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ORIGINAL ARTICLE

Prognostic value of cyclin E expression in patients with ovarian cancer: a Meta-analysis

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Summary

***Purpose**: Cell cycle is mainly mediated by cyclins, cyclin-dependent kinases (CDK), and CDK inhibitors. Cyclin E is the main regulator for transition from G1 to S phase, and is involved in cancer pathogenesis, progression and metastasis. Nevertheless, there is still a controversy of the prognostic value of cyclin E overexpression in ovarian cancer patients. This meta-analysis is the first study aimed at analyzing the effect of cyclin E overexpression on the prognosis of ovarian cancer.*

***Methods:** By systematically searching the PUBMED, EMBASE and MEDLINE databases for relevant articles with publication dates up to January 2016 and selection following inclusion and exclusion criteria, 8 studies with 1470 patients were enrolled in our meta-analysis. The overall survival (OS) of patients with cyclin E overexpression was calculated using hazard ratio (HR) with 95% confidence intervals (CIs). The studies were categorized according to the author and year, demographic data in each study, ovarian cancer related information, and cyclin E cut-off value.*

***Results:** Cyclin E overexpression in ovarian cancer was a poor prognostic factor with statistical significance for OS (HR=1.48, 95%CI: 1.12,1.85). Using confunnel, we found no publication bias in our analysis.*

***Conclusion:** Cyclin E might be considered as a prognostic factor for ovarian cancer, as supported by our meta-analysis. However, more high-quality studies should be conducted to find better clinical use of cyclin E in ovarian cancer.*

***Key words:** cyclin E, meta-analysis, ovarian cancer, prognosis*

Introduction

Ovarian cancer, which has relatively high incidence and mortality among gynecological malignancies, is a serious health issue worldwide [1]. This malignancy is the seventh most common cancer and the eighth cause of death from cancer in women worldwide, especially in developed countries where it is the fifth most common cancer and the sixth cause of death [2]. In 2012, it was estimated that 238,700 women were diagnosed with ovarian cancer and 151,900 died of disease worldwide while these figures in 2003 were 225,500 and 140,200 respectively [2,3]. According to reported studies, the incidence ranges from more than 7.5 cases per 100,000 in developed areas to less than 5 cases per 100,000 in Sub-Saharan Africa [4].

Ovarian cancer can be divided into different histopathological subtypes and epithelial ovarian cancer is the most common and lethal among all kinds of ovarian cancer [1,5]. Since ovarian cancer patients are asymptomatic for a long time, over two-thirds of them are diagnosed with advanced stage, leading to lower OS rate and worse quali-

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ty of life [6]. Cytoreductive surgery and systemic chemotherapy are the current standard treatment of ovarian cancer patients [7]. A platinum compound combined with paclitaxel are first-line agents for ovarian cancer patients and they can effectively reduce tumor burden [8]. However, recurrence is a very common phenomenon and second-line options are not so credible [9]. Therefore, apart from finding specific methods to make early detection, finding specific agents to make treatment of ovarian cancer more effective is one of the most important strategies to improve prognosis of patients with this disease. Until now, studies indicated that anti-angiogenics and polyadenosine diphosphateribose polymerase (PARP) inhibitors are the most effective agents, whereas other approaches target aberrant pathways such as the PI3K/AKT/MTOR network, the epidermal growth factor receptor (EGFR), the WEE1 tyrosine kinase and the folate receptor alpha [10]. Immunotherapy can be used to eliminate regulatory T cells or change them into effector T cells or blocking the activity of plasmacytoid dendritic cells [11,12]. In addition, disturbance of the cell cycle will result in increased proliferation and genomic and chromosomal instability [13]. Mechanisms of regulating the cell cycle mainly consist of cyclins, CDK, and CDK inhibitors [14]. Cyclin E is a key regulator for transition from G1 to S phase of cell division through p21-p27-cyclin E-CDK2 pathway, which is governed by the genes CCNE1 and CCNE2 [13,14]. Overexpression of cyclin E has been found in ovarian cancer, but its prognostic value is controversial [15]. Accumulating evidence shows that cyclin E expression is an important prognostic biomarker in ovarian cancer while other authors don't accept this opinion [16-19]. To figure out the association between cyclin E overexpression and prognosis in ovarian carcinoma, we undertook this meta-analysis.

