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The predictive value of PI3K signaling pathway in ovarian cancer prognosis: a meta-analysis

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Abstract. – OBJECTIVE: The aim of the study was to comprehensively assess the clinical significance of the Phosphoinositide 3-kinase (PI3K) signaling pathway in ovarian cancer patients, we conducted a meticulous meta-analysis utilizing individual studies.

MATERIALS AND METHODS: In this meta-analysis, publications through PubMed, Embase, and Cochrane Library databases were searched from inception to December 2022. In this study, only published studies related to the PI3K signaling pathway and prognosis of ovarian cancer patients were included, excluding unpublished literature, incomplete data, animal experiments, literature reviews, and systematic studies. All data were processed by STATA15.1 statistical software.

RESULTS: Previous studies found that PI3K activation was closely related to poor prognosis of ovarian cancer cells [Hazard Ratio (HR)=1.67, 95% CI: 1.03-2.69, *p*=0.038], but not significantly related to disease-free prognosis (HR=1.07, 95% CI: 0.12-9.54, *p*=0.950). Our previous study found that PI3K pathway activation significantly reduced survival in >50% of stage II/III ovarian cancer cells (HR=2.07, 95% CI: 1.17-3.66, *p*=0.012). Our previous study found that PI3K activation level was not strongly associated with the survival of osteosarcoma in the European population (HR=1.35, 95% CI: 0.24-7.60, *p*=0.733), while in the Asian population, PI3K activation level was not strongly associated with the survival of osteosarcoma (HR=1.47, 95% CI: 1.15-1.87, *p*=0.023).

CONCLUSIONS: PI3K can be used as a predictor of prognosis for ovarian cancer, especially in advanced ovarian cancer and Asian patients. Activation of PI3K signaling is associated with poor prognosis in ovarian cancer.

Key Words:
PI3K, Overall survival, Progression-free survival, Ovarian cancer, Meta-analysis.

Introduction

Ovarian cancer, one of the three primary malignancies affecting the female reproductive system, represents approximately 2.5% of all malignant tumors diagnosed in women[1]. Based on statistics[2], approximately 314,000 new cases of ovarian cancer were reported globally, constituting around 1.6% of all cancer cases. Furthermore, about 207,000 individuals succumbed to ovarian cancer, accounting for 2.1% of all cancer-related deaths. Notably, the mortality rate of ovarian cancer ranked highest among the three primary malignancies affecting the female reproductive system[2]. In recent years, there have been advancements in the diagnosis rate and treatment technologies for ovarian cancer. However, still numerous pressing issues exist that require immediate attention and resolution[3]. Identification of molecular markers predicting the clinical outcomes would be of great value for adjustment of patients' treatment[4].

Phosphoinositide 3-kinase (PI3K) is a family of lipid kinases that generate a second messenger by phosphorylating the 3-hydroxyl group of inositol phospholipids in a specific manner[5]. PI3K is divided into three categories: I-III, in the class I component, the p110 catalytic subunit can affect cell proliferation and participate in the regulation of immune function and inflammation[5]; P85 subunit plays a role in receptor binding, enzyme activation, and other processes[6]. Class II PI3K plays an important role in glucose transport, cell migration, cell growth, and cell survival[7]. Class III PI3K is an important regulator of autophagy and vesicle trafficking, which is widely expressed in human tissues and is essential for cell proliferation[8]. PI3K can be activated by tyrosine

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kinase receptors and G-protein coupled receptors to produce PIP3 that activates AKT[9]. Abnormal PI3K signaling pathway is closely related to the prognosis of ovarian cancer[10-12]. Among them, some studies[10,11] argue that PI3K signaling pathway activation is associated with poor prognosis of ovarian cancer, while other studies[12] state that PI3K signaling pathway may improve the prognosis of ovarian cancer. However, there is no systematic evidence to summarize the effect of the PI3K signaling pathway on prognosis. Therefore, this study intends to conduct a meta-analysis on the relationship between the PI3K signaling pathway and the occurrence and development of ovarian cancer to clarify the relationship between the PI3K signaling pathway and the occurrence and development of ovarian cancer.

Materials and Methods

Literature Inclusion and Exclusion Criteria

The eligibility criteria were as follows: studies that reported the correlation between the PI3K pathway and the prognosis of ovarian cancer, with a language restriction to English. Exclusion criteria: duplicate published studies, incomplete studies, incomplete data or unavailability of data, animal testing, review, systematic review.

Search Strategy

In this meta-analysis, publications from PubMed, Embase, and Cochrane Library were searched from inception to December 2022. The search terms were: "PI3K", "PIK3CA" and "Ovarian Neoplasm", "Ovary Neoplasm", "Ovarian Cancer" and "Ovary Cancer", "prognosis", "prognostic", and "indicator".

Literature Screening and Data Extraction

The two researchers (R. Wei and L. Li) conducted the literature search, data screening, and data extraction, respectively. The study contents include the study author, study time, study region, study type, number of cases, overall survival rate, and disease-free development rate of patients.

Literature Quality Assessment

The Newcastle-Ottawa Scale (NOS) was used to independently evaluate the quality of literature, as in a previous cohort study[13].

