Meta-Analysis

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Prognostic significance of autophagy-related genes *Beclin1* and *LC3* in ovarian cancer: a meta-analysis

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Abstract

Objective: Beclin1 plays a central role in the activation of the autophagy signaling pathway. Beclin1 and LC3-related proteins are involved in the initial steps of autophagy, which are closely related to the occurrence and development of tumors. The current meta-analysis aimed to clarify the correlation between expression of *Beclin1* and *LC3* and prognosis of ovarian cancer.

Methods: We searched PubMed, Embase, The Cochrane Library, Web of Science, and CNKI using predefined selection criteria. Pooled hazard ratios and relative risks with 95% confidence intervals were used to evaluate the correlation between autophagy-related genes *Beclin1* and *LC3* and overall survival (OS), progression-free survival (PFS), and International Federation of Gynecology and Obstetrics (FIGO) stage.

Results: In total, 1497 patients from 10 articles were enrolled in this meta-analysis. Expression of *Beclin1* was significantly correlated with improved OS and PFS, and increased expression of *Beclin1* was correlated with early FIGO stage, but not with lymph node metastasis or histological grade. No association was found between *LC3* expression and prognosis in patients with ovarian cancer.

Conclusions: Expression of *Beclin1* is an independent risk factor for the progression of ovarian cancer. Thus, *Beclin1* is a promising indicator in predicting prognosis in patients with ovarian cancer.

Keywords

Ovarian neoplasm, autophagy, Beclin-1, LC3, meta-analysis, prognosis

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Introduction

Ovarian cancer is the third most common gynecological malignant tumor in the female reproductive system, with about 21,750 new cases worldwide every year. The 5-year survival rate of ovarian cancer patients is only 48%.[1] According to statistics, 59% of patients have distant metastasis when diagnosed with the disease. Despite tumor cell cytoreductive surgery and first-line chemotherapy, about 70% to 80% of stage III–IV patients relapse within 5 years.[2,3] Ovarian cancer is prone to be resistant to chemotherapy drugs, which greatly affects the prognosis and life quality of patients.

Autophagy is a highly conserved degradation mechanism. The autophagy of eukaryotic cells is effected via three pathways: macroautophagy, chaperone-mediated autophagy, and microautophagy.[4,5] The correlation between autophagy and ovarian cancer has gained increasing attention in recent years. Our previous study demonstrated a critical role of the autophagy-related gene *Beclin1* in the process of killing ovarian cancer cells by chemotherapy, whereas regulation of autophagy of abnormal cell autophagy regulation was closely related to chemotherapy resistance.[6–8] Therefore, with the present meta-analysis, we aimed to assess the correlation between the expression of *Beclin1* and *LC3* in ovarian cancer patients and prognosis. This would aid in exploring the role of autophagy in the occurrence and development of ovarian cancer and provide a reference for the diagnosis, treatment, and prognosis of this disease.

Material and methods

This study was conducted according to the guidelines outlined in Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. Ethical approval and informed consent were deemed unnecessary for this meta-analysis.

Search strategy

Publications were retrieved from the PubMed, Embase, The Cochrane Library, Web of Science, and CNKI databases up to 31 October 2019. The keywords in our investigation were (ovarian cancer or ovarian neoplasm or ovarian tumor or ovarian carcinoma) and (autophagy-related protein or Beclin1 or Beclin-1 or BECN1 or LC3). The search was performed independently in duplicate by two investigators (Xinbei Chen and Yang Sun).

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) any human studies that estimated the level of Beclin1 and LC3 expression and prognosis and were published in English and Chinese; (2) the patients in the original research were definitively diagnosed with ovarian cancer by histopathology; (3) the correlation between *Beclin1* and *LC3* expression and the clinicopathological parameters or prognosis of ovarian cancer was reported; (4) hazard ratios (HRs) and 95% confidence intervals (CIs) could be extracted directly from the article or calculated indirectly by the Kaplan–Meier curve. Studies were excluded if they met one of the following criteria: (1) reviews and case reports; (2) studies carried out on cell or animal specimens; (3) in a language other than English or Chinese; or (4) full-text of the article was not available.

Data extraction and quality assessment

The data were independently extracted by two investigators (Xinbei Chen and Yang Sun) from the published literature, according to the prescribed standards. The results were carefully checked by a third investigator (Bingrong Wang). The specific

characteristics were extracted from each study: first author, year, nation, number of patients, average age, International Federation of Gynecology and Obstetrics (FIGO) stage, lymph node metastasis, and HR. The quality of retrieved papers was evaluated using the Newcastle–Ottawa scale (NOS); the scores varied from 0 to 9, and a score of >6 indicated a high-quality study.

