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SYSTEMATIC REVIEW

Selective outcome reporting in root coverage randomized clinical trials

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Abstract

Background: Outcome discrepancies between protocols and respective publications represent a concerning bias. The purpose of this study was to assess the prevalence of selective outcome reporting (SOR) in root coverage randomized clinical trials (RCTs).

Methods: Published root coverage RCTs (July 2005 to March 2020) were included if a corresponding protocol could be identified in a public registry. Discrepancies between protocol and its correspondent publication(s) were compared regarding primary and secondary outcomes and other study characteristics. Associations between trial characteristics and SOR were evaluated.

Results: Forty four studies (54 publications) were included. The majority of studies (77.3%) were retrospectively registered. SOR was frequent (40.9% of trials) and consisted of primary outcome downgrade (22.7%); secondary outcome upgrade (11.4%); new primary outcome introduced in publication (25%); protocol primary outcome omitted from publication (13.6%) and discrepancy in primary outcome timing (18.2%). SOR was unclear in 20.5% of studies and favoured statistical significance in 12 studies (27.3%). SOR was significantly associated with study significance ($p < 0.001$) and unclear outcome definition in the publication ($p < 0.001$). Only a third (32.8%) of primary outcomes were completely defined.

Conclusions: The present study identified high prevalence of SOR in root coverage RCTs.

KEYWORDS
gingival recession, publication bias, randomized controlled trials as topic, surgery

Clinical Relevance

Scientific rationale for study: Selective outcome reporting (SOR) is a threat to evidence-based practice, because it leads to overrepresentation of significant findings and positive conclusions in the scientific literature.

Principal findings: A high rate of SOR was observed in root coverage RCTs, with most trials retrospectively registered. SOR was significantly associated with study significance and unclear outcome definition in the publication.

Practical implications: There is room to improve outcome reporting in root coverage RCTs. Prospective trial registration and evaluation of possible inconsistencies between registered trial protocols and submitted manuscripts should help reduce SOR.

1 | INTRODUCTION

Gingival recession (GR) is highly prevalent (Albandar & Kingman, 1999; Sarfati et al., 2010; Rios et al., 2014) and associated with poor aesthetics, impaired plaque-control, hypersensitivity, caries and non-carious cervical lesions (Santamaria et al., 2018; Seong et al., 2018). Consequently, GR could negatively impact patient quality of life (Wagner et al., 2016). Left untreated, GR defects are highly likely to progress (Chambrone & Tatakis, 2016; Agudio et al., 2017). Strong evidence indicates that most GR defects can be predictably treated with root coverage procedures (Chambrone et al., 2010; Chambrone et al., 2012; Chambrone & Tatakis, 2015; Chambrone et al., 2019). The large number of clinical trials and systematic reviews (Chambrone et al., 2010; Chambrone et al., 2012; Chambrone & Tatakis, 2015; Chambrone et al., 2019) focused on GR treatment indicates the heightened clinical interest in root coverage outcomes.

Various outcomes have been used in randomized clinical trials (RCTs) of root coverage procedures, including recession depth and width reduction, mean root coverage, mean clinical attachment gain and complete root coverage prevalence (Chambrone & Tatakis, 2015; Chambrone et al., 2019). Recently, attention has also focused on patient-centered outcomes, including post-operative discomfort, hypersensitivity perception and aesthetics (Mounssif et al., 2018; Cairo et al., 2020).

In this era of evidence-based practice, research findings have a profound influence on clinical practice and delivery of care. Therefore, any limitations or biases that could alter published research findings represent a significant concern. Publication bias, that is the fact that published studies are more likely to report positive or statistically significant results compared to unpublished research, is well documented (Dickersin & Min, 1993; Thaler et al., 2015). Another type of bias that can be introduced in RCT publications is selective outcome reporting (SOR) (Chan et al., 2004). SOR occurs when the primary outcome is changed or omitted, or when a new outcome is introduced. Evidence suggests that SOR, which is quite common in medicine (Chan et al., 2004; Hannink et al., 2013; Wayant et al., 2017), is associated with statistically significant outcomes (Chan et al., 2004; Zhang et al., 2017; Aggarwal & Oremus, 2019). SOR poses a threat to evidence-based practice, since it distorts the real effect of interventions and thus improperly affects clinician decision-making and public policies (Chan et al., 2004). Another shortcoming regarding the transparency of clinical trial reporting is incomplete outcome specification (Zarin et al., 2011). Outcomes can be incompletely prespecified in the protocol and/or incompletely reported in the publication, which creates opportunities for "cherry-picking", that is reporting only some of the outcome measurements or metrics (Mayo-Wilson et al., 2017).

