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Challenging the Concept that OptiBond FL and Clearfil SE Bond in NCCLs Are Gold Standard Adhesives: A Systematic Review and Meta-analysis

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Clinical Relevance

The concept of gold standard dental materials should be re-evaluated. The evidence in the literature does not support the stating that OptiBond FL and Clearfil SE Bond are better than other materials in NCCLs.

SUMMARY

Purpose: The following PICO (Patient/Population, Intervention, Comparison, and Outcomes) question was proposed: "Are retention rates of composite resin restorations in noncarious cervical lesions (NCCLs) when using adhesives considered "gold standard" (OptiBond FL and Clearfil SE Bond) higher than those obtained with other adhesives brands"? Methods: A search was performed in February 2019 (updated in November 2019) in the PubMed/MEDLINE, EMBASE, LILACS, BBO, Web of Science, Cochrane Library, Grey Literature, and IADR abstracts (1990-2018); unpublished and

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ongoing trial registries, dissertations, and theses were also searched. Only randomized clinical trials (RCTs) conducted in NCCLs that compared either OptiBond FL or Clearfil SE Bond adhesive with other commercially available adhesives were included. The risk of bias (RoB) was applied by using the Cochrane Collaboration tool. A meta-analysis was performed for retention rates at different follow-up times using a random effects model for both the adhesives. Heterogeneity was assessed with the Cochran Q test and I^2 statistics. Grading of Recommendations: Assessment, Development and Evaluation (GRADE) assessed the quality of evidence. Results: After removal of duplicates and noneligible articles, 25 studies remained for qualitative synthesis, as one study was common to the two adhesives, of which 9 studies were used for the OptiBond FL meta-analysis and 14 for the Clearfil SE Bond meta-analysis. No significant differences were observed for retention rates in follow-up periods of 12-24 months (p=0.97), 36-48 months (p=0.72), or 108-156 months (p=0.73) for OptiBond FL; and for 12-24 months (p=0.10) and 36-48 months (p=0.17) for Clearfil SE Bond. A significant difference was only found for OptiBond FL at 60-96 months (p=0.02), but only three studies were included in this meta-analysis. Conclusions: The evidence from available RCTs conducted in NCCLs that compared OptiBond FL or Clearfil SE Bond does not support the widespread concept that these adhesives are better than any other competitive brands available in the dental market.

INTRODUCTION

Two different bonding strategies can be used in adhesive procedures: the etch-and-rinse technique (ER) and the self-etch (SE) approach. ER adhesives require the previous demineralization of the dental substrates with a 32%-40% phosphoric acid etchant, followed by a primer and a bonding resin. If the primer and the bonding resin are separate steps, the adhesive is called a three-step ER system. If the priming and bonding are combined, the adhesive is called a two-step ER system.

The SE approach does not require a separate conditioning step, as the adhesive is theoretically capable of demineralizing and infiltrating the dental substrates simultaneously.[1] In the two-step SE approach, an acidic primer is applied before the application of a bonding resin, whereas, in the 1-step SE approach, the contents of the acidic primer and bonding resin are combined in a single-application solution.

From a clinical perspective, it is important to know which type of adhesive can provide the best performance. Systematic reviews have been published attempting to categorize the efficacy of the adhesive systems based on their bonding strategy and number of steps in noncarious cervical lesions (NCCLs).[2-7] However, all material brands for each bonding strategy were grouped together, ignoring the fact that the efficacy of any adhesive depends on the material's composition, with some of them performing better than others in each bonding strategy.

Among the three-step ER systems, the adhesive named OptiBond FL (Kerr; Orange, USA), has been considered the gold standard material by many researchers[8-11] because of its good performance in immediate and long-term bond strength tests.[12] Some authors claim that the presence of glycerol phosphate dimethacrylate,[13] which can interact chemically with the hydroxyapatite and the highly filled bonding resin layer (48 wt%) over the primed dental surfaces are responsible for this good performance.

As for as the SE strategy, the adhesive Clearfil SE Bond (Kuraray, Tokyo, Japan) is the one considered to be the gold standard material.[10,14] This recognition was achieved because of the high bond strength values obtained in immediate and aged bonded interfaces.[7,15,16] The presence of the 10-MDP monomer, which produces a strong and stable chemical bond, and which is less susceptible to degradation, is held to be the main factor in the good performance of this adhesive brand.[17-19]

If these materials are the gold standard, they should be better than other adhesive brands. Therefore, the aim of this systematic review and meta-analysis was to evaluate whether evidence from randomized clinical trials (RCTs) supports the designation of these products as gold standard materials. The following focused research question was posed based on the PICO acronym (P - participant, I - intervention, C – comparator, and O - outcome): "Are the retention rates of composite resin restorations in NCCLs better when "gold standard" (OptiBond FL or Clearfil SE Bond) adhesives are used compared with other brands?"

METHODS

Protocol and Registration

This study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO acknowledgement of receipt: 158813), and followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[20,21]

Information Sources and Search Strategy

A search strategy for MEDLINE via PubMed based on the concepts of participant and intervention of the focused PICO question was elaborated. The strategy was adapted to other electronic databases (EMBASE, Cochrane Library, LILACS) and citation databases (Scopus and Web of Science) (Table 1). We did not restrict studies based on publication date and/or language.

Additionally, grey literature was investigated by searching the abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (1990-2018), the database System for Information on Grey Literature in Europe and dissertations and theses using the ProQuest Dissertations and Theses full-text database as well as the Periódicos Capes Theses database.

Ongoing studies were searched in the following clinical trial registries: Current Controlled Trials (www.controlled-trials.com), International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/), Clinical Trials Register (http://www.clinicaltrials.gov), ReBEC (www.rebec.gov.br), and European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu). Additionally, we hand searched the reference lists of all primary and eligible studies of this systematic review for additional relevant publications. The first two pages of the related articles link of each primary study in the PubMed database were also examined.

Eligibility Criteria

We included only RCTs that compared the retention rates of the two so-called gold standard adhesives OptiBond FL or Clearfil SE Bond with other adhesive brands in NCCLs. We focused only on RCT in NCCLs, because this type of lesion was the one recommended by the American Dental Association[22] for the evaluation of the clinical performance of adhesives. Studies were excluded if 1) adhesives did not follow the manufacturer's specifications, and 2) a comparative adhesive was not included.

Study Selection and Data Collection Process

The articles retrieved by the literature search were evaluated in three phases. All studies were initially scanned for relevance by title, and the abstracts of those that were not excluded at this stage were appraised. The next step included the abstract reading, and those articles not excluded had their full text retrieved for further evaluation. The full texts were then read by two reviewers to definitively check whether they met the inclusion criteria. Finally, the eligible articles received a study identification (ID) by combining first author and year of publication.

The data were extracted using a standardized form in Excel 2016 (Microsoft; Redmond, WA, USA). Two reviewers independently abstracted information about the intervention from the included articles, including study design, participants, adhesives and composite resin types, mode of isolation of the operative field, cavity preparation (enamel beveling and dentin roughening), and number of examiners/operators and evaluation criteria. In case of disagreement, a decision was reached by consulting a third reviewer. Another worksheet containing the study identification and the outcomes per adhesive group at different follow-up periods was also prepared. If there were multiple reports of the same study (ie, reports with different follow-up times), data from all reports were extracted directly into a single data-collection form to avoid overlapping data.

Risk of Bias (RoB) in Individual Studies

The RoB of the eligible studies was evaluated by two independent reviewers by using the Cochrane Collaboration tool for assessing the RoB in RCTs (RoB version 1.0).[23] Disagreements were resolved by discussion.

