

## REVIEW

# Efficacy and safety of olaparib in the treatment of platinum-sensitive recurrent ovarian cancer: a systematic review and meta-analysis

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**Abstract**

**Background:** Olaparib, an orally active inhibitor, has undergone comprehensive clinical evaluation as either single or combination therapy in several solid tumors. To explore the efficacy and safety of Olaparib versus placebo in the treatment of platinum-sensitive recurrent ovarian cancer, we conducted a systematic review and meta-analysis. **Methods:** We systemically searched through April 30, 2021 PubMed, Cochrane Library, Embase and Web of Science for randomized control trials (RCTs) that compared Olaparib and placebo therapies for platinum-sensitive recurrent ovarian cancer. The primary outcomes were progression-free survival (PFS) and overall survival (OS) evaluated by Hazard ratio (HR) with 95% CI and the secondary outcome was adverse events calculated by the risk ratio (RR) with 95% CI. **Results:** A total of 3 RCTs, involving 592 patients in the Olaparib group and 359 patients in the placebo therapy, were included. The analysis results of RCTs showed that Olaparib had a significantly better PFS than placebo (HR 0.31; 95% CI 0.26–0.37;  $p \leq 0.001$ ), and the pooled OS of the Olaparib group was significantly higher than that of the placebo group (RR 0.73; 95% CI 0.60–0.90;  $p = 0.003$ ). Regarding safety, the main adverse events included nausea, fatigue, vomiting, anemia, diarrhea, abdominal pain, constipation, headache, dysgeusia and decreased appetite. **Conclusions:** Olaparib has a positive effect on platinum-sensitive recurrent ovarian cancer as related to progression and overall survival with an increase in adverse events being noted. This meta-analysis demonstrated that Olaparib maintenance therapy is generally well tolerated by the patients.

**Keywords**

adverse events; efficacy; meta-analysis; ovarian cancer; olaparib; safety

## 1. Introduction

Ovarian cancer accounts for 3–4% of female cancers. Due to the lack of specific clinical symptoms in the early stage of an ovarian malignancy, approximately 70% of patients are diagnosed in the late stage of disease. According to China's cancer statistics in 2015, there are 52,100 new cases of ovarian cancer and 22,500 deaths per year, with an observed increasing trend in mortality of ovarian cancer [1]. Although most patients with ovarian cancer undergo surgery combined with a course of chemotherapy, 75% of the patients relapse within 2 years [2]. Recurrent ovarian cancer refers to the complete remission of patients' clinical symptoms after receiving surgery and chemotherapy with the recurrence of the disease at least 6 months after stopping chemotherapy. Platinum-resistant recurrent ovarian cancer accounts for approximately 25% of patients with first-time recurrent ovarian cancer, and almost all patients with recurrent ovarian cancer will eventually develop platinum resistance [3]. Recently, poly (ADP-ribose) polymerase (PARP) inhibitors have become a new op-

tion for maintenance treatment of ovarian cancer having been approved by the US Food and Drug Administration (FDA). These inhibitors can provide longer survival time for patients with recurrent ovarian cancer [4]. PARP inhibitors are very important for PARP enzymes, mainly in the following two aspects: PARP inhibitors inhibit PARP enzyme activity [5] and capture the PARP enzyme at the DNA single-strand break site [6]. Olaparib is the first PARP inhibitor which has successively obtained priority review qualifications from both the European Medicine Agency (EMA) and FDA and was approved for listing in Europe and the United States in December 2014. The treatment of Olaparib may last for 2–3 years or longer. In order to improve the quality of life for patients and maximize the benefit of treatment, attention must be paid to serious adverse reactions along with the long-lasting mild adverse reactions such as fatigue and nausea. Therefore, it is important to explore the efficacy and safety of Olaparib.

