Systematic Review and Meta-Analysis

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Clinical significance of matrix metalloproteinase-2 in endometrial cancer

A systematic review and meta-analysis

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Abstract

Background: Matrix metalloproteinase-2 (MMP-2), a member of the zinc-dependent metalloproteinase gene family, plays a vital role in cancer invasion, metastasis, and progression. This systematic review and meta-analysis aims to explore the clinical significance of MMP-2 expression in endometrial cancer.

Methods: PubMed, Embase, Cochrane Library, and China National Knowledge Infrastructure databases were systematically searched up to September 30, 2017, supplemented by manual searches of bibliographies. Two reviewers independently identified articles, extracted data, assessed quality, and cross-checked the results. Meta-analysis was conducted to explore the difference in the positive rate of MMP-2 expression between patients with endometrial cancer and those with endometriosis or normal endometrium, and to investigate the associations of MMP-2 expression with clinicopathologic characteristics of patients with endometrial cancer. Weighted mean differences and risk ratios (RRs) with 95% confidence interval (CI) were calculated for continuous and dichotomous variables, respectively.

Results: Totally 20 studies were selected for this systematic review and meta-analysis. Compared with those with endometriosis or normal endometria, the positive rate of MMP-2 expression is significantly higher in patients with endometrial cancer (RR = 2.31, 95% CI: 1.78–3.00, $P < .01$). MMP-2 expression was significantly associated with Federation of Gynecology and Obstetrics stage (RR = 1.19, 95% CI: 1.09–1.31, $P < .01$), histologic grade (RR = 1.10, 95% CI: 1.01–1.19, $P = .02$), lymph node metastasis (RR = 1.32, 95% CI: 1.15–1.51, $P < .01$), and myometrial invasion (RR = 1.25, 95% CI: 1.12–1.38, $P < .01$).

Conclusion: The results showed that MMP-2 was expressed in high percentage of endometrial cancer and its expression may be associated closely with clinical stage, and tumor invasion and metastasis, indicating that MMP-2 overexpression may serve as a predictive factor for poor prognosis of endometrial cancer.

Abbreviations: ACROBAT-NRSI = the Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions, CI = confidence interval, CNKI = China National Knowledge Infrastructure, FIGO = Federation of Gynecology and Obstetrics, MMP-2 = matrix metalloproteinase-2, NR = not reported, RoB = Cochrane Risk of Bias, RRs = risk ratios, SCCs = squamous cell carcinomas, S-P = streptavidin-peroxidase, WMDs = weighted mean differences.

Keywords: clinicopathologic characteristics, endometrial cancer, meta-analysis, matrix metalloproteinase-2

1. Introduction

Endometrial cancer is a common gynecologic malignancy ranked fourth in developed countries and also a common cause of death from female cancers ranked third.[1] It affected approximately 320,000 patients with the estimated death of 76,000 patients in 2012 worldwide.[2] With the industrialization, urbanization, and westernization of lifestyle, the incidence of endometrial cancer increased significantly, especially in developing countries.[3] Although 5-year survival is estimated to be more than 90% in early stage, those women with advanced stage, high-risk histology, poor differentiation, and metastasis to regional nodes may have poor prognosis, with only 57% in patients with stage III (regional diseases) and 19% in stage IV (distant spread diseases), respectively.[4] Therefore, identification of novel and more reliable markers to accurately predict prognosis of patients with endometrial cancer is urgently needed.

Matrix metalloproteinases (MMPs) represent a family of extracellular zinc-dependent endoproteinases, known for their capacity to degrade extracellular matrix components.[5] They play extremely pivotal roles in tumor invasion and infiltration, as well as in tumor angiogenesis.[6,7] Of the several MMPs analyzed in endometrial tumors, MMP-2 acts as a key enzyme that associated with tumor metastasis and physiologic function.[8] A large amount of studies investigated the expression of MMP-2 in endometrial cancer and its association with clinicopathologic characteristics, but the reported results were inconsistent. For instance, researchers suggested that overexpression of MMP-2 in endometrial cancer was correlated with lymph node metastasis,[9] but others failed to give the same results.[10]

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The systematic review and meta-analysis were aimed to explore the difference in the positive rate of MMP-2 between patients with endometrial cancer and the patients with endometriosis or normal endometrium, and to study the associations between MMP-2 expression and clinicopathologic characteristics of patients with endometrial cancer, including clinical stages defined by International Federation of Gynecology and Obstetrics (FIGO) systems,[11] degree of differentiation, depth of myometrial invasion, and metastasis within lymph node.