We evaluated whether the randomization sequence and allocation concealment were adequate. Additionally, we evaluated whether blinding was implemented for participants, personnel, and outcomes assessment. Evidence of incomplete outcome data and selective reporting of outcomes was also checked. At the study level, they were judged to be at low RoB, if all domains were judged to be at low RoB.

Summary Measures and Synthesis of the Results

The main outcome evaluated was retention rate, and the meta-analysis was performed using the Meta package of the software R Analyses were carried out by using the random-effect model, and pooled-effect estimates were obtained by comparing the retention ratios of OptiBond FL and Clearfil SE Bond with those from other commercial brands of adhesives. We estimated the overall risk ratio (RR) for this binary outcome, presenting their 95% confidence intervals (CI) at different follow-up periods for each adhesive. Data from OptiBond FL and Clearfil SE Bond were summarized into the following follow-ups: 12-24 months and 36-48 months. For OptiBond FL, additional follow-ups (60-96 months and 108-156 months) were included, as these data were available. In case a study reported data twice within the range described above, data from the longest follow-up period were used.

Table 1: *Database Search Strategy*

Database, Number of Papers: (5035)	**Search (November 20, 2019)**
PubMed (1588)	dental restoration, permanent[MeSH Terms] OR dentition, permanent[MeSH Terms] OR tooth erosion[MeSH Terms] OR tooth erosion*[Title/Abstract] OR tooth abrasion[MeSH Terms] OR tooth abrasion*[Title/Abstract] OR dental abrasion*[Title/Abstract] OR tooth cervix[MeSH Terms] OR tooth cervix[Title/Abstract] OR abfraction*[Title/Abstract] OR cervical lesion*[Title/Abstract] OR NCCL*[Title/Abstract] OR class V[Title/Abstract] OR class 5[Title/Abstract] AND dentin-bonding agents[Mesh Term] OR adhesive system*[Title/Abstract] OR bonding agent*[Title/Abstract] OR dental adhesive*[Title/Abstract] OR adhesive material*[Title/Abstract] OR "etch-and-rinse adhesive"[Title/Abstract] OR "etch-and-rinse adhesives"[Title/Abstract] OR "total-etch adhesive"[Title/Abstract] OR "total-etch adhesives"[Title/Abstract] OR "self-etch adhesive"[Title/Abstract] OR "self-etching adhesive"[Title/Abstract] OR "self-etch adhesives"[Title/Abstract] OR "self-etching adhesives"[Title/Abstract] OR "all-in-one adhesive"[Title/Abstract] OR "all-in-one adhesives"[Title/Abstract] OR "one-bottle adhesive"[Title/Abstract] OR "one-bottle adhesives"[Title/Abstract] OR "single-bottle adhesive"[Title/Abstract] OR "single-bottle adhesives"[Title/Abstract] OR universal adhesive*[Title/Abstract] OR "multi-mode adhesive"[Title/Abstract] AND randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR singl*[tw] OR doubl*[tw] OR trebl*[tw] AND mask*[tw] OR blind*[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[pt] OR evaluation studies as topic
Scopus (1626)	"t??th erosion" OR "t??th abrasion" OR "dental abrasion" OR "t??th cervix" OR "abfraction*" OR "cervical lesion*" OR "NCCL*" OR "class V" OR "class 5" AND "dentin bonding agent" OR "adhesive system" OR "bonding agent" OR "dental adhesive" OR "adhesive material" OR "etch-and-rinse adhesive" OR "self-etch adhesive" OR "self-etching adhesive" OR "all-in-one adhesive" OR "one-bottle adhesive" OR "single-bottle adhesive" OR "universal adhesive" OR "multi-mode adhesive"
Cochrane Library (543)	#1 MeSH descriptor: [Dental Restoration, Permanent] explode all trees 1288 #2 MeSH descriptor: [Dentition, Permanent] explode all trees 65 #3 MeSH descriptor: [Tooth Erosion] explode all trees 222 #4 (tooth next erosion):ti,ab,kw (Word variations have been searched) 233 #5 MeSH descriptor: [Tooth Abrasion] explode all trees 124 #6 tooth next abrasion (Word variations have been searched) 132 #7 dental next abrasion (Word variations have been searched) 1 #8 MeSH descriptor: [Tooth Cervix] explode all trees 292 #9 tooth next cervix (Word variations have been searched) 306 #10 abfraction (Word variations have been searched) 18 #11 cervical next lesion (Word variations have been searched) 394 #12 NCCL? (Word variations have been searched) 84 #13 class next V (Word variations have been searched) 344 #14 class next 5 (Word variations have been searched) 47 #15 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 1995 #16 MeSH descriptor: [Dentin-Bonding Agents] explode all trees 937 #17 adhesive next system (Word variations have been searched) 505 #18 bonding next agent (Word variations have been searched) 1061 #19 dental next adhesive (Word variations have been searched) 297

Table 1: *Database Search Strategy (cont.)*	
Cochrane Library (543)	#20 adhesive next material (Word variations have been searched) 160 #21 "etch-and-rinse adhesive" (Word variations have been searched) 117 #22 "total-etch adhesive" (Word variations have been searched) 53 #23 "self-etch adhesive" (Word variations have been searched) 356 #24 "all-in-one adhesive" (Word variations have been searched) 25 #25 "one-bottle adhesive" (Word variations have been searched) 36 #26 "single-bottle adhesive" (Word variations have been searched) 13 #27 "universal next adhesive" (Word variations have been searched) 38 #28 "multi-mode adhesive" (Word variations have been searched) 3 #29 #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 1314 #30 #15 AND #29 Total: 545 (-2 reviews) = 543
Web of Science (688)	TS= ("t*th erosion" OR "t*th abrasion" OR "dental abrasion*" OR "tooth cervix" OR "abfraction*" OR "cervical lesion*" OR "NCCL" OR "class V" OR "class 5") AND TS= ("dentin bonding agent*") OR TS= ("adhesive system*") OR TS= ("bonding agent*") OR TS= ("dental adhesive*") OR TS= ("adhesive material*") OR TS= ("etch-and-rinse adhesive") OR TS= ("etch-and-rinse adhesives") OR TS= ("total-etch adhesive") OR TS= ("total-etch adhesives") OR TS= ("self-etch adhesive") OR TS= ("self-etch adhesives") OR TS= ("self-etching adhesive") OR TS= ("self-etching adhesives") OR TS= ("all-in-one adhesive") OR TS= ("all-in-one adhesives") OR TS= ("one-bottle adhesive") OR TS= ("one-bottle adhesives") OR TS= ("single-bottle adhesive") OR TS= ("single-bottle adhesives") OR TS= ("universal adhsesive") OR TS= ("universal adhesives") OR TS= ("multi-mode adhesive")
LILACS (553)	mh:"dental restoration, permanent" OR "restauração dentária permanente" OR "restauración dental permanente" OR mh:"dentition, permanent" OR tw:"dentição permanente" OR "dentición permanente" OR mh:"tooth erosion" OR tw:"erosão dentária" OR tw:"erosión de los dientes" OR mh:"tooth abrasion" OR tw:"abrasão dentária" OR tw:"abrasión de los dientes" OR mh:"tooth cervix" OR tw:"colo do dente" OR tw:"cuello del diente" OR tw:abfrac* OR tw:"cervical lesions" OR tw:"lesões cervicais" OR tw:"lesiones cervicales" OR tw:nccls OR tw:lcncs OR tw:"class V" OR tw:"class 5" OR tw:"classe V" OR tw:"classe 5" AND mh:"dentin bonding agents" OR tw:"adesivos dentinários" OR tw:"recubrimientos dentinarios" OR tw:"adhesive systems" OR tw:"sistemas adesivos" OR tw:"sistemas adhesivos" OR tw:"bonding agents" OR tw:"agentes de união" OR tw:"agentes de unión" OR tw:"dental adhesives" OR tw:"adesivos dentais" OR tw:"adhesivos dentales" OR tw:"adhesives materials" OR tw:"materiais adesivos" OR tw:"materiales adhesivos" OR tw:"etch and rinse adhesives" OR tw:"adesivos convencionais" OR tw:"adhesivos convencionales" OR tw:"total etch adhesives" OR tw:"condicionamento ácido total" OR tw:"adhesivos de grabado total" OR tw:"self etch adhesives" OR tw:"adesivos autocondicionantes" OR tw:"adhesivos autocondicionantes" OR tw:"self etching adhesives" OR tw:"all in one adhesives" OR tw:"adesivos de passo único" OR tw:"one bottle adhesives" OR tw:"adesivos de frasco único" OR tw:"single bottle adhesives" OR tw:"universal adhesives" OR tw:"adesivos universais" OR tw:"multi mode adhesives"
Embase (37)	"tooth erosion" OR "tooth abrasion" OR "dental abrasion" OR "tooth cervix" OR abfraction OR "cervical lesion" OR NCCL OR "class V" OR "class 5" AND "dentin bonding agent" OR "adhesive system" OR "bonding agent" OR "dental adhesive" OR "adhesive material" OR "etch-and-rinse adhesive" OR "self-etch adhesive" OR "self-etching adhesive" OR "all-in-one adhesive" OR "one-bottle adhesive" OR "single-bottle adhesive" OR "universal adhesive" OR "multi-mode adhesive"

