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Review Article

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The prevalence of apical periodontitis in patients prior to hematopoietic cell transplantation: a systematic review

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No potential conflict of interest relevant to this article was reported.

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ABSTRACT

Objectives: This systematic review addressed the question: "What is the prevalence of apical periodontitis in patients prior to hematopoietic cell transplantation?"
Materials and Methods: A systematic search was conducted in MEDLINE/PubMed, Cochrane Library, Scopus, Web of Science, Embase, and Grey Literature Report. Eligibility criteria were based on the condition, content, and population strategy: the condition was the radiographic prevalence of apical periodontitis, the content comprised patients scheduled for hematopoietic stem cell transplantation, and the population consisted of adult and pediatric patients. The revised Risk of Bias in Nonrandomized Studies of Exposure tool was used to assess the quality of studies. The Grading Recommendations Assessments, Development, and Evaluation (GRADE) tool was used to assess the quality of evidence.
Results: Eight studies were included in this review. The average number of patients with apical periodontitis was 15.65% (range, 2.1%–43.34%). One study was classified as having a very high risk of bias, 1 with a high risk of bias, and 6 with some concern for bias. GRADE analysis showed a very low certainty of evidence. Significant limitations concerning the absence of control over confounding variables were identified.
Conclusions: With the caveat of the very low quality of evidence in the studies reviewed, there was a low to moderate prevalence of apical periodontitis in patients prior to undergoing hematopoietic cell transplantation.

Keywords: Apical periodontitis; Bone marrow transplant; Endodontics; Hematopoietic stem cell transplant; Systematic review

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is one of the most common procedures employed to treat blood disorders, autoimmune diseases, and tumors [1]. Nevertheless, HSCT carries a risk of mortality from both early and late complications. In particular, infections play a pivotal role during the initial posttransplantation phase. Patients who undergo transplantation usually require immunosuppressive therapy for several months and, in certain instances, for a lifetime [2].

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After transplantation, patients may also experience alterations in the oral cavity. During the first year, complications such as hyposalivation, taste disorders, and dentin hypersensitivity may arise, often correlating with a reduced quality of life. In more advanced stages, complications such as sicca syndrome, impaired mastication, malabsorption syndrome, and lichen planus lesions may manifest. Other common occurrences include advanced periodontal disease and rapid caries [3].

For individuals with severe hematological abnormalities, dental treatment is imperative before undergoing HSCT. Procedures such as tooth extractions, restorations, periodontal and endodontic treatments, and prosthetic adjustments should be undertaken first to mitigate postoperative complications (*e.g.*, infection, bleeding, and impaired wound healing) [4].

Apical periodontitis is a highly prevalent infectious disease. It is more common in individuals with a systemic condition (63%) than in a healthy population (48%) and more prevalent in hospital samples (51%) than in the general population (40%). In a previous study, patients with systemic conditions were shown to be twice as likely to have apical periodontitis (8%) than healthy individuals (4%) [5]. Apical periodontitis triggers the host's inflammatory and immunological responses to contain progression of the infection [6,7]. However, immunocompromised patients with an increased susceptibility to infection also have a higher potential risk that the local infection will spread and become a systemic infection [8,9].

Therefore, this current systematic review assessed the available literature to address the question: "What is the prevalence of apical periodontitis in patients prior to hematopoietic cell transplantation?"

MATERIALS AND METHODS

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews database with registration number CRD42022354315. Reporting was conducted in line with Preferred Reporting Items for Systematic Review and Meta-Analysis statements (**Supplementary Table 1**) [10].

Search strategy

Two examiners (L.T.O.L and C.H.T.M) performed independent searches in the electronic databases MEDLINE/PubMed, Cochrane Library, Scopus, Web of Science, Embase, and Grey Literature Report. The database searches were conducted from inception to April 2022, without restrictions on language or year of publication. Based on previous publications on the field, the most cited descriptors were used for the searches, combining medical subject heading (MeSH) terms and text words. The following MeSH and text terms were combined, using the Boolean operators "AND" and "OR" to create the search strategy: "bone marrow transplantation," "transplantation, bone marrow cell," "hematopoietic stem cell transplantation," "endodontic," "oral infection," "apical periodontitis," and "periapical periodontitis." Additional manual searches of the reference lists in selected studies were performed. All selected articles were imported into Mendeley Reference Manager (Mendeley Ltd., London, UK) to catalog the references and facilitate exclusion of duplicates.

