Original Article

Expression of Matrix Metalloproteinases in Ameloblastomas and Ameloblastic Carcinoma: Systematic Review and Meta-analysis

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Abstract

Objective: This study aimed to examine the difference in expression of matrix metalloproteinases (MMPs) in ameloblastoma and other benign tumors or normal tissue of the jaw, and ameloblastic carcinoma, and to investigate the correlation of expression of MMPs with patient prognosis.

Methods: Studies were identified in the major electronic databases (Medline, EMBASE and Cochrane Library) using the keywords "matrix metalloproteinases" and "ameloblastoma" OR "ameloblastic carcinoma", and a quantitative meta-analysis was conducted.

Results: Fourteen studies were included in this systematic review. Twelve studies representing a total number of 471 cases qualified for the meta-analysis. The analysis revealed a higher MMP-2 expression in ameloblastoma than in the other benign odontogenic tumors, showing a significant inter-group difference (odds ratio [OR]: 5.33; 95% confidence interval (CI): [1.36, 25.62]; p = 0.02). A lower MMP-2 expression was found for the ameloblastoma than in the ameloblastic carcinoma, with a non-significant inter-group difference (OR: 0.12; 95% CI: [0.01, 1.02]; p = 0.05). Finally, a lower MMP-9 expression was found for the follicular subgroup compared to that in other subgroups of ameloblastoma, showing a significant inter-group difference (OR: 0.15; 95% CI: [0.05, 0.48]; p = 0.001).

Conclusions: We found that MMP-2 expression in ameloblastoma is higher than that in other benign tumors or normal tissue of jaw, and that MMP-9 expression in the follicular subgroup of ameloblastoma is lower than that in other pathology subgroups of ameloblastoma. What is more important, the MMPs expression in ameloblastoma was found to be significantly correlated with many clinicopathologic features of ameloblastoma. However, some limitations weakened the power of this meta-analysis.

Keywords: Ameloblastoma; Ameloblastic carcinoma; MMPs; Immunohistochemistry; Meta-analysis.

Abbreviations: AB, ameloblastoma; AC, ameloblastic carcinoma; CI, confidence interval; ECM, extracellular matrix; MMP, matrix metalloproteinase; NOS, Newcastle-Ottawa Scale; OR, odds ratio; TSA, trial sequential analysis.

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Introduction

Ameloblastoma (AB) is the second most common odontogenic tumor, known to be slow-growing, persistent, and locally aggressive. AB is estimated to account for 11% of all odontogenic tumors on a global scale.[1–4] The World Health Organization has defined AB as a benign odontogenic tumor formed by odontogenic epithelium with fibrous mature stroma but without odontogenic ectomesenchyme.[5] AB cells usually invade into the cancellous bone beyond the tumor margin.[6,7] The operation of performing a radical resection 1–2 cm from the tumor margin is recommended to prevent recurrences.

Although significant advancements have been made in diagnos-

tics and treatment strategies, only modest progress has been made in improving the rates of radical operation in patients with ABs or ameloblastic carcinoma (AC) over the last 20 years.[8,9] ABs are locally destructive aggressive benign tumors. Although this tumor rarely metastasizes, the operative treatment of ABs usually results in maxillofacial deformities. New research has shown, however, that molecular targeted therapy may be useful for treating aggressive and recurrent cases.[10] Promising markers remain the basis for detection and for accurate survival evaluation of ABs or AC patients.

Matrix metalloproteinases (MMPs), a family of zinc- and calcium-dependent proteolytic enzymes,[11–13] mediate extracellular matrix (ECM) breakdown. MMPs play a vital role in AB invasion and metastasis, since they are involved in degradation of the ECM.[11] The degradation of ECM itself is a prerequisite for cell migration into the matrix and represents a key element in the multistage processes of tumor invasion and metastasis.[14–17] Aberrant MMP activity in tumor cells and the surrounding stromal tissues has been implicated in tumor invasion and metastasis.[18,19]

At present, up-regulated expression of MMPs is associated with tumor invasion and poor prognosis in various kinds of tumors, including AB and AC. In addition, a multitude of existing research studies have investigated the observed over-expression of MMPs in AB and AC.[3,20–23] However, some studies have found that the expression of MMPs in AB or AC was not significantly high, and was even low.[24–26] What is worse, most of studies published in the literature are not only small size and heterogeneous but also generally ambivalent in their results.

