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Review

Prevalence of odontogenic cysts and tumors associated with impacted third molars: A systematic review and meta-analysis

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ABSTRACT

Purpose: This systematic review aimed to investigate the prevalence of odontogenic cysts and tumors associated with impacted third molars (ITM).**Methods:** Only studies that performed histopathological diagnosis of lesions were eligible for inclusion. Five main electronic and three grey literature databases were searched. Risk of bias (RoB) of included articles was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data.**Results:** From 1,300 studies identified, 16 met the inclusion criteria. Seven studies were classified as high, seven as moderate, and two as low RoB. The prevalence of odontogenic cysts and tumors associated with ITM was 5.3% (95%CI: 3.1%–8.1%) of ITM. Odontogenic cysts in particular were found in 4.4% (95%CI: 2.5–6.8%) of the extracted ITM, whilst odontogenic tumors in 0.5% (95%CI: 0.2–0.9%). The dentigerous cyst was mentioned in eleven studies with a pooled prevalence of 2.1% (95%CI: 1.4–3.1%). The odontogenic keratocyst was cited by nine studies and had a prevalence of 0.5% (95%CI: 0.2–0.7%). The radicular cyst was mentioned only in three articles and the pooled prevalence was 4.7% (95%CI: 0.0–19.4%).**Conclusion:** Odontogenic cysts and tumors were found in 5.3% of ITM extracted. The most common lesions were the radicular cyst, dentigerous cyst, and odontogenic keratocyst.

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1. Introduction

Tooth impaction is a frequent dental condition with prevalence rates ranging from 0.8 to 3.6% in the general population (Kaszor-Urbanowicz et al., 2016). Impacted teeth can be classified as entirely or partially unerupted teeth (Shoshani-Dror et al., 2018). The most common impacted teeth are the third molars since they are the last to erupt and usually remain impacted due to the lack of space in the dental arch (Kaszor-Urbanowicz et al., 2016). Partially erupted impacted third molars (ITM) have been associated with

odontogenic infections, such as caries, periodontal diseases, and pericoronitis. Due to difficulties in reaching partially erupted teeth during oral hygiene, dental caries and endodontic illnesses are more frequently observed in comparison to entirely unerupted teeth (Shoshani-Dror et al., 2018). On the other hand, non-inflammatory conditions such as the dentigerous cysts (DC), odontogenic keratocysts (OKC), and ameloblastomas are mostly related to entirely unerupted ITM (Rakprasitkul, 2001).

In the United States, approximately 3 billion dollars are spent yearly on the extraction of third molars (Friedman, 2007). The prophylactic removal of asymptomatic ITM is a commonly performed procedure in oral surgery clinics worldwide (Rafetto, 2015; Alves-Pereira et al., 2017). Reasons for extracting ITM include the risk of developing dental caries, pericoronitis, periodontal defects, crowding, and occurrence of different odontogenic cysts and tumors (Steed, 2014). However, there is a lack of substantial evidence supporting the extraction of asymptomatic

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ITM, especially considering the morbidity and the costs of the procedure. Thus, further investigations on this topic are necessary to aid surgeons in the decision-making process (Adeyemo, 2006; Ghaemini et al., 2016).

The presence of odontogenic cysts and tumors in the third molar region can cause severe consequences, such as pathological mandibular fracture and facial asymmetry (Boffano et al., 2013). Nonetheless, surgical removal of ITM might present complications, which might occur in up to 15% of cases, such as nerve injuries, post-operative infections, and iatrogenic mandibular fractures (Gbotolorun et al., 2007; Agrawal et al., 2014). Therefore, the clinical conduct regarding asymptomatic ITM should weigh the risks of removal and benefits of tooth preservation (Gupta and Ahuja, 2018).

The most frequently reported odontogenic cysts in the third molar region are the DC and the OKC, while the most common odontogenic tumor is the ameloblastoma (Rakprasitkul, 2001). Currently, there is no consensus regarding the prevalence of odontogenic cysts and tumors related to ITM. Furthermore, the knowledge of the prevalence regarding these conditions might be useful for both clinicians and health policymakers, as it could guide evidence-based decisions on the management of these lesions. Thus, the aim of this systematic review (SR) and meta-analysis (MA) was to answer the focused question: “What is the prevalence of odontogenic cysts and tumors associated with ITM?”.