Statistical analysis

Results were pooled and expressed as HR and 95% CI using RevMan5.3 (The Nordic Cochrane Centre, www.cochrane.org) to evaluate the correlation between autophagy-related genes *Beclin1* and *LC3* and prognosis. For studies that only provided the Kaplan–Meier curves, we estimated the HR and 95% CI from the curves. Heterogeneity was assessed by the inconsistency index I^2, which was considered significant at >50%. If the heterogeneity was significant, the random-effects model was adopted; otherwise, the fixed-effects model was used. A sensitivity analysis was performed to estimate the reliability of the pooled result.

Results

Inclusion criteria

A total of 1410 studies were identified according to the search strategy. Of these, 163 studies were removed because of duplication. Then, the abstracts were screened, and 1352 studies were excluded due to duplication or because they were case reports, reviews, or laboratory research reports. After screening the full-text of the articles, 48 studies were excluded. Finally, 10 studies were included for further analysis (Figure 1). These studies were published from 2012 to 2017. One article was in Chinese and the others were in English. The studies encompassed 1497 patients. The expression of *Beclin1* and *LC3* expression in ovarian cancer specimens was evaluated by immunohistochemistry (IHC). The HR of five studies was obtained directly from the articles or, in three studies, indirectly calculated from the Kaplan–Meier curves. The NOS score of the enrolled studies ranged from 5 to 8, and the studies were mostly high quality (Figure 2). The baseline characteristics of the included studies[9–18] are shown in Table 1.

Correlation between Beclin1 and prognosis of ovarian cancer

Six studies reported a correlation between *Beclin1* expression and overall survival (OS).[9–11,15–17] Because the samples were not heterogeneous ($I^2 = 0\%$), the fixed-effect model was applied to calculate the accumulated HR and 95% CI. The results indicated that patients with increased *Beclin1* expression showed improved OS (HR = 0.56, 95% CI: 0.44–0.71, $P < 0.00001$) (Figure 3). Two studies evaluated the correlation between *Beclin1* expression and progression-free survival (PFS),[11,17] and because no heterogeneity was observed ($I^2 = 0\%$), we used the fixed-effects model. The pooled results suggested that the PFS was improved in patients with high *Beclin1* expression (HR = 0.50, 95% CI: 0.32–0.79, $P = 0.003$) (Figure 4).

Correlation between Beclin1 and FIGO stage of ovarian cancer

Eight studies included FIGO stage (III/IV vs. I/II) associated with different expression levels of *Beclin1*.[9–11,14–18] Because of the heterogeneity among the included studies ($I^2 = 74\%$), the random-effect model was used to generate cumulative relative risk (RR), together with the corresponding 95% CI. The results demonstrated that ovarian cancer with elevated *Beclin1*

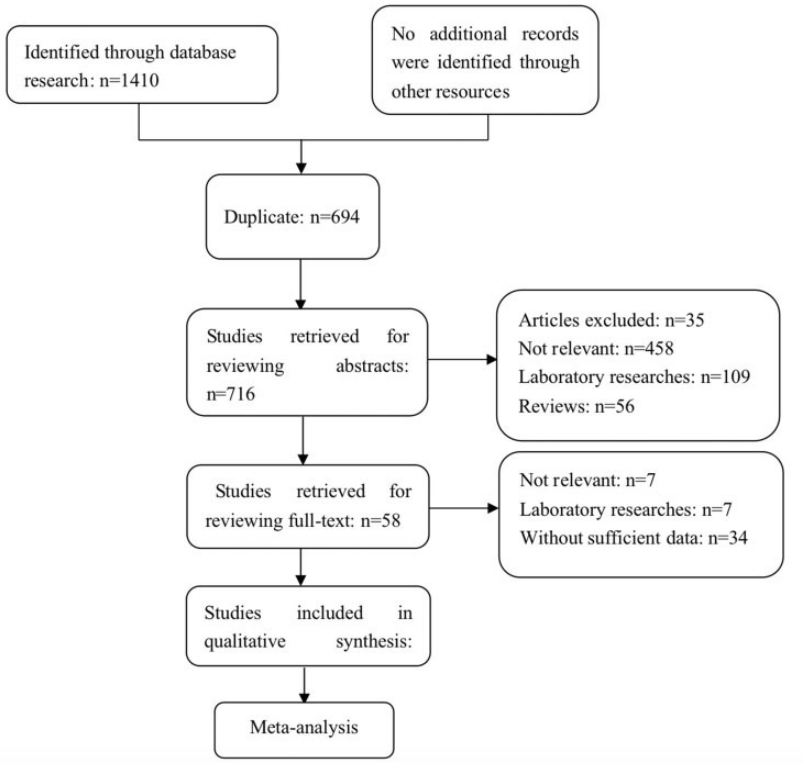

Figure 1. Schematic of the study search and the selection process.