Thus, identification of prognostic values of the MMPs in ABs is of considerable importance to determine the most appropriate therapeutic approach and establish the prognosis of afflicted patients. In respect to this, we designed a systematic review and meta-analysis to systematically estimate the expression and prognostic value of MMPs in AB and AC. The specific aims of this study were to 1) compare the difference in MMPs' expression between AB and other benign tumors or normal tissue of jaw, AB and AC, 2) compare the difference in MMPs' expression among each pathological subtype of AB, and 3) determine the correlation of expression of MMPs and patient prognosis.

Materials and methods

Inclusion criteria

Studies were included if they met all the following inclusion criteria: patients diagnosed with ABs or AC; reported outcome measures having included the expression of MMPs; and summary data being available for the outcomes of interest.

Literature search

Cochrane Library (until September 2015), Medline (until September 2015) and EMBASE (until September 2015) were used to search for original articles analyzing the expression of MMPs in ABs or AC. Each database was searched with the following search terms as keywords: ("matrix metalloproteinases" OR "matrix metalloproteinases" OR "matrix metalloproteinase" OR "MMPs") AND ("ameloblastoma" OR "adamantoma" OR "adamantoblastoma" OR "classic intraosseous ameloblastoma" OR "ameloblastic carcinoma"). Reference lists within the retrieved articles were used as secondary reference sources. If multiple publications from a particular research group reported data from overlapping samples, the study reporting the largest dataset was included.

Exclusion criteria

Research published in languages other than English were excluded. Research studies which did not provide sufficient information on the expression of MMPs were also excluded. Studies did not use immunohistochemistry to assess the expression of MMPs.

Quality assessment

The quality of all the included studies was independently assessed by two of the investigators (Lu and Cao), based on the recommendations from the Newcastle-Ottawa Scale (NOS). The NOS ranged from 0 to 9 stars, with more stars indicating a better quality. The NOS system categorizes studies using three dimensions (selection of cohort, comparability of cohort, and ascertainment of outcome), with each dimension being assessed by eight items. Any inconsistency between the two investigators was solved by discussion with the other authors.

Data extraction

The key information of all the included studies was independently extracted by two investigators (Zhou and Ye). Any disagreements were resolved by discussion. The following data were extracted from each eligible study: first author, publication year, trial site, participants, interventions, controls, outcomes, study design (PICOS), and other relevant information.

Statistical analysis

Data analysis was performed with RevMan 5.3 (Cochrane Collaborative, Oxford, England). The odds ratio (OR) with corresponding 95% confidence interval (CI) was calculated to compare dichotomous outcomes. The inconsistency index *I*-squared was used to estimate the variation caused by heterogeneity. When p was > 0.10 and I^2 was $\leq 25\%$, the fixed-effect model was used, indicating that inter-study heterogeneity was not significant. Otherwise, a random effect model was performed. Subgroup analyses were conducted if there was a significant statistical heterogeneity ($I^2 > 50\%$). Subgroup analyses and sensitivity analyses were performed to assess inter-group differences with respect to primary outcomes.

Trial sequential analysis (TSA)

As is known, systematic reviews and meta-analyses are considered to provide the best available evidence if all eligible trials are included. However, 'the best available evidence' might not be equal to 'sufficient evidence'. To resolve this question, we applied the TSA to estimate the robustness of conclusions.[27] We calculated the required power to collect adequate information and evaluate how many subjects would be necessary to make these robust conclusions. The required power was based on the assumption of a plausible relative risk of 10% with low risk bias, and we adopted the risks for a type I error (a) of 5%, a type II error (b) of 20%. TSA monitoring boundary crossing the Z-curve before the required

