

Overexpression of the cancer stem cell marker CD117 predicts poor prognosis in epithelial ovarian cancer patients: evidence from meta-analysis

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Purpose: Cancer stem cells have recently been identified as a key driving factor for tumor metastasis and chemoresistance. CD117 is a well-established cancer stem cell marker, but its clinical significance in epithelial ovarian cancer (EOC) remains controversial. Therefore, we aimed to identify correlations between CD117 expression and clinical features and outcomes in EOC patients in this meta-analysis.

Materials and methods: A literature search was performed in the PubMed, Cochrane Library, Web of Science, EMBASE, and OVID databases to identify eligible studies. Correlations between CD117 expression and clinicopathological parameters and overall survival or disease-free survival were analyzed. A subgroup analysis was then performed, which was classified by patient ethnicity and age at diagnosis, study sample size, and tumor histological type.

Results: A total of seven studies enrolling 1,247 EOC patients were included in this meta-analysis. Our results demonstrated that CD117 expression was significantly correlated with age (pooled odds ratio [OR] =1.67, 95% confidence interval [CI] =1.05–2.66), International Federation of Gynecology and Obstetrics stage (pooled OR =1.99, 95% CI =1.31–3.02), tumor differentiation grade (pooled OR =2.46, 95% CI =1.48–4.10), and histological type (pooled OR =1.85, 95% CI =1.05–3.26). EOC patients with high CD117 expression had significantly worse OS (hazard ratio [HR] =1.39, 95% CI =1.03–1.90) than patients with low CD117 expression. However, no significant correlation was found between CD117 expression and disease-free survival (HR =1.31, 95% CI =0.79–2.17). In subgroup analysis, CD117 was identified as a significant prognostic factor for overall survival in European patients (HR =1.59, 95% CI =1.13–2.23), younger patients (<60 years) (HR =1.59, 95% CI =1.10–2.30), studies with sample sizes >200 (HR =1.84, 95% CI =1.32–2.56), and the mixed histological types (HR =1.47; 95% CI =1.08–2.00).

Conclusion: Our meta-analysis suggests that CD117 is associated with EOC progression and can serve as a promising prognostic predictor for EOC patients. However, larger scale multicenter clinical trials are still needed to further validate our results.

Keywords: epithelial ovarian cancer, CD117, cancer stem cell, prognosis

Introduction

Worldwide, epithelial ovarian cancer (EOC) is a common gynecologic malignancy.¹ In the USA, there will be an estimated 22,440 new EOC cases and 14,080 EOC-specific deaths in 2017.² Currently, combined radical surgery and platinum-based adjuvant chemotherapy is standard treatment for EOC patients. With the rapid development of biotechnology, numerous breakthroughs have been achieved in the clinical management of EOC, such as precancerous screening programs, personalized

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neoadjuvant chemotherapy, and immunotherapy.³ Despite these encouraging advances, the overall 5-year relative survival rate of EOC patients is only around 46%, with 73% and 29% of patients experiencing regional and distant metastases, respectively.² This clinical dilemma may largely reflect a lack of reliable biomarkers for early diagnosis, prognostic prediction, and targeted therapy. Recent studies have provided an increasing number of molecular candidates that have been proven to be involved in EOC development.^{4,5} However, most of them failed to be further developed as reliable indicators for clinical management owing to insufficient validation studies. Therefore, it is of great practical significance to conduct a comprehensive evidence-based analysis to clearly confirm their clinical utility in EOC.

Cancer stem cells (CSCs) are a distinct subpopulation of cancer cells known for their self-renewal and ability to generate heterogeneity.⁶ Recently, accumulating studies have identified CSCs as a crucial driving factor for EOC tumorigenesis and metastasis.⁷ Moreover, emerging evidence also suggests that CSCs contribute to chemotherapy resistance in EOC patients, thereby leading to worse disease-free survival (DFS).^{8,9} Experimental studies have revealed that CSC-induced malignant characteristics may be conditioned by the activation of oncogenic signaling pathways (such as Wnt signaling) or the epithelial–mesenchymal transition pathway.^{10,11} Specific cell surface markers, including CD44 and CD133, have been extensively investigated as a means of detecting CSCs, not only in EOC but also in other malignancies.^{12,13} In addition to CD44 and CD133, CD117 is commonly used to identify CSCs among EOC cells. CD117 is a type III receptor tyrosine kinase that regulates cell proliferation, apoptosis, and adhesion by binding to its ligand-stem cell factor.¹⁴ Recent studies have found that CD117 is abnormally overexpressed in various human malignancies and that it may play a crucial role in carcinogenesis and metastasis.^{15,16} With regard to its role in EOC, Zhang et al isolated highly tumorigenic and chemoresistant CSCs from primary human EOC tissues and characterized them as CD44⁺CD117⁺.¹⁷ Using serum-free medium, Yan et al identified CD117⁺CD133⁺ CSCs among the human EOC cell line HO8910 and found that this subpopulation was more likely to develop resistance to conventional chemotherapy agents including cisplatin, doxorubicin, and mitoxantrone.¹⁸ Therefore, CD117 is a crucial CSC marker in EOC that has the potential to be an effective therapeutic target.