Eligibility criteria

Eligibility criteria were selected according to the condition, content, and population (CoCoPoP) strategy, which is recommended for systematic reviews that analyze questions relevant to the prevalence or incidence of a disease [11,12]:

- Condition (Co): prevalence of apical periodontitis as assessed radiographically;
- Context (Co): patients who were going to be treated with HSCT;
- Population (PoP): adult and pediatric patients.

Only observational studies that evaluated the prevalence of apical periodontitis in patients before HSCT were included. Studies investigating endodontic treatment outcomes, studies performed in animals, histological studies, randomized and non-randomized clinical trials, systematic reviews with and without meta-analysis, reviews, letters, opinion articles, conference abstracts, case reports, and case series were excluded.

Selection of the studies

Two authors (L.T.O.L and C.H.T.M) independently selected the included studies. After the database searches, duplicates were identified and removed, and titles and abstracts were screened. A third author was consulted to resolve any discrepancies (M.V.R.S.). Potentially eligible studies then underwent full text assessment using the CoCoPoP criteria.

Data extraction

Two authors (L.T.O.L. and C.H.T.M.) independently extracted the data, which included author(s), year of publication, country, number of participants, patient ages, patients' sex, hematologic diagnoses, method used to diagnose apical periodontitis, prevalence of apical periodontitis, age and sex of patients with apical periodontitis, and main findings. Again, discrepancies were resolved by discussion with a third author (M.V.R.S.). In cases with missing information, the authors were contacted 3 times by email at 1-week intervals.

Qualitative assessment

The risk of bias was assessed independently by 2 authors (L.T.O.L. and C.H.T.M.). The Risk of Bias in Non-randomized Studies - of Exposures (ROBINS-E) tool [13] was used. A third author (M.V.R.S.) was consulted to resolve any discrepancies between reviewers. Since blinded operators and participants could not be utilized in this type of intervention, these factors were not included in the assessment. Thus, the following domains were assessed:

1. Risk of bias due to confounding factors: the risk of bias was considered low when all possible confounding factors (*e.g.,* the participants' age, sex, and dental history) were controlled in the study design or statistical analysis; 'some concerns' for risk when confounding factors were partially controlled; high risk when no possible confounding factors were controlled; and very high risk when possible confounding factors were not even discussed.
2. Risk of bias arising from the measurement of exposure: the risk of bias was considered low when all of the participants had the same exposure level or status; some risk when some participants had different exposure levels but those differences did not seem to affect the outcome; high risk when exposure levels were associated with the outcome; and very high risk when exposure levels were not described.
3. Risk of bias in the selection of study participants: the risk of bias was considered low when all eligible participants were included in the study; some risk when participant selection might have affected the outcome; high risk when participant selection did affect the outcome; and very high risk when the selection process was not described.

4. Risk of bias due to postexposure interventions: the risk of bias was considered low when there were no postexposure interventions that might affect the outcome; some risk when postexposure interventions were not likely to affect the outcome; high risk when postexposure interventions could possibly affect the outcome; very high risk when postexposure interventions were directly related to the outcome.
5. Risk of bias due to missing data: the risk of bias was considered low when the outcome was accurately reported for all participants; some risk when some data were missing, but the missing data were not relevant to the outcome of the study; high risk when some relevant data were missing; and very high risk when several relevant data were missing.
6. Risk of bias arising from measurement of the outcome: the risk of bias was considered low when a valid method was used to assess apical periodontitis for all participants; some risk when a valid method was not used, although the method was well described; high risk when a valid method was not used and not well described; and very high risk when the method used was not described.
7. Risk of bias in selection of the reported result: the risk of bias was considered low when all cases of apical periodontitis were accurately reported; some risk when apical periodontitis was reported, but not described; high risk when the authors did not report the prevalence of apical periodontitis; and very high risk when information about apical periodontitis was missing.

The overall risk of bias for each study was classified as low when there were some concerns in domain 1 (residual confounding) but low risk of bias in all other domains; some risk when there was some risk of bias in at least 1 domain, but no domains were considered high or very high risk; high when at least 1 domain was considered high risk but no domains were at very high risk, or when several domains were at some risk; and very high when at least 1 domain was at very high risk of bias or when several domains were at high risk. Furthermore, a sufficiently high risk of bias in 1 domain could threaten conclusions about whether the exposure had an important effect on the outcome. Two authors individually evaluated the methodological quality of the studies (L.T.O.L. and C.H.T.M.), and a third author was consulted (M.V.R.S.) to resolve any disagreements.

