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Review Article

A meta-analysis of the prognostic value of circulating tumor cells in ovarian cancer

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Abstract: Objective: To evaluate the prognostic value of circulating tumor cells (CTCs) in ovarian cancer. Methods: Chinese databases (Wanfang, Cqvip, CNKI) and English databases (PubMed, Web of Science, Embase, SinoMed, Cochrane Library) were retrieved to collect relevant studies on CTCs evaluation of ovarian cancer prognosis. Data were extracted to analyze the effect of CTCs on the overall survival (OS) and progression-free survival (PFS) of patients, and a meta-analysis was performed using Stata 15 software. Results: Nineteen studies were included in this meta-analysis. The results showed that ovarian cancer patients with positive CTCs had a shorter OS and higher death rate, (HR=1.57, 95% CI: 1.30, 1.84), a shorter PFS and an increased risk of disease progression (HR=1.29, 95% CI: 1.04, 1.54) compared with patients with negative CTCs. Subgroup analysis showed that the HRs for death and disease progression were higher in CTCs-positive patients after treatment than those patients with negative CTCs ($P<0.05$). Conclusion: CTCs detection has a high application value in the prognosis assessment of ovarian cancer.

Keywords: Ovarian cancer, prognosis, circulating tumor cells, meta-analysis

Introduction

Ovarian cancer is a gynecological malignancy with high incidence rate, and the data released by International Agency for Research on Cancer (IARC) in 2018 showed that the incidence of ovarian cancer ranked ninth in malignant tumors and eighth in mortality among women in 185 countries or regions worldwide [1]. Early diagnosis and timely treatment are the keys to improve the prognosis of ovarian cancer, but the proportion of early diagnosis of ovarian cancer is low at present, and more than 70% of patients have been already in stage III or IV upon diagnosis, leading to poor prognosis [2]. Despite significant advances in antitumor therapy for ovarian cancer, a high proportion of patients have recurred or progressed within 18 years after treatment [3]. Accurate assessment of the prognosis of patients before and after treatment can provide a reference for the development of follow-up and subsequent intervention plans, which is of great significance to improve the prognosis of patients. At present, the main methods for clinical evaluation of the prognosis of ovarian cancer are serum marker (CA125 and HE4 etc.) tests and imaging analysis, but the accuracy has not yet reached a satisfactory level [4]. Recent studies have shown that circulating tumor cells (CTCs) can assist in the clinical diagnosis and prognosis assessment of various malignancies [5]. CTCs before or after treatment are associated with clinicopathological features and prognosis in patients with ovarian cancer. Ovarian cancer patients with positive CTCs have higher proportion of advanced cancer, poor tumor differentiation, poor prognosis, and a higher risk of recurrence and progression after surgery or antitumor therapy [5]. A variety of studies have shown that CTC is a predictive indicator for ovarian cancer prognosis, and positive CTCs are associated with shorter progression-free survival and overall survival [5-8]. In this study, we intended to investigate the value of CTCs in prognostic assessment of ovarian cancer through meta-

