Systematic Review and Meta-Analysis

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The association between diabetes/hyperglycemia and the prognosis of cervical cancer patients

A systematic review and meta-analysis

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Abstract

Background: The predictive roles of diabetes in the prognosis of many types of cancer have been well studied, but its role in predicting the prognosis of cervical cancer is still controversial. The aim of the study is to evaluate the association between diabetes/hyperglycemia and the prognosis of cervical cancer.

Methods: We conducted a systematic review for peer-reviewed studies indexed in PubMed, Embase, Web of Science, and Wanfang published before December 2016. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were pooled in the meta-analysis.

Results: This systematic review identified 13 studies with a total of 11,091 cervical cancer patients, of which 11 studies were included in the meta-analysis. The study indicated that diabetes was related to poorer overall survival (HR = 1.59, 95% CI: 1.35–1.87, $P < .001$) and poorer recurrence-free survival (HR = 1.98, 95% CI: 1.47–2.66, $P < .001$) in cervical cancer patients. The meta-analysis of adjusted HRs also indicated that diabetes was independently associated with poor overall survival (HR = 1.69, 95% CI: 1.38–2.05, $P < .001$) and poor recurrence-free survival (HR = 1.98, 95% CI: 1.47–2.66, $P < .001$) in cervical cancer patients. Sensitivity analysis and subgroup analyses showed similar results. No significant heterogeneity was observed for the included studies.

Conclusions: The meta-analysis suggests that diabetes is an important predictive factor for cervical cancer prognosis, and it is linked to poorer survival of cervical cancer patients. Diabetes can serve as a useful index in the prognostic evaluation for patients with cervical cancer.

Abbreviations: 95%CIs = 95% confidence intervals, HRs = hazard ratios, T2DM = type 2 diabetes mellitus.

Keywords: cervical cancer, diabetes, prognosis

1. Introduction

Cervical cancer is one of the most common gynecological cancers in the world, and about 454,000 women are newly diagnosed with cervical cancer every year.[1,2] Though many advances have been achieved in the treatment of cervical cancer, a large proportion of patients with advanced cervical cancer still have a poor prognosis.[3,4] Thus, appropriate clinical staging before treatment is vital to improve the prognosis of cervical cancer, and patients with lower survival probability may need more intensive management. Some prognostic factors predicting the survival of cervical cancer patients have been found, whereas the clinical staging of cervical cancer is still mainly based on the clinical exam and clinical imaging.[5,6] Therefore, more useful and effective prognostic factors predicting the survival of cervical cancer patients are needed to establish a more appropriate clinical staging system for cervical cancer patients.

Diabetes is an increasingly common metabolic diseases.[7,8] Recently, the prevalence of type 2 diabetes has risen rapidly due to the epidemic of obesity.[7] Previous studies have suggested that diabetes can promote both tumorigenesis and tumor progression.[9–11] It is well known that diabetes is a risk factor of cancer. A large number of epidemiological studies have shown the predictive role of diabetes in the prognosis of many types of cancers, such as breast cancer, ovarian cancer, and colorectal cancer.[12–16] Considering the prognostic roles of diabetes, numerous studies also have investigated its predictive role in cervical cancer prognosis.[17–26] Some studies reported that diabetes was associated with poor survival in cervical cancer patients,[17,24,25] but others indicated that diabetes had no significant influence on the prognosis of cervical cancer.[20,27] Therefore, the role of diabetes in predicting the prognosis of cervical cancer is still controversial. To address this issue, we performed a systematic review and meta-analysis to comprehensively evaluate the predictive role of diabetes/hyperglycemia in cervical cancer prognosis.

2. Methods

2.1. Data sources and eligibility criteria

The PubMed, Embase, Web of Science, and Wanfang databases were searched to identify relevant studies evaluating the prognostic value of diabetes in cervical cancer. The last updated search was carried out on December 20, 2016. Google Scholar was also searched to find additional studies. The following search

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terms and combinations were used in keyword and subject heading searches: (diabetes or diabetic or T2DM), (cervical cancer or cervical carcinoma or cervix cancer or cervix carcinoma), and (prognosis or prognostic or survival or mortality or outcomes or outcome). There was no language limitation in the literature search. References of relevant studies were checked manually. This study was carried out under the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analysis.[28]

Studies eligible for inclusion met the following criteria: (1) patients had histopathologically confirmed cervical cancer; (2) the exposure was diabetes or hyperglycemia; (3) the controls were those without diabetes or those with normal fasting blood glucose; (4) the outcomes of interests were overall survival or recurrence-free survival; (5) hazard ratios (HRs) with 95% confidence intervals (95% CIs) were reported, or data that could be transferred to risk estimates of cervical cancer prognosis were provided. Studies that did not meet the eligibility criteria were excluded. Studies with overlapping or duplicate data were also excluded.