The Newcastle-Ottawa Scale (NOS) comprises four items related to "subject selection", one item regarding "comparison between groups", two items under "2 items", and three items under "3 items", resulting in a total score of 9 points. Scores exceeding 7 points are considered high, while scores below 7 points are categorized as "3 items". If there is a disagreement, it shall be made by consultation or deliberatioan of a third party. The meta-analysis is performed according to the report items and the relevant items in the PRISMA Checklist[14].

Statistical Analysis

All data were processed with the statistical software STATA 15.1 (Stata Crop LP, College Station, TX, USA)[15] Hazard Ratio (HR) for OS and progression-free survival (PFS) (95% CI) and I^2 were used to assess cell heterogeneity. A heterogeneity test of $p>0.1$, $I^2>50\%$ indicated that all studies were homogeneous and allowed pooled analysis using a fixed effects model. $p<0.1$, $I^2>5\%$ indicated that studies differed, and a difference sensitivity analysis was performed to identify sources of difference. If there was still a significant difference, a random effects model was applied or a descriptive analysis was conducted instead of pooled results. The funnel plot method and the Egger's test were used to investigate publication bias[16].

Results

Literature Search Results

A total of 662 literature articles were collected for this study. After excluding those duplicate trials, 303 studies were obtained. After reading the titles and abstracts, a total of 212 articles were identified. Finally, after a full-text review, 205 articles were excluded, and 7 studies[10,17-22] were incorporated into the meta-analysis (Figure 1).

Baseline Characteristics and Quality Assessment of the Included Studies

Seven retrospective studies were included in this meta-analysis. The sample size of patients ranged from 55 to 835, for a total of 1,547 patients. Among them, 3 studies[19,21,22] were from Asia and 4 studies[10,17,18,20] were from Europe. The age range ranged from 47.5 to 60.0, and most of them were middle-aged patients. The Newcastle-Ottawa Quality Assessment Scale (NOS) scores used for quality assessment were above 7 and meet the requirements (Table I).

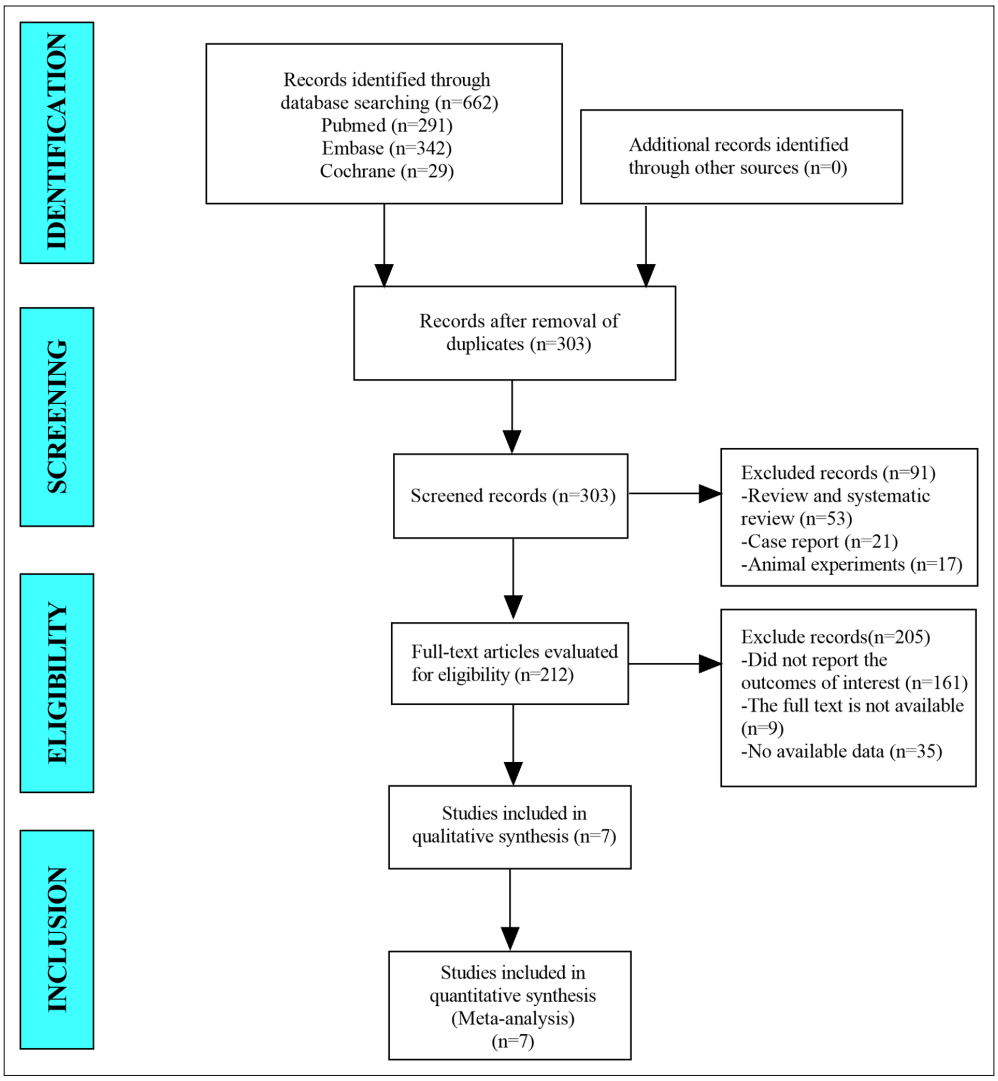

Figure 1. Flow diagram for selection of studies.