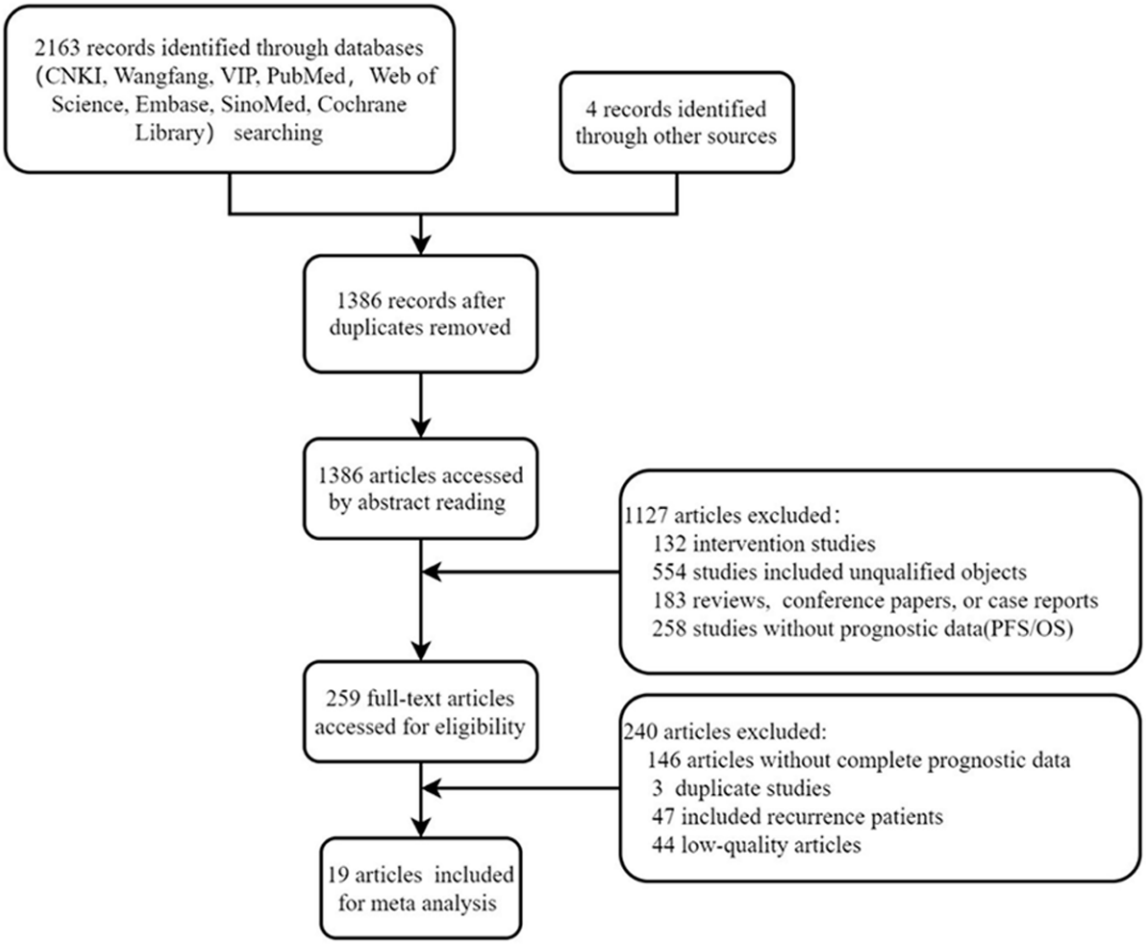

Figure 1. Literature screening process.

Table 1. Basic profile of the included literatures

Authors	Year	Sample size	Detection time	Cell enrichment	Assays	Analysis	Prognostic indicators	NOS
A Poveda [16]	2011	216	Before treatment	IM	Cellsearch	Multifactorial	OS, PFS	7
E Obermayr [12]	2013	35	Before treatment	PM	RT-PCR	Multifactorial	OS, PFS	8
JD Kuhlmann [17]	2014	143	Before treatment	IM	RT-PCR	Multifactorial	OS, PFS	7
MX Sang [7]	2014	80	Before treatment	NA	RT-PCR	Multifactorial	OS	7
M Lee [8]	2017	24	Before treatment	IM	ICC	Multifactorial	OS, PFS	7
T Fehm [18]	2013	30	After treatment	PM	ICC	Multifactorial	OS, PFS	8
M Banys Paluchowski [19]	2020	43	Before treatment	IM	Cellsearch	Multifactorial	OS, PFS	8
M Banys [20]	2009	112	After treatment	PM	ICC	Single factor	OS, PFS	7
MJ Mo [21]	2018	56	After treatment	NA	Cellsearch	Multifactorial	OS, PFS	6
M Thalgott [22]	2015	122	After treatment	IM	Cellsearch	Multifactorial	OS	8
JF Liu [23]	2013	30	Before treatment	IM	Cellsearch	Single factor	OS, PFS	6
T Fan [24]	2009	71	Before treatment	PM	ICC	Single factor	OS, PFS	8
ML Pearl [25]	2013	88	Before treatment	IM	ICC	Single factor	OS, PFS	8
K Behbakht [26]	2011	54	After treatment	PM	Cellsearch	Single Factor	OS	7
SO Gening [27]	2021	31	Before treatment	IM	Cellsearch	Multifactorial	PFS	6
E Obermayr [28]	2017	78	Before treatment	IM	Cellsearch	Multifactorial	OS	8
Yang J [29]	2021	114	Before treatment	PM	ICC	Multifactorial	PFS	7
I Chebouti [30]	2017	65	After treatment	PM	RT-PCR	Single factor	OS	7
ZK Zhao [31]	2019	30	Before treatment	IM	ICC	Single factor	OS	6

Note: PM: physical method; IM: immunological method; ICC: immunocytochemistry; NA: not reported.

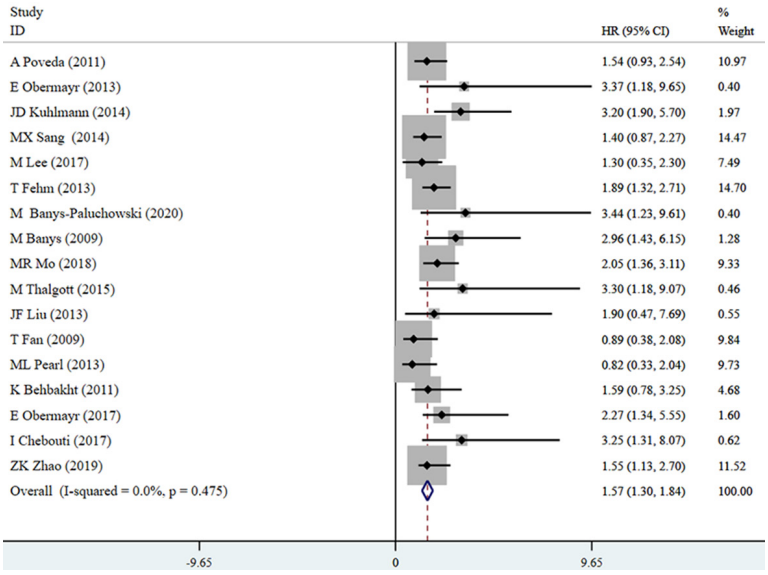

Figure 2. Meta-analysis of the correlation between CTCs and OS in ovarian cancer patients.