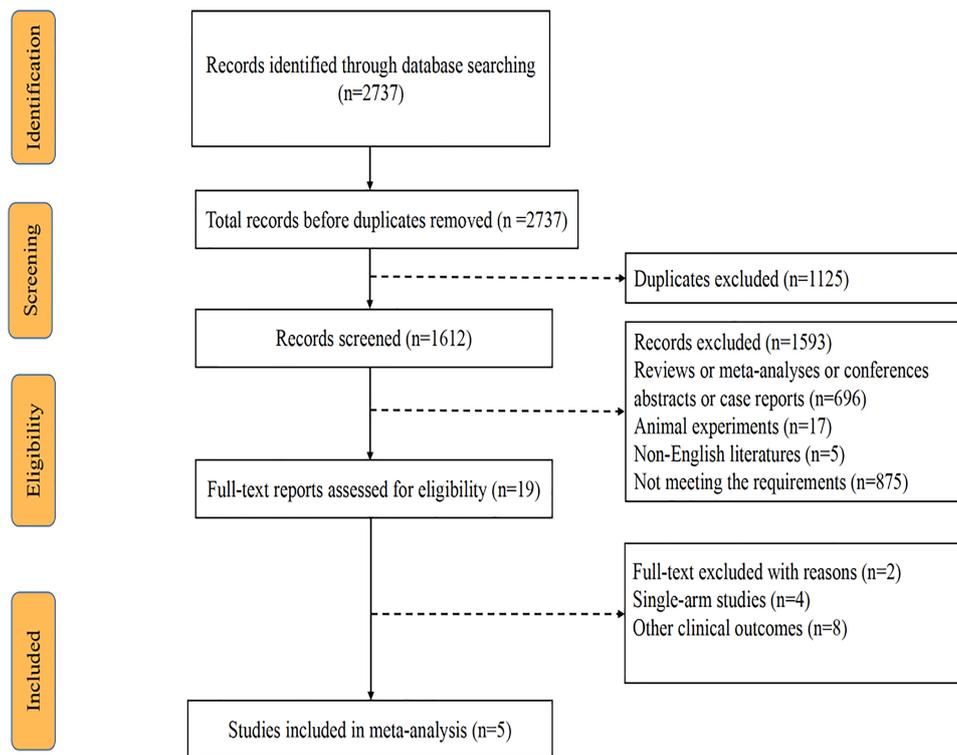


FIGURE 1. Study selection process for the meta-analysis.

## 2. Materials and Methods

### 2.1 Electronic Search

A systematic review and meta-analysis of Olaparib were conducted for this study. A comprehensive search of PubMed, Cochrane Library, Embase and Web of Science was carried out using medical subject heading (MeSH) terms and text words related to Olaparib and Ovarian Neoplasms. The search was completed through April 2021. Relevant articles and abstracts from retrieved articles were browsed for additional eligible studies.

### 2.2 Study Selection

The selection of literature was performed independently by two reviewers. Any discrepancies were discussed and resolved by consensus between both reviewers. The relevant clinical studies of Olaparib maintenance therapy for platinum-sensitive ovarian cancer patients were included according to PICOS criteria if they met all of the following criteria for eligibility: (1) Patients with platinum-sensitive recurrent ovarian cancer; (2) Participants assigned to treatment with Olaparib or placebo; (3) Studies' evaluating the following outcomes: (a) progression-free survival (PFS), (b) overall survival (OS), (c) adverse events; (4) The trial was a RCT design; (5) Articles were published in the English language. Studies were excluded for the following reasons: (1) Treatment of other diseases rather than platinum-sensitive recurrent ovarian cancer; (2) Observational trials, retrospective studies or case reports; (3) Conference abstracts, guidelines, letters, meta-analysis and reviews. Single-arm studies (phase I and II) were excluded due to the lack of control groups.

### 2.3 Data Extraction

The following information was extracted from each trial: first author, publication year, country, clinical Trials.gov number, study design, dosage of Olaparib, age, follow-up time, PFS, OS and adverse events. For publications reporting results from the same trial, the most recent or complete publication reporting the information of interest was considered. According to the third or fourth version of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, high-grade (grade 3 or 4) adverse events (AEs) were defined.

### 2.4 Assessment of Risk of Bias

The risk of bias for included studies was assessed using the Cochrane Collaboration tool RevMan 5.4 (The Cochrane Collaboration, London, England), including the following seven domains [7]: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); (7) Other bias.

