RISK OF BIAS ASSESSMENT OF IN VITRO STUDIES IN ENDODONTICS AND DEVELOPMENT OF ROBENDO TOOL: AN UMBRELLA REVIEW

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1. INTRODUCTION

Systematic reviews (SR) typically are a collective scientific update on a particular topic or intervention based on the synthesis of randomized clinical trials (RCTs), which are ranked at the top of the scientific evidence (GOPALAKRISHNAN; GANESHKUMAR, 2013). The risk of bias (RoB) assessment of the included studies is considered an essential component of an SR (NAGENDRABABU et al., 2022). Bias or systematic error can be defined as any bias in the collection, analysis, interpretation, publication, or data review which leads to conclusions that tend to distance themselves from the evidence (LORSCHEITTER et al., 2017). The findings from studies with good methodological quality are generally considered more reliable, whereas a greater degree of uncertainty is associated with results from studies with a higher RoB (NAGENDRABABU et al., 2022).

Several criteria without standards have been reported to assess the RoB in SR of *in vitro* studies in the endodontic literature (SILVA et al., 2020). These SRs have frequently used criteria adapted from previous reviews, including SRs of clinical studies, to adjust to the complexity of the different factors that can be characterized as bias (RANJAN; RANJAN, 2021). Recently, two RoB tools were developed to assess the risk of bias of *in vitro* studies. One is a tool to evaluate the quality and RoB of in vitro dental studies, called The QUIN (SHETH et al., 2022). In addition, other tool was developed to asssess the RoB in laboratory studies of dental materials, the so-called RoBDEMAT (DELGADO et al., 2022). Thus, the aim of this umbrella review is to map criteria used to assess the RoB of *in vitro* studies in the endodontic scope; as well as propose and evaluate a new standardized RoB tool to evaluate *in vitro* studies in endodontic systematic reviews.

2. METHODS

2.1. Selection criteria

The protocol was previously registered in Open Science Framework (OSF) Registries (https://osf.io/azd8u/).The following research question was established: “What tools are used to assess the RoB in SRs of laboratory studies in endodontics?”. The eligible studies for inclusion in this review were systematic reviews with or without meta-analysis, scoping reviews and umbrella reviews focused on endodontics that evaluated the RoB. The publication period was restricted to 2018 and onwards to obtain the most recent publications in the field. As exclusion criteria, narrative reviews or systematic reviews regarding

endocrowns, intraradicular posts, or post cementation protocols were excluded. Five databases were searched (PubMed, Embase, Web of Science, Scopus, and Cochrane Library) and data were independently extracted by two reviewers (RRG and LPA) using an Excel spreadsheet (Microsoft Corporation, Redmond, WA, United States) with parameters agreed upon by all reviewers. Another reviewer (WLOR) double-checked the extracted data.

2.2. Data extraction

The following data from the included studies were tabulated: demographic data such as authors, year of publication, country, journal, number of studies included, study design, category of the study according to the objective, evaluated tests, reported guideline, databases searched, grey literature assessed, protocol register, risk of bias tool with all criteria used to evaluated RoB in in vitro studies and statistical software used.

2.3. Development of RoBEndo tool

Common criteria used to assess RoB was grouped and analyzed to formulate a new tool: RoBEndo, which was developed in 3 phases: *Analysis of all RoB tools, Criteria grouped to assess RoB in endodontics and Creation of RoBEndo tool*. RoBEndo and RoBDEMAT tools were used to evaluate 9 *in vitro* studies by three endodontic specialists to measure inter-rater reliability with Kappa statistics in IBM SPSS Statistics.

3. RESULTS AND DISCUSSION

The electronic search identified 6418 potentially relevant records and 87 SRs were included (Figure 1). All SR assessed the RoB with criteria adapted for other reviews or by adapting existing tools. The Cochrane Collaboration Tools was the tool most cited to assess RoB (19.5%). Fourteen items were selected for the elaboration RoBEndo tool grouped in 5 main domains. Substantial and nearly perfect agreement were found among examiners using the RoBEndo, and moderate and substantial agreement among examiners in the RoBDEMAT. An Excel spreadsheet (Microsoft Corporation, Redmond, WA, United States) was also developed to automatically generate a figure (Figure 2) to analyze the RoB in in vitro studies in endodontics (available in: https://osf.io/azd8u/).

The RoBENDO tool was developed to specifically analyze in vitro studies in endodontics with their particularities. The inter-rater reliability obtained by this tool was higher than the reliability reported for RoBDEMAT tool (Delgado et al., 2022) with substantial and nearly perfect agreement (Table 1). When the risk of bias of the same nine studies used to evaluate RoBEndo was assessed by the RoBDEMAT tool, a moderate and substantial agreement was found. These findings suggest RoBEndo could facilitate RoB assessment of in vitro studies in endodontics. One difficult in the application of the tool is related to the lack of standardization of in vitro studies reports. Therefore, future in vitro endodontic literature should also better describe the parameters included in RoBEndo tool, which could facilitate RoB assessment and improve the quality of in vitro studies in endodontics. Finally, RoBEndo tool requires perpetual reappraisal and, if necessary, modifications. In the future we may further revise the tool considering comments and criticisms that may raise by researchers.