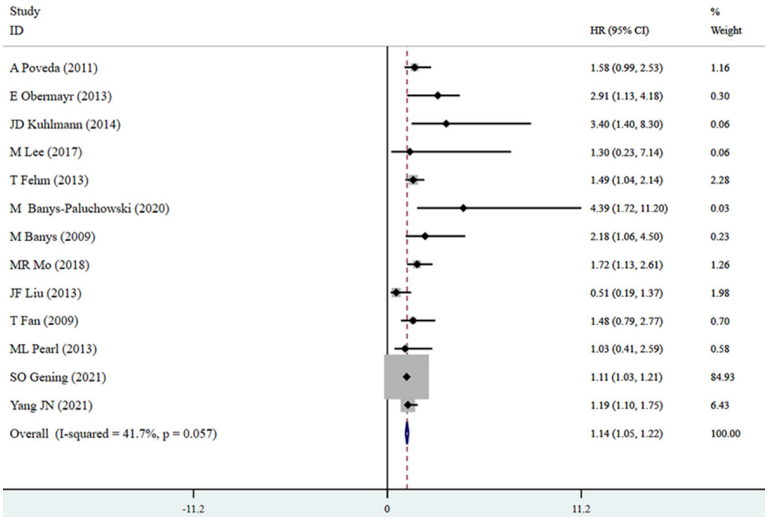

Figure 3. Meta-analysis of the correlation between CTCs and PFS in ovarian cancer patients.

analysis and provided new markers for post-treatment monitoring and assessment.

Materials and methods

Literature inclusion criteria

(1) Research type: clinical observation of CTCs in predicting the prognosis of ovarian cancer. (2) Subjects: patients with ovarian cancer diagnosed by pathological examination. (3) Literature in English and Chinese. (4) Pre-treatment, or (and) post-treatment CTCs assay results were provided. (5) Correlation of CTCs with patient prognosis was assessed, with description of either overall survival (OS) or progression free survival (PFS).

Literature exclusion criteria

(1) Duplicate publications-only include the literature with the largest sample size; (2) Interventional studies; (3) Studies involving patients with relapse; (4) Reviews, abstracts, and conference papers; (5) Incomplete outcome data; (6) Animal studies; (7) Case reports; (8) Those with no access to full text; (9) Low-quality literature (NOS≤5).

Literature search

The Chinese and English electronic databases were searched, and the Chinese databases included China National Knowledge Infrastructure (CNKI), Wanfang database, and Cqvip database, and the English databases included PubMed, Web of Science, Embase, SinoMed, and Cochrane Library. The time frame ranges from January 2005 to December 2021. Chinese keywords: ovarian cancer, circulating tumor cells, prognosis, survival (Chinese translations of these terms); English keywords: ovarian cancer/ovarian carcinoma/ovarian tumor, circulating tumor cells/CTCs/disseminated tumor cells/DTCs. MseSH-related terms, subject terms in association with free words were searched.

Literature screening and data extraction

Literature screening was performed independently by two investigators (two gynecologists, Shenjie Li and Yali Ni in our hospital). Verification was done by a third researcher when there

Table 2. Results of subgroup analysis

Indicators	Subgroup	OS			PFS		
		n	HR (95% CI)	*P*	n	HR (95% CI)	*P*
Analysis method	Univariate	7	1.57 (1.30, 1.84)	0.093	4	0.90 (0.46, 1.35)	0.292
	Multivariate	10	1.75 (1.41, 2.09)		9	1.15 (1.06, 1.23)	
Detection time	Before treatment	11	1.38 (1.06, 1.70)	0.040	10	1.12 (1.03, 1.20)	0.027
	After treatment	6	1.99 (1.31, 2.46)		3	1.61 (1.18, 2.04)	
Cell enrichment methods	IM	9	1.48 (1.08, 1.88)	0.850	7	1.11 (1.02, 1.19)	0.066
	PM	6	1.62 (1.15, 2.10)		5	1.35 (1.09, 1.61)	
Assay method	Cellserach	7	1.82 (1.32, 2.33)	0.346	5	1.11 (1.02, 1.20)	0.015
	RT-PCR	4	1.72 (1.08, 2.35)		2	2.99 (1.60, 4.39)	
	ICC	6	1.39 (1.03, 1.75)		6	1.29 (1.03, 1.55)	

Note: OS: overall survival; PFS: progression-free survival; PM: physical method; IM: immunological method; ICC: immunocytochemistry.