### 2.5 Data handling and statistical Methods

Stata 15.1 software packages (Nets Times Company, Beijing, China) were utilized for data analysis. Based on the data from all trials, pooled PFS and OS evaluated by hazard ratio (HR) with 95% CIs were calculated to assess the efficacy of Olaparib in treating ovarian cancers. In terms of safety, the binary data (adverse events) was calculated by the risk ratio (RR) with 95% CI. Heterogeneity, representing the percentage

**TABLE 1. Characteristics of included studies.**

First Author Year	Country	Study Design	Total N (Olaparib /Placebo)	Dosage	Median Age (Y)	Median duration of follow-up (mo)	Median PFS (mo)	Median OS (mo)
Ledermann 2014	Multiple countries	RCT	136/129	400 mg orally twice daily	58 (21–89) vs 59 (33–84)	37.1 (34.4–39.7) vs 37.6 (34.9–40.3)	8.4 vs 4.8	-
Ledermann 2016	Multiple countries	RCT	136/129	400 mg orally twice daily	58 (21–89) vs 59 (33–84)	71.0 (68.5–72.7) vs 70.8 (38.2–73.0)	-	29.8 vs 27.8
Moore 2018	Multiple countries	RCT	260/131	300 mg orally twice daily	53 (47–60) vs 53 (47–59)	41	51.8 vs 15.1	-
Friedlander 2021	Multiple countries	RCT	260/131	300 mg orally twice daily	53 (47–60) vs 53 (47–59)	40.7 (34.9–42.9) vs 1.2 (32.2–41.6)	-	-
Poveda 2021	Multiple countries	RCT	196/99	1500 mg orally twice daily	56 (51–63) vs 56 (49–63)	65.7 (63.6–69.3) vs 64.5 (63.4–68.7)	19.1 vs 5.5	51.7 vs 38.8

RCT, randomized controlled trial; N, Number; Y, year; mo, month.

of total variation across studies, was considered statistically significant when  $p < 0.1$ . When substantial heterogeneity was not observed or  $I^2 < 50\%$  ( $p \geq 0.1$ ), a fixed-effect model was used. A random-effect model was adopted to obtain more appropriate estimates of the average treatment effect in the case of between-study heterogeneity. A sensitivity analysis was carried out by sequential omission of individual studies to capture whether certain characteristics of the included studies would affect the pooled estimates. A  $p$  value  $< 0.05$  was considered statistically significant.

### 3. Results

#### 3.1 Study Selection and Characteristics

A total of 1736 results were obtained based on the search strategy. According to the initial review of titles, 746 duplicates and 985 articles that did not meet the criteria were excluded. Finally, five studies, including three RCTs, were further assessed for eligibility, and the latest publication of each trial was adopted for the meta-analysis. The detailed selection process is presented in Fig. 1. The three RCTs were multicenter, randomized, double-blind, parallel-group trials, with the clinicalTrials.gov numbers of NCT00753545, NCT01844986 and NCT01874353 respectively. The characteristics of patients are shown in Table 1.

#### 3.2 Risk of Bias

All five included studies were RCTs. The overall risk of selection, allocation, performance, detection, attrition and reporting bias was very low. All trials were double-blind phase III trials, with the exception of Ledermann (2014) and Ledermann (2016) which were double-blind phase II trials. Two trials (Ledermann, 2014 & Ledermann, 2016) were at high risk of attrition bias due to the lack of intention-to-treat basis, as well as the risk of reporting secondary outcomes. Detailed risk of bias assessment is described in Fig. 2 with a review of authors' judgments about each risk of bias item for each included study.

#### 3.3 Progression-Free Survival

Three trials reported the outcome of PFS with pooled data demonstrating a statistically significant improvement in PFS for participants treated with Olaparib when compared with placebo therapy. The fixed-effect model was adopted for the significant heterogeneity among trials ( $I^2 = 0.0\%$ ,  $p = 0.749$ ), and the combined HR for PFS was 0.31 (95% CI 0.26–0.37,  $p < 0.001$ ; Fig. 3).

