per 1,000** (from 25 fewer to 13 more)	-	
Retention 18/24 months												
4	randomized trials	not serious	not serious	not serious	serious [c]	none	8/280 (2.9%)	6/179 (3.4%)	**RR 0.70** (0.25 to 1.95)	**10 fewer per 1,000** (from 25 fewer to 32 more)	⨁⨁⨁◯ MODERATE	
Retention 36 months												
2	randomized trials	not serious	not serious	not serious	very serious [d]	none	3/143 (2.1%)	2/100 (2.0%)	**RR 1.02** (0.17 to 6.12)	**0 fewer per 1,000** (from 17 fewer to 102 more)	⨁⨁◯◯ LOW	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. 95% CI includes appreciable benefit of harm (RR>1.25); wide 95% CI; few events
b. 95% CI is wide; few events
c. 95% CI includes appreciable benefit of harm (RR>1.25); few events

d. 95% CI is wide; small sample size; few events

Table 6.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EAR**	**SEE**	**Relative (95% CI)**	**Absolute (95% CI)**		
Postoperative sensitivity (baseline objective)												
5	randomized trials	not serious	not serious	not serious	serious [a]	none	8/275 (2.9%)	5/194 (2.6%)	**RR 1.03** (0.35 to 3.03)	**1 more per 1,000** (from 17 fewer to 52 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. 95% CI includes appreciable benefit of harm (RR>1.25); wide 95% CI; few events