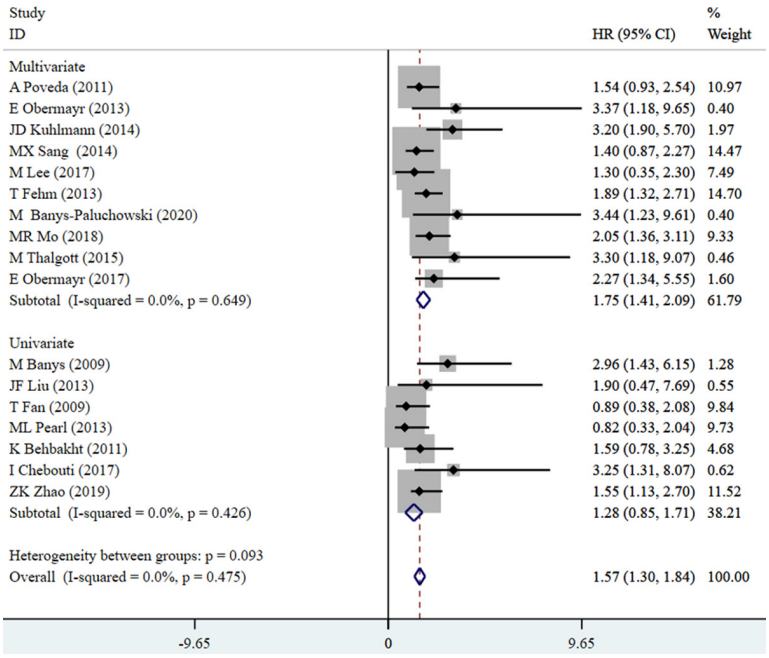

Figure 4. Subgroup analysis of OS-data analysis method.

was a controversary (head of research of this study). Data extraction was performed for the included literature, and differences were recounted by the third researcher. Data collection forms were established, including authors, year of publication, study populations, CTCs enrichment methods and monitoring methods, CTCs detection results, and prognostic parameters. If a correlation between CTCs and prognosis before and after treatment was reported in the literature, both data were applied; if both univariate and multivariate analyses were reported in the literature, only the results of multivariate analysis were included.

Literature quality evaluation

The NOS scale with a range of 0-9 was used to evaluate the quality of literature, and score ≥7 was regarded as high-quality literature [9].

Statistical analysis

Stata 15 software was used for data analysis. Hazard ratio (HR) with 95% confidence interval (CI) was used to describe the correlation between CTCs and OS/PFS in ovarian cancer. Higgins I^2 test was adopted to analyze the heterogeneity of the studies, and prognostic indicators with P≥0.1 or I^2<50% were analyzed using fixed-effect models in meta-analysis, while prognostic indicators with P< 0.1 or I^2≥50% were analyzed using random-effect models. Egger's test was used to calculate publication bias, and funnel plots were drawn to observe its distribution characteristics. Statistical significance was considered at P<0.05.

Results

Literature inclusion process

A total of 19 literatures meeting the inclusion criteria were included in this study, and the literature screening process is shown in **Figure 1**.

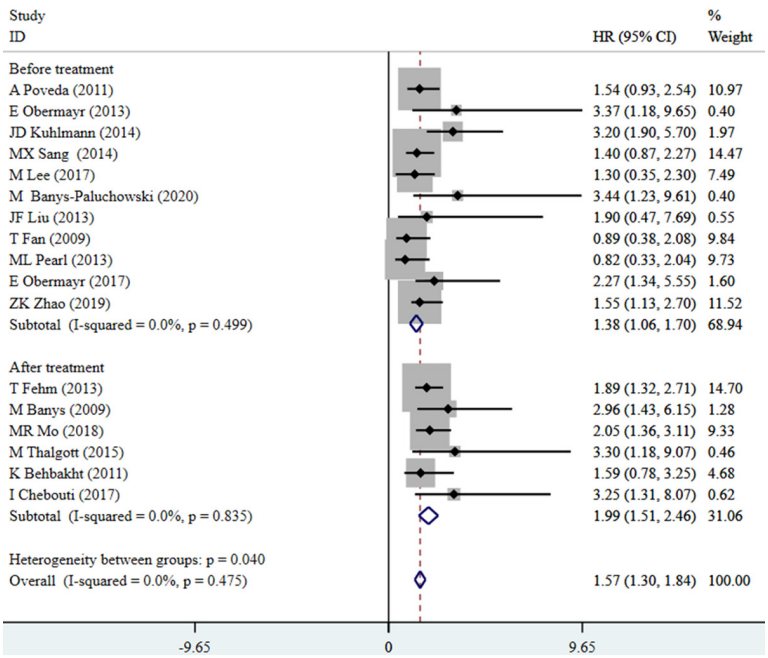

Figure 5. Subgroup analysis of OS-detection time.

