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SYSTEMATIC REVIEW

# Evaluation of the Clinical Outcomes of Regenerative Endodontic Procedures Using Autologous Platelet Concentrate: A Systematic Review and Meta-Analysis

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**ABSTRACT**

**Objective:** To assess the clinical outcomes of regenerative endodontic procedures using autologous platelet concentrate. Both regeneration and apexification procedures were examined and compared with each other. **Material and Methods:** The PRISMA 2020 Checklist has been utilized to carry out the systematic review and meta-analysis for the present study. PubMed, Scopus, Web of Science, EBSCO, Embase, and ISI Web of Knowledge have been reviewed for systematic literature until May 2023. A fixed-effect model and a Mantel-Haenszel methodology have been used to measure the risk ratio's 95% confidence interval. Then, Meta-analyses were carried out utilizing Stata/MP version 17. **Results:** Duplicate studies were eliminated from the first review, 849 studies' abstracts were reviewed, two authors reviewed 103 papers' full texts, and finally, 20 articles were selected. The survival rate in regenerative endodontic procedures between apexification and regenerative endodontic procedures was -0.01 (RR: -0.01, 95% CI: -0.05, 0.02; p=0.35). **Conclusion:** Throughout the present meta-analysis, regenerative endodontic therapy is an effective intervention with a high survival and success rate in managing immature necrotic permanent teeth.

**Keywords:** Autografts; Regenerative Endodontics; Root Canal Obturation; Thrombosis.

## Introduction

In endodontics, root canal treatment is used to treat inflamed pulp tissue or irreversible necrosis, usually damaged by infectious diseases or trauma [1]. However, there is a possibility of re-infection due to microleakage and increased susceptibility to root fracture. Therefore, the goal of regenerative pulp treatment is to maintain the vitality of dental pulp [2].

Traumatic dental injuries are among the most common reasons for pulp necrosis in permanent teeth; Statistics show that its prevalence is 85% [1]. Reports indicate that over one billion people suffer from trauma worldwide, one-third of which suffer from dental injuries that may cause pulp necrosis [2]. In growing children and adolescents, pulp necrosis caused by caries or trauma can cause permanent tooth roots not to grow [3]. Studies show that immature permanent teeth with necrotic pulp have lower survival. After conventional root canal filling treatment, they are also more susceptible to root fracture [4,5].

Early interventions are essential; however, choosing the right interventions is challenging and time-consuming. Apexification and regeneration are the interventions used to treat these patients [6]. Regeneration has been suggested in short roots with thin canal walls and teeth with no root formation potential or open apex. Apexification is performed for teeth that have almost done root formation with an open apex [3]. Biologically based methods known as regenerative endodontic procedures are generally used to restore damaged components like roots and dentin. The purpose of this method is to restore the pulp tissue and grow the root of the tooth. The basic principles of Apexification and regeneration are canal debridement, necrotic pulp removal, and infection control [7]. The current research's objective is to assess the clinical outcomes of regenerative endodontic procedures using autologous platelet concentrate, and both regeneration and apexification procedures were examined and compared with each other.

## Material and Methods

Search Strategy

PRISMA 2020 Checklist was used throughout the systematic review and meta-analysis presented in this study [8]. PubMed, Science Direct, Scopus, ISI, Embase, and Web of Knowledge have been reviewed till May 2023 using keywords regarding the purpose of the study. The Google Scholar search engine has been utilized to locate additional relevant publications. MeSH keywords:

((((((("Dental Implantation, Endosseous, Endodontic"[Mesh]) AND ("Dental Pulp"[Mesh] OR "Dental Pulp Necrosis"[Mesh])) AND "Survival Rate"[Mesh]) AND "Contraceptive Effectiveness"[Mesh]) AND "Periapical Periodontitis"[Mesh]) AND "Apexification"[Mesh]) AND "Regeneration"[Mesh].

Selection Process, Data Items, and Data Collection

A checklist that contained the name of the authors, publication year, study design, size of the sample, follow-up period, pulp necrosis, intracanal medication, recall time, and intervention type were extracted from the studies. Each article was subjected to the inclusion criteria, and each record underwent independent evaluation by two reviewers.

Eligibility Criteria

Inclusion criteria: as seen in Table 1, inclusion criteria have responded to PICO. English-language articles, observational studies, randomized controlled trials, cohort studies, and research evaluating either or both apexification and regeneration. The following exclusion criteria were established: in-vitro, case studies, review articles, and case reports, as well as animal studies; and articles that do not have full-text access.