Certainty of evidence

The certainty of evidence in the included studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, available from https://gdt.gradepro.org/app/handbook/handbook.html [14]. The GRADE tool has 5 domains that can be downgraded and reduce the quality of evidence. The following domains were included in this assessment:

1. Risk of bias: looking for design features and study methods that have been shown by empirical evidence to minimize the risk of bias.
2. Inconsistency: determining whether differences underlying the results of the studies are genuine (heterogeneity) or whether the variation in findings is compatible with chance alone (homogeneity).
3. Indirectness: looking for differences between the population of interest and those who have participated in other relevant studies.
4. Imprecision: focusing on the 95% confidence interval around the best estimate of the absolute effect.
5. Other considerations: publication bias, large magnitude of intervention effect, direction of plausible residual confounding, and dose-response gradient.

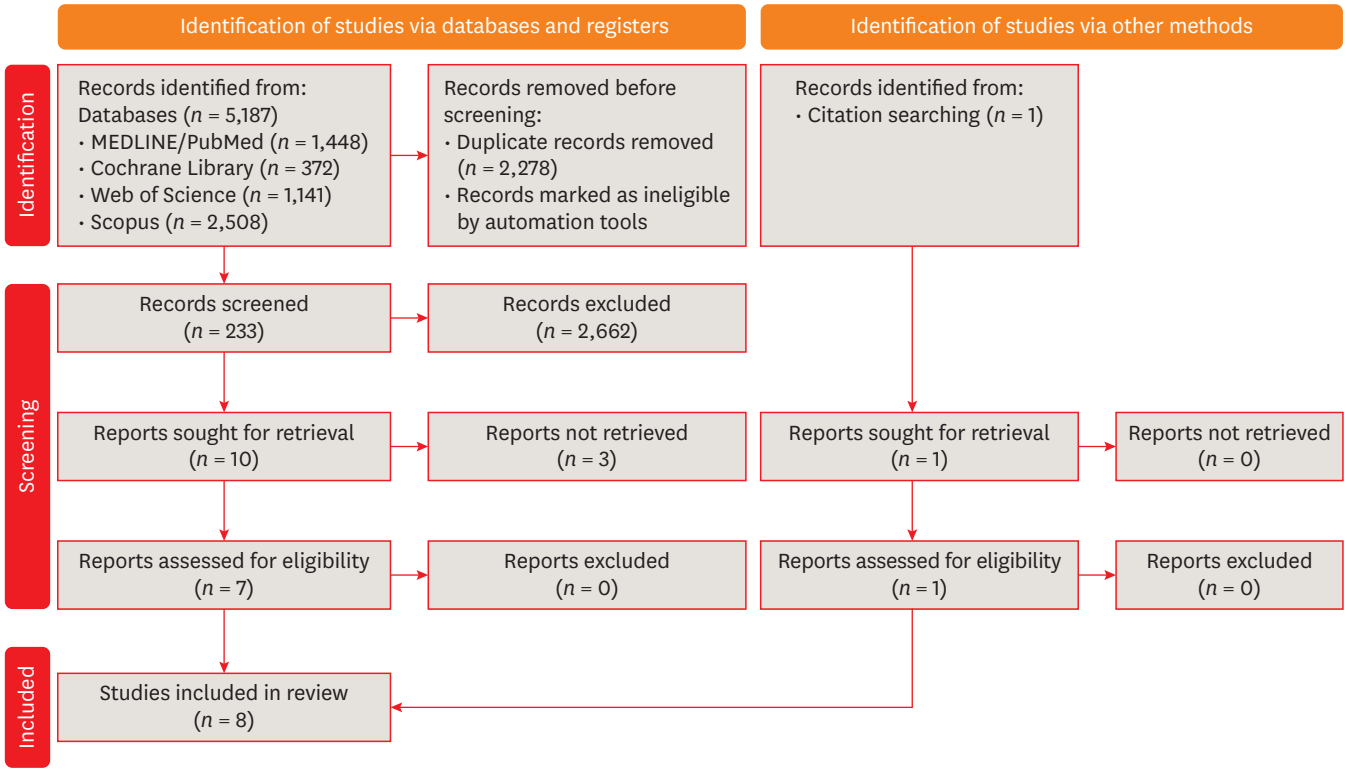

Figure 1. Flow diagram of the systematic literature search according to Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 guidelines.