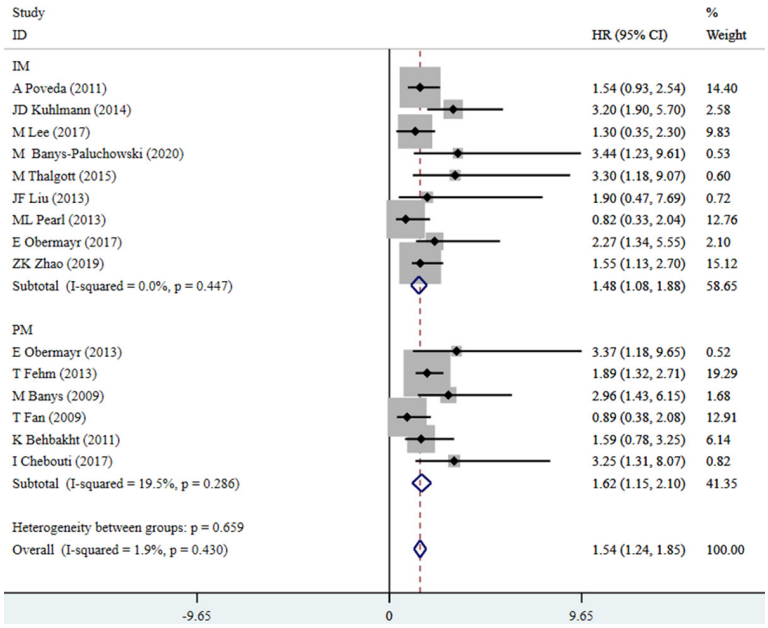

Figure 6. Subgroup analysis of OS-cell enrichment methods.

Basic profile of the included literature

The basic profile of the included literature is shown in **Table 1**. The cumulative number of newly diagnosed ovarian cancer cases included in this study was 1422, with 17 publications in English [7, 8, 12, 16-20, 22-30] and 2 in Chinese [21, 31]. CTCs were detected before treatment in 13 studies and after treatment in 6 studies. Cell enrichment methods: immunological methods were used in 10 studies, physical methods were used in 7 studies, and cell enrichment methods were not reported in 2 studies. CTCs detection methods: RC-PCR was used in 4 studies, Cellsearch was used in 8 studies, and ICC was used in 7 studies. Correlation analysis methods between CTCs and prognostic indicators: univariate analysis was used in 7 studies and multivariate analysis was used in 12 studies. Prognostic indicators: 17 described OS and 13 described PFS. Literature quality: the NOS scores of 19 literatures were of 6-8, and 15 literatures had a NOS score of ≥7 points.

Meta-analysis results

Correlation of CTCs with OS in ovarian cancer patients: The correlation of CTCs with OS was reported in 17 studies. The results of heterogeneity analysis showed I^2=0.0%, P=0.475. Using a fixed-effect model, the results of meta-analysis showed that CTCs-positive ovarian cancer patients had shorter OS and higher morbidity and mortality compared with CTCs-negative ovarian cancer patients (HR= 1.57, 95% CI: 1.30, 1.84) (**Figure 2**).

Correlation of CTCs with PFS in ovarian cancer patients: The correlation of CTCs with PFS was reported in 13 studies. Heterogeneity analysis showed I^2=41.7%, P=0.057. Through a fixed-effect model, meta-analysis showed that CTC-positive ovarian cancer patients had shorter PFS and higher risk of disease progression

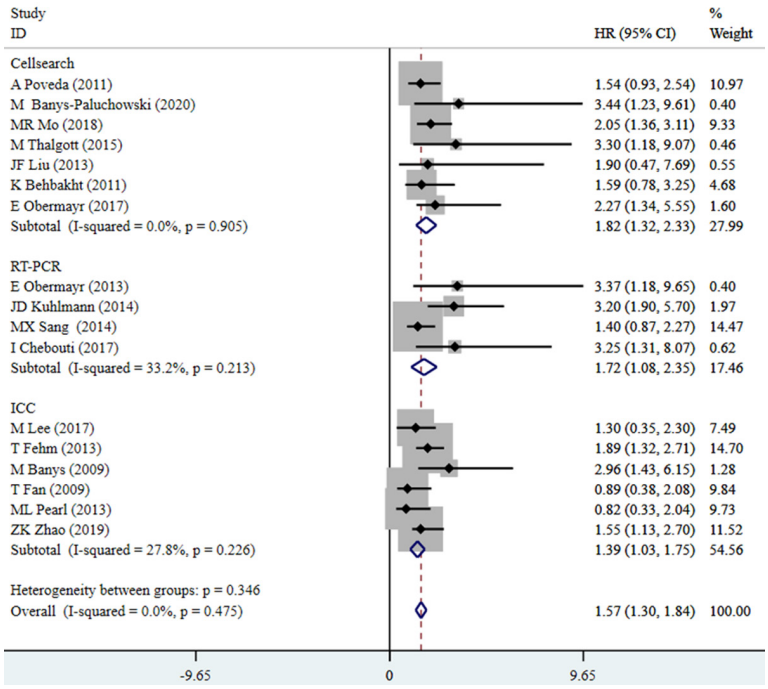

Figure 7. Subgroup analysis of OS-assay methods.