There is little information on SOR in the dental literature. Outcome discrepancies between protocols and respective publications have been observed in oral health systematic reviews (Pandis et al., 2015), in orthodontic RCTs (Koufatzidou et al., 2019) and in dental implant RCTs (Sendyk et al., 2019). However, there are no investigations of SOR in periodontal RCTs. Thus, the aim of this study was to assess the prevalence of SOR in root coverage RCTs and to investigate the possible associations between SOR and specific trial characteristics.

2 | MATERIAL AND METHODS

2.1 | Eligibility criteria and search strategy

We conducted a systematized literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in MEDLINE (PubMed), EMBASE and Cochrane Central Library, from July 1, 2005 to October 10, 2020. The earliest publication date limit was chosen because this was the date when the International Committee of Medical Journal Editors (ICMJE) introduced compulsory registration of RCTs in public registries as a condition for publication in cooperating journals (Angelis et al., 2004). Publications that met the following eligibility criteria were included: (a) study was an RCT, (b) study assessed any root coverage procedure, (c) research protocol was registered in any of the registries enlisted in the International Clinical Trials Registry Platform (ClinicalTrials.gov, 2020).

The following keywords were used: (((((((gingival recession) OR gingiva) OR recession-type defect) OR root exposed) OR root exposure) OR root surface)) AND ((((((((plastic surgery) OR soft tissue graft) OR coronally advanced flap) OR laterally positioned flap) OR connective tissue graft) OR guided tissue regeneration) OR enamel matrix protein) OR dermal matrix) OR root coverage) (Chambrone & Tatakis, 2015). Search was performed with filter for article type (Clinical Trial) and publication date (from July 2005). Further, we conducted a manual search of reference lists from identified studies.

2.2 | Study selection

In the first review phase, two independent reviewers (D.I.S. and N.V.S.) individually screened titles and abstracts of publications identified by the search strategy. A third reviewer (C.M.P.) checked the search and resolved disagreements. In the second phase of the review, studies that met inclusion criteria or that presented unclear information in the title and abstract were selected for assessment of the complete publication. In the third phase, the same reviewers tried to identify the corresponding registered protocol, using the registry number. When no registry was cited in the publication, the corresponding author was contacted. If the author answered that the trial had not been registered, the study was excluded. If the author did not answer after two consecutive tries, the reviewers searched for corresponding protocol at ClinicalTrials.gov, at the registry of the country where the study was conducted, and at the International Clinical Trials Registry Platform, using the publication title or the corresponding author name. If after this search a protocol was not identified, the study was also excluded.

2.3 | Data extraction

Data were recorded independently by the same reviewers using an extraction form that addressed the publication, the corresponding protocol and any discrepancies between the two. A third reviewer (C.M.P.) checked all extracted data and solved disagreements. When two or more publications concerned the same study, data was collected from all publications and grouped under the same study identification.

For each publication the following data was collected: journal name, publication date, name of corresponding and first author, study start date and completion date, trial design, number of arms, interventions, reporting of sample size calculation (and whether it was based on the primary outcome), sample size, number of primary and secondary outcomes, time frame of the primary outcome(s), statistical significance ($p \leq 0.05$) of the primary outcome(s), follow-up period, and industry funding. If no outcome was reported as being the primary, the outcome used for sample size calculation was considered to be the primary. If a primary outcome was not identified in the publication and an outcome was not mentioned in sample size calculation, then the study primary outcome was considered to be unclear. Additionally, the publication was checked for report of trial registration, information on registration number, and reporting of any protocol change.

Each reported primary outcome was defined using five levels: domain, specific measurement, specific metric, method of aggregation and time point (Zarin et al., 2011; Mayo-Wilson et al., 2017; World Health Organization, 2020). Figure 1 shows an example of the five-level definition of an outcome for a root coverage trial. A primary outcome was classified as "completely defined" when all five levels were clearly defined. When the definition of at least one of the five levels was unclear, the outcome was classified as ''not completely defined'' (Mayo-Wilson et al., 2017).

For each corresponding protocol, the following data were extracted: registered protocol number (e.g. ClinicalTrials.gov identifier, or NCT), registry name, date of registration, dates in which the protocol was first received and last updated, study start and completion dates, and name and country of principal investigator. To identify possible protocol changes after initial registration, a specific function of the registry (History of Changes) was used. Trials were judged to be prospectively registered if the registration date preceded enrolment of the first study subject. A trial was considered to be retrospectively registered if it was registered after enrolment of the first subject. In cases where the trial was prospectively registered, but there was an inconsistency between registration date, follow-up period and date of submission to the journal, the registration was judged to be retrospective. Furthermore, information was extracted concerning the following: industry funding, trial design, number of arms and interventions being tested, sample size, follow-up period, number and timing of assessment of the primary and secondary outcomes. Any outcome(s) explicitly reported in the registry as primary outcome(s) was(were) the one(s) considered as primary for the protocol. All other outcomes were classified as secondary. Each registered primary outcome was defined using the same five levels used for the publication and was classified as "completely defined" or ''not completely defined''.