RESULTS

Study selection

A flow diagram of the search strategy is presented in **Figure 1**. The initial screening of databases resulted in 5,187 studies, of which 2,278 duplicates were excluded. Analysis of the titles and abstracts of the remaining 2,909 eligible papers resulted in 10 studies [15-24] that met the inclusion criteria and were selected for full text reading. Three studies were excluded: 1 case report [16] and 2 studies without a full text available [15,20]. A manual search of reference lists in the retrieved articles produced 1 additional study that met eligibility criteria and was included in this systematic review [25]. As a result, 8 studies were included in the present review [17-19,21-25].

Data extraction

The characteristics and main findings of the included studies are presented in **Table 1**. The authors of studies that contained insufficient data were contacted 3 times by e-mail, but no additional information was obtained.

The number of participants evaluated in each study prior to HSCT ranged from 30 to 350. Participant ages ranged from 2 to 75 years, and 7 studies mentioned the distribution of males (n = 406) and females (n = 329) [17,19,21-25]. Only 1 study reported the age (25–58 years) and sex (15 males, 8 females) of participants presenting with apical periodontitis [18].

Hematologic diagnoses varied among the studies. Acute lymphocytic leukemia was the most frequent diagnosis, followed by non-Hodgkin's lymphoma, acute myeloid leukemia, chronic leukemia, Hodgkin's lymphoma, and other less common diseases.

Table 1. Characteristics and main findings in a sytematic review to assess the prevalence of apical periodontitis prior to HSCT

Authors	Study design	Number of participants evaluated	Age of participants	Sex of participants	Hematologic diagnoses	Diagnostic method used to diagnose apical periodontitis	Number of participants with apical periodontitis	Age of patients with apical periodontitis	Sex of patients with apical periodontitis	Main findings
Elad *et al.* [25]	Retro-spective	Dental evaluation of 46 patients prior to HSCT between 1997 and 1998 (31 allogeneic, 15 autologous)	6 to 63 years (mean 37 years)	25 males, 21 females	Acute myelocytic leukemia 14, non-Hodgkins's lymphoma 9, chronic myelocytic leukemia 9, acute lymphocytic leukemia 6, breast carcinoma 4, multiple myeloma 2, Hodgkin's disease 1, multiple sclerosis 1	• Clinical evaluation. • Radiographic examination (when necessary) (*n* = 27) – bite-wing 45.6%, panoramic 39.1%, single periapical X-ray 30.4%, full mouth periapical X-ray 10.9%	9 patients (19.56%), 22 teeth	NI	NI	Data indicate a dense distribution of dental needs preceding HSCT, which accentuates the vital need for cooperation between hospital dentists and treating physicians.
Hansen *et al.* [17]	Prospec-tive	350 patients prior to HSCT (207 autologous, 143 allogeneic)	8 to 75 years (mean 54 years)	207 males, 143 females	Multiple myeloma 104, non-Hodgkin's lymphoma 99, Hodgkin's lymphoma 28, leukemia 95, other 24	• Digital periapical radiographs and, when necessary, selected digital periapical radiographs.	68 patients (19.4%)	NI	NI	Although there was a high percentage of patients that showed moderate and high risk of odontogenic infection before HSCT (58.6%), only 0.57% of patients developed odontogenic complications.
Peters *et al.* [18]	Retro-spective cohort	Dental charts of 276 adult patients who underwent BMT protocols between 1987 and 1991 (13 autogenous and 10 allogeneic)	NI	NI	Chronic myelogenous leukemia, non-Hodgkin's lymphoma, acute myelogenous leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, and testicular and breast malignant conditions.	• Complete intraoral radiographic survey, panoramic radiograph, and hard and soft tissue examination.	23 patients (8.33%) with 1 endodontically treated tooth presenting PE-PARL >1.5 mm	25 to 58 years (mean age 41 years)	15 males, 8 females	Nontreatment of PE-PARLs did not increase the incidence of infectious complications during BMT (neither increased systemic infection).
Reis *et al.* [19]	Prospec-tive	33 patients dental evaluated pre-allogeneic HCT in 2018	28.4 ± 16.37 years	20 males, 13 females	Fanconi's anemia 2, Sickle cell anemia 7, acute lymphocytic leukemia 7, severe aplastic anemia 3, acute myeloid leukemia 8, chronic myeloid leukemia 1, myelodysplastic syndrome 4, non-Hodgkin's lymphoma 1	• Clinical and periapical radiographic examination	5 patients (15%)	NI	NI	Studied population had important incidence of dental pathologies and infectious conditions that could complicate during HCT.