Methods

Search strategy

We extensively searched PUBMED, MEDLINE, EMBASE databases for relevant articles on the relationship between overexpression of cyclin E and prognosis of ovarian cancer up to January 2016. The search strategy was designed as follows: (ovarian cancer or carcinoma) and (cyclin E). 244 publications were retrieved. Two evaluators (Wang and Qi) screened the retrieved articles independently according to the inclusion criteria (see below). Academic divergence between evaluators was resolved by a third researcher (Ming) through discussion.

Inclusion criteria

Inclusion criteria were as follows: (I): The study should be clinical trial investigating the relationship between cyclin E and the prognosis of ovarian cancer patients diagnosed by histopathologic findings; (ii): Cyclin E of tissue or plasma should be evaluated by immunohistochemistry (IHC) or western blot (WB); (iii): The endpoint index should include OS and HR with 95%CI which should be reported or could be calculated by survival curves and p value.

Exclusion criteria

(i): Reviews, editorials, letters, case reports and non-human research were excluded; (ii): Duplicate data or overlapping analyses by the same author(s) or from the same research center or the article with smaller sample size was excluded; (iii): Every study with a population less than 25 patients was excluded. (iv): Studies with incomplete data were excluded.

Extraction of data

The data recorded for each article required first author's name, publication year, country of study, number of patients, specimen source, clinical stage, methods of HR estimation, analytic index, cut-off value , HR and its 95% CI and prognostic value of cyclin E for OS in patients with ovarian cancer. Data were extracted respectively by two researchers (Wang and Qi) and disagreements were resolved by a third researcher (Ming) through discussion.

Quality assessment

The quality of methodology was judged independently by two researchers (Wang and Qi) using the Newcastle-Ottawa Scale (NOS). NOS criteria contain 8 assessment items for nonrandomised studies, including case-control and cohort studies. A 'star system' has been developed in which a study is assessed on three broad perspectives: the selection, the comparability and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. Each of 8 items was identified 'high' quality choices with a 'star'. Items got scores when the studies were consistent with the 'high' quality choices. Study quality was defined as high when the NOS score was 7. Any discrepancy between the two researchers was resolved by a third researcher (Ming) through discussion.

Statistics

Statistical heterogeneity between studies was estimated with the I^2 (inconsistency index) statistic [16]. I^2>50% was considered as statistical heterogeneity significant and a random-effect model would be used; otherwise, a fixed-effect model would be adopted [17-19].

Publication bias was evaluated by confunnel.

When analyzing each eligible study, we marked the results as '+' when overexpression of cyclin E predicted a poorer OS. Otherwise, results were marked as '-' when overexpression of cyclin E didn't show a relationship with poorer OS. The OS of patients with cyclin E overexpression was measured using HR with 95% CI [20]. Survival analysis between cyclin E overexpression positive group and cyclin E overexpression negative group was considered statistically significant when two-sided p value was <0.05.

All statistical analyses were conducted using Statistical Package of Social Sciences (SPSS) Version 22.0 (SPSS Inc., Chicago, IL, USA) software.

Results

Searching results

The PubMed, Medline and Embase search finally yield 244 articles by key words (ovarian cancer or carcinoma) and (cyclin E). Six potentially relevant articles on the association between cyclin E overexpression and ovarian carcinoma patient prognosis studies were excluded following our criteria because they didn't contain HR values and Kaplan-Meier curves. Ultimately, 8 studies were included in this meta-analysis [21-28]. Our selection process is shown in Figure 1.

Characteristics and quality assessment of selected studies

After reviewing full texts for details, 8 studies satisfied the selection criteria. The main characteristics of the 8 eligible studies are presented in Table 1. All selected studies did obtain informed consent from every participant, and every study was approved by an ethics committee or institutional review board. The included studies contained a total of 1470 cases and ranged from 66 to 493 patients.