2. Materials and methods

2.1. Protocol and registration

An SR protocol based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) (Shamseer et al., 2015) was developed and registered on the International Prospective Register of Systematic Reviews under the number CRD42018100413 (Booth et al., 2011). Furthermore, the reporting of this SR was based on the PRISMA checklist (Knobloch et al., 2011).

2.2. Eligibility criteria

The acronym PECOS (Population, Exposition, Comparison, Outcomes, Studies) was used to formulate the focused question of this SR: P) individuals with ITM; E) presence of odontogenic cysts and tumors associated with ITM; C) not applicable; O) prevalence of odontogenic cysts and tumors related with ITM; and S) observational studies. There were no restrictions on the time, sex, age, or language of publication. For the purposes of this SR, ITM included both totally and partially unerupted teeth.

The following exclusion criteria were applied: (1) Studies including other impacted teeth or not reporting data on ITM separately; (2) Studies in which the diagnosis was not confirmed by histopathologic analysis; (3) Studies in which the prevalence of odontogenic cysts and tumors was not clearly reported or could not be calculated; (4) Experimental studies, reviews, case reports, protocols, short communications, personal opinions, letters, posters, conference abstracts, and laboratory research; (5) Full text not available.

2.3. Information sources and search strategy

Search strategies were individually developed for five databases: Embase, Latin American and Caribbean Health Sciences (LILACS), PubMed, Scopus, and Web of Science. An additional search of the grey literature was performed on Google Scholar, Open Grey, and ProQuest (Appendix A). All database searches were conducted

on July 3, 2018. Also, the list of references of included articles was manually screened by two reviewers (F.W.M and P.V.K.) for potentially relevant articles. All references were managed and duplicates were removed using a reference manager software (EndNote X7[®], Thomson Reuters, Philadelphia, PA).

2.4. Study selection and data collection

Study selection was performed in a two-phase process. Phase-1 was carried out using a web application specific for SR (Rayyan[®], Qatar Computing Research Institute), in which two reviewers (F.W.M. and P.V.K.) independently applied the eligibility criteria for titles and abstracts of all identified references. In phase-2, the same reviewers separately applied eligibility criteria to the full-text studies. Any disagreement was resolved in a consensus meeting. The data collection was performed by two reviewers (F.W.M. and G.M.) and consisted of study characteristics, population characteristics, histopathological diagnosis, anatomic location, and outcome measures.

2.5. Risk of bias in individual studies

Two authors (F.W.M. and G.M.) independently performed the risk of bias (RoB) assessment of included articles according to the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (Joanna Briggs Institute, 2014). Studies were categorized as “high RoB” when the study reached up to 49% score “yes”; “moderate RoB” when the study reached 50%–69% score “yes”; and “low RoB” when the study reached more than 70% score “yes”.

2.6. Synthesis of results

A method of proportion MA was performed by using the software R Statistics version 3.5.1 (The R Foundation, Vienna, Austria). The metafor package was used, including the arcsine transformation to calculate overall proportions and the Clopper–Pearson interval to calculate confidence intervals for individual studies. Statistical heterogeneity was calculated by using the I² test, and a random effect model was applied.

2.7. Additional analyses

An alternative funnel plot based on transformed proportion data (log[odds]) against a measure of precision (sample size) was used to investigate publication bias (Hunter et al., 2014). The Egger's test for funnel plot asymmetry, using sample size as a predictor, was also conducted.

3. Results

3.1. Studies selection

The initial searches resulted in 1,300 studies, excluding duplicates. In phase-1, sixty-nine articles met the eligibility criteria and were included for full-text assessment. After phase-2, fifty-three studies were excluded due to several reasons (Appendix B). Sixteen studies were included for qualitative and quantitative analyses (Berge, 1996; Güven et al., 2000; Al-Khateeb and Bataineh, 2006; Akarlan and Kocabay, 2009; Planinić et al., 2010; Stathopoulos et al., 2011; Nuraini et al., 2013; Nazir et al., 2014; Patil et al., 2014; Alamgir et al., 2015; Rosa et al., 2015; Vigneswaran and Shilpa, 2015; Camargo et al., 2016; Shahzad et al., 2016; Shin et al., 2016; Gupta and Ahuja, 2018) (Fig. 1).