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When considering the method used to diagnose apical periodontitis, panoramic radiograph was the most frequent type of examination [17,18,21-24]. Two studies used periapical radiographs only, and 3 studies used both panoramic and periapical radiographs [17-24].

Table 1. (Continued) Characteristics and main findings in a sytematic review to assess the prevalence of apical periodontitis prior to HSCT

Authors	Study design	Number of participants evaluated	Age of participants	Sex of participants	Hematologic diagnoses	Diagnostic method used to diagnose apical periodontitis	Number of participants with apical periodontitis	Age of patients with apical periodontitis	Sex of patients with apical periodontitis	Main findings
Sultan *et al.* [21]	Retrospective	Records of 92 patients pre allogeneic HCT from 2007 to 2011	24 to 66 years (mean 48 years)	44 males, 48 females	Acute myeloid leukemia	• Dental radiographs (full mouth series and panoramic), caries charting, pulp vitality testing in teeth with large restorations, and periodontal status assessment	10 patients (10.87%)	NI	NI	Bacteremia with a potential oral source occurred in 12/92 patients (13%); of these, 11/12 (92%) patients developed bacteremia during HCT.
Uutela *et al.* [22]	Prospective cross-sectional study	143 adults allogeneic HSCT recipient patients from 2008 and 2016	21 to 58 years (mean 44.8 years)	70 males, 73 females	Acute lymphoblastic leukemia 29, acute myeloid leukemia 49, chronic lymphocytic leukemia 8, chronic myeloid leukemia 5, myelodysplastic syndrome 10, Hodgkin's lymphoma 3, myeloproliferative neoplasm 8, non-Hodgkin's lymphoma 18, plasma cell dyscrasia 10, other diseases 3	• Panoramic radiograph and DMFT index	1 patient had fistula, 2 patients had symptomatic periapical process (2.1%)	NI	NI	Oral examinations prior to HSCT showed a higher prevalence of oral disorders in HSCT recipients than in healthy controls.
Yamagata *et al.* [23]	Prospective trial	Dental evaluation of 41 patients pre HSCT from 1998 to 2004 (allogeneic or autologous - not specified)	17 to 58 years (mean 41.3 years)	22 males, 19 females	Chronic myeloid leukemia 14, malignant lymphoma 7, acute myeloid leukemia 4, non-Hodgkin's lymphoma 4, myelodysplastic syndrome 4, multiple myeloma 3, acute lymphoblastic leukemia 3, other malignancies 2	• The dental status of all patients was evaluated by clinical and radiographic examination, including panoramic and occasional periapical films for symptomatic teeth.	19 patients (46.34%), 43 teeth	NI	NI	Among 43 teeth with asymptomatic periapical periodontitis before HSCT, only 12 (apical radiolucencies larger than 5 mm) were treated (extraction or endodontic treatment). No conversions to an acute stage or infectious complications occurred in any patient.
Yamagata *et al.* [24]	Retrospective	Dental evaluation of 30 children prior to HSCT from 2000 to 2003 (allogeneic or autologous – not specified)	2 to 18 years	18 boys, 12 girls	Acute lymphocytic leukemia 20, acute myelocytic leukemia 2, other malignancies 8.	• Clinical examination and panoramic and/or dental radiographic evaluations.	2 children (permanent teeth) (6.66%)	NI	NI	As a dental management program was adopted before HSCT, no odontogenic infections occurred during the immunosuppressive period.

ANC, absolute neutrophil count; PE-PARL, postendodontic asymptomatic periapical radiolucency; BMT, bone marrow transplant; HCT, hematopoietic cell transplantation; HSCT, hematopoietic stem cell transplantation; AlloHCT, allogeneic hematopoietic cell transplantation; DMFT, decayed, missing, and filled teeth; NI, not included.

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One study reported that radiographic evaluations were made when necessary [25]; however, the authors did not specify which criteria were used to determine when it was necessary.

The prevalence of apical periodontitis also varied among studies, with the following percentages reported (in ascending order): 2.1%, 6.66%, 8.33%, 10.87%, 15%, 19.4%, 19.56%, and 43.34% [17-19,21-25]. The number of affected teeth in cases of apical periodontitis was considered high in 2 studies [23,25].