2. Materials and methods

2.1. Search strategy

The systematic review and meta-analysis were performed in accordance with the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12]

To identify clinical data in published studied for trail, we searched the English database including PubMed, Embase, and Cochrane Library, and the Chinese database, including China National Knowledge Infrastructure (CNKI). In English databases, we combined the search terms "matrix metalloproteinases-2" OR "MMP-2" OR "Gelatinase A" OR "collagenase type IV-A" AND "endometrial cancer" OR "endometrial carcinoma". The search terms were translated into Chinese when the CNKI was searched. The search was performed at September 30, 2017. In addition, other relevant studies were selected by screened the bibliographies of included articles and reviews. This study was approved by the Ethics Committee of The First Hospital of Lanzhou University, but not involved patient consents that not required.

2.2. Eligibility criteria

Following criteria were used for included studies: patients with endometrial cancer, endometriosis, or normal endometrium; all cases were histologically diagnosed; and the expression of MMP-2 was detected by streptavidin-peroxidase (S-P) immunohistochemistry. We excluded the cell line study, animal study, letter, editorial, and review. If the same study published more than one paper, only the one with abundant information or with largest cases was included.

2.3. Data extraction and quality assessment

An extraction table was developed to assimilate data from included trials, which include general information regarding the identification of the publication, for example, first author's name, title, publication year, median age, affiliations, sample size, and pathologic characteristics such as clinical stages, degree of differentiation, depth of myometrial invasion, and metastasis of lymph node. When the original study not mentioned those information, "not reported (NR)" were present for the corresponding item. The extracted information was checked by 2 reviewers independently. Inspection of article were further done with discussion if the case with conflicting evaluation.

To evaluate the quality of included studies, the Cochrane Risk of Bias (RoB) Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) was employed in the meta-analysis. The included studies were assessed based on 7 chronologically arranged bias domains (Table 1). Signaling questions flag potential for bias and help review authors judge RoB. Quality assessment was independently conducted by 2 authors and discussed for resolving disagreement.

2.4. Statistical analysis

Risk ratios (RRs) and weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated, respectively, for dichotomous and continuous outcomes. $P < .05$ was considered statistically significant. Meta-analysis was performed using STATA (version 14; Stata Corp, College Station, TX). Heterogeneity analysis was performed by Cochran Q statistic and I^2 statistic. Statistical significance for heterogeneity was considered if $P < .05$ or $I^2 > 50\%$. The fixed-effects model was applied when $P > .05$ and $I^2 < 50\%$, otherwise, the random-effects model was chosen. Additionally, we conducted sensitivity analyses by removing one study each time and recalculating pooled effects. Potential publications bias (considered present if $P \leq .1$) was assessed by conducting statistical tests for funnel plot asymmetry as well as Egger test and Begg test.

Table 1

Consensus ACROBAT-NRSI judgments between two reviewers by domain of bias–component studies.

Component	Domain							
Study	Bias due to judgment confounding	Bias in selection of participants	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results	Overall ROB judgment
Aglund et al (2004)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Wu et al (2004)	Low	Low	Low	Low	Low	Low	Low	Low
Talvensaari-Mattila et al (2005)	Low	Low	Low	Low	Low	Low	Low	Low
Misugi et al (2005)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Liu et al (2005)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Xu et al (2005)	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Yuan et al (2006)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Karahan et al (2007)	Low	Low	Low	Low	Low	Low	Low	Low
Niu and Ge (2009)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Zhang et al (2009)	Low	Low	Low	Low	Low	Low	Low	Low
Zhu et al (2010)	Low	Low	Low	Low	Low	Low	Low	Low
Yilmaz et al (2011)	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Chen (2011)	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Pan et al (2011)	Low	Low	Low	Low	Low	Low	Low	Low
Weigel et al (2012)	Serious	Low	Low	Low	Low	Low	Low	Serious
Zhong and Yan (2014)	Low	Low	Low	Low	Low	Low	Low	Low
Yuan et al (2015)	Low	Low	Low	Low	Low	Low	Low	Low
Sun (2015)	Low	Low	Low	Low	Low	Low	Low	Low
Liu et al (2015)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sun et al (2016)	Low	Moderate	Low	Low	Low	Low	Low	Moderate

ACROBAT-NRSI = the Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions.