Despite its role in promoting EOC development, the clinical significance of CD117 expression for EOC patients remains controversial. Some studies have indicated that

CD117 is an adverse prognostic factor, while other studies found that CD117 expression is unrelated to clinical outcome or may even serve as a favorable prognostic factor.^{19–22} Thus, it is essential to make a comprehensive and objective evaluation of its clinical significance for EOC patients. To achieve this aim, we performed a meta-analysis of seven studies enrolling 1,247 EOC patients to identify correlations between CD117 and clinical features and patient prognosis. This effort will not only provide a novel insight into the clinical significance of CD117 expression in EOC, but also be of great benefit to biomarker-directed precision medicine for this disease.

Materials and methods

Search strategy

The online electronic databases PubMed, Cochrane Library, Web of Science, EMBASE, and OVID were searched for papers regarding clinical correlations between CD117 expression and EOC patients. The deadline for the literature search was December 1, 2016. The search terms used were as follows: “CD117,” “c-kit,” “tyrosine-protein kinase Kit,” “ovarian cancer,” “ovarian carcinoma,” “epithelial ovarian cancer,” “ovarian neoplasm,” “prognosis,” “prognostic,” and “survival.” Other potentially eligible publications were identified by reviewing references from the retrieved papers.

Selection criteria

The inclusion criteria for selecting studies for this meta-analysis were as follows: 1) all patients enrolled in the studies were pathologically confirmed as having EOC; 2) full-length papers provided sufficient data to evaluate CD117 expression and its correlation with patient features and/or prognosis; 3) CD117 expression was detected in the resected tumor tissues instead of other specimen types such as serum; 4) CD117 expression was detected using immunohistochemistry (IHC) instead of Western blot or reverse transcription-polymerase chain reaction; and 5) hazard ratios (HRs) and 95% confidence intervals (CIs) were available, or survival curves and/or *P*-values were given. No limitation was set for the minimum number of enrolled patients during the inclusion process. The exclusion criteria were as follows: 1) studies irrelevant to the research subject; 2) studies that did not involve clinical investigations and only contained cellular assays *in vitro* and/or *in vivo*; 3) reviews or letters without original data; 4) studies lacking accurate information about pathological diagnosis, clinicopathological parameters, or survival data; 5) follow-up periods <2 years; and 6) studies containing duplicate/unextracted clinical data.

Data extraction

All data were extracted and verified independently by two investigators based on the above selection criteria. The general data of the selected studies included first author and publication year. The clinical data of enrolled patients in each study included total number, age at diagnosis, country, follow-up time, histologic type, and International Federation of Gynecology and Obstetrics (FIGO) disease stage. Additionally, other essential details of each study were also extracted, including experimental methods (eg, IHC); IHC cutoff score; ratio of patients with high/low CD117 expression; type of survival analysis; and HRs and corresponding 95% CIs.

Statistical analysis

All statistical analyses were performed using the STATA Software v12.0 (STATA Corp, College Station, TX, USA). Correlations between CD117 expression and clinicopathological parameters, including age FIGO stage, tumor differentiation grade, and histological type, were evaluated using odds ratio (OR) and 95% CI, while correlations with overall survival (OS) and DFS were evaluated using HR and 95% CI. An observed HR >1 suggested that high CD117 expression was associated with poor OS and/or DFS, while a 95% CI >1 indicated that the association was statistically significant. In cases where the HR and 95% CI were not provided directly by the authors, they were estimated using Engauge Digitizer Software v4.1 according to the Kaplan–Meier survival curve data. A random-effect or fixed-effect model was determined by the heterogeneity test across the studies, which was evaluated by the I^2 value. A random-effect model was applied for significant heterogeneity, which was characterized as an I^2 value of >50%, while a fixed-effect model was applied for the remaining cases. Publication bias was evaluated using Begg's and Egger's tests. For all analyses, a P -value <0.05 was considered statistically significant.

Results

Characteristics of the included studies

As shown in Figure 1, a total of 127 potentially relevant papers were initially identified from the electronic databases. Then, 51 papers were excluded owing to duplicate studies, and an additional 60 papers were excluded owing to irrelevant content (27), nonoriginal papers (8), or cellular assays alone (25). Finally, nine papers were excluded owing to insufficient or unextracted clinical data (8) or inconsistent experimental methods (1). The remaining seven papers were used in our meta-analysis.

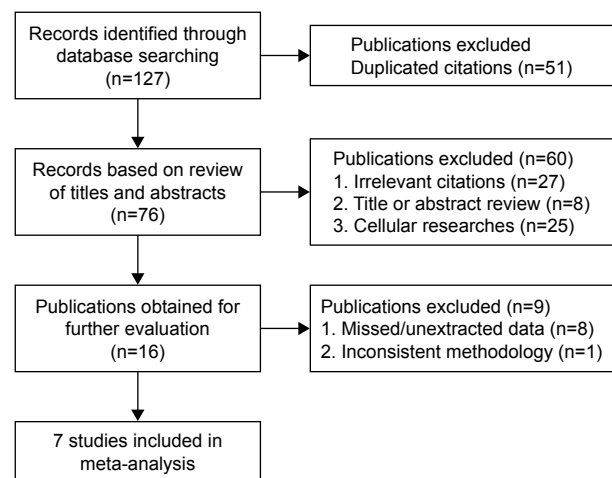


Figure 1 Flowchart of the literature search process.