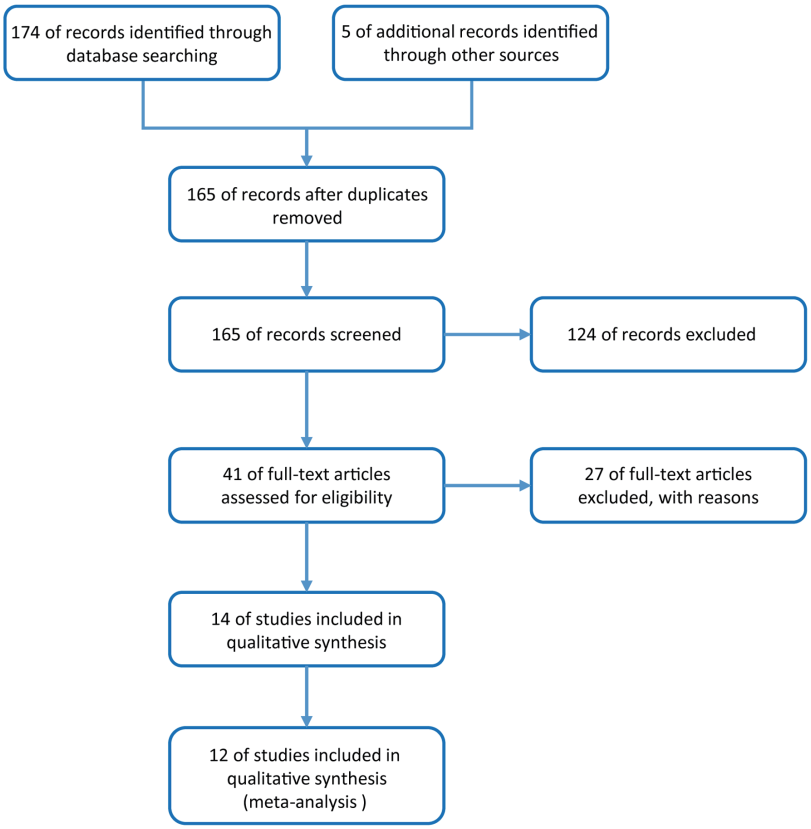

Fig. 1. Flow diagram of the literature search.

power is reached is indicative of a robust verdict, with further research being unnecessary. Otherwise, it is necessary to continue performing more research.

Results

Search findings

This systematic review identified 179 articles including 174 articles from Medline, EMBASE and Cochrane Library, and 5 articles from the reference lists of articles obtained. After deleting the duplications, 165 papers were left. At total of 124 articles were excluded after reviewing the titles and abstracts, and determining irrelevance to AB, AC, or expression of MMPs. The remaining 41 articles were further assessed for eligibility and another 27 articles were eventually excluded. Figure 1 shows the flowchart of studies retrieved and excluded and lists the reasons for their exclusion. Ultimately, 14 studies[2,3,11,20,21,24–26,28–33] were included in this systematic review and 12 studies[2,3,11,20,21,24–26,28–31] representing a total number of 471 cases were eligible for inclusion in the meta-analysis.

Methodological quality of the included studies

The studies by Anne *et al*.,[2] Henriques *et al*.,[24] Ribeiro *et al*.,[25] Nunia *et al*.,[3] and Fregnani *et al*.[31] were identified as being of a higher design quality. The studies by Sah *et al*.,[20] Florescu *et al*.,[28] Kumamoto *et al*.,[11] Souza-Freitas *et al*.,[29] Zhang *et al*.,[30] and Yoon *et al*.[21] were identified as being of a lower design quality because neither the descriptions of case definition nor of outcome assessment were inadequate. The quality of the study by Khalifa *et al*.[26] was the lowest. In addition, the agreement between the two assessors (Lu and Ren) about the quality of these five included studies was high, although there was still a slice of controversy. A third assessor (Wang) was asked to review the study, in case of any controversy in the assessment of the quality of the studies. Please see the data listed in Table 1.[2,3,11,20,21,24–26,28–33] There was no significant publication bias in the nine studies included in the meta-analysis (Fig. 2).

Methodology assessment of MMPs expression

The detection method of MMPs was immunohistochemistry in all included studies, and all provided immunohistochemistry staining figures.

Meta-analysis

MMP-2 in AB or AC

In this meta-analysis, there were four studies that provided data of expression of MMP-2. Therefore, we directly utilized them. There were another two studies from which the expression of MMP-2 could not be calculated according to the data provided by the re-

Table 1. Characteristics of the included studies

Author	Year	Country	Size of study	Tumor locations	MMPs	Cut-off value	Contral	NOS
Nunia *et al.*[3]	2016	India	36	Mandible	MMP9	IHC score ≥ 3	Normal tooth germ	8
Anne *et al.*[2]	2014	Indonesia	40	Mandible	MMP9	IHC score ≥ 1	/	7
Sah *et al.*[20]	2013	India	18	Maxilla and mandible	MMP2, MMP9	IHC score ≥ 3	/	6
Florescu *et al.*[28]	2012	Romania	17	Maxilla and mandible	MMP9	IHC score ≥ 1	/	6
Henriques *et al.*[24]	2011	Brazil	80	/	MMP9	50% stained cells	Dentigerous cysts; radicular cysts; keratocystic odontogenic tumors	7
Yoon *et al.*[21]	2011	South Korea	17	Maxilla and mandible	MMP2, MMP9	IHC score ≥ 1	ameloblastic carcinoma	7
Khalifa *et al.*[26]	2010	Egypt	26	Maxilla and mandible	MMP2	/	Keratocyst odontogenic tumor; radicular cysts	5
Siqueira *et al.*[32]	2010	Brazil	17	/	MMP1, MMP2, MMP9	/	Calcifyingcystic odontogenic tumour	6
Fregnani *et al.*[31]	2009	Brazil	57	Maxilla and mandible	MMP2	50% of positive cells	Ameloblastoma	8
Ribeiro *et al.*[25]	2009	Brazil	30	/	MMP1, MMP2, MMP9	10% of positive tumor cells	Adenomatoid odontogenic tumors	7
Souza-Freitas *et al.*[29]	2009	Brazil	30	/	MMP7, MMP26	Median value	Adenomatoid odontogenic tumors	6
Zhang *et al.*[30]	2009	China	91	/	MMP2	IHC score ≥ 2	Keratocystic odontogenic tumor; ameloblastic carcinoma	6
Pinheiro *et al.*[33]	2004	Brazil	12	/	MMP1, MMP2, MMP9	/	/	5
Kumamoto *et al.*[11]	2003	Japan	29	/	MMP1, MMP2, MMP9	(+) positive	Tooth germ	6