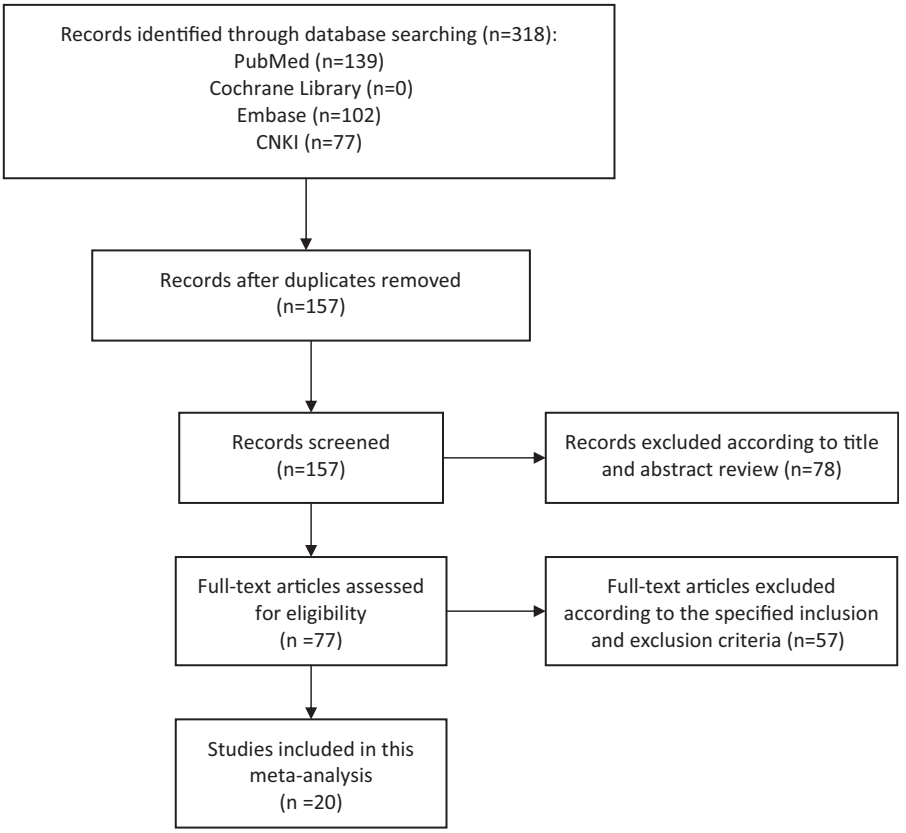

Figure 1. Literature search and selection of articles. CNKI = China National Knowledge Infrastructure.

3. Results

3.1. Characteristics of the included studies

The participant flow diagram for the study inclusion in the meta-analysis is shown in Figure 1. With the initial search strategy mentioned earlier, 318 papers potentially eligible for inclusion were screened. After excluding overlapping studies, irrelevant studies and studies without information of study objectives, 20 articles finally met the inclusion criteria.[9,10,13–30]

The major characteristics of the included studies were summarized in Table 2. These 20 studies involving 1569 cases with endometrial cancer and 333 cases with normal endometria or endometriosis were published from 2004 to 2016. Most studies (14 studies) evaluated patients from China, 2 from

Table 2

Basic characteristics and study quality of included studies.