Data were extracted using intention-to-treat analysis by using the total number of failures for each treatment arm in each follow-up as the nominator and the total number of participants randomized at baseline as the denominator, wherever trial reporting allowed. When trials had more than one adhesive brand being compared with the gold standards, they were included in the meta-analysis separately to provide more than one effect size; however, as in these situations, data from the control group were used more than once, the number of events and the total number of participants were divided among the comparisons to avoid a misleading overpowering of the estimates.[24]

Trials have used several outcome measures; in those applying Vanherle, US Public Health Service or FDI World Dental Federation criteria, we dichotomized Alfa vs. Bravo/Charlie, and these last two were counted as failures.

Only studies classified at low or unclear RoB were meta-analyzed. Heterogeneity was evaluated using the Cochran Q test and I^2 statistics. The 95% prediction interval was calculated in all meta-analyses with at least five studies. Sensitivity analyses were also conducted to investigate the reasons for high heterogeneity whenever detected.

Assessment of the Quality of Evidence Using GRADE

The quality of the evidence was graded for each outcome across studies (body of evidence) using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/). This technique allowed determination of the overall strength of evidence for each meta-analysis.[25] The GRADE grades the evidence into four levels: very low, low, moderate, and high. The "high-quality" level suggests high confidence that the true effect lies close to the estimate of the effect. At the other extreme, "very-low-quality" level suggests very low confidence in the effect estimate, and the estimate reported can be substantially different from what was measured.

For RCTs, the GRADE approach addresses five reasons (RoB, imprecision, inconsistency, indirectness of evidence, and publication bias) for possibly rating down the quality of the evidence by one or two levels. Each of these aspects was assessed as having "no limitation" (0); "serious limitations" (1 level downgraded), and "very-serious limitations" (2 levels downgraded). The GRADEpro Guideline Development Tool, available online (www.gradepro.org), was used to create a summary-of-findings table as suggested in the Cochrane Handbook for Systematic Reviews of Interventions.

RESULTS

Study Selection

The search strategy was conducted initially on February 9, 2019 and was updated on November 20, 2019. A total of 5058 publications were retrieved in all databases. After database screening and duplicate removal, 689 studies were identified, 155 of which were retrieved for further assessment, because they appeared to be relevant. A flowchart outlining the study selection process according to the PRISMA Statement[26] can be seen in Figure 1. Of these, 122 were not included for various reasons (Supplementary Table 1), leaving 33 eligible RCTs. From these 33 articles, 8 studies[9,27-33] reported the same study sample at different follow-ups and, therefore, received the same study ID. Therefore, 25 studies were eligible for inclusion, with one study being common for both adhesives.[34]

Characteristics of the Included Studies

The characteristics of the 25 eligible studies are listed in Table 2. Most studies performed multiple restorations per participant, and only one did not report this information.[35] OptiBond FL was compared with eight different commercial brands of adhesives in the eligible studies as follows:

- Clearfil S3 Bond (Kuraray)[36]
- Clearfil SE Bond (Kuraray)[34]
- G-Bond (GC; Tokyo, Japan)[37,38]
- OptiBond All-in-One (Kerr)[39,40]
- OptiBond Solo Plus (Kerr)[39,40]
- OptiBond XTR (Kerr)[39,41]
- PermaQuick (Ultradent; UT, USA)[42]
- Scotchbond Universal (3M Oral Care; MN, USA)[43]

The adhesive Clearfil SE Bond was compared with 14 different commercial brands as described below:

- AdheSE (Ivoclar Vivadent; Schaan, Liechtenstein)[44]
- Admira Bond (Voco; Cuxhaven, Germany)[45]
- Adper Prompt (3M Oral Care)[46]
- Clearfil S3 Bond (Kuraray)[47]
- G-Bond (GC)[48]
- Hybrid Bond (Sun Medical; Shiga, Japan)[45]
- OptiBond FL (Kerr)[34]
- PQ1 (Ultradent)[49]
- Prime & Bond NT (Dentsply Sirona; Konstanz, Germany)[50]
- Scotchbond Universal (3M Oral Care)[51]
- Single Bond (3M Oral Care)[51-53]
- Xeno III (Dentsply Sirona)[53]