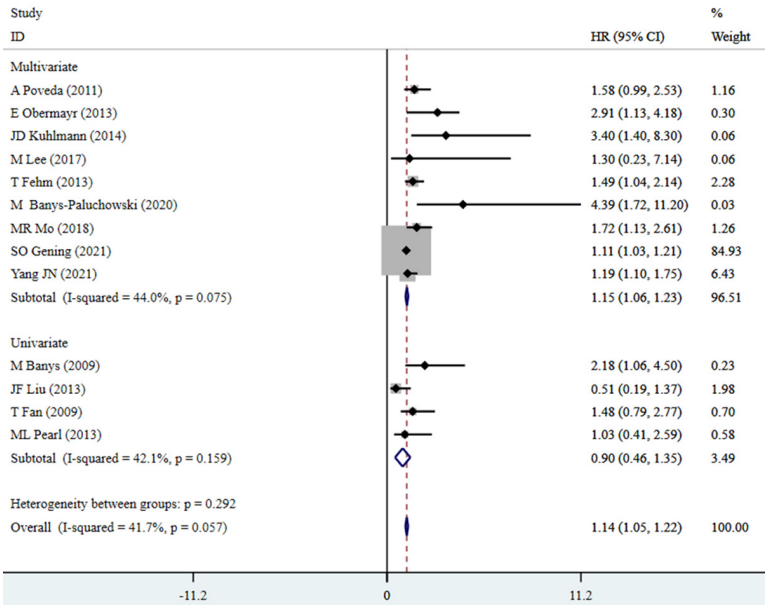

Figure 8. Subgroup analysis of PFS-data analysis method.

compared with CTCs-negative ovarian cancer patients (HR=1.29, 95% CI: 1.04, 1.54) (**Figure 3**).

Subgroup analysis

The results of subgroup analysis showed that there were no statistical differences in OS and PFS between different analysis methods and cell enrichment methods (P>0.05). The prognosis of patients with positive CTCs after treatment was worse, and the HR values of OS and PFS of patients with positive CTCs after treatment were higher than those with positive CTCs before treatment (P<0.05). The HR for PFS was statistically different between the different assays and was significantly higher in those with positive results by RT-PCR assays (P<0.05) (**Table 2**; **Figures 4**-**11**).

Sensitivity analysis

To verify the stability of the results, the correlation analysis was conducted on CTCs with OS/PFS again after excluding each included literature one by one, and the results showed no significant changes in all conclusions.

Publication bias

The OS funnel plot is shown in **Figure 12**. The distribution was basically symmetrical, and egger's test showed P>0.05, suggesting no publication bias. The PFS funnel plot is shown in **Figure 13**, with poor symmetry of the distribution and egger's test of P<0.05, suggesting publication bias.

Discussion

Cells from primary tumor foci or metastases can enter into the blood circulation through the vascular and lymphatic systems, and most of the CTCs are recognized and removed by the immune system, but a small number of cells can acquire a new cell phenotype and survive, and these cells are CTCs. Positive CTCs can indicate high tumor load, and CTC count is positively correlated with tumor load and clinical stage, which

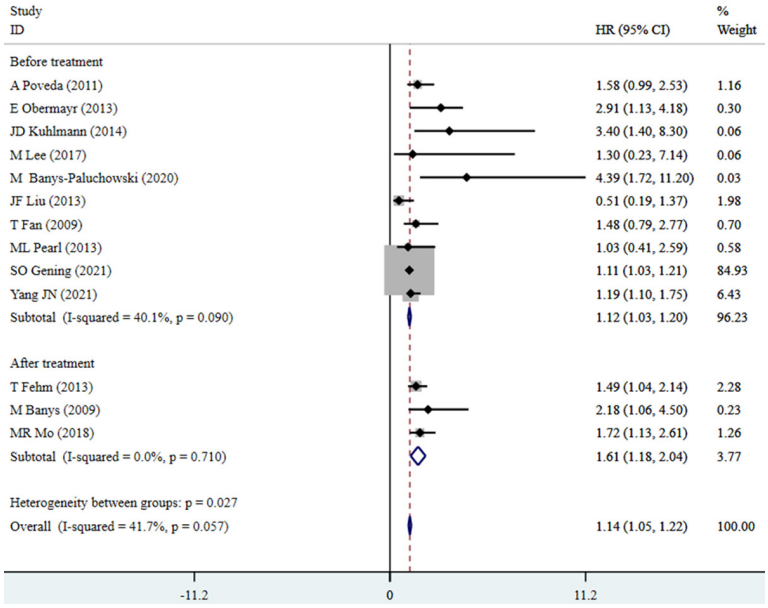

Figure 9. Subgroup analysis of PFS-detection time.