After data extraction, each protocol and the corresponding publication(s) were examined for possible discrepancies between them. Since the study was the statistical unit, when two or more publications were associated with the same registered protocol and a

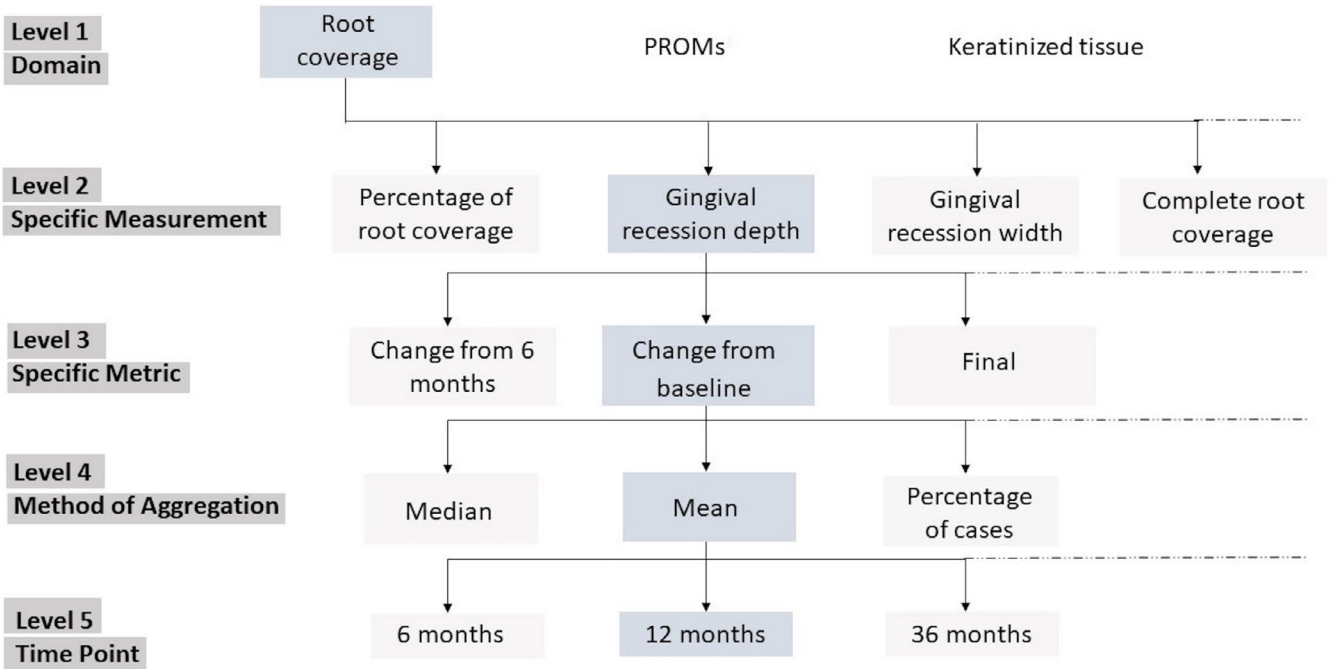


FIGURE 1 Example of complete outcome definition, for a gingival recession treatment trial, using the five-level framework. PROMs, patient-related outcome measures

discrepancy was identified in only one of the publications, then the study was considered to have a discrepancy.

Selective outcome reporting was defined according to a modification of the Chan et al. (2004) criteria:

a. primary outcome in the registry was reported as secondary in the publication (primary outcome downgrade),
b. secondary outcome in the registry was reported as primary in the publication (secondary outcome upgrade),
c. a new primary outcome (i.e. an outcome that was not described in the registry) was introduced in the publication,
d. the primary outcome in the registry was not reported in the paper.
e. there was a difference between the registry and the publication regarding the timing of assessment of the primary outcome

Selective outcome reporting was judged to be unclear when it was not possible to identify primary and secondary outcomes in the publication.

An identified SOR was considered to favour statistically significant results when a secondary outcome in the registry was upgraded to primary and reported as statistically significant in the publication, when a new primary outcome was introduced and reported as statistically significant in the publication, or when a primary outcome in the registry was omitted or downgraded to secondary and reported as non-significant in the publication (Chan et al., 2004).

The reviewers also examined and recorded if in the publication there was a new secondary outcome and if a new outcome (not defined by the authors as primary or secondary) was introduced.

Finally, extracted data were analysed for any discrepancies between registry and publication regarding study start date, industry funding, study design, number of arms, sample size and follow-up period.