The characteristics of these seven papers are summarized in Table 1.^{19,21–26} A total of 1,247 EOC patients from seven countries (Germany, Norway, Serbia, Finland, Austria, Canada, and the USA) were enrolled in our meta-analysis. Patient age ranged from 19 to 89 years, and the longest follow-up time was 420 months. Two papers provided complete HRs and 95% CIs in their survival analysis, while the other five papers did not, and so data were estimated by our researchers. Three papers used both OS and DFS in evaluating the prognostic value of CD117 expression in EOC patients, while the other four papers only used OS.

Correlations between CD117 expression and clinicopathological parameters

As shown in Figure 2 and Table 2, using the fixed-effect model, our meta-analysis indicated that CD117 expression was significantly correlated with FIGO stage (III/IV vs I/II, pooled OR =1.99, 95% CI =1.31–3.02, $P=0.519$, $I^2=0.00\%$) and histological type (serous vs mixed, pooled OR =1.85, 95% CI =1.05–3.26, $P=0.212$, $I^2=35.6\%$). Meanwhile, using the random-effect model, our meta-analysis demonstrated that CD117 expression was also correlated with age (>60 years vs <60 years, pooled OR =1.67, 95% CI =1.05–2.66, $P=0.063$, $I^2=71.0\%$) and tumor differentiation grade (poor vs well, pooled OR =2.46, 95% CI =1.48–4.10, $P=0.008$, $I^2=71.2\%$).

Correlations between CD117 expression and patient prognosis

As shown in Figure 3A, using the random-effects model ($I^2=69.2\%$), our meta-analysis based on seven papers revealed that high CD117 expression was significantly

Table 1 Characteristics of the included studies

Study	No of patients	Country	Age (years)	Follow-up (months)	Histologic type	FIGO stage	Cutoff	Method	CD117 high/low	Survival analysis	HR (95% CI)
Ayub et al, ²¹ 2015	55	Germany	55±8.9	44.81 (17.01–72.61)	S55	III 45 IV 10	NA	IHC	NA	OS	1.17 (0.97–1.42)
Huang et al, ²³ 2014	242	Norway	58 (19–89)	0–348	S163M ¹ +E+C48 U+M ² +O27	I-II 46 III-IV 196	10%	IHC	22/220	DFS OS	1.20 (1.03–1.40) 1.78 (1.09–2.89)
Conic et al, ¹⁹ 2015	240	Serbia	NA	NA	S178 M ¹ 22 E30 C10	I48 II20 III126 IV24	25%	IHC	66/174	DFS OS	2.04 (1.29–3.21) 1.36 (0.88–2.10)
Lassus et al, ²⁴ 2004	516	Finland	NA	0–420	S516	I108 II64 III281 IV60	NA	IHC	63/453	OS	2.34 (1.71–3.19)
Brustmann ²⁵ 2005	41	Austria	68 (37–81)	0–200	S41	I17 III12 IIII2	NA	IHC	30/11	OS	1.62 (0.52–5.10)
Tonary et al, ²² 2000	35	Canada	NA	24 (0–50)	S25 M ¹ I E5 C4	I4 III27 IV4	NA	IHC	25/10	OS	0.92 (0.32–2.65)
Khalifeh et al, ²⁶ 2005	118	USA	63 (38–89)	16.6 (0.5–71.37)	S118	III97 IV21	NA	IHC	25/93	DFS OS	0.51 (0.15–1.74) 0.81 (0.48–1.39)

Note: Age presented as mean ± standard deviation or median (range).
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; DFS, disease-free survival; NA, not available; HR, hazard ratio; CI, confidence interval; S, serous carcinoma; M¹, mucinous carcinoma; E, endometrioid carcinoma; C, clear cell carcinoma; U, undifferentiated carcinoma; M², mixed carcinoma; O, others; IHC, immunohistochemistry.

correlated with poor OS in EOC patients (HR =1.39; 95% CI =1.03–1.90). However, when analyzing data from three papers (Figure 3B), we used the same model ($I^2=70.4\%$) to demonstrate that there was no statistically significant association between CD117 expression and DFS in EOC patients (HR =1.31; 95% CI =0.79–2.17).

To further identify whether CD117 could be a reliable prognostic biomarker for EOC patients, a subgroup analysis was performed based on patient ethnicity, age at diagnosis, sample size, and histological type. As shown in Table 3, CD117 expression was found to be significantly associated with poor OS in European patients (HR =1.59, 95% CI =1.13–2.23), younger patients (<60 years, HR =1.59, 95% CI =1.10–2.30), studies with sample sizes >200 (HR =1.84, 95% CI =1.32–2.56), and patients with mixed histological type (HR =1.47; 95% CI =1.08–2.00), but not in non-European patients (HR =0.83, 95% CI =0.52–1.34), older patients (≥ 60 years, HR =0.95, 95% CI =0.54–1.67), studies with sample sizes <200 (HR =1.13, 95% CI =0.95–1.34), and patients with serous type (HR =1.37, 95% CI =0.84–2.24).

Publication bias analysis

The Begg’s and Egger’s tests were employed to evaluate publication bias in our meta-analysis, and the results are presented as funnel plots in Figure 4 and Table 4. No significant publication bias was observed in our meta-analysis regarding the correlation between CD117 expression and clinical features and patient OS/DFS (Begg’s test, Figure 4; Egger’s test, all $P>0.05$, Table 4).

Sensitivity analysis

To estimate the bias caused by the limited number of papers included in our meta-analysis, a sensitivity analysis was performed, and the results are displayed in Figure 5. We found that the pooled HRs of OS and DFS were not significantly changed owing to the omission of any single paper, demonstrating the statistical robustness of our results.