Results of Meta-Analysis

Overall survival

Six studies[10,17,19-22] reported the correlation between PI3K signaling pathway and OS. Since there is significant heterogeneity (I^2=63.5%, p=0.018), a meta-analysis was conducted through a random effects model. The pooled results show that the activation of the PI3K signaling pathway is significantly associated with lower OS of patients with ovarian cancer (HR=1.67, 95% CI: 1.03-2.69, p=0.038) (Figure 2).

Progression-free survival

Two studies[17,18] reported the correlation between PI3K signaling pathway and PFS. Since there is significant heterogeneity (I^2=89.9%, p=0.002), a meta-analysis was conducted through a random effects model. The pooled results show that there was no significant association between the PI3K signaling pathway and PFS of patients with ovarian cancer (HR=1.07, 95% CI: 0.12-9.54, p=0.950) (Figure 3).

Subgroup Analysis

FIGO Stage

To analyze the different baseline characteristics of patients further, we conducted a subgroup analysis for OS. We first conducted a subgroup analysis based on the FIGO stage of patients. The pooled results show that the activation of the PI3K signaling pathway in patients with I^2>50%

Table I. Baseline characteristics and quality assessment of the included studies.

Author	Year	Study design	Country	Sample size	Age	FIGO Stage	Histotype	NOS score
Despierre et al[17]	2015	Retrospective	Spain	835	59.0 (19-85)	I-IV: 563/62/57/152	Serous/ Mucinous/Endometrioid/Clear cell: 521/14/61/51	7
Kolasa et al[18]	2009	Retrospective	Poland	117	/	I-IV	/	7
Abe et al[19]	2013	Retrospective	Japan	62	53.5 (30-81)	I-IV: 41/8/9/4	Serous/ Mucinous/Endometrioid/Clear cell: 1/1/1/59	8
Woenckhaus et al[10]	2007	Retrospective	Germany	71	/	I-IV: 22/21/24/7	Serous/ Mucinous/Endometrioid/Clear cell: 39/8/6/9	7
Wang et al[20]	2005	Retrospective	Norway	118	60.0 (38-81)	I-IV: 0/9/72/37	Serous/ Non-serous: 96/22	7
Huang et al[21]	2011	Retrospective	China	55	/	/	/	7
Al-Qahtani et al[22]	2021	Retrospective	Saudi	289	47.5 (31-57)	I-IV: 146/64/68/11	Serous/ Mucinous/Endometrioid/Clear cell: 198/21/33/14	8

International Federation of Gynecology and Obstetrics (FIGO); Newcastle-Ottawa Quality Assessment Scale (NOS).