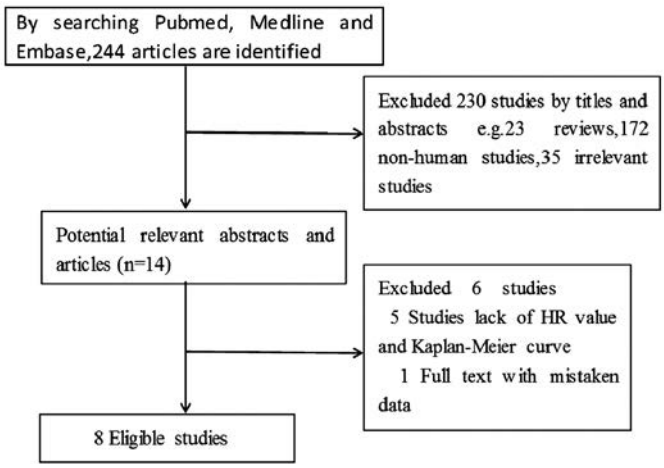

Figure 1. Search results and study selection for all the clinical trials included in our study.

Quantitative data analysis

Significant heterogeneity was observed across the studies with I^2= 57%.

Firstly we analyzed HR of OS between cyclin E positive and cyclin E negative groups. OS was used as prognostic factor in all studies**.** Among these 8 studies, the HRs ranged from 0.183 to 2.4. In the pooled analysis, the combined HR associated with cyclin E positive groups compared to cyclin E negative groups was 1.48 (95%CI:1.12,1.85, p=0.02), demonstrating that high cyclin E expression was related with poor OS (Figure 2).

Publication bias

Publication bias for all pooled HRs with CIs was evaluated using Confunnel. No publication bias was shown in this meta-analysis (Figure 3).

Discussion

In this meta-analysis, a total of 1470 ovarian cancer patients were included in the 8 eligible independent studies. The results of this meta-analysis indicated that the overexpression of cyclin E in ovarian cancer patients is a poor prognostic factor with statistical significance for OS (HR=1.48, 95%CI: 1.12, 1.85, p=0.023), which fits into most of the current research. There have been thousands of studies aimed at finding prognostic factors of ovarian cancer, including genes, mRNA and proteins, e.g. skp2, miRNA, cyclin D1, while there is a controversy of the prognostic value of cyclin E [29-31]. Cyclin E overexpression is recognized as a marker of poor prognosis in several malignancies, such as gastrointestinal cancer, breast cancer, lung cancer, bladder cancer and rectal cancer [32-36]. Cyclin E overexpression is very common in ovarian cancer too which was noted in 30.8-78% in cancer patients with 10% cut off value [22,27]. Nonetheless, whether cyclin E overexpression can be accepted as prognostic factor is still uncertain. As far as we know, this meta-analysis is the first to elucidate a statistically significant association between cyclin E overexpression and prognosis of patients with ovarian cancer.

The prognostic significance of cyclin E levels in patients with ovarian cancer was first presented in 1998 [37]. Cyclin E is the main regulator for transition from G1 to S phase of the cell cycle. Activity of cyclin E–cdk2 complexes is necessary for G1 to S transition, which is inhibited by p27. In mid G1 cyclin E is increasingly expressed and around the G1/S transition it reaches a peak, while

Table 1. Main characteristics of 8 included studies

NOS score	Prognostic p value	HR (95%CI)	HR estimation	Survival analysis	Cutoff value	FIGO stage		Specimen source		Country	First author (Year)
8	-(0.31)	1.5 (0.7-3.1)	given	OS and PFS	>496,553	III–IV:75	WB	Tissue	75	USA	Bedrosian (2007)
8	-(no data)	1.15 (0.89-1.48)	given	OS	10%	I–II:172 III–IV:321	IHC	Tissue and Blood	493	Denmark	Heeran MC (2012)
7	+(0.02)	1.5 (1.1–2.2)	given	OS	40%	III–IV:139	IHC	Tissue	139	USA	Farley J (2003)
8	+(<=0.001)	2.4 (1.8-3.3)	given	OS and PFS	10%	I–II:64 III–IV:341	IHC	Tissue	405	USA	Rosen DG (2006)
8	-(0.21)	1.32 (0.86–2.05)	given	OS and PFS	10%	I–II:14 III–IV:120	IHC	Tissue	134	Australia	Bali A (2004)
7	-(0.75)	0.86 (0.330-2.19)	given	OS and PFS	70%	III–IV:66	IHC	Tissue	66	Japan	Hashimoo T (2011)
7	-(0.821)	0.183 (0.17-4.071)	given	OS	10%	I–II:28 III–IV:50	IHC	Tissue	78	Korea	Leey YH (2011)
7	-(0.54)	0.76 (0.32, 1.83)	given	OS	10%	I–IIA:26 IIB–IV:26	IHC	Tissue	80	USA	Blegen H (2000)