2.2. Data extraction and quality assessment

Two investigators independently extracted data from each included study using a standardized table. Any disagreement was settled by discussion and consensus among all authors. Extracted information included: name of the first author, publication year, study design, country, characteristics of cervical cancer patients, definitions of diabetes or hyperglycemia, duration of follow-up, outcomes of interest, adjustment factors, and HRs with 95% CIs. If both unadjusted HRs and adjusted HRs were provided, only the latter were used. The study quality was assessed according to the Newcastle–Ottawa scale.[29] We evaluated the quality of included studies in terms of the representativeness of recruited cervical cancer patients, the comparability between exposed participants and nonexposed participants, and the adequate assessment of outcome. Studies that scored 6 or more were considered as high quality ones; those with scores of 5 or less were regarded as low quality.

2.3. Statistical analysis

To assess the associations between diabetes and overall survival or recurrence-free survival in cervical cancer patients, HRs with 95% CIs were pooled using meta-analysis. Heterogeneity between studies was examined by Cochran's Q test and I^2.[30,31] A P value on the Q test more than 0.10 or I^2 larger than 50% indicated a high degree of between-study heterogeneity and suggested the use of a random-effects model to pool HRs.[32] Otherwise, a fixed-effect model was utilized.[33] Sensitivity analyses with sequential omission of individual studies were then carried out to test the credibility of the pooled HRs. Sensitivity analysis was also carried out by omitting studies assessing the impact of hyperglycemia on the prognosis of cervical cancer patients. Subgroup analyses were conducted by sample size, adjusted status, and study quality. Publication bias was evaluated by the funnel plot and Egger's test.[34] When publication bias existed, the trim and fill method was performed.[35] STATA 12.0 was used for statistical analysis. A 2-sided P value less than 0.05 was considered to indicate statistical significance. The ethics committee was not applicable to this meta-analysis.

3. Results

3.1. Literature search and included studies

Figure 1 shows a flow chart of the study selection for the meta-analysis. A total of 1080 papers were initially identified in the literature search of 3 databases. After reviewing the titles and abstracts, 1058 obviously irrelevant studies were excluded. After full-text reading, 10 studies not meeting the inclusion criteria were excluded.[36–45] Therefore, 13 studies were included into the systematic review.[17–27,46,47] Two studies without HRs were excluded from the meta-analysis.[17,20] Finally, 11 studies[18,19,21–27,46,47] reporting data for quantitative synthesis were included in the meta-analysis (Fig. 1).

The 13 studies contained a total of 11,091 cervical cancer patients (Table 1). Table 1 summarizes the characteristics of the included studies. All studies used the retrospective cohort design. The majority of the included studies were conducted in Asia and the USA. Ten studies reported overall survival as the primary outcome of interest, and 7 studies reported recurrence-free survival. The follow-up time ranged from 3 to 25 years. Ten studies assessed the impact of diabetes on the survival of cervical cancer patients, and the rest evaluated the impact of hyperglycemia on the survival of cervical cancer patients. Kapp et al[17] reported that diabetes was associated with poor overall survival in cervical cancer after controlling for stage of disease ($P = .026$), but no association was found for recurrence-free survival. However, Chen et al[20] found that diabetes had no adverse effect on the overall survival of cervical cancer patients after controlling for adjusted factors. Neither of these studies reported HRs or data that could be used to calculate the HRs. The remaining 11 studies provided HRs or data that could be used to calculate the HRs, and 8 of them reported adjusted HRs. As to quality assessment, 9 studies had good quality, whereas the other 2 had suboptimal quality (Supplemental Table S1, http://links.lww.com/MD/B860).