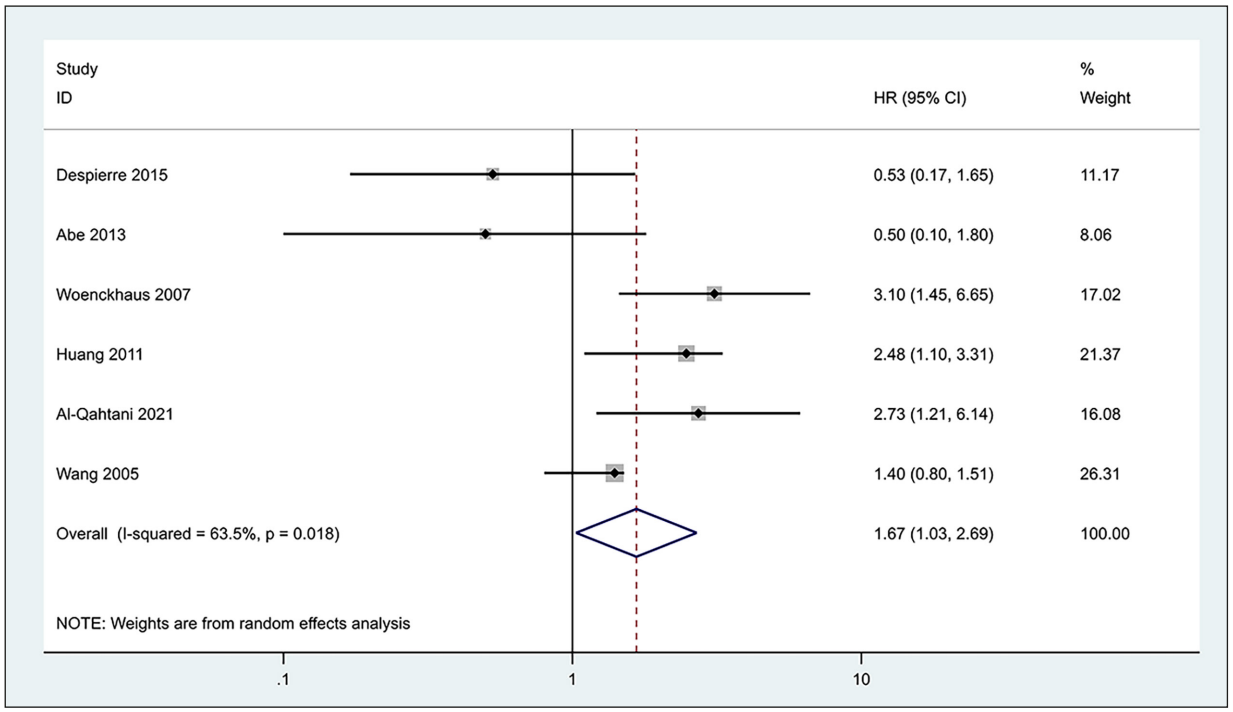

Figure 2. Forest plots on PI3K signaling pathway and OS.

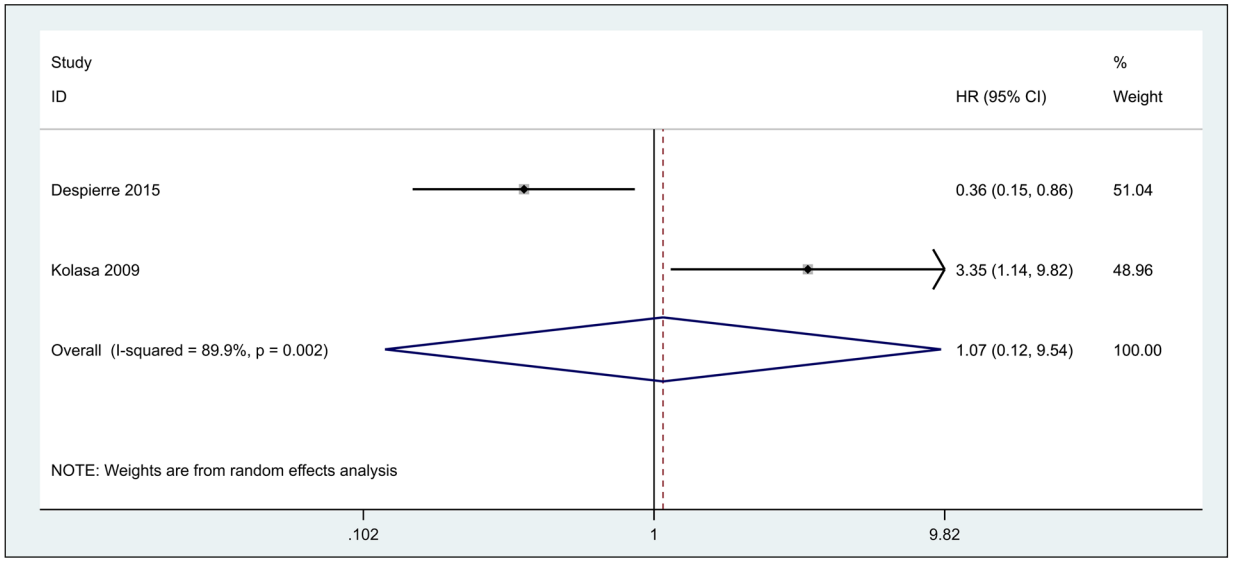

Figure 3. Forest plots on PI3K signaling pathway and PFS.

was not significantly correlated with the patient's OS (HR=0.52, 95% CI: 0.21-1.27, p=0.149). However, the activation of the PI3K signaling pathway in patients with II/III>50% was significantly associated with lower OS of patients with ovarian cancer (HR=2.07, 95% CI: 1.17-3.66, p=0.012) (Figure 4).

Histotype

Then, we explored the differences in OS between different histotypes. The aggregated findings indicated that activation of the PI3K signaling pathway did not show a significant association with overall survival (OS) in ovarian cancer patients. This was true for both patient