2.4 | Risk of bias assessment

Risk of bias of the included studies was assessed using the Cochrane Collaboration tool for assessing risk of bias (Higgins & Green, 2008), as previously described (Chambrone & Tatakis, 2015).

2.5 | Statistical analysis

The statistical unit was the study, except for outcome definition, where the outcome was the unit. Frequency distribution for qualitative variables and mean and standard deviation for quantitative variables were calculated for study characteristics. Presence/absence of SOR was tested for possible association with the following explanatory variables: timing of registration (prospective/retrospective), industry funding (yes/no), study significance of the primary outcome ($p \leq 0.05/p > 0.05$), journal´s impact factor (lower/higher; median impact factor of included journals used as cut-off point) and completeness of primary outcome definition in the publication and in the protocol (primary outcomes completely defined or presented unclear definition in only one level/unclear definition in ≥2 levels). Freeman-Halton extension of Fisher exact probability test was used to test associations. In order to adjust for multiple tests, alpha was adjusted using Bonferroni's procedure, resulting in a level of significance ≤0.0083 for all tests. Statistical analyses were performed using SigmaPlot for Windows version 14.0 (Systat Software, Inc).

3 | RESULTS

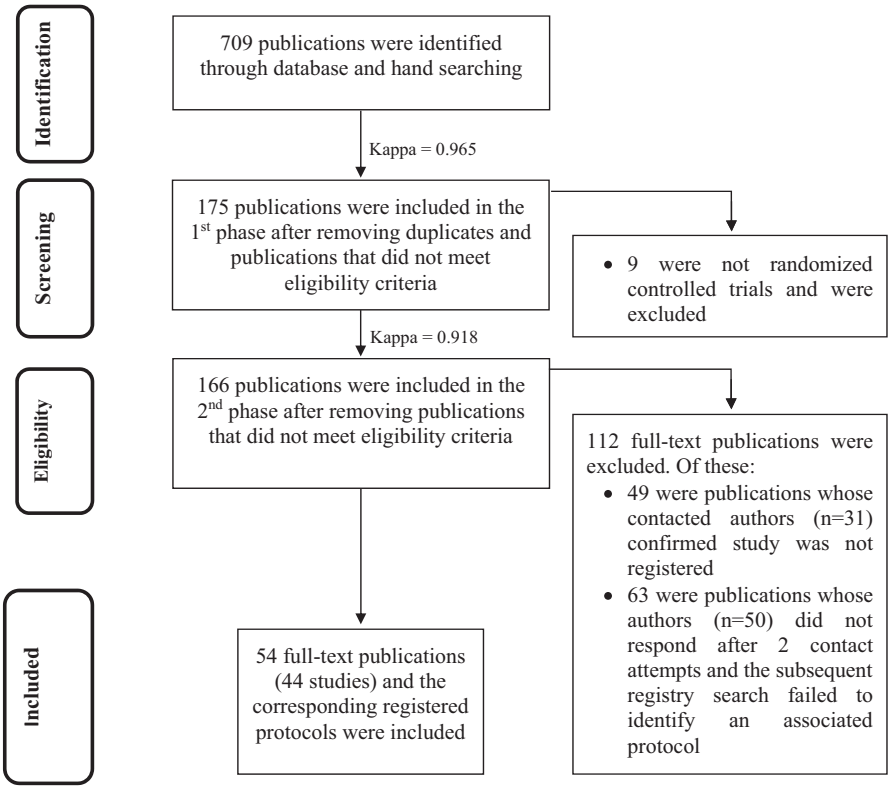
In the first screening phase, 709 potentially relevant articles were retrieved from the electronic databases. After duplicate removal, 687 had their titles and abstracts reviewed. Of those, 175 publications fulfilled eligibility criteria and were included in the first phase. Fifty-four publications reporting 44 RCTs met the eligibility criteria and were included. Reasons for exclusions are shown in Figure 2. Kappa coefficients for inter-examiner agreement were 0.965 (95% CI 0.943–0.988; first phase) and 0.918 (95% CI 0.855–0.982; second phase). The list of included studies is shown in Table S1.

3.1 | Study and protocol characteristics

Table 1 shows characteristics of the publications of the included 44 studies. Most protocols (79.5%) resulted in only one identified publication. Nine studies (20.5%) resulted in more than one publication. Of these, eight reported different follow-up periods in the different papers, and one reported different outcomes in the different publications. The majority of publications cited the registry identification number (93.2%). Although 65.9% of the studies reported only one primary outcome in the publication, 16.5% reported more than one. For eight studies (18.2%) it was not clear which was the primary outcome; therefore, SOR presence was considered unclear. In 61.4% of the studies, sample size calculation was based on the primary outcome. Primary outcome was significant in 38.6% of the studies.