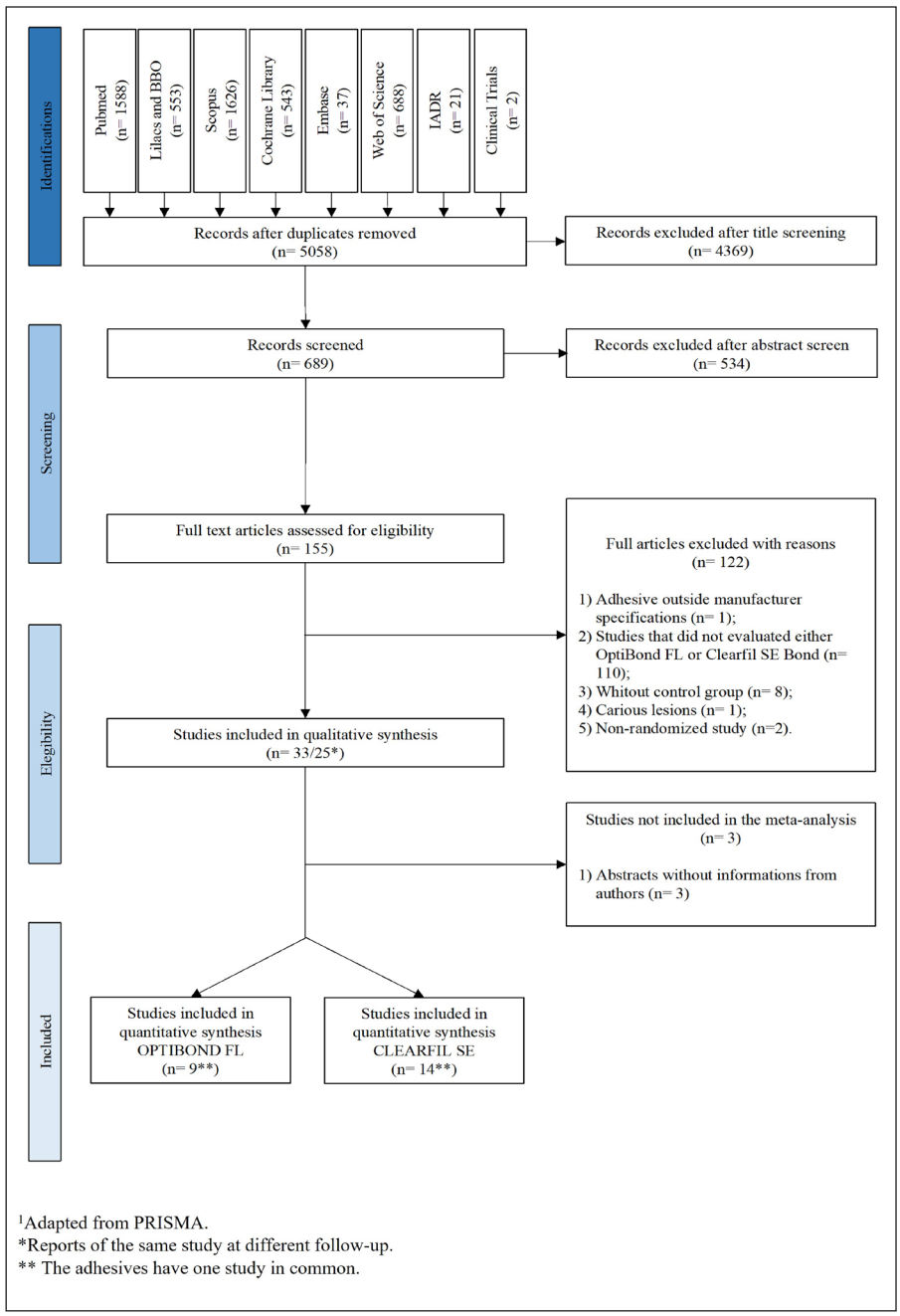

Figure 1. *Flow diagram of study identification (*Reports of the same study at different follow-up; ** The adhesives have one study in common.)*

- Xeno V (Dentsply Sirona)[54,55]
- XP-Bond (Dentsply Sirona)[56]

Most of the composite resins used were microhybrids, nanohybrids, or nanofilled composite resins. The following commercial brands were used: Premise (Kerr),[57] Estelite Sigma Quick (Tokuyama; Tokyo, Japan),[57] CeramX-Duo (Dentsply Sirona),[58] Filtek Z-250 (3M Oral Care),[35,44,54] Filtek Supreme Ultra (3M Oral Care),[39] Clearfil AP-X (Kuraray),[36,45-48,50] Filtek Supreme XTE (3M Oral Care),[43] Herculite XRV (Kerr),[40] Grandio (Voco),[34] Herculite Ultra (Kerr),[41] Venus Diamond (Kulzer; Hanau, Germany),[37] Gradia Direct (GC),[38] Amelogen Hybrid (Ultradent),[42] Amelogen Microfill (Ultradent),[42] Prodigy (Kerr),[42] Filtek A-110 (3M Oral Care),[52] Clearfil ST (Kuraray),[52] Filtek Supreme (3M Oral Care),[51,53] Esthet-X (Dentsply Sirona),[55] Filtek Z-350 (3M Oral Care),[46] TPH Espectrum (Dentsply/De Trey),[50] Tetric Ceram (Ivoclar Vivadent),[49] Point 4 (Kerr),[49] and Ceram X Mono (Dentsply Sirona).[56]

Table 2: *Summary of the Descriptive Characteristics of the Primary Studies Included for Each Adhesive System (n=26/25[a])*

Study ID	**Study Design [setting]**	**Follow-ups (mth)**	**Subject's Age Mean ± SD [range] (yrs)**
OPTIBOND FL			
Armstrong 2012[57]	Paired [university]	6, 12	n.r. ± n.r. [n.r.]
Blunck 2013[58]	Paired [n.r.]	12, 24	n.r. ± n.r. [n.r.]
Dall'orologio 2006,[35] 2008,[27] 2009,[29] 2010[28]	n.r. [n.r.]	Baseline, 6, 12, 18, 24, 36, 60, 78, 84	n.r. ± n.r. [n.r.]
de Paula 2015[39]	Multiple restorations [university]	Baseline, 6, 12	n.r. ± n.r. [20->49]
Ermis 2012[36]	Multiple restorations [university]	Baseline, 6, 12, 24	50 ± 8.3 [39-79]
Haak 2019[43]	Paired [university]	Baseline, 6, 12	65 ± 20.5 [43-84]
Moosavi 2013[40]	Paired [university]	Baseline, 6, 12, 18	n.r. ± n.r. [20-50]
Mortazavi 2012[34a]	Paired [university]	Baseline, 6, 9, 12	n.r. ± n.r. [30-60]
Ritter 2015[41]	Multiple restorations [university]	Baseline, 6, 18	n.r. ± n.r. [n.r.]
Scotti 2016[37]	Multiple restorations [university]	12, 24, 36	52.4 ± n.r. [32-63]
Van Landuyt 2008,[38] 2011,[9] 2014,[30] Peumans 2018[31]	Multiple restorations [university]	Baseline, 6, 12, 24, 36, 60, 108	n.r. ± n.r. [20->80]
Van Meerbeek 2004,[42] Peumans 2007,[32] 2012[33]	Paired [university]	6, 12, 24, 36, 60, 84, 156	n.r. ± n.r. [<18->70]

Abbreviations: #, number; FDI, World Dental Federation; ID, identification; mth, month; n.r., not reported; SD, standard deviation; USPHS, United State Public Health Service.

[a] *One study common to the two adhesives.*

[b] *Depending on access and location of the lesion.*

Table 2: *Summary of the Descriptive Characteristics of the Primary Studies Included for Each Adhesive System (n=26/25[a]) (cont.)*

Groups: Type of Adhesive -Adhesive Brand [Number of Restorations per Group]	Resin Composite per Group	Rubber Dam	Enamel Bevel/ Dentin Prep	# of Operators/ Examinators	Evaluation Criteria
3ER- Optibond FL [30] 1SE- Tokuyama Bond Force [30]	Premise Estelite Sigma Quick	No/Yes[b]	n.r./n.r.	n.r./n/r	USPHS
1SE- iBond [58] 1SE- G-Bond [58] 1SE- Clearfil S3 Bond [58] 3ER- Optibond FL [58]	CeramX-Duo[j]	n.r.	No/No	2/n.r.	USPHS
1SE- iBond [n.r.] 1SE- AQ Bond [n.r.] 3ER- Optibond FL [n.r.]	Filtek Z-250	n.r.	n.r./n.r.	3/1	Modified USPHS
3ER- Optibond FL [46] 2ER- Optibond Solo Plus [44] 2SE- Optibond XTR [44] 1SE- Optibond All-in-One [46]	Filtek Supreme Ultra	Yes	No/No	04/02	FDI/ Modified USPHS
1SE- Clearfil S3 Bond [81] 3ER- Optibond FL [80]	Clearfil AP-X	No	Yes/Yes	01/02	Vanherle
1SE- Scotchbond Universal [110] 3ER- Optibond FL [55]	Filtek Supreme XTE	No	Yes/Yes	01/01	FDI
3ER- Optibond FL [30] 2ER- Optibond Solo Plus [30] 1SE- Optibond All-in-One [30]	Herculite XRV	No	No/No	01/02	USPHS
2SE- Clearfil SE Bond [12] 3ER- Optibond FL [12]	Grandio	Yes	Yes/No	n.r./02	USPHS
2SE- Optibond XTR [41] 3ER- Optibond FL [42]	Herculite Ultra	Yes/No[b]	No/Yes	4/2	Modified USPHS
1SE- G-Bond [46] 3ER- Optibond FL [44]	Venus Diamond	Yes	Yes/Yes	02/02	Modified USPHS
1SE- G-Bond [133] 3ER- Optibond FL [134]	Gradia Direct	No	Yes/Yes	02/02	Vanherle
3ER- PermaQuick [100] 3ER- Optibond FL [50]	Amelogen Hybrid Amelogen Microfill Prodigy	Yes	Yes/No	02/02	Vanherle