Discussion

Recent studies have shown that CSC markers are promising therapeutic targets and prognostic biomarkers for EOC patients, largely owing to their driving role in metastasis and chemotherapy resistance.⁷ To further validate the clinical implications of the CSC marker, a meta-analysis based on previous literature was used to objectively assess correlations between its expression and clinical features/outcome in EOC patients. For example, in a meta-analysis

enrolling 1,051 EOC patients, high CD133 expression was suggested to be associated with advanced tumor stage and reduced 2-year OS rate.²⁷ A similar result was observed in another meta-analysis enrolling 2,161 EOC patients,

which demonstrated CD44 expression was positively correlated with TNM stage and 5-year OS rate.²⁸ With regard to CD117, to the best of our knowledge, no comprehensive evidence-based analysis is currently available to evaluate

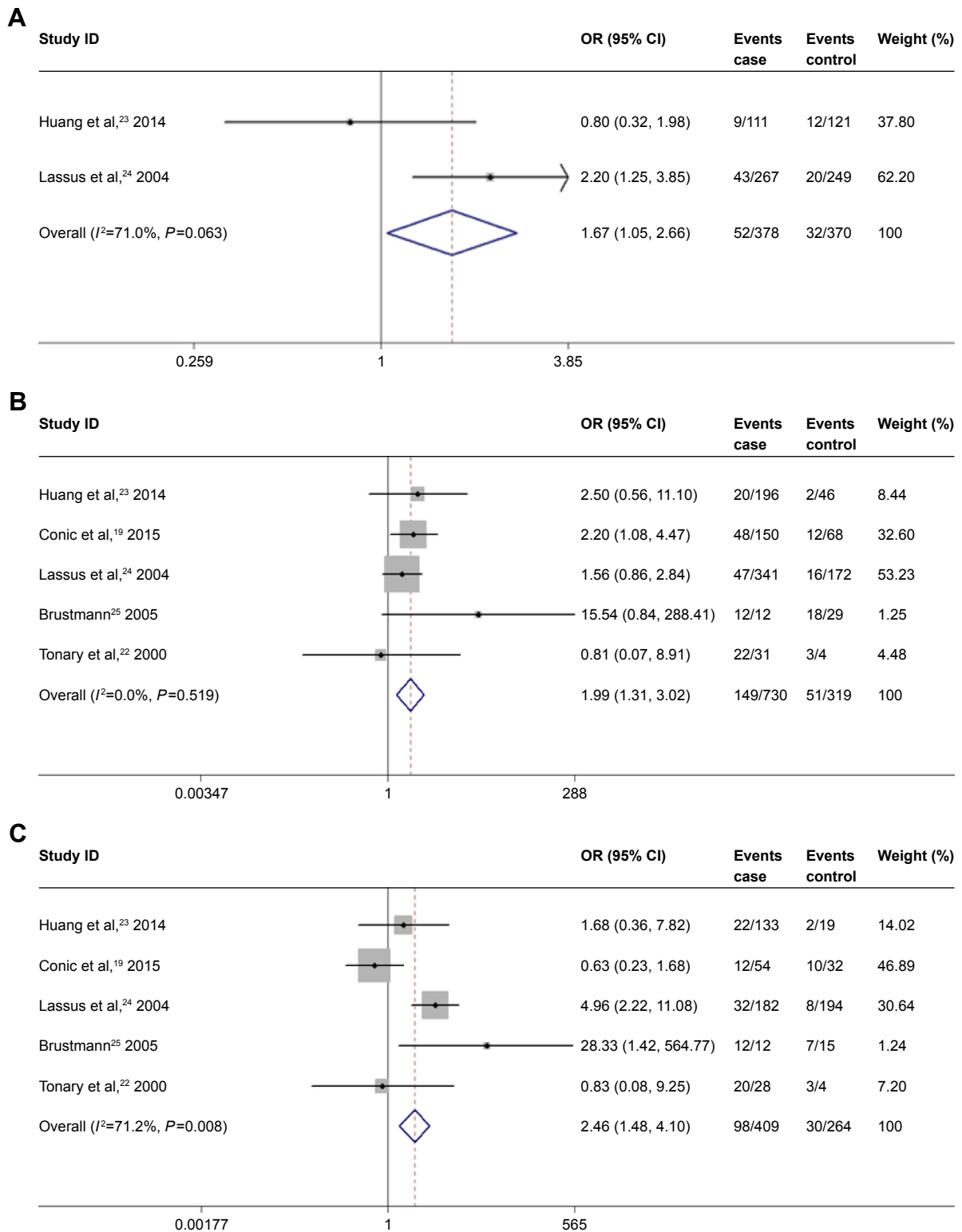


Figure 2 (Continued)