it completely disappears as soon as entering early G2 and in the cdk2 complexes is replaced by cyclin A [38]. Furthermore, cyclin E has correlation with regulating centrosome function at mitosis so chromosomal instability and aneuploidy can be caused by overexpression of cyclin E [39]. What's more, cyclin E-cdk2 complexes are also able to phosphorylate RB protein which is a regulator to start a new round of cell division [40]. Overexpression of cyclin E causes hyperphosphorylation of RB protein so as to decrease the length of G1 and accelerate the transition into S-phase which can promote excessive proliferation [41]. Meanwhile, cyclin E overexpression fortifies phosphorylation of PHF8 (plant homeodomain finger protein 8) so as to promote S phase progression [42]. Hence, disturbance of cell cycle due to abnormal expression of cyclin E may be one of the reasons leading to the development and progression of ovarian cancer with its overexpression being related with poor prognosis. Therefore, drugs targeting cyclin E or its pathway may work for cancer patients. For example resveratrol and a novel proteoglycan (P1) isolated from Phellinus linteus can inhibit cell proliferation by inducing S-phase arrest through activating p27Kip1 which works as cyclin E inhibitor [43,44]. On the other hand, a panel of 7 TAAs (tumor-associated antigens), containing cyclin E, survivin, p53, p16, cyclin B1, cyclin D1 and cyclin A have a little bit higher sensitivity while not decreasing specificity in immunodiagnosis of ovarian cancer than the panel of 6 TAAs without cyclin E and they can differentiate ovarian cancer patient from normal people [45].

In this meta-analysis, effect was undertaken to minimize selection bias. We did our best to avoid selection bias in the literature search and discreet data extraction by three researchers. The methodologic quality of each eligible study was judged by NOS score, showing that the included studies were all of good quality with data extraction scores not lower than 7. Through confunnel, we assured that no publication bias was shown in our meta-analysis.