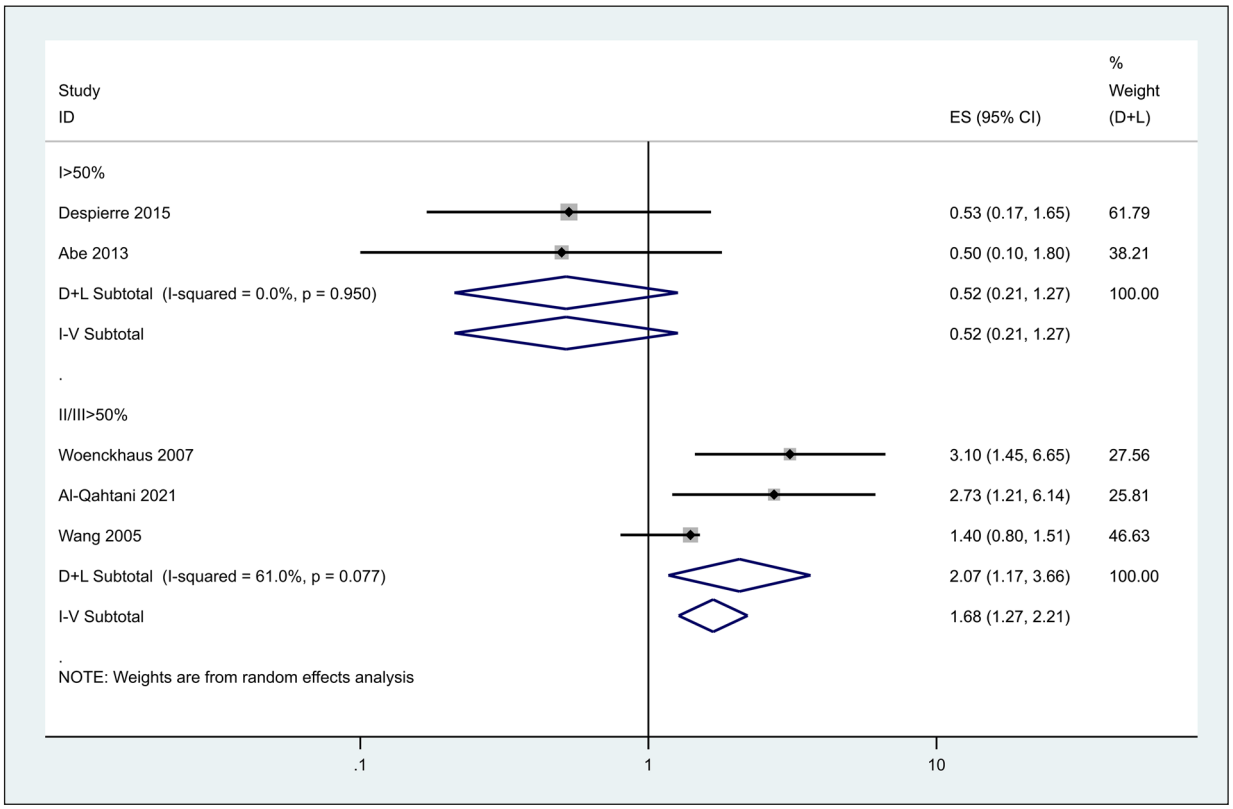

Figure 4. Subgroup analysis of the correlation between PI3K signaling pathway and OS in patients in different FIGO stages.

groups: those with serous histology comprising 50% or more (HR=1.69, 95% CI: 0.93-3.09, p=0.088) and those with less than 50% serous histology (HR=0.50, 95% CI: 0.12-2.12, p=0.347) (Figure 5).

Region

In addition, the pooled results showed no significant correlation between activation of the PI3K signaling pathway and OS in ovarian cancer patients in Europe (HR=1.35, 95% CI: 0.24-7.60, p=0.733), while activation of the PI3K signaling pathway was associated with lower OS of ovarian cancer patients in Asia (HR=1.47, 95% CI: 1.15-1.87, p=0.023) (Figure 6).

Sensitivity Analysis

A sensitivity analysis was performed to exclude each of these trials one by one. Then, a combined analysis of the remaining trials was performed. By doing a meta-analysis, we determined that individual studies did not significantly influence the overall outcome, indicating that the results were stable and reliable (Figure 7).

Publication Bias

Figure 8 shows a funnel-shaped plot of this test. The p-value obtained by Egger's test was 0.854, indicating that no significant publication bias was found in this paper.

Discussion

PI3K is a key molecule that regulates cell proliferation, apoptosis, and other vital activities[23]. Meta-analysis was performed in order to elucidate the important role of the PI3K signaling pathway in the development of ovarian cancer and to provide a theoretical basis for its application in clinical practice. In our preliminary work, we collected 7 papers with 1,547 ovarian cancer patients and analyzed the relationship between PI3K pathway activation and OS and PFS.

Comprehensive studies[24,25] have shown that in ovarian cancer cells, the activation of PI3K signaling is significantly associated with reduced OS levels. PI3K plays an important role in tumorigenesis and its role in tumor development