3.2. Meta-analysis

In the meta-analysis of overall survival, between-study heterogeneity was not obvious ($P = .265$; $I^2 = 20.7\%$). The meta-analysis indicated that diabetes predicted poorer overall survival in cervical cancer patients (HR = 1.59, 95% CI: 1.35–1.87, $P < .001$) (Fig. 2). Sensitivity analysis proved the credibility of the pooled HRs for overall survival (Supplemental Figure S1, http://links.lww.com/MD/B860). After excluding studies addressing hyperglycemia, diabetes was still significantly associated with shorter overall survival time (HR = 1.57, 95% CI: 1.33–1.85, $P < .001$). In the subgroup analysis by adjusted status, after controlling other adjusted factors, diabetes independently predicted shorter overall survival time (HR = 1.69, 95% CI: 1.38–2.05, $P < .001$). The meta-analysis of 3 studies with unadjusted HRs also showed that diabetes was linked to shorter overall survival time (HR = 1.39, 95% CI: 1.04–1.87, $P = .027$). In the subgroup analysis by study quality, studies both with or without good quality suggested that diabetes could predict poorer overall survival in cervical cancer prognosis.

In the meta-analysis of recurrence-free survival, between-study heterogeneity was not significant ($P = .745$; $I^2 = 0\%$). The meta-analysis indicated that diabetes could predict poorer recurrence-free survival in cervical cancer prognosis (HR = 1.98, 95% CI: 1.47–2.66, $P < .001$) (Fig. 3). Sensitivity analysis proved the pooled HRs of recurrence-free survival was credible (Supplemental Figure S2, http://links.lww.com/MD/B860). Similarly, after excluding studies assessing the impact of hyperglycemia on

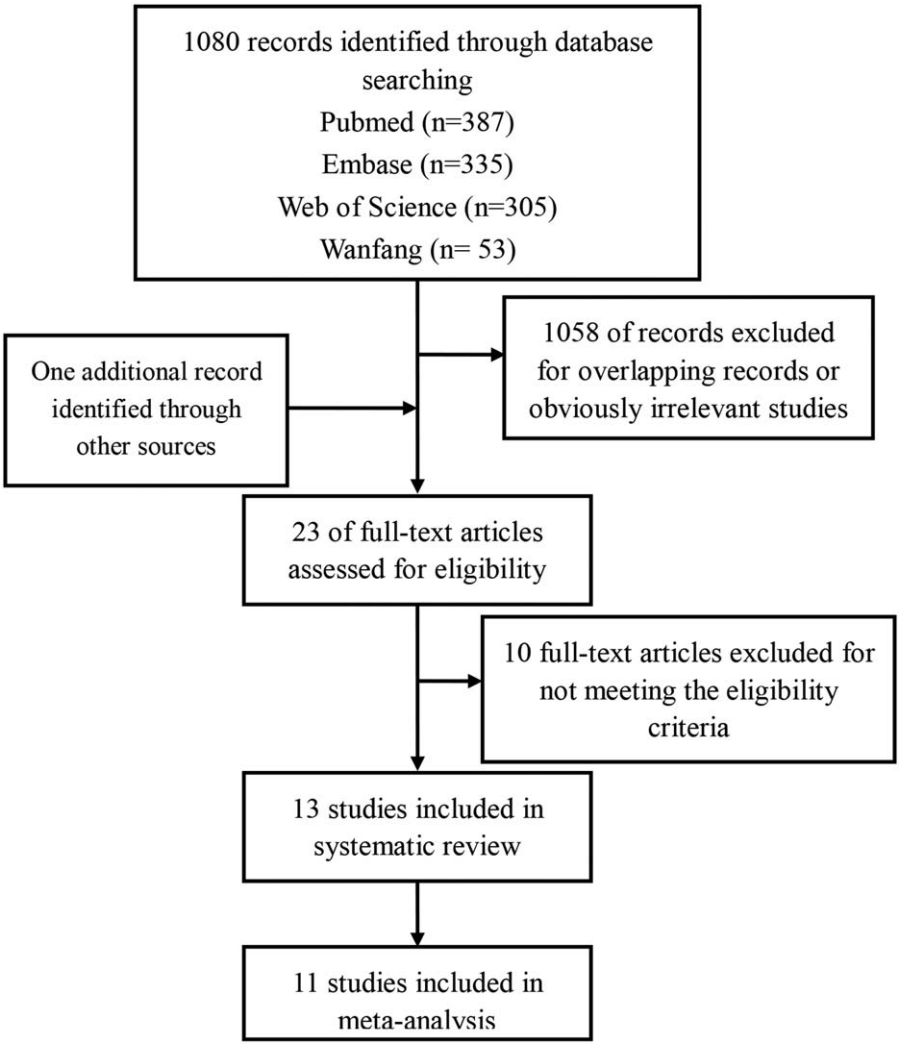

Figure 1. Flow chart of study selection for the meta-analysis.

the prognosis of cervical cancer, diabetes could still significantly predict poorer recurrence-free survival in cervical cancer (HR = 2.09, 95% CI: 1.28–3.41, $P = .003$). All the included studies reported adjusted HRs. In the subgroup analysis by study quality, high-quality studies and those with suboptimal quality both suggested that diabetes could predict poorer recurrence-free survival in cervical cancer, and the pooled HRs were 1.89 (1.40–2.56; $P = .000$) and 4.30 (1.23–15.03; $P = .022$), respectively.