#### 3.4 Overall Survival

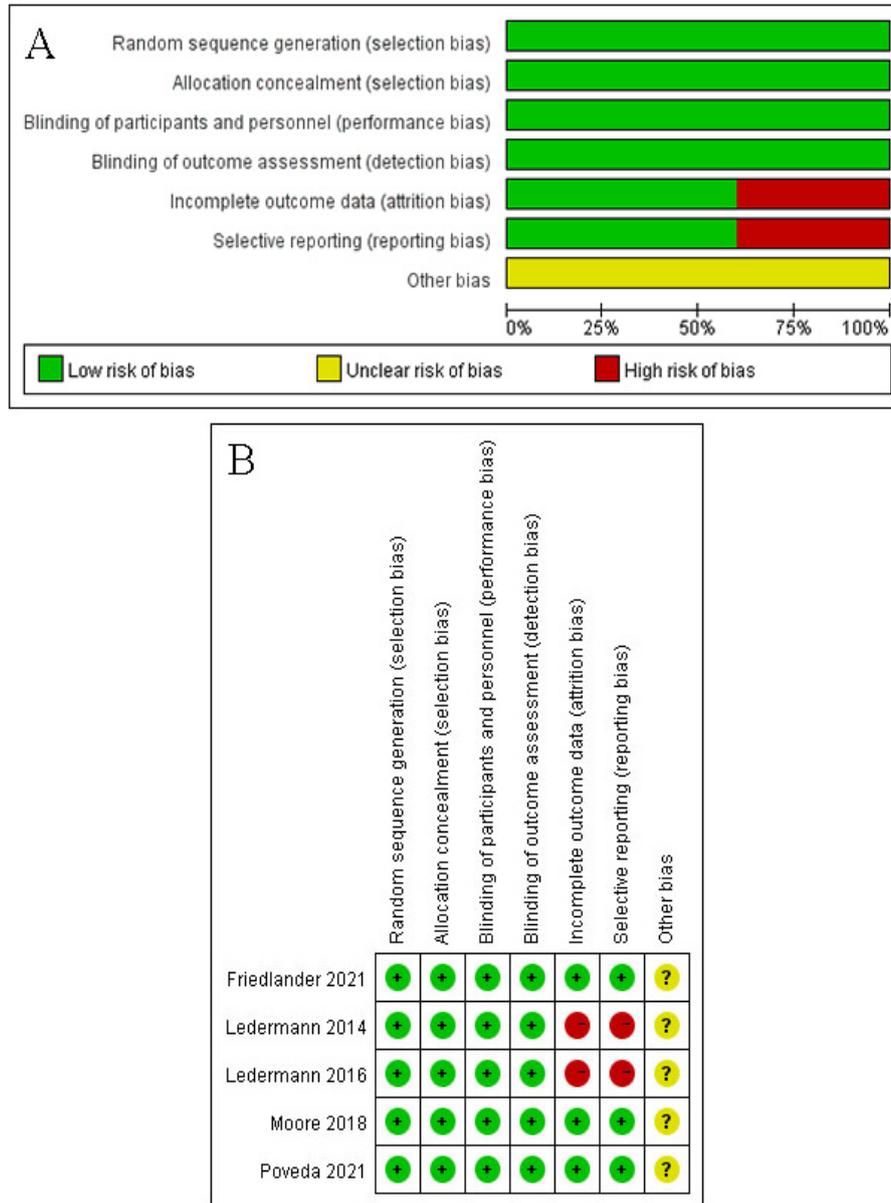
Two of three trials reported data on OS. A statistically significant improvement in OS (HR: 0.73; 95% CI 0.60–0.90;  $p = 0.003$ ; Fig. 3), was observed in patients treated with Olaparib in contrast to placebo, which was revealed by the fixed-effect model for significant heterogeneity ( $I^2 = 0.0\%$ ,  $p = 0.949$ ).

#### 3.5 Adverse Events

It is critical to identify and manage adverse events which may impair patients' quality of life. Adverse events that led to the discontinuation of treatment were reported in the included studies, as well as high-grade AEs (Table 2). Compared with the placebo group, some patients in the Olaparib group experienced dose interruptions or dose reductions. Meanwhile, adverse events were more likely to occur or lasted longer in the Olaparib group than in the placebo group.