Study	Country	Endometrial cancer				Normal endometria/ endometrial hyperplasia		Study quality (NOS score)
		N	Median age (range)	FIGO stage (I/II/III/IV)	Histologic grade (G1/G2/G3)	N	Median age (range)	
Aglund et al (2004)	Sweden	82	–	–	18/53/11	–	–	7
Wu et al (2004)	China	121	57 (32–71)	96/15/9/1	64/37/20	20	–	7
Talvensaari-Mattila et al (2005)	Finland	112	66 (37–86)	84/12/14/2	58/43/11	–	–	6
Misugi et al (2005)	Japan	196	55 (24–82)	131/17/42/6	74/83/39	–	–	8
Liu et al (2005)	China	42	–	19/15/8/0	18/13/11	12	–	7
Xu et al (2005)	China	30	56 (26–73)	–	–	46	42 (25–51)	6
Yuan et al (2006)	China	44	55 (33–78)	18/14/9/3	G1/G2+G3: 10/34	18	–	6
Karahan et al (2007)	Turkey	42	57 (37–80)	23/5/14/0	25/10/7	–	–	8
Niu and Ge (2009)	China	75	51	32/20/17/0	22/35/18	28	45	5
Zhang et al (2009)	China	80	55	60/15/5/0	42/24/14	80	–	6
Zhu et al (2010)	China	60	56 (38–73)	26/19/15/0	29/19/12	42	–	8
Yilmaz et al (2011)	Turkey	95	61 (34–87)	73/6/16/0	30/26/29	–	–	6
Chen (2011)	China	73	57 (37–79)	–	26/23/24	27	54 (37–79)	7
Pan et al (2011)	China	52	53 (29–73)	20/12/14/6	17/17/18	41	–	7
Weigel et al (2012)	Germany	38	36–89	–	–	49	24–56	6
Zhong and Yan (2014)	China	100	51 (37–68)	I/II/III-IV: 58/22/20	65/24/11	50	–	7
Yuan et al (2015)	China	107	35–76	I-II/III-IV: 77/30	–	–	–	7
Sun (2015)	China	72	59 (36–72)	I-II/III-IV: 39/33	35/21/16	–	–	6
Liu et al (2015)	China	96	–	I/II/III-IV: 38/29/29	G1/G2+G3: 40/56	–	–	7
Sun et al (2016)	China	52	54 (34–77)	I/II/III-IV: 28/14/10	14/21/17	–	–	6

FIGO = Federation of Gynecology and Obstetrics.

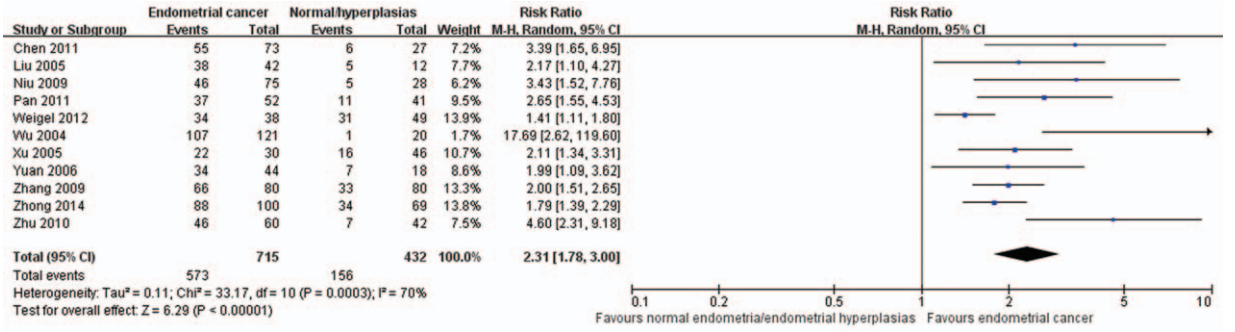

Figure 2. Comparison of positive rate of matrix metalloproteinase-2 expression between patients with endometrial cancer and those with endometriosis or normal endometria. CI = confidence interval.

Turkey, and other 4 from Sweden, Finland, Japan, and Germany, respectively. Bias in most studies were low or moderate (Table 1). The bias due to confounding in the studies conducted by Niu and Ge[18] and Weigel et al[22] were serious as they reported neither the baseline distribution between groups nor previous treatment before the surgery. Difference in the positive rate of MMP-2 expression between patients with endometrial cancer and patients with endometriosis or normal endometria.

A total of 11 studies compared the positive rate of MMP-2 expression between patients with endometrial cancer and patients with endometriosis or normal endometria. Figure 2 shows that there is substantial between-study heterogeneity in this meta-analysis of 11 studies ($I^2 = 70\%$, Cochran Q statistic $P < .01$), indicating that a random effect model should be employed. Compared with those with endometriosis or normal endometria, the proportion of cases expressing positive MMP-2 is higher in patients with endometrial cancer (RR = 2.31, 95% CI: 1.78–3.00, $P < .01$).