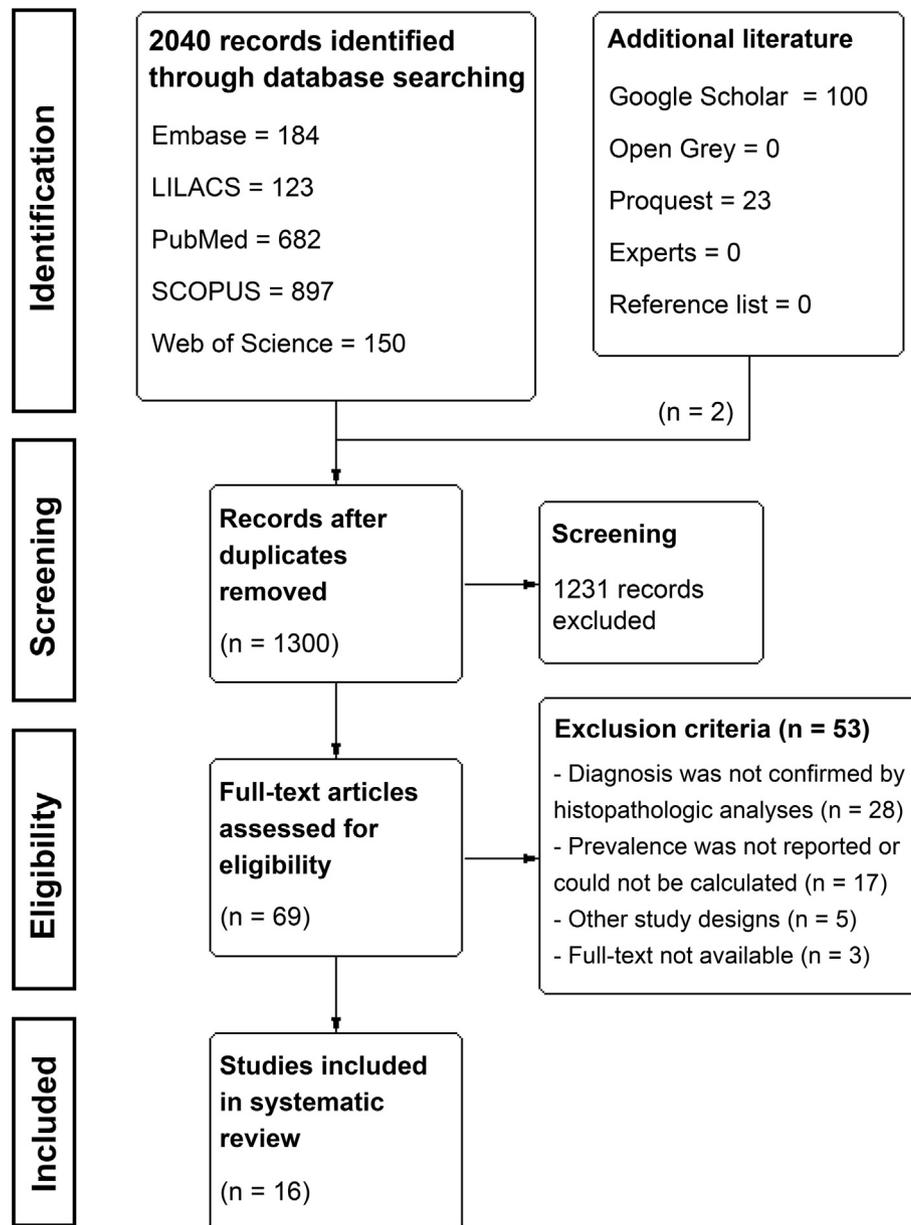


Fig. 1. Flow diagram of literature search and selection criteria*. Legend: *Adapted from PRISMA.