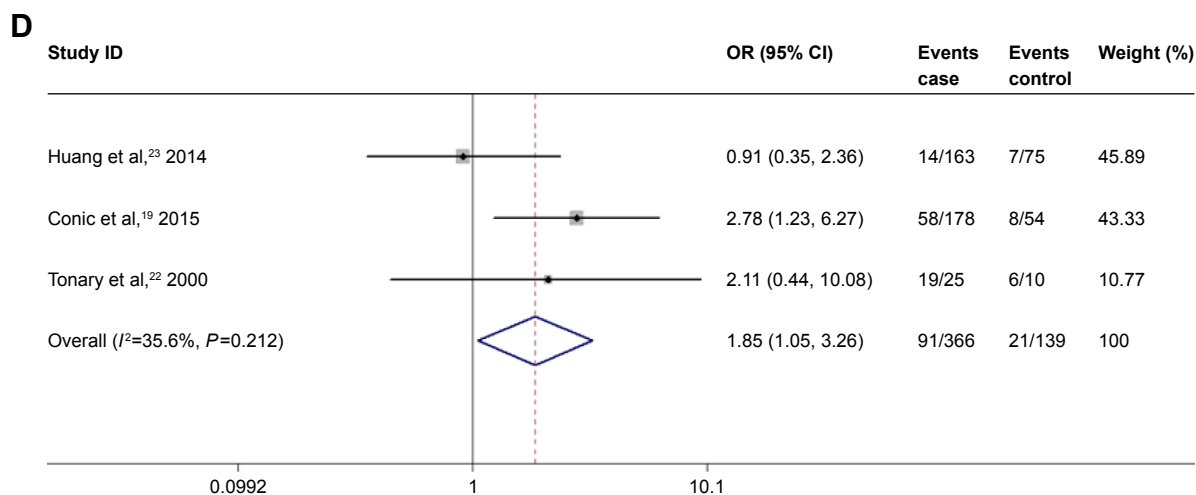


Figure 2 Forest plots of ORs for correlations between CD117 expression and clinicopathological parameters. **Notes:** ORs for the correlations between CD117 expression and (A) age, (B) FIGO stage, (C) differentiation grade, and (D) histological type. X-axis: OR (95% CI). **Abbreviations:** OR, odds ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

its clinical significance in EOC patients, although controversial correlations with clinical outcomes have been found in several recent studies.^{19,22} Therefore, it is necessary to perform a meta-analysis to identify whether CD117 can serve as a predictive biomarker for the clinical management of EOC patients.

In this study, a meta-analysis enrolling 1,247 EOC patients was carried out to assess correlations between CD117 expression and clinical features and postoperative survival. We found that CD117 expression was significantly correlated with FIGO stage and tumor differentiation grade, suggesting that CD117 might be involved in the malignant progression of EOC. This speculation can be partly supported by a previous study that demonstrated that CD117 enhanced the tumorigenicity of EOC cells by conferring a CSC phenotype.²⁹ Additionally, other mechanistic investigations have revealed that CD117 might contribute to EOC development by inducing epithelial–mesenchymal transition, a well-established molecular event that is involved in cell invasion and metastasis.^{30,31} Chene et al recently even have detected high expression of CD117 in the premalignant lesions of EOC, suggesting its potential role as a diagnostic marker for early ovarian tumorigenesis.³² Collectively, these

data suggested that CD117 might serve not only as a helpful indicator for EOC progression but also as a potential target for EOC treatment.

Given its positive correlation with EOC development, it is reasonable to propose that CD117 expression might have some prognostic significance for EOC patients. Based on the extracted survival data from the seven included studies, our meta-analysis demonstrated that CD117 overexpression is significantly associated with worse postoperative OS, suggesting that it is an adverse prognostic factor for EOC patients. However, this conclusion is inconsistent with two included studies, which indicated that CD117 expression was uncorrelated or positively correlated with postoperative OS.^{21,22} Therefore, we subsequently performed a subgroup meta-analysis to further identify correlations between CD117 expression and the OS of EOC patients. We found that CD117 expression was significantly correlated with OS in European patients but not in non-European patients, suggesting that its prognostic value may vary with ethnicity. This is not the first study to report the prognostic inconsistency of CSC markers in EOC patients within different ethnicities. For example, Liu et al recently reported that the CSC marker aldehyde

Table 2 Correlations between CD117 expression and clinicopathological parameters

Clinical variables	Number of studies	Pooled OR (95% CI)	P-value	I^2 (%)
Age (≥ 60 years vs < 60 years)	2	1.67 (1.05–2.66)	0.063	71.0
FIGO stage (III/IV vs I/II)	5	1.99 (1.31–3.02)	0.519	0.00
Differentiation grade (poor vs well)	5	2.46 (1.48–4.10)	0.008	71.2
Histological type (serous vs mixed)	3	1.85 (1.05–3.26)	0.212	35.6

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; OR, odds ratio; CI, confidence interval.