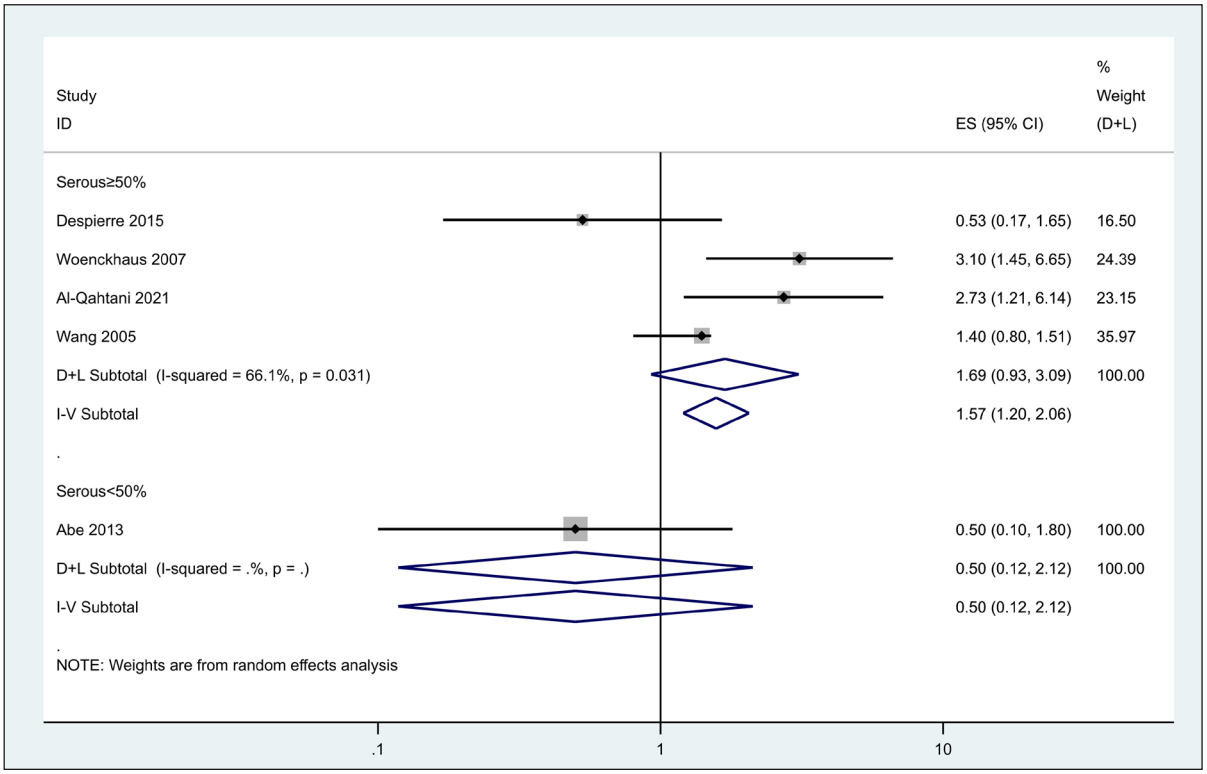

Figure 5. Subgroup analysis of the correlation between PI3K signaling pathway and OS in patients in different histotypes.

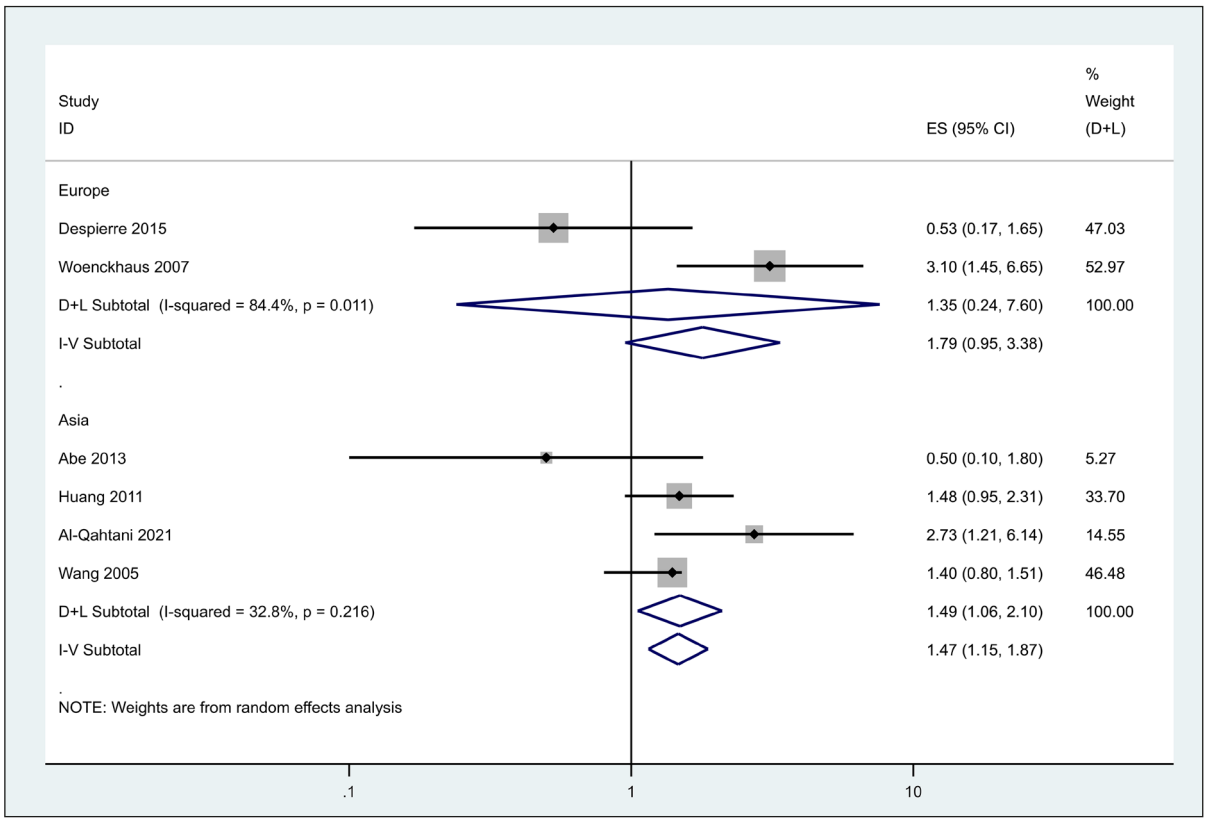

Figure 6. Subgroup analysis of the correlation between PI3K signaling pathway and OS in patients in different regions.