3.2. Study characteristics

In 15 studies the number of individuals was reported as sample size unit (Berge, 1996; Güven et al., 2000; Al-Khateeb and Bataineh, 2006; Akarslan and Kocabay, 2009; Planinić et al., 2010; Stathopoulos et al., 2011; Nuraini et al., 2013; Nazir et al., 2014; Patil et al., 2014; Alamgir et al., 2015; Rosa et al., 2015; Vigneswaran and Shilpa, 2015; Camargo et al., 2016; Shahzad et al., 2016; Shin et al., 2016), ranging from 26 (Camargo et al., 2016) to 40,235 individuals (Nuraini et al., 2013). In 12 studies, sample size unit was reported as the number of ITM (Güven et al., 2000; Al-Khateeb and Bataineh, 2006; Akarslan and Kocabay, 2009; Planinić et al., 2010; Stathopoulos et al., 2011; Nazir et al., 2014; Patil et al., 2014; Alamgir et al., 2015; Camargo et al., 2016; Shahzad et al., 2016; Shin et al., 2016; Gupta and Ahuja, 2018), ranging from 41 (Camargo et al., 2016) to 20,802 ITM (Shin et al., 2016).

Nine studies presented prevalence data of both odontogenic cysts and tumors (Güven et al., 2000; Al-Khateeb and Bataineh,

2006; Akarslan and Kocabay, 2009; Stathopoulos et al., 2011; Nazir et al., 2014; Patil et al., 2014; Alamgir et al., 2015; Shahzad et al., 2016; Shin et al., 2016). Two articles only investigated the prevalence of cysts (Planinić et al., 2010; Rosa et al., 2015), two reported the prevalence of only of DC (Nuraini et al., 2013; Camargo et al., 2016), and one grouped both cysts and tumors and did not report their prevalence separately (Vigneswaran and Shilpa, 2015). Furthermore, one article separated the lesions into cysts, OKC, and ameloblastoma (Berge, 1996); and one study reported the prevalence of DC, OKC, ameloblastoma, and calcifying odontogenic cyst but did not cluster into groups of cyst and tumor (Gupta and Ahuja, 2018) (Appendix C).

3.3. Risk of bias within studies

Two included studies were classified as “low RoB” (Planinić et al., 2010; Alamgir et al., 2015), seven as “moderate RoB” (Al-Khateeb and Bataineh, 2006; Akarslan and Kocabay, 2009;

Stathopoulos et al., 2011; Nuraini et al., 2013; Patil et al., 2014; Rosa et al., 2015; Shin et al., 2016), and seven as “high RoB” (Berge, 1996; Güven et al., 2000; Nazir et al., 2014; Vigneswaran and Shilpa, 2015; Camargo et al., 2016; Shahzad et al., 2016; Gupta and Ahuja, 2018). Significant concerns regarding bias were related to convenience samples and outcome assessment (such as lack of information regarding the calibration of personnel for histopathological diagnosis and diagnostic criteria adopted) (Appendix D).

3.4. Results of individual studies

The total number of individuals included in the analyses was 83832, and the total number of ITM was 50969. This conflicted number can be explained because some studies did not report the number of ITM included in their samples. The total number of odontogenic cysts or tumors associated with ITM in the included studies was 1600. The number of cysts (classification based on the 2017 World Health Organization [WHO] criteria - El-Naggar et al., 2017) included in the sample was 1371, of which 783 were DC, 400 radicular cysts, and 150 OKC. The total number of tumors (classification based on the 2017 WHO criteria - El-Naggar et al., 2017) included in the sample was 186, of which 126 were ameloblastomas, 31 odontomas, and 22 odontogenic myxomas. Also, the majority of lesions reported were associated with mandibular ITM,

ranging from 73.9% (Güven et al., 2000) to 84.9% (Rosa et al., 2015) of the pathologies.

Four included studies (Berge, 1996; Nuraini et al., 2013; Rosa et al., 2015; Vigneswaran and Shilpa, 2015) reported the prevalence of odontogenic cysts and tumors per number of individuals, which ranged from 35.1% (Rosa et al., 2015) to 0.02% (Nuraini et al., 2013). Due to the limit number of studies reporting data in regard to the number of individuals affected, these studies were excluded from the pooled analyses of results.