3.3. Publication bias

In the study of overall survival, there was evidence of publication bias (Supplemental Figure S3, http://links.lww.com/MD/B860; $P_{Eggertest} = .04$). After using the trim and fill method of adding 4 unpublished studies, the pooled HR was 1.49 (95% CI 1.27 = 1.75; $P < .001$). In the meta-analysis of recurrence-free survival, no significant publication bias existed (Supplemental Figure S4, http://links.lww.com/MD/B860; $P_{Eggertest} = .23$).

4. Discussion

The predictive roles of diabetes in the prognosis of many types of cancer have been well studied, but its role in predicting the prognosis of cervical cancer is still controversial. This systematic review and meta-analysis was performed to evaluate the association between diabetes and cervical cancer prognosis. Thirteen studies with a total of 11,091 cervical cancer patients were identified in the systematic review. This study indicated that diabetes could predict poor overall survival and recurrence-free survival in cervical cancer. Sensitivity analyses and subgroup analyses proved the credibility of the pooled HRs. Therefore, the systematic review and meta-analysis suggested that diabetes is an important prognostic factor in patients with cervical cancer, and it is associated with the poor survival of cervical cancer patients.

There are other prognostic factors associated with the survival of cervical cancer patients, such as FIGO stage, histologic subtypes, and some biomarkers.[48–51] In this meta-analysis, we performed subgroup analyses by the adjustment status of HRs reported by included studies. Studies reporting adjusted HRs controlled the risk of bias caused by confounders to evaluate the independent prognostic role of diabetes in cervical cancer. Upon pooling adjusted HRs, we found that diabetes was independently related to shorter overall survival (HR = 1.69, $P < .001$) as well as recurrence-free survival in cervical cancer patients (HR = 1.98, $P < .001$). Therefore, the findings above suggest that diabetes is an independent prognostic factor in cervical cancer. Since

Table 1

Summary of included studies on the association between diabetes and the prognosis in cervical cancer.

First author, year	Country	Study design	Sample characteristics	Follow-up	Definition of DM /hyperglycemia	Comparisons	Outcomes	Adjusted factors	Quality
Chen et al 2016[47]	Taiwan	Retrospective cohort	3388 cervical cancer patients	Not reported	FBG >126 mg/dL or postprandial glucose >200 mg/dL	Diabetes versus nondiabetes	OS	Age	6
Li et al 2016[26]	China	Retrospective cohort	347 patients with early stage cervical cancer	37 months	FBG ≥126 mg/dL	Hyperglycemia	RFS	Age, BMI, tumor stage, cocurrent chemoradiotherapy, cholesterol, lymphatic vascular space involvement, neoadjuvant chemotherapy, and triglyceride	6
Jiamset and Hanprasertpong 2016[25]	Thailand	Retrospective cohort	444 patients with early stage cervical cancer	5 years	Medical records	Diabetes versus nondiabetes	OS; RFS	Age, histology, deep stromal invasion, lymphovascular space invasion, tumor size or stage, node metastasis, and adjuvant therapy.	7
Kuo et al 2015[24]	Taiwan	Retrospective cohort	2,946 patients with stage I-IIA cervical cancer patients	5 years	ICD-9-CM code 250.x	Diabetes versus nondiabetes	OS	Age, tumor size, lymph node, histology, stage, treatment, and comorbidity	8
Choi et al 2015[27]	Korea	Retrospective cohort	494 patients with cervical cancer	61.6 months	Medical records or laboratory test	Diabetes versus nondiabetes	OS; RFS	Age, BMI, cancer stage, histological subtype, tumor markers, treatment method, and any combined disease	7
Ahn et al 2015[23]	Korea	Retrospective cohort	84 patients with early-stage cervical cancer	3 years	FBG ≥100 mg/dL	Hyperglycemia	RFS	Age, lymph node involvement, tumor involvement of resection margin, parametrial invasion, cancer stage, and adjuvant treatment	5
Byun et al 2013[22]	Korea	Retrospective cohort	218 patients with cervical cancer of Stage IB2-III	5 years	Medical records	Diabetes versus nondiabetes	RFS	Age, cancer stage, initial hemoglobin, and adjuvant treatment	7
Lee et al 2010[21]	Korea	Retrospective cohort	134 patients with locally advanced cervical cancer	38 months	FBG ≥102 mg/dL	Hyperglycemia	OS; RFS	Age, histology, stages, performance status, concurrent chemoradiation therapy, radiation therapy and	6
Hopkins and Morley 1993[19]	USA	Retrospective cohort	175 patients with stage III-IV cervical cancer	5 years	Medical records	Diabetes versus nondiabetes	OS	None	5
Hopkins and Morley 1991[46]	USA	Retrospective cohort	345 patients with stage IB squamous cell carcinoma of the cervix	5 years	Medical records	Diabetes versus nondiabetes	OS	None	5
Kucera et al 1987[18]	Austria	Retrospective cohort	1304 patients with invasive cervix carcinoma	5 years	FBG >120 mg/dL	Diabetes versus nondiabetes	OS	None	5
Chen et al 1998[20]	Taiwan	Retrospective cohort	302 patients with primary cervix carcinoma	5 years	FBG ≥140 mg/dL or postprandial glucose ≥200 mg/dL	Diabetes versus nondiabetes	OS	Age, tumor grade, histologic subtypes, lymph node status, bulky tumor, presence of hypertension, obesity and oral contraceptive use	7
Kapp et al 1983[17]	USA	Retrospective cohort	910 previously untreated patients with cervix carcinoma (Stages IB-IVB)	25 years	Medical records	Diabetes versus nondiabetes	OS; RFS	Tumor stages	6