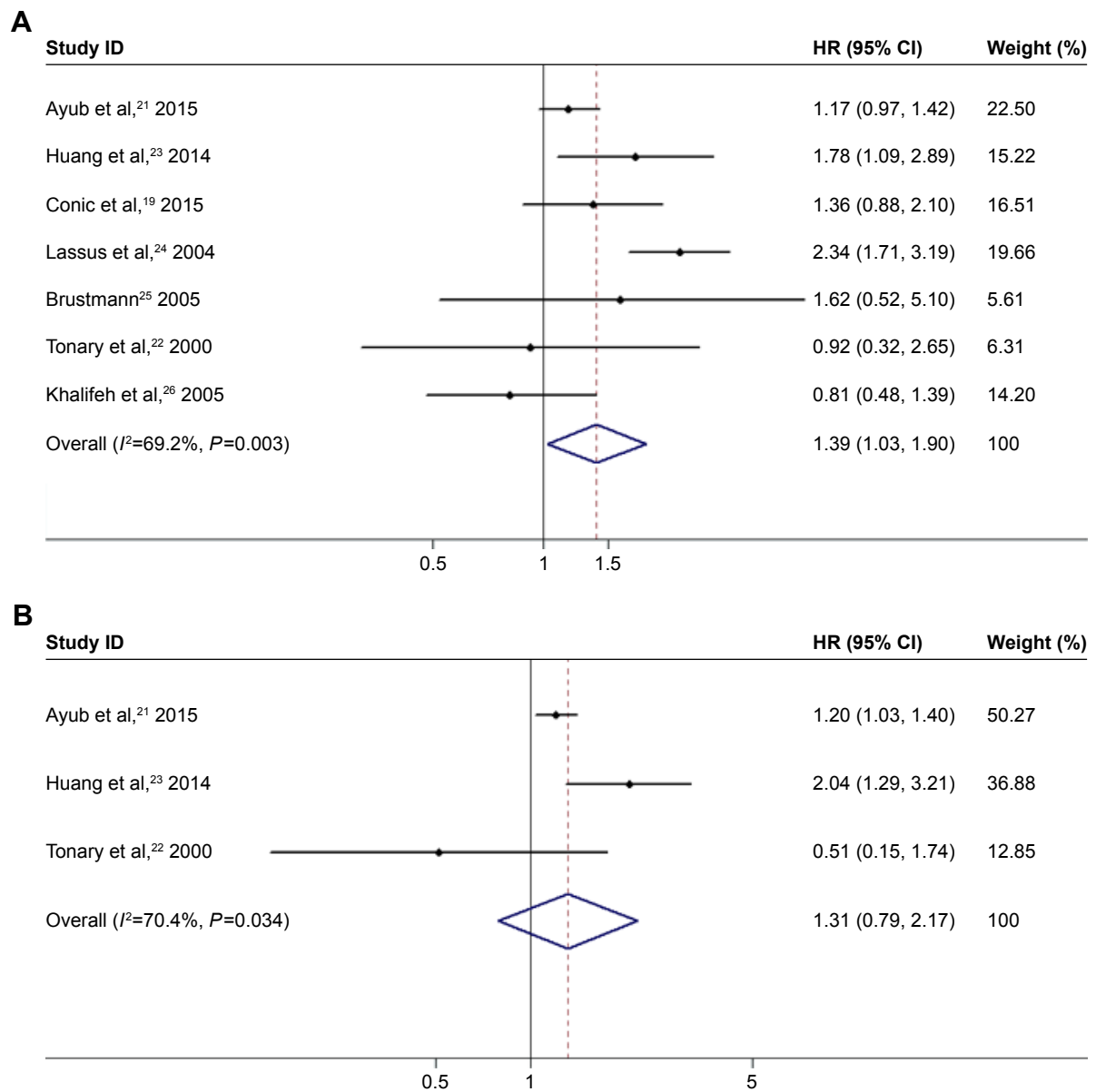


Figure 3 Forest plots of HRs for the correlations between CD117 expression and patient prognosis.

Notes: HRs for the correlations between CD117 expression and **(A)** overall survival and **(B)** disease-free survival. X-axis: HR (95% CI).

Abbreviations: HR, hazard ratio; CI, confidence interval.

Table 3 Prognostic significance of CD117 in subgroup analysis

Variables	Subgroup	No of studies	No of patients	HR (95% CI)	I^2 (%)	P-value
Ethnicity	Europe	5	1,094	1.59 (1.13–2.23)	72.8	0.005
	Non-Europe	2	153	0.83 (0.52–1.34)	0.00	0.833
Age (years)	≥ 60	2	159	0.95 (0.54–1.67)	14.1	0.281
	< 60	4	1,053	1.59 (1.10–2.30)	79.5	0.002
Sample size	≥ 200	3	998	1.84 (1.32–2.56)	50.6	0.132
	< 200	4	249	1.13 (0.95–1.34)	0.00	0.540
Histological type	Serous	4	730	1.37 (0.84–2.24)	83.1	0.000
	Mixed	3	517	1.47 (1.08–2.00)	0.00	0.480

Abbreviations: HR, hazard ratio; CI, confidence interval.