3.2. Association between MMP-2 expression and clinicopathologic characteristics in patients with endometrial cancer

There are 15, 17, 14, and 18 studies reported the association of MMP-2 expression with FIGO stage (Fig. 3), histologic grade (Fig. 4), lymph node metastasis (Fig. 5), and depth of myometrial invasion (Fig. 6), respectively. Due to the significant heterogeneity among studies, random effect models were applied in all analyses. It is noted that MMP-2 staining was significantly associated with FIGO stage (RR = 1.19, 95% CI: 1.09–1.31, $P < .01$), histologic grade (RR = 1.10, 95% CI: 1.01–1.19, $P = .02$), lymph node metastasis (RR = 1.32, 95% CI: 1.15–1.51, $P < .01$), and myometrial invasion (RR = 1.25, 95% CI: 1.12–1.38, $P < .01$).

3.3. Sensitivity analysis

The effect of each study on the overall estimate was verified by calculating the combined results for the remaining studies with omitting the study. Finally, we found that the pooled RR was not significantly affected by individual study. In addition, the removal of 2 studies with serious bias did not significantly affect the outcomes.

3.4. Publication bias

To assess the possibility of publication bias for the association of MMP-2 expression with FIGO stages (Fig. 7A), histologic grades (Fig. 7B), lymph node metastasis (Fig. 7C), and depth of myometrial invasion (Fig. 7D) among the studies, funnel plots were generated. The funnel plot showed no obvious asymmetry, indicating that there was no obvious publication bias in our study, which was supported by Egger test ($P = .27$, $P = .28$,

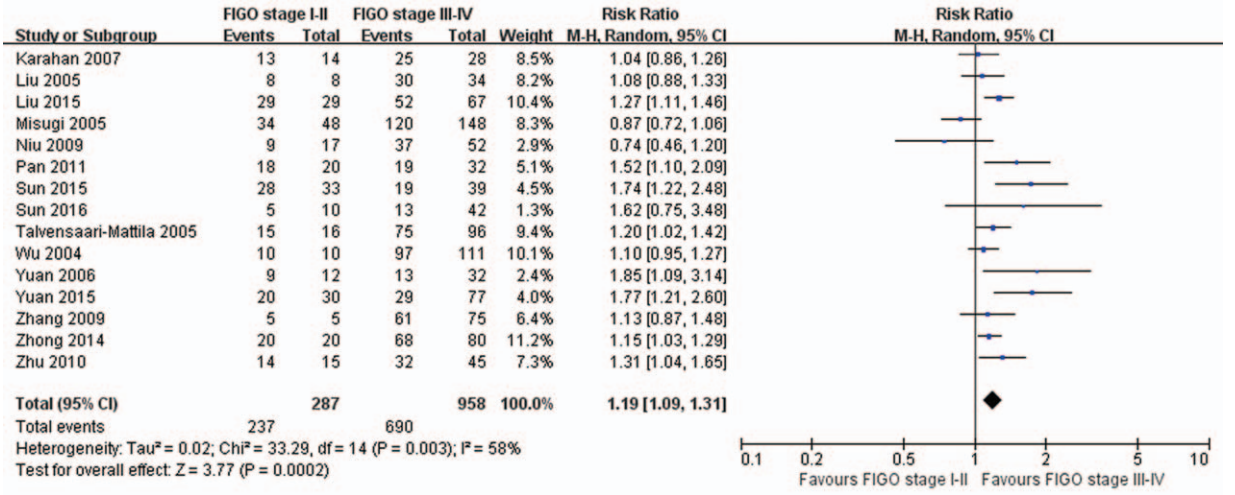

Figure 3. The association of matrix metalloproteinase-2 expression and Federation of Gynecology and Obstetrics (FIGO) stage. CI = confidence interval.