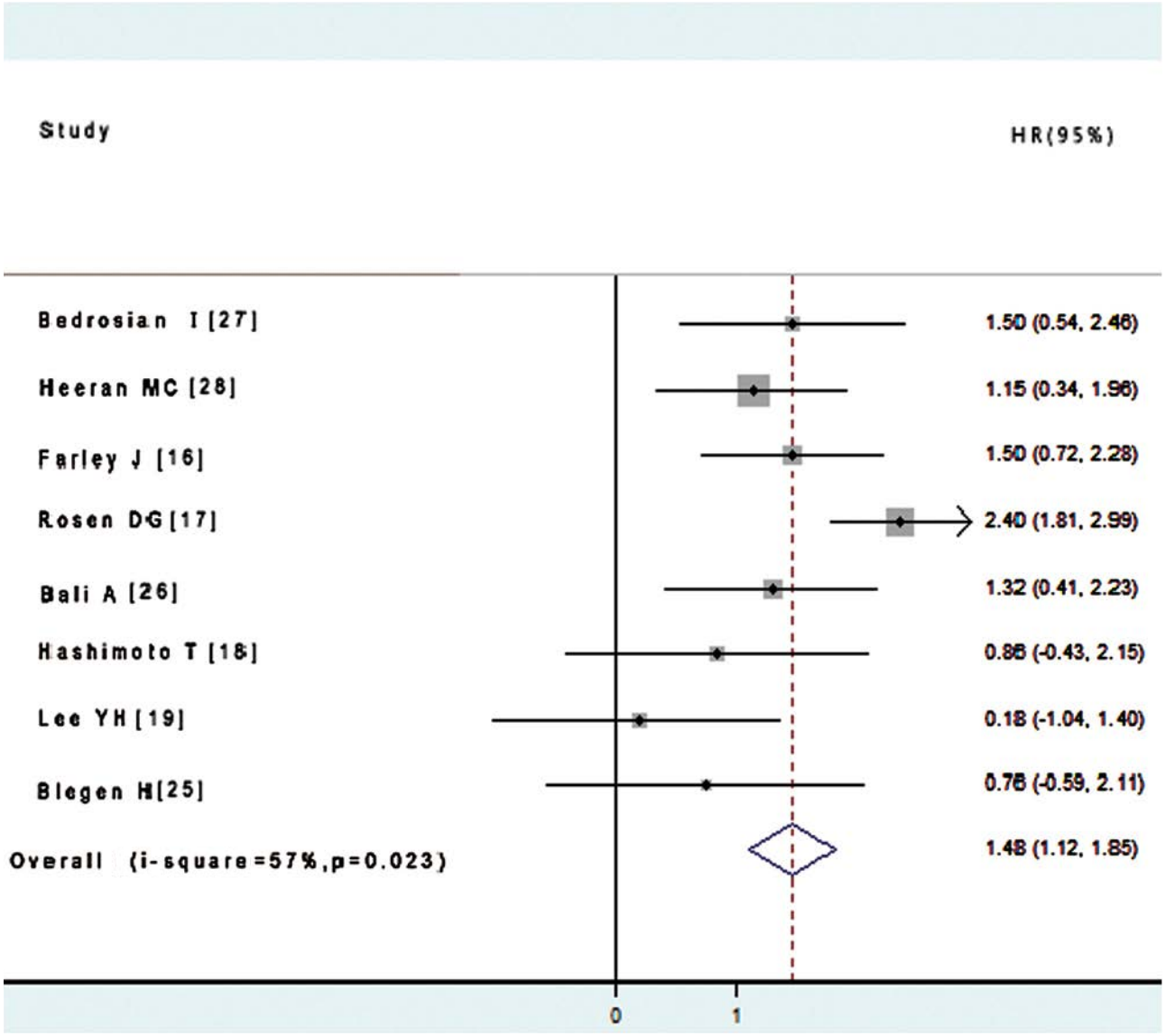

Figure 2. Forrest plot of the association between cyclin E and overall survival of ovarian cancer stratified by hazard ratio estimation.

The results of this meta-analysis are challenging as they may provide further basis of developing new markers for ovarian cancer prognosis and for the development of new therapy strategies. Nevertheless, the real effect of cyclin E in ovarian cancer should be further supported by more clinical trials.

Admittedly, there are several limitations of this meta-analysis. First, all of the studies evaluating the association between cyclin E and prognosis were observational studies, which would not be as reliable as prospective studies, especially when compared with randomized controlled trials. Second, no standardized cutoff value defined variability for cyclin E positive and negative studies. A study included even cyclin E expression levels as continuous variables other than cutoff value because it's more accurate [25]. Another study used 70% as cutoff value according to published reports but it didn't give the references, and the overexpression of cyclin E was noted in only 16.7% of ovarian cancer patients based on 70% cutoff value [26]. Third, the sample size was relatively limited in this meta-analysis so as to lead to insufficient statistical power to assess the prognostic performance of cyclin E in ovarian cancer patients. Fourth, we failed to perform meta-analysis in regard to ovarian cancer histologic subtypes. Finally, notable heterogeneity existed between the individual studies and this was probably caused by differences in study design, study population and statistical methods. Considering these limitations, though our results indicated that cyclin E overexpression is an available prognostic factor for OS in ovarian cancer patients, we could not identify an independent prognostic role. Hence, it is necessary to handle these results with