Abbreviations: MMP, Matrixmetalloproteinase; IHC, immunohistochemistry; NOS, Newcastle-Ottawa Scale. (/ means information could not obtained from the article).

searchers. There was insignificant heterogeneity among each study (I^2 = 44%, p = 0.15). Therefore, a random effect model was applied. Meta-analysis of these four studies revealed a higher MMP-2 expression in the AB group as compared to that in the other benign odontogenic tumors group, with a significant inter-group difference (OR: 5.33; 95% CI: [1.36, 25.62]; p = 0.02; four trials, 170 participants) as shown in Figure 3a.

There were two studies that provided the data of expression of MMP-2 both in AB and AC. There was insignificant heterogeneity between each study (I^2 = 25%, p = 0.25). Therefore, a fixed effect model was applied. Meta-analysis of these two studies revealed a lower MMP-2 expression in the AB group as compared to that in the AC group, with a non-significant inter-group difference (OR: 0.12; 95% CI: [0.01, 1.02]; p = 0.05; two trials, 92 participants) as shown in Figure 3b.

MMP-9 in AB and the pathology subgroups of AB

There were four studies that provided data for the expression of MMP-9. Therefore, we directly utilized them. There were another two studies from which the expression of MMP-9 could not be calculated according to the data provided by the researchers. There was significant heterogeneity in this meta-analysis (I^2 = 51%, p = 0.11). Therefore, a random effect model was applied. Meta-analysis of these four studies revealed that there was an insignificant inter-group difference between the AB group and the other benign odontogenic tumors group (OR: 0.86; 95% CI: [0.17, 4.47]; p = 0.86; four trials, 175 participants) as shown in Figure 4a.

Most articles were rarely able to provide the data of MMPs' expression in the pathological subgroups of AB. In this meta-analysis, there were only three studies that provided information for MMP-9 in each of the pathological subgroups of AB. Therefore, we directly utilized them. There was insignificant heterogeneity between these three studies (I^2 = 0%, p = 0.48). Therefore, a fixed effect model was applied. Meta-analysis of these three studies revealed a lower MMP-9 expression in the follicular subgroup as compared to that in the other subgroups of the AB group, with a significant inter-group difference (OR: 0.15; 95% CI: [0.05, 0.48]; p = 0.001; two trials, 77 participants) as shown

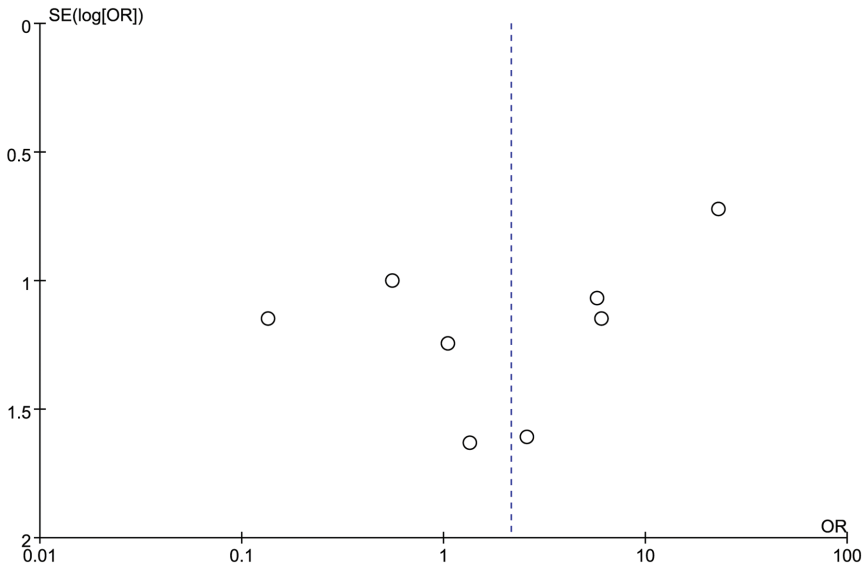

Fig. 2. Funnel plot of publication bias in this study.

in Figure 4b.