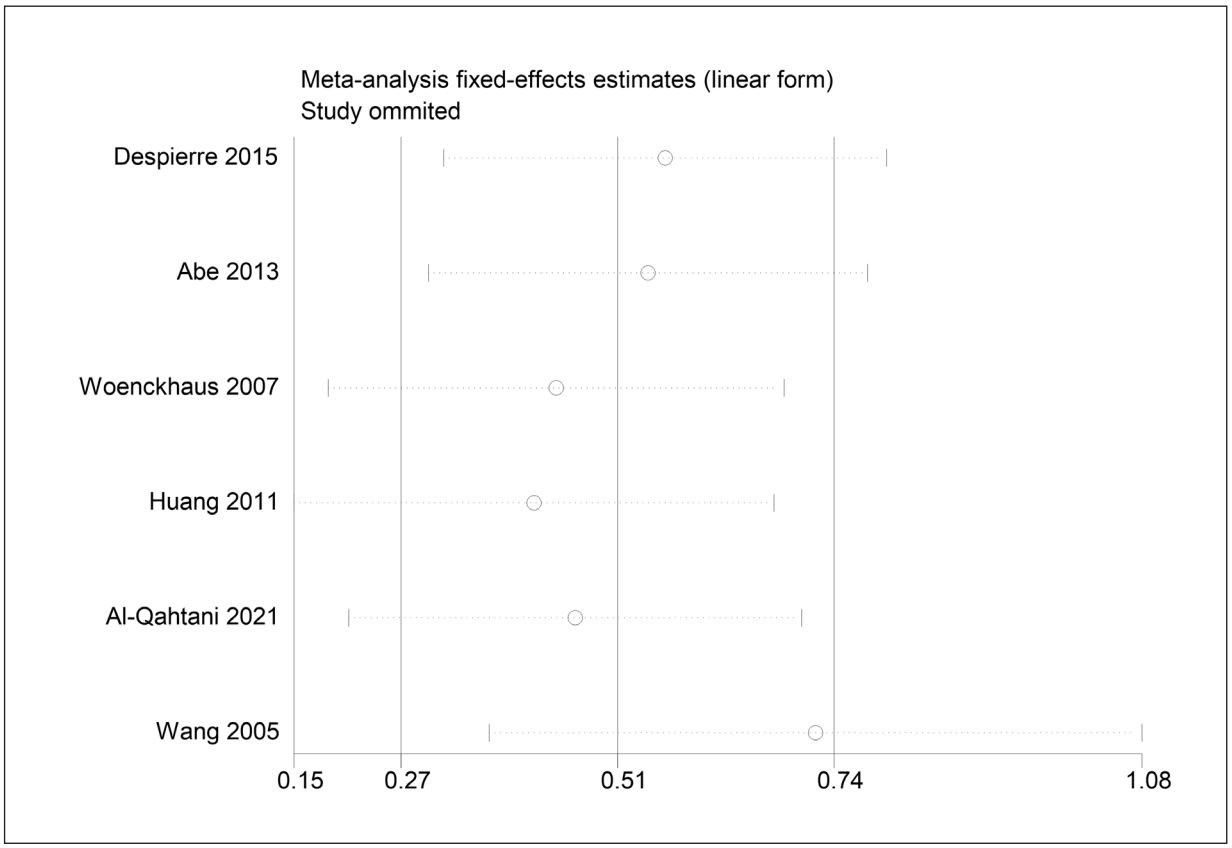

Figure 7. Sensitivity on PI3K signaling pathway and OS.

is of great interest. It has been reported in the literature[26] that PI3K pathway activation induces epithelial-mesenchymal transition (EMT), but the exact mechanism is unclear. In addition, PI3K is one of the important molecular mechanisms of apoptosis, and apoptosis is due to cell autophagy, but the exact mechanism is not clear[27].

To explore its molecular mechanism in depth, researchers performed three-dimensional structural resolution of PI3K protein and high expression of its regulatory protein PIK3R3. Ovarian cancer cell spheres became smaller after the *PIK3R3* gene knockdown, suggesting that the *PIK3R3* gene has the potential to be a new tumor-targeting drug[28]. It was suggested that PI3K and its subunits could be used as predictors of prognosis in tumor patients. However, overall, the findings did not show that PI3K was associated with PFS in ovarian cancer cells. Due to the inconsistency in the results of the two studies[17,18] included in this research, it will be necessary to conduct further large-scale clinical trials in future studies to explore the relationship between PI3K activation status and PFS in ovarian cancer patients.