**Table 1. PICO strategy.**

| PICO | Description |
|---|---|
| P | Patients with immature necrotic permanent teeth |
| I | Platelet concentrate /regenerative endodontic procedures |
| C | Blood clot/apexification procedure |
| O | Dentinal wall thickness, Root length, Apical foramen width, Vitality response, Success rate, Survival rate |

Study Risk of Bias Assessment

The Cochrane Collaboration's instrument has been utilized to assess the quality of the research in the present analysis, which only comprised randomized control clinical trial works [9]. Each item in this tool is scored between 0 and 6, with the 1 score demonstrating low risk and the 0 score demonstrating high and unclear risk. The higher score indicates a higher quality study.

ROBINS-I tool [10] has been used to assess quality in the Non-randomized control clinical trial works; this scale measures seven domains. Studies with ROBINS-I tool scores of 1-3, 4-6, and 7-9 have been categorized as having high, medium, and low risk of bias in the analysis.

Data Analysis

Data analysis has been carried out utilizing STATA/MP V17 software. The confidence interval of 95% for mean differences has been determined using inverse-variance and the fixed effect model methodology. The risk ratio has been calculated using the fixed effect model and the Mantel-Haenszel methodology. Random effects have been utilized to address potential heterogeneity, and $I^2$ revealed heterogeneity. $I^2$ levels over 50% suggest moderate to high heterogeneity, whereas $I^2$ values under 50% indicate low heterogeneity.

## Results

Study Selection

The first search found 849 research studies regarding the mentioned keywords. There were 15 duplicate studies, 12 articles were eliminated because of ineligibility by the automation instruments, and 18 research were eliminated for other acceptable reasons. Accordingly, we reviewed abstracts of 804 papers, and ultimately, using the exclusion criteria, 701 articles were excluded from the study. After reviewing 85 papers, 20 articles were chosen after 65 articles were eliminated based on inclusion criteria (Figure 1).

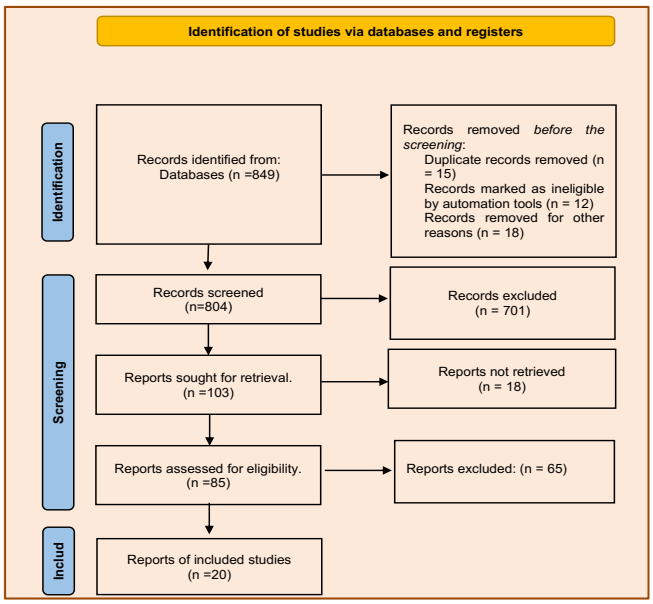


**Figure 1. PRISMA 2020 flow diagram.**

Study Characteristics

Table 2 presents the study data that were extracted. The sample size was 855, the range of recall time was 2 to 4 weeks, and the range of follow-up period was 12 to 36 months.