Other MMPs in AB

Most of these included studies provided data for MMP-2 and MMP-9. The data of MMP-2 and MMP-9 used in our meta-analysis are presented in Figure 4c. Systematic review of the literature identified four formal papers that discussed the expression of MMP-1 in AB and one paper that discussed the expression of MMP-7 and MMP-26 in AB. In a retrospective review of 12 cases of AB, Pinheiro *et al*.[33] reported MMP-1 located in both tumor cells and stromal cells. In a similar study, Siqueira *et al*.[32] reported MMP-1 was not significantly different in AB compared with the calcifying cystic odontogenic tumor. In the other two studies,[11,25] the expression of MMP-1 was also not significantly different in AB compared with other odontogenic tumor or tooth germ. However, Kumamoto *et al*.[11] reported that expression of MMP-1 was detected in stromal cells but not in tumor cells. Souza-Freitas *et al*.[29] reported that both MMP-7 and MMP-26 were located in both tumor cells and stromal cells. There was no statistically significant difference in MMP-7 and MMP-26 expression between the ABs and adenomatoid odontogenic tumors. Stromal staining for MMP-7 was evident in all cases. For MMP-26, stromal staining was observed in 65% of ABs and 50% of adenomatoid odontogenic tumors, and this difference was not statistically significant.

Furthermore, some studies reported the association between MMPs' expression and the clinicopathologic features of patients with AB. Fregnani *et al*.[31] reported the expression of MMP-2 had obvious correlation with rupture of the osseous cortical and histo-

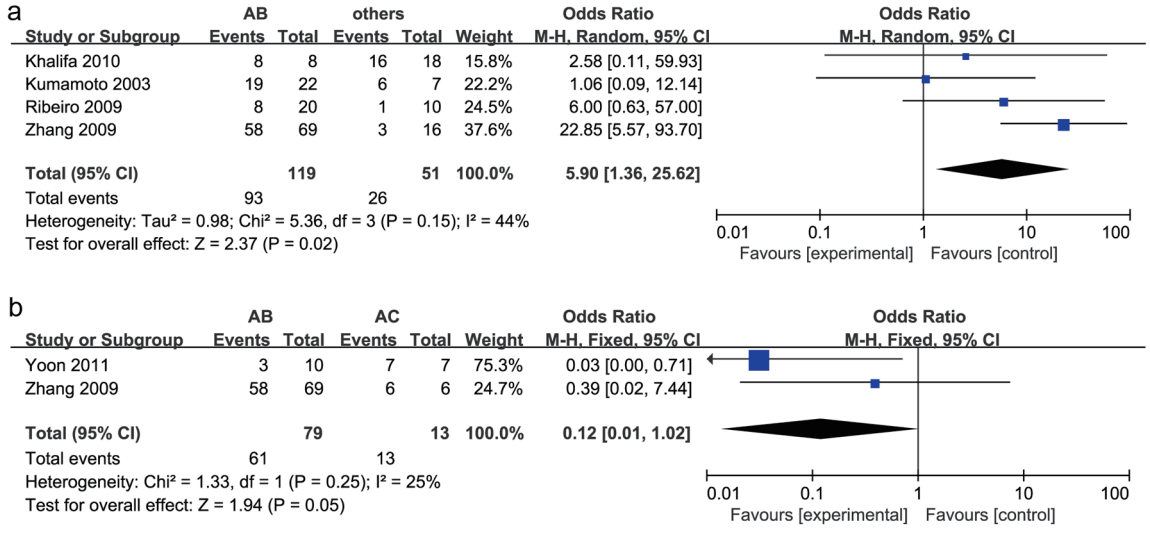

Fig. 3. Forest plots for MMP-2. (a) For AB, the difference between the two groups was significant (OR: 5.33; 95% CI: [1.36, 25.62]; $p = 0.02$; four trials, 170 participants) and the heterogeneity was acceptable ($I^2 = 44\%$, $p = 0.15$). (b) For AC, the difference between the two groups was not significant (OR: 0.12; 95% CI: [0.01, 1.02]; $p = 0.05$; two trials, 92 participants). Abbreviations: AB, ameloblastoma; AC, ameloblastic carcinoma; CI, confidence interval; OR, odds ratio.