Four studies (Berge, 1996; Planinic et al., 2010; Nuraini et al., 2013; Shin et al., 2016) presented data in regard to the age of patients affected by odontogenic cysts or tumors associated with ITM. All studies reported that individuals with more than 40 years presented higher frequencies of lesions associated with ITM.

3.5. Synthesis of results

3.5.1. Overall prevalence

The pooled prevalence rate of odontogenic cysts and tumors associated with ITM was 5.3% (95%CI: 3.1%–8.1%) (Fig. 2). Considering odontogenic cysts, the MA showed that the overall prevalence was 4.4% (95%CI: 2.5–6.8%) (Fig. 3). It is worth mentioning that for this MA, OKC was grouped within cystic lesions, as proposed by the most recent WHO criteria (El-Naggar et al., 2017). Furthermore,

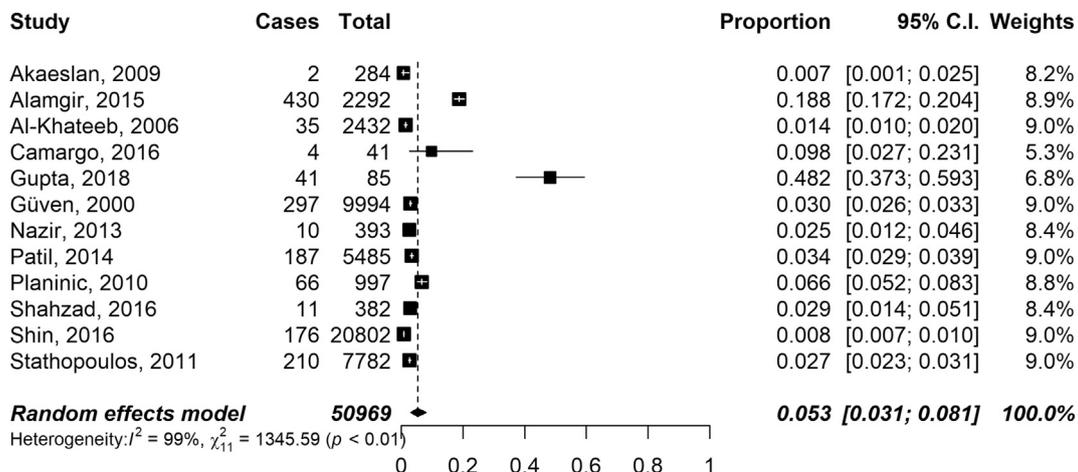


Fig. 2. Forest plot with the pooled prevalence of the odontogenic cysts and tumors associated with ITM.

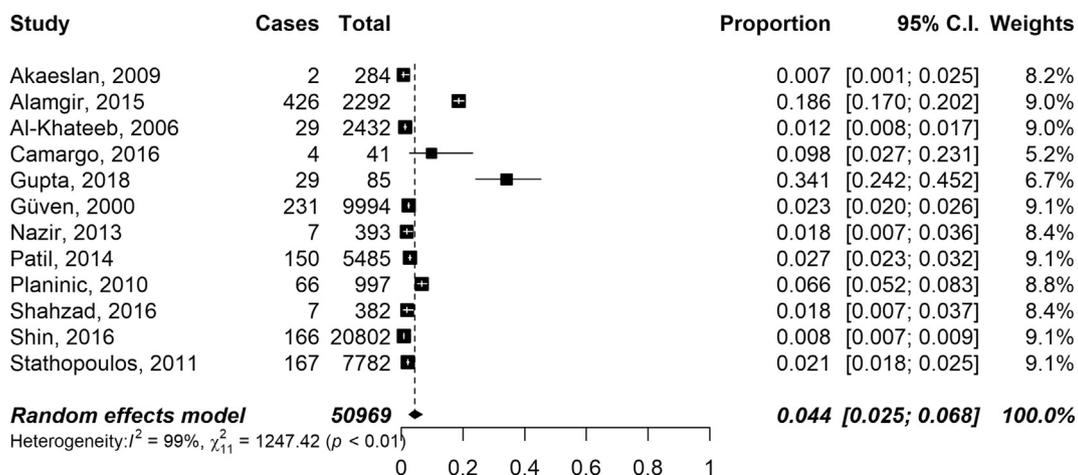


Fig. 3. Forest plot with the pooled prevalence of odontogenic cysts associated with ITM.

pooled data in regard to tumors revealed an overall prevalence rate of 0.5% (95%CI: 0.2–0.9%) (Fig. 4).