### 4. Discussion

The development of first-in-class PARP inhibitors has changed the therapeutic management of platinum-sensitive recurrent ovarian cancer. Olaparib is an orally active inhibitor, which has undergone comprehensive clinical evaluation both as single and combination therapy in various malignancies including ovarian cancer, breast cancer and gastric cancer. Although previous meta-analyses have demonstrated the efficacy and controllable toxicity of Olaparib, previous studies mostly focused on phase II RCT with incomplete OS data with some



**FIGURE 2. Risk of bias map.** (A) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

controversies existing on the interpretation of OS. Therefore, in order to increase the statistical ability to evaluate the impact on OS and provide more reliable estimates of efficacy and safety, we systematized the available information in order to proceed with this meta-analysis.

Our study indicated that Olaparib maintenance therapy provided substantial benefit in terms of PFS (HR 0.31 [95% CI 0.26–0.37],  $p < 0.001$ ) and led to a significantly longer OS (HR 0.73 [95% CI 0.60–0.90],  $p = 0.003$ ) compared to placebo. A previous meta-analysis of three RCTs demonstrated that Olaparib maintenance therapy had significant advantage on PFS (HR 0.50, 95% CI 0.32–0.80), especially in patients with *BRCA1* or *BRCA2* mutations (HR 0.32, 95% CI 0.11–0.94), but had no significant benefit on OS in patients with recurrent serous ovarian cancer [8]. Gao found that olaparib still had high therapeutic activity and good tolerance for

wild-type *BRCA* in Asian ovarian cancer patients [9]. Ma [10] published a meta-analysis including four RCTs to find that Olaparib maintenance therapy significantly improved PFS (HR 0.31, 95% CI 0.15–0.62) while slightly improving OS (HR 0.75, 95% CI 0.56–0.99) in the patients with platinum-sensitive *BRCA*-mutated ovarian cancer as compared to other interventions (placebo or chemotherapy drugs). In the analyses of toxicity profile, they found the common adverse events included anemia, fatigue, vomiting, diarrhea and nausea [10]. Another meta-analysis evaluated eight trials and confirmed that Olaparib treatment significantly improved PFS (HR 0.62, 95% CI 0.47–0.82;  $p = 0.001$ ), OS (HR 0.82, 95% CI 0.73–0.93;  $p = 0.001$ ), and ORR (RR 1.38, 95% CI 1.16–1.65;  $p < 0.001$ ), when compared with controls in various cancers (ovarian cancer, small-cell lung cancer, breast cancer and gastric cancer) [11]. However, OS was not the primary endpoint