Quality assessment

The risk of bias in the included studies is summarized in **Figure 2**. Of the 8 included studies, 6 were classified as having some risk, with 1 domain (risk of bias due to confounding factors) presenting some concern [17-19,21,23,24]. One study was classified as high risk of bias in 2 domains (missing data and measurement of outcomes) [25]. One study was directly classified as having very high risk of bias, since on preliminary considerations, method of measuring outcome was inappropriate [22].

Strength of evidence

The GRADE results are presented in **Table 2**. Overall, a very low quality of evidence was found for the included studies. Based on guidelines for the assessment of certainty of evidence in observational studies, the initial certainty was low [14]. Because the selected studies received a "serious" classification for risk of bias and inconsistency, the overall certainty was downgraded. Imprecision and indirectness were classified as "not serious," and there were no other areas of concern.

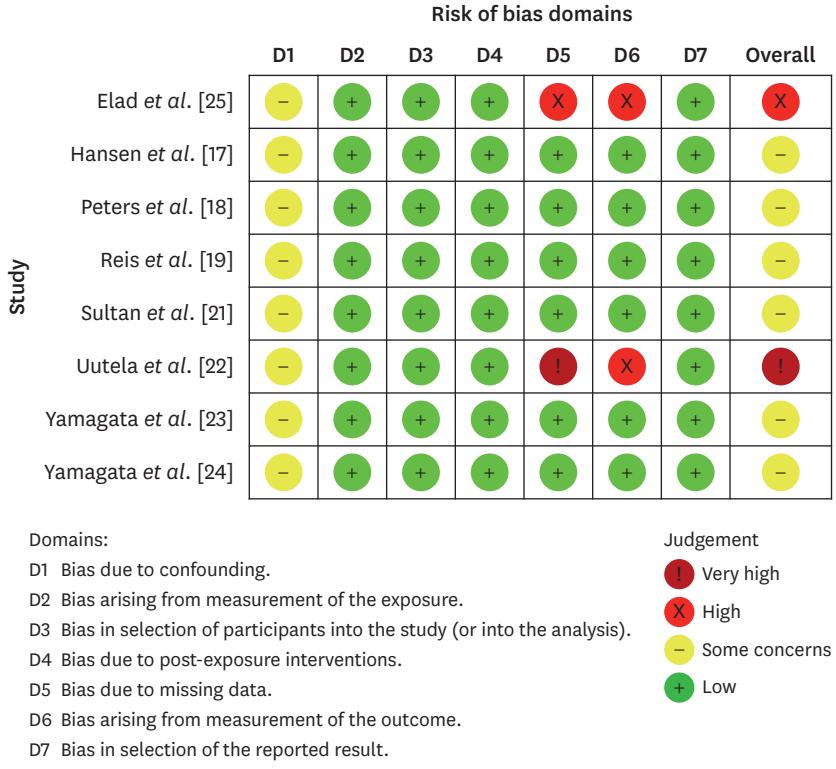

Figure 2. The quality assessment of included studies according to the Cochrane Collaboration common scheme for bias and the Risk of Bias in Non-randomized Studies - of Exposure tool.

Table 2. Quality of evidence assessment for the studies included in a systematic review

Certainty assessment						
Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence
8 Observational studies	Serious[a]	Serious[b]	Not serious	Not serious	None	⨁◯◯◯ Very low

[a]One domain showed 'some concern' for all studies; 2 studies showed high/very high risk of bias.
[b]There was heterogeneity in the results that could not be explained by the information given in the studies.

DISCUSSION

The present systematic review evaluated the existing literature to determine the prevalence of apical periodontitis in patients requiring HSCT and found a varied prevalence. Infections can play a crucial role in patients undergoing HSCT, as transplanted patients require the administration of immunosuppressive drugs for several months or throughout their lives.

Infections occurring in the oral cavity are of particular significance, as they can compromise the outcomes of the established treatment. Specifically, apical periodontitis is directly linked to the host's inflammatory and immunological responses, which help control the progression of infection. Dental clinicians should be aware of the paramount importance of assessing for infection foci in these patients and addressing these infections prior to HSCT.