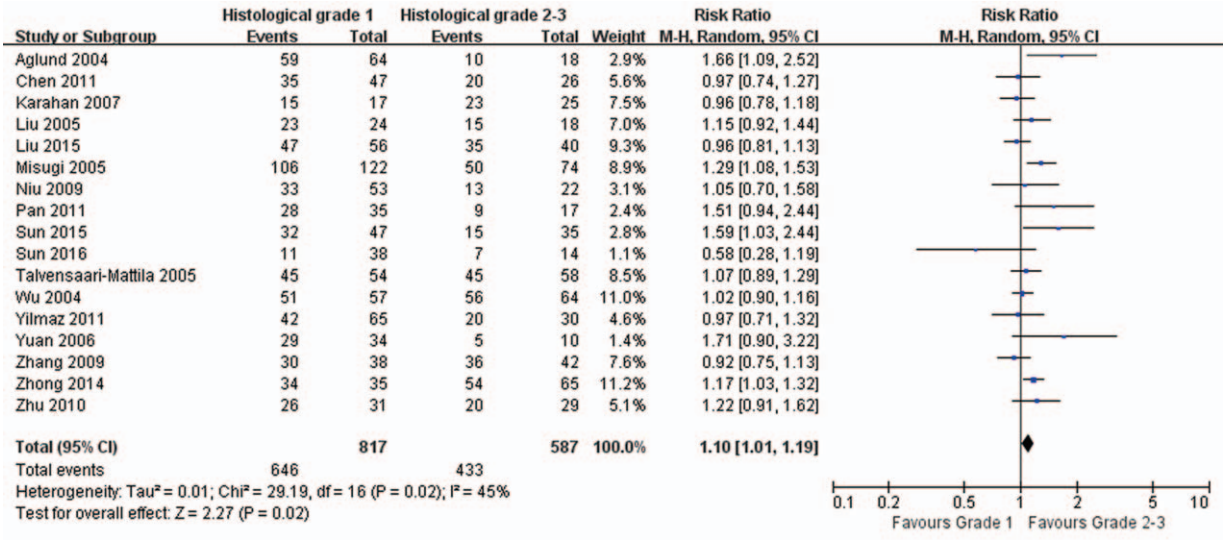

Figure 4. The association of matrix metalloproteinase-2 expression and histologic grade. CI = confidence interval.

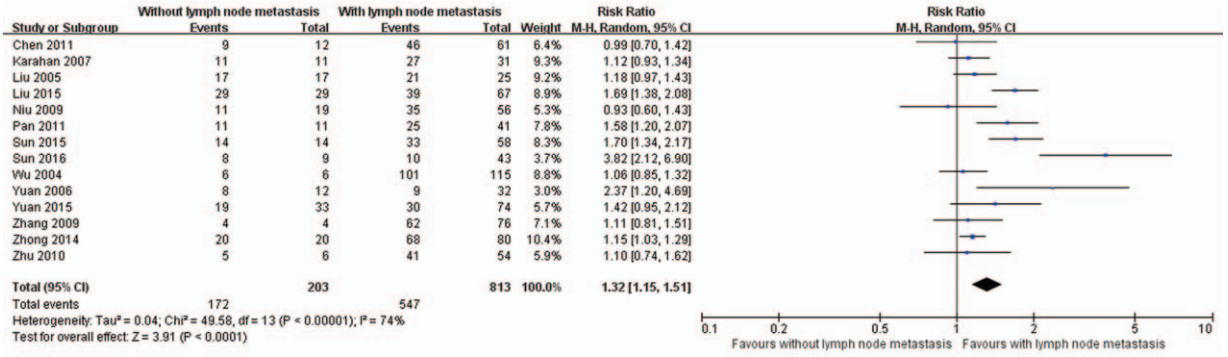

Figure 5. The association of matrix metalloproteinase-2 expression and lymph node metastasis. CI = confidence interval.

P=.73, and P=.27 for FIGO stages, histologic grades, lymph node metastasis, and depth of myometrial invasion, respectively) and Begg test (P=.92, P=.08, P=.58, and P=.32 for FIGO stages, histologic grades, lymph node metastasis, and depth of myometrial invasion, respectively).

4. Discussion

The mechanisms underlying the development and progression of endometrial cancer have not been fully elucidated.[31] Therefore, endometrial cancer is still a serious female health problem in the