Table 2: *Summary of the Descriptive Characteristics of the Primary Studies Included for Each Adhesive System (n=26/25[a]) (cont.)*

Study ID	**Study Design [setting]**	**Follow-ups (mth)**	**Subject's Age Mean ± SD [range] (yrs)**
CLEARFIL SE BOND			
Abdalla & Garcia-Godoy 2006[45]	Paired [n.r.]	12, 24	n.r. ± n.r. [35-52]
Araújo 2015[44]	Multiple restorations [university]	Baseline, 24	45 ± 8 [n.r.]
Brackett 2010[47]	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [31-58]
Burrow & Tyas 2007[52]	Multiple restorations [university]	6, 12, 24, 36	61 ± n.r. [n.r.]
Dalkilic e Omurlu 2012[53]	Multiple restorations [university]	Baseline, 3, 12, 24	n.r. ± n.r. [30-70]
Jang 2017[54]	Multiple restorations [university]	Baseline, 6, 12, 18, 24	55 ± n.r. [30-73]
Mortazavi 2012[34b]	Paired [university]	Baseline, 6, 9, 12	n.r. ± n.r. [30-60]
Pena 2016[55]	Paired [university]	Baseline, 3, 6, 12, 18, 24	n.r. ± n.r. [n.r.]
Qin 2013[46]	Multiple restorations [university]	Baseline, 6, 12, 24	44.1 ± n.r. [27-66]
Türkün 2003[50]	Paired [university]	Baseline, 6, 12, 24	46 ± n.r. [26-60]
van Dijken 2010[49]	Multiple restorations [university]	Baseline, 6, 12, 18, 24, 36, 48, 60, 72, 84, 96	60.1 ± n.r. [42-84]
Yaman 2014[56]	Paired [university]	Baseline, 6, 12, 24, 36	45.12 ± n.r. [32-58]
Zanatta 2019[51]	Paired [university]	Baseline, 6, 12, 24	n.r. ± n.r. [<20->60]
Zhou 2009[48]	Multiple restorations [university]	Baseline, 3, 6, 12	n.r. ± n.r. [n.r.]

Table 2: *Summary of the Descriptive Characteristics of the Primary Studies Included for Each Adhesive System (n=26/25[a]) (cont.)*

Groups: Type of Adhesive -Adhesive Brand [Number of Restorations per Group]	Resin Composite per Group	Rubber Dam	Enamel Bevel/ Dentin Prep	# of Operators/ Examinators	Evaluation Criteria
2ER- Admira Bond [65] 2SE- Clearfil SE Bond [65] 1SE- Hybrid Bond [65]	Clearfil AP-X	Yes	No/Yes	01/02	USPHS
2SE- Clearfil SE Bond [32] 2SE- AdheSE [32]	Filtek Z-250	No	No/No	01/02	Modified USPHS
2SE- Clearfil SE Bond [40] 1SE- Clearfil S3 Bond [40]	Clearfil AP-X	No	No/No	02/02	Modified Ryge/ USPHS
2ER- Single Bond [30] 2SE- Clearfil SE Bond [30]	Filtek A-110 Clearfil ST	n.r.	No/No	02/01	n.r.
2ER- Single Bond [60] 2SE- Clearfil SE Bond [71] 1SE- Xeno III [60]	Filtek Supreme	No	No/Yes	01/01	Modified USPHS
2SE- Clearfil SE Bond [83] 1SE- Xeno V [81]	Filtek Z-250	No	No/No	n.r./02	Modified FDI
2SE- Clearfil SE Bond [12] 3ER- Optibond FL [12]	Grandio	Yes	Yes/No	n.r./02	USPHS
2SE- Clearfil SE Bond [56] 1SE- Xeno V [56]	Esthet-X	No	Yes/No	01/02	Modified USPHS
2SE- Clearfil SE Bond [58] 1SE- Adper Prompt [56]	Clearfil AP-X Filtek Z-350	No	Yes/Yes	02/02	Modified USPHS
2SE- Clearfil SE Bond [49] 2ER- Prime & Bond NT [49]	Clearfil AP-X TPH Spectrum	No	No/Yes	01/02	USPHS
2SE- Clearfil SE Bond [55] 2ER- PQ1 [64]	Tetric Ceram Point 4	No	No/Yes	01/03	Modified USPHS
2SE- Clearfil SE Bond [48] 2ER- XP Bond [48]	Ceram X mono	No	Yes/Yes	02/02	Modified USPHS
2ER- Scotchbond Universal [38] 1SE- Scotchbond Universal [38] 2ER- Single Bond [38] 2SE- Clearfil SE Bond [38]	Filtek Supreme	No	No/No	04/02	FDI
1SE- Clearfil 3S Bond [124] 2SE- Clearfil SE Bond [124] 1SE- G-Bond [94]	Clearfil AP-X	Yes	Yes/Yes	n.r./02	Modified USPHS

The majority of the studies reported that no rubber dam had been applied,[a] six studies reported the use of rubber dam,[34,37,39,42,45,48] another three did not report this information,[35,52,58] and two studies stated that rubber dam was used depending on the location and access to the lesion.[41,57]

Ten studies[b] prepared a small enamel bevel at the incisal/occlusal margin of the lesion, 11 studies[c] superficially roughened the exposed dentin with a coarse diamond rotatory instrument, 8 studies[d] did not prepare either the enamel or dentin, and 2 studies[35,57] did not report this information.

Risk of Bias in the Included Studies

The quality assessment of the RoB of included studies both for OptiBond FL and Clearfil SE Bond is presented in Figures 2 and 3. From the 12 eligible studies that evaluated OptiBond FL, only 1[39] was considered at low RoB, while the other 11 were considered at unclear RoB. From the 14 studies that evaluated the Clearfil SE Bond studies, 2 studies[44,51] were considered low RoB, and the remaining were at unclear risk.

Meta-analyses

OptiBond FL

Nine studies were included in the meta-analysis, as three studies were excluded because of lack of data (they were abstracts).[35,57,58] One study provided three effect sizes, as OptiBond was compared with three different adhesives,[39] and another provided two effect sizes.[40] The results are presented in Figure 4. No significant differences in the retention rates between groups (OptiBond FL vs other adhesive brands) were observed at the follow-ups of 12-24 months, 36-48 months, and 108-156 months (p>0.72). The risk ratio (RR) and the 95% confidence interval at 12-24 months was 0.99 (0.56-1.75; p=0.97), the RR and the 95% confidence interval at 36-48 months was 1.12 (0.61-2.03; p=0.72), and the RR and the 95% confidence interval at 108-156 months was 0.94 (0.67-1.32; p=0.73), respectively. A significant difference was found between the groups at 60-96 months, with an average RR of 1.65 (1.07-2.53; p=0.02) in favor of the OptiBond FL. Heterogeneity was not observed in any of the follow-up periods (I^2=0; p>0.50).

Clearfil SE Bond

All the 14 studies were included in the meta-analysis, and the results are presented in Figure 5. Four studies provided two effect sizes.[45,48,51,53] No significant differences in the retention rates between groups (Clearfil SE Bond vs other adhesives) were observed in any of the different follow-up periods (p>0.10). The RR and the 95% confidence interval at 12-24 months was 1.21 (0.97-1.53; p=0.10) and the RR and the 95% confidence interval at 36-48 months was 1.49 (0.84-2.67; p=0.17), respectively. Heterogeneity was observed at the follow-up periods to 36-48 months (p=0.09; I^2=59%).