The results of outcome definition analysis of the 61 published primary outcomes are shown in Table S2. Root coverage was the most frequently used domain (55.7%). GR depth was the most common specific measurement (21.3%). The most common specific metric was “change from baseline” (55.7%). The mean was the most frequent method of aggregation (64%). Most primary outcomes were presented as 6-month (32.8%) or 12-month (32.8%) measurements. Unclear definitions were common in all five levels of outcome definition, including domain (24.6%), specific measurement (39.3%), specific metric (34.4%), aggregation method (32.8%), and time point (24.6%). Table S3 shows the distribution of primary outcomes according to completeness of outcome definition and number of unclear levels in the publications. Only 32.8% (n = 20) of primary outcomes were completely defined (i.e. clear definition in all five levels).

FIGURE 2 Flow of studies



Characteristics of the corresponding 44 protocols are shown in Table 2. Studies were registered from May 2008 onwards, and 27 (61.4%) between 2015 and 2019. About half of the studies were conducted in Europe. The majority were retrospectively registered (77.3%) and not industry-sponsored (90.9%). Most registered protocols (72.7%) described only one primary outcome. For 12 studies (27.3%), the number of primary outcomes in the protocols ranged from 2 to 5. In one protocol it was not clear which was the primary outcome.

Table S4 shows the outcome definition analysis of the 67 primary outcomes described in the 44 protocols. Root coverage was the most frequently used domain (67.2%). The most common specific measurement was root coverage percentage (29.9%). Change from baseline was the specific metric used in 28.4% of primary outcomes. Aggregation method was unclear in 97% of the outcomes. Most protocol outcomes were intended to be analysed after 6 (37.3%) and 12 months (20.9%). Unclear definition varied by level, with domain the least likely to be unclear (3%) and aggregation method the most likely (97%). For the other three levels, unclear definition fell between these extremes, with specific measurement, specific metric, and time point being unclear in 17.9%, 62.6%, 26.9% of the primary outcomes, respectively (Table S4). Only 2 (2.9%) primary outcomes were completely defined in the protocols (Table S5).

Risk of bias of the included studies is shown in Table S6. Kappa coefficient for inter-examiner agreement in risk of bias evaluation was 0.864 (95% Confidence Interval: 0.715–1.000). The majority of publications reported randomization (80%), allocation concealment (54%) and examiner masking (76%) adequately. Follow-up completeness was adequate in 74% of the papers. As regards other bias, risk was low in all publications. Five (9.3%), 29 (53.3%) and 20 (37%) of the publications presented high, unclear and low overall risk of bias, respectively.

3.2 | Outcome discrepancies between protocols and corresponding publications

Outcome discrepancies were identified in 40.9% of the trials (*n* = 18; Table 3). In nine studies (20.5%) SOR was unclear, because of lack of primary outcome identification either in the publication (*n* = 8) or in the registry (*n* = 1). The identified discrepancies between protocol and publication were: primary outcome in protocol described as secondary in publication (*n* = 10; 22.7%); secondary outcome in protocol described as primary in publication (*n* = 5; 11.4%); primary outcome in protocol omitted from publication (*n* = 6; 13.6%); new primary outcome introduced in publication (*n* = 11; 25%), and discrepancy in primary outcome timing of assessment (*n* = 8; 18.2%). SOR favoured statistical significance in 12 studies (27.3%). Remarkably, a new secondary outcome was introduced in 25 studies (56.8%) and a new outcome, not defined by the authors as primary or secondary, was introduced in 30 trials (68.2%) (Table 3).

Regarding discrepancies in other study aspects (Table S7), three studies showed discrepancy in funding (6.8%), nine studies had discrepancies in study design (20.5%), four trials (9.1%) had sample size discrepancies and nine (20.5%) had follow-up period discrepancies. There were no identifiable discrepancies in study start date or number of arms.