3.5.2. Prevalence per pathology

Within cystic lesions, DC was cited by eleven articles and the pooled prevalence was 2.1% (95%CI: 1.4–3.1%). OKC was cited by nine studies and had a prevalence of 0.5% (95%CI: 0.2–0.7%). The radicular cyst was mentioned only in three articles and the pooled prevalence was 4.7% (95%CI: 0.0–19.4%). Furthermore, the COC was cited by two studies and had a prevalence of 0.06% (95%CI: 0.0–4.2%).

In regard to odontogenic tumors, the ameloblastoma was cited by seven articles and had a prevalence of 0.4% (95%CI: 0.2–0.7%). The odontoma was mentioned in three studies and the pooled prevalence was 0.1% (95%CI: 0.1–0.2%). In addition, the odontogenic myxoma was cited by two included studies and had a prevalence of 0.1% (95%CI: 0.1–0.2%) (Appendix E). The statistics regarding the prevalence of other cysts and tumors were not calculated due to an insufficient amount of data in the included studies.

3.5.3. Additional analyses

The funnel plot with regard to the overall MA of ITM is available in Appendix E. The Egger’s test suggested that funnel plot asymmetry was not present (p = 0.1058). Funnel plots regarding other MA were not appropriate due to the limited amount of included studies (Lau et al., 2006).

4. Discussion

Although there are plenty of clinical studies on this topic, conflicting results were often observed, which might explain the lack of consensus among oral surgeons in regard to the prevalence of odontogenic cysts and tumors related with ITM. Pooled data from included studies showed that the prevalence of odontogenic cysts and tumors associated with ITM was approximately 5%. Considering that this SR did not investigate the prevalence of other pathologies (e.g., dental caries, pericoronitis, and periodontal diseases) the total prevalence of pathologies related to ITM might be considerably higher (Stella et al., 2017; Venta et al., 2017; Gloria et al., 2018).

The radicular cyst was the most frequently reported lesion among odontogenic cysts and tumors by a previous SR (Johnson et al., 2014). Similarly, the radicular cyst was the most common lesion associated with ITM in the present SR. It should be emphasized that only three of the 16 included articles presented data about the prevalence of radicular cysts, therefore these results should be interpreted with caution. Although accurate

information was not available in the majority of included studies, it is hypothesized that this finding might be related to partially unerupted ITM. Usually, difficulties in maintaining good oral hygiene in the presence of semi-erupted teeth are associated with increased risk of inflammatory conditions (such as dental caries, pulp necrosis, and recurrent pericoronitis), which could lead to development of chronic inflammation in the apex, leading to the development of radicular cyst (Al-Khateeb and Bataineh, 2006). The paradental cyst is another cyst with inflammatory etiology, which is associated with the crown of a partially erupted ITM, frequently with history of recurrent pericoronitis (Al-Khateeb and Bataineh, 2006). However, in this SR only one included study (Al-Khateeb and Bataineh, 2006) reported the prevalence of the paradental cyst (0.08%) and, therefore, a meta-analysis in regard to this cyst information could not be performed.

Non-inflammatory cysts associated with ITM were considerably less frequent than radicular cysts in this SR. The most commonly reported developmental cyst was the DC, followed by the OKC. The higher proportion of both DC and OKC in comparison to other developmental cysts was predictable since it is well established in the literature that the posterior region of the mandible is the anatomical site most frequently affected by these pathologies (Bilodeau and Collins, 2017). It should be mentioned that, as opposed to semi-erupted teeth, completely unerupted ITM are associated with developmental odontogenic cysts, since no inflammatory etiology is present.