**Table 2. Data extraction from included articles.**

| No | Study | Study Design | Sample Size | Intervention Type | Presence of Periapical Lesion | Recall Time (Weeks) | Cause of Pulp Necrosis | Follow-up (Months) |
|---|---|---|---|---|---|---|---|---|
| 1 | Li et al. [11] | Non-RCT | 112 | REP *vs.* APP | Yes | 2 | Trauma | 12 |
| 2 | Casey et al. [12] | Non-RCT | 211 | REP *vs.* APP | Yes | 2 | Trauma | 32 |
| 3 | Caleza-Jiménez et al. [13] | Non-RCT | 18 | REP *vs.* APP | Yes | 2 | Trauma, Caries | 25 |
| 4 | Cheng et al. [14] | Non-RCT | 62 | REP | No | 2 | Trauma | 16 |
| 5 | Meschi et al. [15] | RCT | 19 | REP | Yes | 2 | Trauma | 36 |
| 6 | Jayadevan et al. [16] | RCT | 21 | REP | No | 4 | Trauma | 12 |
| 7 | Pereira et al. [17] | Non-RCT | 44 | REP *vs.* APP | No | 4 | Trauma | 16 |
| 8 | Mittal et al. [18] | RCT | 8 | REP | Yes | 4 | Trauma, Caries | 12 |
| 9 | Ulusoy et al. [19] | RCT | 73 | REP | Yes | 4 | Trauma | NR |
| 10 | Ragab et al. [20] | RCT | 22 | REP | Yes | 3 | Trauma | 12 |
| 11 | Xuan et al. [21] | RCT | 30 | REP *vs.* APP | Yes | 4 | Trauma | 12 |
| 12 | Shivashankar et al. [22] | RCT | 39 | REP | No | 3 | Trauma, Caries | 12 |
| 13 | Lin et al. [23] | RCT | 103 | REP *vs.* APP | Yes | 3 | Trauma, Caries | 12 |
| 14 | Alagl et al. [24] | RCT | 30 | REP | Yes | 3 | Trauma, Caries | 12 |
| 15 | Silujjai et al. [25] | Non-RCT | 43 | REP *vs.* APP | Yes | - | Trauma, Caries | 30 |
| 16 | Bezgin et al. [26] | RCT | 20 | REP | Yes | 3 | Trauma, Caries | 18 |
| 17 | Narang et al. [27] | RCT | 20 | REP | Yes | 4 | Trauma, Caries | 18 |
| 18 | Alobaid et al. [28] | Non-RCT | 31 | REP *vs.* APP | Yes | 3 | Trauma | 20 |
| 19 | Jadhav et al. [29] | RCT | 20 | REP | No | - | Trauma, Caries | 12 |
| 20 | Jeeruphan et al. [30] | Non-RCT | 41 | REP *vs.* APP | No | 3 | Trauma, Caries | 24 |

RCT: Randomized Controlled Trial; Non-RCT: Non-Randomized Controlled Trial; REP: Regenerative Endodontic Procedure; APP: Apexification Procedure.

Risk of Bias in Studies

Based on the bias assessment tool, it was determined that all studies had a minimal risk of bias.

Dentinal Wall Thickness

Subgroup meta-analysis showed that the overall risk ratio of dentinal wall thickness in regenerative endodontic procedure between the two groups was -0.16 (RR: 0.16, 95% CI: -0.36, 0.04; p=0.56), having minimal heterogeneity ($I^2$=0%; p =0.74). These findings show that among the two groups, there has been no statistically substantial difference (Figure 2).

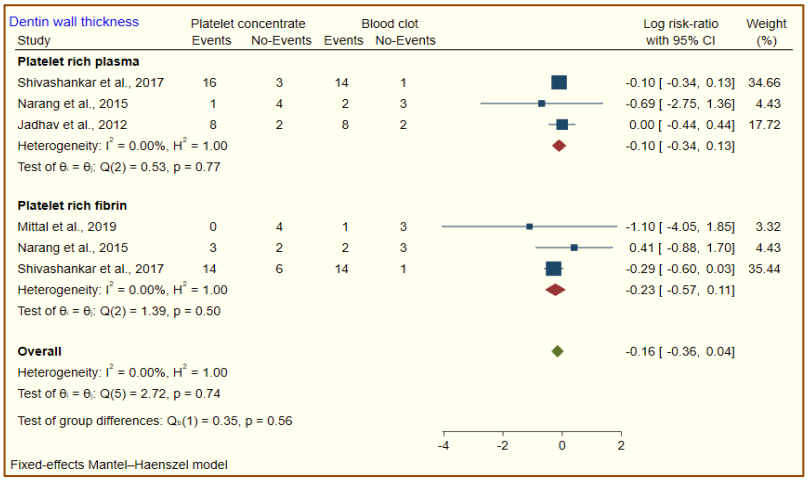


**Figure 2. The dentinal wall thickness in the regenerative endodontic procedure. Platelet concentrate.**

Root Length

Subgroup meta-analysis showed that the overall risk ratio of raised root length throughout regenerative endodontic procedure among the two groups had been -0.02 (RR: -0.02, 95% CI: -0.25, 0.21; p=0.58), having minimal heterogeneity ($I^2$=38.14%; p=0.15). These results show that between the two groups, there has been no statistically substantial difference (Figure 3).