TABLE 1 Characteristics of publications of the included studies

Characteristic	Studies (*n* = 44)
Number of publications from same study protocol—*n* (%)	
One	35 (79.5)
Two	8 (18.2)
Three	1 (2.3)
Registry identifier cited in publication—*n* (%)	
Yes	41 (93.2)
No	3 (6.8)
Change in protocol cited in publication—*n* (%)	
Yes	0 (0.0)
No	44 (100.0)
Industry funding as reported in publication—*n* (%)	
Yes	7 (15.9)
No	37 (84.1)
Design of trial as reported in publication – *n* (%)	
Parallel	28 (63.6)
Split-mouth	16 (36.4)
Number of arms as reported in publication – *n* (%)	
Two	40 (90.9)
Three	3 (6.8)
Four	1 (2.3)
Sample size calculation reported in publication—*n* (%)	
Yes	34 (77.3)
No	10 (22.7)
Sample size calculation based on protocol primary outcome—*n* (%)	
Yes	27 (61.4)
No	17 (38.6)
Sample size—*n*	
Min-max	12–187
Mean (SD)	35 (28.3)
Median (IQR)	29 (20–40)
Period of follow-up (months)	
Min-max	6–240
Mean (SD)	18.1 (36.4)
Median (IQR)	12 (6–12)
Number of primary outcomes in publication—*n* (%)	
One	29 (65.9)
Two	5 (11.9)
Three	1 (2.3)
Five	1 (2.3)
Unclear	8 (18.2)
Time frame of primary outcome[a]	
Min-max	3 days–240 months
Mean (SD), in months	19.5 (39.7)
Median (IQR), in months	12 (6–12)
Primary outcome significant—*n* (%)	
Yes	17 (38.6)
No	19 (43.2)
Unclear	8 (18.2)

Abbreviations: IQR, inter-quartile range; SD, standard deviation.

[a]Time frame of primary outcome was unclear in seven studies.

TABLE 2 Characteristics of trial protocols of the included studies

Characteristic	Studies (*n* = 44)
Region of principal investigator—*n* (%)	
Europe	21 (47.7)
South America	14 (31.8)
North America	4 (9.1)
Asia	4 (9.1)
Oceania	1 (2.3)
Registry—*n* (%)	
ClinicalTrials.gov	41 (93.2)
Clinical Trial Register (DRKS)	2 (4.5)
New Zealand Clinical Trial Registry (ANZCTR)	1 (2.3)
Change in protocol—*n* (%)	
Yes	3 (6.8)
No	38 (86.4)
Unclear	3 (6.8)
Timing of registration—*n* (%)	
Prospective	10 (22.7)
Retrospective	34 (77.3)
Industry Funding—*n* (%)	
Yes	4 (9.1)
No	40 (90.9)
Design of the trial as reported in protocol—*n* (%)	
Parallel	38 (86.4)
Split mouth	5 (11.3)
Crossover	1 (2.3)
Number of arms as reported in protocol—*n* (%)	
Two	39 (88.6)
Three	3 (6.8)
Four	1 (2.3)
Unclear	1 (2.3)
Sample size—*n*	
Min-max	12–187
Mean (SD)	34.7 (28.1)
Median (IQR)	30 (19–40.5)
Period of follow-up	
Min-max	14 days–240 months
Mean (SD), in months	15.4 (35.8)
Median (IQR), in months	6 (6–12)
Number of primary outcomes in protocol—*n* (%)	
One	32 (72.7)
Two	05 (11.4)
Three	04 (9.1)
Five	02 (4.5)
Unclear	01 (2.3)
Time frame of primary outcome	
Min-max	3 days–240 months
Mean (SD), in months	15.0 (35.9)
Median (IQR), in months	6 (6–12)

Abbreviations: IQR, inter-quartile range; SD, standard deviation.

TABLE 3 Outcome discrepancies between protocol and publication

Characteristic	Studies (n = 44)
Trials with Selective Outcome Reporting[a]	
Yes	18 (40.9)
No	17 (38.6)
Unclear	9 (20.5)
Primary outcome in protocol described as secondary in the publication	
Yes	10 (22.7)
No	25 (56.8)
Unclear	9 (20.5)
Secondary outcome in protocol described as primary in the publication	
Yes	5 (11.4)
No	30 (68.2)
Unclear	9 (20.5)
Primary outcome in protocol omitted from publication	
Yes	6 (13.6)
No	37 (84.1)
Unclear	1 (2.3)
New primary outcome introduced in the publication	
Yes	11 (25.0)
No	24 (54.5)
Unclear	9 (20.5)
Discrepancy in primary outcome timing of assessment	
Yes	8 (18.2)
No	36 (81.8)
Selective outcome reporting favours statistical significance	
Yes	12 (27.3)
No	23 (52.3)
Unclear	9 (20.5)
New secondary outcome	
Yes	25 (56.8)
No	10 (22.7)
Unclear	9 (20.5)
New outcome	
Yes	30 (68.2)
No	14 (31.8)

Note: All variables are reported as *n* (%).

[a]According to a modification of Chan et al. (2004) classification.

Table 4 shows that SOR was significantly associated with study significance in the publication ($p < 0.001$). SOR was also associated with unclear definition of the outcome(s) in two levels or more in the publication ($p < 0.001$), but not in the protocol ($p = 0.16$). There was no SOR association with timing of registration ($p = 0.37$), industry funding ($p = 0.66$) or journal impact factor ($p = 0.13$). Introduction of a new outcome (not defined by the authors as primary or secondary) was associated with a significant result ($p = 0.007$).