Among the selected studies, 3 reported a low prevalence of apical periodontitis [17,22,23]. However, certain methodological characteristics might explain these findings. Peters *et al.* [18] reported exclusively on endodontic infections in teeth that had undergone endodontic treatment; Yamagata *et al.* [23] only evaluated patients between 2 and 18 years of age; and Uutela *et al.* [22] did not provide the total number of teeth with apical periodontitis and focused solely on symptomatic cases.

Conversely, 2 studies demonstrated a significantly high prevalence of apical periodontitis [24,25]. Analysis of the number of teeth affected by apical periodontitis showed an average of 3 affected teeth per patient [24,25]. Consequently, the variability in results could potentially be attributed to unreported confounding factors, such as socioeconomic status, dietary habits, access to dental care, oral hygiene practices, and the patient's dental history.

Results of the risk of bias assessment ranged from some concerns of bias to a very high risk of bias. None of the included studies reported or evaluated the participants' dental history. For this reason, in domain 1A (risk of bias due to confounding factors) 'some concern' was attributed to all studies. In addition, 1 study did not perform radiographic examinations with all participants [25]. There were missing data for 19 out of 46 participants. Therefore, a high risk of bias in the domains 'risk of bias due to missing data' and 'risk of bias arising from measurements of outcome' was attributed to this study. One study did not look for apical periodontitis with radiographic examination and only recorded the presence of acute infection [22]. Therefore, it was considered to have used a diagnostic method that did not account for all foci of infection and was classified as a very high risk of bias.

Guidelines for assessing the certainty of evidence in observational studies recommend that the initial certainty be classified as low [14]. Because of the limitations found in the risk of bias assessment for GRADE domain 1, it was classified as serious as the initial certainty of evidence was downgraded in 2 studies [26]. Domain 2 (inconsistency) was classified as serious in the included studies because they presented heterogeneous results

[27]. Domain 3 (indirectness) was classified as not serious since they directly compared the intervention with the population of interest [28]. For domain 4 (imprecision), we followed the recommendations of Murad *et al.* [29]. A single pooled estimate of the effect could not be assessed since a meta-analysis could not be conducted. Therefore, we considered the total number of participants (*i.e.*, the pooled sample size) in the included studies and the confidence interval (CI) of the largest studies [29]. A pooled sample size of < 400 was concerning for imprecision, and the results might be imprecise when the CIs of the largest studies included no effect and no meaningful benefits or harms [29]. Based on these recommendations, domain 4 was classified as not serious. In addition, domain 5 (other considerations) included the assessment of publication bias, which can downgrade the overall certainty of evidence, as well as large effect, plausible confounding, and dose-response gradient, which can upgrade the overall certainty of evidence [30]. None were verified and, therefore, the certainty of the evidence was not downgraded or upgraded. Overall, the GRADE analysis for this systematic review demonstrated a very low certainty of evidence.

As previously noted, the included studies were significantly limited by a risk of bias due to confounding factors (*i.e.*, incomplete or unreported dental history assessments). Thus, despite the prevalence of apical periodontitis in many patients scheduled to undergo HSCT, it remained uncertain whether the need for HSCT directly contributed to the presence of apical periodontitis. Furthermore, because we included all studies with patients who would subsequently undergo HSCT, the hematologic diagnoses and patient ages varied. Future systematic reviews that stratify these variables and correlate them with the presence of apical periodontitis are needed. Another major limitation involved the method employed to detect apical periodontitis. Panoramic radiographs significantly underestimate the occurrence of apical periodontitis when compared to periapical radiographs. Similarly, periapical radiographs underestimate the occurrence when compared to cone beam computed tomography. Additional longitudinal cohort studies employing the more appropriate and sensitive methods for detecting apical periodontitis are necessary to establish a stronger relationship between the presence of apical periodontitis and the need for HSCT.

A meta-analysis was not possible due to methodological differences among the studies (the diagnostic methods for apical periodontitis in particular), which can also be considered a limitation of the present systematic review. Lastly, it is worth noting that this systematic review did not include a control or comparison group, given the inherent difficulty in obtaining a suitable standard comparison group for the conditions under investigation.

CONCLUSIONS

Overall, based on a very low certainty of evidence, this systematic review indicated that patients referred to hospital centers for hematopoietic cell transplantation showed a low to moderate prevalence of apical periodontitis (mean, 15.65%; range, 2.1% to 43.34%). Given the potential for this condition to worsen and progress to an acute stage under immunosuppression, a thorough dental examination is strongly recommended prior to undergoing HSCT.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Search strategy in each database

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