Odontogenic tumors associated with ITM were overall 8.8 times less frequent compared to odontogenic cysts. It is worth mentioning that OKC was reclassified as an odontogenic cyst according to the 2017 WHO criteria (El-Naggar et al., 2017), which might have contributed to these results. Also, the most common odontogenic tumor in this SR was the ameloblastoma. Although information regarding the classification of ameloblastoma was not available in the included studies, the proportion of unicystic ameloblastomas associated with impacted teeth (52–100%) is considerably higher than solid ameloblastomas (15–40%) (Philipsen and Reichart, 1998). Radiographically, unicystic ameloblastomas, OKC, and DC often present similar characteristics. However, both OKC and ameloblastoma can present recurrences after surgical treatment (McClary et al., 2016; Karaca et al., 2018). Therefore, the histopathological examination of pericoronal tissues associated with extracted ITM is highly recommended.

It is important to emphasize that studies investigating ITM with normal radiographic follicular space were not included in this SR. This decision was made due to a possible bias related to the misdiagnosis of DC in these studies. Some researchers claim that a radiographically normal dental follicle may present cystic changes

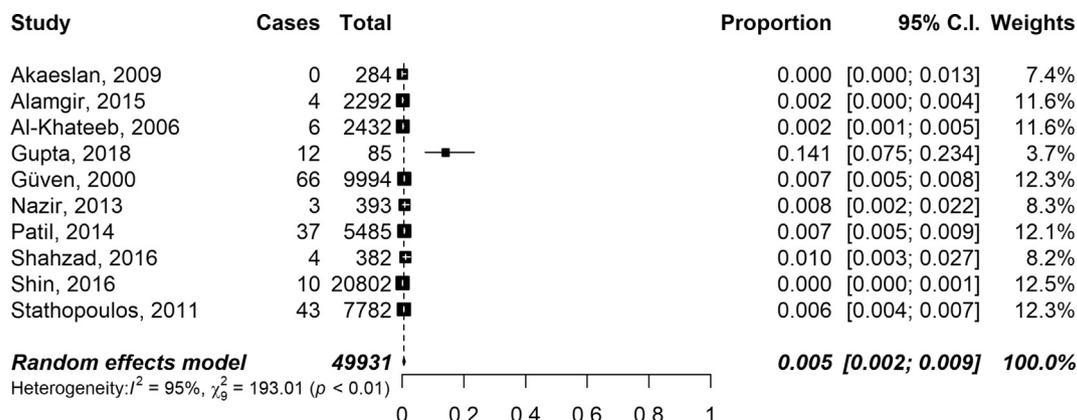


Fig. 4. Forest plot with the pooled prevalence of the tumors associated with ITM.

on histopathological analysis (Glosser and Campbell, 1999). On the other hand, others propose that radiographic changes are necessary to confirm the diagnosis of odontogenic cysts, since normal follicular tissue and DC in early stages of development can present similar histopathological characteristics (Al-Khateeb and Bataineh, 2006). The criteria for the definition of a normal follicular space are not well established in literature, although there is some agreement regarding the radiographic appearance of pathology as a pericoronal space larger than 2.5 mm (Eliasson et al., 1989). Therefore, it is worth emphasizing that the definitive diagnosis of odontogenic cysts and tumors can only be confirmed by the correlation of clinical, radiographic, and histopathological analyses.

Since inflammatory odontogenic cysts were considerably more prevalent, the surgical extraction of partially unerupted ITM, especially in cases with poor oral health and recurrent pericoronitis, might be recommended. Considering completely unerupted ITM, however, the risks involved in the surgical procedure (e.g., paresthesia, hemorrhage, dry socket, and periodontal damage) should be taken into account, as the prevalence of non-inflammatory cysts and tumors were considerably lower compared to inflammatory odontogenic cysts (Friedman, 2007; Azenha et al., 2014; Huang et al., 2014). In addition, although only four studies reported data on the age of individuals, the frequency of cysts and tumors associated with ITM was higher in individuals more than 40 years of age. This could suggest that the early removal of ITM may reduce the prevalence of lesions associated with these teeth. However, further high-quality prospective studies are needed for a more definitive conclusion on this topic.

5. Conclusion

In conclusion, within the limitations of this SR and MA, the overall prevalence of odontogenic cysts and tumors associated with ITM was 5.3% (95%CI: 3.1%–8.1%). The most frequent lesions were the radicular cyst, DC, OKC, and ameloblastoma.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcms.2019.03.026>.

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