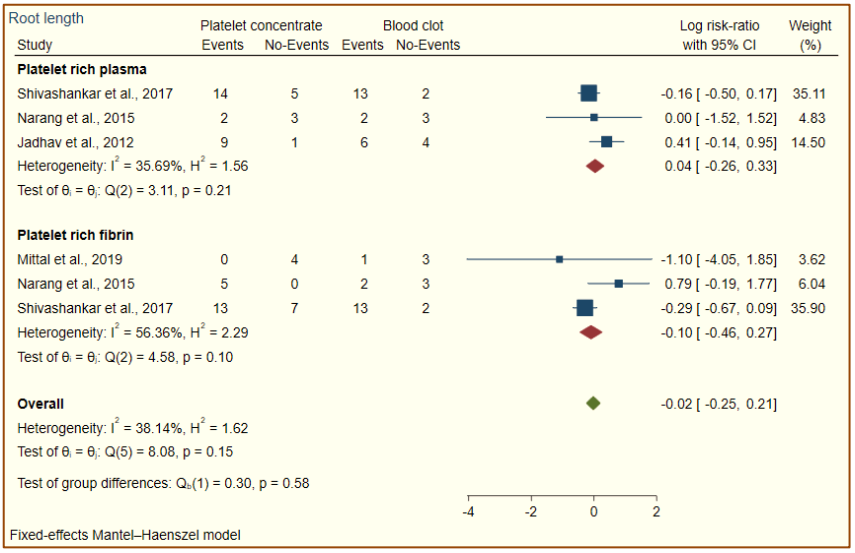


**Figure 3. The increased root length.**

Apical Foramen Width

Subgroup meta-analysis showed that the overall risk ratio of apical foramen width in regenerative endodontic procedure between the two groups was 0.08 (RR: 0.08, 95% CI: -0.06, 0.21; p=0.95), having minimal heterogeneity ($I^2$=26.75%; p=0.19). These results show that among the two groups, there has been no statistically substantial difference (Figure 4).

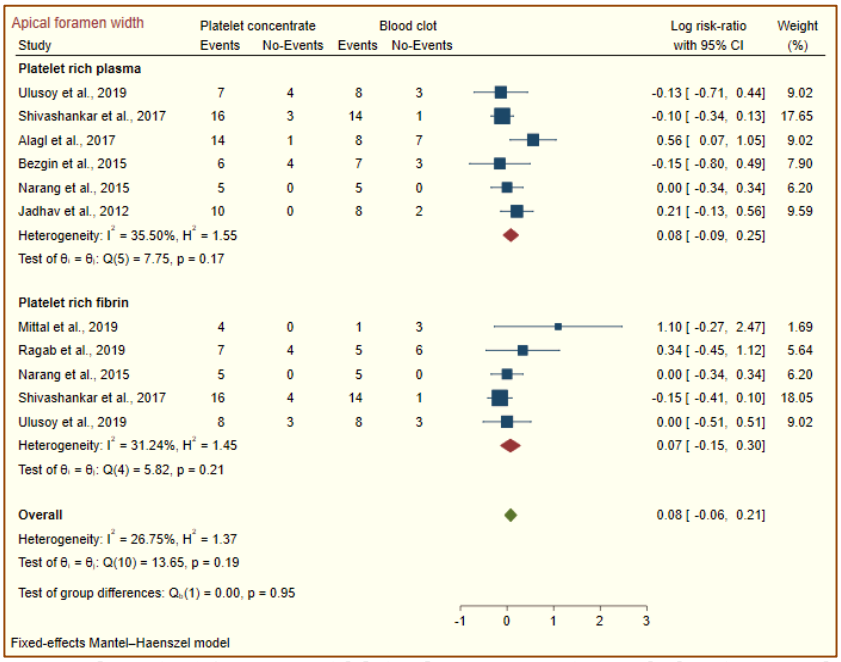


**Figure 4. The apical foramen width in the regenerative endodontic procedure.**

Vitality Response

Subgroup meta-analysis showed vitality response's overall risk ratio in regenerative endodontic procedure between the two groups was 0.70 (RR: 0.70, 95% CI: 0.13, 1.27; p=0.02) having minimal heterogeneity ($I^2$=0%; p=0.77). These results show that among the two groups, there has been no statistically substantial difference (Figure 5).