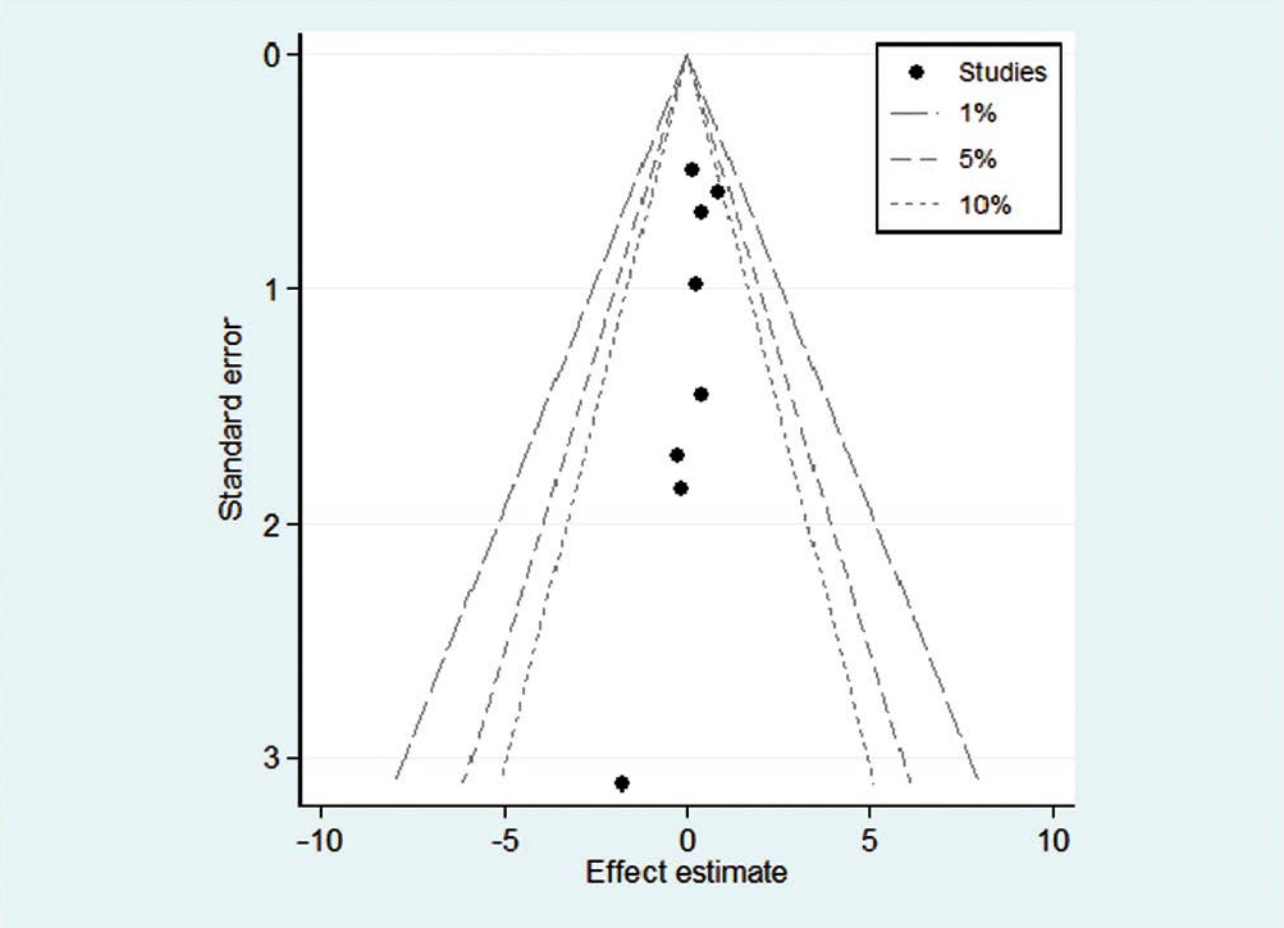

Figure 3. Funnel plot of publication bias showing no significant bias.

caution.

In conclusion, our meta-analysis revealed for the first time that cyclin E is a negative prognostic factor in ovarian cancer on account of patients with cyclin E positive ovarian cancer having a poor OS. Based on these results, cyclin E can be a prognostic factor for ovarian cancer to guide the use of adjuvant therapy after cytoreductive surgery. In addition, in order there is a need for more high-quality studies to find a reliable clinical use of cyclin E in ovarian cancer, following agreed research approaches or standards.

Conflict of interests

The authors declare no confict of interests.

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