BMI = body mass index, DM = diabetes mellitus, FBG = fasting blood glucose, OS = overall survival, RFS = recurrence-free survival.

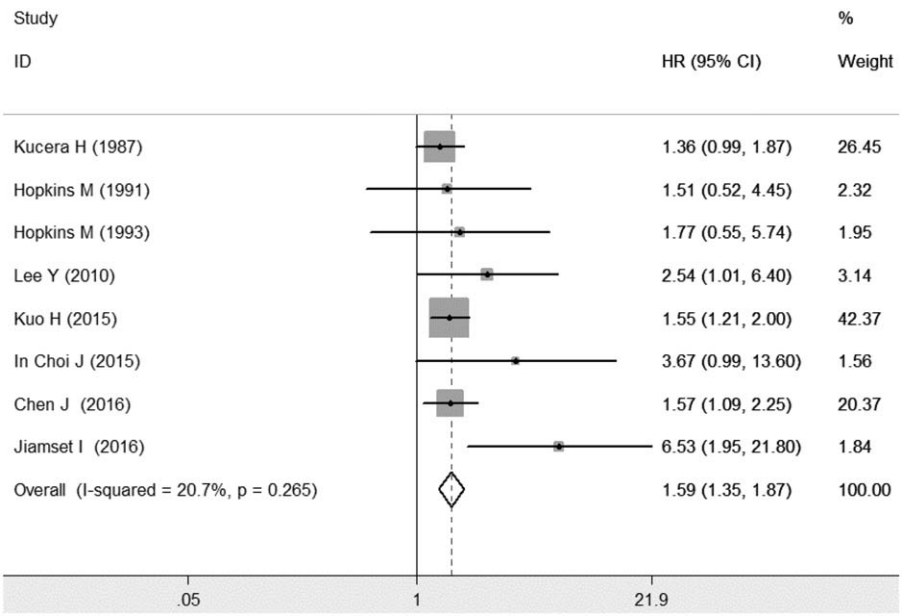

Figure 2. Meta-analysis indicated that diabetes predicted poorer overall survival in cervical cancer patients.

diabetes can be easily diagnosed, it can be a convenient and useful index in the prognostic evaluation of cervical cancer.

A major strength of the systematic review and meta-analysis was the large pooled sample size. Because of the inconsistent findings of the 13 included studies, a meta-analysis was necessary to summarize the predictive role of diabetes in cervical cancer prognosis. A total of 11,091 cervical cancer patients were included into the meta-analysis, which was enough to yield a reliable pooled HR and to appropriately estimate the association between diabetes and cervical cancer prognosis. Another strength was the novelty of this study. To our knowledge, this was the first meta-analysis focusing on the predictive role of diabetes in cervical cancer prognosis. Thus, the findings from the meta-analysis provided a comprehensive evaluation of diabetes as the prognostic factor of cervical cancer for the first time.