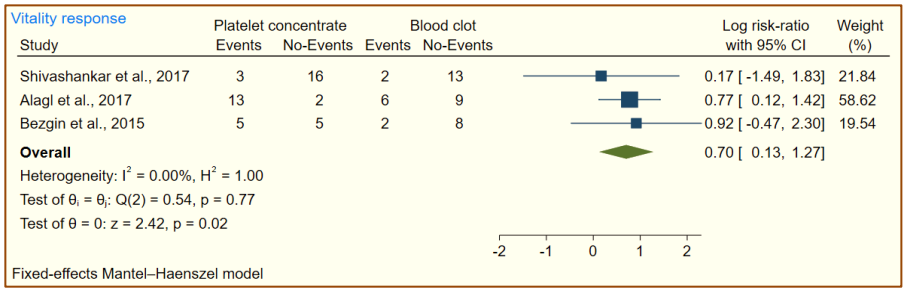


**Figure 5. The vitality response in the regenerative endodontic procedure.**

Success Rate

The regenerative endodontic procedure's success rate between the two groups has been 0.03 (RR: 0.03, 95% CI: -0.06, 0.12; p=0.57), having minimal heterogeneity ($I^2$=0%; p=0.75). These results show that between the two groups, there has been no statistically substantial difference (Figure 6).

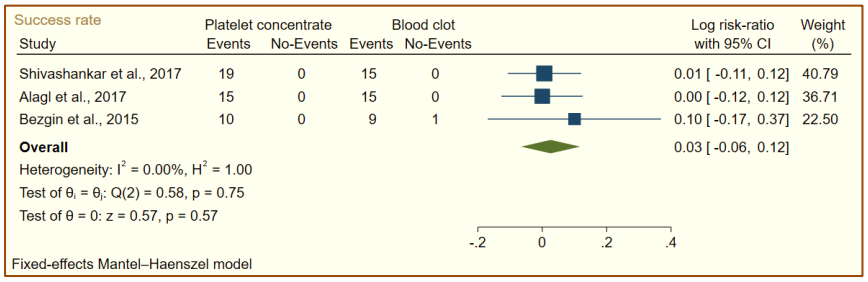


**Figure 6. The success rate.**

Survival Rate

The survival rate in regenerative endodontic procedure between the two groups was -0.01 (RR: -0.01, 95% CI: -0.05, 0.02; p=0.35) with minimal heterogeneity ($I^2$=0%; p=0.62). These results show that between the two groups, there has been no statistically substantial difference (Figure 7).

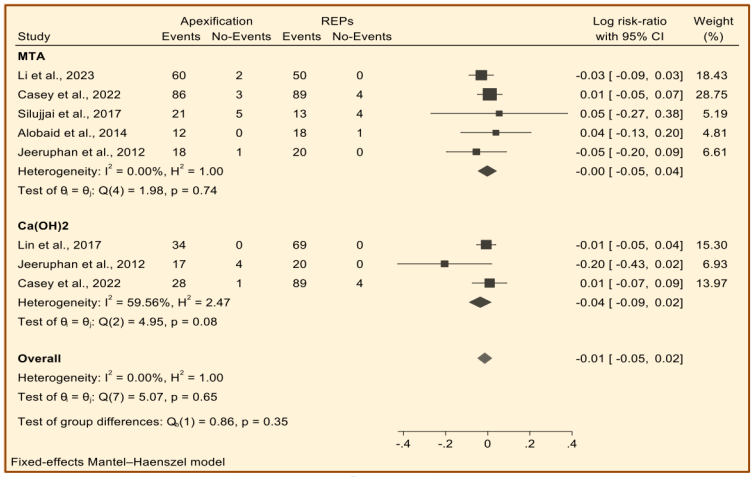


**Figure 7. The survival rate.**

The Success Rate of Regenerative Endodontic Procedure *vs.* Apexification Procedure

The success rate in the regenerative endodontic procedure *vs.* apexification procedure was 0.07 (RR: 0.07, 95% CI: 0.00, 0.14; p=0.05) with minimal heterogeneity ($I^2$=14.53%; p=0.32). These data show no difference between the apexification and regenerative endodontic procedures (Figure 8).

