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 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: ACRB-NSI = 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 endoproteases, 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 over-expression of MMP-2 in endometrial cancer was correlated with lymph node metastasis,[9] but others failed to give the same results.[10]
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 trial, 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 on 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 with 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.

| Component | Bias due to | Bias in | Bias in | Bias due to | Bias due to | Bias in | Bias in | Overall ROB |
|-----------|------------|---------|---------|-------------|-------------|---------|---------|-------------|
|           | judgment   | selection | measurement | departures | missing    | measurement | reported | judgment    |
| Study     | confounding | of participants | of interventions | from intended | data       | of outcomes | results |            |
| Agyiand 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 | Moderate |
| Mitus et al (2009) | Moderate | Low | Low | Low | Low | Low | Low | Moderate |
| Liu et al (2010) | Moderate | Low | Low | Low | Low | Low | Low | Moderate |
| Xu et al (2005) | Low | Moderate | Low | Low | Low | Low | Low | Moderate |
| Yuan et al (2008) | 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 |
| Wegel 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.
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

![Figure 1. Literature search and selection of articles. CNKI = China National Knowledge Infrastructure.](image-url)

Table 2

| Study                        | Country   | Endometrial cancer | Normal endometria/endometrial hyperplasia | Study quality (NOS score) |
|------------------------------|-----------|--------------------|------------------------------------------|--------------------------|
| Aglund et al (2004)          | Sweden    | 82                 | 18/53/11                                 | 7                        |
| Xu et al (2004)              | China     | 121 (32–71)       | 96/15/9/1                                | 7                        |
| Takensu-Matia et al (2005)   | Finland   | 112 (37–49)       | 84/12/4/2                                | 6                        |
| Mitugi et al (2005)          | Japan     | 196 (24–82)       | 131/17/42/6                              | 8                        |
| Liu et al (2005)             | China     | 42                 | 18/15/8/0                                | 7                        |
| Xu et al (2005)              | China     | 30 (26–73)        | –                                        | 6                        |
| Yuan et al (2006)            | China     | 44 (33–78)        | 18/14/9/3 G1/G2+G3: 10/34               | 6                        |
| Karahan et al (2007)         | Turkey    | 42 (37–80)        | 23/5/14/0                                | 7                        |
| Xu and Ge (2009)             | China     | 75                 | 32/20/17/0                               | 5                        |
| Zhang et al (2009)           | China     | 80                 | 60/15/5/0                                | 6                        |
| Zhu et al (2010)             | China     | 60 (36–78)        | 26/19/15/0                              | 6                        |
| Yilmaz et al (2011)          | Turkey    | 95 (34–87)        | 73/8/16/0                                | 6                        |
| Chen et al (2011)            | China     | 73                 | 57 (37–79)                               | 7                        |
| Pan et al (2011)             | China     | 52 (29–73)        | 20/12/14/6                               | 7                        |
| Weigel et al (2012)          | Germany   | 38                 | 36–89                                    | 7                        |
| Zhang and Yan (2014)         | China     | 100 (37–68)       | –                                        | 50 (56–59)               |
| Yuan et al (2015)            | China     | 107 (35–76)       | 1–7                                      | 7                        |
| Sun (2015)                   | China     | 72 (36–72)        | 1–7                                      | 7                        |
| Liu et al (2015)             | China     | 96                 | –                                        | 7                        |
| Sun et al (2016)             | China     | 52 (34–77)        | –                                        | 6                        |

FIGO = Federation of Gynecology and Obstetrics.
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 ($P=.27$, $P=.28$, $P=.27$, $P=.28$, $P=.27$).
\[ P = .73, \] 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).

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.

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

4. Discussion

The mechanisms underlying the development and progression of endometrial cancer have not been fully elucidated. Therefore, endometrial cancer is still a serious female health problem in the
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 collagens 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. Cymbaluk-Ploska et al 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) and bladder cancer (0.83). 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. 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. 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, 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 clinicopathologic 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 of endometrial cancer. MMP-2 is a potential useful biomarker for predicting the prognosis of patients with endometrial cancer.

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