expression was predisposed to early (I/II) FIGO stage (RR = 0.78, 95% CI: 0.62–0.99, $P = 0.04$) (Figure 5).

Correlation between Beclin1 and lymph node metastasis

Four studies elucidated the link between *Beclin1* expression and lymph node metastasis.[9,10,14,16] With obvious heterogeneity among the included studies ($I^2 = 76\%$), the random-effects model was used to generate the cumulative RR and corresponding 95% CI, which showed statistical significance (RR = 0.83, 95% CI: 0.50–1.37) (Figure 6). Although ovarian cancer patients with upregulated *Beclin1* expression had a lower incidence of lymph node metastasis, the difference was not statistically significant.

Correlation between Beclin1 and histological grade

Herein, four studies investigated the association between *Beclin1* expression and histological grade.[9,10,14,16] Because the samples were heterogeneous ($I^2 = 87\%$), the random-effects model was applied to calculate the accumulated RR and 95% CI (Figure 7). No significant association was detected between *Beclin1* expression and histological grade.

Correlation between LC3 and prognosis of ovarian cancer

To further understand the prognosis of LC3, we investigated the correlation between *LC3* expression and OS.[11–13,16] As shown in Figure 8, heterogeneity was

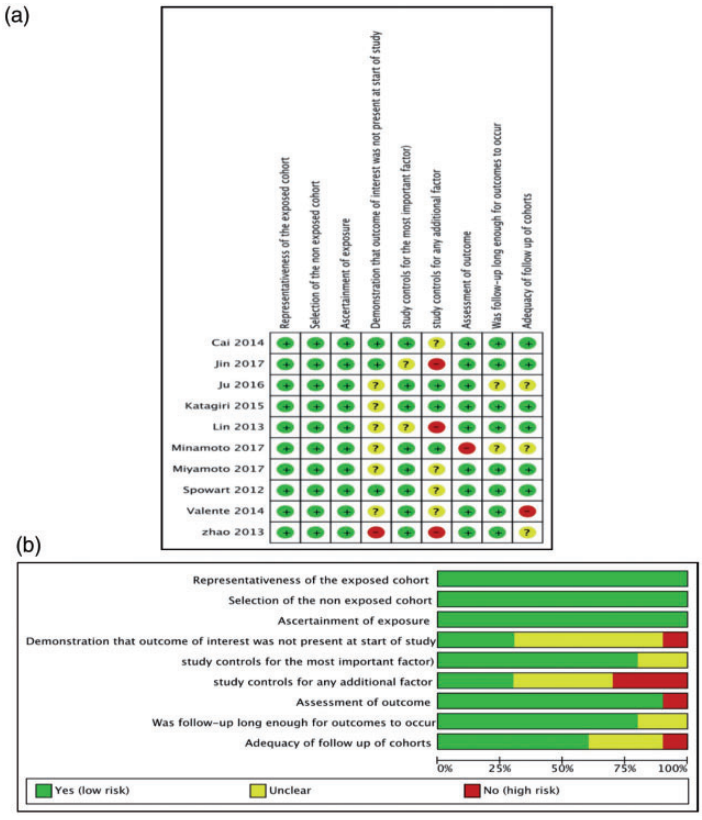

Figure 2. Risk of bias graph, including (A) risk of bias items for each included study, and (B) judgments about each risk of bias item.

observed ($I^2 = 72\%$) and the random-effects model was applied. The pooled results showed no association between *LC3* expression and prognosis of ovarian cancer patients.

Subgroup analysis

Subgroup analyses were stratified by region, sample size, and method of extraction (direct extraction of HRs and 95% CI from the published paper versus indirect extraction from Kaplan–Meier curves) for OS. As shown in Table 2, the combined HRs for China and other regions were 0.59 (95% CI: 0.45–0.79, $P = 0.0004$) and 0.48 (95% CI: 0.30–0.76, $P = 0.002$). The combined HRs for small and large sample sizes were 0.56 (95% CI: 0.39–0.81, $P = 0.002$) and 0.56 (95% CI: 0.40–0.77, $P = 0.0005$), respectively, when 100 patients were used as the threshold. In addition, the summary HR was 0.52 for direct extraction group (95% CI: 0.37–0.73, $P = 0.0001$) and 0.56 for the indirect extraction group (95% CI: 0.40–0.77, $P = 0.006$). The heterogeneity of the indirect extraction group was larger than that of the direct extraction group, albeit not significantly.