Assessment of the Quality of Evidence (GRADE)

The quality of evidence assessed for both the OptiBond FL and Clearfil SE Bond in all study follow-ups was considered to be low due to limitations in the RoB of the eligible studies (most were at unclear risk) and due to imprecision (Table 3). Although the short-term meta-analysis included more than 10 comparisons, the number of events in the short-term follow-ups was quite low, leading to imprecision. In the medium- to long-term follow-ups, imprecision was mainly attributed to the low number of studies and the consequent wide confidence interval around the point estimate.

DISCUSSION

Well-done systematic reviews, with or without meta-analysis, are generally considered to provide the best evidence for the type of study design summarized, as they are based on the findings of multiple studies identified in comprehensive and systematic literature searches. As stated in the introduction section, pairwise meta-analysis involving adhesive systems in NCCLs commonly compare adhesive strategies[4,5,7,59] rather than specific material brands. In these reviews, the so-called 'gold standard' adhesives were grouped with other adhesive brands within their classification group, and, therefore, their individual performance cannot be assessed. That is, variables such as solvents, initiator systems, functional monomers, structural monomers, hydrophilic monomers, number of steps, and mode of application of each adhesive present in the primary studies were not evaluated in the present review. Any attempt to associate one of these factors with the findings of this article could lead to spurious results of an observational nature and be subject to several confounding factors.

Other issues such as enamel beveling and dentin roughening could not be investigated in the present systematic reviews; however, an earlier systematic review showed that we do not have evidence to state that enamel beveling has any role on restoration retention in NCCL.[60] Similarly, a RCT comparing dentin roughening with not dentin roughening ended up with the conclusion that this procedure does not affect the retention rates of composite resins in NCCLs.[61]

[a] *36,38,40, 43,44,46,47,49-51,53-56*
[b] *34,36-38,42,43,46,48,55,56*
[c] *36-38,41,43,45,46,48-50,53*
[d] *39,40,44,47,51,52,54,58*

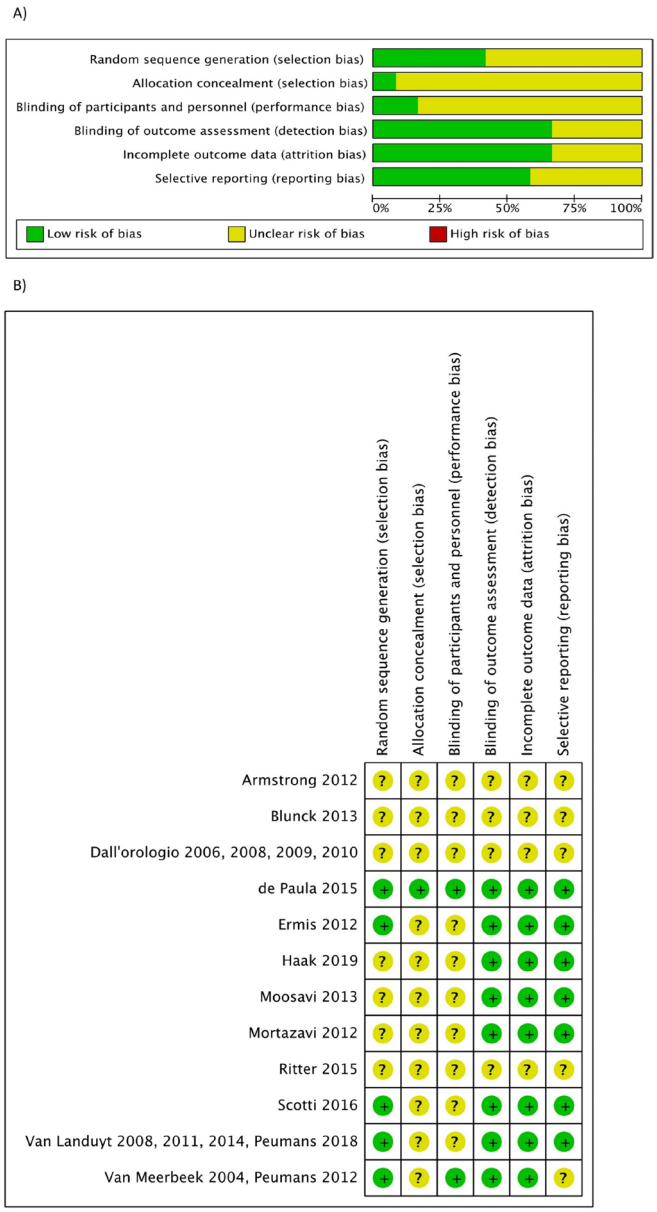

Figure 2. (A): Risk of bias graph for OptiBond FL according to the Cochrane Collaboration Tool. (B): Risk of bias summary for OptiBond FL.

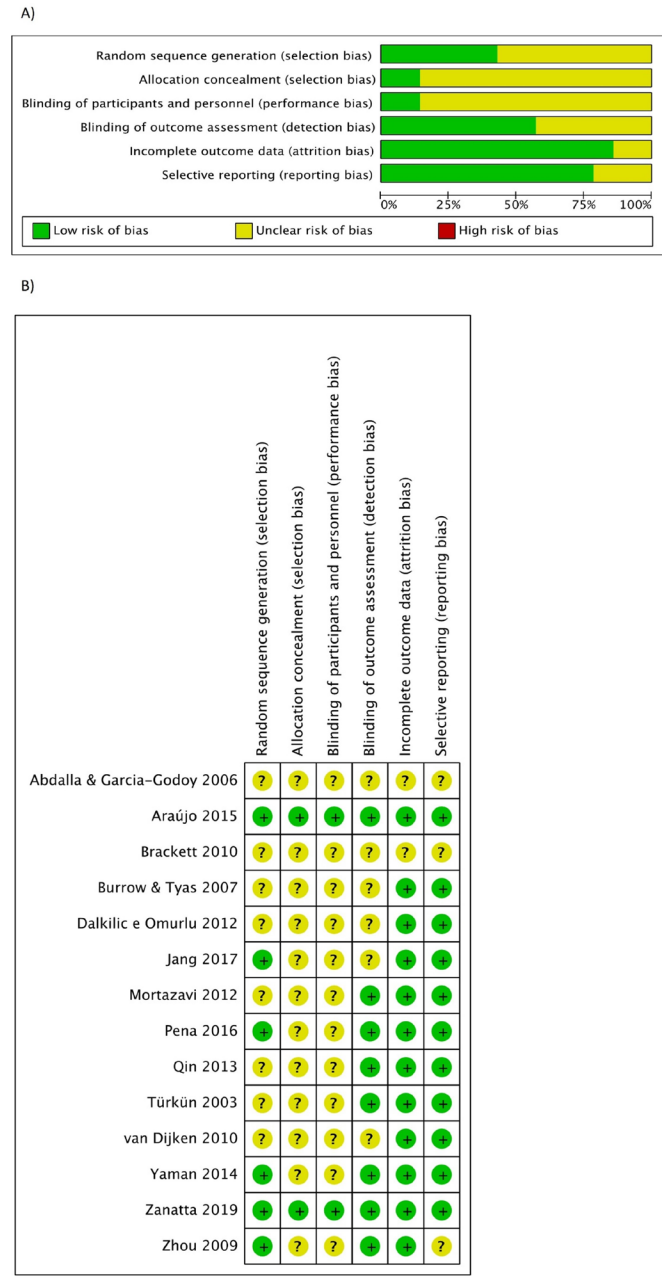

Figure 3. *(A): Risk of bias graph for Clearfil SE Bond according to the Cochrane Collaboration Tool. (B): Risk of bias summary for Clearfil SE Bond.*

The authors are unaware of a previous systematic review that compared retention rates of specific brands of adhesive systems with other competitive adhesive materials. Studies ranging from 2003 to 2019 were found and the results contained in them challenge the widespread concept that the three-step ER OptiBond FL, and the two-step SE Clearfil SE are "gold standard" materials. Their overall retention rates were not better than the overall retention rates of other competitive adhesive brands with which they were compared, except at 60-96 months for OptiBond FL. In this follow-up, only two studies were included, therefore providing an imprecise estimate.