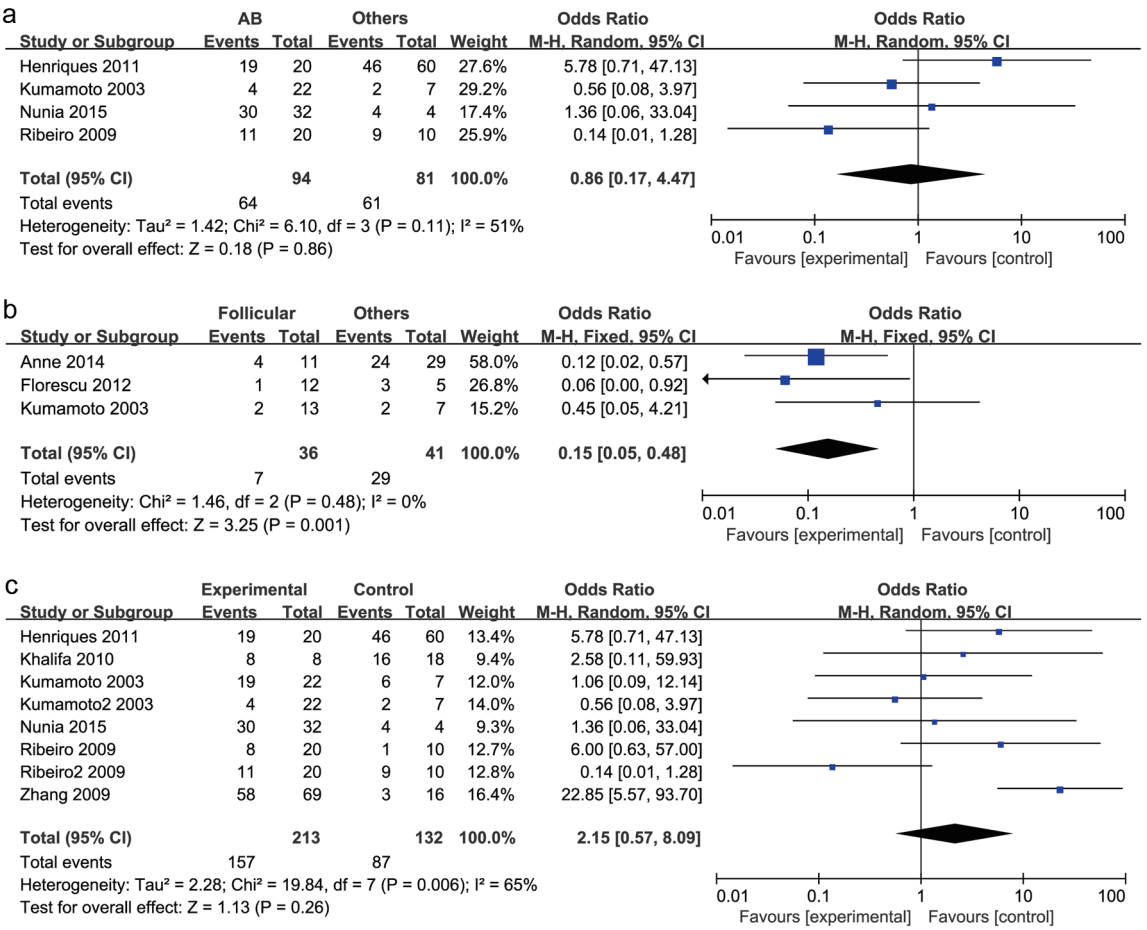

Fig. 4. Forest plots for MMP-9. (a) For AB, the difference between the two groups was not significant (OR: 0.86; 95% CI: [0.17, 4.47]; $p = 0.86$; four trials, 175 participants). (b) For the various pathological subgroups of AB, the difference between the two groups was significant (OR: 0.15; 95% CI: [0.05, 0.48]; $p = 0.001$; two trials, 77 participants) and the heterogeneity was acceptable ($I^2 = 0\%$, $p = 0.48$). (c) MMP-2 and MMP-9 in AB. Abbreviations: AB, ameloblastoma; CI, confidence interval; OR, odds ratio; MMP, matrix metalloproteinase.

logical type.

TSA

Data from all 12 studies were used to investigate whether the expressions of MMPs in AB were different from that in other benign odontogenic tumors, whether MMPs in AB were different from that in AC, or whether the expression of MMPs was different among the various pathological subgroups of AB. Using the TSA (taking the data of MMP-2 in AB for example), the required sample size for adequate power was 1,033 events. There were just 119 events only in this meta-analysis. The cumulative Z-curve does not cross the trial monitoring boundary before reaching the required information size, which indicates that the cumulative evidence is insufficient and further trials are necessary (Fig. 5a). The results for the other groups are not shown, as the study methods were similar. Please see the data listed in Figure 5b and c.