Sensitivity analysis

Sensitivity analysis was performed to determine the reliability of the pooled results.

Table 1. Baseline characteristics of the included studies.

Author	Region	Sample size	Age (years)	Assay method	TNM stage (I–II/III–IV)	Lymph node metastasis (yes or no)	Histological grade (G1+G2/G3)	Research object	HR statistic
Valente et al., 2014[14]	Italy	61	50.8 (19–84)	IHC	34/27	NA	23/38	*Beclin1*, *LC3*	NA
Katagiri et al., 2015[17]	Japan	60	NA	IHC	45/15	51/9	NA	*Beclin1*	Survival curve
Lin et al., 2013[10]	China	169	61 (46–76)	IHC	50/119	83/86	129/40	*Beclin1*	Data in paper
Spowart et al., 2012[13]	Canada	485	51.2 (20–81)	IHC	NA	NA	NA	*LC3*	Data in paper
Jin et al., 2017[16]	China	63	48 (25–72)	IHC	20/43	47/16	17/46	*Beclin1*, *LC3*	Survival curve
Ju et al., 2016[18]	China	39	57 (29–89)	IHC	19/20	NA	NA	*Beclin1*	NA
Cai et al., 2014[9]	China	148	NA	IHC	65/83	90/24	94/54	*Beclin1*	Data in paper
Miyamoto et al., 2017[12]	Japan	100	48 (35–58)	IHC	63/37	55/15	NA	*LC3*	Data in paper
Minamoto et al., 2017[11]	Japan	141	50.3 (19–79)	IHC	80/61	NA	NA	*Beclin1*	Data in paper
Zhao et al., 2013[15]	China	231	NA	IHC	86/145	NA	NA	*Beclin1*	Survival curve

IHC, immunohistochemistry; TNM, tumor node metastases; HR, hazard ratio.

The pooled HR for OS and FIGO stage was not influenced by the sequential exclusion of studies, indicating the consistency of the results.

Discussion

Autophagy is a highly conserved process of programmed cell death. Under stress, autophagy can also degrade proteins, glycogen, and damaged organelles in lysosomes via a series of pathways and provide energy for cell survival.[19] Abnormal autophagy regulation may lead to tumors. Intriguingly, autophagy plays a dual role in malignant tumors. In early stages, it often inhibits the progression of tumors, whereas in later stages, it resists stress environments such as hypoxia and nutritional deficiency and induces drug resistance to promote tumor development.[20]

Recent studies have demonstrated that the autophagy-related genes *Beclin1* and *LC3* could be used to predict the prognosis of malignant tumors. Beclin1 was found to be associated with the clinical prognosis of patients (breast cancer and gastric cancer), and patients with high expression of *Beclin1* exhibited a satisfactory outcome.[21,22] Researchers are paying more attention to the correlation between autophagy and gynecological malignancies. Our previous study discovered that the upregulation of Beclin1 was related to the downregulation of vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP-9); both proteins inhibit cell proliferation, invasion, and metastasis. In addition, cervical cancer patients with high expression of *Beclin1* show a higher 3-year OS.[23] Studies concerning autophagy and ovarian cancer in the SKOV3/DDP cell line demonstrated that Beclin1 regulates antitumor activity through a mitochondrial-dependent pathway. Cells with high expression of *Beclin1* showed an increasing number of apoptotic cells under

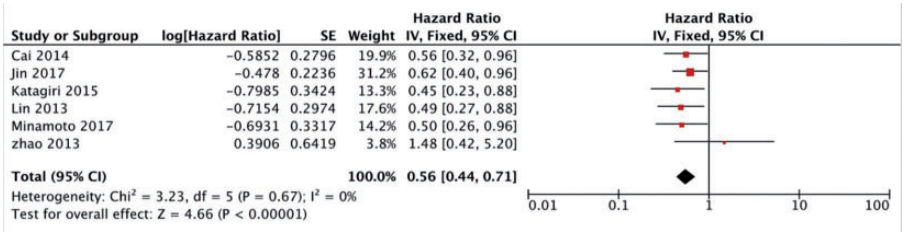

Figure 3. Forest plot for the association between *Beclin1* expression and overall survival. CI, confidence interval.