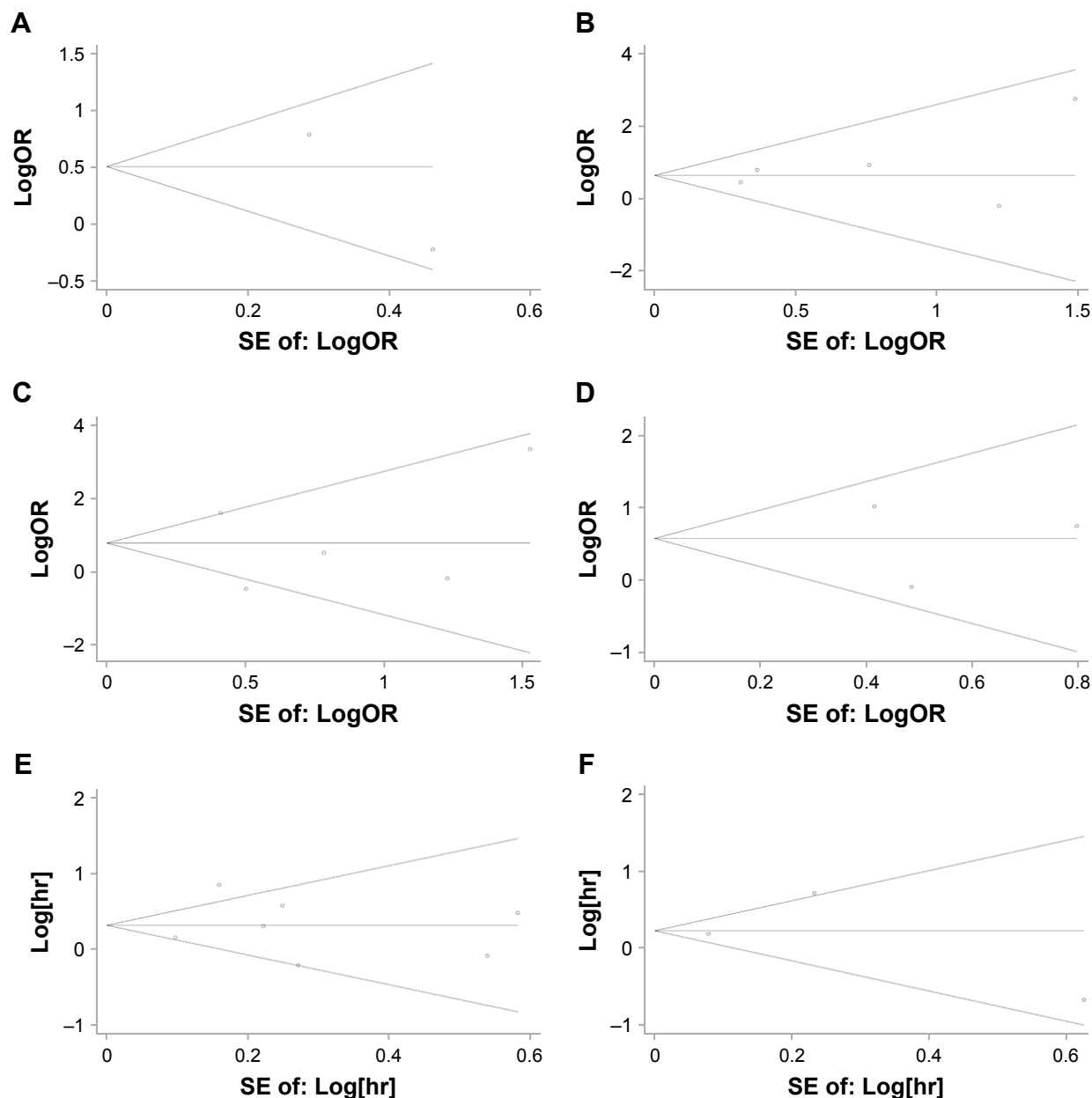


Figure 4 Begg's funnel plots (with pseudo 95% confidence limits) for evaluating publication bias in analyses of clinical features and outcomes.

Notes: Publication bias for (A) age, (B) FIGO stage, (C) differentiation grade, (D) histological type, (E) OS, and (F) DFS analyses.

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; DFS, disease-free survival.

Table 4 Egger's test of funnel plot asymmetry

Variables	t-value	Degrees of freedom	P-value
Overall survival	0.11	6	0.91
Disease-free survival	0.05	2	0.96
FIGO stage	0.85	4	0.45
Differentiation grade	0.05	4	0.96
Histological type	0.13	2	0.91

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

dehydrogenase is correlated with OS and DFS in Asian EOC patients, but not in non-Asian EOC patients.³³ In addition to CSC markers, prognostic inconsistency caused by patient ethnicity has also been found for other molecular biomarkers, such as Matrix metalloproteinase-9 (MMP-9), a well-established molecule that regulates cell invasion and migration.³⁴ Based on these data, we further hypothesized that CD117 may be a specific prognostic