**TABLE 2. Adverse events and safety profile.**

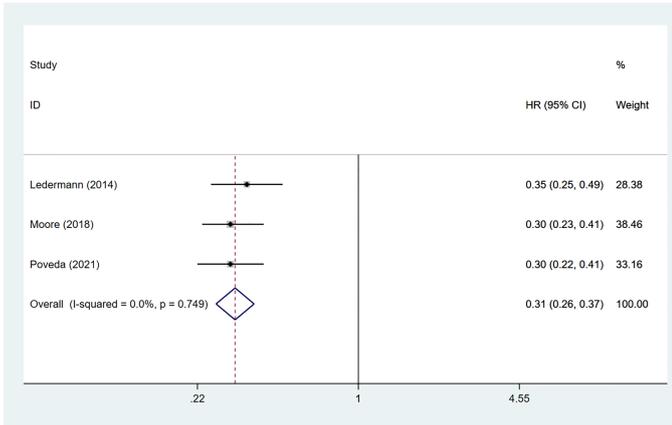
Adverse events	Olaparib (N = 592)	Placebo (N = 359)	RR (95% CI)	<i>p</i>	I <sup>2</sup>	P <sub><i>h</i></sub>	Model used
Nausea	445	130	2.06 (1.78, 2.38)	<0.001	0.0	0.915	Fixed
Fatigue	366	143	1.52 (1.32, 1.76)	<0.001	0.0	0.494	Fixed
Vomiting	228	57	2.37 (1.83, 3.07)	<0.001	0.0	0.578	Fixed
Anemia	219	30	4.12 (2.87, 5.89)	<0.001	0.0	0.929	Fixed
Diarrhea	193	83	1.39 (1.11, 1.74)	0.004	0.0	0.412	Fixed
Abdominal pain	153	90	1.03 (0.82, 1.30)	0.789	0.0	0.419	Fixed
Constipation	146	62	1.36 (1.04, 1.77)	0.023	33.0	0.225	Fixed
Headache	137	61	1.36 (0.88, 2.11)	0.164	58.2	0.092	Random
Dysgeusia	128	19	4.04 (2.51, 6.52)	<0.001	30.1	0.239	Fixed
Decreased appetite	123	41	1.84 (1.32, 2.57)	<0.001	0.0	0.785	Fixed
Arthralgia	120	67	1.04 (0.80, 1.36)	0.760	0.0	0.723	Fixed
Neutropenia	113	26	2.35 (1.56, 3.54)	<0.001	29.3	0.243	Fixed
Dizziness	105	35	1.70 (1.18, 2.43)	0.004	34.0	0.220	Fixed
Cough	102	47	1.53 (0.65, 3.63)	0.332	83.1	0.003	Random
Dyspepsia	96	36	1.61 (1.12, 2.30)	0.010	0.0	0.613	Fixed
Upper abdominal pain	94	40	1.40 (0.99, 1.97)	0.054	41.9	0.179	Fixed
Back pain	93	44	1.27 (0.91, 1.77)	0.160	0.0	0.809	Fixed

of most included trials in this study, probably leading to the problem of incomplete OS data. In this current study, the median chemotherapy-free time of 51.8 months for women treated with Olaparib is a remarkable achievement, since the overall time to relapse is about 1.5 years [12]. Germline mutations in the tumor suppressor *BRCA1* and *BRCA2* genes are closely associated with an increased risk of newly diagnosed ovarian cancer [13], which have been identified in approximately 10–15% of cases with the incidence in those with the platinum-sensitive malignancy being higher [14]. Recent research has shown that women without the *BRCA* mutations have a lifetime risk of ovarian cancer of about 1.3% [15]. For women carrying harmful *BRCA1* or *BRCA2* mutations, the risk is estimated to reach 44% [16] and 17% [17] respectively. Compared with wild-type cells, *BRCA1* and *BRCA2*-deficient cells were up to 1,000-fold more sensitive to PARP inhibition [18]. Studies have confirmed that Olaparib can be used for patients with heavily pretreated ovarian cancer related to *BRCA* gene defects [19], and it has been widely used in clinical practice, especially in the treatment of solid tumors. PARP inhibition has also been proved to be an effective treatment for patients with a germline *BRCA* mutation and metastatic pancreatic cancer [20], and contributes to a longer PFS for patients with breast cancer who are likely to benefit from PARP beyond *BRCA1* and 2 mutation carriers [21]. Olaparib may act as a potential therapy for hepatocellular carcinoma (HCC) [22]. Furthermore, Olaparib can exert an antitumor effect in recurrent glioblastoma [23] and effectively acts on human stomach adenocarcinoma (STAD) treatment, as the enhanced Olaparib-induced antitumor effect by CIC-3/SGK1 regulatory axis may provide promising therapeutic potential for the clinical application of Olaparib in STAD treatment [24].

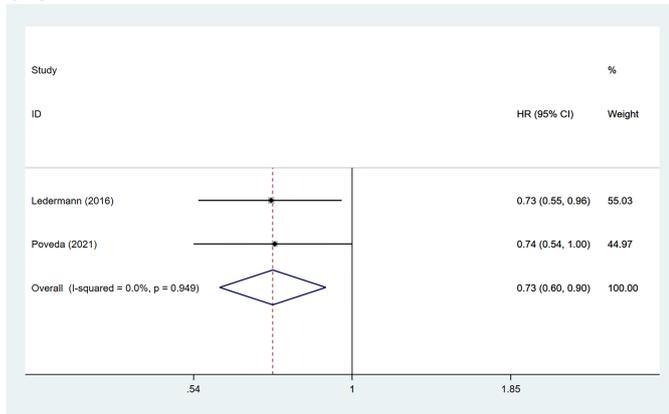
Analysis results of the present study demonstrates that Ola-