Although this concept has been used for more than 20 years in the literature, it became a stronger evidence for the publication of a meta-analytical review of parameters on bond strength values.[10] In their review of laboratory studies,[10] the authors concluded that the best-performing adhesive both in short- and long-term studies was the three-step ER OptiBond FL, while the

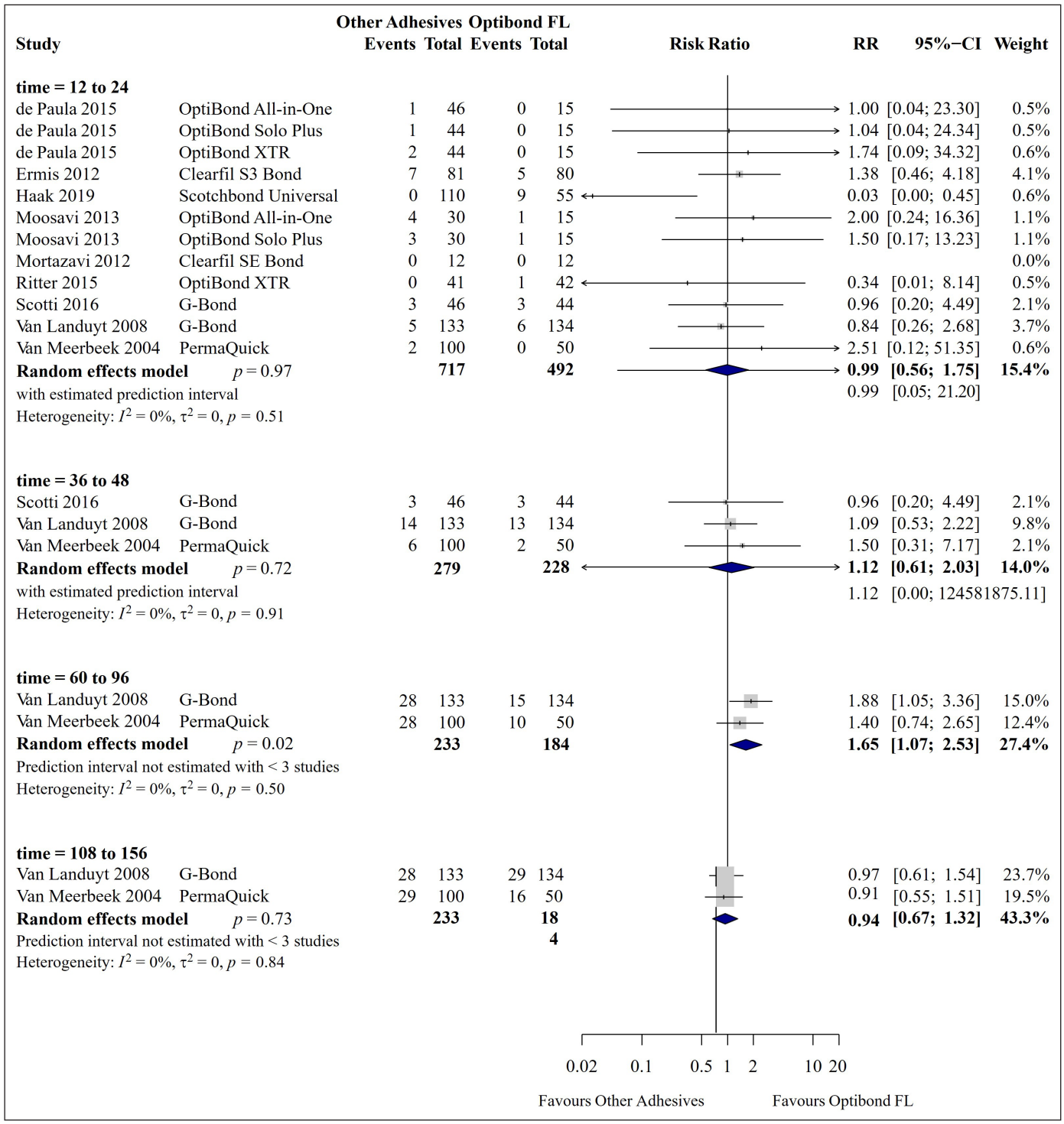

Figure 4. *Forest plots of the retention rates for OptiBond FL at 12 to 24-month, 36 to 48- month, 60 to 96-month and 108 to 156-month.*

second-best performance adhesive was the two-step SE Clearfil SE Bond.

The lack of agreement between the meta-analytical review[10] and the present meta-analysis of RCTs suggests that laboratory and clinical findings are not consistent. While an earlier study reported correlation between laboratory and clinical data, one cannot exclude the fact that this reported correlation was spurious, as it was only found between "aged" bond-strength data with medium-term retention rates of adhesives.[14]