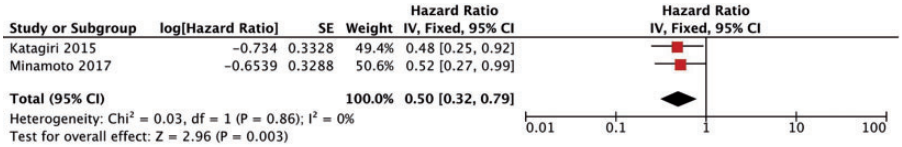

Figure 4. Forest plot for the association between *Beclin1* expression and progression-free survival. CI, confidence interval.

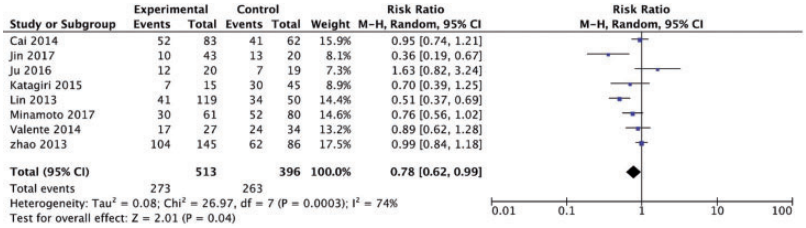

Figure 5. Forest plot for the association between *Beclin1* expression and International Federation of Gynecology and Obstetrics (FIGO) stage. CI, confidence interval; M-H, Mantel-Haenszel.

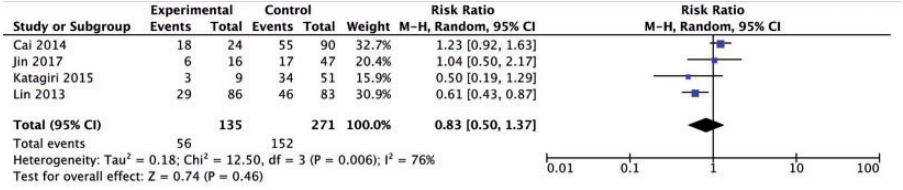

Figure 6. Forest plot for the association between *Beclin1* expression and lymph node metastasis. CI, confidence interval; M-H, Mantel-Haenszel.

a specific concentration of cisplatin.[8] Recent studies have found that autophagy may be related to targeted therapy of ovarian cancer. Wen et al.[24] proposed a human-derived monoclonal antibody MORAB-003 (farletuzumab) against folate receptor-α (FRα) by regulating autophagy-related genes *Beclin1* and *LC3-II*, which can

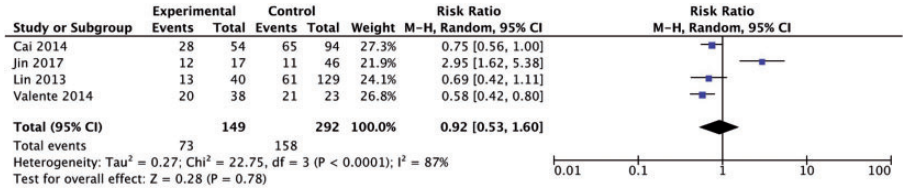

Figure 7. Forest plot for the association between *Beclin1* expression and histological grade. CI, confidence interval; M-H, Mantel-Haenszel.

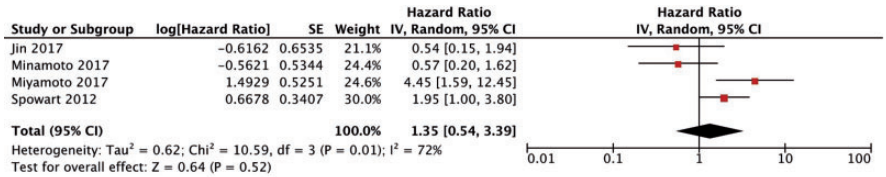

Figure 8. Forest plot for the association between LC3 expression and overall survival. CI, confidence interval.

Table 2. Results of subgroup analyses for *Beclin1* expression and overall survival.