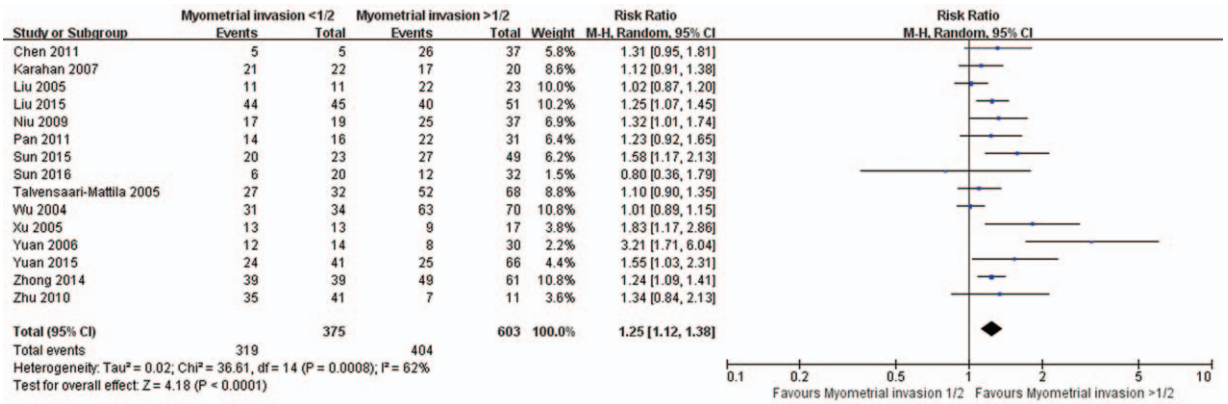

Figure 6. The association of matrix metalloproteinase-2 expression and depth of myometrial invasion. CI = confidence interval.

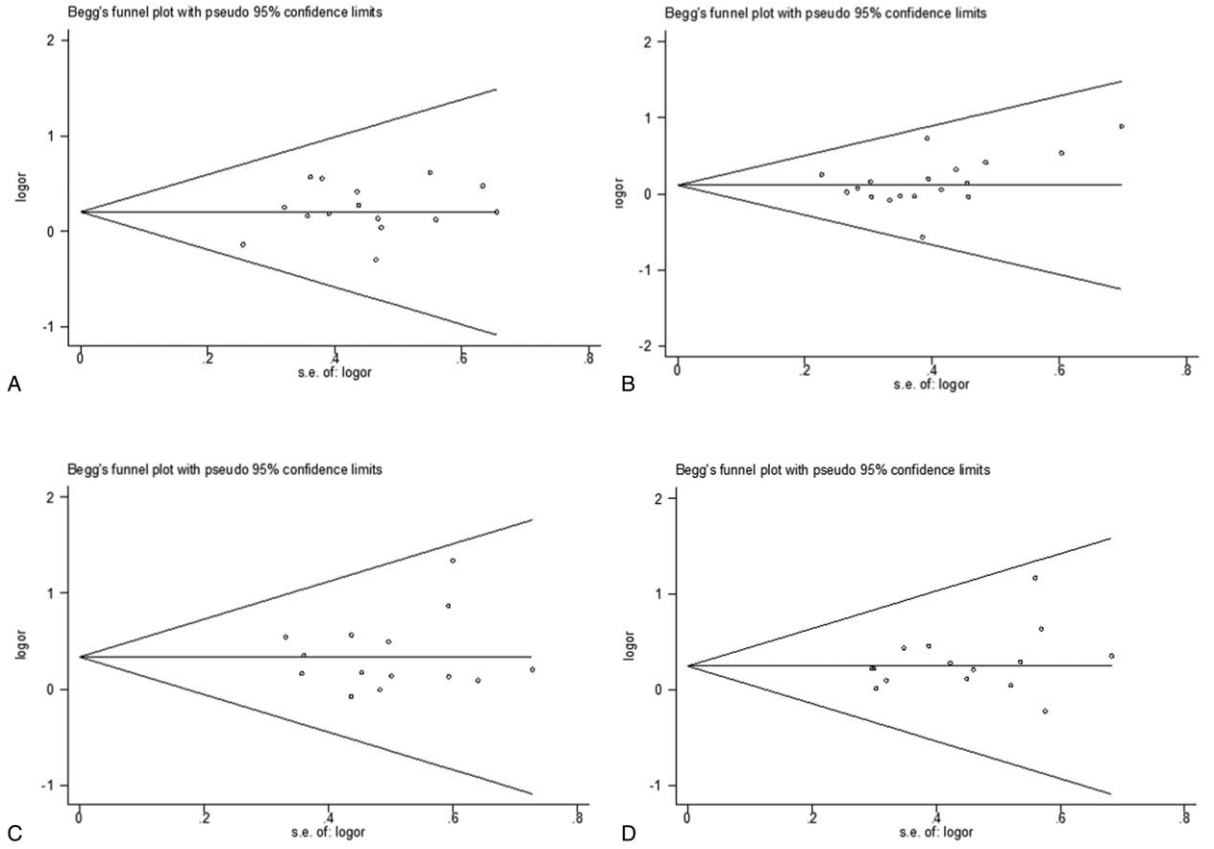

Figure 7. Funnel plots of the meta-analysis assessing the association of matrix metalloproteinase-2 expression with (A) Federation of Gynecology and Obstetrics (FIGO) stage; (B) histologic grade; (C) lymph node metastasis; and (D) depth of myometrial invasion.

coming decades, and effective biomarkers with clinical significance are urgently needed.