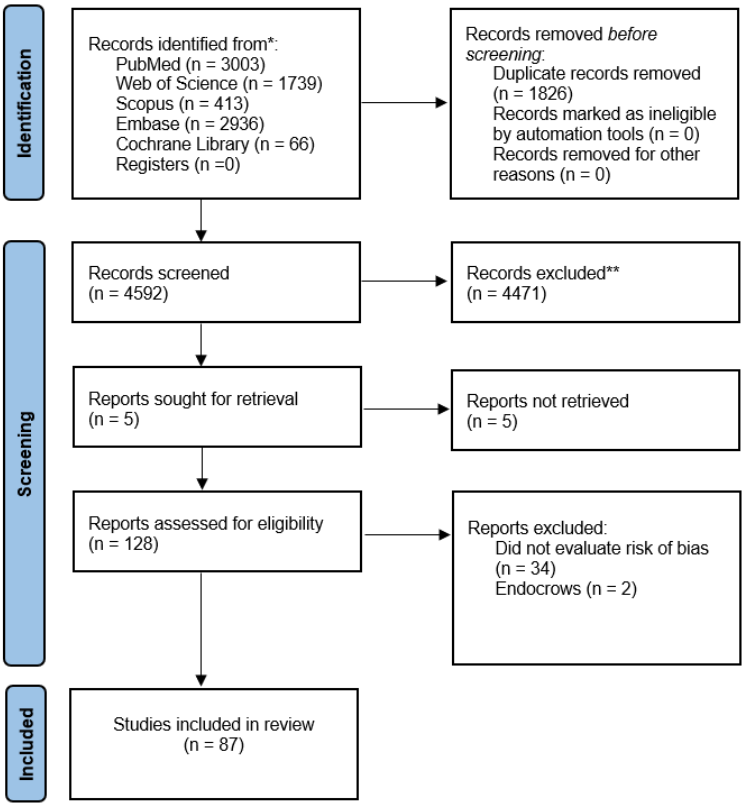

Figure 1. The PRISMA 2020 flow diagram

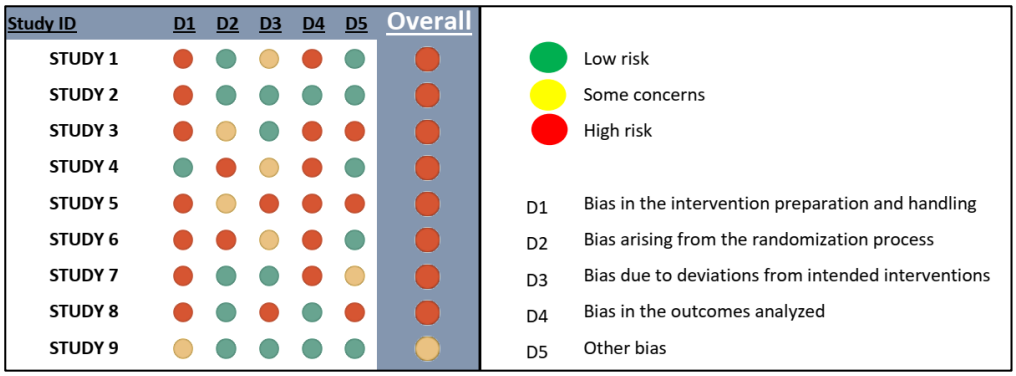

Figure 2. Example of figure generated for analysis of RoB in in vitro studies in endodontics

Table 1. Reliability analysis showing inter-rater reliability test Cohen's k (n=9)

IRR	RoBEndo Cohen's k (SE)	Interpretation	RoBDEMAT Cohen's k (SE)	Interpretation
Examiner 1 and 2	0.74 (0.06)	Substantial	0.54 (0.09)	Moderate
Examiner 1 and 3	0.94 (0.03)	Nearly perfect	0.61 (0.08)	Substantial
Examiner 2 and 3	0.75 (0.06)	Substantial	0.42 (0.10)	Moderate

4. CONCLUSIONS

This umbrella review mapped the criteria used to assess the risk of bias (RoB) of in vitro studies by systematic reviews (SRs) in endodontics. The criteria used to assess RoB were divergent and, in some reviews, inadequate. In this perspective, a new standardized RoB tool was developed, the so called RoBEndo tool, and high agreement between examiners was found. The RoBEndo synthesized common criteria used in recent SRs, and may significantly improve the RoB assessment of in vitro endodontic studies.

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