Discussion

The most important biological feature of the AB is its locally invasive behavior that is responsible for the higher postoperative recurrence rate, even following radical surgery.[34,35] However, both the pathogenesis and invasive growth of AB remains incompletely understood. ECM is a dynamic reticulated structure present between cell to cell, which plays a crucial role in both physiological and pathological processes, such as tumor invasion, angiogenesis, wound healing, and inflammation.[36,37] MMPs are capable of ECM remodeling, favoring the invasion and proliferation of tumor cells.[38,39] MMPs have been detected in both cyst fluids and wall tissue extracts of various odontogenic cysts and odontogenic tumors, including ABs, suggesting that these enzymes play a key role in regulation of tumor and cyst growth.[40–43]

In the present research, the expression of MMP in AB and its effect on tumor cell invasion and the prognosis of patients were varied. Thus, identification of prognostic values of the MMPs in ABs is of considerable importance to determine the most appropriate therapeutic approach and establish the prognosis of patient. With respect to this, the primary purpose of this systematic review was to clarify the difference in the expression of MMPs between AB and other benign tumors or normal tissue of jaw, the effect of MMPs on tumor cell invasion and the prognosis of patients with AB. The secondary purpose was to compare the expression of MMPs in AB to AC, and explore the possible role of MMPs in metastasis of cancer cells.