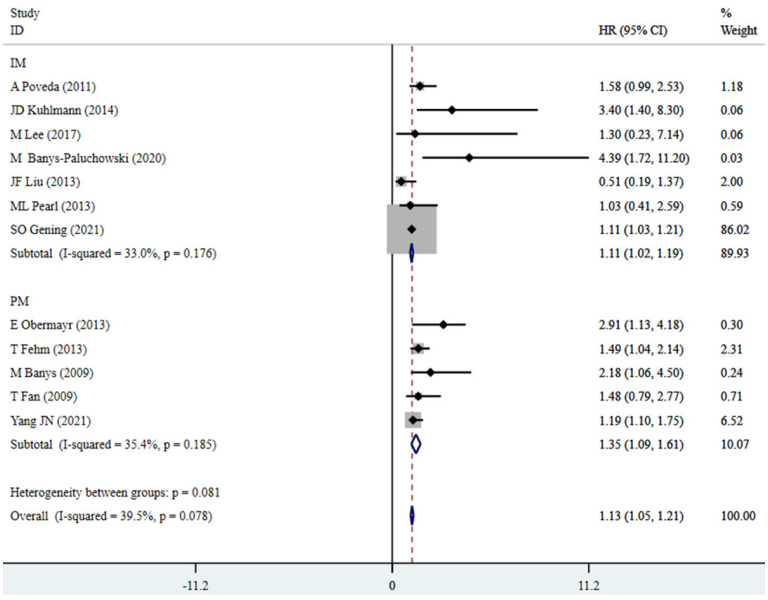

Figure 10. Subgroup analysis of PFS-cell enrichment methods.

can assist in malignancy diagnosis, assessment and monitoring, molecular sequencing and prognostic assessment [6]. Several studies on malignancies, including ovarian cancer, have found that CTCs are correlated with tumor clinicopathological features and may be useful in assessing the efficacy of antitumor treatment and the risk of recurrence [10, 11]. There are few indicators available for real-time monitoring of tumor progression during ovarian cancer treatment and follow-up. CTCs, as non-invasive, reproducible and sensitive markers, have high application potential in the prediction of recurrence, progression and prognosis of ovarian cancer after treatment [7, 8, 12].

CTC is one of the important mechanisms of tumor recurrence and metastasis, which can form microscopic cancer emboli through migration and adhesion under the interaction of microenvironment and tumor growth factors, and the latter further develop into tumor metastases, resulting in worsened prognosis [13]. It has been found that CTCs have the characteristics of epithelial-mesenchymal transition (EMT), which are highly homologous with stem cells, and have strong metastatic ability, and the higher the tumor stage and load, the greater the CTC count in patients and the higher the positive detection rate [14]. Studies related to gastric cancer have shown that CTC counts can be used as a predictor of OS and PFS after chemotherapy, with patients with CTCs <2 having significantly longer OS and PFS than those with ≥2 [15]. The current meta-analysis for ovarian cancer yielded similar results. In this analysis, a positive CTCs test before/after treatment could indicate poor prognosis for ovarian cancer patients, with significantly shorter OS and PFS and an increased risk of disease progression and death in those with positive CTCs compared with those with negative CTCs. These results suggest that pre-treatment or post-treatment CTCs detection has high clinical significance and can assist in prognostic assessment and late management planning.

However, CTCs have not been widely used in tumor diagnosis and treatment due to its high

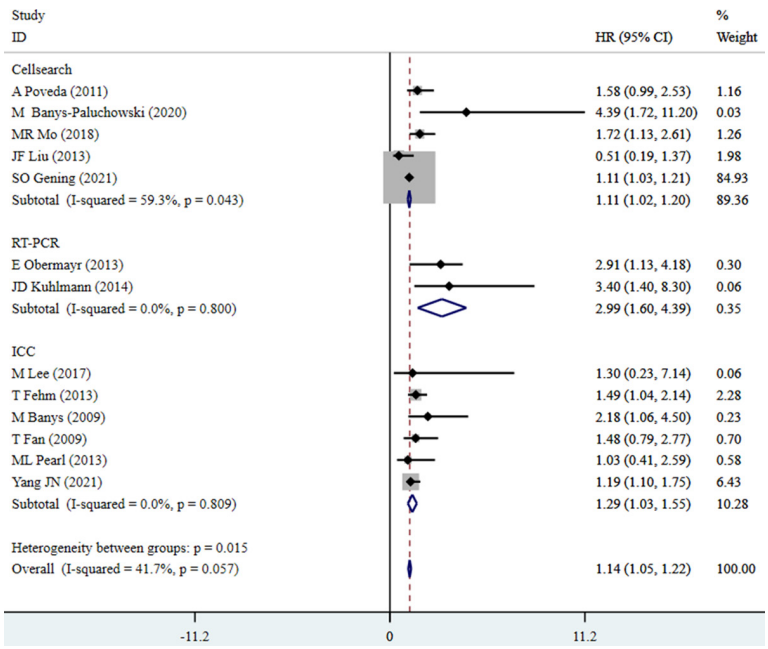

Figure 11. Subgroup analysis of PFS-assay methods.