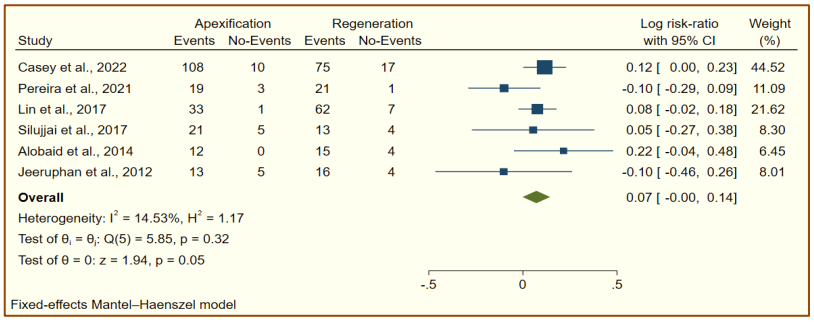


**Figure 8. The forest plot showed the success rate of the regenerative endodontic procedure *vs.* the apexification procedure.**

## Discussion

The present study investigated clinical parameters and immature necrotic teeth' success and survival rate in the oral cavity after regeneration and apexification. The studies' low heterogeneity resulted from the selection of 19 publications that matched the study's inclusion requirements, so the current study's findings provide strong evidence. Also, the studies' quality was high.

Platelet-rich plasma is a method based on tissue engineering that supports the differentiation and proliferation of stem cells. As platelet-rich plasma scaffolds, autologous platelet concentrates, as well as blood clots, have been used [31]. Blood clots are a natural clotting process with many advantages, including low cost, no allergic reaction, and patient comfort. Autologous platelet concentrates are products derived from blood with a concentration higher than the basic level of platelets, which act as a stable scaffold due to the high concentration of growth factors and dense fibrin matrix [32,33]. After the patient's blood is centrifuged, a small amount of platelet-rich plasma is suspended in plasma and plays an essential role in treating damaged tissue [34]. Platelet-rich fibrin is obtained without anticoagulant drugs and biochemical blood manipulation [35].

Based on the selected studies, the teeth selected for intervention were due to trauma and secondary caries. A meta-analysis showed that autologous platelet concentrates significantly improve the response to vital pulp tests. However, no difference was observed between autologous platelet concentrates and blood clots in other clinical parameters. The findings informed the results of Panda et al. 2020 of the current investigation [36]. According to studies, regenerative endodontic therapy thickens canal walls to support fragile, immature, permanent teeth. It can restore the pulp-dentin complex to repair the damaged tissue in the canal area [37,38]. The current meta-analysis revealed that Platelet-rich plasma, compared to Platelet-rich fibrin, has better results throughout endo repair methods. These results require confirmation by additional research using a bigger sample size and an extended follow-up time. According to the outcomes of the meta-analysis, which examined the survival rate between the two regeneration and apexification groups in the $Ca(OH)_2$ and MTA subgroups, it was observed that there had been no significant difference regarding survival.

Moreover, the survival rates in $Ca(OH)_2$ and MTA are similar. $Ca(OH)_2$ is cheap and generally used in clinical procedures [39]. A systematic review study observed that MTA is better than the $Ca(OH)_2$ apposition [40]. According to a systematic review study, whereas pulpal revascularization methods may lengthen and

widen roots, there should be an effort to assess the "true benefit" of root growth using standardized methodologies [41].

## Conclusion

Regenerative endodontic therapy is an effective intervention with a survival and success rate in managing immature necrotic permanent teeth. In general, autologous platelet concentrates and Blood clots showed similar successful results in the regeneration process. As it is noticeable in the findings of this work and other investigations, it is necessary to conduct more studies to provide stronger evidence and confirm the results; a longer follow-up period is also needed.

## Authors' Contributions

| | | |
|---|---|---|
| EM | https://orcid.org/0000-0001-9442-5509 | Methodology, Validation, Writing - Original Draft and Writing - Review and Editing. |
| NN | https://orcid.org/0000-0002-6365-6619 | Data Curation, Writing - Original Draft and Writing - Review and Editing. |
| SJ | https://orcid.org/0000-0003-3803-1235 | Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing - Original Draft and Writing - Review and Editing. |
| AH | https://orcid.org/0009-0001-5982-2362 | Data Curation, Writing - Original Draft and Writing - Review and Editing. |

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

## Financial Support

None.

## Conflict of Interest

The authors declare no conflicts of interest.

## Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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