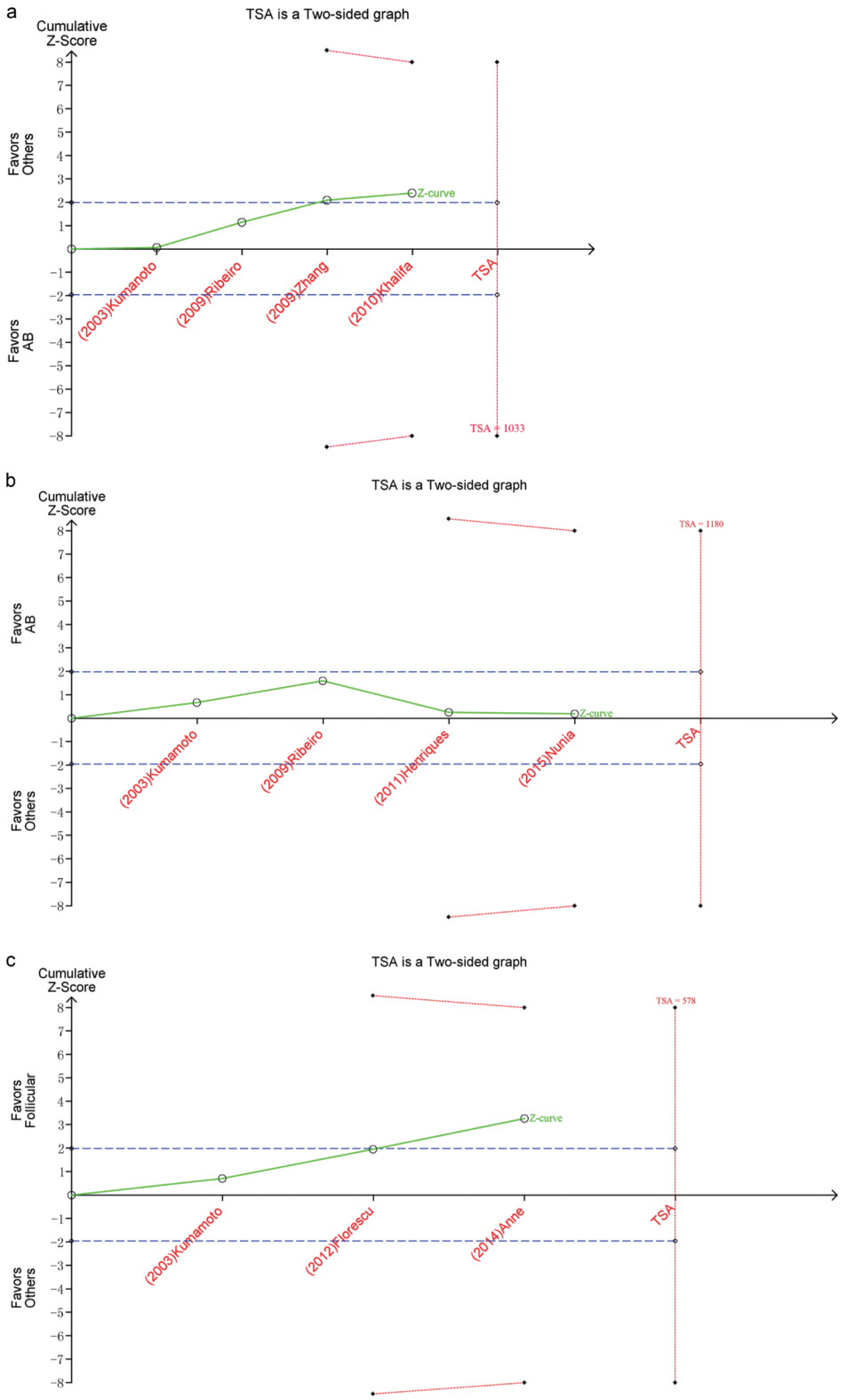

Fig. 5. Trial sequential analysis of this meta-analysis. (a) Data on the MMP-2 expression in AB. (b) Data on the MMP-9 expression in AB. (c) Data on the MMP-9 expression in pathology subgroups of AB. For all, the solid green line represents the cumulative *Z*-curve. The dashed red line represents the trial sequential monitoring boundary. TSA indicates that further trials are required. Abbreviations: AB, ameloblastoma; MMP, matrix metalloproteinase; TSA, Trial sequential analysis.

Although all the studies included in this meta-analysis are retrospective and the sample sizes in each were small, the quality of the included studies is quite high according to the results of NOS.[44,45] The fact that all the included studies are retrospective with small sample sizes is perhaps indicative of the inherent challenges in conducting a methodologically robust prospective study with large sample size in general and in particular when involving AB patients. What is more, this fact also implies that the study of this subject was not enough, and this research direction did not cause enough attention of scholars.

The results of this systematic review and meta-analysis supported the findings of expression of MMP-2 in AB being higher than that in other benign odontogenic tumors, but being lower than in AC. The expression of MMP-9 in the follicular subgroup of AB was lower than that in other subgroups. What is more, this systematic review also supported the findings that the expression of MMPs is significantly correlated with many clinicopathologic features of AB. However, the results of TSA showed that the statistical results of this meta-analysis are likely to be false positive or false negative, and further trials are necessary in this respect.[27,46–49]

Heterogeneity of the studies in this meta-analysis is acceptable, except that in the meta-analysis of MMP-9 in AB (I^2 = 51% > 50%). This statistical heterogeneity is driven by the study of Henriques *et al*.[24] The cut-off value of staining evaluation of that study is different from the other three studies considered. This appears to be the main reason for the heterogeneity. In addition, there may be a large difference in the amount and type of cases in the control group between this trial and the others. The types of cases in the control group of Henriques's study are multifarious, while the types in the other studies are monotonous. This may be another reason contributing to the large statistical heterogeneity between this study and others.

Every meta-analysis, including this one, has its limitations.[27,50] Firstly, all the included studies were of retrospective design, rather than prospective. What is more, the staining evaluations of these studies were various. Due to various reasons, the evaluation results would be expected to deviate. Secondly, the sample sizes of these included studies were rather small. Sample size was one of most important factors that limited the quality of this research. Last but not least, there was unacceptably great heterogeneity among these studies. Apart from heterogeneity, selective reporting among the individual research studies also limited this meta-analysis. Due to various reasons, obtaining all the data for a complete review of MMPs in AB or AC is impossible. All the above factors have an impact on the outcomes measured and might have influenced the findings. More studies are required to further confirm our results.

In conclusion, this systematic review showed that there is evidence that the expression of MMP-2 in AB is higher than that in other benign tumors or normal tissue of jaw, the expression of MMP-2 in AB is lower than that in AC, and the expression of MMP-9 in the follicular subgroup of AB is lower than that in other pathological subgroup of AB. What is more important, the expression of MMPs (including MMP-1, MMP-2, MMP-7, MMP-9, and MMP-26) in AB was significantly correlated with many clinicopathologic features of AB, such as the growth rate, invasion, and metastasis. However, some limitations weakened the power of this meta-analysis. That is to say, further studies are required to substantiate our findings.

Hypothesis

The protein expression levels of MMP-2 and MMP-9 may be an important reference indicator for predicting the invasiveness of AB and the prognosis of patients. In the future, it is expected to use the protein expression of MMPs to establish a prediction model for the recurrence of AB. Of course, the establishment of a prediction model requires a lot of high-quality data as support. It is believed that with the continuous development of science and technology and the continuous improvement of related technology, our prediction is likely to be realized. At present, single-cell sequencing is a promising technique to help us build predictive models.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Project design (ZHR), literature search and quality assessment (YMZ); quality assessment and data extraction (QBZ); data extraction and writing articles (ZHR, HYW, KNY).

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