Though the prognostic role of diabetes in cervical cancer has been identified, the association between diabetes and cervical cancer risk is still poorly understood. Currently, there is still a lack of well-designed epidemiologic studies to provide evidence for the causal role of diabetes in the development of cervical cancer. In addition, few studies have explored the mechanisms underlying the prognostic role of diabetes in cervical cancer. Previous studies concluded that hyperinsulinemia in diabetes patients might explain the poor prognosis of cancer.[13,52,53]

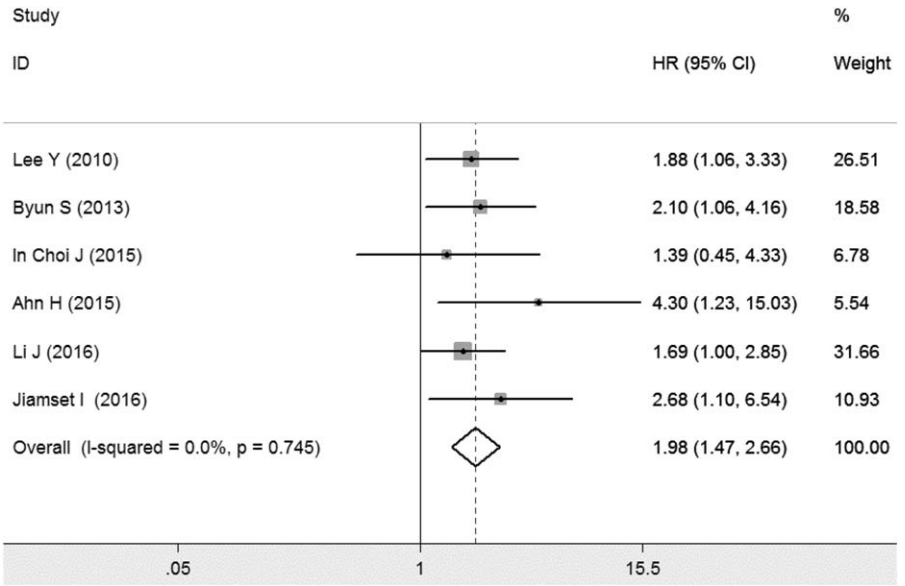

Figure 3. Meta-analysis indicated that diabetes predicted poorer recurrence-free survival in cervical cancer patients.

However, it is still unclear whether hyperinsulinemia can promote the development and progression of cervical cancer. Thus, further experimental studies are needed to explore the related mechanisms.

Several limitations existed in the current meta-analysis. First, all included studies were retrospective cohort studies and thus had possible risk of bias caused by residual confounders. Prospective cohort studies that are well designed and control more confounders are needed to validate recent findings via meta-analysis. Second, there were significant differences in the characteristics of recruited cervical cancer patients, such as age, follow-up period, and adjusted factors. These differences may explain the heterogeneity to some extent. However, the analysis suggested that no significant heterogeneity existed in the meta-analysis. Thus, these differences had limited influence on the association between diabetes and cervical cancer prognosis. Also, under the inclusion and exclusion criteria, most studies included in this meta-analysis were conducted in Eastern Asia, which may led to selective bias of the population and could not be corrected by literature research. Besides, the study carried out by Chen et al did not clearly state their follow-up period. However, the follow-up period is an important factor related to survival rate. Thus, the inclusion of this study may induce some extent of uncertainty in this review. Finally, various therapeutic methods were used and patients with different clinical stages were recruited in the included studies. Because of the small number of studies with a certain therapy or clinical stage, we were not unable to conduct subgroup analyses by therapies and clinical stages to identify the prognostic roles of diabetes in patients receiving a certain therapeutic method and people with different clinical stages of cancer. With more studies conducted in the future, subgroup analyses by therapies and clinical stages are needed to validate the prognostic roles of diabetes in patients receiving different types of treatment or those with different stages.

In conclusion, the meta-analysis suggests that diabetes is an important prognostic factor in patients with cervical cancer, and it is associated with poor survival in cervical cancer patients. The easy diagnosis of diabetes makes it a convenient and useful index for the prognostic evaluation of cervical cancer. However, more prospective studies with larger sample sizes are needed to validate the prognostic roles of diabetes in patients receiving different types of treatments or those with different clinical stages.

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