The extracellular matrix and the basement membrane together constitute the first barrier in the process of tumor metastasis. The components of extracellular matrix are complex. It was reported that type IV collagen is the main component, which could be degrade by MMP-2 after fibrillar collages cleavaged by collagenases. It has been intensively investigated as a potential biomarker and unfavorable factor in a variety of systematic and multi-loci malignant tumors, such as laryngeal, breast, ovarian, and endometrial cancers.[6,32–34] Cymbaluk-Ploska et al[35] indicated that the area under the curve value for identifying patients with endometrial cancer with MMP-2 was 0.79, which was similar to the data for identify the lung cancer (0.75)[36] and bladder cancer (0.83).[37] Though the specificity values were reported in these studies, they cannot be directly compared due to inconsistent cutoff value, which need to be further explored by a large, well-designed clinical study. MMP-2 expression correlates also with tumor progression in neuroblastoma and papillary thyroid carcinoma.[38,39] This systematic review and meta-analysis found that MMP-2 is a potential biomarker for endometrial cancer as the positive rate of MMP-2 expression for patients with endometrial cancer is significantly higher than those with normal endometria or endometriosis.

During cell invasion and migration, extracellular matrix between cell–cell interaction or cell–extracellular matrix attachment were proteolytic modified by MMPs, which facilitated cancer cells metastasis.[40,41] High expression level of MMP-2 has been reported to be associated with in vivo invasion of tumors including oral squamous cell carcinomas (SCCs) and bladder carcinoma.[42,43] The levels of certain MMPs were important predictor of the risk of metastasis in primary tumor. The MMP-2 levels in tumor cells in uveal melanoma and SCC of tongue were associated with increased risk of metastasis.[44,45] Our study illustrated that the MMP-2 level was significantly correlated to myometrial invasion and metastasis within lymph node.

Recent studies have shown that MMPs also contribute to other processes in tumor progression such as cell growth and angiogenesis besides their roles in migration and invasion.[46] Our study demonstrated that the MMP-2 expression was positively associated with the clinical stages. Previous studies have indicated that the upregulation of MMP-2 is associated with the transition from histologic grade 1 to grades 2 and 3,[47,48] which is consistent with our result, that the MMP-2 correlate to the histopathologic grade of the endometrial cancer.

The analysis of the correlation between MMP-2 level and clinicopahologic characteristics revealed no publication bias. The sensitivity analysis showed that the estimation of risk in all the outcomes was not significantly affected by any single study omission. Thus, the results are reliable in the meta-analysis.

Although we have conducted a comprehensive analysis, there are still some limitations that need to be resolved. First, there is no consistent threshold for determining the positive MMP-2 expression in patients with endometrial cancer. The predicted value for MMP-2 should be decided before it used as biomarker. In addition, inaccurate conclusion might obtain due to the

potential heterogeneity between studies which was the inherent limitation of meta-analysis.

In summary, the meta-analysis showed that MMP-2 is positively associated with the clinicopathologic characteristics in endometrial cancer. MMP-2 is a potential useful biomarker for predicting the prognosis of patients with endometrial cancer.

Author contributions

Conceptualization: Chang Liu, Ying Li, Shasha Hu, Yongxiu Yang.
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Funding acquisition: Yongxiu Yang.
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Methodology: Chang Liu, Yao Chen, Li Gao, Dajiang Liu, Hongtao Guo.
Project administration: Chang Liu.
Resources: Chang Liu, Shasha Hu.
Software: Chang Liu.
Writing – original draft: Chang Liu, Ying Li, Shasha Hu, Yao Chen, Li Gao, Dajiang Liu, Hongtao Guo, Yongxiu Yang.
Writing – review & editing: Chang Liu, Ying Li, Shasha Hu, Yao Chen, Li Gao, Dajiang Liu, Hongtao Guo, Yongxiu Yang.

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