Stratified analysis	Number of studies	HR (95% CI)	*P*-value	Heterogeneity I^2 (%)	Heterogeneity *P*-value
Region					
China	4	0.59 (0.4–0.79)	0.0004	0	0.47
Other	2	0.48 (0.30–0.76)	0.002	0	0.83
Sample size					
<100	2	0.56 (0.39–0.81)	0.002	0	0.43
≥100	4	0.56 (0.40–0.77)	0.0005	0	0.46
Extracted method					
Direct	3	0.52 (0.37–073)	0.0001	0	0.94
Indirect	3	0.61 (0.43–0.86)	0.006	26	0.26

HR, hazard ratio; CI, confidence interval.

promote the expression of LC3-II and the formation of autophagic vacuoles. We found a meta-analysis that evaluated the prognostic role of autophagy-related proteins in epithelial ovarian cancer in 2017,[25] but the number of studies included was smaller and the quality was average compared with those of the current meta-analysis. It found that the expression of *Beclin1* and *LC3* was not related to the prognosis of ovarian cancer, a finding that is inconsistent with recent clinical studies. In our meta-analysis, we included a larger number of recent clinical studies of higher quality to better reflect the relationship between the expression of *Beclin1* and *LC3* and the prognosis of ovarian cancer. Our results showed that ovarian cancer

patients with high expression of *Beclin1* had better prognosis, longer OS and PFS, and earlier FIGO stage than those with low expression. However, expression of *LC3* was not significantly correlated with prognosis of ovarian cancer. In our study, *Beclin1* expression was not associated with lymph node metastasis or histopathological grade. Thus, additional studies focusing on the correlation between autophagy and ovarian cancer are essential. Zhou et al.[26] conducted cell experiments and found that tanshinone I promotes *Beclin1* expression and increases autophagy to suppress the proliferation of the ovarian cancer cell lines A2780 and ID-8 by inhibiting the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway. Liang et al.[27] proposed that the transfection of STAT-DN (dominant negative signal transducer and activator of transcription) in SKOV3 ovarian cancer cells inhibits the mitogen-activated protein kinase (MAPK) and PI3K/AKT/mTOR signaling pathways, activates the expression of autophagy-related molecules, reduces the resistance of cells to cisplatin therapy, and promotes cell death. These studies suggested a putative mechanism for the prognosis of ovarian cancer with the highly expressed *Beclin1*. Bhattacharjee et al.[28] demonstrated that ormeloxifene promotes the expression of *Beclin1* and *LC3-II* by inhibiting the PI3K/AKT/mTOR signaling pathway, which in turn, significantly reduces the size of ovarian cancer tumors in mice. As described earlier, several studies have found that the drug-elevated expression of *Beclin1* promotes the death of ovarian cancer cells, reduces tumor volume, and improves the prognosis of ovarian cancer patients, which is consistent with the results of the current meta-analysis. Beclin1, a protein that interacts with either BCL-2 or PI3k class III, plays a critical role in the regulation of both autophagy and cell death, and LC3 is an autophagy-related protein considered to be a sign of ongoing autophagy.[14] Usually, the expression of *Beclin1* and *LC3* is highly consistent. However, in the current meta-analysis, expression of *LC3* was not significantly correlated with the prognosis of ovarian cancer. This might be due to the high expression of BCL-2, which may cause *Beclin1* to lose the effect of autophagy and decrease autophagy, which might show that the expression of LC3 was negative.[14] Minamoto et al.[11] noted that cancers that are *Beclin1*-positive but *LC3*-negative may be associated with a function of Beclin1 outside its involvement in autophagy. In a previous study, Rohatgi et al.[29] reported that Beclin1 regulates growth factor signaling, including AKT and the extracellular signal-regulated kinase (ERK) pathway. More in-depth clinical research is required to explore this issue.

The present study has some limitations. First, the studies included were all cohort-based, which represents a medium quality of clinical evidence; the meta-analysis lacked non-public published literature. Second, the IHC methods and scoring criteria adopted in each study were slightly different. The evaluation methods were qualitative and not quantitative. Moreover, the samples investigated in this meta-analysis were obtained intraoperatively, making it impossible to investigate longitudinal changes in expression of *Beclin1* and *LC3* before and after chemotherapy. Furthermore, for some studies, we extracted HR values using the Kaplan–Meier curve, which might have introduced some errors in the results. Our study was not registered in PROSPERO.

Conclusion

The expression of the autophagy-related gene *Beclin1* is an independent risk factor that affects the prognosis of ovarian cancer

patients. It can be applied to screen patients for poor prognosis and would provide a basis for clinicians to develop personalized treatment plans. prospective and large-scale studies are essential to confirm the correlation between autophagy and the prognosis of ovarian cancer. We hope to explore the correlation between autophagy and chemotherapy resistance through clinical trials in the future.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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