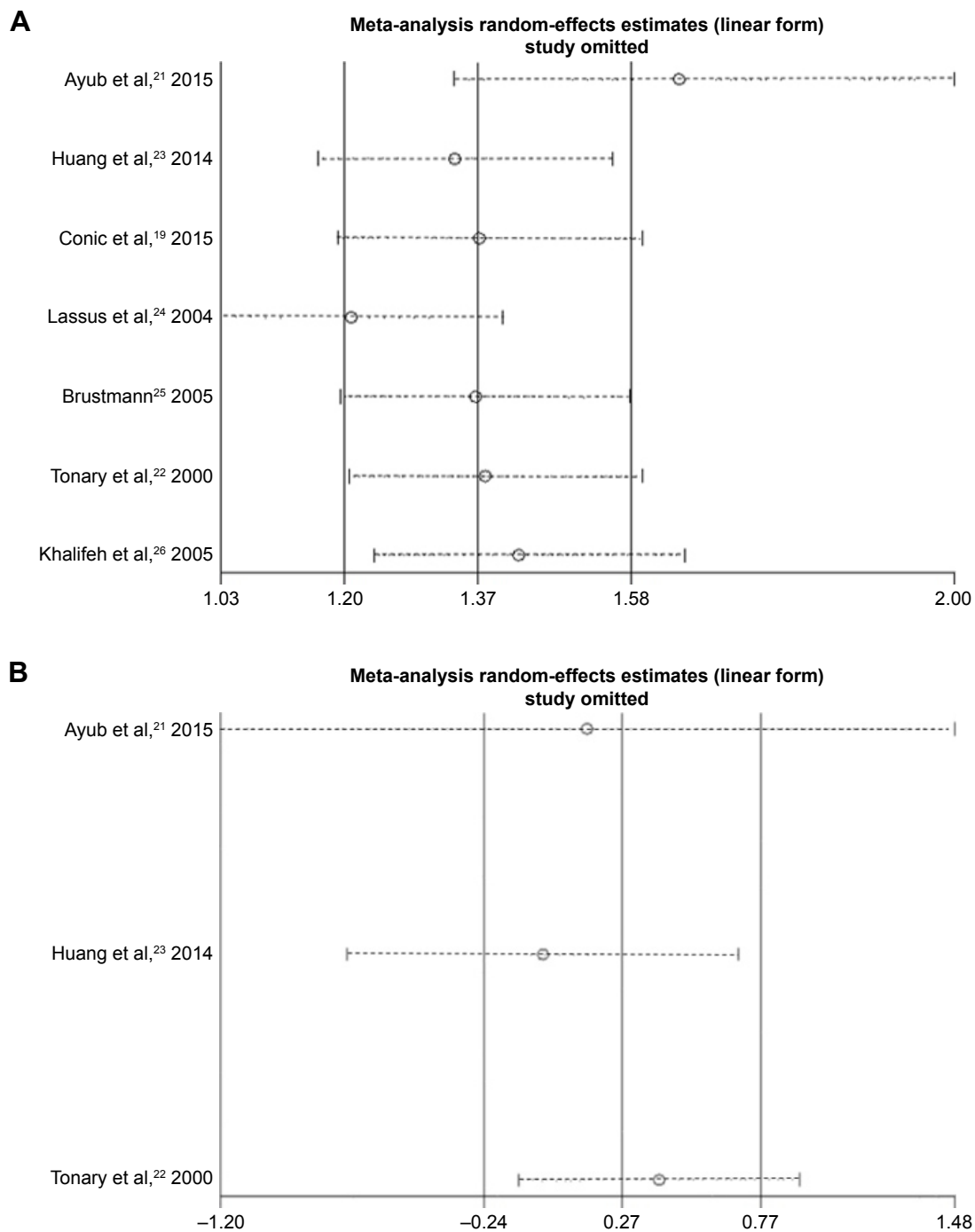


Figure 5 Sensitivity analyses of the studies assessing overall survival (A) and disease-free survival (B).

biomarker for European EOC patients. However, large-scale multicenter retrospective studies will be required to validate this hypothesis. In addition, we found that CD117 is a significant prognostic factor in younger patients, implying that its prognostic significance may also depend on age at diagnosis. Moreover, a significant correlation between CD117 expression and OS was only observed in

studies enrolling >200 patients, strongly supporting the necessity of utilizing large sample sizes in future clinical validations. Finally, we noted that the prognostic impact of CD117 was contradictory in two included studies only enrolling patients with stage III and IV disease, indicating that its clinical utility for late-stage EOC also requires more related validations.^{21,26}

Chemotherapy resistance is a major threat to EOC prognosis, and accumulating evidence suggests a close link between chemoresistance and the presence of CSCs.^{35,36} Thus, detecting CSC markers in EOC patients can help predict benefits of chemotherapy to some degree. For example, Conic et al have recently found that EOC patients with positive CD117 expression were more likely to resist paclitaxel/carboplatin treatment, resulting in a higher recurrence than patients negative for CD117 expression.¹⁹ However, by analyzing CSCs isolated from EOC patients, Ayub et al found that CD117 was uncorrelated with platinum resistance and OS, although it was identified as a significant factor affecting recurrence.²¹ In our meta-analysis of the three available studies, we found that CD117 expression was uncorrelated with DFS in EOC patients. DFS is a widely used criteria for evaluating chemotherapy response; thus, our results suggested that CD117 may not be a predictive factor for assessing the chemotherapy benefits for EOC patients, which is somewhat inconsistent with our knowledge about CSC markers. However, considering the limited number of studies (n=3) included in our analysis, we are unable to make a definite conclusion with regard to that, and therefore strongly advocate for more clinical validations based on large-scale samples.

It must be noted that there are several inherent limitations to our meta-analysis. First, the number of included studies was relatively small, which can be attributed to two reasons: 1) we restricted studies to those published in English, which may have omitted potentially eligible studies published in other languages. Furthermore, compared with other CSC markers, such as CD133 and CD44, CD117 is relatively poorly investigated, not only in EOC but also in other cancer types. Therefore, relevant studies were limited. 2) There are various inherent factors affecting study heterogeneity, such as patient selection, experiment procedures, and staining evaluation. This deficiency is expected to be improved by stricter selection criteria upon sufficient available studies in our following work. Finally, a considerable part of the patient survival data was not provided in the included studies, and therefore was estimated by a digitizing software, which may also be partly responsible for analytical deviations in our study.

Conclusion

In conclusion, our findings demonstrated that CD117 expression is positively correlated with advanced FIGO stage and tumor differentiation grade in EOC patients. In addition, we also found that EOC patients with high CD117 expression have significantly worse OS than those with low CD117

expression. Collectively, these data suggest that CD117 is not only a promising therapeutic target but also a potential prognostic indicator for EOC patients. Larger scale multicenter clinical trials are strongly advocated to further validate our meta-analysis.

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Disclosure

The authors report no conflicts of interest in this work.

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