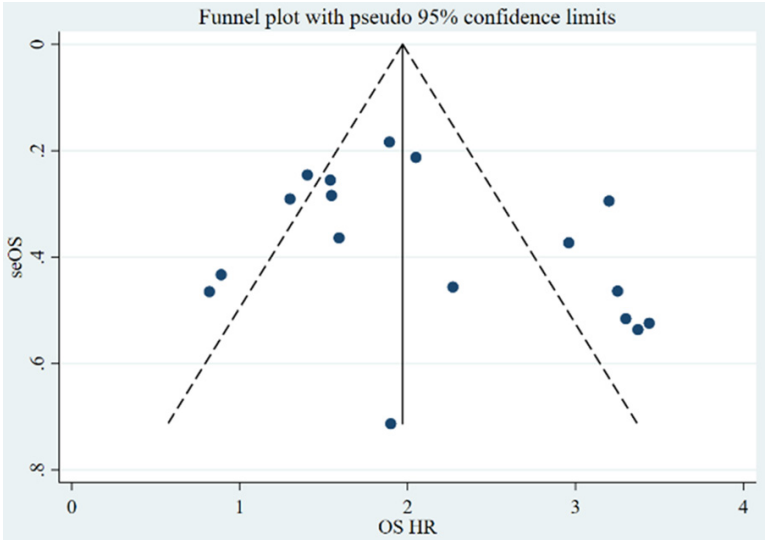

Figure 12. OS funnel diagram.

cost and inconsistent timing and procedures. The detection is usually performed before the start of treatment and after the completion of antitumor treatment regimen, and the detection process mainly includes the isolation, enrichment, detection and identification of CTCs. It can be found from this retrospective analysis that cell enrichment methods in clinical studies mainly include physical and immunological methods. The latter is more widely used, and detection methods mainly include ICC, RT-PCR and Cellsearch detection systems. In this study, subgroup analysis was conducted to explore the correlation between CTCs and the prognosis of ovarian cancer under different detection timing and methods, and the results showed that patients who tested positive for CTCs after treatment had poorer prognosis, higher tumor malignancy, and higher risk of disease progression and death. This suggested that CTCs detection after treatment may have higher clinical value in prognostic assessment. There was no significant difference in the correlation between CTCs and prognosis of ovarian cancer under different cell enrichment methods, but a statistical difference was found between different detection methods. PFS was shorter in those with positive RT-PCR detection, and the specific reasons for this are not clear, but only few literatures in this study adopted RT-PCR detection, which needs to be further analyzed by expanding the sample.

The present study still has some limitations: (1) only Chinese and English literatures were included, which may be under-representative, and there is publication bias in PFS; (2) the impact of CTC count on the prognosis of patients was not evaluated, and medical reference values were not provided; (3) the number of included literatures was insufficient and the number of cases was small, which should be further expanded in future studies.

In conclusion, the present study included more risks compared to similar studies and performed a subgroup analysis to explore the

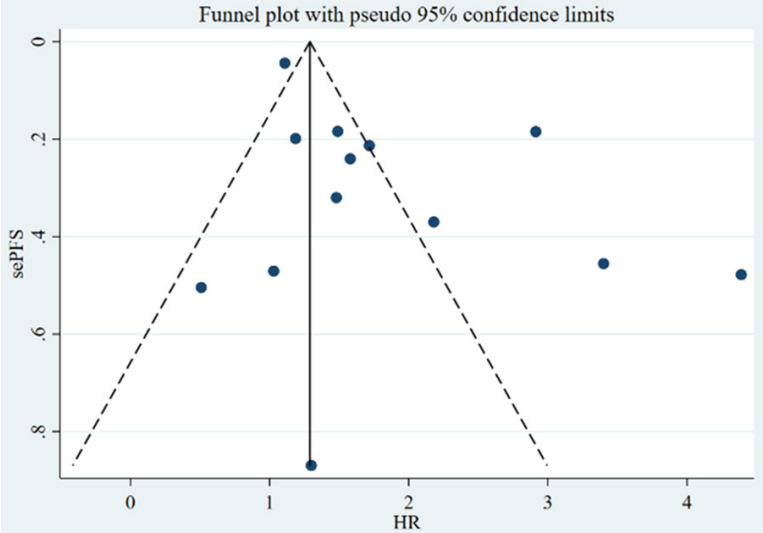

Figure 13. PFS funnel diagram.

effects of assay methods and different assay times on the correlation between CTCs and prognosis. CTCs can be used as biomarkers to evaluate the prognosis of ovarian cancer patients and have high application value.

Disclosure of conflict of interest

None.

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