parib therapy is well-tolerated with the most common adverse events associated with Olaparib being nausea, fatigue, vomiting, anemia, diarrhea, abdominal pain, constipation, headache, dysgeusia and decreased appetite with most of events being mild to moderate in severity. Moreover, risks of severe hematologic and non-hematologic toxicities were discovered between Olaparib therapy and placebo therapy. It is worth noting that three common adverse events in clinical practice being nausea, fatigue and vomiting can limit the administration of ovarian cancer treatment and affect the quality of life of patients. We evaluated all grades of adverse events as most previous publications only focused on the high-grade adverse events. In the included trials, the RR of all levels of nausea, fatigue, and vomiting remained statistically significant, but due to the unavailability of individual patient data, we were unable to further explore the connections between various adverse reactions. Fatigue, commonly referred to as motivation loss, a persistent lack of energy and decreased mental work capacity and exhaustion [25] is very subjective and might be associated with endocrine changes or altered muscle metabolism [26]. Pharmacological interventions (exercise, sleep hygiene, massage, maintenance of physical fitness, distractions) and non-pharmacologic approaches (sleep-aid medication, psychostimulants) are required for those suffering from severe fatigue [27]. Compared with placebo, Olaparib has the highest risk of causing anemia (RR 4.12 [2.87, 5.89],  $p < 0.001$ ), which is supported by the fact that PARP is related to the regulation of red blood cell production [28]. In addition, great effort should be made to identify patients who are more susceptible to myelodysplastic syndrome and small intestinal obstruction. The efficacy of subsequent PARP inhibitors after chemotherapy progression needs to be further addressed and additional data needs to be collected in ongoing as well as real-world ex-

## (A) Progression-Free Survival



## (B) Overall Survival



**FIGURE 3. Forest plots of pooled HRs for PFS (A) and OS (B) by fixed-effect model.** Note: HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

perience to determine the optimal treatment. Although the use of PARP inhibitors marks a new era for patients with or without *BRCA*-mutant ovarian cancer, the inevitable development of resistance to PARP inhibitors indicates that new combination therapies need to be discovered to overcome the resistance mechanism and enhance the efficacy of PARP inhibitors [29], taking into account the possible overlapping toxicity caused by the combination of PARP and chemotherapeutics resulting in neutropenia [30]. There are still some limitations that need to be considered in our meta-analysis. First, only three RCTs were included in the current meta-analysis, weakening the applicability of this study. Second, variables such as race and age were confounded at the patient level with a lack of individual patient data preventing subgroup analyses. In addition, the efficacy and safety of Olaparib have only been confirmed from short-term treatment and still needs to be investigated during long-term studies. Lastly, different doses of the drugs adopted in the clinical trials had also affected the results of the meta-analysis. More clinical trials about Olaparib are still in progress and the safety of different doses of drugs needs to be further explored.

## 5. Conclusions

Our meta-analysis confirms that Olaparib can significantly prolong PFS as well as OS in patients as compared with placebo. Nevertheless, some questions remain to be resolved, such as when and how to use PARP inhibitors in patients before chemotherapy, whether to use them alone or in combination with other therapies (such as immunotherapy and anti-angiogenesis drugs), how to choose the best treatment based on molecular subgroups and how to enable patients to benefit most from PARP inhibitors in the absence of any defined predictive biomarker of PARP inhibitors. Moreover, further studies are required to determine whether patients with disease progression and relapse after being treated with Olaparib need to continue the use of PARP inhibitors. At present, how to overcome the mechanism of PARP inhibitors resistance is a priority for future clinical research.

## AUTHOR CONTRIBUTIONS

YW and YC drafted the initial manuscript, designed study and analyzed data. QW reviewed the image processing results and provided extensive critical insights and revisions. All authors contributed to the final version of the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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