4 | DISCUSSION

The present study sought to determine the prevalence of selective outcome reporting (SOR) in root coverage RCTs. SOR was frequent (40.9%; 18 of 44) and it was associated with statistical significance in the publication and with unclear definition of the outcome in the publication. SOR was not associated with timing of registration, industry funding, journal impact factor, or unclear definition in the protocol. This is the first study to examine SOR in periodontal RCTs of any therapeutic modality.

Evidence suggests that SOR prevalence in the scientific literature is highly variable; a recent systematic review (Li, Abbade, et al., 2018) reported that SOR ranged from 14% to 95%, varying by medical field. The 40.9% SOR rate identified in the included root coverage trials is lower than those reported by studies on medical trials: 62% in the milestone paper from Chan and co-workers (Chan et al., 2004), 49% in haematology journals (Wayant et al., 2017), 49% in surgical intervention trials (Hannink et al., 2013) and 95% in eczema treatment trials (Nankervis et al., 2012). In addition, SOR in root coverage trials was also lower than in other dental fields: 47% in orthodontic trials (Koufatzidou et al., 2019) and 55.1% in dental implant literature (Sendyk et al., 2019). It is important to point out that in 20.5% of the studies included herein SOR was unclear, because authors did not identify the primary outcome in either the publication or the protocol. This considerable percentage of unclear SOR raises the possibility that actual SOR prevalence could be higher than 40.9%. The ubiquitous and frequent identification of SOR, regardless of field of investigation, is informative and underscores the challenges associated with conducting and reporting RCTs.

A third of the studies (34.1%) reported two or more outcomes in the publications, and 27.3% registered two or more in the protocol. Most RCT registries, like ClinicalTrials.gov, allow the inclusion of more than one primary outcome. However, use of many outcomes in a trial increases the probability of type I error, that is the chance of finding a significant result just by chance (Dmitrienko & D'Agostino, 2018). Such an error may lead to the wrong conclusion that a treatment has an effect, when in fact it doesn't (Goodman et al., 2016; Li et al., 2018). In this context, it should be noted that CONSORT (Schulz et al., 2010) advises authors to include only one outcome, in order to avoid problems with multiplicity.

In 2005, the International Committee of Medical Journal Editors (ICMJE) introduced a policy mandating registration of RCTs in a public registry (Angelis et al., 2004). Such initiatives help decrease the risk of SOR, since prospectively registered trials present lower SOR risk (Farquhar et al., 2017). Registered trials are also less likely to report significant results than non-registered ones (Kaplan & Irvin, 2015). However, registration of the protocol per se might have limited impact in preventing SOR unless authors define outcomes completely. Incomplete outcome definition may lead to multiplicity, if under the domain (e.g. root coverage) there are variations in the other 4 levels. These variations offer the possibility for post hoc selectively reporting a specific measurement or metric (e.g. reduction in recession depth after 12 months) associated with the most

TABLE 4 Association between selective outcome reporting (SOR) and study characteristics

Characteristic	SOR			Total	*p*-value
	Yes	No	Unclear		
Timing of registration, per protocol					
Retrospective	12 (35.3)	15 (44.1)	7 (20.6)	34 (100.0)	0.37
Prospective	6 (60.0)	2 (20.0)	2 (20.0)	10 (100.0)	
Industry funding, per protocol					
Yes	2 (50.0)	2 (50.0)	0 (0.0)	4 (100.0)	0.66
No	16 (40.0)	15 (37.5)	9 (22.5)	40 (100.0)	
Study significance					
Yes	8 (47.1)	8 (47.1)	1 (5.9)	17 (100.0)	**<0.001***
No	10 (52.6)	9 (47.4)	0 (0.0)	19 (100.0)	
Unclear	0 (0.0)	0 (0.0)	8 (100.0)	8 (100.0)	
Journal impact factor					
Below median	9 (40.9)	6 (27.3)	7 (31.8)	22 (100.0)	0.13
Above median	9 (40.9)	11 (50.0)	2 (9.1)	22 (100.0)	
Definition of primary outcome(s) in the publication					
Unclear definition of the outcome(s) in two levels or more	17 (50)	16 (47.1)	1 (2.9)	34 (100.0)	**<0.001***
Completely defined outcome(s) or unclear definition in only one level	1 (10)	1 (10)	8 (80)	10 (100.0)	
Definition of primary outcome(s) in the protocol					
Unclear definition of the outcome(s) in two levels or more	13 (43.3)	9 (30.0)	8 (26.7)	30 (100.0)	0.16
Completely defined outcome(s) or unclear definition in only one level	5 (35.7)	8 (57.1)	1 (7.1)	14 (100.0)	

Note: All variables are reported as *n* (%). Bold numbers indicate statistically significant *p*-value.