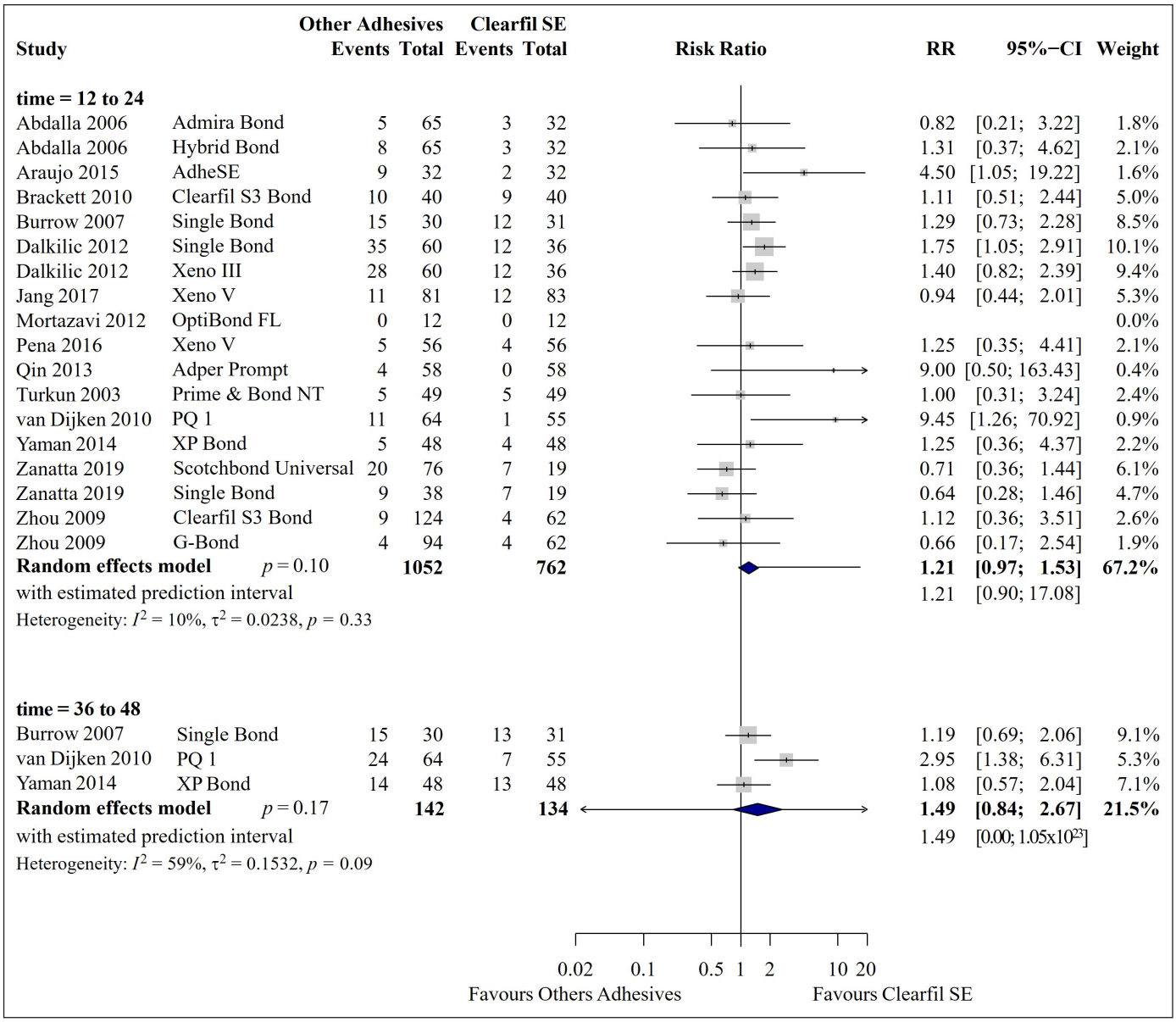

Figure 5. *Forest plots of the retention rates for Clearfil SE Bond at 12 to 24-month and 36 to 48-month.*

Nevertheless, this conclusion does not mean that the adhesives OptiBond FL and Clearfil SE Bond are not good adhesives. Indeed, they have good clinical performance with clinical data of up to 13 years of follow-up.[62,63] Very few adhesive systems have been followed up for such a long time. However, the merged data of OptiBond FL and Clearfil SE Bond from eligible RCTs in short- to long-term studies have not shown superiority of these materials over other brands, suggesting that there are other adhesives as good as these two. We do agree with some authors[17,64] that the clinical performance of the adhesive system is not related to the bonding strategy but to the product chemical composition. Therefore, any attempt to categorize the efficacy of adhesives based on their classification may be misleading. This may explain why systematic reviews grouping brands of adhesive systems from the same category failed to reach a consensus.[5,7,59]

Some considerations about the RCTs included in this systematic review are required. Authors of RCTs of bonding studies have not reported the study findings in a standardized way, and this may lead to misleading conclusions. In some clinical trials, events at the shortest follow-ups are not carried forward to the longest follow-ups, which may lead to the reporting of misleading results. This misleading report probably

Table 3: *Summary of Findings Table for OptiBond FL and Clearfil SE Bond*

Retention Rates		Anticipated Absolute Effects[a] (95% CI)		Relative Effect (95% CI)[a]	Number of Participants (Studies)	Certainty of the Evidence (GRADE)[b]
		Risk with Other Competitive Brands	Risk with Optibond FL			
OptiBond FL	Follow up range 12-24 month	39 per 1000	39 per 1000 (22-68)	RR 0.99 (0.56-1.75)	1209 (12 RCTs)	□□□□ LOW a,b
	Follow up range 36-48 month	82 per 1000	92 per 1000 (50-167)	RR 1.12 (0.61-2.03)	507 (3 RCTs)	□□□□ LOW a,c
	Follow up range 60-96 month	240 per 1000	397 per 1000 (257-608)	RR 1.65 (1.07-2.53)	417 (2 RCTs)	□□□□ LOW a,d
	Follow up range 108-156 month	245 per 1000	230 per 1000 (164-323)	RR 0.94 (0.67-1.32)	417 (2 RCTs)	□□□□ LOW a,e
Clearfil SE Bond	Follow up range 12-24 month	183 per 1000	222 per 1000 (178-281)	RR 1.21 (0.97-1.53)	1814 (18 RCTs)	□□□□ LOW a,e
	Follow up range 36-48 month	373 per 1000	556 per 1000 (314-997)	RR 1.49 (0.84-2.67)	276 (3 RCTs)	□□□□ LOW a,e

Abbreviations: CI, confidence interval; RR, risk ratio.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

occurred because the recall rate drops drastically in long-term follow-ups. In these situations, the review authors calculated the retention rates based on the number of recalled restorations and not based on the total number of restorations placed at baseline.

When we collected data for this meta-analysis, we used the total number of restorations at baseline as a reference for all studies. This approach assumes that none of those missed at the follow-up suffered the target outcome, ie, debonding. Making this assumption, we presented the study results as the best estimate, as we do not know (like the authors of the eligible studies) what happened to the unseen restorations. Although this approach may overestimate the retention rates of the adhesives, it does not break the random assignment to the treatment groups in the studies.

The other alternative would be to use the number of restorations recalled at each follow-up as a denominator of the retention rate; however, this number is not always provided. Some authors report an overall recall rate and not the recall rate per group,[55] which does not help in data extraction; others do not report the recall rate at all.[34,40] To make the scenario harder, some study authors report the percentage of events instead of the raw numbers, without specifying whether the denominator of such percentages is the total number of placed restorations at baseline or the total number of evaluated restorations at any follow-up.

All these concerns regarding data extraction indicate an urgent need for standardization of the report of studies conducted on NCCLs. Instead of providing retention rates per follow-up, the use of survival analysis could provide better estimates of what occurs to the adhesives over time.

Another important issue to be addressed is that the great majority of the studies had an unclear RoB. To prevent selection bias, the randomization process should be adequately performed, and the random sequence should be protected from foreknowledge until the implementation of the intervention. The latter procedure is called allocation concealment. Only 30%-40% of eligible studies from this review reported the randomization process used in their study, and only 10%-15% of the studies adequately reported the allocation concealment.

The poor reporting of the random sequence generation and the allocation concealment in studies conducted in NCCLs has been highlighted in a previous review that assessed the compliance of bonding studies in NCCLs to the CONSORT statement,[65] which is a set of recommendations for reporting clinical trials in biomedical literature. This fact led us to downgrade the quality of evidence by one level for the RoB.

Another important consideration is that most of the RCTs focused on short- and medium-term follow-ups, ie, 12-48 months for both the adhesives. In these short-term follow-ups, the number of events, ie, debonded restorations, was low for both the groups, leading to imprecise estimates. The body of evidence produced at these follow-ups was also downgraded for imprecision due to the low number of events. Similarly, the long-term follows up were downgraded for imprecision, but due to the low number of studies and wide 95% confidence interval.

Only three medium- to long-term studies (5 years or more) for OptiBond FL were found. Clearfil SE Bond was not compared with other adhesive brands in follow-ups equal to or longer than 5 years. The studies of Van Meerbeek 2005[66] and Peumans 2005,[8] 2007,[67] 2010,[68] 2015[63] evaluated the long-term performance of this two-step SE adhesive, but the authors did not compare it with other adhesive brands, which prevented a meta-analysis of these data.

Based on the available RCTs meta-analyzed in this systematic review, there are adhesives whose performance is similar to that of those currently considered "gold standard" adhesives in the dental market. However, the quality of the body of evidence was considered low, and further RCTs, mainly with a long-term record of performance, are required.

CONCLUSION

We have no evidence from the available RCTs that compared OptiBond FL or Clearfil SE Bond, used in NCCLs, to support the widespread concept that these adhesives are better than other competitive brands available in the dental market.

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Conflict of Interest

The authors of the present study certify that they have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in the present article.

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