In view of the differences in the expression levels of PI3K in different patients, this study proposes a subgroup analysis of PI3K expression levels in patients. This is the first subgroup analysis of patients using the FIGO classification method. This study found that PI3K signaling pathway activation was closely related to ovarian cancer prognosis, suggesting that PI3K signaling pathway activation could be an important indicator for predicting ovarian cancer prognosis. We also analyzed the distribution characteristics of osteosarcoma in different tissues. Although it has been reported in the literature that the degree of PI3K activation is closely related to the malignancy of ovarian plasma cells[29,30], this study found that PI3K was not involved. Ultimately, pooled results have shown that activation of the PI3K signaling pathway is closely associated with its reduced survival in the Asian population. This phenomenon may be related to the unique genetic factors of Asians, and more experimental confirmation is needed.

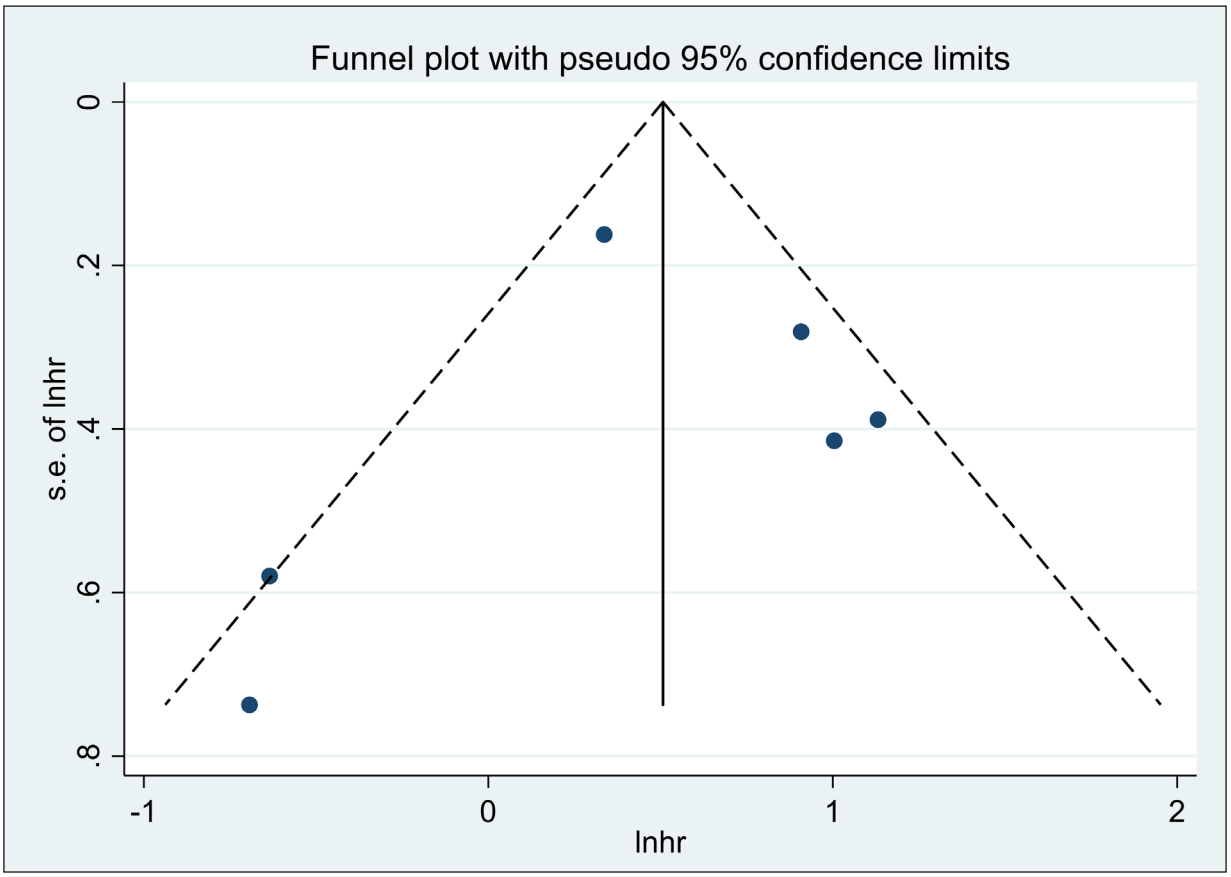

Figure 8. Funnel plot for evaluating the publication bias of this meta-analysis.

Limitations

This meta-analysis has some limitations. First, given that all the studies included in this research are retrospective, there is variability in the quality of the literature, which could lead to selection bias. Second, the lack of research on the analysis of PFS challenges the objectivity of existing studies, which requires further analysis by continuing to include relevant studies in the future.

Conclusions

PI3K can be used as a predictor of prognosis for ovarian cancer, especially in advanced ovarian cancer and Asian patients. Activation of PI3K signaling is associated with poor prognosis in ovarian cancer.

Ethics Approval and Informed Consent

This study is a meta-analysis that synthesizes data from previously published studies. As such, it did not involve direct interaction with human subjects or the collection of new patient data. The data used in this meta-analysis were extracted from studies that had already obtained ethics approval and informed consent from their respective institutional review boards and participants. Therefore, additional ethics approval and informed consent were not required for this study.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflicts of interest.

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Authors' Contributions
Renji Wei participated in the acquisition of the data, performed the data analyses, and drafted the manuscript; Li Li helped perform the analysis with constructive discussions and conceived the study.

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