*Significant association according to the Freeman-Halton extension of the Fisher exact probability test. All tests were performed considering alpha ≤0.0083 (Bonferroni procedure for multiplicity adjustment).

favourable results (Zarin et al., 2011; Mayo-Wilson et al., 2017; Li, Mayo-Wilson, et al., 2018). In the included studies, 17.9% of the primary outcomes in the protocols and 37.9% of the primary outcomes in the publication described the domain, but not the specific measurement. Interestingly, 8 of the 12 protocols that included two or more primary outcomes had more than one specific measurement under the same domain (e.g. recession depth reduction, root coverage percentage and complete root coverage). Of these, 6 (75%) presented SOR or unclear SOR. Incomplete outcome definition may have allowed for cherry-picking favourable results. Indeed, incomplete outcome definition (≥2 levels) in the publication was significantly associated with study significance and SOR.

Selective outcome reporting favoured statistically significant results in 27.3% of the RCTs. Furthermore, SOR was significantly associated with study significance. This is in agreement with numerous medical studies (Chan et al., 2004; Mathieu et al., 2009; Jones & Platts-Mills, 2012; Wayant et al., 2017; Zhang et al., 2017; Aggarwal & Oremus, 2019). A plausible explanation for this association is that authors pursue changes between protocol and publication in an attempt to report significance or to meet editors´ expectations (Li, Abbade, et al., 2018). This practice, combined with multiplicity, can lead to wrong conclusions about the true efficacy of a treatment.

Selective outcome reporting was not associated with journal impact factor and was frequent even in journals with the highest impact factor, in agreement with another study (Calméjane et al., 2018) and consistent with the fact that even leading medical journals are not immune to SOR (Fleming et al., 2015).

In the present study, SOR was not associated with registration timing (prospective or retrospective), in agreement with other studies (Jones & Platts-Mills, 2012; Fleming et al., 2015; Aggarwal & Oremus, 2019; Koufatzidou et al., 2019). Most RCTs included herein (77.3%) were retrospectively registered. This finding raises concerns, because retrospective registration may undermine the main objective of trial registration, that is to guard against publication and reporting bias, such as omission of non-significant results. Trials are recommended to be registered before onset of participant enrolment (Angelis et al., 2004); this avoids the possibility of protocol registration after changes have been introduced in the study.

In agreement with previous studies on dental (Koufatzidou et al., 2019), drug (van den Bogert et al., 2017), and medical intervention (Chan et al., 2004; Wayant et al., 2017) trials, the present study did not find association between SOR and industry funding. However, a recent study on dental implant trials reported an association between industry funding and SOR (Sendyk et al., 2019). Further, annual implant failure for sponsored trials is significantly lower when compared with non-sponsored studies, which could also bias the clinical decision-making (Popelut et al. 2010). This discrepancy between dental implant and root coverage trials regarding SOR association with industry funding may reflect the different nature of the two therapies in terms of reliance on an industry product, that is dental implant versus autogenous graft or flap.

A limitation of the present study was the inability to identify a corresponding registered protocol for a large number of RCTs (67% of identified trials). Some publications did not refer to registry number and for other studies publication title and registry title did not match. Additionally, the response rate of contacted authors was low (40%). A trend was observed between publication date and existence of a protocol registry, with 61.4% of the 44 included RCTs being registered between 2015 and 2019. In this context, it is notable that a 2015 report indicated that among 78 leading dental journals only 40% required or recommended trial registration (Smaïl-Faugeron et al., 2015). Publication of unregistered trials and trials registered after inclusion of the first participant is concerning because it allows for post hoc changes and SOR.

5 | CONCLUSION

The high rate of SOR for root coverage RCTs identified in the present study suggests that there is room to improve outcome reporting in periodontal therapy trials. Prospective trial registration, complete definition of trial outcomes (five-level framework), and evaluation of possible inconsistencies between registered trial protocols and submitted manuscripts should help reduce SOR among periodontal RCT publications.

CONFLICT OF INTEREST

The authors report no conflicts of interest related to this study. The study was supported by the authors' institutions.

AUTHOR CONTRIBUTIONS

D.I.S. conceived and designed the study and contributed to data collection, data interpretation, and drafting, editing and revising manuscript. N.V.S. contributed to data collection, preparation of tables and figures, and drafting, editing and revising manuscript. J.B.C.N. contributed to editing and revising manuscript. D.N.T. contributed to data interpretation and editing and revising manuscript. C.M.P. conceived and designed the study and contributed to data analysis and interpretation, and drafting, editing and revising manuscript. All authors approved the final version of manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

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

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